Conceptrichtlijn Melanoom

(15 modules)

INITIATIEF
Nederlandse Internisten Vereniging
Nederlandse Vereniging voor Heelkunde

IN SAMENWERKING MET
Nederlandse Vereniging voor Nucleaire geneeskunde
Nederlandse Vereniging voor Dermatologie en Venereologie
Nederlandse Vereniging voor Radiologie
Nederlandse Vereniging van Pathologie
Verpleegkundigen & Verzorgenden Nederland

MET ONDERSTEUNING VAN
Kennisinstituut van de Federatie Medisch Specialisten

FINANCIERING
De ontwikkeling van de richtlijnmodule werd gefinancierd uit de Stichting Kwaliteitsgelden Medisch Specialisten (SKMS)

Colofon

Commentaarfase december 2024

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In dit document vindt u <u>modulaire updates en nieuw ontwikkelde modules</u> die in de richtlijn Melanoom ingebed worden

De volledige richtlijn Melanoom vindt u op de Richtlijnendatabase:

https://richtlijnendatabase.nl/richtlijn/melanoom/melanoom_-_startpagina.html

of in de app:

https://richtlijnendatabase.nl/app.html

Inhoudsopgave

Samenstelling van de werkgroep

Huidige samenstelling van de werkgroep:

- Dr. A.A.M. (Astrid) van der Veldt, voorzitter, internist-oncoloog, werkzaam in het Erasmus Medisch Centrum, NIV
- Dr. M.J.B. (Maureen) Aarts, internist-oncoloog, werkzaam in het Maastricht Universitair Medisch Centrum, NIV
- Prof. dr. A.J.M. (Fons) van den Eertwegh, internist-oncoloog, werkzaam in het Amsterdam Universitair Medisch Centrum, NIV
- Dr. M. (Hilde) Jalving, internist-oncoloog, werkzaam in het Universitair Medisch Centrum Groningen, NIV
- Dr. S. (Sofie) Wilgenhof, internist-oncoloog, werkzaam in het Antoni van Leeuwenhoek, NIV
- Dr. J.J. (Han) Bonenkamp, chirurgisch oncoloog, werkzaam in het Radboudumc, NVvH
- Dr. D.J. (Dirk) Grünhagen, chirurgisch oncoloog, werkzaam in het Erasmus Medisch Centrum, NVvH
- Dr. A.B. (Anne Brecht) Francken, chirurgisch oncoloog, werkzaam in het Isala, NVvH
- Dr. E.I. (Elsemieke) Plasmeijer, dermatoloog, werkzaam in het Antoni van Leeuwenhoek, NVDV
- Dr. R. (Remco) van Doorn, dermatoloog, werkzaam in het Leids Universitair Medisch Centrum, NVDV
- Dr. Q.G. (Quido) de Lussanet de la Sablonière, nucleair radioloog, werkzaam in het Erasmus Medisch Centrum, NVvR
- Dr. E.H.J.G. (Erik) Aarntzen, nucleair geneeskundige, werkzaam in het Universitair Medisch Centrum Groningen, NVNG
- Drs. B.A. (Beatrijs) Seinstra, radioloog, werkzaam in het Antoni van Leeuwenhoek, NVvR
- H.C. (Hanna) van der Pol, MSC, verpleegkundig specialist melanoom, werkzaam in het Antoni van Leeuwenhoek, V&VN
- Dr. T.P. (Thomas) Potjer, klinisch geneticus, werkzaam in het Leids Universitair Medisch Centrum, VKGN
- Dr. W.A.M. (Willeke) Blokx, patholoog, werkzaam in het Universitair Medisch Centrum Utrecht, NVVP
- Dr. A.M.L. (Anne) Jansen, klinisch moleculair bioloog in de pathologie, werkzaam in het Universitair Medisch Centrum Utrecht, NVVP

Met speciale dank aan:

- Dr. B. Leeneman, Universitair docent, werkzaam in het Erasmus Medisch Centrum (bijdrage aan de doelmatigheidsmodule)

Met ondersteuning van:

- Dr. D. (Dagmar) Nieboer, senior adviseur, Kennisinstituut van de Federatie Medisch Specialisten
- Drs. R.J.S. (Rayna) Anijs, adviseur, Kennisinstituut van de Federatie Medisch Specialisten
- Dr. L. (Lisanne) Verbruggen, adviseur, Kennisinstituut van de Federatie Medisch Specialisten
- Drs. F. (Fieke) Pepping, junior adviseur, Kennisinstituut van de Federatie Medisch Specialisten

Voormalig betrokken werkgroepleden:

- Drs. J.G.M. (Anne) van den Hoek, radiotherapeut, werkzaam in het Universitair Medisch Centrum Groningen, NVRO (tot en met juni 2024)

Verantwoording

Leeswijzer

Deze verantwoording zal op de Richtlijnendatabase (Richtlijnendatabase.nl) bij elk van de in deze richtlijn opgenomen modules worden geplaatst.

Autorisatie en geldigheid

De richtlijnmodules zullen worden geautoriseerd door de: Nederlandse Vereniging voor Heelkunde, Nederlandse Vereniging voor Dermatologie en Venereologie, Nederlandse Internisten Vereniging, Nederlandse Vereniging voor Nucleaire Geneeskunde, Nederlandse Vereniging voor Radiologie, Nederlandse Vereniging voor Pathologie, Verpleegkundigen & Verzorgenden Nederland. Op dit moment is er nog geen consensus bereikt over het patiëntperspectief binnen deze modules.

Algemene gegevens

De ontwikkeling/herziening van deze richtlijnmodule werd ondersteund door het Kennisinstituut van de Federatie Medisch Specialisten (www.demedischspecialist.nl/kennisinstituut) en werd gefinancierd uit de Kwaliteitsgelden Medisch Specialisten (SKMS).
De financier heeft geen enkele invloed gehad op de inhoud van de richtlijnmodule.

Samenstelling werkgroep

Voor het ontwikkelen van de richtlijnmodule is in 2017 een multidisciplinaire werkgroep ingesteld, bestaande uit vertegenwoordigers van alle relevante specialismen (zie hiervoor de Samenstelling van de werkgroep) die betrokken zijn bij de zorg voor patiënten met Melanoom.

Belangenverklaringen

De Code ter voorkoming van oneigenlijke beïnvloeding door belangenverstrengeling is gevolgd. Alle werkgroepleden hebben schriftelijk verklaard of zij in de laatste drie jaar directe financiële belangen (betrekking bij een commercieel bedrijf, persoonlijke financiële belangen, onderzoeksfinanciering) of indirecte belangen (persoonlijke relaties, reputatiemanagement) hebben gehad. Gedurende de ontwikkeling of herziening van een module worden wijzigingen in belangen aan de voorzitter doorgegeven. De belangenverklaring wordt opnieuw bevestigd tijdens de commentaarfase.

Een overzicht van de belangen van werkgroepleden en het oordeel over het omgaan met eventuele belangen vindt u in onderstaande tabel. De ondertekende belangenverklaringen zijn op te vragen bij het secretariaat van het Kennisinstituut van de Federatie Medisch Specialisten.

Werkgroeplid	Functie	Nevenfuncties	Gemelde belangen	Ondernomen actie
Veldt, van der (voorzitter)	Internist-oncoloog, afdeling Interne Oncologie (0,8 fte) en afdeling Radiologie & Nucleaire Geneeskunde (0,2 fte) Erasmus MC, Rotterdam	Adviesraden: BMS, MSD, Merck, Novartis, Pfizer, Eisai, Sanofi, Pierre-Fabre en Ipsen. Betaald aan het instituut (Erasmus MC) Roche (ook betaald aan het instituut Erasmus MC)	A.A.M. van der Veldt is principal investigator van meerdere studies van firma's (BMS, Exelexis, Novartis, Roche) en investigator-initiated studies (o.a. Safe Stop Trials) die financieel worden ondersteund door onder andere de	Actie ondernomen bij modules over systemische behandelingen Zie hiervoor 'Werkwijze en toelichting belangen richtlijn Melanoom'

			zorgverzekeraars en non-profit organisaties Participatie aan NADINA-trial	
Bonenkamp	Chirurgisch oncoloog, RadboudUMC Nijmegen	* Lid DB TFG Melanoom (onbetaald) * Lid bestuur WIN-O (onbetaald) * Lid DB DMTR (onbetaald) * Lid DB Dutch sarcoma Group	Geen	Geen actie
Aarts	Internist-oncoloog Maastricht Universitair Medisch Centrum	* Bestuurslid WIN-O (Werkgroep Immunotherapie Nederland voor Oncologie) melanoom en nierkanker (onbetaald) * Bestuurslid TFG (tumor focus groep)-melanomen (Integraal kankercentrum Nederland) (onbetaald) * Bestuurslid PRO-RCC (Prospectief Nederlands Nierkanker Cohort) * Bestuurslid OncoZON (Oncologisch netwerk Zuid-Oost Nederland) melanoom * Adviesraad (betaald) BMS, Novartis, AMGEN, MSD, Roche, Ispen, Pfizer, Eisai, Merck, Sanofi, Astellas	* Pfizer - Tyrosine Inhibitor effect op trombocyten - Co-promotor Participatie aan NADINA-trial	Actie ondernomen bij modules over systemische behandelingen Zie hiervoor 'Werkwijze en toelichting belangen richtlijn Melanoom'
Doorn, van	Dermatoloog, Leids Universitair Medisch Centrum	Onbetaald lid van enkele besturen (European Society for Dermatological Research, Nederlandse Vereniging voor Experimentele Dermatologie) adviseur van Stichting Melanoom (onbetaald)	Stichting KiKA - Therapeutic targeting of congenital melanocytic naevus and childhood melanoma using FOXO4 anti-senescence peptides - Projectleider Zeldzame Ziekten Fonds, onderzoek naar Familial Atypical Multiple Mole Melanoma syndrome	Geen actie

			-Stichting Dioraphte, onderzoek naar farmacologische therapie voor congenitale melanocytaire nevi	
Francken	Chirurgisch oncoloog, Isala	* Voorzitter werkgroep audit NVvH * Lid werkgroep endocriene chirurgue * Lid werkgroep mammachirurgie	Geen	Geen actie
Jalving	Internist-oncoloog, UMCG Groningen	Adviesraden: Bristol-Myers Squibb, AstraZenica,Pierre Fabre (betaald aan instituut (UMCG)	* KWF - TAMIC: Dichloroacetate in patients with metastatic melanoma prior to treatment with immune-checkpoint inhibition - Projectleider * KWF - FORCE: Infrastructure for rare Cancers in the Netherlands - Geen projectleider	Actie ondernomen bij modules over systemische behandelingen Zie hiervoor 'Werkwijze en toelichting belangen richtlijn Melanoom'
Wilgenhof	Internist-oncoloog in het Antoni van Leeuwenziekenhuis	Adviesraden: Eisai, Bristol-Myers Squibb, Pierre Fabre, Novartis, Pfizer en lpsen (betaald aan instituut (AVL)); educatief symposium: MSD en Bristol-Myers Squibb (betaald aan insituut (AVL))	* EU Horizon 2020 (no 875052) - CAPABLE: Pilot study of the eHealth application Cancer Patients Better Life Experience - Geen Projectleider * EU (101104801) - CARE-1: Optimizing Treatmensts for Metastatic Renal Carcinoma - Geen Projectleider Studies: principal investigator: CA224020 studie (Clinicalîrials.gov number, NCT01968109) R3767-ONC-2011 studie (NCT05352672) E2139 (NCT05270044) vorinostat studie (NCT02836548) subinvestigator: TIL studie (Clinicalîrials.gov number, NCT02278887) NADINA studie (Clinicalîrials.gov number, NCT04949113) safe stop studie	Actie ondernomen bij modules over systemische behandelingen Zie hiervoor 'Werkwijze en toelichting belangen richtlijn Melanoom'

			safe stop ipi-nivo (NCT05652673) E1325 (NCT02362594) NIVEC studie (NCT04330430) NKTR-214 + nivolumab (NCT03635983) EBIN (NCT03235245) DONIMI (NCT04133948) MASTERKEY-115 (NCT04068181) IOB-013 (NCT05155254)	
Grünhagen	Chirurg, Erasmus MC	Lid bestuur WIN-O melanoom, onbetaald	Deelname NADINA-trial	Geen actie
Plasmeijer	Dermatoloog, AVL	* Bestuurslid Win-O: onbetaald * Lid JongCBG: 1500 EUR/jaar onkostenvergoeding * Bestuurslid SCOPE (Skin Care in organ transplantrecipients Europe): onbetaald * Lid NCI Keratinocyte Cancer Consortium (KeraCon) Immunosuppression Group: onbetaald * Lid domeingroep NVDV dermatotherapie: onbetaald * Raad van Advies HUKA's: onbetaald * Raad van Advies Lacune NVDV (kennisagenda)	Geen	Geen actie
Eertwegh, van den	Medisch-oncoloog, afdeling medische oncologie, Cancer Center Amsterdam, Amsterdam UMC, Vrije Universiteit Amsterdam Voorzitter DMTR (Dutch Melanoma Treatment registry)(vacatiegeld aan Amsterdam UMC)	Adviesraad (betaald aan Amsterdam UMC): Bristol-Myers Squibb, MSD Oncology, Ipsen, Pierre Fabre, Janssen Cilag BV	* Sanofi - Prostaat studies (cabazipet en RECAB) - Projectleider * TEVA - prostaat studie (RECAB) - Projectleider * Bristol-Myers Squibb - Onco-kompas - Geen projectleider Huidig:" * Idera - INTRIM melanoom studie - Projectleider * Roche - REPOSIT melanoom studie - Projecteider * Novartis, Pierre Fabre, MSD, BMS en ziektekosten - DMTR - Geen projectleider PI NADINA-trial	Actie ondernomen bij modules over systemische behandelingen Zie hiervoor ‘Werkwijze en toelichting belangen richtlijn Melanoom’

Potjer	Klinisch Geneticus, LUMC	Cluster expertisegroep Maligniteiten van de huid	Geen	Geen actie
Blokx	Klinisch patholoog, UMC Utrecht	Geen	Geen	Geen actie
Jansen	Klinisch Moleculair Bioloog in de Pathologie, UMC Utrecht	Bestuurslid Stichting PALGA (vacatiegelden)	Geen	Geen actie
Seinstra	Radioloog - Antoni van Leeuwenhoek Ziekenhuis	Betrokken bij NADINA-trial als mede-auteur	Geen	Geen actie
Lussanet de la Sablonière	Nucleair- en Abdomen radioloog, Erasmus Medisch Centrum, Rotterdam	Geen	Geen	Geen actie
Aarntzen	Nucleair geneeskundige, UMC Groningen (0,8 fte) * UMCGroningen, nucleair geneeskundige (0,8 fte) * Radboudumc, post-doc onderzoeker (0,1 fte) * Eberhard Karls University, Tuebingen, Duitsland (0,5 fte)	* Post-doc onderzoeker Radboudumc, betaald (0,1 fte) * Post-doc onderzoeker Eberhard Karls University Tuebingen (Duitsland), betaald (0,05 fte)	* EU Innovatieve Health Initiative (IHI) - IMAGIO - IMAGING and advanced guidance for workflow optimalization in interventionaal oncology - Projectleider * Bergh in het Zadel/ Radboud oncologie Fonds - 'Breek de barrière: 'een nieuwe lokale en gerichte behandelmethode voor alvleesklierkanker' - Projectleider * ImaginAB Inc - iPREDICT, Trial: A phase IIB, Open Label, Study of 89Zr-crefmirlimab berdoxam PET/CT in Subjects with Selected Advanced or Metastetic Malignancies to ? - Geen projectleider site PI * Bergh in het Zadel/Radboud oncologie Fonds - Inzet AI voor betere overleving niet-kleincellig longkanker - Projectleider * ImaginAB Inc - (89Zr)Df-IAB22MC anti-CD8 minibody PET/CT-imaging to assess the in vivo distribution of CD8+ T-cells in COVID-19 patienst (NCT04874818) - Projectleider * KWF - Imaging tumor-infiltrating CD8+ T-cells in	Geen actie

			non-small cell lung cancer patienst upon neo-adjuvant treatment with Durvalumab - Projectleider	
Leeneman	Universitair docent, Erasmus Universiteit Rotterdam	Geen	* ZIN - Ontwikkeling van ziektemodel voor melanoom - Geen projectleider * ZIN - Actualisatie van ziektemodel voor melanoom - Projectleider	Geen actie
Van der Pol	Verpleegkkundig specialist, Antoni van Leeuwenhoekziekenhuis, Amsterdam	Geen	Geen	Geen actie

Werkwijze en toelichting belangen richtlijn Melanoom

De Code ter voorkoming van oneigenlijke beïnvloeding door belangenverstrengeling is gevolgd. Alle werkgroepleden hebben schriftelijk verklaard of zij in de laatste drie jaar directe financiële belangen (betrekking bij een commercieel bedrijf, persoonlijke financiële belangen, onderzoeksfinanciering) of indirecte belangen (persoonlijke relaties, reputatiemanagement) hebben gehad. Gedurende de ontwikkeling of herziening van een module worden wijzigingen in belangen aan de voorzitter doorgegeven. De belangenverklaring wordt opnieuw bevestigd tijdens de commentaarfase.

De NIV heeft vastgesteld dat het niet mogelijk was werkgroepleden af te vaardigen met voldoende expertise zonder potentiële belangenverstrengeling. Het gaat daarbij met name om werkgroepleden die deelnemen aan adviesraden/kennisuitwisselingsbijeenkomsten met de farmaceutische industrie of deel nemen of hebben genomen als onderzoeker van een klinische studie. Gedurende de ontwikkeling van de [richtlijn / modules] heeft daarom afstemming plaatsgevonden tussen de werkgroepvoorzitter, de belangencommissie van het Kennisinstituut van de Federatie Medisch Specialisten en de NIV over passende acties naar aanleiding van de gemelde belangen.

Restricties voor de modules over onderwerpen (medicamenteuze behandeling) waar de adviesraden betrekking op hebben:

- Werkgroeplid werkt niet als enige inhoudsdeskundige aan de module;
- Werkgroeplid werkt tenminste samen met een werkgroeplid met een vergelijkbare expertise in alle fasen (zoeken, studieselectie, data-extractie, evidence synthese, Evidence-to-decision, aanbevelingen formuleren) van het ontwikkelproces. Indien nodig worden werkgroepleden toegevoegd aan de werkgroep;
- In alle fasen van het ontwikkelproces is een onafhankelijk methodoloog betrokken;
- Overwegingen en aanbevelingen worden besproken en vastgesteld tijdens een werkgroepvergadering onder leiding van een onafhankelijk voorzitter (zonder gemelde belangen).

Aansluitend op de reguliere commentaarronde bij de achterban van de bij de richtlijn betrokken wetenschappelijke verenigingen, hebben (een aantal) leden van richtlijn- en kwaliteitscommissie van de NIV en een methodoloog van het Kennisinstituut die niet betrokken waren bij ontwikkeling van de modules, aanvullend beoordeeld of de aanbevelingen logischerwijs aansluiten bij het gevonden bewijs en de overwegingen, om de onafhankelijkheid van de richtlijn te waarborgen.

Wellicht ten overvloede willen wij erop wijzen dat medisch specialistische richtlijnen niet worden vastgesteld door de betreffende richtlijnwerkgroep maar door de besturen/ledenvergadering van de betrokken verenigingen.

Een overzicht van de belangen van werkgroepleden en het oordeel over het omgaan met eventuele belangen vindt u in onderstaande tabel. De ondertekende belangenverklaringen zijn op te vragen bij het secretariaat van het Kennisinstituut van de Federatie Medisch Specialisten.

Inbreng patiëntenperspectief

Bij elke module is het patiëntperspectief meegenomen door de werkgroep.
Stichting melanoom is uitgenodigd om te participeren tijdens de herziening van de richtlijn. Op deze uitnodiging is vooralsnog niet ingegaan. De conceptrichtlijn wordt voorgelegd aan de Nederlandse Federatie van Kankerpatiëntorganisaties (NFK), Patiëntfederatie Nederland (PFN) en de Stichting Melanoom.

NHG-standaard Verdachte huidafwijkingen

Voor huisartsen is de NHG-Standaard Verdachte huidafwijkingen leidend. Deze sluit aan op de richtlijn Melanoom.

Kwalitatieve raming van mogelijke financiële gevolgen in het kader van de Wkkgz

Bij de richtlijnmodule is conform de Wet kwaliteit, klachten en geschillen zorg (Wkkgz) een kwalitatieve raming uitgevoerd om te beoordelen of de aanbevelingen mogelijk leiden tot substantiële financiële gevolgen. Bij het uitvoeren van deze beoordeling is de richtlijnmodule op verschillende domeinen getoetst (zie het stroomschema op de Richtlijnendatabase).

Module	Uitkomst raming	Toelichting
Module 3.1 familiaire risicofactoren	Geen substantiële financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (5.000-40.000 patiënten), volgt ook uit de toetsing dat het geen nieuwe manier van zorgverlening of andere organisatie van zorgverlening betreft. Er worden daarom geen substantiële financiële gevolgen verwacht.

Module	Uitkomst raming	Toelichting
Module 4.1 pTNM-classificatie en AJCC stadiëring	Geen substantiële financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (5.000-40.000 patiënten), volgt ook uit de toetsing dat het geen nieuwe manier van zorgverlening of andere organisatie van zorgverlening betreft. Er worden daarom geen substantiële financiële gevolgen verwacht.

Module	Uitkomst raming	Toelichting
Module 7.1.5. Moleculaire diagnostiek bij gelokaliseerde ziekte (Stadium III)	Geen substantiële financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (5.000-40.000 patiënten), volgt ook uit de toetsing dat het geen nieuwe manier van zorgverlening of andere organisatie van zorgverlening betreft. Er worden daarom geen substantiële financiële gevolgen verwacht.

Module	Uitkomst raming	Toelichting
Module 7.2.1. Neoadjuvante behandeling bij	Geen substantiële financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (5.000-40.000

locoregionale ziekte (Stadium III)		patiënten), volgt ook uit de toetsing dat het geen nieuwe manier van zorgverlening of andere organisatie van zorgverlening betreft. Er worden daarom geen substantiële financiële gevolgen verwacht.

Module	**Uitkomst raming**	**Toelichting**
Module 8.1.4. Moleculaire diagnostiek bij gemetastaseerde en irresectabele ziekte (irresectabel stadium III en IV)	Geen substantiële financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (5.000-40.000 patiënten), volgt ook uit de toetsing dat het geen nieuwe manier van zorgverlening of andere organisatie van zorgverlening betreft. Er worden daarom geen substantiële financiële gevolgen verwacht.

Module	**Uitkomst raming**	**Toelichting**
Module 8.2.2. Behandeling van oligometastase(n) bij stadium IV	Geen substantiële financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (5.000-40.000 patiënten), volgt ook uit de toetsing dat het geen nieuwe manier van zorgverlening of andere organisatie van zorgverlening betreft. Er worden daarom geen substantiële financiële gevolgen verwacht.

Module	**Uitkomst raming**	**Toelichting**
Module 8.3. – 8.3.2.2. Systemische therapie bij gemetastaseerde en irresectabele ziekte (irresectabel stadium III en IV)	Geen substantiële financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (5.000-40.000 patiënten), volgt ook uit de toetsing dat het geen nieuwe manier van zorgverlening of andere organisatie van zorgverlening betreft. Er worden daarom geen substantiële financiële gevolgen verwacht.

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Module	Uitkomst raming	Toelichting
Module 8.3.3. Doelmatig voorschrijven systemische therapieën	Geen substantiële financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (5.000-40.000 patiënten), volgt ook uit de toetsing dat het geen nieuwe manier van zorgverlening of andere organisatie van zorgverlening betreft. Er worden daarom geen substantiële financiële gevolgen verwacht.

Module	Uitkomst raming	Toelichting
Module 9.4. Onbekende primaire tumor melanoom	Geen substantiële financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (5.000-40.000 patiënten), volgt ook uit de toetsing dat het geen nieuwe manier van zorgverlening of andere organisatie van zorgverlening betreft. Er worden daarom geen substantiële financiële gevolgen verwacht.

Module	Uitkomst raming	Toelichting
Module 10. Palliatieve zorg	Geen substantiële financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (5.000-40.000 patiënten), volgt ook uit de toetsing dat het geen nieuwe manier van zorgverlening of andere organisatie van zorgverlening betreft. Er worden daarom geen substantiële financiële gevolgen verwacht.

Module	Uitkomst raming	Toelichting
Module 11. Ondersteunende zorg	Geen substantiële financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (5.000-40.000 patiënten), volgt ook uit de toetsing dat het geen nieuwe manier van zorgverlening of andere organisatie van zorgverlening betreft. Er

		worden daarom geen substantiële financiële gevolgen verwacht.

Module	Uitkomst raming	Toelichting
Module Organisatie van zorg	Geen financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (5.000-40.000 patiënten), volgt ook uit de toetsing dat het geen nieuwe manier van zorgverlening of andere organisatie van zorgverlening betreft. Er worden daarom geen substantiële financiële gevolgen verwacht.

Werkwijze

AGREE

Deze richtlijnmodule is opgesteld conform de eisen vermeld in het rapport Medisch Specialistische Richtlijnen 2.0 van de adviescommissie Richtlijnen van de Raad Kwaliteit. Dit rapport is gebaseerd op het AGREE II instrument (Appraisal of Guidelines for Research & Evaluation II; Brouwers, 2010).

Knelpuntenanalyse en uitgangsvragen

De werkgroep beoordeelde de aanbeveling(en) uit de eerdere richtlijnmodules op noodzaak tot revisie.

Uitkomstmaten

Na het opstellen van de zoekvraag behorende bij de uitgangsvraag inventariseerde de werkgroep welke uitkomstmaten voor de patiënt relevant zijn, waarbij zowel naar gewenste als ongewenste effecten werd gekeken. Hierbij werd een maximum van acht uitkomstmaten gehanteerd. De werkgroep waardeerde deze uitkomstmaten volgens hun relatieve belang bij de besluitvorming rondom aanbevelingen, als cruciaal (kritiek voor de besluitvorming), belangrijk (maar niet cruciaal) en onbelangrijk. Tevens definieerde de werkgroep tenminste voor de cruciale uitkomstmaten welke verschillen zij klinisch (patiënt) relevant vonden.

Methode literatuursamenvatting

Een uitgebreide beschrijving van de strategie voor zoeken en selecteren van literatuur is te vinden onder ‘Zoeken en selecteren’ onder Onderbouwing. Indien mogelijk werd de data uit verschillende studies gepoold in een random-effects model. Review Manager 5.4 werd gebruikt voor de statistische analyses. De beoordeling van de kracht van het wetenschappelijke bewijs wordt hieronder toegelicht.

Beoordelen van de kracht van het wetenschappelijke bewijs

De kracht van het wetenschappelijke bewijs werd bepaald volgens de GRADE-methode. GRADE staat voor ‘Grading Recommendations Assessment, Development and Evaluation’ (zie http://www.gradeworkinggroup.org/). De basisprincipes van de GRADE-methodiek zijn: het

benoemen en prioriteren van de klinisch (patiënt) relevante uitkomstmaten, een systematische review per uitkomstmaat, en een beoordeling van de bewijskracht per uitkomstmaat op basis van de acht GRADE-domeinen (domeinen voor downgraden: risk of bias, inconsistentie, indirectheid, imprecisie, en publicatiebias; domeinen voor upgraden: dosis-effect relatie, groot effect, en residuele plausibele confounding).
GRADE onderscheidt vier gradaties voor de kwaliteit van het wetenschappelijk bewijs: hoog, redelijk, laag en zeer laag. Deze gradaties verwijzen naar de mate van zekerheid die er bestaat over de literatuurconclusie, in het bijzonder de mate van zekerheid dat de literatuurconclusie de aanbeveling adequaat ondersteunt (Schünemann, 2013; Hultcrantz, 2017).

GRADE	Definitie
Hoog	• er is hoge zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt; • het is zeer onwaarschijnlijk dat de literatuurconclusie klinisch relevant verandert wanneer er resultaten van nieuw grootschalig onderzoek aan de literatuuranalyse worden toegevoegd.
Redelijk	• er is redelijke zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt; • het is mogelijk dat de conclusie klinisch relevant verandert wanneer er resultaten van nieuw grootschalig onderzoek aan de literatuuranalyse worden toegevoegd.
Laag	• er is lage zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt; • er is een reële kans dat de conclusie klinisch relevant verandert wanneer er resultaten van nieuw grootschalig onderzoek aan de literatuuranalyse worden toegevoegd.
Zeer laag	• er is zeer lage zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt; • de literatuurconclusie is zeer onzeker.

Bij het beoordelen (graderen) van de kracht van het wetenschappelijk bewijs in richtlijnen volgens de GRADE-methodiek spelen grenzen voor klinische besluitvorming een belangrijke rol (Hultcrantz, 2017). Dit zijn de grenzen die bij overschrijding aanleiding zouden geven tot een aanpassing van de aanbeveling. Om de grenzen voor klinische besluitvorming te bepalen moeten alle relevante uitkomstmaten en overwegingen worden meegewogen. De grenzen voor klinische besluitvorming zijn daarmee niet één op één vergelijkbaar met het minimaal klinisch relevant verschil (Minimal Clinically Important Difference, MCID). Met name in situaties waarin een interventie geen belangrijke nadelen heeft en de kosten relatief laag zijn, kan de grens voor klinische besluitvorming met betrekking tot de effectiviteit van de interventie bij een lagere waarde (dichter bij het nuleffect) liggen dan de MCID (Hultcrantz, 2017).

<u>Overwegingen (van bewijs naar aanbeveling)</u>

Om te komen tot een aanbeveling zijn naast (de kwaliteit van) het wetenschappelijke bewijs ook andere aspecten belangrijk en worden meegewogen, zoals aanvullende argumenten uit bijvoorbeeld de biomechanica of fysiologie, waarden en voorkeuren van patiënten, kosten (middelenbeslag), aanvaardbaarheid, haalbaarheid en implementatie. Deze aspecten zijn systematisch vermeld en beoordeeld (gewogen) onder het kopje ‘Overwegingen’ en kunnen (mede) gebaseerd zijn op expert opinion. Hierbij is gebruik gemaakt van een gestructureerd

format gebaseerd op het evidence-to-decision framework van de internationale GRADE Working Group (Alonso-Coello, 2016a; Alonso-Coello 2016b). Dit evidence-to-decision framework is een integraal onderdeel van de GRADE methodiek.

Formuleren van aanbevelingen

De aanbevelingen geven antwoord op de uitgangsvraag en zijn gebaseerd op het beschikbare wetenschappelijke bewijs en de belangrijkste overwegingen, en een weging van de gunstige en ongunstige effecten van de relevante interventies. De kracht van het wetenschappelijk bewijs en het gewicht dat door de werkgroep wordt toegekend aan de overwegingen, bepalen samen de sterkte van de aanbeveling. Conform de GRADE-methodiek sluit een lage bewijskracht van conclusies in de systematische literatuuranalyse een sterke aanbeveling niet a priori uit, en zijn bij een hoge bewijskracht ook zwakke aanbevelingen mogelijk (Agoritsas, 2017; Neumann, 2016). De sterkte van de aanbeveling wordt altijd bepaald door weging van alle relevante argumenten tezamen. De werkgroep heeft bij elke aanbeveling opgenomen hoe zij tot de richting en sterkte van de aanbeveling zijn gekomen.

In de GRADE-methodiek wordt onderscheid gemaakt tussen sterke en zwakke (of conditionele) aanbevelingen. De sterkte van een aanbeveling verwijst naar de mate van zekerheid dat de voordelen van de interventie opwegen tegen de nadelen (of vice versa), gezien over het hele spectrum van patiënten waarvoor de aanbeveling is bedoeld. De sterkte van een aanbeveling heeft duidelijke implicaties voor patiënten, behandelaars en beleidsmakers (zie onderstaande tabel). Een aanbeveling is geen dictaat, zelfs een sterke aanbeveling gebaseerd op bewijs van hoge kwaliteit (GRADE gradering HOOG) zal niet altijd van toepassing zijn, onder alle mogelijke omstandigheden en voor elke individuele patiënt.

Implicaties van sterke en zwakke aanbevelingen voor verschillende richtlijngebruikers		
	Sterke aanbeveling	*Zwakke (conditionele) aanbeveling*
Voor patiënten	De meeste patiënten zouden de aanbevolen interventie of aanpak kiezen en slechts een klein aantal niet.	Een aanzienlijk deel van de patiënten zouden de aanbevolen interventie of aanpak kiezen, maar veel patiënten ook niet.
Voor behandelaars	De meeste patiënten zouden de aanbevolen interventie of aanpak moeten ontvangen.	Er zijn meerdere geschikte interventies of aanpakken. De patiënt moet worden ondersteund bij de keuze voor de interventie of aanpak die het beste aansluit bij zijn of haar waarden en voorkeuren.
Voor beleidsmakers	De aanbevolen interventie of aanpak kan worden gezien als standaardbeleid.	Beleidsbepaling vereist uitvoerige discussie met betrokkenheid van veel stakeholders. Er is een grotere kans op lokale beleidsverschillen.

Organisatie van zorg

In de knelpuntenanalyse en bij de ontwikkeling van de richtlijnmodule is expliciet aandacht geweest voor de organisatie van zorg: alle aspecten die randvoorwaardelijk zijn voor het verlenen van zorg (zoals coördinatie, communicatie, (financiële) middelen, mankracht en infrastructuur). Randvoorwaarden die relevant zijn voor het beantwoorden van deze specifieke uitgangsvraag zijn genoemd bij de overwegingen. Meer algemene, overkoepelende, of

bijkomende aspecten van de organisatie van zorg worden behandeld in de module Organisatie van zorg.

Commentaar- en autorisatiefase

De conceptrichtlijnmodule werd aan de betrokken (wetenschappelijke) verenigingen en (patiënt) organisaties voorgelegd ter commentaar. De commentaren werden verzameld en besproken met de werkgroep. Naar aanleiding van de commentaren werd de conceptrichtlijnmodule aangepast en definitief vastgesteld door de werkgroep. De definitieve richtlijnmodule werd aan de deelnemende (wetenschappelijke) verenigingen en (patiënt) organisaties voorgelegd voor autorisatie en door hen geautoriseerd dan wel geaccordeerd.

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5

Aanpassingen richtlijn

Ten opzichte van de vorige richtlijn Melanoom, is de structuur van huidige richtlijn aangepast. Hieronder volgt informatie, en waar nodig verantwoording, van deze aanpassingen.

Nieuw voorstel richtlijnindeling Melanoom

Module
1. STARTPAGINA
2. EPIDEMIOLOGIE EN CLASSIFICATIE
3. RISICOFACTOREN
3.1. Familiare risicofactoren
3.2. Niet-familiare risicofactoren
4. STADIËRING
4.1 TNM
4.2 AJCC 8e editie
5. GELOKALISEERDE ZIEKTE (STADIUM I)
5.1. Diagnostiek gelokaliseerde ziekte
5.1.1. Klinische diagnostiek
5.1.2. Laboratoriumonderzoek
5.1.3. Beeldvormende diagnostiek
5.1.4. Pathologisch onderzoek
5.1.5. Moleculaire diagnostiek
5.2. Behandeling
5.2.1. Neoadjuvante behandeling
5.2.2. Chirurgie
5.2.3. Adjuvante behandeling
5.3. Follow-up
6. GELOKALISEERDE ZIEKTE (STADIUM II)
6.1. Diagnostiek
6.1.1. Klinische diagnostiek
6.1.2. Laboratoriumonderzoek
6.1.3. Beeldvormende diagnostiek
6.1.4. Pathologisch onderzoek
6.1.5. Moleculaire diagnostiek
6.2. Behandeling
6.2.1. Neoadjuvante behandeling

6.2.2. Chirurgie
6.2.3. Adjuvante behandeling
6.3. Follow-up
7. LOCOREGIONALE ZIEKTE (STADIUM III)
7.1. Diagnostiek
7.1.1. Klinische diagnostiek
7.1.2. Laboratoriumonderzoek
7.1.3. Beeldvormende diagnostiek
7.1.4. Pathologisch onderzoek
7.1.5. Moleculaire diagnostiek
7.2. Behandeling
7.2.1. Neoadjuvante behandeling
7.2.3. Locoregionale behandeling
7.2.3. Adjuvante behandeling
7.3. Follow-up
8. GEMETASTASEERDE EN IRRESECTABELE ZIEKTE (IRRESECTABEL STADIUM III EN IV)
8.1. Diagnostiek
8.1.1. Klinische diagnostiek
8.1.2. Laboratoriumonderzoek
8.1.3. Beeldvormende diagnostiek
8.1.4. Moleculaire diagnostiek
8.2. Behandeling
8.2.1. Systemische therapie
8.2.2 Behandeling van oligometastase(n) bij stadium IV
8.2.3. Adjuvante behandeling
8.3. Follow-up
9. BIJZONDERE ZORGPADEN
9.1. Lentigo maligna
9.2. MELTUMP/STUMPS
9.3. Onbekende primaire tumor melanoom
9.4. Melanoom op kinderleeftijd
9.5. Zwangerschap, hormonale anticonceptiva en hormonale substitutiemiddelen
9.6 Mucosaal melanoom
10. PALLIATIEVE ZORG

11. ONDERSTEUNENDE ZORG
12. ORGANISATIE VAN ZORG

Dermatologische modules die ontwikkeld worden door de NDVD (binnen het cluster Maligniteiten van de Huid)

Module	Titel / uitgangsvraag	Ontwikkeld in:	Uiterlijke herziening in:	Regie-houder
3.	**RISICOFACTOREN**			
3.2.	Niet-familiare risicofactoren			NVDV
9.	**BIJZONDERE ZORGPADEN**			
9.1.	Lentigo maligna			NVDV
9.2.	MELTUM/STUMPS			**NVDV**

5

Modules die teruggetrokken worden in huidige vorm en eventueel ondergebracht dienen te worden in de nieuwe boomstructuur

Huidige Module	Titel / uitgangsvraag
3. Preventie	Het voorstel is om de volgende module uit 2012 op de Richtlijnendatabase terug te trekken vanwege de verouderde inhoud.
4.1. Screening van de algemene bevolking	Het voorstel is om de volgende module uit 2012 op de Richtlijnendatabase terug te trekken vanwege de verouderde inhoud.
4.2. Personen met verhoogd risico & 4.3. Genetisch verhoogd risico	Het voorstel is om deze informatie onder te brengen in de nieuwe Module 3. Risicofactoren
5.1. Diagnostiek gelokaliseerde ziekte	Het voorstel in om deze module te updaten en de informatie voor de aparte stadia op te nemen in de module diagnostiek van stadium I en stadium II (Module 5.1 en 6.1)
5.2. Diagnostische excisie	Het voorstel is om de informatie uit deze module in te bedden in de nieuwe diagnostiek modules.
5.3. Behandeling gelokaliseerde ziekte	Het voorstel is om de volgende module uit 2012 op de Richtlijnendatabase terug te trekken en de aanbeveling die hier gedaan wordt op te nemen in de Module Behandeling bij Stadium III (Module 7.2)
5.4. Schildwachtklierprocedure	Het voorstel is om deze module in te bedden in module die betrekking hebben op de lokale behandeling van stadium I en stadium II (module 5.2 en 6.2)
5.6. In opzet curatieve radiotherapie	Het voorstel is om de volgende module uit 2012 op de Richtlijnendatabase terug te trekken en de aanbeveling die hier gedaan wordt op te nemen in de Module Behandeling bij Stadium III (Module 7.2)
7.1. Diagnostiek bij primair melanoom met verdenking op locoregionale kliermetastasen/satellieten/in-transitmetastasen	Het voorstel is om deze module in te bedden in module die betrekking hebben op de lokale behandeling van stadium I en stadium II (module 5.2 en 6.2)
7.2. Aanvullende beeldvormend onderzoek / rol PET/CT in de follow-up	Het voorstel is om deze module deels in te bedden in de beeldvormende modules die terugkomen bij elk stadium. Een aantal van de huidige aanbevelingen hebben nu plaatst gekregen in de conceptmodules follow-up (ter commentaar aangeboden).
7.3. Onbekende primaire tumor	Het voorstel is om deze module te laten vervallen (het beschrijft geen klinisch knelpunt). Het onderwerp wordt behandeld in het hoofdstuk ‘bijzondere zorgpaden’.
7.4. Adjuvante systemische behandeling na initiële behandeling	Het voorstel is om deze module in te bedden in de modules die betrekking hebben op de adjuvante behandeling.
7.6. Regionaal geïsoleerde perfusie	Het voorstel is om dit onderwerp in te bedden bij de lokale behandeling van stadium III.
8.1. Diagnostiek systemische ziekte	Het voorstel is om de rol van diagnostiek in elk stadium van de behandeling terug te laten komen.
8.2. BRAF gen-mutatie	Het voorstel is om de rol van BRAF gen-mutatie terug te laten komen bij de moleculaire diagnostiek binnen elk stadium.

8.3. Systemische behandeling	Het voorstel is om de rol van systemische behandeling terug te laten komen bij elk stadium.
8.4. Chirurgische behandeling systemische ziekte	Deze module is in ontwikkeling. Het voorstel is dat deze module straks onder adjuvante behandeling stadium III/IV (Module 8.2.3.)
8.5. Radiotherapie	Het voorstel is om de rol/plek van radiotherapie terug te laten komen bij elk stadium.
9.1. Diagnostische excisie	Het voorstel is om de rol van de pathologie terug te laten komen bij elk stadium.
9.2. Procedure bij onzekerheid	Het voorstel is om de rol van de pathologie terug te laten komen bij elk stadium.
9.3. Re-excisiepreparaat	Het voorstel is om de rol van de pathologie terug te laten komen bij elk stadium.
9.4. Schildwachtklier	
9.5. Lymfeklierdissectiepreparaat	Het voorstel is om dit onderwerp aan bod te laten komen bij stadium III (7.2.3.)
9.7. Protocollaire verslaglegging PALGA	Het voorstel is om de rol van de pathologie terug te laten komen bij elk stadium.
11.1. Detectie nieuwe kankermanifestaties	Het voorstel is om deze module te laten vervallen. De beschreven knelpunten hebben een plaatst gekregen in de conceptmodules follow-up (ter commentaar aangeboden).
11.1. Detectie nieuwe kankermanifestaties	Het voorstel is om deze module te laten vervallen. De beschreven knelpunten hebben een plaatst gekregen in de conceptmodules follow-up (ter commentaar aangeboden).
11.3. Evaluatie van medisch handelen	Het voorstel is om deze module te laten vervallen. Deze module behandeld geen (klinisch) knelpunt.
13.1 Maximaal aanvaardbare wachttijden	Het voorstel is om deze module te laten vervallen. Dit onderwerp wordt ondervangen door de Treeknormen waar de NZa op toeziet en valt buiten het bestek van de richtlijn.
13.2 Multidisciplinair overleg voor stadium III en IV	Het voorstel is om deze module te laten vervallen. Dit onderwerp is ingebed in de module follow-up en deels onder te brengen onder de module organisatie van zorg (module 12)
13.3 Organisatie van zorg	Het voorstel is om deze module in de huidige vorm te laten vervallen. De huidige aanbevelingen zijn nu onderdeel van de follow-up module. Het voorstel is om deze module te herzien.

Modules die nu ter commentaar aangeboden worden
Nieuwe / updates modules

	Titel
3.1	Familiaire risicofactoren
4.1	pTNM-classificatie en AJCC stadiëring
7.1.5.	Moleculaire diagnostiek bij locoregionale ziekte (stadium III)
7.2.1	Neoadjuvante behandeling stadium III
8.1.4.	Moleculaire diagnostiek bij gemetastaseerde en irresectabele ziekte (irresectabel stadium III en IV)
8.2.2.	Behandeling van oligometastase(n) bij patiënten met stadium IV
8.3.	Systemische therapie
8.3.1.1	Eerstelijnsbehandeling BRAF-V600E/K gemuteerd irresectabel of gemetastaseerd stadium III/IV
8.3.1.2.	Tweedelijnsbehandeling BRAF-V600E/K gemuteerd irresectabel of gemetastaseerd stadium III/IV
8.3.2.1.	Eerstelijnsbehandeling BRAF-wild type gemuteerd irresectabel of gemetastaseerd stadium III/IV
8.3.2.2.	Tweedelijnsbehandeling BRAF-wild type gemuteerd irresectabel of gemetastaseerd stadium III/IV
8.3.3.	Doelmatigheidsmodule behorend bij systemische behandelingsmodules stadium III/IV
9.3.	Onbekende primaire tumor melanoom
10	Palliatieve zorg
11	Ondersteunende zorg
12	Organisatie van zorg

3.1. Familiaire risicofactoren

Uitgangsvraag

Welke personen hebben een genetisch verhoogd risico op melanoom en hoe dient periodiek onderzoek bij deze personen plaats te vinden?

De uitgangsvraag omvat de volgende deelvragen:

1. Hoe kunnen personen met een genetisch verhoogd risico op melanoom worden geïdentificeerd?
2. Welke medische (controle)adviezen dienen te worden gegeven aan personen met een genetisch verhoogd risico op melanoom?

Introductie

Ongeveer 10% van alle melanomen komt voor in een familiaire setting. Aan de hand van de familiegeschiedenis kan worden beoordeeld of er in de familie van een patiënt met melanoom een genetisch verhoogd risico op melanoom kan zijn. Het is daarom van belang om bij elke patiënt met melanoom een gestructureerde familiegeschiedenis af te nemen, gericht op het vóórkomen van melanoom én andere vormen van kanker bij eerste- en tweedegraads verwanten. Eerstegraads verwanten zijn ouders, kinderen, broers en zussen. Tweedegraads verwanten zijn kleinkinderen, grootouders, ooms en tantes en kinderen van broers en zussen. Deze module beoogt hierin uniformiteit te brengen.

Zoeken en selecteren

Voor het beantwoorden van deze uitgangsvraag is er geen systematische literatuuranalyse verricht, maar heeft de werkgroep de criteria en adviezen die hier verder worden besproken grotendeels overgenomen uit het in 2021 herziene hoofdstuk *Erfelijk en familiair melanoom* in de VKGN-StOET richtlijnen voor erfelijke en familiaire tumoren op https://vkgn.stoet.nl/.

Samenvatting literatuur

Een belangrijke risicofactor voor melanoom is het voorkomen van melanoom in de familie. Het hebben van een eerstegraads verwant met melanoom verhoogt het *lifetime* risico van 1,5% (populatierisico) naar 2,5% en bij 2 of meer aangedane eerstegraads verwanten stijgt dit aanzienlijk naar 6,5% en zelfs 13,5% als de diagnoseleeftijd <30 jaar is (Fallah, 2014]. Aan de hand van de diagnostische criteria voor familiair melanoom kan bepaald worden in welke families het risico dusdanig hoog is dat er een indicatie is voor periodieke huidcontrole. Daarbij wordt uitgegaan van de *regel van drie*, wat wil zeggen het voorkomen van tenminste drie melanomen bij (tenminste twee) naaste verwanten. Historisch gezien wordt deze regel van drie ook, in bredere zin, toegepast voor de indicatiestelling voor genetisch onderzoek, waaronder dan ook het voorkomen van 3 of meer melanomen bij één persoon valt, én waarbij ook een diagnose alvleesklierkanker in plaats van melanoom in de familie mee kan tellen. In regio's met een lagere melanoom incidentie zoals Zuid-Europa houdt men meestal een vergelijkbare regel van twee aan. Deze personen/families worden verondersteld een kans van 10% of meer te hebben op een onderliggende genmutatie (Leachman, 2009; Delaunay, 2017). Omdat deze relatief hoge grens van 10% voor het doen van genetisch onderzoek in elk geval in Nederland al enige tijd is losgelaten zijn de Nederlandse criteria voor genetisch onderzoek ook wat soepeler dan deze oorspronkelijke regel van drie. Hierdoor komen bijvoorbeeld ook families met 2 melanomen bij eerstegraadsverwanten in aanmerking voor genetisch onderzoek, mits er

tenminste één melanoom <50 jaar is vastgesteld (zie Richtlijnen VKGN-StOET, hoofdstuk *Erfelijk en familiair melanoom* op https://vkgn.stoet.nl/). Het kan dus voorkomen dat er in een familie met melanomen wel een reden is voor genetisch onderzoek maar geen reden voor periodieke huidcontrole als niet wordt voldaan aan de diagnostische criteria voor familiair melanoom (mits er geen onderliggende genmutatie wordt aangetroffen).

Hoog-risico genmutaties

Veruit het belangrijkste hoog-risico melanoomgen is *CDKN2A* (OMIM 600160). In ongeveer 10 tot maximaal 40% van de families die voldoen aan de diagnostische criteria voor familiair melanoom kan een kiembaan mutatie in het *CDKN2A*-gen worden aangetoond (Read, 2016). Vanwege een founder populatie in de omgeving van Leiden komt een specifieke 19bp deletie in exon 2 van het *CDKN2A* gen (p16-*Leiden* mutatie) relatief veel voor. *CDKN2A* mutatiedragers hebben een sterk verhoogd *lifetime* risico op melanoom (tot 70%) (Bishop, 2002; Cust, 2011) en krijgen vaak meerdere primaire melanomen (30-40%). Patiënten met drie tot vijf melanomen worden regelmatig gezien in deze setting. De gemiddelde leeftijd waarop (het eerste) melanoom wordt vastgesteld is ongeveer 40 jaar (van der Rhee, 2011). Daarnaast is er een verhoogd lifetime-risico op pancreascarcinoom (15-20%) en komen ook andere vormen van kanker vaker voor in deze families, met name hoofd-halskanker en longkanker (de Snoo, 2008; Potjer, 2015; Helgadottir, 2015; Klatte, 2022; Sargen, 2022). Voor de zeldzamere *CDKN2A*-mutaties met uitsluitend een effect op het p14ARF-eitwit (meestal exon 1β) lijkt er geen verhoogd risico op pancreascarcinoom te zijn (Overbeek, 2021).

Kiembaan mutaties in overige bekende hoog-risico melanoomgenen zijn veel zeldzamer. Mutaties in het *BAP1*-gen worden in ongeveer 1% van de melanoomfamilies gevonden, mutaties in *CDK4*, *POT1*, *TERT*, *TERF2IP* en *ACD* in minder dan 1% van de families (Potrony, 2015; Potjer, 2018). Hoe vaak mutaties in het *TINF2*-gen in melanoomfamilies worden gevonden is nog niet goed bekend, maar mogelijk is dit vaker dan 1% (Jensen, 2023). De specifieke E318K mutatie in het *MITF*-gen komt in ongeveer 3% van de families voor en geeft een matig verhoogd risico op melanoom (ongeveer 2 tot 5 maal verhoogd ten opzichte van het risico in de algemene bevolking) (Potjer, 2018; Guhan, 2020). Anders dan voor de hoog-risicogenen hangt bij het *MITF*-gen de hoogte van het individuele melanoomrisico sterker samen met de aanwezigheid van andere bekende/onbekende risicofactoren en de mate van familiaire belasting voor melanoom (Berwick, 2014).

De zeldzame erfelijke huidaandoeningen Xeroderma Pigmentosum (XP) en Oculocutaan Albinisme (OCA) gaan daarnaast ook gepaard met een sterk verhoogd risico op huidkanker in het algemeen (basaalcelcarcinoom, plaveiselcelcarcinoom, melanoom) door de sterke overgevoeligheid voor Uv-straling bij deze personen. Bij een milder subtype van XP veroorzaakt door kiembaan *POLH* genmutaties (XP-V) kan melanoom soms echter meer op de voorgrond staan dan andere huidkankers of andere symptomen van XP, waardoor een DNA-onderzoek van het *POLH*-gen soms ook overwogen kan worden bij personen met multipele primaire melanomen op jonge leeftijd (Opletalova, 2014).

Screening bij familiair/erfelijk melanoom

Als in een familie sprake is van erfelijk of familiair melanoom, dan geldt er een indicatie voor screening van de huid een à tweemaal per jaar door een dermatoloog voor zowel patiënten met een melanoom/mutatiedragers als hun eerstegraads verwanten. Onderzoeken hebben aangetoond dat melanomen die bij personen met een genetisch verhoogd risico door screening

worden ontdekt significant dunner zijn (lagere Breslowdikte) (Hansson, 2007; van der Rhee, 2011; Sargen, 2021).

Tweedegraads verwanten in *CDKN2A*-families hebben ook een verhoogd risico op melanoom omdat soms een kind eerder een melanoom krijgt dan zijn/haar ouder. De hoogte van dit risico is ongeveer vergelijkbaar met het hebben van 5 of meer atypische nevi, of meer dan 100 banale nevi, waarvoor relatieve indicaties gelden voor screening en waarbij instructie voor zelfonderzoek wordt aanbevolen (Van der Rhee, 2013). Er wordt daarom geadviseerd dat ook deze tweedegraads verwanten uit *CDKN2A*-families periodiek onderzoek van de huid laten verrichten, vanaf de leeftijd van 20 jaar.

Vanwege het verhoogde risico op pancreascarcinoom is er voor *CDKN2A* mutatiedragers, met uitzondering van personen met zeldzamere mutaties in exon 1β (Overbeek, 2021), een indicatie voor periodiek onderzoek van de pancreas vanaf de leeftijd van 40 jaar. Onderzoeken hebben aangetoond dat d.m.v. jaarlijks MRI gecombineerd met Magnetic Resonance Cholangio-Pancreatography (MRCP) en/of Endo-Echografie (EUS) pancreascarcinoom in een vroeger (en operabel) stadium kan worden vastgesteld en dat de prognose van patiënten hierdoor significant verbetert (Klatte, 2022; Klatte, 2023). Omdat pancreassurveillance complex is en er nog geen universeel surveillanceprotocol is, dient het alleen plaats te vinden in een gespecialiseerd centrum door een multidisciplinair expertise team, en met wetenschappelijke evaluatie van de uitkomsten (Goggins, 2019).

<u>Laagrisico genvarianten en polygene overerving</u>

In families met melanoom waarin geen oorzakelijk gendefect wordt gevonden, speelt polygene overerving van laagrisico varianten (risico-allelen; SNPs), tezamen met niet-genetische risicofactoren zoals blootstelling aan Uv-straling, waarschijnlijk een belangrijke rol. Laagrisico varianten komen frequent voor in de populatie en hebben afzonderlijk een beperkt effect op het melanoomrisico, maar een ongunstige combinatie van risicovarianten kan het risico aanzienlijk verhogen. In families waarin relatief veel van dit soort erfelijke risicovarianten aanwezig zijn, zal melanoom dus ook vaker voorkomen. Risicovarianten in het bij huidpigmentatie en haarkleur betrokken *MC1R* gen zijn hiervan het bekendst en zijn in meer of mindere mate geassocieerd met roodharigheid. Het hebben van een of twee van deze *MC1R* risicovarianten verhoogt het risico op melanoom met een RR van 1,42-2,45 (Raimondi, 2008). Inmiddels zijn er ook tientallen andere laagrisico varianten geïdentificeerd middels grote population-based Genome Wide Association Studies (GWAS), waarvan een groot deel in, of in de buurt van, genen ligt die betrokken zijn bij huidpigmentatie, het aantal naevi, DNA-reparatie of telomeerlengte. Het gecombineerde effect van al deze risicovarianten wordt uitgedrukt in een polygene risicoscore (PRS) en kan per familielid sterk verschillen. Hoewel een melanoom-specifieke PRS nu nog niet diagnostisch beschikbaar is, zal het naar verwachting in de nabije toekomst een belangrijke rol kunnen gaan spelen in de risicostratificatie binnen melanoomfamilies (Roberts, 2019; Potjer, 2020; Steinberg, 2022).

Overwegingen

Professioneel perspectief

Diagnostische criteria

Er is sprake van *familiair melanoom* als een familie voldoet aan de volgende diagnostische criteria:

- Familie met 3 verwanten met invasief melanoom waarvan 2 eerstegraads verwanten (de aangedane personen moeten eerste- of tweedegraads verwanten zijn)
- Familie met 2 eerstegraads verwanten met invasief melanoom van wie 1 verwant met multipele melanomen

Er is sprake van *erfelijk melanoom* als er een kiembaan mutatie (pathogene genvariant) is vastgesteld in het *CDKN2A*-gen of een van de zeldzamere geassocieerde genen (*CDK4*, *BAP1*, *POT1*, *ACD*, *TERF2IP*, *TINF2, TERT*, *MITF*).

Verwijscriteria Klinische Genetica

Patiënten met een melanoom/families die voldoen aan de volgende criteria dienen te worden verwezen naar een polikliniek klinische genetica voor erfelijkheidsonderzoek en -advisering:

- De familie van de patiënt voldoet aan de diagnostische criteria voor *familiair melanoom*
- Invasief melanoom bij 2 eerstegraads verwanten, waarbij tenminste één melanoom <50 jaar is vastgesteld
- Invasief melanoom bij 2 eerste- of tweedegraads verwanten EN
    - een eerste of tweedegraads verwant met pancreascarcinoom OF
    - een eerste of tweedegraads verwant met hoofd-halskanker (larynx, farynx, mondholte, tong, lip)
- Invasief melanoom <18 jaar
- ≥3 invasieve melanomen bij 1 persoon ongeacht leeftijd
- Invasief melanoom én pancreascarcinoom bij 1 persoon ongeacht leeftijd
- Invasief melanoom met in de familie specifieke aanwijzingen voor het *BAP1* tumorpredispositiesyndroom (met name bij voorkomen van uveamelanoom en/of maligne mesothelioom en/of BAP1-inactieve naevi). Voor de diagnostische criteria en verwijscriteria van dit tumorsyndroom verwijst de werkgroep naar het betreffende hoofdstuk in de VKGN-StOET richtlijnen voor erfelijke en familiaire tumoren op https://vkgn.stoet.nl/

NB: het heeft altijd de sterke voorkeur dat, indien mogelijk, een *aangedaan persoon* (patiënt met melanoom) in de familie wordt verwezen voor erfelijkheidsonderzoek

Voorheen werd de term Familial Atypical Multiple Mole-Melanoma (FAMMM) syndroom wisselend gebruikt voor familiair melanoom met of zonder *CDKN2A* genmutatie. Bij de revisie van deze richtlijn is ervoor gekozen om deze term niet meer te gebruiken, omdat de correlatie tussen atypische naevi en melanoom complexer is en niet alle patiënten met een melanoom uit *CDKN2A*-families multipele atypische naevi hebben (Nielsen, 2010; Ipenburg, 2016). Ook de term *mogelijk familiair melanoom* als diagnostische entiteit om de groep patiënten aan te duiden die niet voldoet aan de familiair melanoom criteria, maar wel vanwege verdenking van een eventuele erfelijke aanleg voor melanoom doorverwezen moet worden naar de klinisch geneticus, kan leiden tot verwarring en wordt daarom niet meer gebruikt.

Medische adviezen

Voor personen met een genetisch verhoogd risico op melanoom is er een indicatie voor levenslange periodieke huidcontrole (tenminste jaarlijks, CDK2NA mutatiedragers halfjaarlijks) door een dermatoloog vanaf de leeftijd van 12 jaar. De volgende personen komen daarvoor in aanmerking:

Erfelijk melanoom

- Dragers van een kiembaan mutatie in het *CDKN2A*-gen of een ander hoog-risico melanoomgen, en hun eerstegraads verwanten die nog geen presymptomatisch (voorspellend) DNA-onderzoek hebben laten verrichten [#] [%]
- Dragers van de *MITF* E318K kiembaan mutatie die zelf een melanoom hebben gehad of een eerstegraads verwant hebben met melanoom

[#] de startleeftijd voor periodieke huidcontrole bij *BAP1* mutatiedragers is 16 jaar

[%] tweedegraads verwanten van *CDKN2A* mutatiedragers komen in aanmerking voor periodieke huidcontrole vanaf 20 jaar

Familiair melanoom

- Patiënten met een melanoom en hun eerstegraads verwanten

Het is daarnaast van belang om bovengenoemde personen én hun (minderjarige) kinderen goed te instrueren over adequate zonbescherming vanaf jonge leeftijd, en duidelijke instructies te geven voor regelmatig zelfonderzoek van de huid (met hulp van derden).
De werkgroep is daarnaast van mening dat een tenminste eenmalige dermatologische controle ook overwogen kan worden bij eerstegraads verwanten van een persoon met ≥3 invasieve melanomen zonder verdere belaste familiegeschiedenis.

In families met erfelijk melanoom is vanaf jongvolwassen leeftijd presymptomatisch (voorspellend) DNA-onderzoek mogelijk. Als verwanten de bekende aanleg niet hebben geërfd dan vervalt de indicatie voor periodieke huidcontrole, tenzij er een andere reden voor huidcontrole is (bijv. 5 of meer atypische naevi, meer dan 100 naevi of andere risicofactoren voor melanoom).

Voor de E318K mutatie in het *MITF*-gen geldt echter een uitzondering; als een *MITF*-familie voldoet aan de diagnostische criteria voor familiair melanoom, dan is er voor alle patiënten met een melanoom en hun eerstegraads verwanten een indicatie voor periodieke huidcontrole ongeacht mutatiestatus (conform advies *familiair melanoom*).

Soms wordt in een melanoomfamilie een variant in een melanoomgen gevonden waarvan de klinische betekenis vooralsnog onduidelijk is, een zogeheten *variant of uncertain significance* (VUS). In dergelijke families is presymptomatisch DNA-onderzoek bij verwanten (nog) niet mogelijk en wordt meestal een periodiek controle advies gegeven conform advies *familiair melanoom.*

Vanwege het verhoogde risico op pancreascarcinoom komen *CDKN2A* mutatiedragers vanaf 40-jarige leeftijd in aanmerking voor periodiek onderzoek van de pancreas d.m.v. jaarlijks MRI gecombineerd met Magnetic Resonance Cholangio- Pancreatography (MRCP) en/of Endo-Echografie (EUS). Pancreassurveillance dient uitsluitend plaats te vinden in een gespecialiseerd centrum door een multidisciplinair expertise team en met wetenschappelijke evaluatie van de

uitkomsten. De specialist die de pancreassurveillance uitvoert (meestal maag-darm-leverarts) zal de voor- en nadelen van surveillance met de patiënt bespreken.

Vanwege het verhoogde risico op pancreascarcinoom, hoofd-halskanker en longkanker is het voor *CDKN2A* mutatiedragers van groot belang om niet te roken en dit dient dan ook stellig te worden afgeraden. Voor hoofd-halskanker en longkanker is er (nog) geen periodiek onderzoek beschikbaar, maar bij klachten van de mondholte (zweren), slikklachten, heesheid en andere klachten van de bovenste luchtwegen is het voor *CDKN2A* mutatiedragers raadzaam om in een vroeg stadium contact met hun (huis)arts op te nemen.

Voor de medische adviezen anders dan huidcontrole bij het *BAP1* tumorpredispositiesyndroom verwijst de werkgroep naar het betreffende hoofdstuk in de VKGN-StOET richtlijnen voor erfelijke en familiaire tumoren op https://vkgn.stoet.nl/

Voorkeuren en waardes van patiënten.

Uit een eerder verstuurde online enquête vanuit de VSOP (patiëntenkoepel voor zeldzame en genetische aandoeningen) bleek dat ondersteuning bij het infomeren van familieleden door indexpatiënten als positief beoordeeld wordt. Het bleek onvoldoende duidelijk in welke situaties er behoefte is aan psychosociale ondersteuning bij het infomeren van familieleden en waaruit de geboden zorg precies zou moeten bestaan [zie richtlijnendatabase.nl/richtlijn/informeren_van_familieleden_bij_erfelijke_aandoeningen/psychosociale_begeleiding_bij_informeren_familieleden.html] .

Kosten

Er is geen informatie bekend over kosten en/ of kosteneffectiviteit. De werkgroep kan dit aspect daarom niet meewegen bij de onderbouwing van de aanbeveling.

Haalbaarheid en implementatie

De werkgroep voorziet geen problemen ten aanzien van de haalbaarheid en de implementatie van de aanbevelingen.

Aanbevelingen

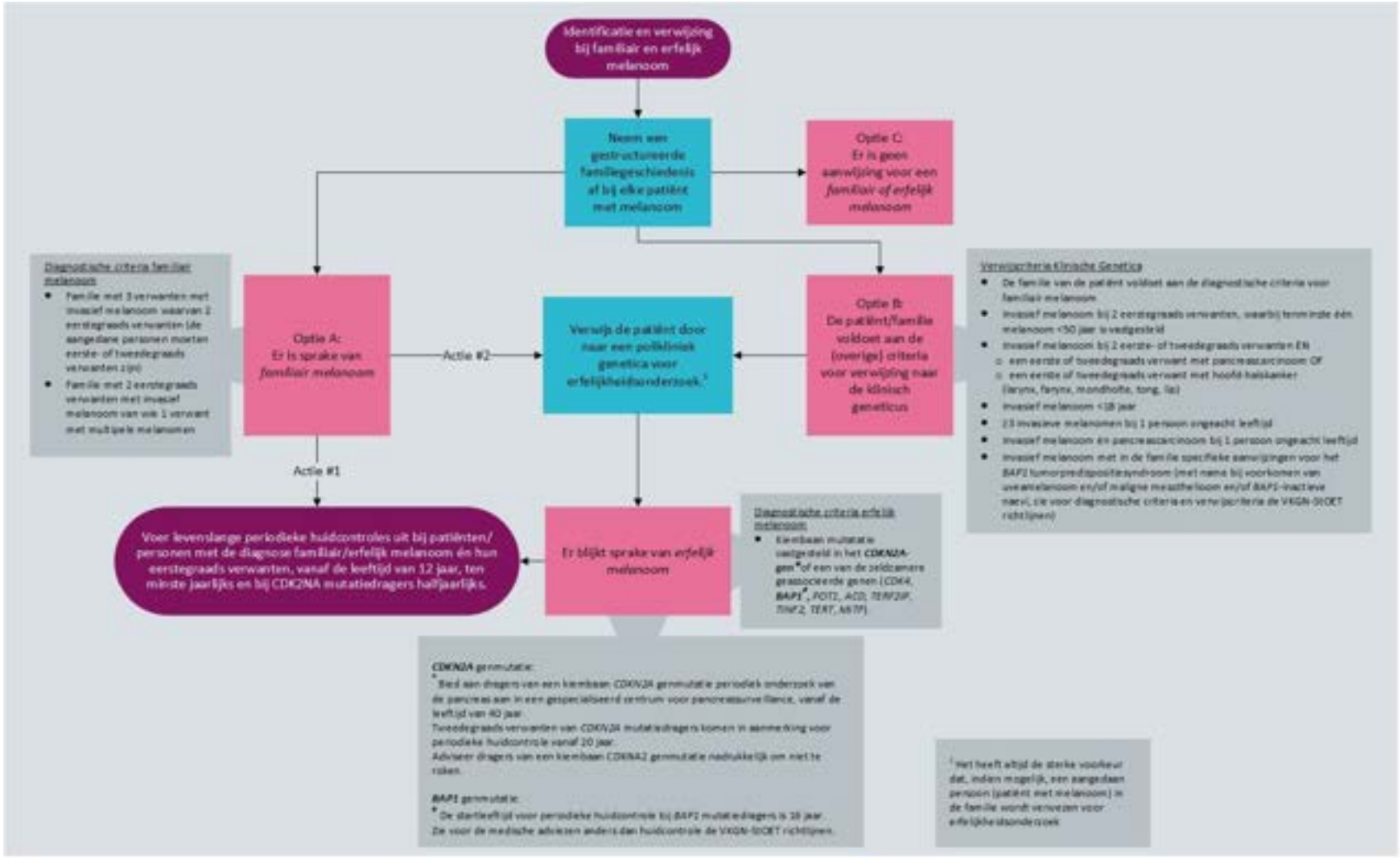
Neem bij elke patiënt met melanoom een familieanamnese af, gericht op het vóórkomen van melanoom en andere vormen van kanker bij eerste- en tweedegraads verwanten.

Bied een verwijzing aan naar een polikliniek klinische genetica voor erfelijkheidsonderzoek en -advisering indien

- de familie van de patiënt voldoet aan de diagnostische criteria voor familiair melanoom, óf
- de patiënt voldoet aan andere verwijscriteria voor erfelijk melanoom.

Voer levenslange periodieke huidcontrole uit bij patiënten/personen met de diagnose familiair/erfelijk melanoom én hun eerstegraads verwanten, vanaf de leeftijd van 12 jaar.

Bied aan dragers van een kiembaan *CDKN2A* genmutatie periodiek onderzoek van de pancreas aan, in een gespecialiseerd centrum voor pancreassurveillance met evaluatie van de uitkomsten, vanaf de leeftijd van 40 jaar.



NVDV NIV

initiatiefnemende verenigingen

NB1: Dit stroomschema hoort bij de module Familiair/Erfelijk melanoom van de richtlijn Melanoom. Lees altijd de overwegingen en aanbevelingen van de betreffende module voor nuances, eventuele afwijkende situaties en extra achtergrondinformatie.

NB2: Betrek de patiënt bij de besluitvorming.

Federatie Medisch Specialisten

Ontwikkeld door het Kennisinstituut van de Federatie Medisch Specialisten

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4.1. pTNM-classificatie en AJCC stadiëring

Uitgangsvraag

Welke pTNM classificatie en AJCC-stadiumindeling dient gebruikt te worden voor de stadiëring van melanoom?

Introductie

Nauwkeurige stadiëring van melanoom is cruciaal voor het bepalen van de prognose en het plannen van de behandeling. Een essentieel aspect van dit proces is het gebruik van het TNM-stadiëringssysteem, een wereldwijd erkend classificatiesysteem dat de histologische kenmerken van het primaire melanoom (T), de betrokkenheid van de regionale lymfeklieren (N), en de aanwezigheid van metastasen op afstand (M) classificeert. De huidige standaard voor de stadiëring van melanoom is gebaseerd op de 8e editie van de AJCC (American Joint Committee on Cancer) stadiumindeling. Deze editie introduceert belangrijke updates in de TNM-classificatie, zoals de differentiatie van T-stadia op basis van de Breslow-dikte en ulceratie, evenals aanpassingen in de N-stadia die rekening houden met de aanwezigheid van microscopische versus macroscopische lymfeklierbetrokkenheid. Deze AJCC-stadiumindeling is van groot belang bij het pathologisch stadiëren van melanoom, omdat het zorgt voor een nauwkeurige inschatting van de ziektelast en daarmee de keuze van de behandeling en prognose bepaalt. Echter, met verschillende edities van het de pTNM-classificatie en de AJCC-stadiumindeling rijst de vraag welke editie het meest geschikt is voor de stadiëring van melanoom. Deze module geeft hier een antwoord op.

Zoeken en selecteren

De werkgroep heeft besloten om geen systematisch literatuuronderzoek (PICO) uit te voeren voor deze vraag.

Overwegingen – van bewijs naar aanbeveling

Samenvatting literatuur

In 2017 verscheen de achtste editie van de pTNM Classification of Malignant Tumours. Deze nieuwe editie bevat herzieningen met betrekking tot pT1 (Keung, 2018; Gershenwald; 2017).

Tabel 1 pTNM classificatie melanoom (8e editie, 2017)

T – Primaire tumor		
TX	Primaire tumor kan niet worden bepaald	
T0	Geen bewijs van primaire tumor	
Tis	Melanoom in situ	
T1	Tumor ≤ 1.0 mm in dikte	T1a: <0.8 mm en zonder ulceratie T1b: 0.8 – 1.0 mm met of zonder ulceratie
T2	Tumor > 1.0 – 2.0 mm in dikte	T2a: zonder ulceratie T2b: met ulceratie
T3	Tumor > 2.0 – 4.0 mm in dikte	T3a: zonder ulceratie T3b: met ulceratie
T4	Tumor > 4.0 mm in dikte	T4a: zonder ulceratie T4b: met ulceratie
N – Regionale lymfeklieren		

NX	Regionale lymfeklieren kunnen niet worden bepaald	
N0	Geen regionale lymfekliermetastasen	
N1	Metastase in één regionale lymfeklier of loco regionale metastase zonder lymfekliermetastasen	N1a: Micrometastase (klinisch occult) N1b: Macrometastase (Klinisch detecteerbaar) N1c: In transit metastasen of satellieten zonder aangedane lymfeklieren
N2	Metastase in twee of drie regionale lymfeklieren of locoregionale metastasen met lymfekliermetastasen	N2a: Micrometastase (klinisch occult) N2b: Macrometastase (Klinisch detecteerbaar) N2c: In transit metastasen of satellieten met enkel één regionale lymfekliermetastase
N3	Metastase in vier of meer regionale lymfeklieren, of gematteerde metastatische regionale lymfeklieren, of satelliet(en) of in-transit-metastasen met twee of meer regionale lymfeklier(en)	N3a: Micrometastase (klinisch occult) N3b: Macrometastase (Klinisch detecteerbaar) N3c: In transit metastasen of satellieten met twee of meer regionale lymfekliermetastase
M – Metastasen op afstand		
M0	Geen metastasen op afstand	
M1	Metastasen op afstand*	M1a: Huid-, subcutane of lymfekliermetastasen op afstand M1b: long metastasen M1c: andere niet-centrale zenuwstelsel locaties M1d: Centrale zenuwstelsel locaties
* Suffixen voor categorie M: (0) lactaatdehydrogenase (LDH) - niet verhoogd (1) LDH - verhoogd zodat M1a(1) een metastase is in de huid, het onderhuidse weefsel of de lymfeklier(en) buiten de regionale lymfeklieren met verhoogde LDH . Er wordt geen suffix gebruikt als LDH niet is geregistreerd of niet is gespecificeerd.		

Veranderingen T-classificatie

- Voor het onderscheid tussen T1a en T1b wordt - in de 8e versie - de tumordikte nader gedifferentieerd (<0.8 mm, 0.8-1.0mm); de mitose-index (aantal mitosen/1 mm^2) is vervallen als indelingscriterium.

Veranderingen N-classificatie

- De classificatie N1c (satelliet of in-transit metastase zonder aangedane lymfeklieren) is nieuw toegevoegd.
- De classificatiesN3a, N3b en N3c zijn nieuw toegevoegd.

Veranderingen M-classificatie

- De classificatie M1d (metastasen in centraal zenuwstelsel) is nieuw toegevoegd.

- Verhoogd LDH betekent niet langer per definitie M1c. Achter elke M1 (zowel a, b, c als ook d) kan nu (0) - oftewel niet-verhoogd LDH - of (1) - oftewel verhoogd LDH - worden toegevoegd. De toevoeging ontbreekt als LDH niet gerapporteerd c.q. gespecificeerd wordt.

Bij de onderstaande tabel wordt de indeling van het pathologische en klinische stadium van melanoom weergegeven volgens de richtlijnen van het TNM-systeem (8e editie 2017) en de AJCC-stadiumindeling versie 2017. Het TNM-systeem (Tumor, Node, Metastasis) wordt wereldwijd gebruikt om de ernst van kanker in te delen, waarbij de grootte en uitgebreidheid van de tumor (T), de betrokkenheid van de lymfeklieren (N), en de aanwezigheid van metastasen (M) worden geëvalueerd. Deze tabel geeft een gedetailleerd overzicht van de verschillende stadia van melanoom, variërend van stadium 0 (in situ melanoom) tot en met stadium IV (uitgezaaide melanoom), met bijbehorende T-, N-, en M-classificaties.

Tabel 2 Pathologisch en klinisch stadium melanoom volgens pTNM (8e editie 2017) en AJCC-stadiumindeling 2017.

AJCC	T	N	M
Stadium 0	Tis	N0	M0
Stadium IA	T1a	N0	M0
	T1b	N0	M0
Stadium IB	T2a	N0	M0
Stadium IIA	T2b	N0	M0
	T3a	N0	M0
Stadium IIB	T3b	N0	M0
	T4a	N0	M0
Stadium IIC	T4b	N0	M0
Stadium IIIA	T1a/b, T2a	N1a, N2a	M0
Stadium IIIB	T0	N1b, N1c	M0
	T1a/b, T2a	N1b/c, N2b	M0
	T2b, T3a	N1a/b/c, N2a/b	M0
Stadium IIIC	T0	N2b/c, N3b/c	M0
	T1a/b, T2a/b, T3a	N2c, N3a/b/c	M0
	T3b, T4a	Elke N ≥ N1	M0
	T4b	N1a/b/c, N2a/b/c	M0
Stadium IIID	T4b	N3a/b/c	M0
Stadium IV	Elke T, Tis	Elke N	M1

Overwegingen

In 2017 verscheen de achtste editie van de TNM Classification of Malignant Tumours. Het effect van de 8e stadiëringseditie van de American Joint Committee on Cancer (AJCC) lijkt geen significante impact te hebben op de onderverdeling in T1a en T1b van dunne melanomen (<1.0 mm) in Nederland (Verver, 2017).

Voor de stadiëring van melanoom wordt daarom aanbevolen om de meest recente editie van het TNM-stadiëringssysteem te gebruiken, zoals die werd gepubliceerd door de American Joint Committee on Cancer (AJCC) (Keung, 2018; Gershenwald; 2017). Deze editie biedt de meest actuele classificaties en richtlijnen voor het beoordelen van de omvang van de tumor (T), de betrokkenheid van de regionale lymfeklieren (N), en de aanwezigheid van metastasen op afstand (M) bij melanoom.

Aanbeveling

Gebruik voor de stadiering van melanoom de 8e editie van de pTNM-classificatie (2017) en de 8e editie van de AJCC (2017).

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7.1.5. Moleculaire diagnostiek bij locoregionale ziekte (stadium III)

Uitgangsvraag

Wat is het juiste moment en wijze waarop mutatieanalyse ten behoeve van systeemtherapie bij patiënten met stadium III melanoom dient te worden verricht?

Inleiding

De systemische behandeling van patiënten met melanoom is in Nederland gecentraliseerd in landelijk aangewezen melanoomcentra. Op dit moment wordt moleculaire diagnostiek voor melanoom op verschillende momenten in het beloop van de ziekte, met verschillende diagnostische testen en in een grote verscheidenheid van pathologie laboratoria verricht. Er is hierbij een sterke variatie in de uitgebreidheid en gevoeligheid van de moleculaire testen die worden ingezet. Genoemde situatie leidt tot inefficiëntie door vertraging en opnieuw testen bij verwijzing naar een melanoomcentrum. Centralisatie van moleculaire diagnostiek in de melanoomcentra reduceert kosten en doorlooptijden en verbetert uniformiteit en continuïteit van zorg.

Zoeken en selecteren

Voor deze vraagstelling werd geen PICO geformuleerd.

Overwegingen – van bewijs naar aanbeveling

<u>Samenvatting van (systematische) reviews, internationale richtlijnen en consensusdocumenten</u>

Tot circa 60% van de melanomen op intermitterend aan zon blootgestelde huid heeft een somatische *BRAF* mutatie. De meeste *BRAF* mutaties zijn missense variaties die leiden tot een verandering van het aminozuur valine op codon 600 (Vanni, 2020; Elder, 2020; WHO, 2023).

Een recente Europese richtlijn (Garbe, 2022) geeft aan dat *BRAF* V600 mutatie analyse vereist is bij besluit over de behandeling van patiënten met melanoom met afstandsmetastasen of niet-reseceerbare regionale metastasen en indien BRAF/MEK remmers worden overwogen voor de adjuvante behandeling van gereseceerd hoog-risico stadium III melanoom.

Bij metastasen verdient het testen van een recente of nog aanwezige metastase de voorkeur, maar indien dit niet mogelijk is kan ook de primaire tumor worden gebruikt, in verband met hoge -maar niet complete - concordantie t.a.v. de BRAF status tussen het primair melanoom en de metastase (Valeachis, 2017; Vanni, 2020). Ter overweging: benoemen dat patiënten meerdere primaire melanomen kunnen hebben en dat de kliniek ten aanzien van metastaserings patroon bij eventuele meerdere primaire melanomen van belang is.

Naast *BRAF* mutaties komen bij melanomen in huid en slijmvlies ook andere mutaties voor in genen van de MAP-kinase signaaltransductieroute zoals *NRAS, NF1* en *KIT.* Verder komen relatief zeldzame fusies in *NTRK, ALK, ROS1* en *RET* voor in met name Spitz melanoom, acraal melanoom en mucosaal melanoom. In oogmelanoom worden met name *GNAQ* en *GNA11* mutaties aangetroffen (Elder, 2020; WHO, 2023).

Op dit moment is er alleen voor melanoom met een *BRAF* V600 mutatie een behandeling beschikbaar buiten trial verband, met ook bewezen effectiviteit. *KIT* mutaties zijn vrij zeldzaam (1-3%), en komen met name voor in melanomen van slijmvlies, en in acraal melanoom en melanoom van chronisch zonbeschadigde huid voor. Van *KIT* remmers is wel klinische benefit beschreven bij geselecteerde patiënten (Meng, 2019).

De ge-update Europese en op consensus gebaseerde richtlijn voor melanoom uit 2022 doet geen aanbeveling om tumor mutational burden (TMB) standaard als predictieve marker voor immuuntherapie te bepalen. Tevens is er geen aanbeveling om een gen expressie profiel (GEP) test als prognostische marker voor recidief of metastasering van melanoom uit te voeren (Garbe, 2022) .

De verwachting is wel dat het belang van meer uitgebreid screenen van relevante genen in melanoom middels next-generation-sequencing (NGS) in de toekomst zal toenemen en een test die alle actionable targets in een analyse kan detecteren lijkt kosten- en tijds-efficiënt in een diagnostische setting.

BRAF mutaties en testen

BRAF mutaties worden ingedeeld in 3 klassen op basis van het mechanisme waarop ze de MAPK signaaltransductie route activeren: klasse I mutaties zijn de *BRAF* V600 mutaties en hebben een hoge kinase activiteit, klasse II betreft non-V600 *BRAF* mutaties met hoge of intermediaire kinase activiteit en klasse III mutaties hebben geen kinase activiteit, en worden ook wel kinase-dood mutaties genoemd (Vanni, 2020).

Er zijn diverse testen voor detectie van een *BRAF* mutatie waarbij NGS een hoge sensitiviteit en specificiteit heeft, ook bij een laag tumorcelpercentage. NGS heeft tevens het voordeel dat simultaan meerdere genen kunnen worden geanalyseerd. Het nadeel van NGS is dat de analyse meerdere werkdagen duurt.

Bij gebruik van NGS als moleculaire test is het advies bij additionele bevindingen (zoals bijvoorbeeld een pathogene variant in *CDKN2A* of *BAP1*) Tabel 3 “Leidraad voor het rapporteren van een advies over kiembaandiagnostiek in het PA-verslag en tijdens de MTB bij de analyse van solide tumoren van volwassenen” te raadplegen. Conform tabel 3 kan besloten worden de patiënt te bespreken in het lokale Moleculaire Tumor Board, dan wel in het pathologie-verslag te attenderen op een mogelijke kiembaanvariant (zie, tabel 3 via www.artsengenetica.nl).

<u>Waarden en voorkeuren van patiënten</u>

Patiënten met stadium III melanoom hechten waarde aan tijdige en accurate mutatieanalyse voor het bepalen van de juiste systeemtherapie en willen dat dit proces toegankelijk is. Het is belangrijk dat patiënten goed geïnformeerd worden over het doel van het uitvoeren van deze moleculaire testen en van eventuele consequenties die daarmee gepaard gaan.

<u>Kosten</u>

Hoewel NGS een duurdere techniek is dan immuunhistochemie of een moleculaire sneltest, is de werkgroep van mening dat gezien de hogere gevoeligheid en de vele extra informatie die NGS oplevert direct inzetten van NGS voldoende kosteneffectief is.

<u>Haalbaarheid en implementatie</u>

De werkgroep voorziet geen probleem ten aanzien van de haalbaarheid en implementatie.

Aanbevelingen

Verricht moleculaire diagnostiek bij patiënten die in aanmerking komen voor systeemtherapie.

Verricht moleculaire diagnostiek ten behoeve van behandeling in een van de melanoomcentra die landelijk aangewezen zijn voor de systemische behandeling van melanoom.

Verricht bij voorkeur de moleculaire diagnostiek middels een NGS test in verband met hogere gevoeligheid.

Verricht alleen een moleculaire sneltest voor detectie van een BRAFV600 mutatie of BRAFV600E immuunhistochemie indien een snelle uitslag gewenst is.

Verricht meer uitgebreid moleculair onderzoek (o.a. *KIT* mutatie status) indien er geen mogelijkheid (meer) is tot BRAF-gerichte therapie of een andere behandeling.

Verricht moleculaire diagnostiek bij voorkeur op een recente of nog aanwezige melanoom metastase.

Gebruik een gevalideerde moleculaire test uitgevoerd door een moleculair diagnostisch laboratorium dat hiertoe is uitgerust en deelneemt aan kwaliteitsrondzendingen en daarbij goed scoort.

Het is wenselijk dat de uitslag van de BRAF-test binnen vijf werkdagen na binnenkomst van het tumormateriaal bij het uitvoerend laboratorium bekend is. Rapporteer de uitslag van de moleculaire test volgens de vigerende HGVS (Human Genome Variation Society) nomenclatuur.

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7.2.1. Neoadjuvante behandeling stadium III

Uitgangsvraag

Wat zijn de indicaties voor neoadjuvante behandeling bij patiënten met een resectabel stadium III melanoom?

De uitgangsvraag omvat de volgende deelvragen:

1. Wat is de rol van neoadjuvante systemische therapie?
2. Welk schema systemische therapie heeft de voorkeur, en van welke factoren is dit afhankelijk?
3. Wanneer dient responsevaluatie/restadiëring plaats te vinden?
4. Welke operatie volgt na neoadjuvante behandeling?
5. Hoe wordt het resectiepreparaat na neoadjuvante behandeling beoordeeld en wat staat erin het pathologieverslag?
6. Welke adjuvante behandeling wordt gegeven na neoadjuvante behandeling en is dit altijd nodig?

Introductie:

Adjuvante behandeling met anti-PD1 monotherapie (pembrolizumab of nivolumab) of dabrafenib-trametinib was tot 2024 de standaardbehandeling voor patiënten met een stadium III melanoom (zie module adjuvante therapie). Ondanks dit intensieve adjuvante behandeltraject van een jaar krijgt een aanzienlijk deel van de patiënten nog steeds een lokaal recidief of metastasen (Weber, 2016; Eggermonet, 2018; Long, 2017). De afgelopen jaren zijn er meerdere studies uitgevoerd waarin patiënten voorafgaand aan de operatie werden behandeld met immuuntherapie. De resultaten van verschillende studies laten zien dat neoadjuvante behandeling de recidief vrije overleving verbetert, een aanzienlijke gezondheidswinst oplevert en mogelijk minder belastend is voor de patiënt.

Search and select

P (patients): patients with resectable stage III melanoma
I (intervention): neoadjuvant treatment given
C (control): no neoadjuvant treatment given (Note: adjuvant treatment with immunotherapy or BRAF/MEK-i is allowed)
O (outcome measure): recurrence-free survival, event-free survival, overall survival, adverse events
Other selection criteria; randomized controlled trials

Relevant outcome measures

The guideline development group considered recurrence-free survival, event-free survival and overall survival as a critical outcome measure for decision making; and adverse events as an important outcome measure for decision making.

Per outcome measure:

The working group defined a difference of 10% as a minimal clinically (patient) important difference.

Results

Two randomized studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias

is summarized in the risk of bias tables. The results are stratified by type of medication, pembrolizumab (Patel, 2023) and nivolumab plus ipilimumab (Blank, 2024).

Summary of literature

Description of studies

Pembrolizumab

Patel (2023)

Described a randomized, open-label, phase II trial, which was conducted at 90 sites in the United States with a medium follow-up duration of 14.7 months. They evaluated the efficacy and safety of neoadjuvant and adjuvant therapy with pembrolizumab versus adjuvant therapy with pembrolizumab only in patients with resectable stage III or IV melanoma. A total of 313 patients were randomized to receive either three doses of 3-weekly neoadjuvant pembrolizumab, followed by surgery, followed by 15 doses of 3-weekly adjuvant pembrolizumab (neoadjuvant-adjuvant group, n=154), or surgery followed by 18 doses of adjuvant pembrolizumab (adjuvant-only group, n=159). One dosage consisted of an intravenous infusion of 200 mg of pembrolizumab. The median age (range) was 64 (19-90) in the neoadjuvant-adjuvant group, compared with 62 (22-88) in the adjuvant-only group. In the neoadjuvant group 92/154 (60%) were males, compared with 111/159 (70%) in the adjuvant-only group. The distribution of the BRAF mutation status and the disease stage were similar between the two groups. The following relevant outcomes were reported: event-free survival, event-free survival at 2 years, and the treatment-related adverse events.

Ipilimumab plus nivolumab

Blank (2024)

Described a randomized, multicentre, international, phase III trial which was conducted in 27 centres in Australia, France, Italy, Poland, the Netherlands, and the USA with a medium follow-up duration of 10.6 months in the neoadjuvant group and 9.9 months in the adjuvant group. They compared the efficacy and safety of neoadjuvant ipilimumab plus nivolumab with adjuvant nivolumab in patients with resectable, macroscopic stage III melanoma. A total of 423 patients were randomized to receive either two cycles of neoadjuvant ipilimumab (at a dose of 80 mg) plus nivolumab (at a dose of 240 mg) every three weeks followed by surgery (neoadjuvant group, n = 212); or surgery followed by 12 cycles of adjuvant nivolumab (at a dose of 480 mg) every 4 weeks (adjuvant group, n=211). In the neoadjuvant group, patients who had a locally assessed major pathological response (≤10% residual viable tumor) did not receive any adjuvant treatment, and patients who had a pathological partial response (11 to 50% residual viable tumor) or a pathological nonresponse (>50% residual viable tumor) received adjuvant dabrafenib (at a dose of 150 mg twice daily) plus trametinib (at a dose of 2 mg once daily) for 46 weeks if the melanoma had a BRAF V600E or V600K mutation or received an additional 11 cycles of adjuvant nivolumab (at a dose of 480 mg) every 4 weeks if the melanoma was BRAF wild type. The median age was 60 years (22-84) in the neoadjuvant group, compared with 59 years (19-87) in the adjuvant group. In the neoadjuvant group, 141/212 (66.5%) were males, compared with 135/211

(64.0%) in the adjuvant group. The baseline characteristics of the patients were balanced between the groups. The following relevant outcomes were reported: 12-month event-free survival, recurrence-free survival at 12 months and adverse events.
N.B.: Follow-up is ongoing for the assessment of long-term event-free and distant metastasis-free survival, health-related quality of life, and ultimately overall survival. Data on overall survival remain blinded until the prespecified final analysis at 3 years after the last patient is enrolled.

Results

Pembrolizumab

Event-free survival

Patel (2023) reported the outcome event-free survival in the intention-to-treat population. Events were defined as disease progression or toxic effects that precluded surgery; the inability to resect all gross disease; disease progression, surgical complications, or toxic effects of treatment that precluded the initiation of adjuvant therapy within 84 days after surgery; recurrence of melanoma after surgery; or death from any cause. After a median duration of follow-up of 14.7 months in both groups, a total of 105 events occurred, 38 (24.7%) events in the neoadjuvant-adjuvant group and 67 (42.1%) events in the adjuvant-only group. This difference is considered clinically relevant.

Event-free survival at 2 years

Patel (2023) reported the outcome event-free survival in the intention-to-treat population at 2 years. Events were defined as disease progression or toxic effects that precluded surgery; the inability to resect all gross disease; disease progression, surgical complications, or toxic effects of treatment that precluded the initiation of adjuvant therapy within 84 days after surgery; recurrence of melanoma after surgery; or death from any cause. Event-free survival at 2 years was 72% (95% CI: 64-80) in the neoadjuvant-adjuvant group and 49% (95% CI: 41-59) in the adjuvant-only group. The article by Patel (2023) lacks data regarding time-to-event outcomes, as well as information on the risk of mortality within the various groups during the follow-up period. Consequently, there is insufficient data available to calculate a hazard ratio.

Recurrence-free survival

No data on recurrence-free survival was reported.

Adverse events

Patel (2023) reported the outcome treatment-related adverse event (grade 3 or higher) in the 152 patients in the neoadjuvant-adjuvant group who had received at least one dose of pembrolizumab. 11 (7%) patients had at least one grade 3 or 4 adverse event that was deemed by the investigators to be related to pembrolizumab. Furthermore, the incidence of treatment-related adverse events of grade 3 or higher during adjuvant therapy in both groups was assessed. This outcome was similar in the two groups (12% in the neoadjuvant-adjuvant group and 14% in the adjuvant-only group). No new toxic effects of pembrolizumab were observed in either trial group, or no deaths attributed by the investigators to pembrolizumab occurred in either group. This difference is not considered clinically relevant.

Ipilimumab plus nivolumab

Event-free survival

Blank (2024) reported the outcome event-free survival in the intention-to-treat population. Event-free survival was described as the time from randomization to the occurrence of progression to unresectable melanoma before surgery; disease recurrence; or death due to melanoma or due to treatment. After a median duration of follow up of 10.6 months in the neoadjuvant group and 9.9 months in the adjuvant group respectively, a total of 100 events occurred, 28 (13.2%) events in the neoadjuvant group and 72 (34.2%) in the adjuvant group. The

hazard ratio for progression, recurrence, or death was 0.32 (99.9% CI: 0.15 to 0.66), favoring the neoadjuvant group. This difference is considered clinically relevant.

Event-free survival at 12 months

Blank (2024) reported the outcome event-free survival in the intention-to-treat population at 12 months. Event was defined as the time from randomization to the occurrence of progression to unresectable melanoma before surgery; disease recurrence; or death due to melanoma or due to treatment. Event-free survival at 12 months was 83.7% (99.9% CI: 73.8 – 94.8) in the neoadjuvant group and 57.2% (99.9% CI: 45.1-72.7) in the adjuvant group respectively. This difference is considered clinically relevant.

Recurrence-free survival

Blank (2024) reported the recurrence-free survival by pathological response among patients in the neoadjuvant treatment group. The hazard ratio for progression, recurrence, or death was 0.32 (99.9% CI: 0.15 to 0.66), favoring the neoadjuvant group. This difference is considered clinically relevant.

Adverse events

Blank (2024) reported the outcome adverse events of grade 3 and higher that were related to systemic treatment. This occurred in 63 (29.7%) patients in the neoadjuvant group and 25 (14.7%) patients in the adjuvant group. This difference is considered clinically relevant.

<u>Level of evidence of the literature</u>

Pembrolizumab

There are four levels of evidence: high, moderate, low, and very low.
The evidence was derived from an RCT, therefore the level of evidence of all outcomes started at 'high'.

The level of evidence regarding the outcome measure **event-free survival** was downgraded by one level because of study limitations (-1 risk of bias, because of incomplete information about the allocation concealment, and the lack of blinding of the data analysist). Therefore, the level of evidence was graded as moderate.

The level of evidence regarding the outcome measure **event-free survival at two years** was downgraded by one level because of study limitations (-1 risk of bias, because of incomplete information about the allocation concealment, and the lack of blinding of the data analysist). Therefore, the level of evidence was graded as moderate.

The level of evidence could not be graded for the outcome **recurrence-free survival**, as it was not reported in the included study.

The level of evidence regarding the outcome measure **treatment-related adverse events** was downgraded by one level because of study limitations (-1 risk of bias, because of incomplete information about the allocation concealment, and the lack of blinding of the data analysist). Therefore, the level of evidence was graded as moderate.

Conclusions
Pembrolizumab

Moderate **GRADE**	Pembrolizumab both before surgery (neoadjuvant therapy) and after surgery (adjuvant therapy) probably results in an improved **event-free survival** compared with adjuvant pembrolizumab only in patients with high-risk resectable stage III melanoma. *Source: Patel, 2023*

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Moderate **GRADE**	Pembrolizumab both before surgery (neoadjuvant therapy) and after surgery (adjuvant therapy) probably results in an improved **event-free survival at two years** compared with adjuvant pembrolizumab only in patients with high-risk resectable stage III melanoma. *Source: Patel, 2023*

- **GRADE**	No evidence was found regarding the effect of receiving pembrolizumab both before surgery (neoadjuvant therapy) and after surgery (adjuvant therapy) on recurrence-free survival in patients with high-risk resectable stage III melanoma.

Moderate **GRADE**	Pembrolizumab both before surgery (neoadjuvant therapy) and after surgery (adjuvant therapy) probably does not result in an increase in **treatment-related adverse events** compared with pembrolizumab given as adjuvant therapy only in patients with high-risk resectable stage III melanoma. *Source: Patel, 2023*

10 **Ipilimumab plus nivolumab**
The evidence was derived from an RCT, therefore the level of evidence of all outcomes started at 'high'.

The level of evidence regarding the outcome measures **event-free survival, event-free survival at 12 months, recurrence-free survival** and **adverse events** was not downgraded.

15 Therefore, the level of evidence was graded as high for all outcome measures.

Conclusions
Ipilimumab plus nivolumab

HIGH GRADE	Neoadjuvant ipilimumab plus nivolumab followed by surgery and response-driven adjuvant therapy* results in an improved **event-free survival** compared to surgery followed by adjuvant nivolumab only in patients with high-risk resectable stage III melanoma. *Source: Blank, 2024*

HIGH GRADE	Neoadjuvant ipilimumab plus nivolumab followed by surgery and response-driven adjuvant therapy* results in an improved **event-free survival at 12 months** compared to surgery followed by adjuvant nivolumab only in patients with high-risk resectable stage III melanoma. *Source: Blank, 2024*

HIGH GRADE	Neoadjuvant ipilimumab plus nivolumab followed by surgery and response-driven adjuvant therapy* results in an improved **recurrence-free survival** compared to surgery followed by adjuvant nivolumab in patients with high-risk resectable stage III melanoma. *Source: Blank, 2024*

HIGH GRADE	Neoadjuvant ipilimumab plus nivolumab followed by surgery and response-driven adjuvant therapy* results in a higher percentage of **adverse events of any cause of grade 3 or higher** compared to surgery followed by adjuvant nivolumab only in patients with high-risk resectable stage III melanoma. *Source: Blank, 2024*

*Patients who had a locally assessed major pathological response (≤10% residual viable tumor) did not receive any adjuvant treatment, and patients who had a pathological partial response (11 to 50% residual viable tumor) or a pathological nonresponse (>50% residual viable tumor) received adjuvant dabrafenib (at a dose of 150 mg twice daily) plus trametinib (at a dose of 2 mg once daily) for 46 weeks if the melanoma had a BRAF V600E or V600K mutation or received an additional 11 cycles of adjuvant nivolumab (at a dose of 480 mg) every 4 weeks if the melanoma was BRAF wild type.

Overwegingen – van bewijs naar aanbeveling

Balans tussen gewenste en ongewenste effecten

Neoadjuvante behandeling met anti-PD1 gebaseerde therapie resulteert in een betere event-free survival bij patiënten met resectabel stadium III melanoom, wanneer wordt vergeleken met alleen adjuvante therapie. Daarom wordt neoadjuvante behandeling met anti-PD1 gebaseerde therapie als standaardbehandeling beschouwd. Adjuvante behandeling zonder neoadjuvante behandeling is daarmee geen standaardbehandeling meer tenzij bij operatie en/of pathologisch onderzoek onverwacht sprake blijkt van een melanoom stadium III of patiënten overduidelijk geen kandidaat zijn voor neoadjuvante behandeling met anti-PD1 gebaseerde therapie vanwege bijvoorbeeld pre-existente auto-immuunziekten.

Aangezien de patiëntenpopulatie, de diagnostiek van pathologische response, de adjuvante behandelstrategie en de definitie van event-free survival enigszins verschillend waren tussen de twee gerandomiseerde studies, kunnen de verschillende strategieën niet met elkaar vergeleken worden. Daarnaast is combinatietherapie met ipilimumab-nivolumab geassocieerd met een hogere frequentie van adverse events, welke ernstig en irreversibel kunnen zijn. Daarom dienen de mogelijke voor- en nadelen van neoadjuvante behandeling met combinatietherapie (ipilimumab-nivolumab) en monotherapie (pembrolizumab) weloverwogen met de patiënt besproken te worden om samen te besluiten tot neoadjuvante behandeling. In deze besluitvorming dienen ook de verschillende adjuvante behandelstrategieën van deze neoadjuvante behandelstrategieën meegenomen te worden.

Kwaliteit van bewijs:
De overall kwaliteit van bewijs is redelijk voor de neoadjuvante behandeling met monotherapie (pembrolizumab). Dit betekent dat we redelijk zeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaten.

De overall kwaliteit van bewijs is hoog voor de neoadjuvante behandeling met combinatietherapie (ipilimumab-nivolumab) gevolgd door chirurgie en response-driven behandeling. Dit betekent dat we zeer zeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaten.

Voor de combinatietherapie met ipilimumab-nivolumab was een response driven adjuvante behandeling onderdeel van de onderzochte behandeling strategie in de experimentele arm. Derhalve maakt de response driven adjuvante behandeling onderdeel uit van de neoadjuvante behandelstrategie met ipilimumab-nivolumab en dient neoadjuvante behandeling met ipilimumab-nivolumab na operatie gevolgd te worden door een response driven adjuvante behandeling zoals gedefinieerd in de studie. Dat betekent dat patiënten die een *major* pathologische respons (<10% residuele vitale tumor) hebben na neoadjuvante behandeling met ipilimumab-nivolumab geen adjuvante therapie meer krijgen.

De ‘response-driven’ adjuvante behandeling is na neoadjuvante behandeling met pembrolizumab niet onderzocht. Daarom wordt adjuvante behandeling met pembrolizumab beschouwd als de standaard behandelstrategie na neoadjuvante behandeling met

pembrolizumab. Bij patiënten die een *major* pathologische respons hebben na neoadjuvante behandeling met pembrolizumab is het denkbaar dat afzien van adjuvante behandeling besproken zou kunnen worden met de patiënt, waarbij vermeld dient te worden aan de patiënt dat dit na neoadjuvante behandeling met pembrolizumab niet is onderzocht en daarom niet als standaardzorg wordt beschouwd. Voor patiënten die een BRAF-gemuteerd melanoom hebben en geen *major* pathologische respons na neoadjuvante behandeling met pembrolizumab is adjuvante behandeling met dabrafinib-trametinib niet onderzocht.

Wanneer dient responsevaluatie/restadiëring plaats te vinden?

Voor de rol van beeldvormende technieken tijdens de stadiering van hoog-risico stadium II en stadium III melanoom wordt verwezen naar de module Beeldvorming [In ontwikkeling LINK].

Indien bij stadiering een [^{18}F]FDG-PET met alleen een low-dose CT is verricht, kan deze low-dose CT tevens als uitgangsscan voor response evaluatie na neoadjuvante behandeling dienen, mits de gevonden laesies betrouwbaar te meten zijn volgens RECIST1.1. In de twee gerandomiseerde studies zijn de behandelstrategieën en de momenten van respons evaluatie verschillend. In de studie van Patel et al. 2023 wordt de radiologische respons op neoadjuvante behandeling gerapporteerd volgens RECIST1.1, na drie 3-wekelijkse doses pembrolizumab. Van de 142 evalueerbare patiënten hadden 9 (6%) patiënten een radiologisch complete respons, en 58 (41%) patiënten een partiële respons. Er is geen correlatie met de pathologische respons beschreven. In de studie van Blank (2024) worden geen radiologische responsen beschreven. In een eerdere multicenter, gerandomiseerde, gecontroleerde fase 2 studie van Rozeman (2019) werden patiënten met een resectabel stadium III met alleen lymfeklierbetrokkenheid gerandomiseerd tussen 3 verschillende combinaties van ipilimumab en nivolumab. De radiologische respons na 6 weken neoadjuvante behandeling en vooraf aan operatie werd niet gerapporteerd volgens RECIST1.1 (Eisenhauer, 2009) en is niet centraal gereviewd. Van de 86 evalueerbare patiënten hadden tussen 4% en 7% van de patiënten een complete radiologische respons en tussen 31% en 57% van de patiënten een partiële radiologische respons. Dit is vergelijkbaar met de radiologische response in de studie van Patel (2023). In vergelijking met de pathologische respons, gemeten over alle drie de behandelarmen, lijkt de radiologische evaluatie volgens RECIST1.1 het aantal pathologische responsen te onderschatten (radiologisch 52%, pathologisch 74%). Concluderend is er op dit moment geen rol voor beeldvormende technieken voor het (vervangen van) beoordelen van pathologische respons op neoadjuvante behandeling.

In de studie van Blank (2024) werd bij 5 van 212 (2,4%) patiënten afgezien van chirurgische resectie na neoadjuvante behandeling vanwege progressieve ziekte, in de studie van Patel (2023) was dit bij 12 van 14 patiënten (8,3%). In beide studies wordt niet beschreven of progressieve ziekte is vastgelegd door lichamelijk onderzoek of door radiologische evaluatie, of beide, en of dit progressie van bekende lokale ziektelast is of nieuwe metastasen op afstand. In de studie van Rozeman et al. 2019 werd in de drie neoadjuvante behandelarmen bij 9 van 86 patiënten (10%) progressieve ziekte vastgesteld bij radiologische evaluatie. Dit betrof bij 7 patiënten locoregionale progressie van lymfekliermetastasen en bij 2 patiënten metastasen op afstand. Desalniettemin ondergingen alle 9 patiënten een (partiële) lymfeklierdissectie voor lokale controle. Concluderend is het aan te bevelen om na neoadjuvante behandeling, na 9-12 weken afhankelijk van het behandelschema, en vooraf aan chirurgische resectie patiënten te evalueren met anatomische beeldvorming (CT-thorax en abdomen met intraveneuze contrasttoediening)

ter detectie van progressieve ziekte. Er zijn geen data beschikbaar over een aanvullende rol voor [18F]FDG-PET/CT in de evaluatie van neoadjuvante behandeling.

Hoe wordt het resectiepreparaat na neoadjuvante behandeling beoordeeld en wat staat erin het pathologieverslag?

In principe kan de beoordeling van het pathologie preparaat na neoadjuvante behandeling van melanoom in elk pathologie laboratorium worden verricht. Hierbij dient eenzelfde protocol te worden gevolgd zoals gehanteerd in beide reeds genoemde studies.
Van een lymfklierdissectie dienen de afmetingen van de grootste macroscopisch positieve lymfklier in 3 dimensies te worden gemeten. Indien de grootste lymfklier kleiner dan 5 cm is, dan dient elke lymfklier volledig te worden gelamelleerd (in plakjes van 3-4 mm) en ingesloten. Indien de macroscopisch tumorpositieve lymfklier > 5 cm is, dienen volledige doorsnedes van deze klier per 1 cm te worden ingesloten. Alle andere lymfklieren worden eveneens volledig gelamelleerd en ingesloten.

Naast de standaard AJCC parameters, dient het effect van de therapie te worden beschreven en gekwantificeerd. Het tumorbed wordt gedefinieerd als het oppervlak dat ingenomen wordt door vitale tumor en door tekenen van tumorregressie (necrose, melanofagen, fibrose/fibroinflammatoir stroma).

Het pathologie rapport dient de volgende items te bevatten:

- Totaal aantal lymfklieren en het aantal tumorpositieve lymfklieren
- Percentage vitale tumor t.o.v. van het totale tumorbed (bij meerdere positieve lymfklieren, een percentage geven van het oppervlak vitale tumor t.o.v. het totale oppervlak van het tumorbed in alle betrokken lymfklieren)
- Pathologische respons categorie aangeven:
    - pCR (pathologische complete respons): complete afwezigheid van vitale tumor in het behandelde tumorbed
    - pnCR (near-pCR): 1-10% vitale tumor in het behandelde tumorbed
    - MPR (major pathologische respons): 10% of minder vitale tumor in het behandelde tumorbed (dit omvat dus zowel de categorie pCR en pnCR)
    - pPR (partiële pathologische respons): > 10%, maar 50% of minder vitale tumor in het behandelde tumorbed
    - pNR (geen pathologische respons): > 50% vitale tumor in het behandelde tumorbed.
- Grootste tumordepositie vermelden (continue vitale tumor)
- Aan-/afwezigheid van extranodale uitbreiding
- Separaat in-transit metastasen beschrijven indien aanwezig: aantal, percentage vitale tumor, diameter van de grootste in-transit metastase.

Dit verslag dient uiteindelijk voorgelegd te worden aan een internist-oncoloog in één van de 14 melanoomcentra om de adjuvante behandelstrategie te bepalen na neoadjuvante behandeling met immuuntherapie. Bij voorkeur gebeurt dit in een MDO huid/melanoom van het centrum waar de neoadjuvante immuuntherapie is gegeven (zie Organisatie van zorg).

Welke operatie volgt na neoadjuvante behandeling?

Voor de-escalatie van chirurgie van melanoom na neoadjuvante therapie is weinig wetenschappelijke onderbouwing. In de setting van neoadjuvante behandeling van resectabele ziekte gaan we ervan uit dat de resectie niet anders zou moeten zijn dan vooraf gepland. Dit is ook de basis van de SWOG studie, waarvan het chirurgische protocol hier is overgenomen.

Bij een radiologische en/of klinische respons kan een dilemma ontstaan als de geplande chirurgie technisch lastig is of tot forse morbiditeit leidt. In de SWOG studie was de-escalatie van chirurgie geen optie hoewel er geen data zijn die dat bevestigen. Meerdere proof-of-concept studies (OpACIN (Rozeman, 2019) en PRADO (Reijers, 2022)) laten zien dat resectie van een 'indexklier' geen slechtere resultaten geeft dan een regionale klierdissectie, maar dat is nog niet bevestigd in grotere studies. Naar verwachting zullen die wel binnenkort gestart worden. Tot die tijd is het advies voor chirurgie na neoadjuvante behandeling van melanoom hieronder beschreven.
Chirurgische procedures na neoadjuvante therapie:

1. Resectie primaire tumor: conform huidige richtlijn (marge 1 dan wel 2 cm tenzij in functioneel of cosmetisch te belastend gebied (acra, gelaat).
2. Locoregionale ziekte (primair dan wel recidief): conform huidige richtlijn: resectie met tumorvrije marges.
3. Voor lymfekliermetastasen wordt een regionale lymfeklierdissectie geadviseerd.

Bij cervicale lymfekliermetastasen wordt geen radicale halsklierdissectie geadviseerd, selectieve halsklierdissectie is wel geaccepteerd. Uitgebreide klierdissecties (level 3 oksel, ilioinguinaal) zonder aanwijzingen voor metastasen in die regio's worden ook niet geadviseerd.
Extra aandacht bij de voorbereiding is nodig als er immuungerelateerde complicaties zijn, hoewel dat in de meeste gevallen geen contraindicatie is voor chirurgie.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

De mogelijke voor- en nadelen van neoadjuvante behandeling met combinatietherapie (ipilimumab-nivolumab) en monotherapie (pembrolizumab) dienen weloverwogen met de patient besproken te worden om samen tot een shared deciscion te komen voor neoadjuvante behandeling. Daarbij dient de hogere kans op (irreversible) bijwerkingen van de combinatietherapie met ipilimumab-nivolumab meegenomen te worden. Momenteel zijn er nog geen data over de kwaliteit van leven van de twee gerandomiseerde studies gepubliceerd die kunnen bijdragen aan deze besluitvorming.

Kosten (middelenbeslag)

De interventie levert minder kosten op. Voor neoadjuvante behandeling met pembrolizumab is response driven adjuvante behandeling niet onderzocht.
Neoadjuvante behandeling met ipilimumab-nivolumab gevolgd door een response driven adjuvante behandeling is kostenbesparend, omdat een groot deel van de patiënten (60%) geen adjuvante behandeling zal krijgen.

Aanvaardbaarheid, haalbaarheid en implementatie

Vergeleken met de adjuvante behandelstrategie wordt bij neoadjuvante behandeling met pembrolizumab alleen het tijdstip van chirurgie aangepast naar een later moment tijdens de behandelstrategie. Daarom gaat deze behandelstrategie niet gepaard met hogere kosten voor

medicatie. Van de combinatietherapie met ipilimumab-nivolumab is ipilimumab momenteel nog geen vergoede zorg.

Aanbevelingen

Medicamenteuze behandeling

Kies bij voorkeur voor neoadjuvante behandeling met combinatietherapie (ipilimumab-nivolumab) of monotherapie (pembrolizumab) boven adjuvante behandeling voor resectabel stadium III melanoom.

Bespreek neoadjuvante behandeling met de patiënt met resectabel stadium III melanoom alvorens te opereren, tenzij er evidente contra-indicaties zijn voor deze behandeling en bespreek dit met de patiënt.

Verwijs een patiënt met resectabel stadium III melanoom -nog voor chirurgie- naar een internist-oncoloog in één van de 14 melanoomcentra om te beoordelen of de patiënt kandidaat is voor neoadjuvante behandeling.

Bespreek de mogelijke voor- en nadelen van neoadjuvante behandeling met combinatietherapie (ipilimumab-nivolumab) en monotherapie (pembrolizumab) weloverwogen met de patiënt om samen te besluiten tot neoadjuvante behandeling. In deze besluitvorming dienen de grotere kans op bijwerkingen bij ipilimumab-nivolumab en de verschillende adjuvante behandelstrategieën meegenomen te worden.

Overweeg het gebruik van pembrolizumab vanwege minder bijwerkingen en de voorkeur van de patiënt.

Neem in overweging dat van alle (neo)adjuvante behandelingen vooralsnog geen overlevingsvoordeel is aangetoond.

Responsevaluatie/restadiëring

Verricht na neoadjuvante behandeling en vóór chirurgie een diagnostische CT-thorax en abdomen na intraveneuze contrasttoediening voor het uitsluiten van afstandsmetastasen en het bevestigen van operabiliteit.

Pathologie

Verwerk en beoordeel het resectiepreparaat na neoadjuvante therapie met gebruikmaking van de gestandaardiseerde macroscopie en verslaglegging volgens het protocol zoals gehanteerd in de NADINA studie.

Operatie

Verricht bij patiënten met lymfekliermetastasen een regionale lymfeklierdissectie.

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Kennisvragen:

- Het is nog onbekend of afzien van adjuvante behandeling veilig en effectief is voor patiënten die een major pathologische respons hebben na neoadjuvante behandeling met pembrolizumab.
- Het is nog onbekend wat de beste timing en modaliteit is voor responsevaluatie/restadiering (en responsvoorspelling) bij neoadjuvante therapie.

Bijlagen

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?** Definitely yes	**Was the allocation adequately concealed?**	**Blinding: Was knowledge of the allocated** **interventions adequately prevented?** **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	**Was loss to follow-up (missing outcome data) infrequent?**	**Are reports of the study free of selective outcome reporting?**	**Was the study apparently free of other problems that could put it at a risk of bias?** Definitely yes Probably yes	**Overall risk of bias** **If applicable/necessary, per outcome measure**

	Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no		Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Probably no Definitely no	**LOW** **Some concerns** **HIGH**
Patel, 2023	Definitely yes: Reason: Central randomization in a 1:1 ratio and according to a dynamic balancing method with the use of the National Cancer Institute Web-based Oncology Patient Enrollment Network platform.	Definitely yes: Reason: Central randomization.	Definitely no: Reason: Open-label trial (patients and health care providers not blinded). No information on blinding data collectors, outcome assessors, and data analysts.	Probably yes: Reason: Loss to follow-up was infrequent in intervention and control group. No adequate imputation methods (multiple imputation) were used	Definitely yes: Reason: All relevant outcomes were reported.	Definitely yes: Reason: No other problems noted	Some concerns
Blank, 2024	Probably yes: Reason: Randomization in a 1:1 ratio.	Definitely no: Reason: no information reported	Definitely no: Reason: No information reported on blinding data collectors, outcome assessors, and data analysts.	Probably yes: Reason: Loss to follow-up was infrequent in intervention and control group.	Definitely yes: Reason: All relevant outcomes were reported.	Definitely yes: Reason: No other problems noted	Some concerns

Evidence table for intervention studies (randomized controlled trials and non-randomized *observational* studies [cohort studies, case-control studies, case series])[1]

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Patel, 2023	Type of study: Open-label, Phase 2, Randomized clinical controlled trial. Setting and country: This study was conducted at 90 sites in the United States. Patients were enrolled from February 2019 to May 2022.	Inclusion criteria: Patients ≥ 18 years with histologically confirmed cutaneous, acral, or mucosal melanoma; clinically detectable, measurable disease according to RECIST; and stage IIIB to IIID melanoma or oligometastatic resectable stage IV (M1a, M1b, and M1c) melanoma. Patients with metastases in multiple regional nodal basins were eligible.	Describe intervention (treatment/procedure/test): Neoadjuvant-adjuvant group Three doses[1] of neoadjuvant pembrolizumab, surgery, and 15 doses of adjuvant pembrolizumab. The interval between the last dose and surgery was expected to be no longer than 5 weeks. [1]One dose: intravenous infusion of 200 mg of pembrolizumab every 3 weeks	Describe control (treatment/procedure/test): Adjuvant-only group Surgery followed by pembrolizumab every 3 weeks for a total of 18 doses[1].	Length of follow-up: Median follow-up of 14.7 months in both groups. Loss-to-follow-up: Reason: Withdrawal of consent I: N= 2/154 C: N=7/159 Incomplete outcome data: At time of data cut-off (2 years) Reason: still being on therapy. Intervention:	Outcome measures and effect size (include 95%CI and p-value if available): *Event[2]-free survival in the intention-to-treat population at 2 years. (Two-sided p-value and 95% CI [3]):* I: 72% (95% CI, 64%-80%) C: 49% (95% CI, 41% - 59%)	Authors conclusion: *"The percentage of patients with event-free survival at 2 years was 23 percentage points higher among those who received neoadjuvant pembrolizumab followed by adjuvant pembrolizumab than among those who received adjuvant pembrolizumab alone."*

	<u>Funding and conflicts of interest:</u> The study received funding from the National Cancer Institute and Merck Sharp and Dohme.	<u>Exclusion criteria</u>: If the patient had local recurrences in the scar or surgical bed of the primary melanoma as the sole site of disease. If the patient received previous immunotherapy for melanoma, active autoimmune disease in patients who had received systematic treatment within 2 years before trial entry, uveal melanoma, and any history of brain metastasis. <u>N total at baseline</u>:			N (%) 43 (28%) Control: N (%) 41 (27%) <u>Discontinued data</u>: Intervention: N (%) 59 (39%) - Death (n=14) - Did not underwent surgery due to multiple reasons (n=15) • Toxic effects (n=1) • Disease progression (n=12) • Coexisting conditions (n=1) • Had a clinical complete response and declined surgery (n=1) - Patients who underwent surgery but did not receive adjuvant therapy because of a defined event (n=18) • Declined receiving adjuvant therapy (n=1) • Neoadjuvant toxic effects (n=3)	[2] Events were defined as disease progression or toxic effects that precluded surgery; the inability to resect all gross disease; disease progression, surgical complications, or toxic effects of treatment that precluded the initiation of adjuvant therapy within 84 days after surgery; recurrence of melanoma after surgery; or death from any cause. [3] Confidence intervals were not corrected for multiplicity.	

		Intervention: 154 Control: 159 <u>Important prognostic factors</u>[2]: *For example* *Median age (range):* *I: 64 (19-90)* *C: 62 (22-88)* *Sex:* *I: 60 % M* *C: 70 % M* Groups comparable at baseline? Yes			• Disease progression (n=9) • Residual disease (n=1) • Clinical trials closed because of COVID-19 (n=1) • Concerns regarding exposure to Covid-19 (n=1) • Disease other than melanoma identified at surgery (n=2) - Lost during adjuvant therapy (n=26) Control: N (%) 73 (48%) Reasons (describe) - Death (n=22) - Did not underwent surgery due to multiple reasons (n=1) • Scheduling issues (n=1) - Patients who underwent surgery but did not receive adjuvant therapy because of a defined event (n=21) • Declined to receive adjuvant therapy (n=2) • Disease progression (n=16) • Residual disease (n=2)		

					• Radiotherapy-related delays (n=1) - Lost during adjuvant therapy (n=51)		
Blank et al, 2024	Type of study: Phrase 3, randomized controlled trial. Setting and country: This study was conducted at 27 sites in Australia, France, Italy, The Netherlands and the USA. Patients were enrolled from July 2021 to December 2023.	Inclusion criteria: Patients ≥ 16 years with resectable, macroscopic stage III cutaneous or acral melanoma or melanoma of unknown primary origin with at least one pathologically proven lymph-node metastasis and a maximum of three additional intransit metastases. Patients with concurrent primary melanoma were eligible for inclusion.	Describe intervention (treatment/procedure/test): Neoadjuvant group: two cycles of neoadjuvant ipilimumab (at a dose of 80 mg) plus nivolumab (at a dose of 240mg) every three weeks followed by surgery.	Describe control (treatment/procedure/test): Adjuvant group: Surgery followed by 12 cycles of adjuvant nivolumab (at a dose of 480 mg) every 4 weeks.	Length of follow-up: Median follow-up of 10.6 months in the neoadjuvant group and 9.9 months in the adjuvant group. Lost-to-follow-up: Intervention: n= 1/212 Control: n= 6/211 Incomplete outcome data: Reason: still being on treatment at cut-off. Intervention: N=31 Control:	Outcome measures and effect size *Event-free survival in the intention-to-treat population at 12 months. (Two-sided p-value and 99.9% CI)* Intervention: 83.7% (99.9% CI, 73.8%-94.8%) Control: 57.2% (99.9% CI, 45.1%-72.7)	Authors conclusion: *"Neoadjuvant treatment resulted in longer event-free survival than adjuvant treatment with an absolute reduction of 27 percentage points in the risk of an event in the first 12 months."*

	<u>Funding and conflicts of interest:</u> The study received funding form Bristol Meyers Squibb, the National Health and Medical Research Council and Melanoma Institute Australia and University of Sydney Medical Foundation,	<u>Exclusion Criteria:</u> *See article.* <u>N total at baseline</u>: Intervention: 212 Control: 211 <u>Important prognostic factors</u>: Median age (range): Intervention: 64 (19-90) Control: 62 (22-88) Sex: Intervention: 66.5% male Control: 64.0% male			N=68 <u>Discontinued data:</u> Intervention: N= 44 Reasons: - Progression before surgery (n=5) - Recurrence (n=12) - Adverse event (n=19) - Refused further treatment (N=8) Control: N= 100 Reasons: - Progression/recurrence (n=62) - Adverse events (n=29) - Refused further treatment (n=6) - Physician's choice (n=1) - Death due to toxicity (n=1) - Death due to other reason (n=1)	The hazard ratio for progression, recurrence, or death was 0.32 (99.9% CI: 0.15 to 0.66), favoring the neoadjuvant group. This difference is considered clinically relevant.	

		Groups comparable at baseline? Yes					

8.1.4. Moleculaire diagnostiek bij gemetastaseerde en irresectabel ziekte (irresectabel stadium III en IV)

Uitgangsvraag

Wat is het juiste moment en wijze waarop mutatieanalyse ten behoeve van systeemtherapie bij patiënten met irresectabel stadium III en IV melanoom dient te worden verricht?

Inleiding

De systemische behandeling van patiënten met melanoom is in Nederland gecentraliseerd in landelijk aangewezen melanoomcentra. Op dit moment wordt moleculaire diagnostiek voor melanoom op verschillende momenten in het beloop van de ziekte, met verschillende diagnostische testen en in een grote verscheidenheid van pathologie laboratoria verricht. Er is hierbij een sterke variatie in de uitgebreidheid en gevoeligheid van de moleculaire testen die worden ingezet. Genoemde situatie leidt tot inefficiëntie door vertraging en opnieuw testen bij verwijzing naar een melanoomcentrum. Centralisatie van moleculaire diagnostiek in de melanoomcentra reduceert kosten en doorlooptijden en verbetert uniformiteit en continuïteit van zorg.

Zoeken en selecteren

Voor deze vraagstelling werd geen PICO geformuleerd.

Overwegingen – van bewijs naar aanbeveling

Samenvatting van (systematische) reviews, internationale richtlijnen en consensusdocumenten

Tot circa 60% van de melanomen op intermitterend aan zon blootgestelde huid heeft een somatische *BRAF* mutatie. De meeste *BRAF* mutaties zijn missense variaties die leiden tot een verandering van het aminozuur valine op codon 600 (Vanni, 2020; Elder, 2020; WHO, 2023).

Een recente Europese richtlijn (Garbe, 2022) geeft aan dat *BRAF* V600 mutatie analyse vereist is bij besluit over de behandeling van patiënten met melanoom met afstandsmetastasen of niet-reseceerbare regionale metastasen en indien BRAF/MEK remmers worden overwogen voor de adjuvante behandeling van gereseceerd hoog-risico stadium III melanoom.

Bij metastasen verdient het testen van een recente of nog aanwezige metastase de voorkeur, maar indien dit niet mogelijk is kan ook de primaire tumor worden gebruikt, in verband met hoge -maar niet complete - concordantie t.a.v. de BRAF status tussen het primair melanoom en de metastase (Valeachis, 2017; Vanni, 2020). Ter overweging: benoemen dat patiënten meerdere primaire melanomen kunnen hebben en dat de kliniek ten aanzien van metastaserings patroon en eventuele meerdere primaire melanomen van belang is.

Naast *BRAF* mutaties komen bij melanomen in huid en slijmvlies ook andere mutaties voor in genen van de MAP-kinase signaaltransductieroute zoals *NRAS, NF1* en *KIT.* Verder komen relatief zeldzame fusies in *NTRK, ALK, ROS1* en *RET* voor in met name Spitz melanoom, acraal melanoom en mucosaal melanoom. In oogmelanoom worden met name *GNAQ* en *GNA11* mutaties aangetroffen (Elder, 2020; WHO, 2023).

Op dit moment is er alleen voor melanoom met een *BRAF* V600 mutatie een behandeling beschikbaar buiten trial verband, met ook bewezen effectiviteit. *KIT* mutaties zijn vrij zeldzaam (1-3%), en komen met name voor in melanomen van slijmvlies, en in acraal melanoom en melanoom van chronisch zonbeschadigde huid voor. Van *KIT* remmers is wel klinische benefit beschreven bij geselecteerde patiënten (Meng, 2019).

De ge-update Europese en op consensus gebaseerde richtlijn voor melanoom uit 2022 doet geen aanbeveling om tumor mutational burden (TMB) standaard als predictieve marker voor immuuntherapie te bepalen. Tevens is er geen aanbeveling om een gen expressie profiel (GEP) test als prognostische marker voor recidief of metastasering van melanoom uit te voeren (Garbe, 2022) .

De verwachting is wel dat het belang van meer uitgebreid screenen van relevante genen in melanoom middels next-generation-sequencing (NGS) in de toekomst zal toenemen en een test die alle actionable targets in een analyse kan detecteren lijkt kosten- en tijds-efficiënt in een diagnostische setting.

BRAF mutaties en testen
BRAF mutaties worden ingedeeld in 3 klassen op basis van het mechanisme waarop ze de MAPK signaaltransductie route activeren: klasse I mutaties zijn de *BRAF* V600 mutaties en hebben een hoge kinase activiteit, klasse II betreft non-V600 *BRAF* mutaties met hoge of intermediaire kinase activiteit en klasse III mutaties hebben geen kinase activiteit, en worden ook wel kinase-dood mutaties genoemd (Vanni, 2020).

Er zijn diverse testen voor detectie van een *BRAF* mutatie waarbij NGS een hoge sensitiviteit en specificiteit heeft, ook bij een laag tumorcelpercentage. NGS heeft tevens het voordeel dat simultaan meerdere genen kunnen worden geanalyseerd. Het nadeel van NGS is dat de analyse meerdere werkdagen duurt. In geval van spoed bij snel progressieve ziekte van een gemetastaseerd melanoom, kan een minder sensitieve en specifieke immunohistochemische BRAFV600E kleuring of moleculaire sneltest worden ingezet.
Bij gebruik van NGS als moleculaire test is het advies bij additionele bevindingen (zoals bijvoorbeeld een pathogene variant in *CDKN2A* of *BAP1*) Tabel 3 “Leidraad voor het rapporteren van een advies over kiembaandiagnostiek in het PA-verslag en tijdens de MTB bij de analyse van solide tumoren van volwassenen” te raadplegen. Conform tabel 3 kan besloten worden de patiënt te bespreken in het lokale Moleculaire Tumor Board, danwel in het pathologie-verslag te attenderen op een mogelijke kiembaanvariant (zie, tabel 3 via www.artsengenetica.nl).

<u>Waarden en voorkeuren van patiënten</u>
Patiënten met met irresectabel stadium III en IV melanoom hechten waarde aan tijdige en accurate mutatieanalyse voor het bepalen van de juiste systeemtherapie en willen dat dit proces toegankelijk is. Het is belangrijk dat patiënten goed geïnformeerd worden over het doel van het uitvoeren van deze moleculaire testen en van eventuele consequenties die daarmee gepaard gaan.
<u>Kosten</u>

Hoewel NGS een duurdere techniek is dan immuunhistochemie of een moleculaire sneltest, is de werkgroep van mening dat gezien de hogere gevoeligheid en de vele extra informatie die NGS oplevert direct inzetten van NGS voldoende kosteneffectief is.

5 Haalbaarheid en implementatie

De werkgroep voorziet geen probleem ten aanzien van de haalbaarheid en implementatie

Aanbevelingen

Verricht moleculaire diagnostiek bij patiënten die in aanmerking komen voor systeemtherapie.

Verricht moleculaire diagnostiek ten behoeve van behandeling in één van de melanoomcentra die landelijk aangewezen zijn voor de systemische behandeling van melanoom.

Verricht bij voorkeur de moleculaire diagnostiek middels een NGS test in verband met hogere gevoeligheid.

Verricht alleen een moleculaire sneltest voor detectie van een BRAFV600 mutatie of BRAFV600E immuunhistochemie indien een snelle uitslag gewenst is.

Verricht meer uitgebreid moleculair onderzoek (o.a. *KIT* mutatie status) indien er geen mogelijkheid (meer) is tot BRAF-gerichte therapie of een andere behandeling.

Verricht moleculaire diagnostiek bij voorkeur op een recente of nog aanwezige melanoom metastase.

Gebruik een gevalideerde moleculaire test uitgevoerd door een moleculair diagnostisch laboratorium dat hiertoe is uitgerust en deelneemt aan kwaliteitsrondzendingen en daarbij goed scoort.

Het is wenselijk dat de uitslag van de BRAF-test binnen vijf werkdagen na binnenkomst van het tumormateriaal bij het uitvoerend laboratorium bekend is. Rapporteer de uitslag van de moleculaire test volgens de vigerende HGVS (Human Genome Variation Society) nomenclatuur.

Literatuur

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8.2.2. Behandeling van oligometastase(n) bij stadium IV

Uitgangsvraag

Wat is de waarde van lokale behandeling voor patiënten met op afstand gemetastaseerd (stadium IV) melanoom?

Introductie

De behandeling van patiënten met een op afstand gemetastaseerd melanoom heeft zich de afgelopen jaren aanzienlijk ontwikkeld. Door de komst van zeer effectieve systeemtherapie is de rol van lokale behandeling in deze setting veranderd. Hoewel lokale behandeling soms wordt overwogen vooraf aan systeemtherapie, is dit nu vaak vooral op het moment van (oligo)progressie op systeemtherapie of bij klachten. Ook zijn er ontwikkelingen geweest in de lokale behandelingen waardoor indicaties en contra-indicaties veranderen. Het ontbreken van een consensus over de rol en timing van lokale behandeling alsmede over welke modaliteit het beste kan worden toegepast bij patiënten met op afstand gemetastaseerd melanoom kan leiden tot ongewenste praktijkvariatie en mogelijk suboptimale resultaten voor patiënten. Om deze reden is in deze module het bewijs ter ondersteuning van lokale behandelingen bij patiënten met een op afstand gemetastaseerd melanoom beschreven en worden aanbevelingen gedaan.

Search and select

A systematic review of the literature was performed to answer the following question: What is the effect of local treatment in comparison to wait and see policy, systemic therapy (continued, switch, or restart), or other type of treatment for metastatic patients with stadium IV melanoma?

P (patients): Patients with metastatic (stage IV) melanoma
I (intervention): local treatment: radiotherapy, surgery, ablative treatments (RFA)
C (control): wait and see policy, systemic therapy (continued, switch, or restart), other type of treatment
O (outcome measure): progression free survival, overall survival, time to next treatment, (surgical) complications, complications due to radiotherapy

<u>Relevant outcome measures</u>

The guideline development group considered progression free survival, overall survival, time to next treatment, (surgical) complications, and complications from radiotherapy as important outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

<u>Search and select (Methods)</u>

On the 7th of November 2022, relevant search terms were used to search for systematic reviews, randomized controlled trials and observational studies about the best local therapy for patients with stage IV melanoma in the databases Embase.com and Ovid/Medline. The search resulted in 936 unique hits. The detailed search strategy is depicted under the tab Methods.

Studies were selected based on the following criteria:

- Systematic reviews or randomized controlled trials
- Patients with metastatic (stage IV) cutaneous melanoma
- Local treatment
- Published in English

Studies were excluded if the following criteria were fulfilled:

- Articles reporting on solely ocular or mucosal melanoma
- Studies in patients with brain metastases
- Articles in which the effect of radiotherapy and immunotherapy synergy is studied

For brain metastases a separate guideline exists, which can be find trough the following link:
https://richtlijnendatabase.nl/richtlijn/hersenmetastasen/startpagina_-_hersenmetastasen.html
This literature analysis is restricted to studies reporting outcomes for local treatment of patients with metastatic (stage IV) focusing on other treatment sites than the brain. Studies only analyzing local treatment of the brain were excluded.

Twelve studies were initially selected based on title and abstract screening. After reading the full text, seven studies were excluded (see the table with reasons for exclusion under the tab Methods), and five studies were included.

Additionally, in cases where a systematic review included randomized controlled trials (RCTs) or prospective studies detailing outcomes for subgroups fulfilling our inclusion criteria, only such studies were included in the literature analysis and subjected to the GRADE approach.

Results

Five studies were included in the literature analysis. The assessment of the risk of bias is summarized in the risk of bias tables (under the tab Evidence tables).

Summary of literature

Description of studies

The PICO and important study characteristics of the included systematic reviews can be found in table 1.

Surgical intervention

Wankhede (2022) performed a systematic review and meta-analysis of studies comparing survival for patients who had malignant melanoma (MM) treated with curative metastasectomy versus incomplete metastasectomy or nonsurgical treatment. The literature search was performed from inception until 30 September 2021. Studies with fewer than 30 patients and reporting ocular or mucosal melanoma exclusively were excluded. In total, 40 studies were included, of which 38 retrospective trials, one multicentric randomized phase 3 trial, and one prospective phase 2 trial. The metastatic sites were skin, subcutaneous tissue or distant lymph nodes (27%); lung (30%); abdominal visceral (33%); and brain (10%). Wankhede included two prospective trials (Sosman, 2011 and Howard, 2012). One of the prospective trials (Howard, 2012) compared outcomes between two treatment arms.

Howard (2012) randomized patients to treatment surgery plus systemic medical therapy (SMT) versus SMT alone for melanoma patients developing distant metastases. In total, 291 patients (<60 years) had detailed records of treatment for stage IV recurrence. Patients were treated with surgery alone (n=43, 15%), surgery followed by SMT (n=85, 29%, SMT followed by surgery (n=33, 11%), and SMT alone (n=130, 45%).

Yeo (2022) performed a systematic review and meta-analysis to identify whether surgical or non-surgical therapy has better outcomes in the management of liver metastases in malignant melanoma. The search covered the period from inception to July 17, 2022. Articles that did not utilize a control were excluded. Thirteen non-randomized studies were included, of which eleven retrospective studies, and two prospective studies. One study conducted case–control matching One study did not report the primary tumor site and one study reported unknown location for some cases. The other included studies consisted of cutaneous (55.9%) and uveal (37.6%) melanoma.

Versluis* (2021) performed a retrospective, international, multicentre study to determine the role of local therapy in patients with metastatic melanoma experiencing solitary progression after initial response to immune checkpoint inhibition (ICI). In total, 294 patients treated with ICI between 2010-2019 were included from 17 centres in 9 countries. Patients were treated with a combination of local and systemic treatment in 42%, systemic therapy in 18%, local therapy in 36%, or active surveillance in 4%. The median duration of follow-up was 43 months and median time to solitary progression 13 months. Median OS was not reached. The estimated 3-year OS was 79%. The study showed that in 44% of patients treated for melanoma solitary progression after initial response to ICI, no subsequent progression occurred. Based on the results, the authors suggest that local therapy can benefit patients and may be associated with favourable long-term outcomes. This study did not compare treatment arms in a randomized manner. Therefore, the level of evidence of this study is not graded and this study is not described in more detail in the literature analysis.*

Urbanski* (2023) studied the influence of a surgical approach in treatment of advanced malignant melanoma with visceral metastases. A retrospective analysis was performed of 351 patients treated between 2006 and 2017 at single hospital with a follow-up time of 60 months. Of the included patients 121 had visceral metastases, of which 18 patients with oligometastatic disease (defined as <=5 metastases) and 103 patients with a diffuse pattern (defined as >5 metastases). Of the patients with oligometastatic disease, 13 patients were treated with visceral resection. Of the patients with a diffuse pattern 5 patients were treated with visceral resection. The results demonstrated a significant difference in median overall survival time (13.6 vs. 34.2 months) and in progression-free survival (9.6 vs. 3.8 months) in favor of those patients with resection of visceral metastases. The authors conclude that resection of visceral metastases is a rational treatment option in advanced malignant melanoma, in particular for patients in an oligometastatic stage.

Mor* (2022) undertook a retrospective cohort study of patients with metastatic melanoma undergoing abdominal resection of metastases. The study was performed at a single center tertiary national referral site for malignant melanoma and included all patients who underwent abdominal resection of metastatic melanoma metastases between 2009–2021 (n=80). The therapeutic group (n=43) which mainly included resections resulting in no evidence of disease, had a median age of 62 years (range 19.1–77.3). The palliative group, including patients which resection of one of several lesions due to symptoms or for harvest of tumor material for cell-based therapy, had a median age of 64 years (range 33–90.6). Median follow-up was 13.48 months (range: 0.5–107). The estimated 2- and 5- years survival of the therapeutic group was 76.61% and 69.65%, and 49.01% and 28.01% in the palliative group (p = 0.005). In multivariate analysis, therapeutic resection (HR 2.53, p = 0.042) and major complication score (HR 1.62, p = 0.004) were significant independent factors correlated with survival. The authors state that based on the results, abdominal metastasectomy is a safe and oncologically efficacious therapy in selected patients. They suggest that stage IV patients with isolated disease site, limited resectable progression on therapy, or patients with symptomatic metastases should be considered for surgical resection.

Malissen* (2021) performed a retrospective cohort study to assess the context and outcomes of small bowel melanoma metastases (SBMM) resections. In total, 20 patients who underwent resection of SBMM between 2011 and 2017, in a single referral center were included. Retrospective analyses were carried out by studying the melanoma-specific survival (MSS) defined as the time from small bowel resection to the last assessment or to the date of death from melanoma. Median follow-up was 47.8 months. Three groups were classified by surgical indications: (1) surgery as a pivotal treatment for mono- or oligo-metastases limited to the small bowel (n = 6); (2) salvage surgery for symptomatic patients in order to preserve their chances to switch to an active line of medical treatment (n = 8); (3) surgery of small bowel dissociated metastatic progression for patients otherwise controlled (n = 6), aiming at keeping patients with the same treatment or active follow-up. This study described that in all these three situations, the objective of surgery was usually met, and most patients had a long median MSS after surgery: 70.3 months, 89.5 months and 72.4 months, respectively. The authors conclude that although medical treatments have dramatically improved survival in metastatic melanoma, surgical control of life-threatening localization like small bowel metastases is often a condition for long survival.

Lwin* (2023) performed a follow-up analysis to characterize national trends and outcomes after surgical resection used for stage IV melanoma, with or without the use of immunotherapy. Patients who received surgery were compared to those who did not. The study identified 9800 patients with stage IV melanoma from the National Cancer Database (NCDB) data from 2012 to 2017. Of these patients, 2160 (22%) underwent surgery. The patients who received both surgery and immunotherapy had a better overall survival rate (hazard ratio [HR], 0.41; 95 % CI, 0.36–0.46; P < 0.01) than the patients who received neither immunotherapy nor surgery. The authors conclude that the use of immunotherapy was associated with a lower use of surgery for patients with stage IV melanoma. The patients with stage IV disease who received both surgery and immunotherapy had the highest overall survival rates, likely representing selection of a patient population more favorable for surgical resection.

Li*(2021) performed a retrospective cohort study to study the outcomes of salvage metastasectomy for patients who had undergone systemic therapy. The study identified 190 patients with stage 3 or 4 melanoma with extracranial disease progression after at least 4 weeks of systemic treatment between 2009 and 2020. The patients were categorized as resected to no evidence of disease (NED), non-progressive residual disease (NPRD), or progressive residual disease (PRD). Systemic therapy comprised BRAF-targeted therapy, immune checkpoint inhibitor immunotherapy, or both. The study showed a 5-year OS from metastatectomy of 52%, and a 3-year PFS of 21%. After resection to NED, NPRD, and PRD, the 5-year OS was 69%, 62% and 8%, and the 3-year PFS was 23%, 24% and 10%, respectively. The authors conclude that salvage metastasectomy was associated with durable survival and disease control, particularly after resection to NED, preoperative immunotherapy, and fewer lines of preoperative systemic therapy. They observed that histologically clear margins were not significantly associated with local disease control The authors believe that inability to obtain clear margins should not be a barrier to palliative debulking surgery.

Guerra (2022) performed a comprehensive literature search to assess the evidence of outcomes of resection in patients with melanoma metastasis to the pancreas. The study included 109 patients that were surgically treated for pancreatic metastases, identified from 72 articles. Mean age was 51.8 years at diagnosis of pancreatic disease. The 1, 3 and 5 years cumulative survival was 71%, 38%, and 26%, with an estimated median survival of 24 months. The authors conclude that within the limitations of a review of non-randomized reports, curative surgical resection confers a survival benefit in carefully selected patients with pancreatic dissemination of melanoma. This study did not perform a systematic literature review. Therefore, the level of evidence of this study is not graded and this study is not described in more detail in the literature analysis.

Asare* (2023) performed a retrospective case series of consecutive patients (n=74) that were treated with adrenalectomy between 1/1/2007–1/1/2019. The patients were compared to patients treated with systemic therapy alone (n=69) in the same time period. A longer survival was observed among patients that were surgically treated (116.9 vs. 11.0 months after adrenal metastasis diagnosis, p < 0.001). The authors conclude that selective application of adrenal metastasectomy is associated with prolonged survival benefit and remains an important consideration in the multidisciplinary management of patients with metastatic melanoma.

Radiotherapy

Versluis (2021): see study description above under the heading 'surgical intervention'

***Damen 2022** performed a retrospective study of to determine the long-term efficacy and toxicity of combined (stereotactic) body radiotherapy and anti-PD1 In consecutive oligoprogressive melanoma and non-small cell lung cancer (NSCLC) patients (n=361) who were irradiated for 1 to 3 progressive metastasis during anti-PD-1 between January 2017 and January 2019. Eleven melanoma patients and five NSCLC patients were included in this series. Radiotherapy was applied after a median 11 months (range: 1-30 months) from the start of the anti-PD1 treatment. This retrospective study did not compare treatment arms in a randomized manner. Therefore, the level of evidence of this study is not graded and this study is not described in more detail in the literature analysis.

*This study did not compare treatment arms in a randomized manner. Consequently, the level of evidence of this study is not graded, and it is not described in detail in the literature analysis. The results of this study were solely used for the consideration section.

Laser and light-based therapy

Austin (2017) performed a systematic review to evaluate the evidence about laser and light-based palliative therapy for metastatic melanoma patients. The literature search was conducted on March 10, 2016 and included RCTs, cohort studies, case series and case reports. Articles studying non-cutaneous melanoma and stage I/II cutaneous melanomas were excluded. Treatment site of the included studies were not specified in this review. The study characteristics are described in table 1. For more details about the included studies, please see Austin (2017). Twenty-seven articles were included, of which 17 case series and 10 case reports. They found no RCTs or cohort studies evaluating the safety and efficacy of LLBT for the palliative care of metastatic melanoma. The article provides a narrative summary of the results. The study results are therefore not described in this literature analysis.

Electrochemotherapy

Aguado-Romeo (2016) performed a systematic review with qualitative synthesis to study the effectivity and safety of electrochemotherapy for the treatment of unresectable locally advanced cutaneous melanoma at any site in adults. The literature search was conducted during February 2015 and included studies in English, Spanish, French, and German. Studies published before the year 2000 were excluded. Seven studies were included, of which three systematic reviews and four case series. The study characteristics are described in table 1. For more details about this review, please see Aguado-Romeo (2016). The article provides a narrative summary of the results. The study results are therefore not described in this literature analysis.

Radioembolization

Jia (2017) performed a systematic review of clinical evidence to study the effectiveness of 90Y radioembolization for the treatment of unresectable liver metastasis of melanoma. The literature search covered the period between January 1, 1991 and March 15. 2016. Articles were included if the overall survival or 1-year survival rate (with overall survival calculated from the date of first 90Y treatment to the date of death or

last follow-up) was reported. Review articles, animal studies, laboratory investigations, case series, case reports, and duplicated clinical studies were excluded. This systematic review included 12 articles, of which three studied cutaneous melanoma. These three studies (Piduru, 2012; Memon, 2014, Xing, 2017) are used in this literature analysis and the study characteristics are described in table 1. For more details about the included studies, please see Jia (2017).

Piduru (2012), Memon (2014) and Xing (2017) reported an overall survival of 10, 7.6, and 10.1 months respectively, after treatment with 90Y radioembolization. Piduru (2012), Memon (2014), and Xing (2017) reported a 1-year survival rate of 23.0%, 31.0%, and 34.6%.

Table 1. Study characteristics of systematic reviews for local therapy in metastatic melanoma

Author, Year, Study design	Number of included studies in this literature analyses and study design	Patients, age	Intervention vs control	Follow-up	Outcomes	Author's conclusion
Surgical intervention						
Wankhede, 2022 SR & MA	Total: n=40 • Retrospective: n=38 • Prospective phase 2 trial n=1 • Multicentric randomized phase 3 trial n=1	Patients with metastatic melanoma with cutaneous melanoma as the primary subtype. n= 31.282 Median age: 46 - 70 years	<u>Intervention:</u> Curative metastasectomy (complete resection of metastatic deposit from the organ site under investigation) n= 9.958 <u>Control:</u> Non-curative treatment (R1/R2 resection, palliative surgery, systemic therapy, radiotherapy, and end-of-life care) n=21.324	Median: 6.3 to 93 months	• Overall mortality • Median survival • 5-year OS	*"Curative metastasectomy for MM is associated with a lower risk of death than non-curative treatment methods. Selection bias and underlying weakness of studies reduced the strength of evidence in this review. However, CM should be a part of the multimodality treatment of MM whenever technically feasible."*
Yeo, 2022 SR & MA	Total: n=13 • Retrospective: n=11	Patients with liver metastases from malignant melanoma.	<u>Intervention:</u> Liver resection n= 749 (21.9%)	Mean in months: • Surgery: 54.6 ± 11.6 • Non-surgery:	• Postoperative mortality • 30-day mortality	*"This study suggests that surgical treatment of melanoma liver*

Author, Year, Study design	Number of included studies in this literature analyses and study design	Patients, age	Intervention vs control	Follow-up	Outcomes	Author's conclusion
	• Prospective: n=2	n= 3.422 Mean age, years: • Surgery: 43.5 ± 10.9 • Non-surgery: 53.1 ± 16.1	<u>Control:</u> Non-surgical arm n= 2.673 (78.1%)	52.9 ± 16.4.	• median OS • 1-year OS • 2-year OS • 3-year OS • 4-year OS • 5-year OS	*metastases could offer better OS outcomes compared with non-surgical treatment."*
Laser and light-based therapy						
Austin, 2017 SR	Total: n=27 • Case-report: n=10 • Not specified: n=17	Metastatic melanoma patients. n= 397 Age: NR	<u>Intervention:</u> • Ablative laser therapy: 10 studies including n=318 patients • Non-ablative laser therapy: 9 studies including n=50 patients • Photodynamic therapy: 8 studies including n=29 patients <u>Control:</u> Not applicable	• Ablative laser therapy: Between 1 month – 10 y • Non-ablative laser therapy: 8 weeks – 6.5 y • Photodynamic therapy: 4 weeks – 2 y	• Response • Recurrences • Adverse events	*"Additional clinical research with standardized outcome measures involving contemporary LLBT devices may yield promising results. The evidence demonstrates that LLBT could an be effective palliative option in combination with standard of care treatment for MM*

Author, Year, Study design	Number of included studies in this literature analyses and study design	Patients, age	Intervention vs control	Follow-up	Outcomes	Author's conclusion
						and may improve patient's quality-of-life and MM burden without subjecting patients to costly procedures, long hospital stays and significant AEs."
Electrochemotherapy						
Aguado-Romeo, 2016 SR	Total: n=7 • Systematic reviews=3 Spratt (2014): 47 studies of which 11 with ECT AETS (2011): 26 studies (13 case series, 13 with control group) Mali (2013): 9 studies • Case series: n=4 (Caracò 2013, Ricotti	Unresectable cutaneous and/or subcutaneous metastatic melanoma (in transit, satellite, distant) at any site. Number of patients, mean age in years • Sprat (2014): n=176, age: NR	<u>Intervention:</u> ECT as monotherapy and as therapy combined with isolated limb perfusion in patients with high tumor load n=1.181 <u>Control:</u> NR	• Systematic reviews: NR • Case series range: 6-67 months	• Effectiveness • Clinical response (measured as complete response, partial response , disease-free Period, overall survival, recurrence rate, stable disease) • Safety	*"There is no evidence that electrochemotherapy alters the natural course of the disease and it should therefore be considered a palliative treatment. With an evidence level of 1- (minus), electrochemotherapy can be recommended for the palliative*

Author, Year, Study design	Number of included studies in this literature analyses and study design	Patients, age	Intervention vs control	Follow-up	Outcomes	Author's conclusion
	2013, Solari 2014, Skarlatos 2011)	• AETS (2011) n=693, age 56.9 • Mali (2013) n=197, age: NR • Caracò (2013): n=60, age 62 • Ricotti (2013): n=30, age 75 • Solari (2014) : n=20, age 72 • Skarlatos (2011): n=5, age 69.8			• Adverse effects associated with the procedure • Toxicity	*treatment of unresectable, locally advanced melanoma (grade B recommendation)."*

Author, Year, Study design	Number of included studies in this literature analyses and study design	Patients, age	Intervention vs control	Follow-up	Outcomes	Author's conclusion
Radioembolization						
Jia, 2017 SR	Total: n=3 • Observational: n=3 (Piduru, 2012; Memon, 2014; Xing, 2017)	Patients with unresectable liver metastasis of melanoma. Number of patients, age in years • Piduru, 2012: n=12 (5 cutaneous and 7 ocular), age: 53 • Memon, 2014 n=16 (4 cutaneous and 7 ocular, 3 rectal, 2 unknown), age: 57 • Xing, 2017 n=28 (13 cutaneous and 15 ocular), age: 49.5	<u>Intervention:</u> 90Y radioembolization n=56 <u>Control:</u> Not applicable	• Piduru, 2012: NR • Memon, 2014: NR • Xing, 2017 39.6 months	• Disease control rate, % • Cases of CR, PR, SD, PD, n • Overall survival, mo • 1-year survival rate % • Side effects	*"In conclusion, 90Y radioembolization therapy is an effective treatment for unresectable liver metastases of melanoma, with encouraging effects on disease control and survival. However, prospectively gathered data are needed to further demonstrate the benefit of 90Y radioembolization in this patient population.*

SR: Systematic review; MA: Meta-analysis; NR: Not reported; ICI: Immunotherapy; stereotactic radiation therapy (SRS/SBRT); ECT: Electrochemotherapy

Results

Surgical intervention

Two studies reported outcomes after surgical intervention (Wankhede, 2022 and Yeo, 2022).

Overall survival - Critical outcome

The systematic review of Wankhede (2022) reported the median overall survival of 31 of the 40 included studies. The median survival of patients with curative metastasectomy was 4–53 months. Patients without curative metastasectomy had a median survival of 0–31 months. The 5-year OS was 10–75% for patients with curative metastasectomy and 0–38.9% for patients without curative metastasectomy. Full details of the meta-analyses can be found in Wankhede (2022).

In the prospective study by Howard (2012) a median survival of 15.8 months was reported for patients receiving surgery plus SMT vs. 6.9 months for patients receiving SMT alone. The 4-year survival was 20.8% vs. 7.0% for patients receiving surgery plus SMT vs. SMT alone ($p<0.0001$; HR 0.406).

The meta-analysis of Yeo (2022) showed that patients who underwent liver resection had a longer overall survival than patients without liver resection. 10 of the 13 included studies reported the 3-year OS, of which 6 studies were included in the meta-analysis. The meta-analysis indicated a statistically significant difference in 3-year OS, favouring patients undergoing liver resection as compared with patients without liver resection (HR = 0.07, 95%CI 0.03–0.19, $p < 0.00001$). 12 of the 13 included studies reported the 5-year OS, of which 4 were included in the meta-analysis. The meta-analysis showed a statistically significant difference in 5-year OS, favouring patients undergoing liver resection as compared with patients without liver resection (HR = 0.07, 95%CI 0.02–0.22, $p < 0.00001$). Full details of the meta-analyses can be found in Yeo (2022).

Progression free survival - Critical outcome

The included systematic reviews did not report the effect of surgical intervention on PFS.

Time to next treatment – Important outcome:

The included systematic reviews did not report the effect of surgical intervention on time to next treatment.

(Surgical) complications– Important outcome:

The included systematic reviews did not report the effect of surgical intervention on surgical complications.

Radiotherapy

No study reported the effect of radiotherapy on overall survival, progression free survival, time to next treatment and complications.

Laser and light-based therapy

The included systematic reviews did not (quantitively) report the overall survival, progression free survival, time to next treatment and complications.

Electrochemotherapy

The included systematic reviews did not (quantitively) report the overall survival, progression free survival, time to next treatment and complications.

Radioembolization

The systematic review by Jia (2017) reported outcomes after treatment with 90Y radioembolization.

Overall survival - Critical outcome

Piduru (2012), Memon (2014) and Xing (2017) reported an overall survival of 10, 7.6, and 10.1 months respectively, after treatment with 90Y radioembolization. Piduru (2012), Memon (2014), and Xing (2017) reported a 1-year survival rate of 23.0%, 31.0%, and 34.6%.

Progression free survival - Critical outcome

The included systematic review did not report the effect of treatment with 90Y radioembolization on progression free survival.

Time to next treatment – Important outcome:

The included systematic review did not report the effect of treatment with 90Y radioembolization on time to next treatment.

Complications – Important outcome:

Memon (2014) reported side effects in 16 cases. Most reported side effects were fatigue (n=7, 44%), nausea (n=3, 19%), vomiting (n=2, 12%), and abdominal pain (n=1, 7%). Xing (2017) reported side effects in 28 cases. Fatigue was reported in 4 cases (14.3%) and abdominal pain in 5 cases (17.8%).

Level of evidence of the literature

Surgical intervention

Overall survival - Critical outcome

The level of evidence for the outcome measure overall survival was based on observational studies and therefore started as low. The level of evidence was downgraded by one level because of risk of bias (selection bias, -1). The level of evidence is therefore *very low.*

Progression free survival - Critical outcome

The level of evidence was not assessed for the outcome progression free survival because of the lack of studies reporting this outcome.

Time to next treatment – Important outcome:

The level of evidence was not assessed for the outcome time to next treatment, because of the lack of studies reporting this outcome.

Complications – Important outcome:

The level of evidence was not assessed for the outcome complications, because of the lack of studies reporting this outcome.

Radiotherapy

The level of evidence was not assessed for the outcome overall survival, progression free survival, time to next treatment and complications.

Laser and light-based therapy

The included systematic reviews did not (quantitively) report the overall survival, progression free survival, time to next treatment and complications.

Electrochemotherapy

The included systematic reviews did not (quantitively) report the overall survival, progression free survival, time to next treatment and complications.

Radioembolization

Overall survival - Critical outcome

The level of evidence for the outcome measure overall survival was based on observational studies and therefore started as low. The level of evidence was downgraded by one level because of imprecision (low number of participants, -1). The level of evidence is therefore *very low.*

Progression free survival - Critical outcome

The level of evidence was not assessed for the outcome progression free survival because of the lack of studies reporting this outcome.

Time to next treatment – Important outcome:

The level of evidence was not assessed for the outcome time to next treatment, because of the lack of studies reporting this outcome.

Complications – Important outcome:

The level of evidence for the outcome measure overall survival was based on observational studies and therefore started as low. The level of evidence was downgraded by one level because of imprecision (low number of participants, -1). The level of evidence is therefore *very low.*

5

Conclusions

Surgical interventions

Very Low GRADE	Curative metastasectomy is associated with long **overall survival** in very selected metastatic patients with stage IV melanoma, but the evidence is very uncertain. *Source: Wankhede, 2022; Howard, 2012*

Very Low GRADE	Liver resection is associated with long **overall survival** in metastatic patients with stage IV melanoma, but the evidence is very uncertain. *Source: Yeo, 2022*

No GRADE	No evidence was found regarding the effect of local treatment on **progression free survival**, **time to next treatment**, or **(surgical) complications** in metastatic patients with stage IV melanoma. *Source: -*

Radiotherapy

No GRADE	No evidence was found regarding the effect of radiotherpy on **overall survival, progression free survival, time to next treatment, or (surgical) complications** in metastatic patients with stage IV melanoma. Source: -

Laser and light-based therapy

No GRADE	No evidence was found regarding the effect of light-based therapy on **overall survival, progression free survival, time to next treatment, or (surgical) complications** in metastatic patients with stage IV melanoma. Source: -

Electrochemotherapy

No GRADE	No evidence was found regarding the effect of light-based therapy on **overall survival, progression free survival, time to next treatment, or (surgical) complications** in metastatic patients with stage IV melanoma. Source: -

Radioembolization

Very low GRADE	The evidence is very uncertain about the effect of treatment with 90Y radioembolization on **overall survival** in metastatic patients with stage IV melanoma. *Source: Jia, 2017*

Very low GRADE	The evidence is very uncertain about the effect of treatment with 90Y radioembolization on **complications** in metastatic patients with stage IV melanoma.

	Source: Jia, 2017

No GRADE	No evidence was found regarding the effect of treatment with 90Y radioembolization on progression free survival or time to next treatment in metastatic patients with stage IV melanoma. *Source: -*

Overwegingen – van bewijs naar aanbeveling

Er zijn geen gerandomiseerde studies of kwalitatief goede vergelijkende observationele studies gevonden die de effecten van radiotherapie, laseren, light-based therapie, electrochemotherapie of de behandeling met 90Y radioembolisatie onderzochten bij patiënten met een gemetastaseerd stadium IV melanoom op overall survival, progressie vrije overleving, complicaties en tijd tot volgende behandeling. Voor deze lokale behandelingen kunnen daarom geen conclusies worden getrokken op basis van de wetenschappelijke literatuur.

Er werden twee systematische reviews gevonden die de effecten van chirurgische interventies op overall survival onderzochten (Wankhede, 2022; Yeo, 2022). Wankhede (2022) concludeerde dat er een curatieve metastasectomie een positief effect had op de overall survival. Wankhede (2022) includeerde 1 RCT (Howard, 2012) die liet zien dat meer dan de helft van de patiënten met een melanoom stadium IV die in aanmerking komen voor een operatie een verbetering lieten zien in overall survival, ten opzichte van patiënten die alleen systemische behandeling krijgen, ongeacht de locatie(s) en het aantal metastasen. De mediane overleving was 15,8 versus 6,9 maanden en de overleving na 4 jaar was respectievelijk 20,8% versus 7,0% voor patiënten die alleen systemische behandeling kregen. Een operatie met of zonder systemische therapie gaf een overlevingsvoordeel voor patiënten met M1a (mediaan >60 maanden versus 12,4 maanden. Vierjaarsoverleving 24,1% versus 14,3%) en M1c (mediaan 15,0 versus 6,3 maanden; vierjaarsoverleving 10,5% versus 4,6%). Patiënten met meerdere uitzaaiingen die chirurgisch werden behandelend, hadden een overlevingsvoordeel, en het aantal operaties verminderde de overleving niet bij de 67% patiënten (42%) die meerdere operaties hadden voor metastasen op afstand.

De studie van Yeo (2022) bekeek de effecten van leverresectie op overall survival en deze studie suggereerde een positief effect hiervan op de overall survival. Beide systematic reviews includeerde veelal retrospectieve en niet-gerandomiseerde studies, waardoor de overall bewijskracht op zeer laag uitkomt.

Na de zoekdatum van de geïncludeerde systematic review werden nog een aantal relevante publicaties bekeken (Versluis, 2021; Damen, 2022; Urbanski, 2023; Mor, 2022; Malissen, 2021; Lwin, 2023; Li, 2021; Guerra, 2022; Asare, 2023). Deze publicaties werden niet opgenomen in de literatuuranalyse, maar zullen kort besproken worden ter overweging. Deze korte bespreking geeft wellicht geen compleet literatuuroverzicht van de periode na de systematisch zoekopdracht in deze richtlijnmodule en bevat geen GRADE-beoordelingen.

De gevonden onderzoeken tonen aan dat lokale therapieën, zoals chirurgische resectie van metastasen, gunstige langetermijnresultaten kunnen opleveren voor patiënten met gemetastaseerd melanoom, vooral in een oligometastatische setting (Versluis, 2021; Damen, 2021; Urbanski, 2023). Chirurgische resectie wordt aanbevolen voor patiënten met geïsoleerde ziekteplaatsen, beperkte progressie die resectabel is na therapie, of symptomatische metastasen (Mor, 2022). Ondanks de vooruitgang in medicamenteuze behandelingen, blijft chirurgische controle van levensbedreigende metastasen, zoals die in de dunne darm, van cruciaal belang voor langdurige overleving (Malissen, 2021). Immuuntherapie kan het gebruik van chirurgie verminderen, maar patiënten die zowel chirurgie als immuuntherapie ondergaan, vertonen de hoogste overlevingspercentages, waarbij opgemerkt moet worden dat dit wellicht te wijten valt aan mogelijke selectiebias (Lwin, 2023).

Zelfs wanneer het niet mogelijk is om duidelijke marges te behalen, blijft palliatieve debulkingchirurgie een optie (Li, 2021). Curatieve chirurgische resectie bij patiënten met melanoom dat zich verspreidt naar de alvleesklier of de bijnieren gaat gepaard met lange overleving bij zorgvuldig geselecteerde patiënten (Guerra, 2022; Asare, 2023).

Aangezien het totale bewijs van zeer lage kwaliteit is (ernstige methodologische beperkingen) en onvoldoende is om tot harde conclusies te komen, is het belangrijk dat hier verder onderzoek naar gedaan wordt. Een goede behandelingskeuze heeft aanzienlijke gevolgen voor de kwaliteit van leven en het goed inzetten van de (beschikbare) behandelingsmogelijkheden.

<u>Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)</u>
Een goed oncologisch resultaat met een goede uitkomst zijn belangrijk. De belasting voor de patiënt is wel verschillend en zal meegewogen moeten worden. De vormen van belasting die in de besluitvorming moeten worden meegenomen zijn oa. effectiviteit, korte termijn en lange termijn bijwerkingen van de gekozen behandeling en tijdsbelasting voor patiënt en mantelzorgers.

<u>Kosten (middelenbeslag)</u>
Er zijn geen studies gevonden over de kosteneffectiviteit van de verschillende lokale behandelingen. Het is bekend dat systeemtherapie met immune checkpoint remmers en doelgerichte therapie hoge effectiviteit maar ook hoge kosten met zich meebrengen. In situaties waar een lokale behandeling mogelijk even effectief is als systeemtherapie kan dit een kosten voordeel hebben.

<u>Aanvaardbaarheid, haalbaarheid en implementatie</u>
Alle onderzochte behandelingen worden al langer toegepast in Nederland en zijn in de behandelprotocollen van de melanoomcentra opgenomen. De beschikbaarheid van de beschreven behandelingen is wijd verspreid.

Aanbevelingen

Beschouw een patiënt met progressieve oligometastatische ziekte tijdens of na eerdere immuuntherapie als een potentiële kandidaat voor lokale behandeling (chirurgie of radiotherapie) van de groeiende laesie(s) met als doel langdurige ziektevrije overleving. Bespreek deze behandelopties in een MDO van een melanoomcentrum en in een proces van gedeelde besluitvorming.

Overweeg bij een patiënt die zich primair presenteert met oligometastatische ziekte in eerste instantie immuuntherapie. Bespreek lokale opties als alternatief. Bespreek deze behandelopties in een MDO van een melanoomcentrum en in een proces van gedeelde besluitvorming.

Bespreek met de patiënt met een gemetastaseerd stadium IV melanoom met nog systemische behandelopties lokale behandelopties in de vorm van chirurgie of radiotherapie in geval van te palliëren klachten met als doel symptoombestrijding of preventie symptomen in afwachting van effect van systeemtherapie. Wijs daarbij op de voor- en nadelen van deze behandelmogelijkheden.

Bespreek met patiënten met te palliëren klachten van een gemetastaseerd stadium IV melanoom zonder systeemtherapie opties lokale behandelopties in de vorm van chirurgie of radiotherapie met als doel symptoombestrijding en wijs daarbij op de voor- en nadelen van deze behandelmogelijkheden.

Kennisvraag

Er is een duidelijke behoefte aan goed opgezette prospectieve studies over de waarde van lokale behandeling bij patiënten met een uitgezaaid melanoom die ook systeembehandeling krijgen of hebben gehad.

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Table of excluded studies

Nr.	Reference	Reason for exclusion
1	Alexander H, Wen D, Chu M, Han C, Hadden P, Thomas R, Bartlett A. Selective internal radiation therapy for hepatic metastases of uveal melanoma: a systematic review. Br J Radiol. 2022 Jan 1;95(1129):20210200. doi: 10.1259/bjr.20210200. Epub 2021 Nov 10. PMID: 34757824; PMCID: PMC8722257.	Wrong population
2	Ben Shimol J, Guzman-Prado Y, Karlinskaya M, Davidson T. Effectiveness and safety of immune checkpoint inhibitors in combination with palliative radiotherapy in advanced melanoma: A systematic review. Crit Rev Oncol Hematol. 2021 Nov;167:103499. doi: 10.1016/j.critrevonc.2021.103499. Epub 2021 Oct 20. PMID: 34687896.	Wrong intervention
3	Hameed AM, Ng EE, Johnston E, Hollands MJ, Richardson AJ, Pleass HC, Lam VW. Hepatic resection for metastatic melanoma: a systematic review. Melanoma Res. 2014 Feb;24(1):1-10. doi: 10.1097/CMR.0000000000000032. PMID: 24300091.	Systematic review with more recent literature search and similar PICO available
4	Aubin JM, Rekman J, Vandenbroucke-Menu F, Lapointe R, Fairfull-Smith RJ, Mimeault R, Balaa FK, Martel G. Systematic review and meta-analysis of liver resection for metastatic melanoma. Br J Surg. 2013 Aug;100(9):1138-47. doi: 10.1002/bjs.9189. Epub 2013 Jun 17. PMID: 23775340.	Systematic review with more recent literature search and similar PICO available.
5	Baker JJ, Stitzenberg KB, Collichio FA, Meyers MO, Ollila DW. Systematic review: surgery for patients with metastatic melanoma during active treatment with ipilimumab. Am Surg. 2014 Aug;80(8):805-10. PMID: 25105403.	Systematic review with more recent literature search and similar PICO available
6	Anahid, S. M., & Afra, O. (2020). The Combination of Radiotherapy with Pembrolizumab in the Treatment of Metastatic Melanoma Patients: a Systematic Review. SN Comprehensive Clinical Medicine, 2(4), 432-438.	Wrong intervention
7	Rodríguez Plá M, Dualde Beltrán D, Ferrer Albiach E. Immune Checkpoints Inhibitors and SRS/SBRT Synergy in Metastatic Non-Small-Cell Lung Cancer and Melanoma: A Systematic Review. Int J Mol Sci. 2021 Oct 27;22(21):11621. doi: 10.3390/ijms222111621. PMID: 34769050; PMCID: PMC8584181.	Wrong intervention

Table of quality assessment for systematic reviews of RCTs and observational studies

Based on AMSTAR checklist (Shea, 2007; BMC Methodol 7: 10; doi:10.1186/1471-2288-7-10) and PRISMA checklist (Moher, 2009; PLoS Med 6: e1000097; doi:10.1371/journal.pmed1000097)

Study **First author, year**	**Appropriate and clearly focused question?[1]** **Yes/no/unclear**	**Comprehensive and systematic literature search?[2]** **Yes/no/unclear**	**Description of included and excluded studies?[3]** **Yes/no/unclear**	**Description of relevant characteristics of included studies?[4]** **Yes/no/unclear**	**Appropriate adjustment for potential confounders in observational studies?[5]** **Yes/no/unclear/ Not applicable**	**Assessment of scientific quality of included studies?[6]** **Yes/no/unclear**	**Enough similarities between studies to make combining them reasonable?[7]** **Yes/no/unclear**	**Potential risk of publication bias taken into account?[8]** **Yes/no/unclear**	**Potential conflicts of interest reported?[9]** **Yes/no/unclear**
Surgical interventions									
Wankhede, 2022	Yes Reason: A systematic review and meta-analysis was performed to ascertain the role of CM compared with incomplete or nonsurgical treatment for	Yes Reason: Multiple databases were searched. Search period was described.	No (partially) Reason: Excluded studies were not described or referenced, however reasons for exclusion were	Yes Reason: Table 2 provides the study characteristics.	No Reason: There was no adjustment for confounding variables in the multivariate analysis.	Yes Reason: The Newcastle-Ottawa Scale (NOS) for cohort studies was used.	Yes Reason: The meta-analysis of all 40 studies indicated a significantly decreased risk of death after CM, with a pooled HR of 0.42 (95% CI,	No Reason: Publication bias was assessed with the Egger's and Begg's test. Publication bias was detected in the final	No Reason: It was reported for the systematic review authors, but not for the included studies.

	patients with MM.		provided in the study selection flow diagram.				0.38–0.47; p<0.00001), although it was associated with significant heterogeneity (I^2 = 76%; p<0.00001; Fig. 2).	results, with a deficiency of studies showing negative results.	
Yeo, 2022	Yes Reason: A systematic review and meta-analysis was performed to evaluate the difference in surgical versus non-surgical options for melanoma liver metastases.	Yes Reason: Multiple databases were searched. Search period was described.	No (partially) Reason: Excluded studies were not described or referenced, however reasons for exclusion were provided in the study selection flow diagram.	Yes Reason: Table 1 provides the study characteristics.	No Reason: There was no adjustment for confounding variables in the multivariate analysis.	Yes Reason: The Newcastle-Ottawa Scale (NOS) for cohort studies was used.	Yes Reason: The Meta-analysis of eight studies showed a statistically significant difference in 1-year OS, favouring patients undergoing surgery as compared with non-surgery (HR=0.29, 95%CI 0.19–0.44,	No Reason: Publication bias could not be assessed as there were fewer than ten studies reporting each outcome.	No Reason: It was reported for the systematic review authors, but not for the included studies.

							p<0.00001, I^2 = 33%; Fig. 2)		
Laser and light-based therapy									
Austin, 2017	Yes Reason: A systematic review was performed to evaluate the published literature and provide evidence-based recommendations regarding LLBT for MM.	Yes Reason: Multiple databases were searched. Search period was described.	No (partially) Reason: Excluded studies were not described or referenced, however reasons for exclusion were provided in the study selection flow diagram.	Yes Reason: Table 2 provides the study characteristics.	No Reason: There was no adjustment for confounding variables in the multivariate analysis.	No Reason: No quality assessment was performed.	No Reason: Authors were unable to perform a meta-analysis. The systematic review include non-uniform inclusion/exclusion criteria, subjects treated with multiple previous therapies, and few validated palliative/quality-of-life outcome measures. Ten of the twenty-seven reviewed clinical studies	No Reason: Publication bias was not assessed	No Reason: It was reported for the systematic review authors, but not for the included studies.

							are case reports, and conclusions from these studies are limited due to a small sample size of one or two patient outcomes.		
Electrochemotherapy									
Aguado-Romeo, 2017	Yes Reason: A systematic review was performed to evaluate the evidence that supports the use of electrochemotherapy as a therapeutic strategy in melanoma.	Yes Reason: Multiple databases were searched. Search period was described.	No (partially) Reason: Excluded studies were not described or referenced, however reasons for exclusion were provided in the study selection flow diagram.	Yes Reason: Table 2 provides the study characteristics.	No Reason: There was no adjustment for confounding variables in the multivariate analysis.	No Reason: The AMSTAR checklist was applied to assess the quality of the included SR. However, no quality assessment was performed for the observational studies.	No Reason: The study populations were small, and the studies were not designed to compare effectiveness with other alternatives.	No Reason: Publication bias was not assessed	No Reason: It was reported for the systematic review authors, but not for the included studies.

Radioembolization									
Jia, 2017	Yes Reason: A systematic review was performed to assess the effectiveness of yttrium-90 (90Y) radioembolization in the treatment of unresectable liver metastases of melanoma.	Yes Reason: Multiple databases were searched. Search period was described.	No (partially) Reason: Excluded studies were not described or referenced, however reasons for exclusion were provided in the study selection flow diagram.	Yes Reason: Table 2 provides the study characteristics.	No Reason: There was no adjustment for confounding variables in the multivariate analysis.	No Reason: The quality of the included reports were assessed.	No Reason: The heterogeneous patient selection, treatment algorithms, and combinations with other therapies in these studies may have also affected the results.	No Reason: Publication bias was not assessed	No Reason: It was reported for the systematic review authors, but not for the included studies.

Literature search strategy

Zoekperiode: 2010 - 7 november 2022.

5

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	77	68	92
RCT	114	102	141
Observationele studies	550	430	703
Totaal	741	600	**936**

Embase.com

No.	**Query**	**Results**
#19	#16 OR #17 OR #18	741
#18	#11 AND #15 NOT (#16 OR #17)	550
#17	#11 AND #14 NOT #16	114
#16	#11 AND #13	77
#15	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat*	13545102

	NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	
#14	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	1839814
#13	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab	733409

	OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	
#12	#5 AND #11	4
#11	#6 AND (#7 OR #8 OR #9 OR #10) AND ([english]/lim OR [dutch]/lim) AND [2010-2022]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	1343
#10	'radiofrequency ablation'/exp OR 'tumor ablation'/exp/mj OR ablation:ti,kw OR ablative:ti,kw OR rfa:ti,kw	109109
#9	'metastasis resection'/exp/mj OR 'surgery'/exp/mj OR 'surgical patient'/exp/mj OR 'surgical risk'/exp/mj OR surgic*:ti,kw OR surger*:ti,kw OR operation*:ti,kw OR operative:ti,kw OR resect*:ti,kw OR dissect*:ti,kw OR metastasectom*:ti,kw	3495339
#8	'radiotherapy'/exp/mj OR 'bioradiant therapy':ti,kw OR 'bucky ray':ti,kw OR 'bucky therapy':ti,kw OR 'radio therapy':ti,kw OR 'radio treatment':ti,kw OR 'radiohypophysectomy':ti,kw OR 'radiotherapy':ti,kw OR 'roentgen therapy':ti,kw OR 'roentgen treatment':ti,kw OR 'rontgen therapy':ti,kw OR 'therapeutic radiology':ti,kw OR 'x radiotherapy':ti,kw OR 'x ray therapy':ti,kw OR 'x ray treatment':ti,kw OR 'x-ray therapy':ti,kw OR irradiati*:ti,kw OR radiati*:ti,kw	534736
#7	'local therapy'/exp OR (((local OR locoregional) NEAR/3 (treat* OR therap*)):ti,kw)	19333
#6	'metastatic melanoma'/exp/mj OR (('metastasis'/exp/mj OR metasta*:ti,kw OR ((stage NEAR/3 ('iv*' OR four OR '4*')):ti,ab,kw) OR advanced:ti,kw) AND ('melanoma'/exp/mj OR melanoma*:ti,kw))	32389

Ovid/Medline

#	Searches	Results
16	13 or 14 or 15	600
15	(9 and 12) not (13 or 14)	430
14	(9 and 11) not 13	102

13	9 and 10	68
12	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	5283487
11	exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	1559694
10	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid)	628085

	adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	
9	limit 8 to ((english language or dutch) and yr="2010 -Current")	1314
8	7 not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/))	2296
7	1 and 6	2575
6	2 or 3 or 4 or 5	3305121
5	exp Radiofrequency Ablation/ or (ablation or ablative or RFA).ti,kf.	70644
4	exp *Surgical Procedures, Operative/ or exp *Specialties, Surgical/ or surgic*.ti,kf. or surger*.ti,kf. or operation*.ti,kf. or operative.ti,kf. or *Metastasectomy/ or (resect* or dissect* or metastasectom*).ti,kf.	2934647
3	exp *Radiotherapy/ or exp *Radiotherapy Dosage/ or (bioradiant therapy or bucky ray or bucky therap* or radio therap* or radio treatment or radiohypophysectomy or radiotherap* or roentgen therap* or roentgen treatment or rontgen therap* or therapeutic radiology or x radiotherapy or x ray therap* or x ray treatment or x-ray therapy or irradiati* or radiati*).ti,kf.	370972
2	((local or locoregional) adj3 (treat* or therap*)).ti,ab,kf.	40166
1	(exp *Melanoma/ or melanoma*.ti,kf.) and (exp *Neoplasm Metastasis/ or metasta*.ti,kf. or (stage adj3 ('iv*' or four or '4*')).ti,kf. or advanced.ti,kf.)	18556

8.3. Systemische therapie

Uitgangsvraag

Wat is de plaats van systemische therapie in de behandeling van patiënten met irresectabel of gemetastaseerd stadium III/IV melanoom?

Introductie

Systemische therapie speelt een cruciale rol in de behandeling van patiënten met een irresectabel of gemetastaseerd stadium III/IV melanoom. Deze therapievorm is een primaire optie en richt zich op het beheersen van de ziekte en het verlengen van de overleving. Het belang van systemische therapie binnen deze context komt voort uit de noodzaak om effectieve behandelingsstrategieën te bieden voor deze patiëntengroep. Hierbij wordt de keuze voor een specifieke behandeling bepaald door verschillende factoren, waaronder de genetische kenmerken van de tumor, aantal en locatie van de metastasen, lactaatdehydrogenase in het bloed en de algehele gezondheid van de patiënt.

Search and select

A systematic review of the literature was performed to answer the following question: What is the effect of systemic therapy compared to placebo, other systemic therapy or best supportive care in patients with unresectable or metastatic stadium III/IV melanoma?

Table 1. PICO

Patients	Patients with unresectable or metastatic stadium III/IV melanoma
Intervention	Targeted therapy, BRAF/MEK inhibition, immunotherapy, anti-CTLA4, anti-pd-1, anti-CTLA4+anti PD-1, dabrafenib/trametinib, encorafenib/binimetinib, vemurafenib/cobimetinib, ipilimumab, nivolumab, nivolumab+ ipilimumab, atezoluzumab + vemurafenib + cobimetinib, T-VEC-, DTIC (dacarbazine), T-VEC+ANTI-PD1, anti-LAG3+anti-PD1, imatinib, anti-PDL1, TIL
Control	Placebo, other systemic therapy, or best supportive care
Outcomes	1. overall survival, 2. progression free survival, 3. adverse events, 4. quality of life
Other selection criteria	Study design: systematic reviews and randomized controlled trials

Submodules

Systemische behandeling van stadium III/IV melanoom verschilt afhankelijk van de behandellijn en de BRAF-mutatiestatus. Daarom is deze module opgedeeld in vier submodules.

De eerste twee submodules beschrijven de systemische therapie bij patiënten met een BRAF-V600E/K-mutatie en een onresectabel of gemetastaseerd stadium III/IV melanoom. Submodule 8.3.1.1 beschrijft de eerstelijnsbehandeling en submodule 8.3.1.2 de tweedelijnsbehandeling.

De laatste twee submodules beschrijven de systemische therapie bij patiënten met een BRAF-wildtype en een onresectabel of gemetastaseerd stadium III/IV melanoom. Submodule 8.3.2.1 beschrijft de eerstelijnsbehandeling en submodule 8.3.2.2 de tweedelijnsbehandeling.

Relevant outcome measures

The guideline panel considered overall survival as a **critical** outcome measure for decision making; and progression free survival, adverse events, and quality of life as **important** outcome measures for decision making.

The working group defined clinically relevant differences based on the PASKWIL criteria https:www.nvmo.org

If median overall survival in control group ≤12 months:

Overall survival: >12 weeks and hazard ratio (HR)<0.7

Or > 10% profit in the 2-year OS (provided that > 20% of the patients in the intervention group are still alive after 2 years)

If median overall survival in control group >12 months:

Overall survival: >16 weeks and HR<0.7

Or > 10% profit in the 3-year OS (provided that > 20% of the patients in the intervention group are still alive after 3 years)

Progression-free survival: >16 weeks and HR<0.7

Adverse events: absolute difference <5% for lethal complications, or <25% for serious complications

Quality of life: A minimal clinically important difference of 10 points on the quality-of-life instrument EORTC QLQ-C30 or a difference of a similar magnitude on other quality of life instruments

Search and select (Methods)

On the 17th of April 2023, relevant search terms were used to search for systematic reviews and RCTs about systemic therapy for patients with stage III/IV melanoma in the databases Embase.com and Ovid/Medline. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 977 unique hits.

Studies were selected based on the following criteria:

- Phase III randomized controlled trials
- Including patients with unresectable or metastatic stadium III/IV melanoma
- Comparing targeted therapy, BRAF/MEK inhibition, immunotherapy, anti-CTLA4, anti-pd-1, anti-CTLA4+anti PD-1, dabrafenib/trametinib, encorafenib/binimetinib, vemurafenib/cobimetinib, ipilimumab, nivolumab, nivolumab+ ipilimumab, atezoluzumab + vemurafenib + cobimetinib, T-VEC-, DTIC (dacarbazine),T-VEC+ANTI-PD1, anti-LAG3+anti-PD1, imatinib, anti-PDL1, TIL with placebo, other systemic therapy, or best supportive care.

Thirty-eight studies were initially selected based on title and abstract screening. After reading the full text, twenty-two studies were excluded (see the table with reasons for exclusion under the tab Methods), and sixteen studies were included (CHECKMATE-066; RELATIVITY-047; CHECKMATE-067; CA184-024; MDX010-20; KEYNOTE-006; MASTERKEY-265; OPTiM; NCT02278887; CHECKMATE-037; COBRIM; COMBI-V; COLUMBUS; COMBI-d; DREAMseq; IMspire150). (see exclusion table).

Summary of literature

Description of studies

A total of 16 studies were included in the analysis of the literature. Important study characteristics and results are summarized in table 2. The assessment of the risk of bias is summarized in the risk of bias tables (under the tab 'Evidence tabels').

For the literature analysis, considerations and recommendations see submodules 8.3.1.1, 8.3.1.2, 8.3.2.1, and 8.3.2.2.

8.3.1. BRAF-V600E/K mutated metastatic melanoma:

- Submodule 8.3.1.1: First line treatment
- Submodule 8.3.1.2: Second line treatment

8.3.2. BRAF-wild type metastatic melanoma:

- Submodule 8.3.2.1.: First line treatment
- Submodule 8.3.2.2: Second line treatment

Table 2. Study characteristics of 16 included studies assigned to one or more of the four submodule: A) first line treatment in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma; B) second line treatment in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma; C) first line treatment in patient with BRAF-wild type with unresectable or metastatic stadium III/IV melanoma; and D) second line treatment in patient with BRAF-wild type with unresectable or metastatic stadium III/IV melanoma.

Study (Author, Year)	Study design	Patients	Intervention	Control	Reported outcomes	8.3.1.1	8.3.1.2	8.3.2.1,	8.3.2.2.
CHECKMATE-066	Phase III, randomized, controlled, double blind study.	Confirmed, unresectable, previously untreated stage III or IV melanoma without a BRAF mutation.	Nivolumab n=210	Dacarbazine n=208	• OS (primary outcome) • PFS • AEs				
RELATIVITY-047	Phase 2-3, global, double-blind, randomized controlled trial	Previously untreated, histologically confirmed, unresectable stage III or IV melanoma.	Relatlimab and nivolumab n=355	Nivolumab n=359	• PFS (primary outcome) • AEs • QoL				
CHECKMATE-067	Multicentre, randomized, double-blind, phase 3 study.	Histologically confirmed stage III (unresectable) or stage IV melanoma.	Nivolumab plus ipilimumab. n=314	Nivolumab n=316 Ipilimumab n=315	• OS (coprimary end point) • PFS (coprimary end point) • AEs				

CA184-024	Multinational, randomized, double-blind, phase 3 study.	Previously untreated stage III (unresectable) or stage IV melanoma with measurable lesions.	Ipilimumab plus dacarbazine n=250	Dacarbazine n=252	• OS (primary outcome) • PFS • AEs				
MDX010-20	Randomized, double-blind, phase 3 study.	Unresectable stage III or IV melanoma who received a previous therapeutic regimen containing one or more of the following: dacarbazine, temozolomide, fotemustine, carboplatin, or interleukin-2.	Ipilimumab, plus a gp100 peptide vaccine n= 403	Ipilimumab n=137 gp100 n=136	• OS (Primary endpoint) • PFS, Median • AEs • QoL				

KEYNOTE-006	International, randomized, open-label phase 3 study.	Histologically confirmed, unresectable stage III or IV melanoma who received no more than one previous systemic therapy for advanced disease.	Pembrolizumab every 2 weeks n= 279 Pembrolizumab every 3 weeks n=277	Ipilimumab every 3 weeks n=278	• OS (primary outcome) • PFS (primary outcome) • AEs				
MASTERKEY-265	A multicenter, double-blind, placebo controlled, randomized phase III study.	Histologically confirmed stage IIIB-IV M1c unresectable melanoma	A combination of T-VEC plus pembrolizumab n=346	Placebo plus pembrolizumab n=346	• OS (primary outcome) • PFS (primary outcome) • AEs				

OPTiM	A randomized open-label phase III trial.	Histologically confirmed, unresectable, bidimensionally measurable stage IIIB/C/IV melanoma with ≥1 cutaneous, subcutaneous or nodal lesions that was suitable for direct or ultrasound-guided injection.	Intratumoral Talimogene laherparepvec (T-VEC) (at the approved dose) n= 295 (68%)	Subcutaneous recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) n= 141 (32%)	• OS (secondary endpoint) • AEs				
NCT02278887	Multicenter, open-label, phase 3, randomized trial.	Histologically confirmed, unresectable or metastatic stage IIIC or IV cutaneous melanoma, one or more lesions that could be surgically removed for generation of TILs.	Adoptive cell therapy with tumor-infiltrating lymphocytes (TILs). n=84	Ipilimumab: n=84	• OS • PFS (primary outcome) • AEs • QoL				

CHECKMATE-037	A multicentre, randomized, controlled, phase III, open-label study, at 90 sites in 14 countries.	Histologically confirmed, unresectable stage IIIC or IV metastatic melanoma.	Nivolumab 3 mg/kg intravenously every 2 weeks. n=272	Investigator's choice chemotherapy (ICC), which consisted of dacarbazine 1,000 mg/m2 every 3 weeks or carboplatin area under the curve 6 plus paclitaxel 175 mg/m2 every 3 weeks intravenously. n:133	• OS (co-primary outcome) • PFS • AEs • QoL				
COBRIM	A multicentre, randomized, controlled, double-blind, phase 3 study, at 135 centres worldwide.	Histologically confirmed, unresectable, locally advanced stage IIIC or stage IV metastatic melanoma with BRAF V600 mutations.	Oral vemurafenib and cobimetinib N= 247	Oral vemurafenib and placebo N= 248	• OS • PFS (primary outcome) • AEs				

COMBI-V	A multicentre, open-label, randomized, phase 3 study, at 193 centers worldwide.	Metastatic melanoma with BRAF V600E or V600K mutations. N= 352	Oral dabrafenib and trametinib N= 352	Oral vemurafenib N= 352	• OS (primary outcome) • PFS • AEs				
COLUMBUS	A multicentre, two-part, randomised, open-label, phase 3 study, at 162 centres worldwide.	Histologically confirmed locally advanced, unresectable, or metastatic cutaneous melanoma or unknown primary melanoma stage IIIB, IIIC, or IV, with BRAF V600E or BRAF V600K mutations.	Oral encorafenib and binimetinib N = 192	Oral encorafenib N= 194 Or Oral vemurafenib N= 191	• OS • PFS (primary outcome) • AEs				
COMBI-d	A double-blind, randomized, phase 3 study without crossover, at 113 centres worldwide.	Histologically confirmed, unresectable stage IIIC or stage IV metastatic melanoma with BRAF V600E or V600K mutations.	Dabrafenib and oral trametinib n=211	Dabrafenib. n=212	• OS • PFS (primary outcome) • AEs				

DREAMseq	A two-arm, two-step, open-label, randomized phase 3 trial.	Step 1: • Unresectable stage III/IV melanoma with a BRAFV600E/K mutation. • Treatment-naive for metastatic disease. To enroll onto step 2: • Progressive disease and meeting the relevant step 1 eligibility criteria.	**Arm A:** nivolumab/ipilimumab n=133 At disease progression patients were enrolled in step 2 to receive the alternate therapy: **Arm C:** dabrafenib/ trametinib n=27	**Arm B:** dabrafenib/trametinib n=132 At disease progression patients were enrolled in step 2 to receive the alternate therapy: **Arm D:** nivolumab/ ipilimumab n=46	• PFS • OS (primary outcome: 2-year landmark OS rate among patients followed for >2 yrs) • AEs				

IMspire150	A multicentre, double blind, placebo-controlled, randomised, phase 3 study done in 108 academic and community hospitals in 20 countries.	Untreated, histologically confirmed stage IV or unresectable stage IIIc melanoma, with BRAFV600 mutation-positive tumours.	Atezolizumab, vemurafenib, and cobimetinib n= 256	Placebo, vemurafenib, and cobimetinib n= 258	• PFS (primary outcome) • OS • AEs				

Tabe 3. Exclusion table

Nr.	Study name	Reason for exclusion
1	KEYNOTE-001	Wrong intervention
2	Systematic review Ascierto (2014); Lipson (2014); Johnson (2015); Johnson (2016); Jamal (2017); Afzal (2018); Dupuis (2018); Kirchberger (2018); Sheng (2019); Loo (2020); Tang (2020); Byeon (2021); Guida (2021); Li (2021); Zhou (2021); Zhang (2022)	Wrong study design
3	Systematic review IMSpire 150, KEYNOTE-022, IMPemBra, COMBI-i, NCT02027961	Wrong study design
4	Systematic review NCT02519322, CheckMate 069, Checkmate 067, NCT01844505, NCT01927419, NCT02374242, NCT02731729	Wrong study design
5	ABC	Wrong study design
6	Systematic review	Wrong study design
7	Systematic review BRAF-targeted therapies: BREAK-3, BRF113220 Part C, BRIM-3, coBRIM, COLUMBUS, COMBI-d, COMBI-i, COMBI-v, EUDRACT, Imspire 150, KEYNOTE-022, METRIC, NCT02314143, S1320 Immunotherapy trials: CA 184-024, CheckMate 037, CheckMate 066, CheckMate 067, CheckMate 069, CheckMate 511, EUDRACT2016-001941-26, KEYNOTE-002, KEYNOTE-006, KEYNOTE-029, KEYNOTE-252/ECHO-301, NCCTG N0879, NCT01152788, NCT01258855, NCT01515189, NCT01740297, NCT02545075, NCT03273153	Wrong study design
8	Systematic Review Immune checkpoint inhibitors: Hodi (2010); Larkin (2015); Robert (2015); Weber (2015); Ascierto (2017); Lebbe (2019); Long (2019); Gogas (2021); Tawbi (2022); Eggermont (2015); Weber (2017); Eggermont (2018); Grossmann (2021) Targeted therapy: Chapman (2011); Flaherty (2021); Hauschild (2012); Larkin (2014); Long (2015); Robert	Wrong study design

	(2015); Dummer (2018); Gutzmer (2020); Long (2017); Maio (2018)	
9	European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment - Update 2019	Wrong study design
10	Immunotherapy discontinuation - how, and when? Data from melanoma as a paradigm	Wrong study design
11	Current and Emerging Options for Patients With Melanoma Brain Metastases	Wrong study design
12	Nivolumab/Relatlimab: A Novel Addition to Immune Checkpoint Inhibitor Therapy in Unresectable or Metastatic Melanoma	Wrong study design
13	KEYNOTE-001, KEYNOTE-002 and KEYNOTE-006	No comparison between the interventions with regard to outcomes of interest
14	Systematic review Eggermont (2015); Ribas (2015); Weber (2015); Robert (2015); Larkin (2015); Postow (2015); Eggermont (2018); Long (2018)	Wrong study design
15	Systematic review IMspire150, KEYNOTE-022, COMBI-i	Wrong study design
16	TEAM	Wrong study design
17	BREAK-2 and BREAK-3	Wrong intervention
18	BREAK-3	Wrong intervention
19	BRIM-3	Wrong intervention
20	COMBI-d and COMBI-v	Original studies included
21	KEYNOTE-002	Wrong study design
22	SECOMBIT	Wrong study design

Zoekopbrengst

	EMBASE	OVID/MEDLINE	Ontdubbeld
SRs	299	204	332
RCT	449	433	558
Totaal	748	637	**890 + 87**

Zoekstrategie

Embase.com

No.	Query	Results
#9	#7 OR #8	748
#8	#4 AND #6 NOT #7 **= RCT**	449
#7	#4 AND #5 **= SR**	299
#6	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	1942912
#5	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	733409
#4	#1 AND (#2 OR #3) AND ([english]/lim OR [dutch]/lim) AND [2010-2022]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	5884
#3	'nivolumab'/exp/mj OR 'nivolumab':ti,ab,kw OR 'ipilimumab'/exp/mj OR 'ipilimumab':ti,ab,kw OR ipilumumab:ti,ab,kw OR 'vemurafenib'/exp/mj OR 'vemurafenib':ti,ab,kw OR 'cobimetinib'/exp/mj OR 'cobimetinib':ti,ab,kw OR 'binimetinib'/exp/mj OR 'binimetinib':ti,ab,kw OR 'encorafenib'/exp/mj OR 'encorafenib':ti,ab,kw OR	131232

	'trametinib'/exp/mj OR 'trametinib':ti,ab,kw OR 'dabrafenib'/exp/mj OR 'dabrafenib':ti,ab,kw OR 'imatinib'/exp/mj OR 'imatinib':ti,ab,kw OR 'dacarbazine'/exp/mj OR 'dacarbazine':ti,ab,kw OR dtic:ti,ab,kw OR 'talimogene laherparepvec'/exp/mj OR 'talimogene laherparepvec':ti,ab,kw OR 't vec':ti,ab,kw OR 'b raf kinase inhibitor'/exp/mj OR 'mitogen activated protein kinase kinase inhibitor'/exp/mj OR (((braf OR 'b raf' OR mek) NEAR/3 (inhibit* OR block*)):ti,ab,kw) OR 'cytotoxic t lymphocyte antigen 4 antibody'/exp OR 'cytotoxic t lymphocyte antigen 4'/exp OR (((anti OR inhibit* OR block*) NEAR/3 ('ctla4' OR 'ctla 4' OR 'pd 1' OR 'pd1' OR 'lag3' OR 'pdl1')):ti,ab,kw)	
#2	'molecularly targeted therapy'/exp/mj OR ((target* NEAR/3 (therap* OR treat*)):ti,kw) OR 'immunotherapy'/exp/mj OR 'immunotherap*':ti,kw OR ((immun* NEAR/3 (therap* OR treat*)):ti,kw)	246571
#1	'metastatic melanoma'/exp/mj OR (('metastasis'/exp OR metasta*:ti,kw OR ((stage NEAR/3 ('iii*' OR 'iv*' OR three OR four OR '3*' OR '4*')):ti,ab,kw) OR advanced:ti,kw) AND ('melanoma'/exp/mj OR melanoma*:ti,kw))	48219

Ovid/Medline

#	Searches	Results
11	9 or 10	637
10	(6 and 8) not 9 **= RCT**	433
9	6 and 7 **= SR**	204
8	exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	1535592
7	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	610138
6	limit 5 to ((english language or dutch) and yr="2010 -Current")	4294

5	4 not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/))	5883
4	1 and (2 or 3)	6634
3	Imidazoles/ or MAP Kinase Kinase Kinases/ai or Oximes/ or Protein Kinase Inhibitors/ or Proto-Oncogene Proteins B-raf/ai or Pyridones/ or Pyrimidinones/ or exp Nivolumab/ or 'nivolumab'.ti,ab,kf. or exp Ipilimumab/ or 'ipilimumab'.ti,ab,kf. or ipilumumab.ti,ab,kf. or exp Vemurafenib/ or 'vemurafenib'.ti,ab,kf. or 'cobimetinib'.ti,ab,kf. or 'binimetinib'.ti,ab,kf. or 'encorafenib'.ti,ab,kf. or 'trametinib'.ti,ab,kf. or 'dabrafenib'.ti,ab,kf. or exp Imatinib Mesylate/ or 'imatinib'.ti,ab,kf. or exp Dacarbazine/ or 'dacarbazine'.ti,ab,kf. or dtic.ti,ab,kf. or 'talimogene laherparepvec'.ti,ab,kf. or 't vec'.ti,ab,kf. or ((braf or 'b raf' or mek) adj3 inhibit*).ti,ab,kf. or ((anti or inhibit* or block*) adj3 ('ctla4' or 'ctla 4' or 'pd 1' or 'pd1' or 'lag3' or 'pdl1')).ti,ab,kf.	187834
2	exp Molecular Targeted Therapy/ or (target* adj3 (therap* or treat*)).ti,kf. or exp Immunotherapy/ or 'immunotherap*'.ti,kf. or (immun* adj3 (therap* or treat*)).ti,kf.	433288
1	(exp Melanoma/ or melanoma*.ti,kf.) and (exp Neoplasm Metastasis/ or metasta*.ti,kf. or (stage adj3 ('iii*' or 'iv*' or three or four or '3*' or '4*')).ti,kf. or advanced.ti,kf.)	27134

8.3.1.1. Eerstelijnsbehandeling BRAF-V600E/K gemuteerd irresectabel of gemetastaseerd stadium III/IV

Uitgangsvraag

Wat is de plaats van systemische therapie in de eerste lijns-behandeling van patiënten met een BRAF-V600E/K gemuteerd irresectabel of gemetastaseerd stadium III/IV melanoom?

Search and select

The search and selection methods can be found in the main module 8.3 [Link XXX]

Summary of literature

Twelve randomized controlled trials that studied clinical outcomes of first line systemic therapy in patients with unresectable or metastatic stadium III/IV melanoma with a BRAF-V600E/K mutation were included in the literature analysis.

Description of studies

The study characteristics of the included trials are summarized in Table 2 in the main module 8.3 [Link XXX].

Tawbi (2022) – RELATIVITY-047 described a phase 2-3 global, double-blind, randomized study, which was conducted in 111 sites in North America, Central America, South America, Europe, Australia, and New Zealand. They evaluated the efficacy and safety of the combination of relatlimab, a LAG-3–blocking antibody, and nivolumab in patients with previously intreated metastatic or unresectable melanoma. A total of 714 patients were randomized to receive a relatlimab and nivolumab combination (160 mg of relatlimab and 480 mg of nivolumab in a fixed-dose combination administered in a single 60-minute intravenous infusion every 4 weeks) versus nivolumab alone (480 mg of nivolumab administered in a single 60-minute intravenous infusion every 4 weeks). The median age was 63 (20-94) years in the relatlimab + nivolumab group and 62.0 (21–90) years in the control group. In the relatlimab + nivolumab group 59% was male, compared to 57% in the nivolumab alone group. 136 of the 355 (38.3%) patients that were randomized in the relatlimab + nivolumab group, and 139 of the 359 (38.7%) patients that were randomized in the nivolumab alone group, had a BRAF mutation. The following relevant outcomes were reported progression free survival (PFS), adverse events (AEs), and quality of life (QoL). In this literature analysis the median PFS is analysed.

Larkin (2015), Larkin (2019), Wolchock (2017), Wolchok (2022), Hodi (2018) - CHECKMATE 067 is a phase 3, randomized, double-blind study, which is conducted in 137 centres in Australia, Europe, Israel, New Zealand, and North America. They evaluated the efficacy and safety of the use of Nivolumab and Ipilimumab as combination therapy in patients with untreated unresectable stage III or stage IV melanoma. A total of 945 patients were randomized to receive nivolumab 1 mg/kg plus ipilimumab 3 mg/kg once

every 3 weeks followed by nivolumab 3 mg/kg once every 2 weeks (n=314, of which 101 patients (32.2%) had a BRAF mutation), or nivolumab 3 mg/kg once every 2 weeks (n=316, of which 100 patients (31.6%) had a BRAF mutation), or ipilimumab 3 mg/kg once every 3 weeks (n=315, of which 97 patients (30.8%) had a BRAF mutation). The median age, of both patients with and without BRAF mutation, was 59 (18-88) years in the combination group, 59 (25-90) in the nivolumab group and 61 (18-89) in the Ipilimumab group. In the combination group, 66% was male, compared to 64% in the nivolumab alone group and 64% in the Ipilimumab group. The following relevant outcomes were reported, overall survival (OS), PFS, and number of patients with serious AEs. The study was not powered for a formal statistical comparison between the nivolumab group and the nivolumab-plus-ipilimumab group. In this literature analysis the median outcomes for OS and PFS are analysed and the last endpoint for OS (6.5-year OS rates) are described.

Robert (2011), Maio (2015) - CA184-024 is a multinational, randomized, double-blind, phase 3 study. This trial compared ipilimumab plus dacarbazine with dacarbazine and placebo in patients with previously untreated stage III (unresectable) or stage IV melanoma with measurable lesions. Tumors were not routinely assessed for the presence of the BRAF V600E mutation and therefore no sub analyses was possible in this study. Patients were randomized to receive ipilimumab at a dose of 10 mg per kg plus dacarbazine at a dose of 850 mg per square meter (n=250) or dacarbazine at a dose of 850 mg per square meter plus placebo (n=252). The mean age was 57.5 years in the intervention group and 56.4 years in the control group. In the intervention group 60.8% and in the control group 59.1% were male. Robert (2011) reported on OS, PFS, and AEs after a follow up time of 54 months between the start of the study (first visit of first patient) and end of the study. Maio (2015) reported updated results after a median survival follow-up of 11 months (range, 0.4 to 71.9 months) for the intervention group and 8.9 months (range, 0.1 to 73.2 months) for the control group. In this literature analysis the median outcomes for OS and PFS are analysed and the last endpoint for OS (5-year OS rates) are described.

Robert (2019), Carlino (2018), Schachter (2017), Robert (**2015)** - KEYNOTE-006 is an international, randomized, open-label phase 3 study performed in 16 countries. In this trial treatment with pembrolizumab versus ipilimumab was studied, to compare PD-1 inhibition with CTLA-4 blockade in patients with unresectable stage III/IV melanoma. Patients were randomized to pembrolizumab at a dose of 10 mg/kg of body weight every 2 weeks (n= 279); pembrolizumab at a dose of 10 mg/kg every 3 weeks (n=277); or ipilimumab at a dose of 3 mg/kg every 3 weeks (n=278). The mean age was 61 years in the pembrolizumab every 2 weeks group, 63 years in the pembrolizumab every 3 weeks group and 62 years in the ipilimumab group. The percentage of males was 57.7 %, 62.8%, and 58.3% for the three groups, respectively. Robert (2015) reported on OS, PFS, and AEs after a median follow-up of 7.9 months. Schachter (2017) reported updated results after a median follow-up of 22.9 months. Carlino (2018) reported updated outcomes by line of therapy and programmed death ligand 1 expression after a median follow-up of 33.9 months. Robert (2019) reported updated results of OS, PFS, and AES

after a median follow-up of 57.7 months. In this literature analysis the median outcomes for OS and PFS are analysed and the last endpoints for OS and PFS (2-year OS rates and 2-year PFS rates) are described.

Chesney (2023) - MASTERKEY-265 is a multicenter, double-blind, placebo controlled, randomized phase 3 study in 21 countries. This trial evaluated the efficacy and safety of T-VEC-pembrolizumab versus placebo-pembrolizumab in patients with stage IIIB-IV M1c unresectable melanoma. Patients were randomized to a combination of T-VEC plus pembrolizumab 200 mg once every 3 weeks (n=346) or placebo plus pembrolizumab 200 mg once every 3 weeks (n=346). The median age was 64 years in both study groups. The percentage of males was 57.5% in the T-VEC-pembrolizumab group and 63.3% placebo-pembrolizumab group. Chesney (2023) reported OS, PFS, and AES, after a median follow-up of 25.6 months for the primary PFS analysis, 31.0 months for the second OS interim analysis, and 35.6 months for the final analysis. In this literature analysis the median outcomes for OS and PFS are analysed.

Andtbacka (2019), Andtbacka (2015) – OPTiM is a randomized open-label phase 3 trial at 64 sites in the United States, the United Kingdom, Canada, and South Africa. This trial evaluated outcomes after treatment with talimogene laherparepvec (T-VEC) compared with granulocyte macrophage colony-stimulating factor (GM-CSF) in patients with unresectable, stage IIIB/C/IV melanoma with ≥1 lesion that was suitable for direct or ultrasound-guided injection. Patients were randomized to T-VEC (at the approved dose) (n=295 (68%)) of subcutaneous recombinant GM-CSF (n=141 (32%)). The median age was 63 years in the T-VEC group and 64 years in the GM-CSF group. The percentage of males was 59% in the T-VEC group and 55% in the GM-CSF group. Of 204 of the 295 (69%) in the T-VEC group, and 95 of the 141 (67%) in the GM-CSF group, the BRAF mutation status was unknown. For 138 of the 295 (47%) patients in the T-VEC group, and 65 of the 141 (46%) in the GM-CSF group, this was a first line therapy. OS and AEs were reported after a median follow-up of 49 months in the final analysis of OS. In this literature analysis the median OS is analysed.

Larkin (2014), Ascierto (2016), Ascierto (2021) - CoBRIM described an international, multicentre, double-blind, randomized phase 3 study, which was conducted in 135 sites in the United States, Canada, Australia, New Zealand, Europe, Russia, Turkey, and Israel. The authors evaluated efficacy and safety of using cobimetinib combined with vemurafenib, versus vemurafenib and placebo, in previously untreated patients with advanced BRAF-mutated melanoma. A total of 495 patients were randomized in a 1:1 ratio to receive vemurafenib orally (at a dose of 960 mg twice daily) together with either placebo (control group) or cobimetinib (at a dose of 60 mg once daily for 21 days, followed by 7 days off) (combination group). The median age was 56 (23-88) years in the combination group and 55 (25-85) years in the control group. In the combination group 59% was male, compared to 56% in the control group. The following relevant outcomes were reported, OS, PFS and number of patients with serious AEs. In this literature analysis, the median outcomes for OS were analysed and the last endpoint (5-year OS and 3-year PFS) for the outcomes OS and PFS are described.

Robert (2015), Robert (2016) - COMBI-v described an open-label, randomized, phase 3 study performed at 193 centres worldwide, where they evaluated the efficacy and safety of using combination therapy with dabrafenib plus trametinib versus vemurafenib monotherapy in patients with previously untreated patients with unresectable stage IIIC or IV melanoma with BRAF V600E or V600K mutations. A total of 704 patients were randomized in a 1:1 ratio to receive either a combination of dabrafenib (150 mg orally twice daily) and trametinib (2 mg orally once daily) or vemurafenib (960 mg orally twice daily). The median age was 55 (18–91) years in the combination group and 54 (18–88) years in the control group. In the combination group 59% was male, compared to 51% in the control group. The following relevant outcomes were reported, OS, PFS, and number of patients with serious AEs. In this literature analysis the median outcomes for OS and PFS are analysed and the last endpoints (3-year OS and 3-year PFS) of the outcomes are described.

Dummer (2018), Dummer (2018-2), Ascierto (2020) - COLUMBUS described a two-part, randomised, open-label, phase 3 study, performed at 162 sites in 28 countries. They evaluated the efficacy and safety of encorafenib plus binimetinib versus encorafenib alone and versus vemurafenib alone in patients with histologically confirmed, locally advanced, unresectable, or metastatic cutaneous melanoma, or unknown primary melanoma. In part 1 of the study, 577 patients were randomly assigned (1:1:1) to receive oral encorafenib 450 mg once daily plus oral binimetinib 45 mg twice daily (encorafenib plus binimetinib group), oral encorafenib 300 mg once daily encorafenib group), or oral vemurafenib 960 mg twice daily (vemurafenib group). The median age was 57 (20–89; 48–66) years in the combination group, 54 (23–88; 46–63) years in the encorafenib control group and 56 (21–82; 45–65) years in the vemurafenib control group. In the combination group 60% was male, compared to 60% and 56% in the two control groups, respectively. The following relevant outcomes were reported, OS, PFS and number of patients with serious AEs. In this literature analysis the median outcomes for OS and PFS are analysed and the last endpoint (3-year OS) for the outcome OS is described.

Long (2014), Long (2015), Long (2017) – COMBI-d is a double-blind, randomized, phase 3 study without crossover that is carried out at 113 centres worldwide. This trial compared the combination of dabrafenib and trametinib with dabrafenib alone as first-line therapy in patients with metastatic melanoma with BRAF V600E or V600K mutations. Participants were randomized (1:1) to receive a combination of oral dabrafenib (150 mg twice daily) and oral trametinib (2 mg once daily) (n=211), or oral dabrafenib (150 mg twice daily) and placebo (n=212). The median age (range) was 55.0 (22–89) in the dabrafenib and trametinib group and 56.5 (22–86) in the dabrafenib alone group. In the dabrafenib and trametinib group and the dabrafenib alone group 53% and 54% were male respectively. Long (2014) reported on PFS, OS, and number of patients with AEs. At that time, the median duration of follow-up was 9 months (range, 0 to 16). Long (2015) reported updated results of PFS, OS, and AEs after a median follow-up of 20 months (range 0–30) for the dabrafenib and trametinib group and 16 months (range 0–32 months) for the dabrafenib only group. Long (2017) reported an updated 3-year landmark analysis of PFS,

OS, and AEs. In this literature analysis the median outcomes for OS and PFS are analysed and the last endpoint (3-year OS, 3-year PFS) of the outcomes are described.

Atkins (2022) – DREAMseq is a two-arm, two-step, open-label, randomized phase 3 trial. This trial compared the combination of nivolumab/ipilimumab with the combination dabrafenib/trametinib in patients with histologically confirmed, unresectable stage III or IV melanoma containing a BRAFV600E/K mutation. Patients were randomized (1:1) to receive step 1 with either nivolumab/ipilimumab (Arm A, n=133) or dabrafenib/trametinib (Arm B, n=132). At disease progression patients were enrolled in step 2 to receive the alternate therapy (Arm C (n=27) and D (=46)). Patients in arms A and D received nivolumab 1 mg/kg and ipilimumab 3 mg/kg once every 3 weeks for four doses followed by nivolumab 240 mg intravenously once every 2 weeks for up to 72 weeks. Patients in arms B and C received dabrafenib 150 mg twice a day and trametinib 2 mg orally once daily. The median age (range) was 61 (25-85) in arm A, and 61 (30-84) in arm B. In arm A 81% were male and in arm B 86% were male. The following outcomes are reported PFS, OS, and AEs. Median follow-up was 27.7 months (IQR, 41.9-11.9). In this literature analysis the median outcomes for PFS is analysed and the last endpoints (3-year OS and 2-year PFS) of the outcomes are described. The median OS was not reported.

Ascierto (2023) - IMspire150 is a multicentre, double blind, placebo-controlled, randomised, phase 3 study performed in 108 academic and community hospitals in 20 countries. This trial studied the combination of atezolizumab with vemurafenib and cobimetinib in patients with untreated, histologically confirmed stage IV or unresectable stage IIIc melanoma, with BRAFV600 mutation-positive tumours. Patients were randomized (1:1) to receive atezolizumab, vemurafenib, and cobimetinib (atezolizumab group, n=256) or placebo, vemurafenib, and cobimetinib (control group, n=258). In cycle 1 all patients received oral cobimetinib 60 mg once daily plus oral vemurafenib 960 mg twice daily for 21 days then vemurafenib 720 mg twice daily (atezolizumab group) or 960 mg twice daily (control group) for 7 days. From cycle 2 onwards atezolizumab or placebo was added. Patients in the atezolizumab group received intravenous atezolizumab 840 mg (day 1 and 15), once-daily cobimetinib 60 mg (21 days on and 7 days off), and twice-daily vemurafenib 720 mg. Patients in the control group received intravenous placebo (day 1 and 15), once-daily cobimetinib 60 mg (21 days on and 7 days off), and twice-daily vemurafenib 960 mg. The median age (range) was 54.0 years (44.8-64.0 years) in the atezolizumab group, and 53.5 years (43.0-63.8 years) in the control group. In the atezolizumab group 59% was male and in the control group 58% was male. The following outcomes are reported PFS, OS, and AEs. Median follow-up was 29.1 months (IQR 10.1–45.4) in the atezolizumab group and 22.8 months (10.6–44.1) in the control group. OS was not fully met. In this literature analysis the median outcomes for OS and PFS are analysed and the last endpoints (2-year OS and 1.5-year PFS) of the outcomes are described.

Results

Overall survival (OS) – Critical outcome measure

Eleven of the twelve included studies reported on OS.

Checkmate-067 reported the effect of **nivolumab plus ipilimumab** versus **nivolumab** versus **ipilimumab** on OS in patients with BRAF-mutant tumors. The study was not powered for a formal comparison between the nivolumab plus ipilimumab and the nivolumab treatment groups. The 6.5-year OS rates in patients with BRAF-mutant tumors were 57% for the nivolumab plus ipilimumab group, 43% for the nivolumab group, and 6% for the ipilimumab group. The median OS in the nivolumab plus ipilimumab group was not reported, and therefore no clinical relevance could be assessed according to the PASKWIL criteria. The absolute difference in median OS between the group treated with nivolumab (45.5 months) versus those treated with ipilimumab (24.6 months) was 20.9 months with a HR of 0.63 (95% CI 0.44 to 0.90) favoring treatment with nivolumab. This difference was considered clinically relevant according to the PASKWIL criteria.

CA184-024 reported the effect of **ipilimumab plus dacarbazine** versus **dacarbazine** plus placebo on OS. The 5-year OS rates were 18.2% for the ipilimumab plus dacarbazine group and 8.8% for the dacarbazine group. Treatment with ipilimumab plus dacarbazine resulted in a longer median OS compared to treatment with dacarbazine only. The absolute difference in median OS between the group treated with ipilimumab plus dacarbazine (11.2 months) versus those treated with dacarbazine (9.1 months) was 2.1 months with a HR of 0.69 (95% CI 0.57 to 0.84) favoring treatment with ipilimumab plus dacarbazine. This difference was not considered clinically relevant according to the PASKWIL criteria.

KEYNOTE-006 reported the effect of **pembrolizumab every 2 weeks** or **pembrolizumab every 3 weeks** compared to **ipilimumab every 3 weeks** on OS. The 2-year OS rates were 55% in the pembrolizumab-every-2-weeks group, 55% in the pembrolizumab-every-3-weeks group, and 43% in the ipilimumab-every-3-weeks group. Treatment with pembrolizumab resulted in a longer median OS than treatment with ipilimumab. The absolute difference between the combined pembrolizumab groups (32.7 months) and the ipilimumab group (15.9 months) was 16.8 months with a HR of 0.73 (95% CI 0.61–0.88). This difference was not considered clinically relevant according to the PASKWIL criteria.

MASTERKEY-265 reported the effect of a combination of **T-VEC plus pembrolizumab** versus placebo plus **pembrolizumab** on OS. Treatment with T-VEC-pembrolizumab did not result in a longer OS compared with treatment with placebo-pembrolizumab. The median OS was not estimable in the T-VEC plus pembrolizumab group and 49.2 months (40.57 to not estimable) in the pembrolizumab group with a HR of 0.96 (95% CI 0.76 to 1.22; P =0 .74). This difference was not considered clinically relevant according to the PASKWIL criteria.

OPTiM reported the effect of **T-VEC** versus **GM-CSF** on OS in first line treatment, without subgroup analyses on BRAF mutation. Treatment with T-VEC resulted in a longer median OS than treatment with GM-CSF. The median follow-up in the final OS analysis was 49 months. Median OS weas 23.3 months (CI, 19.5-29.6) and 18.9 months (95% CI, 16.0-23.7) in the TVEC and GM-CSF arm, respectively (HR, 0.79; 95% CI, 0.62-1.00). This difference was not considered clinically relevant according to the PASKWIL criteria.

CoBRIM reported the effect of **cobimetinib combined with vemurafenib** versus **vemurafenib and placebo** on median OS. Treatment with cobimetinib combined with vemurafenib resulted in a longer median OS than treatment with vemurafenib and placebo. The absolute difference between the cobimetinib combined with vemurafenib group (22.5 months) and the vemurafenib and placebo group (17.4 months) was 5.1 months with a HR of 0.70 (95% 0.55 – 0.89). This difference was not considered clinically relevant according to the PASKWIL criteria.

COMBI-v did not reported the effect of **dabrafenib and trametinib** versus **vemurafenib** on median OS. However, the absolute difference in median 3-year survival between dabrafenib and trametinib (45%) versus vemurafenib (32%) was 13%, with a higher 3-year survival in the dabrafenib and trametinib group. This difference was considered clinically relevant according to the PASKWIL criteria.

COLUMBUS reported the effect of **encorafenib and binimetinib** versus **encorafenib** versus **vemurafenib** on median OS. Treatment with encorafenib and binimetinib resulted in the longest median OS. The absolute difference between encorafenib and binimetinib (33.6 months) and encorafenib (23.5 months) was 10.1 months with a HR of 0.81 (95% 0.61 to 1.06). This difference was not considered clinically relevant according to the PASKWIL criteria. The absolute difference between encorafenib and binimetinib (33.6 months) and vemurafenib (16.9 months) was 16.7 months with a HR of 0.61 (95% 0.47 to 0.79). This difference was considered clinically relevant according to the PASKWIL criteria. The absolute difference between encorafenib (23.5 months) and vemurafenib (16.9 months) was 6.6 months with a HR of 0.76 (95% CI 0.58 to 0.98).
This difference was not considered clinically relevant according to the PASKWIL criteria.

COMBI-d reported the effect of **dabrafenib and trametinib** versus **dabrafenib** on median OS. Treatment with dabrafenib and trametinib resulted in a longer median OS than treatment with dabrafenib alone. The absolute difference between the dabrafenib and trametinib group (25.1 months) and dabrafenib group (18.7 months) was 6.4 months with a HR of 0.71 (95% 0.55 to 0.92). This difference was not considered clinically relevant according to the PASKWIL criteria.

In the DREAMseq trial, combination treatment with **nivolumab and ipilimumab** versus **dabrafenib and trametinib** resulted in a longer OS. The absolute difference between the intervention and control group was 23.4% after 3 years of follow-up. According to the PASKWIL criteria we could not assess clinical relevance (median OS in the control group not reported).

In the IMspire150 trial, combination treatment with **atezoluzumab and vemurafenib and cobimetinib versus vemurafenib and cobimetinib** did not show a significant survival

benefit.The absolute difference between the intervention and control group was 9% after 2 years of follow-up. The median OS was 39 months (29.9–not estimable) in the intervention group, versus 25.8 months (22.0-34.6 months) in the control group, with a HR of 0.84 (95% CI 0.66–1.06). This difference was not considered clinically relevant according to the PASKWIL criteria.

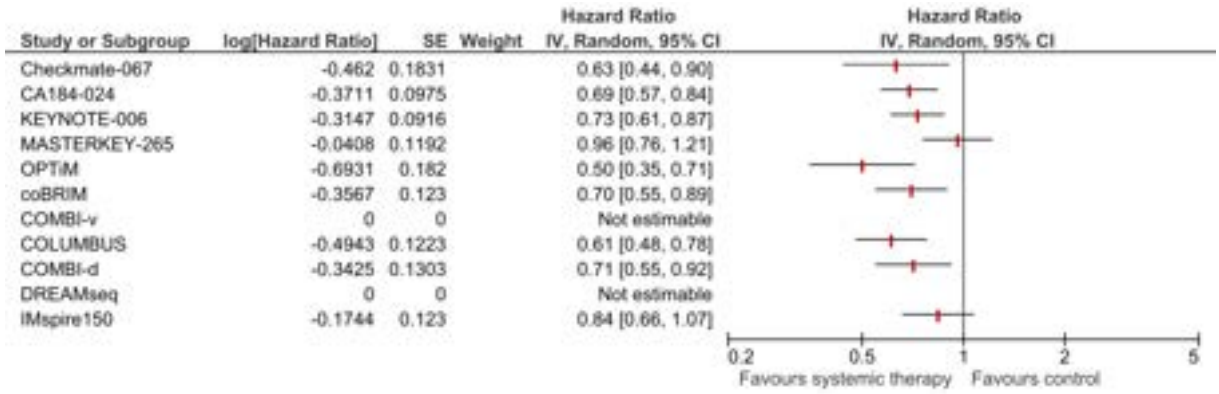

Figure 1. Forest plot of median overall survival for first line systemic therapy versus placebo, other systemic therapy, or best supportive care in patients with a BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma.

[a] For Checkmate-067 the HR for nivolumab versus ipilimumab is shown.
[b] For KEYNOTE-006 the HR for combined pembrolizumab versus ipilimumab is shown.
[c] For COLOMBUS the HR for encorafenib and binimetinib versus vemurafenib is shown.
[d] COMBI-v and DREAMseq did not report the HR for median OS and is therefore not shown in this figure.

Progression free survival – important outcome measure

Eleven of the twelve included studies reported on PFS.

RELATIVITY-047 reported the effect of **relatlimab and nivolumab** versus **nivolumab** on PFS. In the subgroup of patients with BRAF mutations, the median PFS was 10.1 months (95% CI, 4.6 to 23.1) in the relatlimab and nivolumab group and 4.6 months (95% CI, 3.0 to 6.5) in the nivolumab group. The absolute difference between the group treated with relatlimab and nivolumab and the group treated with nivolumab was 5.5 months with a HR of 0.74 (95%CI 0.54-1.03) favoring treatment with relatlimab and nivolumab. According to the PASKWIL criteria we could not assess clinical relevance (median OS in the control group not reported).

Checkmate-067 reported the effect of **nivolumab plus ipilimumab** versus **nivolumab** versus **ipilimumab** on PFS in patients with a BRAF mutant. Treatment with nivolumab plus ipilimumab resulted in a longer median PFS compared to treatment with nivolumab only. The absolute difference in median PFS between the group treated with nivolumab plus ipilimumab (16.8 months) versus those treated with nivolumab (5.6 months) was 11.2 months with a HR of 0.62 (0.44 to 0.89) favoring treatment with nivolumab plus ipilimumab. This difference was considered clinically relevant according to the PASKWIL

criteria. This outcome was observed, but the study was not designed or powered to detect it initially. The absolute difference in median PFS between the group treated with nivolumab plus ipilimumab (16.8 months) versus those treated with ipilimumab (3.4 months) was 13.4 months with a HR of 0.44 (0.31 to 0.62) favoring treatment with nivolumab plus ipilimumab. This difference was considered clinically relevant according to the PASKWIL criteria. The absolute difference in median PFS between the group treated with nivolumab versus those treated with ipilimumab was 2.2 months with a HR of 0.71 (0.51 to 0.98) favoring treatment with nivolumab. This difference was not considered clinically relevant according to the PASKWIL criteria.

CA184-024 reported the effect of **ipilimumab plus dacarbazine** versus **dacarbazine** plus placebo on PFS. The median PFS was comparable between the ipilimumab-dacarbazine group and the dacarbazine-only group. After the first assessment of progression at week 12 (after the true median), the Kaplan-Meier curves separated and there was a 24% reduction in the risk of progression in the ipilimumab plus dacarbazine group compared to the dacarbazine only group with a HR of 0.76 (95% CI 0.63–0.93). According to the PASKWIL criteria we could not assess clinical relevance (median OS in the control group was < 12 months).

KEYNOTE-006 reported the effect of **pembrolizumab every 2 weeks** or **pembrolizumab every 3 weeks** compared to **ipilimumab every 3 weeks** on PFS. The 2-year PFS rates were 31% in the pembrolizumab-every-2-weeks group, 28% in the pembrolizumab-every-3-weeks group, and 14% in the ipilimumab-every-3-weeks group. Treatment with pembrolizumab resulted in a longer median PFS than treatment with ipilimumab. The absolute difference between the combined pembrolizumab groups and the ipilimumab group was 5.0 months with a HR of 0.57 (95% CI 0.48–0.67). This difference was considered clinically relevant according to the PASKWIL criteria.

MASTERKEY-265 reported the effect of a combination of **T-VEC plus pembrolizumab** versus placebo plus **pembrolizumab** on PFS. Treatment with T-VEC-pembrolizumab resulted in a longer PFS compared with treatment with placebo-pembrolizumab. The absolute difference between the combined pembrolizumab groups and the ipilimumab group was 5.8 months with a HR of 0.86 (95% CI, 0.71 to 1.04). This difference was not considered clinically relevant according to the PASKWIL criteria.

CoBRIM reported the effect of **cobimetinib combined with vemurafenib** versus **vemurafenib and placebo** on PFS. Treatment with cobimetinib combined with vemurafenib resulted in a longer median PFS than treatment with vemurafenib and placebo. The absolute difference between the cobimetinib combined with vemurafenib group (12.6 months) and the vemurafenib and placebo group (7.2 months) was 5.4 months with a HR of 0.51 (95% 0.39 to 0.67). This difference was considered clinically relevant according to the PASKWIL criteria.

COMBI-v reported the effect of **dabrafenib and trametinib** versus **vemurafenib** on PFS. Treatment with dabrafenib and trametinib resulted in a longer PFS than treatment with vemurafenib. The absolute difference between the dabrafenib and trametinib group (11.4 months) and the vemurafenib group (7.3 months) was 4 months with a HR of 0.56

(95% 0.46 to 0.69). This difference was considered clinically relevant according to the PASKWIL criteria.

COLUMBUS reported the effect of **encorafenib and binimetinib** versus **encorafenib** versus vemurafenib on PFS. Treatment with encorafenib and binimetinib resulted in the longest PFS. The absolute difference between the encorafenib and binimetinib group (14.9 months) and the encorafenib group (9.6 months) was 5.3 months. According to the PASKWIL criteria, clinical relevance could not be assessed as the HR and 95% CI were not provided. The absolute difference between the encorafenib and binimetinib group (14.9 months) and the vemurafenib group (7.3 months) was 7.6 months, with an HR of 0.51 (95% CI: 0.39 to 0.67). This difference was considered clinically relevant according to the PASKWIL criteria. The absolute difference between the encorafenib group (9.6 months) and the vemurafenib group (7.3 months) was 2.3 months. The PASKWIL-criteria could not be assessed (HR and 95% CI not provided).

COMBI-d reported the effect of **dabrafenib and trametinib** versus **dabrafenib** on PFS. Treatment with dabrafenib and trametinib resulted in a longer PFS than treatment with dabrafenib alone. The absolute difference in PFS between the dabrafenib and trametinib group (11.0 months) and dabrafenib group (8.8 months) was 2.2 months with a HR of 0.67 (95% 0.53 to 0.84). This difference was not considered clinically relevant according to the PASKWIL criteria.

DREAMseq reported a longer PFS when using combination treatment with **nivolumab and ipilimumab** versus **dabrafenib and trametinib**. The absolute difference between the intervention and control group was 22.7% after 2 years of follow-up. The median PFS was 11.8 months (95%CI, 5.9 - 33.5) versus 8.5 months (95%CI 6.5 to 11.3). No HR was reported for the median PFS.

IMspire150 reported a longer PFS when using combination treatment with **atezoluzumab and vemurafenib and cobimetinib versus vemurafenib and cobimetinib**. The absolute difference between the intervention and control group was 12% after 1.5 years of follow-up. The median PFS was 15.1 months (95%CI, 11.4-18.4) versus 10.6 months (95%CI 9.3 to 12.7), with a HR of 0.79 (95%CI 0.64 to 0.97), favouring the intervention group. This difference was considered not clinically relevant according to the PASKWIL criteria.

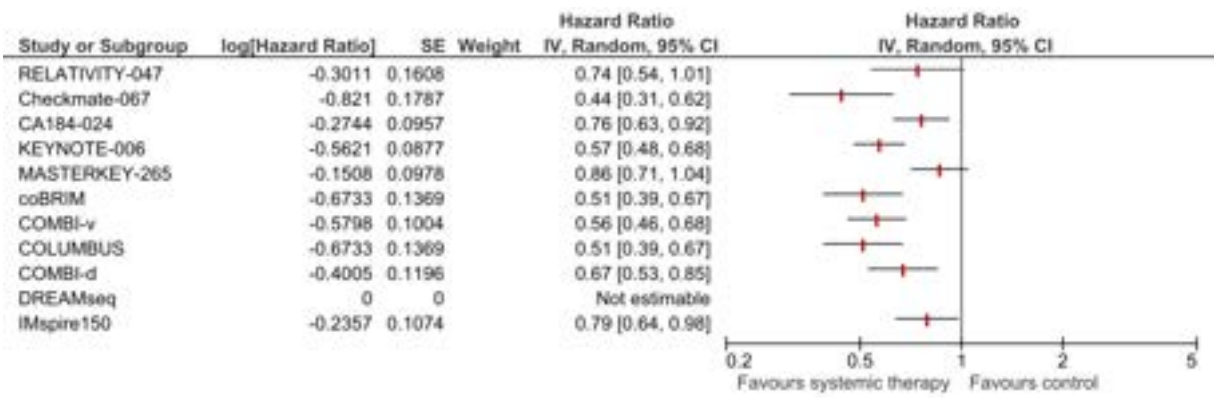

Figure 2. Forest plot of median progression free survival for first line systemic therapy versus placebo, other systemic therapy, or best supportive care in patients with a BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma.

[a] For Checkmate-067 the HR for nivolumab versus ipilimumab is shown.
[b] For KEYNOTE-006 the HR for combined pembrolizumab versus ipilimumab is shown.
[c] For COLOMBUS the HR for encorafenib and binimetinib versus vemurafenib is shown.
[d] DREAMseq did not report the HR for median OS and is therefore not shown in this figure.

Treatment related adverse events (AEs) grade ≥ 3 - Important outcome

Twelve studies reported on AEs.

RELATIVITY-047 reported the effect of **relatlimab and nivolumab** versus **nivolumab** on AEs. No sub group analyses were used while analyzing this outcome. Treatment with relatlimab and nivolumab resulted in a higher percentage of treatment related AEs grade ≥3 compared to treatment with nivolumab only. The risk difference is 0.07 (95%CI -0.00, 0.14; NNH= 14) favoring treatment with nivolumab. This difference is not considered clinically relevant according to the PASKWIL criteria.

Checkmate-067 reported the effect of **nivolumab plus ipilimumab** versus **nivolumab** versus **ipilimumab** on AEs without using sub analyses. Treatment with nivolumab plus ipilimumab resulted in a higher percentage of treatment related AEs grade ≥3 compared to treatment with nivolumab or ipilimumab only. The risk difference between nivolumab plus ipilimumab and nivolumab is 0.36 (95%CI 0.29, 0.43; NNH= 2.8) favoring treatment with nivolumab. This difference is considered clinically relevant. The risk difference between nivolumab plus ipilimumab and ipilimumab is 0.32 (95% CI 0.25, 0.39; NNH= 3.1) favoring treatment with ipilimumab. This difference is considered clinically relevant. The risk difference between nivolumab and ipilimumab is 0.04 (95% CI -0.03, 0.11; NNH= 25) favoring treatment with nivolumab. This difference is not considered clinically relevant according to the PASKWIL criteria.

CA184-024 reported the effect of **ipilimumab plus dacarbazine** versus **dacarbazine** plus placebo on AEs. Treatment with ipilimumab plus dacarbazine resulted in a higher percentage of treatment related AEs grade ≥3 compared to treatment with dacarbazine only. The risk difference between ipilimumab plus dacarbazine and dacarbazine is 0.34 (95% CI 0.27, 0.40; NNH= 2.9) favoring treatment with dacarbazine. This difference is considered clinically relevant according to the PASKWIL criteria.

KEYNOTE-006 reported the effect of **pembrolizumab every 2 weeks** or **pembrolizumab every 3 weeks** compared to **ipilimumab every 3 weeks** on AEs. Treatment with pembrolizumab (pooled groups) resulted in a lower percentage of treatment related AEs grade ≥3 compared to treatment with ipilimumab. The risk difference between pembrolizumab (pooled groups) and ipilimumab is -0.01 (95% CI -0.06, 0.05; NNH=100) favoring treatment with pembrolizumab. This difference is not considered clinically relevant according to the PASKWIL criteria.

MASTERKEY-265 reported the effect of a combination of **T-VEC plus pembrolizumab** versus placebo plus **pembrolizumab** on AEs. Treatment with T-VEC-pembrolizumab resulted in a higher percentage of treatment related AEs grade ≥3 compared to treatment with placebo-pembrolizumab. The risk difference between T-VEC plus pembrolizumab and placebo-pembrolizumab is 0.05 (95% CI -0.01, 0.10; NNH=20) favoring treatment with placebo plus pembrolizumab. This difference is not considered clinically relevant according to the PASKWIL criteria.

OPTiM reported the effect of **T-VEC** versus **GM-CSF** on AEs. Treatment with T-VEC resulted in a higher percentage of treatment related AEs grade ≥3 compared to treatment with GM-CSF. The risk difference between T-VEC and GM-CSF is 0.07 (95% CI 0.02, 0.12; NNH=14) favoring treatment with GM-CSF. This difference is not considered clinically relevant according to the PASKWIL criteria.

CoBRIM reported the effect of **cobimetinib combined with vemurafenib** versus **vemurafenib and placebo** on AEs. Treatment with cobimetinib combined with vemurafenib resulted in a higher percentage of treatment related AEs grade ≥3 compared to treatment with vemurafenib and placebo. The risk difference between the cobimetinib combined with vemurafenib group (78%) and the vemurafenib and placebo group (63%) was 15%. This difference was not considered clinically relevant according to the PASKWIL criteria.

COMBI-v reported the effect of **dabrafenib and trametinib** versus **vemurafenib** on AEs. Treatment with dabrafenib and trametinib resulted in less AEs than treatment with vemurafenib. The risk difference between the dabrafenib and trametinib group (48%) and the vemurafenib group (57%) was 9%. This difference was not considered clinically relevant according to the PASKWIL criteria.

COLUMBUS reported the effect of **encorafenib and binimetinib** versus **encorafenib** versus **vemurafenib** on AEs. There was no risk difference in the percentage of AEs between encorafenib and binimetinib (68%) and encorafenib (68%). The risk difference in AEs between encorafenib and binimetinib (68%) and vemurafenib (66%) was 2%. This difference was not considered clinically relevant according to the PASKWIL criteria. The risk difference between encorafenib (68%) and vemurafenib (66%) was also 2%. This difference was not considered clinically relevant according to the PASKWIL criteria.

COMBI-d reported the effect of **dabrafenib and trametinib** versus **dabrafenib** on AEs. The risk difference in percentage of AEs between the dabrafenib and trametinib group (48%) and dabrafenib group (50%) was 2%. This difference was not considered clinically relevant according to the PASKWIL criteria.

DREAMseq reported the severe adverse events grade ≥3 after treatment with **nivolumab and ipilimumab** versus dabrafenib and trametinib. The risk difference is 0.06 (95%CI -0.06, 0.18, NNH=17), favoring treatment with nivolumab and ipilimumab. This difference is not considered clinically relevant according to the PASKWIL criteria.

IMspire150 reported the severe adverse events grade ≥3 after treatment with **atezoluzumab and vemurafenib and cobimetinib versus vemurafenib and cobimetinib.**

The risk difference is -0.09 (95%CI -0.17, -0.01, NNH=11), favoring treatment with atezoluzumab and vemurafenib and cobimetinib. This difference is not considered clinically relevant according to the PASKWIL criteria.

Study or Subgroup	Systemic therapy Events	Total	Control Events	Total	Weight	Risk Difference M-H, Random, 95% CI
RELATIVITY-047	143	355	120	359		0.07 [-0.00, 0.14]
Checkmate-067	184	313	86	311		0.31 [0.24, 0.39]
CA184-024	139	247	69	251		0.29 [0.20, 0.37]
KEYNOTE-006	96	555	50	256		-0.02 [-0.08, 0.04]
MASTERKEY-265	25	346	27	346		-0.01 [-0.05, 0.03]
OPTiM	33	292	6	127		0.07 [0.01, 0.12]
coBRIM	194	248	155	245		0.15 [0.07, 0.23]
COLUMBUS	131	192	122	186		0.03 [-0.07, 0.12]
COMBI-v	167	350	198	349		-0.09 [-0.16, -0.02]
COMBI-d	100	209	106	211		-0.02 [-0.12, 0.07]
DREAMseq	79	133	70	132		0.06 [-0.06, 0.18]
IMspire150	184	280	173	231		-0.09 [-0.17, -0.01]

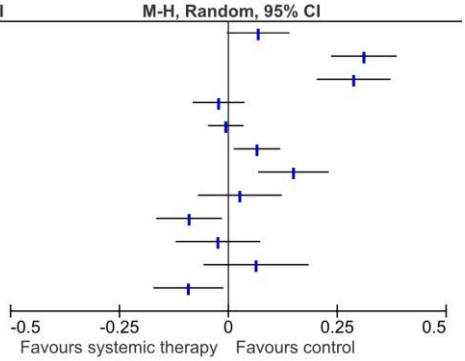

Figure 3. Forest plot of treatment related adverse events grade ≥3 after first line systemic therapy versus placebo, other systemic therapy, or best supportive care in patients with a BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma.

[a] For Checkmate-067, the risk difference for nivolumab versus ipilimumab is shown.
[b] For KEYNOTE-006, the the risk difference for combined pembrolizumab versus ipilimumab is shown.
[c] For COLOMBUS, the the risk difference for encorafenib and binimetinib versus vemurafenib is shown.

Quality of life (QoL) - Important outcome

One study reported the effect of first line systemic therapy on QoL.

RELATIVITY-047 reported the effect of **relatlimab and nivolumab** versus **nivolumab** on QoL. In this study, the changes from baseline in FACT-M total score and EQ-5D-3L health utility index were analysed without using subgroup analyses based on BRAF mutation status. The authors considered minimal clinically important differences of 5 in the FACT-M total score and 0.08 in the EQ-5D-3L health utility index to be clinically meaningful. The least-squares mean changes from baseline over time in the FACT-M total score ranged between 1 and -4 and did not exceed the minimal clinically important differences. The least-squares mean changes from baseline over time in the EQ-5D-3L utility index ranged between -0.025 and -0.08 and did not exceed the minimal clinically important differences.

<u>Level of evidence of the literature</u>

There are four levels of evidence: high, moderate, low, and very low. RCTs start at a high level of evidence.

Relatlimab plus nivolumab versus nivolumab
The level of evidence regarding the outcome measure **progression free survival** was downgraded by two levels because of study limitations (risk of bias) and because we

could not asses clinical relevance according to the PASKWIL criteria (imprecision). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by two levels because of study limitations (risk of bias) and the lack of a subgroup analysis (indirectness). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **quality of life** was downgraded by two levels because of study limitations (risk of bias) and the lack of a subgroup analyses (indirectness). Therefore, the level of evidence was graded as low.

Nivolumab plus ipilimumab versus nivolumab versus ipilimumab

Nivolumab plus ipilimumab versus nivolumab

The level of evidence regarding the outcome measure **overall survival** was downgraded by two levels because of study limitations (risk of bias) and because the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by two levels because of study limitations (risk of bias), and because the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by two levels because of study limitations (risk of bias), and the lack of a subgroup analysis (indirectness). Therefore, the level of evidence was graded as low.

Nivolumab plus ipilimumab versus ipilimumab

The level of evidence regarding the outcome measure **overall survival** was graded as high.

The level of evidence regarding the outcome measure **progression free survival** the level of evidence was graded as high.

The level of evidence regarding the outcome measure **adverse events** was downgraded by one level due to the lack of a subgroup analysis (indirectness). Therefore, the level of evidence was graded as moderate

Nivolumab versus ipilimumab

The level of evidence regarding the outcome measure **overall survival** was downgraded by one level because the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision). Therefore, the level of evidence was graded as moderate.

The level of evidence regarding the outcome measure **progression free survival** was graded as high.

The level of evidence regarding the outcome measure **adverse events** was downgraded by two levels because the optimal information size is not met (imprecision), and the lack of a subgroup analysis (indirectness). Therefore, the level of evidence was graded as low.

Ipilimumab plus dacarbazine versus dacarbazine

The level of evidence regarding the outcome measure **overall survival** was downgraded by four levels because of study limitations (risk of bias -2), the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision), and the lack of a subgroup analysis (indirectness). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by four levels because of study limitations (risk of bias -2), the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision), and the lack of a subgroup analysis (indirectness). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by three levels because of study limitations (risk of bias -2) and the lack of a subgroup analysis (indirectness). Therefore, the level of evidence was graded as very low.

Pembrolizumab every 2 weeks or every 3 weeks compared to ipilimumab

The level of evidence regarding the outcome measure **overall survival** was downgraded by four levels because of study limitations (risk of bias -2); the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision), and the lack of a subgroup analysis (indirectness). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by three levels because of study limitations (risk of bias -2), and the lack of a subgroup analysis (indirectness). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by four levels because of study limitations (risk of bias -2), because the optimal information size is not met (imprecision), and the lack of a subgroup analysis (indirectness). Therefore, the level of evidence was graded as very low.

T-VEC plus pembrolizumab versus placebo plus pembrolizumab

The level of evidence regarding the outcome measure **overall survival** was downgraded by four levels because of study limitations (risk of bias -2), the optimal information size is not met (imprecision), and the lack of a subgroup analysis (indirectness). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by four levels because of study limitations (risk of bias -2), the optimal information size is not met (imprecision), and the lack of a subgroup analysis (indirectness). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by four levels because of study limitations (risk of bias -2), the optimal information size is not met (imprecision), and the lack of a subgroup analysis (indirectness). Therefore, the level of evidence was graded as very low.

T-VEC versus GM-CSF

The level of evidence regarding the outcome measure **overall survival** was downgraded by four levels because of study limitations (risk of bias -2), the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision), and the lack of a subgroup analysis (indirectness). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by four levels because of study limitations (risk of bias -2), was downgraded by one level because the optimal information size is not met (imprecision), and the lack of a subgroup analysis (indirectness). Therefore, the level of evidence was graded as very low.

Cobimetinib plus vemurafenib versus vemurafenib and placebo

The level of evidence regarding the outcome measure **overall survival** was downgraded by one level because the confidence interval encloses the threshold for a clinically relevant effect (imprecision -1). Therefore, the level of evidence was graded as moderate.

The level of evidence regarding the outcome measure **progression free survival** was graded as high.

The level of evidence regarding the outcome measure **adverse events** was graded as high.

Dabrafenib plus trametinib versus vemurafenib

The level of evidence regarding the outcome measure **overall survival** was downgraded by one level because of study limitations (risk of bias -1). Therefore, the level of evidence was graded as moderate.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by one level because of study limitations (risk of bias -1). Therefore, the level of evidence was graded as moderate.

The level of evidence regarding the outcome measure **adverse events** was downgraded by two level because of study limitations (risk of bias -2). Therefore, the level of evidence was graded as low.

Encorafenib plus binimetinib versus encorafenib versus vemurafenib

Encorafenib and binimetinib versus encorafenib

The level of evidence regarding the outcome measure **overall survival** was downgraded by two levels because of study limitations (risk of bias -1) and because the confidence interval encloses the threshold for a clinically relevant effect (imprecision -1). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by two level because of study limitations (risk of bias -1), and no clinically relevant effect could be established (imprecision -1). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by two level because of study limitations (risk of bias -2). Therefore, the level of evidence was graded as low.

Encorafenib plus binimetinib versus vemurafenib

The level of evidence regarding the outcome measure **overall survival** was downgraded by two levels because of study limitations (risk of bias -1) and because the confidence interval encloses the threshold for a clinically relevant effect (imprecision -1). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by one level because of study limitations (risk of bias -1). Therefore, the level of evidence was graded as moderate.

The level of evidence regarding the outcome measure **adverse events** was downgraded by two level because of study limitations (risk of bias -2). Therefore, the level of evidence was graded as low.

Encorafenib plus vemurafenib

The level of evidence regarding the outcome measure **overall survival** was downgraded by two levels because of study limitations (risk of bias -1) and because the confidence interval encloses the threshold for a clinically relevant effect (imprecision -1). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by two level because of study limitations (risk of bias -1), and no clinically relevant effect could be established (imprecision -1). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by two level because of study limitations (risk of bias -2). Therefore, the level of evidence was graded as low.

Dabrafenib plus trametinib versus dabrafenib

The level of evidence regarding the outcome measure **overall survival** was downgraded by one level because of study limitations (risk of bias -1) and because the confidence interval encloses the threshold for a clinically relevant effect (imprecision -1). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by one level because of study limitations (risk of bias -1). Therefore, the level of evidence was graded as moderate.

The level of evidence regarding the outcome measure **adverse events** was downgraded by two level because of study limitations (risk of bias -2). Therefore, the level of evidence was graded as low.

Nivolumab plus ipilimumab versus dabrafenib plus trametinib.
The level of evidence regarding the outcome measure **overall survival** was downgraded by two levels because we could not asses clinical relevance according to the PASKWIL criteria (imprecision -1). Therefore, the level of evidence was graded as moderate.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by two levels because we could not asses clinical relevance according to the PASKWIL criteria (imprecision -1). Therefore, the level of evidence was graded as moderate.

The level of evidence regarding the outcome measure **adverse events** was downgraded by two levels because of study limitations (risk of bias -2). Therefore, the level of evidence was graded as low.

Atezolizumab plus vemurafenib plus cobimetinib versus vemurafenib plus cobimetinib.
The level of evidence regarding the outcome measure **overall survival** was downgraded by one level because the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision -1). Therefore, the level of evidence was graded as moderate.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by one level because the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision -1). Therefore, the level of evidence was graded as moderate.

The level of evidence regarding the outcome measure **adverse events** was downgraded by two levels because of study limitations (risk of bias -2). Therefore, the level of evidence was graded as low.

Conclusions

Relatlimab plus nivolumab versus nivolumab
Progression free survival

Low GRADE	Relatlimab plus nivolumab may result in a small increase in progression free survival compared to nivolumab in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Tawbi, 2022*

Adverse events

Low GRADE	Relatlimab plus nivolumab may result in little to no difference in adverse events compared to nivolumab in patients with BRAF-V600E/K mutated unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Tawbi, 2022*

5 *Quality of Life*

Low GRADE	Relatlimab plus nivolumab may result in little to no difference in quality of life compared to nivolumab in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Tawbi, 2022*

Nivolumab plus ipilimumab versus nivolumab versus ipilimumab

Overall survival

Low GRADE	Nivolumab plus ipilimumab may result in little to no difference in overall survival compared to treatment with nivolumab only in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Larkin, 2015; Wolchock, 2017; Hodi, 2018; Larkin, 2019; Wolchok, 2022*
High GRADE	Nivolumab plus ipilimumab results in a large increase in overall survival compared to treatment with ipilimumab only in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Larkin, 2015; Wolchock, 2017; Hodi, 2018; Larkin, 2019; Wolchok, 2022*

Moderate GRADE	Nivolumab likely results in a large increase in overall survival compared to treatment with ipilimumab only in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Larkin, 2015; Wolchock, 2017; Hodi, 2018; Larkin, 2019; Wolchok, 2022*

Progression free survival

Low GRADE	Nivolumab plus ipilimumab may result in little to no difference in progression free survival compared to treatment with nivolumab only in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Larkin, 2015; Wolchock, 2017; Hodi, 2018; Larkin, 2019; Wolchok, 2022*
High GRADE	Nivolumab plus ipilimumab results in a large increase in progression free survival compared to treatment with ipilimumab only in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Larkin, 2015; Wolchock, 2017; Hodi, 2018; Larkin, 2019; Wolchok, 2022*
High GRADE	Nivolumab versus ipilimumab result in an increase in progression free survival compared to treatment with ipilimumab only in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Larkin, 2015; Wolchock, 2017; Hodi, 2018; Larkin, 2019; Wolchok, 2022*

5 *Adverse events*

Low GRADE	Nivolumab plus ipilimumab may result in an increase of adverse events compared to treatment with nivolumab only in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Larkin, 2015; Wolchock, 2017; Hodi, 2018; Larkin, 2019; Wolchok, 2022*

Moderate GRADE	Nivolumab plus ipilimumab likely result in an increase of adverse events compared to treatment with ipilimumab only in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Larkin, 2015; Wolchock, 2017; Hodi, 2018; Larkin, 2019; Wolchok, 2022*
Low GRADE	Nivolumab may result in little to no difference in adverse events compared to treatment with ipilimumab in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Larkin, 2015; Wolchock, 2017; Hodi, 2018; Larkin, 2019; Wolchok, 2022*

Ipilimumab plus dacarbazine versus dacarbazine

Overall survival

Very low GRADE	The evidence is very uncertain about the effect of ipilimumab plus dacarbazine on overall survival compared to treatment with dacarbazine only in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Maio, 2015; Robert, 2011*

Progression free survival

Very low GRADE	The evidence is very uncertain about the effect of ipilimumab plus dacarbazine on progression free survival compared to treatment with dacarbazine only in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Maio, 2015; Robert, 2011*

Adverse events

Very low GRADE	The evidence is very uncertain about the effect of ipilimumab plus dacarbazine on the incidence of adverse events compared to treatment with dacarbazine only in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Maio, 2015; Robert, 2011*

Pembrolizumab every 2 weeks or every 3 weeks compared to ipilimumab

Overall survival

Very low GRADE	The evidence is very uncertain about the effect of pembrolizumab every 2 weeks or every 3 weeks on overall survival compared to treatment with ipilimumab in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Robert, 2019; Carlino, 2018; Schachter, 2017; Robert, 2015*

Progression free survival

Very low GRADE	The evidence is very uncertain about the effect of pembrolizumab every 2 weeks or every 3 weeks on progression free survival compared to treatment with ipilimumab in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Robert, 2019; Carlino, 2018; Schachter, 2017; Robert, 2015*

Adverse events

Very low GRADE	The evidence is very uncertain about the effect of pembrolizumab every 2 weeks or every 3 weeks on adverse events compared to treatment with ipilimumab in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Robert, 2019; Carlino, 2018; Schachter, 2017; Robert, 2015*

T-VEC plus pembrolizumab versus placebo plus pembrolizumab

Overall survival

Very low GRADE	The evidence is very uncertain about the effect of T-VEC plus pembrolizumab on overall survival compared to treatment with placebo plus pembrolizumab in patients with BRAF-V600E/K mutation with unresectable or metatsatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Chesney, 2023*

Progression free survival

Very low GRADE	The evidence is very uncertain about the effect of T-VEC plus pembrolizumab on progression free survival compared to treatment with placebo plus pembrolizumab in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Chesney, 2023*

Adverse events

Very low GRADE	The evidence is very uncertain about the effect of T-VEC plus pembrolizumab on adverse events compared to treatment with placebo plus pembrolizumab in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Chesney, 2023*

T-VEC versus GM-CSF

Overall survival

Very low GRADE	The evidence is very uncertain about the effect of T-VEC on overall survival compared to treatment with GM-CSF in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Andtbacka, 2019; Andtbacka, 2015*

Adverse events

Very low GRADE	The evidence is very uncertain about the effect of T-VEC on adverse eventscompared to treatment with GM-CSF in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Andtbacka, 2019; Andtbacka, 2015*

Cobimetinib plus vemurafenib versus vemurafenib and placebo

Overall survival

Moderate GRADE	Cobimetinib plus vemurafenib likely results in an increase in overall survival when compared with vemurafenib and placebo in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Larkin (2014), Ascierto (2016), Ascierto (2021)*

Progression free survival

High GRADE	Combimetinib plus vemurafenib results in an increase in progression free survival when compared with vemurafenib and placebo in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Larkin (2014), Ascierto (2016), Ascierto (2021)*

Adverse events

High GRADE	Combimetinib plus vemurafenib results in little to no difference in adverse events when compared with vemurafenib and placebo in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Larkin (2014), Ascierto (2016), Ascierto (2021)*

Dabrafenib plus trametinib versus vemurafenib

Overall survival

Moderate GRADE	Dabrafenib plus trametinib likely result in an increase in overall survival when compared with vemurafenib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Robert (2015), Robert (2016)*

Progression free survival

Moderate GRADE	Dabrafenib plus trametinib likely result in an increase in progression free survival when compared with vemurafenib and placebo in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Robert (2015), Robert (2016)*

Adverse events

Moderate GRADE	Dabrafenib plus trametinib likely results in little to no difference in adverse events when compared with vemurafenib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Robert (2015), Robert (2016)*

Encorafenib plus binimetinib versus encorafenib versus vemurafenib

Encorafenib and binimetinib versus encorafenib

Overall survival

Moderate GRADE	Encorafenib plus binimetinib likely result in little to no difference in overall survival when compared with encorafenib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Dummer (2018), Dummer (2018-2), Ascierto (2020)*

Progression free survival

Low GRADE	Encorafenib plus binimetinib may result in little to no difference in progression free survival when compared with encorafenib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy.

	Source: Dummer (2018), Dummer (2018-2), Ascierto (2020)

Adverse events

Low GRADE	Encorafenib plus binimetinib may result in little to no difference in adverse events when compared with encorafenib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Dummer (2018), Dummer (2018-2), Ascierto (2020)*

Encorafenib plus binimetinib versus vemurafenib
Overall survival

Moderate GRADE	Encorafenib plus binimetinib likely result in an increase in overall survival when compared with vemurafenib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Dummer (2018), Dummer (2018-2), Ascierto (2020)*

Progression free survival

Moderate GRADE	Encorafenib plus binimetinib likely result in an increase in progression free survival when compared with vemurafenib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Dummer (2018), Dummer (2018-2), Ascierto (2020)*

Adverse events

Low GRADE	Encorafenib plus binimetinib may result in little to no difference in adverse events when compared with vemurafenib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Dummer (2018), Dummer (2018-2), Ascierto (2020)*

Encorafenib versus vemurafenib
Overall survival

Moderate GRADE	Encorafenib likely results in little to no difference in overall survival when compared with vemurafenib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Dummer (2018), Dummer (2018-2), Ascierto (2020)*

Progression free survival

Low GRADE	Encorafenib may result in little to no difference in overall survival when compared with vemurafenib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Dummer (2018), Dummer (2018-2), Ascierto (2020)*

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Adverse events

Low GRADE	Encorafenib may result in little to no difference in adverse events when compared with vemurafenib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Dummer (2018), Dummer (2018-2), Ascierto (2020)*

Dabrafenib plus trametinib versus dabrafenib

10 *Overall survival*

Low GRADE	Dabrafenib plus trametinib may result in little to no difference in overall survival when compared with dabrafenib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Long (2014), Long (2015), Long (2017)*

Progression free survival

Moderate GRADE	Dabrafenib plus trametinib likely result in little to no difference in progression free survival when compared with dabrafenib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Long (2014), Long (2015), Long (2017)*

Adverse events

Low GRADE	Dabrafenib plus trametinib may result in little to no difference in adverse events when compared with dabrafenib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Long (2014), Long (2015), Long (2017)*

Dabrafenib and trametinib versus nivolumab and ipilimumab.

Overall survival

Moderate GRADE	Nivolumab plus ipilimumab likely result in a large increase in overall survival compared to dabrafenib and trametinib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Atkins (2022)*

Progression free survival

Moderate GRADE	Nivolumab plus ipilimumab likely result in a large increase in progression free survival compared to dabrafenib and trametinib TKI in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Atkins (2022)*

Adverse events

Low GRADE	Nivolumab and ipilimumab may result in little to no difference in adverse events compared to dabrafenib and trametinib TKI in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Atkins (2022)*

Atezolozumab plus vemurafenib plus cobimetinib versus vemurafenib plus cobimetinib.

Overall survival

Moderate GRADE	Atezolizumab plus vemurafenib plus cobimetinib likely result in little to no difference in overall survival compared to vemurafenib and cobimetinib TKI in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Ascierto (2023)*

5 *Progression free survival*

Moderate GRADE	Atezolizumab plus vemurafenib plus cobimetinib likely result in little to no difference in progression free survival compared to vemurafenib and cobimetinib TKI in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Ascierto (2023)*

Adverse events

Low GRADE	Atezolizumab plus vemurafenib plus cobimetinib may result in little to no difference in adverse events compared to vemurafenib and cobimetinib TKI in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Ascierto (2023)*

Overwegingen – van bewijs naar aanbeveling

RELATIVITY-047 rapporteerde het effect van **relatlimab plus nivolumab** versus **nivolumab** op progression free survival, adverse events en kwaliteit van leven bij patiënten met unresectable of gemetastaseerd stadium III/IV melanoom (Tawbi, 2022). Het absolute verschil in mediane progression free survival was 5.5 maanden met een HR van 0.75 (95% CI 0.62-0.92). De klinische relevantie van dit verschil kan niet worden beoordeeld op basis van de PASKWIL criteria (mediane overall survival in de controle groep < 12 maanden). De bewijskracht van deze studie is laag, dit heeft te maken met het risico op bias (door de rol van de sponsor in deze studie) en door imprecisie.

Relatlimab plus nivolumab resulteert waarschijnlijk niet of nauwelijks in een vermindering of toename van adverse events of kwaliteit van leven vergeleken met nivolumab.

CHECKMATE-067 rapporteerde het effect **van nivolumab plus ipilimumab versus nivolumab versus ipilimumab** op overall survival bij patiënten met niet-receerbaar of gemetastaseerd stadium III/IV melanoom (Larkin 2015, Wolchock 2017, Hodi 2018, Larkin 2019, Wolchok 2022). Er werd daarbij een klinisch relevant voordeel gevonden voor het gebruik van nivolumab plus ipilimumab. Het absolute verschil in mediane overall survival tussen behandeling met nivolumab plus ipilimumab versus behandeling met alleen ipilimumab was 52.2 maanden met een hazard ratio van 0.52 (95% CI 0.43-0.63). De bewijskracht hiervan is hoog. Het absolute verschil in mediane overall survival tussen behandeling met nivolumab plus ipilimumab versus behandeling met alleen nivolumab was 35.2 maanden met een hazard ratio van 0.84 (95% CI 0.67 to 1.04). De bewijskracht hiervan is redelijk tot laag, dit heeft te maken met imprecisie, omdat de confidence interval de grens voor klinische besluitvorming omvat en het risico op bias (doordat de studie niet gepowered was voor de vergelijking van deze middelen).

De studie rapporteerde ook het effect op progression free survival en adverse events. Een langere mediane progression free survival werd gevonden voor patiënten die behandeld warden met nivolumab plus ipilimumab, met een verschil van 8.6 maanden (HR 0.42; CI 0.35-0.51) met patiënten die behandeld warden met alleen ipilimumab en een verschil van 4.6 maanden (HR 0.79; CI 0.65 to 0.97) met patiënten die behandeld warden met alleen nivolumab. Behandeling met nivolumab plus ipilimumab resulteerde in een hoger percentage behandelingsgerelateerde adverse events grade ≥3 in vergelijking met behandeling met alleen nivolumab of alleen ipilimumab.

CA184-024 rapporteerde het effect van **ipilimumab plus dacarbazine versus dacarbazine** op overall survival bij patiënten met unresectable of gemetastaseerd stadium III/IV melanoom (Maio, 2015; Robert, 2011). Er werd daarbij geen klinisch relevant voordeel gevonden voor het gebruik van ipilimumab plus dacarbazine. Het absolute verschil in mediane overall survival tussen behandeling met ipilimumab plus dacarbazine versus behandeling met alleen dacarbazine was 2.12 maanden met een hazard ratio van 0.69 (95% CI 0.57 to 0.84). De bewijskracht van deze studie is zeer laag. Dit heeft te maken met het risico op bias (onduidelijke behandelings allocatie en doordat meer patiënten in de interventie groep stopten vanwege behandelingsgerelateerde adverse events) en door imprecisie omdat de confidence interval de grens voor klinische besluitvorming omvat.

De studie rapporteerde ook het effect op progression free survival en adverse events. Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor

de uitkomst progression free survival. Het ontstaan van adverse events. Behandeling ipilimumab plus dacarbazine resulteerde in een hoger percentage behandelingsgerelateerde adverse events grade ≥3 in vergelijking met behandeling met alleen dacarbazine.

KEYNOTE-006 rapporteerde het effect van **pembrolizumab (iedere 2 of 3 weken) in vergelijking met ipilimumab (iedere 3 weken**) op overall survival bij patiënten met unresectable of gemetastaseerd stadium III/IV melanoom (Robert, 2019; Carlino, 2018; Schachter, 2017; Robert, 2015). Er werd daarbij geen klinisch relevant voordeel gevonden voor het gebruik van pembrolizumab volgens de PASWKIL-criteria. Het absolute verschil in mediane overall survival tussen behandeling met pembrolizumab versus behandeling met ipilimumab was 16.8 maanden met een hazard ratio van 0.73 (95% CI 0.61–0.88). De bewijskracht van deze studie is zeer laag. Dit heeft te maken met het risico op bias (open-label studie design; meer patiënten stopten in de controle groep; de rol van de sponsor) en door imprecisie, omdat de confidence interval de grens voor klinische besluitvorming omvat.

De studie rapporteerde ook het effect op progression free survival en adverse events. Voor de uitkomst progression free survival werd een klinisch relevant voordeel gevonden voor behandeling met pembrolizumab. Het absolute verschil in mediane progressievrije overleving was 5.0 maanden (HR 0.57; 95% CI 0.48–0.67). Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor de uitkomst adverse events.

MASTERKEY-265 rapporteerde het effect van **T-VEC plus pembrolizumab** in vergelijking met **placebo plus pembrolizumab** op overall survival bij patiënten met unresectable of gemetastaseerd stadium III/IV melanoom (Chesney, 2023). Er werd daarbij geen klinisch relevant voordeel gevonden voor het gebruik van T-VEC plus pembrolizumab (HR 0.96; 95% CI 0.76 to 1.22). De bewijskracht van deze studie is zeer laag. Dit heeft te maken met het risico op bias (meer patiënten stopten in de controle groep; studie werd vroegtijdig gestopt) en door imprecisie.

De studie rapporteerde ook het effect op progression free survival en adverse events. Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor de uitkomsten progression free survival en adverse events.

OPTiM rapporteerde het effect van **T-VEC** in vergelijking met **GM-CSF** op overall survival bij patiënten met niet-receerbaar of gemetastaseerd stadium III/IV melanoom (Andtbacka, 2019; Andtbacka, 2015). Er werd daarbij geen klinisch relevant voordeel gevonden voor het gebruik van T-VEC. Het absolute verschil in mediane overall survival tussen behandeling met T-VEC versus behandeling met GM-CSF was 4.4 maanden met een hazard ratio 0.79 (95% CI 0.62–1.00). De bewijskracht van deze studie is zeer laag. Dit heeft te maken met het risico op bias (open-label studie design; meer patiënten stopten in de interventie groep; de rol van de sponsor) en door imprecisie, omdat het betrouwbaarheidsinterval de grens voor klinische besluitvorming omvat.

De studie rapporteerde ook het effect op adverse events. Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor de uitkomst adverse events.

CoBRIM rapporteerde het effect van **cobimetinib plus vemurafenib versus vemurafenib** en placebo op de mediane OS. Behandeling met cobimetinib plus vemurafenib resulteerde in een langere mediane OS dan behandeling met vemurafenib en placebo. Het absolute verschil tussen de cobimetinib plus vemurafenib groep (22,5 maanden) en de vemurafenib en placebo groep (17,4 maanden) was 5,1 maanden met een HR van 0,70 (95% BI: 0,55 – 0,89). Dit verschil werd volgens de PASKWIL-criteria niet als klinisch relevant beschouwd. De bewijskracht hiervan is redelijk, dit heeft te maken met de imprecisie, omdat de confidence interval de grens voor klinische besluitvorming omvat.
De studie rapporteerde ook het effect op progression free survival en adverse events. Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor de uitkomsten progression free survival en adverse events.

COMBI-v rapporteerde niet het effect van dabrafenib plus trametinib versus vemurafenib op de mediane OS. Echter, het absolute verschil in mediane 3-jaarsoverleving tussen dabrafenib plus trametinib (45%) en vemurafenib (32%) was 13%, met een hogere 3-jaarsoverleving in de dabrafenib en trametinib groep. Dit verschil werd volgens de PASKWIL-criteria als klinisch relevant beschouwd. De bewijskracht hiervan is redelijk, dit heeft te maken met het risico op bias.
De studie rapporteerde ook het effect op progression free survival en adverse events. Voor de uitkomst progression free survival werd een klinisch relevant voordeel gevonden voor behandeling met cobimetinib plus vemurafenib. Het absolute verschil in mediane progressievrije overleving was 5.4 maanden (HR 0.51; 95% CI 0.39–0.67). Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor de uitkomst adverse events.

COLUMBUS rapporteerde het effect van encorafenib plus binimetinib versus encorafenib versus vemurafenib op de mediane OS. Behandeling met encorafenib plus binimetinib resulteerde in de langste mediane OS. Het absolute verschil tussen encorafenib plus binimetinib (33,6 maanden) en encorafenib (23,5 maanden) was 10,1 maanden met een HR van 0,81 (95% BI: 0,61 tot 1,06). Dit verschil werd volgens de PASKWIL-criteria niet als klinisch relevant beschouwd. Het absolute verschil tussen encorafenib plus binimetinib (33,6 maanden) en vemurafenib (16,9 maanden) was 16,7 maanden met een HR van 0,61 (95% BI: 0,47 tot 0,79). Dit verschil werd volgens de PASKWIL-criteria als klinisch relevant beschouwd. Het absolute verschil tussen encorafenib (23,5 maanden) plus vemurafenib (16,9 maanden) was 6,6 maanden met een HR van 0,76 (95% BI: 0,58 tot 0,98). Dit verschil werd volgens de PASKWIL-criteria niet als klinisch relevant beschouwd. De bewijskracht hiervan is redelijk, dit heeft te maken met de imprecisie, omdat de confidence interval de grens voor klinische besluitvorming omvat.
De studie rapporteerde ook het effect op progression free survival en adverse events. Voor de uitkomst progression free survival werd een klinisch relevant voordeel gevonden voor behandeling met encorafenib plus binimetinib vergeleken met vemurafenib. Het absolute verschil in mediane progressievrije overleving was 7.6 maanden (HR en CI niet gegeven). Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor de uitkomst adverse events.

COMBI-d rapporteerde het effect van dabrafenib plus trametinib versus dabrafenib op de mediane OS. Behandeling met dabrafenib plus trametinib resulteerde in een langere mediane OS dan behandeling met alleen dabrafenib. Het absolute verschil tussen de dabrafenib plus trametinib groep (25,1 maanden) en de dabrafenib groep (18,7 maanden) was 6,4 maanden met een HR van 0,71 (95% BI: 0,55 tot 0,92). Dit verschil werd volgens de PASKWIL-criteria niet als klinisch relevant beschouwd. De bewijskracht hiervan is laag, dit heeft te maken met risk of bias en imprecisie, omdat de confidence interval de grens voor klinische besluitvorming omvat.

De studie rapporteerde ook het effect op progression free survival en adverse events. Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor de uitkomsten progression free survival en adverse events.

DREAMseq rapporteerde het effect van **nivolumab plus ipilimumab** versus **dabrafenib plus trametinib** op overall survival bij patiënten met irresectabele of gemetastaseerd stadium III/IV melanoom (Atkins 2022). Een langere survival werd gevonden bij het gebruik van nivolumab plus ipilimumab, maar de klinische relevantie van dit verschil kan niet worden beoordeeld op basis omdat er geen mediane survival is gerapporteerd. Hierdoor is de bewijskracht redelijk.

De studie rapporteerde ook het effect op progression free survival en adverse events. Een langere mediane progression free survival werd gevonden voor patiënten in de groep met nivolumab plus ipilimumab , met een absoluut verschil van 3.3 maanden met patiënten in de nivolumab plus ipilimumab groep. De klinische relevantie van dit verschil kan niet worden beoordeeld op basis van de PASKWIL criteria (geen HR gerapporteerd). Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor het ontstaan van adverse events. Behandeling met nivolumab plus ipilimumab resulteerde in een hoger percentage behandeling gerelateerde adverse events grade >3 in vergelijking met behandeling met dabrafenib plus trametinib.

IMspire150 rapporteerde het effect van **atezoluzumab plus vemurafenib plus cobimetinib** versus **vemurafenib plus cobimetinib** op overall survival bij patiënten met irresectabele of gemetastaseerd stadium III/IV melanoom (Ascierto 2023). Het absolute verschil in mediane overall survival tussen behandeling met atezoluzumab en vemurafenib en cobimetinib versus behandeling met vemurafenib en cobimetinib was 13.2 maanden met een hazard ratio van 0.84 (95% CI 0.66–1.06), maar dit verschil was niet klinisch relevant. De bewijskracht hiervan is redelijk, dit heeft te maken met imprecisie, omdat de confidence interval de grens voor klinische besluitvorming omvat.

De studie rapporteerde ook het effect op progression free survival en adverse events. Een langere mediane progression free survival werd gevonden voor patiënten die behandeld warden met behandeling met atezoluzumab en vemurafenib en cobimetinib versus behandeling met vemurafenib en cobimetinib, met een absoluut verschil van 4.5 maanden (HR 0.79 (95%CI 0.64-0.97), dit was niet klinisch relevant.

Behandeling met atezoluzumab en vemurafenib en cobimetinib resulteerde in een hoger percentage behandeling gerelateerde adverse events grade ≥3 in vergelijking met behandeling met alleen vemurafenib en cobimetinib, dit verschil was niet klinisch relevant.

Kwaliteit van bewijs

Relatlimab plus nivolumab versus nivolumab

De overall kwaliteit van bewijs is laag. Dit betekent dat we onzeker zijn over het gevonden geschatte effect van de belangrijke uitkomstmaten (cruciale uitkomstmaat overall survival werd niet gerapporteerd).

Nivolumab plus ipilimumab versus nivolumab versus ipilimumab

Nivolumab plus ipilimumab versus nivolumab

De overall kwaliteit van bewijs is laag. Dit betekent dat we onzeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Nivolumab plus ipilimumab versus ipilimumab

De overall kwaliteit van bewijs is hoog. Dit betekent dat we zeer zeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Nivolumab versus ipilimumab

De overall kwaliteit van bewijs is redelijk. Dit betekent dat we redelijk zeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Ipilimumab plus dacarbazine versus dacarbazine

De overall kwaliteit van bewijs is laag. Dit betekent dat we onzeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Pembrolizumab every 2 weeks or every 3 weeks versus ipilimumab

De overall kwaliteit van bewijs is zeer laag. Dit betekent dat we zeer onzeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

T-VEC plus pembrolizumab versus placebo plus pembrolizumab

De overall kwaliteit van bewijs is zeer laag. Dit betekent dat we zeer onzeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

T-VEC plus pembrolizumab versus GM-CSF

De overall kwaliteit van bewijs is zeer laag. Dit betekent dat we zeer onzeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Cobimetinib plus vemurafenib versus vemurafenib plus placebo

De overall kwaliteit van bewijs is redelijk. Dit betekent dat we redelijk zeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Dabrafenib plus trametinib versus vemurafenib

De overall kwaliteit van bewijs is redelijk. Dit betekent dat we redelijk zeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Encorafenib plus binimetinib versus encorafenib versus vemurafenib

Encorafenib plus binimetinib versus encorafenib
De overall kwaliteit van bewijs is redelijk. Dit betekent dat we redelijk zeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Encorafenib plus binimetinib versus vemurafenib
De overall kwaliteit van bewijs is laag. Dit betekent dat we onzeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Encorafenib plus vemurafenib
De overall kwaliteit van bewijs is laag. Dit betekent dat we onzeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Dabrafenib plus trametinib versus dabrafenib
De overall kwaliteit van bewijs is laag. Dit betekent dat we onzeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Nivolumab plus ipilimumab versus **dabrafenib plus trametinib**.
De overall kwaliteit van bewijs is redelijk. Dit betekent dat we redelijk zeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Atezoluzumab plus vemurafenib and cobimetinib versus vemurafenib pluscobimetinib.
De overall kwaliteit van bewijs is redelijk. Dit betekent dat we redelijk zeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Overwegingen- van bewijs naar aanbeveling
Ondanks de vooruitgang in de behandeling van irresectabel of gemetastaseerd melanoom, blijven veel vragen onbeantwoord en voor een belangrijke deel van de patiënten blijft de prognose slecht. Inclusie in klinische studies blijft daarom de hoogste prioriteit in alle settings.

<u>Waarden en voorkeuren van patiënten (en eventueel hun naasten/verzorgers)</u>
Bij het kiezen van een behandelstrategie is het van belang om de waarden en voorkeuren van de patiënt centraal te stellen en de beslissing te individualiseren op basis van zowel het gewenste behandeldoel (kortetermijnvoordeel versus langetermijnvoordeel) als klinische kenmerken zoals lactaatdehydrogenase (LDH)-niveau, betrokken organen, performance status, tumorlast, de snelheid van ziekteprogressie en de bijwerkingen van de behandelingen.

<u>Professioneel perspectief</u>
Immuuntherapie (PD-1-blokkade of PD-1-blokkade gecombineerd met ipilimumab) heeft de voorkeur, omdat het na het stoppen langdurige ziektecontrole kan bieden. Bij patiënten met een BRAFV600- gemuteerd melanoom heeft immuuntherapie in deze situatie ook de voorkeur boven BRAF-/MEK-remmers omdat aangetoond is dat deze volgorde een betere overleving geeft.

De keuze tussen monotherapie en combinatiebehandeling wordt mede bepaald door klinische factoren; bijvoorbeeld, patiënten met asymptomatische hersenmetastasen

en/of een verhoogd LDH kunnen meer baat hebben bij combinatiebehandeling. In fase 2 studies (ABC studie en Checkmate 204) werd bij patiënten met asymptomatische hersenmetastasen een hogere responskans en betere overleving vastgesteld met ipilimumab + nivolumab (Long, 2019).

Voor patiënten met een BRAFV600-gemuteerd melanoom waarbij immuuntherapie in de eerste maanden niet mogelijk is, zoals bij snel progressieve metastasen die vitale organen of functies bedreigen of gebruik van dexamethason bij symptomatische hersenmetastasen wordt aangeraden om in de eerstelijn doelgerichte therapie (BRAF + MEK-inhibitie) te overwegen. In dit geval zou vervolgens na 8 tot 12 weken behandeling met BRAF+MEK-inhibitie een switch naar ipilimumab + nivolumab kunnen overwogen worden (conform de SECOMBIT (arm C) en EBIN (arm B) studie) (Ascierto, 2023; Robert, 2024 (meeting abstract: 2024 ASCO Annual Metting II)

Kostenaspecten

Vanwege geheime prijsafspraken, kan de exacte impact op het geneesmiddelenbudget niet worden vastgesteld, maar het staat vast dat deze impact hoog is. Het huidig prijsniveau wordt echter acceptabel geacht in verhouding tot de effectiviteit van de behandeling. Een lagere prijs van de behandelingen zou desondanks in alle opzichten zeer wenselijk en naar mening van de werkgroep zelfs noodzakelijk zijn, mede met het oog op de komende ontwikkelingen en het betaalbaar houden en borgen van een goede kwaliteit van de zorg in de nabije toekomst.

Haalbaarheid/aanvaardbaarheid

Bij de behandeling van patiënten met een irresectabel of gemetastaseerd stadium III/IV melanoom is het van belang niet alleen te kijken naar klinische effectiviteit en patiëntvoorkeuren, maar ook naar de haalbaarheid en aanvaardbaarheid van de aanbevolen behandelopties. Deelname aan klinische studies kan voor sommige patiënten een haalbare optie zijn, mits er toegang is tot geschikte onderzoeksfaciliteiten en de patiënt bereid is de mogelijk intensieve studieverplichtingen te dragen.

Rationale

De werkgroep is van mening dat deelname aan klinische studies in de behandeling van irresectabel of gemetastaseerd stadium III/IV melanoom de hoogste prioriteit heeft, gezien de sombere prognose voor een groot deel van de patiënten en de noodzaak om effectiviteit en aanvaardbaarheid van behandelingen verder te optimaliseren. Hierbij is het essentieel om patiëntwaarden en individuele klinische kenmerken leidend te laten zijn, zodat behandelbeslissingen aansluiten bij zowel haalbaarheid als de persoonlijke voorkeuren van de patiënt.

Aanbevelingen

Overweeg behandeling in studieverband.

Individualiseer de behandelbeslissing rekening houdend met het behandeldoel (kortetermijnvoordeel versus langetermijnvoordeel) en klinische kenmerken [lactaatdehydrogenase (LDH), betrokken organen waaronder de hersenen, algehele conditie (performance status), tumorlast, snelheid van ziekteprogressie], comorbiditeiten, bijwerkingen en patiëntvoorkeuren.

Overweeg immuuntherapie bij patiënten die dit in de eerste maanden kunnen verdragen, ongeacht de BRAF-status, omdat PD-1 blokkade, eventueel gecombineerd met ipilimumab, langdurige ziektecontrole kan bieden, zelfs na het beëindigen van de behandeling. Bovendien is aangetoond dat ipilimumab/nivolumab in deze situatie superieur is aan dabrafenib/trametinib.

Baseer de keuze tussen monotherapie en combinatiebehandeling op klinische parameters. Combinatiebehandeling is meer voorbehouden voor patiënten met hersenmetastasen en/of verhoogd serum LDH.

Overweeg bij patiënten met een BRAFV600 gemuteerd melanoom bij wie immuuntherapie gedurende de eerste paar maanden vanwege snelle progressie en/of bedreiging van een belangrijk orgaan of functie, doelgerichte therapie (BRAF + MEK-inhibitie) in de eerstelijn.

Kies bij doelgerichte behandeling altijd voor de combinatie van BRAF- en MEK-remmers; gebruik BRAF-inhibitor alleen als monotherapie bij een absolute contra-indicatie voor MEK-remmers. Gelijktijdig combineren van doelgerichte behandeling (BRAF + MEK remmers) met immuuntherapie wordt niet aanbevolen buiten studieverband.

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Evidence tabellen

Tawbi 2022, RELATIVITY-047	Type of study: phase 2-3, global, double-blind, randomized controlled trial Setting and country: Multicentre, 111 sites in North America, Central America, South America, Europe, Australia, and New Zealand. Funding and conflicts of interest: Funded by Bristol-Meyers Squibb. The funder participated in data collection and medical writing support. Detailed declarations of interests are provided in the article.	Inclusion criteria: -Previously untreated, histologically confirmed, unresectable stage III or IV melanoma -Aged >= 12 years -Measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 -Expression of LAG-3 and programmed death ligand 1 (PD-L1) that could be evaluated in tumor tissue -Patients who had received previous adjuvant or neoadjuvant therapies containing a PD-1, CTLA-4, BRAF, or MEK inhibitor (or a combination of BRAF and MEK inhibitors) were eligible if the therapy was completed at least 6 months before the date of recurrence -Patients who received previous treatment with interferon were	Describe intervention (treatment/procedure/test): 160 mg of relatlimab and 480 mg of nivolumab in a fixed-dose combination administered in a single 60-minute intravenous infusion every 4 weeks	Describe control (treatment/procedure/test): 480 mg of nivolumab administered in a single 60-minute intravenous infusion every 4 weeks	<u>Median follow-up:</u> 13.2 months <u>Loss-to-follow-up</u>: Intervention: 237 (66.8%) discontinued treatment. *129 disease progression* *63 AE related to study drug* *19 request to discontinue* *12 AE unrelated to study drug* Control: 233 (64.9%) discontinued treatment. *165 disease progression* *32 AE related to study drug* *12 request to discontinue*	Outcome measures and effect size (include 95%CI and p-value if available): <u>Overall survival:</u> Not reported. <u>Median progression-free survival:</u> I: 10.1 months (95%CI, 6.4 to 15.7) C: 4.6 months (95%CI 3.4 to 5.6) HR 0.75 (95%CI 0.62-0.92)? <u>Adverse events:</u> I: 345 (97.2%) C: 339 (94.4%) Treatment related grade 3 and 4: I: 143 (40.3%) C: 120 (33.4%)	Authors' conclusion: *The inhibition of two immune checkpoints, LAG-3 and PD-1, provided a greater benefit with regard to progression-free survival than inhibition of PD-1 alone in patients with previously untreated metastatic or unresectable melanoma. Relatlimab and nivolumab in combination showed no new safety signals.* -Outcome overall survival: *At the final analysis of progression-free survival, the data monitoring committee conducted a prespecified interim analysis of overall survival, which at that time point had*

		eligible if the last dose was received at least 6 weeks before randomization Exclusion criteria: -Active untreated brain or leptomeningeal metastases -Uveal melanoma -A history of serious autoimmune disease. <u>N total at baseline</u>: 714 Intervention: 355 Control: 359 <u>Important prognostic factors</u>[2]: Median age (IQR) *I:* 63 (20-94) *C:* 62.0 (21–90)			*14 AE unrelated to study drug*	<u>Quality of life:</u> No substantial differences in health-related quality of life were noted between the treatment groups.	*not reached significance.* -A subgroup analysis was performed for BRAF positive mutants. The benefit of treatment with relatlimab–nivolumab was observed regardless of patients' BRAF mutation status. In the subgroup of patients with BRAF mutations, the median progression-free survival was 10.1 months (95% CI, 4.6 to 23.1) in the relatlimab–nivolumab group and 4.6 months (95% CI, 3.0 to 6.5) in the nivolumab group (hazard ratio for progression or death, 0.74 [95% CI, 0.54 to 1.03]); in the subgroup of patients with wild-type BRAF,

		Sex: *I:* 59.2% M *C: 57.4%* M ECOG performance status: *I:* 66.5% 0 C: 67.4% 0 No BRAF mutation: *I:* 219 (61.7) *C:* 220 (61.3) LAG-3 expression >=1% I: 268 (75.5) C: 269 (74.9) PD-L1 expression >=1% I: 146 (41.4) C: 147 (40.9)					the median progression-free survival was 10.1 months (95% CI, 5.9 to 17.0) with relatlimab–nivolumab and 4.6 months (95% CI, 2.9 to 6.6) with nivolumab (hazard ratio, 0.76 [95% CI, 0.59 to 0.98]).

		Groups comparable at baseline? Yes.					
Larkin 2015, **Wolchock 2017,** **Hodi 2018,** **Larkin 2019,** **Wolchok 2022** **CheckMate 067**	Type of study: multicentre, randomized, double-blind, phase 3 study. Setting and country: Multicentre, 137 centres in Australia, Europe, Israel, New Zealand, and North America. Funding and conflicts of interest: Funded by Bristol-Meyers Squibb.	Inclusion criteria: -histologically confirmed stage III (unresectable) or stage IV melanoma -no prior systemic treatment for advanced disease. -age >= 18 years -ECOG performance-status score of 0-1 -measurable disease as assessed by means of computed tomography or magnetic resonance imaging according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1	Describe intervention (treatment/procedure/test): Nivo + ipi: 1 mg of nivolumab per kilogram every 3 weeks plus 3 mg of ipilimumab per kilogram every 3 weeks for 4 doses, followed by 3 mg of nivolumab per kilogram every 2 weeks for cycle 3 and beyond. Administered by means of intravenous infusion.	Describe control (treatment/procedure/test): Nivo: 3 mg of nivolumab per kilogram of body weight every 2 weeks (plus ipilimumab-matched placebo). Ipi: 3 mg of ipilimumab per kilogram every 3 weeks for 4 doses (plus nivolumab-matched placebo). Administered	**Larkin 2015** <u>Median follow-up:</u> Clinical data cutoff February 17, 2015. Range 12.2-12.5 months <u>Loss-to-follow-up</u>: Nivo: 3 (0.95%) *1 no longer met study criteria* *1 withdrew consent* *1 request to discontinue* Nivo + ipi: 1 (0.32%)	Outcome measures and effect size (include 95%CI and p-value if available): **Larkin 2015** <u>Median progression-free survival:</u> Nivo: 6.9 months (95% CI 4.3-9.5) Nivo + ipi: 11.5 months (95% CI 8.9-16.7) Ipi: 2.9 months (95% CI 2/8-3.4) HR nivo+ipi vs ipi 0.42; 99.5% CI, 0.31 to 0.57	-Subgroup analyses performed on PD-L1 status, BRAF mutation status, and metastasis stage.

	Detailed declarations of interests are provided in the article.	-availability of tissue collected from metastatic or unresectable tumors (archival or recently biopsied samples) for the assessment of PD-L1 status -known BRAF V600 mutation status Exclusion criteria: -ECOG score of 2 or higher -presence of active brain metastases -ocular melanoma -autoimmune disease. <u>N total at baseline</u>: 945 Nivolumab: 316 Nivolumab + ipilimumab: 314 Ipilimumab: 315		by means of intravenous infusion.	*1 no longer met study criteria* Ipi: 4 (1.27%) *2 no longer met study criteria* *1 withdrew consent* *1 disease progression* **Wolchok 2017** <u>Median follow-up:</u> Clinical data cutoff May 24, 2017. Nivo: 35.7 months Nivo+ipi: 38.0 months Ipi: 18.6 months <u>Loss-to-follow-up</u>: Nivo: 265 (84.7%)	HR nivo+ipi vs nivo 0.74 (95% CI, 0.60 to 0.92) HR nivo vs ipi HR, 0.57; 99.5% CI, 0.43 to 0.76. <u>Adverse events:</u> Nivo: 257 (82.1%) Nivo+ipi: 299 (95.5%) Ipi: 268 (86.2%) Treatment related grade 3 and 4: Nivo: 51 (16.3%) Nivo+ipi: 172 (55.0%) Ipi: 85 (27.3%) <u>Quality of life:</u> Not reported.	

		<u>Important prognostic factors</u>[2]: Median age (IQR) nivo: 59 (25-90) nivo+ipi: 59 (18-88) ipi: 61 (18-89) Sex: nivo: 202 (63.9%) M nivo+ipi: 206 (65.6%) M ipi: 202 (64.1%) M ECOG performance status 0: nivo: 238 (75.3%) nivo+ipi: 230 (73.2%) ipi: 224 (71.1%)			*174 disease progression* *42 study drug toxicity* *1 death* *8 adverse events* *24 patient request* *1 lost to follow-up* *12 maximum clinical* *benefit* *1 poor/noncompliance* *2 other* Nivo + ipi: 288 (92.0%) *90 disease progression* *131 study drug toxicity* *4 deaths*	**Wolchock 2017** <u>Median progression-free survival:</u> Nivo: 6.9 months (95% CI, 5.1 to 9.7) Nivo + ipi: 11.5 months (95% CI 8.9-19.3) Ipi: 2.9 months (95% CI 2.8-3.2) HR nivo+ipi vs ipi 0.43 (95% CI, 0.35 to 0.52) HR nivo+ipi vs nivo 0.78 (95% CI, 0.64 to 0.96) HR nivo vs ipi HR, 0.55 (95% CI, 0.45 to 0.66) <u>Overall survival at 2 years:</u> Nivo: 59% Nivo+ipi: 64%	

		No BRAF mutation: nivo: 216 (68.4%) nivo+ipi: 213 (67.8%) ipi: 218 (69.2%) Increased serum lactate dehydrogenase <ULN: Nivo: 112 (35.4%) nivo+ipi: 114 (36.3%) ipi: 115 (36.5%) Brain metastases nivo: 8 (2.5%) nivo+ipi: 11 (3.5%) ipi: 15 (4.8%) PD-L1 status positive: nivo: 80 (25.3%) nivo+ipi: 68 (21.7%) ipi: 75 (23.8%)			*18 adverse events* *24 patient request* *3 withdrew consent* *12 maximum clinical* *benefit* *1 poor/noncompliance* *1 no longer met study* *criteria* *4 other* Ipi: 303 (97.4%) *224 disease progression* *52 study drug toxicity* *1 death* *6 adverse events* *13 patient request*	Ipi: 45% <u>Overall survival at 3 years:</u> Nivo: 52% Nivo+ipi: 58% Ipi: 34% <u>Median overall survival:</u> Nivo: 37.6 months; 95% CI, 29.1 to not reached Nivo+ipi: not reached Ipi: 19.9 months; 95% CI, 16.9 to 24.6 <u>Adverse events:</u> Nivo: 270 (86) Nivo+ipi: 300 (96)	

		Groups comparable at baseline? Yes			*1 withdrew consent* *3 maximum clinical benefit* *1 poor/noncompliance* *2 other* **Hodi 2018** <u>Median follow-up (IQR):</u> Clinical data cutoff May 10, 2018. Nivo: 36.0 months (10.5-51.4 months) Nivo+ipi: 46.9 months (10.9-51.8 months) Ipi: 18.6 months (7.6-49.5 months) <u>Loss-to-follow-up</u>:	Ipi: 268 (86) Treatment related grade 3 and 4: Nivo: 67 (21) Nivo+ipi: 184 (59) Ipi: 86 (28) <u>Quality of life:</u> Not reported. **Hodi 2018:** <u>Median progression-free survival:</u> Nivo: 6.9 months (95% CI, 5.1 to 10.2) Nivo + ipi: 11.5 months (95% CI 8.7–19.3) Ipi: 2.9 months (95% CI 2.8-3.2)	

					Nivo: 280 *177 disease progression* *44 study drug toxicity* *1 death* *8 adverse events* *29 patient request* *1 lost to follow-up* *16 achieved maximum* *clinical benefit* *1 poor or non-compliance* *3 other* Nivo + ipi: 295 *90 disease progression* *134 study drug toxicity* *4 deaths* *19 adverse events*	HR nivo+ipi vs ipi 0.42 (95% CI, 0.35 to 0.51) HR nivo+ipi vs nivo 0.79 (95% CI, 0.65 to 0.97) HR nivo vs ipi HR, 0.53 (95% CI, 0.44 to 0.64) <u>Median overall survival</u> Nivo: 36·9 months (28·3–not reached) Nivo+ipi: not reached (95% CI 38·2–not reached) Ipi: 19·9 months (16·9–24·6) <u>Overall survival at 4 years:</u> Nivo: 46% (41−52) Nivo+ipi: 53%	

					27 patient request *3 withdrew consent* *13 achieved maximum* *clinical benefit* *1 poor or non-compliance* *1 no longer met study* *criteria* *3 other* Ipi: 311 *224 disease progression* *52 study drug toxicity* *1 death* *6 adverse events* *13 patient request* *1 withdrew consent*	(95% CI 47−58) Ipi: 30% (25−35) <u>Adverse events:</u> Nivo: 270 (86) Nivo+ipi: 300 (96) Ipi: 268 (86) Treatment related grade 3 and 4: Nivo: 70 (22%) Nivo+ipi: 185 (59%) Ipi: 86 (28%) <u>Quality of life:</u> Not reported. **Larkin 2019** <u>Median progression-free survival:</u>	

					4 achieved maximum *clinical benefit* *1 poor or non-compliance* *6 administrative reason** *3 other* **Larkin 2019** <u>Median follow-up:</u> Clinical data cutoff July 2, 2019. Nivo: 54.6 months Nivo+ipi: 36.0 months Ipi: 18.6 months <u>Loss-to-follow-up</u>: Nivo: 289 (92.3%) *179 disease progression*	Nivo: 6.9 months (95% CI, 5.1 to 10.2) Nivo + ipi: 11.5 months (95% CI, 8.7 to 19.3) Ipi: 2.9 months (95% CI 2.8-3.2) <u>Median overall survival</u> Nivo: 36.9 months (95% CI, 28.2 to 58.7) Nivo+ipi: 60.0 months (median not reached; 95% confidence interval [CI], 38.2 to not reached) Ipi: 19.9 months (95% CI, 16.8 to 24.6)	

					45 study drug toxicity *1 death* *8 adverse events* *33 patient request* *1 lost to follow-up* *18 maximum clinical* *benefit* *1 poor/non-compliance* *3 other* Nivo + ipi: 301 (96.2%) *90 disease progression* *139 study drug toxicity* *4 death* *18 adverse events* *27 patient request*	<u>Overall survival at 5 years:</u> Nivo: 44% Nivo+ipi: 52% Ipi: 26% <u>Adverse events:</u> Nivo: 271 (87) Nivo+ipi: 300 (96) Ipi: 268 (86) Treatment related grade 3 and 4: Nivo: 73 (23%) Nivo+ipi: 186 (59%) Ipi: 86 (28%) <u>Quality of life:</u> Not reported. **Wolchok 2022**	

					3 withdrew consent *15 maximum clinical* *Benefit* *1 poor/non-compliance* *1 no longer meets study* *criteria* *3 other* Ipi: 311 (100%) *224 disease progression* *52 study drug toxicity* *1 death* *6 adverse events* *13 patient request* *1 withdrew consent*	<u>Median progression-free survival:</u> Nivo: 6.9 months (95% CI, 5.1 to 10.2) Nivo + ipi: 11.5 months (95% CI, 8.7 to 19.3) Ipi: 2.9 months (95% CI 2.8-3.2) <u>Median overall survival</u> Nivo: 36.9 months (95% CI, 28.2 to 58.7) Nivo+ipi: 72.1 months (38.2 to not reached) Ipi: 19.9 months (95% CI, 16.8 to 24.6)	

					4 maximum clinical *benefit* *1 poor/non-compliance* *6 administrative* *reasons* *3 other* **Wolchok 2022** <u>Median follow-up:</u> Clinical data cutoff October 19, 2020. Nivo: 57.5 months Nivo+ipi: 36.0 months Ipi: 18.6 months <u>Loss-to-follow-up</u>: Nivo: 305 (97.4%) *180 disease progression*	<u>Overall survival at 6.5 years:</u> Nivo: 42% Nivo+ipi: 49% Ipi: 23% <u>Adverse events:</u> Nivo: 271 (87) Nivo+ipi: 300 (96) Ipi: 268 (86) Treatment related grade 3 and 4: Nivo: 73 (23%) Nivo+ipi: 186 (59%) Ipi: 86 (28%) <u>Quality of life:</u> Not reported.	

					49 study drug toxicity *1 death* *8 adverse events* *39 patient request* *2 withdrew consent* *1 lost to follow-up* *21 maximum clinical* *benefit* *1 poor/non-compliance* *3 other* Nivo + ipi: 306 (97.8%) *91 disease progression* *139 study drug toxicity* *4 death* *18 adverse events*		

					30 patient request *3 withdrew consent* *16 maximum clinical* *Benefit* *1 poor/non-compliance* *1 no longer meets study* *criteria* *3 other* Ipi: 311 (100%) *224 disease progression* *52 study drug toxicity* *1 death* *6 adverse events* *13 patient request* *1 withdrew consent*		

					4 maximum clinical *benefit* *1 poor/non-compliance* *6 administrative* *reasons* *3 other*		
Maio, 2015 **Robert, 2011** **CA184-024** **NCT00324155**	Multinational, randomized, double-blind, phase 3 study. Patient enrolment between: August 8, 2006, and January 22, 2008. <u>Funding and conflicts of interest:</u> • The sponsor, Bristol-Myers Squibb contributed to:	Inclusion criteria: • Age ≥18 years • Previously untreated stage III (unresectable) or stage IV melanoma with measurable lesions • ECOG PS of 0 or 1 • Life expectancy of 16 weeks or more • Patients were eligible regardless of baseline serum lactate dehydrogenase	Ipilimumab (dose: 10 mg per kg) plus dacarbazine (850 mg per square meter) n=250	Dacarbazine (850 mg per square meter) plus placebo. n=252	**Maio, 2015** Remained on ipilimumab treatment as of the last database lock: n=7 Alive at a minimum follow-up of 5 years: I: n=40 C: n=20 Median survival follow-up:	**Maio, 2015** Median OS, months (95% CI) I: 11.2 (9.5 to 13.8) C: 9.1 (7.8 to 10.5) HR, 0.69; 95% CI, 0.57 to 0.84 1-Year OS, months (95% CI): I: 47.6% (41.2 to 53.7) C: 36.4% (30.4 to 42.4)	• Database lock Maio, 2015: March 2013 • Primary outcome: OS • Efficacy analyses were performed on the ITT population. • The safety analysis included all patients who underwent randomization and received at least one

	• Trial design • Data collection • Initial draft of the manuscript • All authors signed a confidentiality disclosure agreement with the sponsor. Disclosure forms provided by the authors are available with the full text of this article.	level or BRAF mutation status. Exclusion criteria: • Prior treatment for metastatic disease (Patients who received prior adjuvant therapy were not excluded) • Concomitant treatment with immunosuppressive agents or long-term use of systemic glucocorticoids • Brain metastasis (based on imaging) • Primary ocular or mucosal melanoma • Autoimmune disease.			I: 11 months (range, 0.4 to 71.9 months) C: 8.9 months (range, 0.1 to 73.2 months) **Robert, 2011** Follow-up time between the start of the study (first visit of first patient) and end of the study (last visit of last patient): 54 months Follow-up time between the time the last patient underwent randomization (the first visit of the last patient) and the end of the study: 36.6 months.	2-Year OS, months (95% CI): I: 28.9% (23.3 to 34.7) C: 17.8% (13.3 to 22.8) 3-Year OS, months (95% CI): I: 21.3% (16.3 to 26.6) C: 12.1% (8.4 to 16.5) 4-Year OS, months (95% CI): I: 19.1% (14.4 to 24.3) C: 9.7% (6.4 to 13.7) 5-Year OS, months (95% CI):	dose of the assigned study drug (498 patients). • Initial study design: 500 patients were to undergo randomization, and PFS was to be the primary end point. An amendment was approved on October 9, 2008, to change the primary end point to OS. <u>Authors conclusions:</u> **Robert 2011:** Ipilimumab (at a dose of 10 mg per kilogram) in combination with dacarbazine, as compared with dacarbazine plus placebo, improved overall survival in patients with

		Mean age, years I: 57.5 C: 56.4 Male, n (%) I: 152 (60.8%) C: 149 (59.1%) ECOG PS: 0 – I: 177 (70.8%) 0 – C: 179 (71.0%) 1 – I: 73 (29.2%) 1 – C: 73 (29.0%) Groups were comparable at baseline.			A survival analysis was performed after 414 deaths occurred, 37 months after the last patient was enrolled. Discontinuation due to treatment related AEs, n (%): I: 89/247 (36%) C: 10/251 (4%)	I: 18.2% (13.6 to 23.4) C: 8.8% (5.7 to 12.8) (P=0.002) irAEs with onset during ipilimumab maintenance therapy in patients who survived ≥ 5 years: n=7. Grade 3 to 4 irAEs were observed exclusively in the skin, and both of the reported grade 3 to 4 irAEs (rash, pruritus) occurred in the same patient. Grade 5 irAEs: None.	previously untreated metastatic melanoma. The types of adverse events were consistent with those seen in prior studies of ipilimumab; however, the rates of elevated liver-function values were higher and the rates of gastrointestinal events were lower than expected on the basis of prior studies. **Maio, 2015:** The additional survival benefit of ipilimumab plus dacarbazine is maintained with twice as many patients alive at 5 years compared with those who initially received

						Robert, 2011 Deaths I: 196/250 (78.4%) C: 218/252 (86.5%) Median OS, months (95% CI) I: 11.2 (9.4 to 13.6) C: 9.1 (7.8 to 10.5) HR for death 0.72; P<0.001. 1-Year OS, months (95% CI): I: 47.3% C: 36.3% 2-Year OS, months (95% CI): I: 28.5% C: 17.9%	placebo plus dacarbazine. These results demonstrate a durable survival benefit with ipilimumab in advanced melanoma.

						3-Year OS, months (95% CI): I: 20.8% C: 12.2% Disease progression, n: I: 203 C: 223 HR for progression, 0.76; P = 0.006. AEs grade 3 or 4: I: 56.3% C: 27.5% P<0.001 Immunemediated adverse reactions grade ≥ 3	

						I: 38.1% C: 4.4% Drug-related deaths, n: I: 0 C: 1 (gastrointestinal Hemorrhage) For more information on AEs see results section of the article.	
Robert, 2019 **Carlino, 2018 Schachter, 2017** **Robert, 2015** **KEYNOTE-006**	International, randomized, open-label phase 3 study. In 16 countries. Patient enrolment: From September	Inclusion criteria: • Age ≥ 18 years • Histologically confirmed, unresectable stage III or IV melanoma who received no more than one previous systemic therapy	Ia: pembrolizumab at a dose of 10 mg per kilogram of body weight every 2 weeks n= 279 Ib: pembrolizumab at a dose of 10 mg per kilogram of	C: Four cycles of ipilimumab at a dose of 3 mg per kilogram every 3 weeks n=278	**Robert, 2019:** Median follow-up for survival: 57.7 months (IQR 56.7–59.2). **Carlino, 2018:** Median follow-up: 33.9 months.	**Robert, 2019:** Median OS: I (pooled groups): 32.7 months (95% CI 24·5–41·6) C: 15.9 months (13.3–22.0) HR: 0.73 (95% CI 0.61–0.88, p=0·00049).	Co-primary endpoints were OS and PFS. **Robert, 2019:** • Data cutoff: Dec 3, 2018. **Carlino, 2018:** • Data cutoff: 03 Nov 2016.

NCT01866319	18, 2013, to March 3, 2014. <u>Funding and conflicts of interest:</u> • The sponsors, Merck Sharp & Dohme, contributed to: • Trial design • Statisticians and a science writer were employed by the sponsor. Disclosure forms provided by the authors are available with the full text of this article.	for advanced disease • Known BRAF V600 mutational status was required; • previous BRAF inhibitor therapy was not required for patients with normal lactate dehydrogenase levels • no clinically significant tumor-related symptoms or evidence of rapidly progressive disease. • ECOG PS of 0 or 1 • Provision of a tumor sample adequate for assessing PD-L1 expression. Exclusion criteria:	body weight either every 3 weeks n=277		**Schachter, 2017:** Median follow-up: 22.9 months Discontinued treatment: Ia: *147 progressive disease* *29 adverse events* *2 deaths* *2 complete responses* *21 other* Ib: *139 progressive disease* *45 adverse events* *1 death* *5 complete responses* *23 other*	Median PFS: I (pooled groups): 8.4 months (95% CI 6.6–11.3) C: 3.4 months (2.9–4.2) HR 0.57, 95% CI 0.48–0.67, p<0.0001. Grade 3–4 treatment-related AEs: I (pooled groups): 96 (17%) C: 50 (20%) Treatment-related sepsis. C: n=1 **Schachter, 2017:** Death: n=383	• Reported outcomes by line of therapy and PD-L1 expression **Schachter, 2017:** • Data cutoff: Dec 3, 2015. **Robert, 2015:** • Data cutoff 1st interim analysis: Sep 3, 2014 (PFS and AEs) • Data cutoff 2nd interim analysis: Mar 3, 2015 (OS). • OS results for the pembrolizumab groups were superior to those for the ipilimumab group. The independent data and safety monitoring committee

		• Patients who had received previous therapy with CTLA-4, PD-1, or PD-L1 inhibitors • Ocular melanoma • Active brain metastases • History of serious autoimmune disease. Mean age, years Ia: 61 (18–89) Ib: 63 (22–89) C: 62 (18–88) Male, n (%) Ia: 161 (57.7) Ic: 174 (62.8) C: 162 (58.3) ECOG PS:			C: *46 progressive disease* *35 adverse events* *5 deaths* *24 other* Withdrew consent and did not receive treatment: Ia: n=1 C: n=22 **Robert, 2015:** Median follow-up at data cutoff (with 502 events reported), months: 7.9 (range: 6.1 to 11.5) March 3, 2015:	Median OS: Ia: not reached (range 22.1 months–not reached) Ib: not reached (23.5 months–not reached) C: 16.0 months (range 13.5–22.0) HR pembro every 2 weeks vs ipi: 0.68, 95% CI 0·53–0·87; p=0·0009 HR pembro every 3 weeks vs ipi: 0.68, 0·53–0·86; p=0·0008. 2 year OS rate: Ia: 55% (95% CI 49–61) Ib: 55% (95% CI 49–61) C: 43% (95% CI 37–49)	recommended stopping the study early. <u>Authors conclusions:</u> **Robert, 2019:** Pembrolizumab continued to show superiority over ipilimumab after almost 5 years of follow-up. These results provide further support for use of pembrolizumab in patients with advanced melanoma. **Carlino, 2018:** Findings support pembrolizumab monotherapy as standard of care in patients with advanced melanoma, regardless of first- or

		0 – Ia: 196 (70.3) 0 – Ib: 189 (68.2) 0 – C: 188 (67.6) 1 – Ia: 83 (29.7) 1 – Ib: 88 (31.8) 1 – C: 90 (32.4) PD-L1-positive tumours: 80.6% Groups were comparable at baseline.			Follow-up for OS: Minimum follow-up: 12 months with 289 deaths occurred Mean duration of exposure, days: Ia: 164 Ib: 151 C: 50 Rate discontinuation of a study drug because of treatment related AEs: Ia: 4.0%, Ib: 6.9%, C: 9.4%,	PFS events: n= 566 I (pooled groups): 364 (65%) C: 202 (35%) Median PFS, months: Ia: 5.6 months (range 3.4–8.2) Ib: 4.1 months (range 2.9–7.2) C: 2.8 months (range 2.8–2.9) HR for both Pembro schedules vs ipi: 0.61; 95% CI 0·50–0·75; p<0·0001 HR for Ia vs Ib: 0.95; 95% CI 0·77–1·17; p=0·62). 2-year PFS rate: Ia: 31%	second-line therapy or PD-L1 status. **Schachter, 2017:** Substantiating the results of the interim analyses of KEYNOTE-006, pembrolizumab continued to provide superior overall survival versus ipilimumab, with no difference between pembrolizumab dosing schedules. These conclusions further support the use of pembrolizumab as a standard of care for advanced melanoma. **Robert, 2015:** The anti–PD-1 antibody pembrolizumab prolonged progression-free

						Ib: 28% C: 14% Treatment related AEs grade 3 to 5: Ia: 47 (17%) of 278 Ib: 46 (17%) of 277 C: 50 (20%) of 256 **Robert, 2015:** Median overall survival was not reached in any study group. 1-Year OS: Ia: 74.1% Ib: 68.4% C: 58.2% • HR for death for pembrolizumab every 2 weeks versus	survival and overall survival and had less high-grade toxicity than did ipilimumab in patients with advanced melanoma.

						ipilimumab: 0.63; 95% CI, 0.47 to 0.83; P<0.0005 • HR for death for pembrolizumab every 3 weeks versus ipilimumab: 0.69; 95% CI, 0.52 to 0.90; P = 0.0036 Median PFS, months (95% CI): Ia: 5.5 (95% CI, 3.4 to 6.9) Ib: 4.1 (95% CI, 2.9 to 6.9) C: 2.8 (95% CI, 2.8 to 2.9) • HR for progression for pembrolizumab every 2 weeks versus ipilimumab:	

						0.58 (95% CI, 0.46 to 0.72; P<0.001) • HR for pembrolizumab every 3 weeks versus ipilimumab: 0.58 (95% CI, 0.47 to 0.72; P<0.001). 6-month PFS, months: Ia: 47.3% Ib: 46.4% C: 26.5% Treatment related AEs grade 3 to 5: Ia: 13.3% Ib: 10.1% C: 19.9%	

						Drug-related deaths, n: Ia: 0 Ib: 0 C: 1 For more information on AEs see results section of the article.	
Chesney, 2023 **MASTERKEY-265** **NCT02263508**	A multicenter, double-blind, placebo controlled, randomized phase III study in 21 countries. Patient enrolment between: March 17, 2016, through April 26, 2018. <u>Funding and conflicts of interest:</u>	Main Inclusion criteria: • Histologically confirmed stage IIIB-IV M1c unresectable melanoma • Age ≥ 18 years • ECOG PS 0 or 1 • At least one visceral or nodal/soft tissue melanoma lesion for which the longest diameter was ≥ 10 mm	I: A combination of T-VEC plus pembrolizumab (T-VEC-pembrolizumab) n=346 T-VEC was administered at ≤ 4 x 106 plaque-forming unit followed by ≤ 4 x 108 PFU 3 weeks later and once every 2 weeks until dose 5 and once every 3 weeks thereafter.	C: Placebo plus pembrolizumab (placebo-pembrolizumab n=346 Pembrolizumab was administered intravenously 200 mg once every 3 weeks.	Median follow-up in months: • 25.58 (range, 0.3-45.8) for the PFS primary analysis. • 31.0 (range, 0.3-53.0) for the second OS interim analysis. • 35.56 (range, 0.3-58.4) for the final analysis	Deaths at planned second interim OS analysis: I: 136 (39.3%) C: 146 (42.2%) Median OS, months (95% CI): I: Not estimable C: 49.2 (40.57 to not estimable) HR of 0.96 (95% CI, 0.76 to 1.22; P = .74)	• The dual primary end points were PFS and OS. • Data cutoff dates: Mar 2, 2020, for the PFS primary analysis; Sep 29, 2020, for the second interim OS analysis; Mar 26, 2021, the final analysis.

	- Supported by Amgen Inc and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc, Rahway, NJ. The sponsors contributed to: • Medical writing support - Authors' disclosures of potential conflict of interest is provided at the end of the full text article.	• In/exclusion criteria with regard to prior therapy for patients with BRAF-mutated melanoma is specified in the article. Exclusion criteria: • Active untreated brain metastases • Primary uveal or mucosal melanoma • Prior therapy with T-VEC or any other oncolytic viruses • Prior therapy with anti–PD-1/PD-L1/PD-L2 agents • Prior therapy with tumor vaccine in the nonadjuvant setting	Pembrolizumab was administered intravenously 200 mg once every 3 weeks.		Discontinued study: I: n = 152 *Death n = 131* *Withdrawal of consent n = 15* *Lost to follow-up n=6* C: n = 170 *Death n = 142* *Withdrawal of consent n = 22* *Lost to follow-up n = 6* April 2020, all patients discontinued study treatments. The final analysis was performed early given the futility noted in	The primary analysis of PFS was to be performed after 407 PFS events occurred. Median PFS (95% CI) (months): I: 14.3 (10.25 to 22.11) C: 8.5 (5.72 to 13.54) Stratified log-rank: HR, 0.86 (95% CI, 0.71 to 1.04), P=.13 Treatment related AEs grade 3 or 4: I: 70 (20.3%) C: 54 (15.7%) Fatal AEs: I: 45 (13.1%)	• On June 12, 2020, the DMC met to review data from the PFS primary analysis and recommended that the study continues as planned. • On December 22, 2020, the DMC reviewed the efficacy and safety data from the second OS interim analysis. The DMC indicated that the futility boundary for OS was crossed and recommended that no further study-related procedures are conducted. • On January 8, 2021, the study was unblinded and proceeded

		• History of autoimmune diseases • Evidence of immunosuppression therapy for > 2 weeks or < 7 days prior to the first dose of study • Active herpetic skin lesions • Current treatment with antiherpetic drug. For more information on in-/exclusion see the article. Median age, years (range) I: 64 (26-92) C: 64 (19-94) Male, n (%)			the second interim analysis and included an additional follow-up of 6 months.	C: 42 (12.2%) Treatment related fatal AEs, n: I: 4 (1.2%) C: 1 (0.3%) Immune-related AEs: I: 27.5% C: 24.8% For more information on AEs see results section of the article At final analysis: - PFS overall stratified HR, 0.87; 95% CI, 0.72 to 1.06 - OS: overall stratified HR,	directly to a final analysis conducted in an unblinded manner. • All patients were off study treatment as of April 2020. The last visit date for the final analysis was March 11, 2021. • No improvement in OS was observed in any of the predefined subgroups. • Sensitivity analysis were performed: - which censored patients at the time of subsequent anticancer therapy

		I: 199 (57.5) C: 219 (63.3) ECOG PS: 0 – I: 259 (74.9) 0 – C: 249 (72.0) 1 – I: 87 (25.1) 1 – C: 97 (28.0) Groups were comparable at baseline.				0.97; 95% CI, 0.77 to 1.21) No new safety signals were observed.	- excluding patients with stage IVM1c disease - second-line therapies were generally balanced between the arms, and the crossover rate from the placebo arm to receive subsequent T-VEC treatment was<5% <u>Authors conclusions:</u> This randomized, double-blinded, placebo-controlled, multicenter, international phase

							III trial did not show improved PFS or OS for the combination of T-VEC plus pembrolizumab compared with placebo plus pembrolizumab for immunotherapy-naïve patients with advanced melanoma in the frontline setting. There were no new safety concerns with the addition of T-VEC to pembrolizumab, and the safety profile of the combination was consistent with the known safety profile of each drug.
Andtbacka, 2019; Andtbacka, 2015 **OPTiM NCT00769704**	A randomized open-label phase III trial at 64 sites in the United States, the United Kingdom, Canada, and South Africa.	Main inclusion criteria: • ≥ 18 years • Histologically confirmed, unresectable, bidimensionally measurable stage IIIB/C/IV melanoma with	I: intratumoral Talimogene laherparepvec (T-VEC) (at the approved dose) n= 295 (68%)	C: subcutaneous recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) n= 141 (32%)	Median follow-up in the final analysis of OS: 49 months. Median duration of treatment in weeks (range):	**Intent-to treat population (stage IIIB–IVM1c melanoma):** Median OS, months (95% CI): I: 23.3 (19.5–29.6)	• Primary end point: durable response rate (objective response lasting continuously ≥ 6 months) per independent

	Patient enrolment between: 2009 and 2011 <u>Funding and conflicts of interest:</u> - Funded by BioVex, who were subsequently acquired by Amgen Inc. during the OPTiM trial. The sponsor contributed to: • Design of the trial • Data collection • Data analysis • Interpretation of data • Development of the manuscript. - A competing interests statement is provided at the end	≥1 cutaneous, subcutaneous or nodal lesions that was suitable for direct or ultrasound-guided injection; • ECOG PS ≤1 • Serum lactate dehydrogenase ≤1.5 × upper limit of normal; • ≤3 visceral lesions (excl. lung or nodal lesions associated with visceral organs) with none > 3 cm; • Adequate organ function. • Patients with history of autoimmune disease, but not use of high-dose steroids. Exclusion criteria:			I: 23.1 (0.1–176.7) C: 10.0 (0.6–120.0) **Andtbacka, 2015:** Discontinued T-VEC: n=291 *Disease progression:* *n=191* *PR or CR for ≥ 6 continuous months:* *n=42* *Maximum allowed dose without* *PR/CR: n=26* *Adverse event: n=11* *Consent withdrawn: n=10* *Physician decision: n=6* *Death: n=5*	C: 18.9 (16.0–23.7) unstratified HR for death, 0.79 (95% CI,0.62–1.00); P = 0.0494). Estimated 5-year survival I: 33.4% C: Not estimable **Stage IIIB–IVM1a disease** Effect of T-VEC on OS vs GM-CSF: • Stage IIIB/C: HR, 0.48, P < 0.05 Effect of T-VEC on OS vs ITT population including stage IVM1b/c disease: • Stage IIIB–IVM1a: HR, 0.56; 95% CI,	assessment. Key secondary end points: OS and overall response rate • Data cut-off for this final analysis of OPTiM was 5 September 2014. • 4 patients in the T-VEC arm and 14 in the GM-CSF arm did not receive T-VEC or GM-CSF. • When the 18 patients who did not receive allocated treatment were excluded (T-VEC arm, n =4; GM-CSF arm, n = 14), median OS in the final analysis dataset was 24.5 versus 18.9 months for T-VEC versus

	of the full text article.	• Requiring intermittent or chronic treatment with an antiviral agent (eg, acyclovir) or high-dose steroids • Primary ocular or mucosal melanoma • Bone metastases • Active cerebral metastases • > 3 visceral metastases • Any visceral metastasis >3 cm • Liver metastases had to be stable for 1 month before random assignment. For more information on in-/exclusion see the article.			Discontinued GM-CSF: n=127 *Disease progression: n=95* *PR or CR for ≥ 6 continuous months: n=0* *Maximum allowed dose without* *PR/CR: n=9* *Adverse event: n=3* *Consent withdrawn: n=12* *Physician decision: n=5* *Death: n=3*	0.40–0.79; P < 0.001 Estimated 5-year survival with T-VEC: • Stage IIIB–IVM1a melanoma: 48.9% (95% CI, 40.6–56.7) • Stage IVM1b/c disease: 15.1% (95% CI, 9.3–22.2). Treatment related AEs grade 3/4: I: 33 (11.3%) C: 6 (4.7%) Immune-related AEs: I: 24/295 C: ?	GM-CSF (HR, 0.78; P = 0.0439). • Ad-hoc sensitivity analysis for OS accounting for subsequent systemic anti-cancer treatment, there was a 27% reduction in the risk of death for T-VEC versus GM-CSF (unadjusted HR, 0.73; 95% CI, 0.59–0.92; P = 0.0069). <u>Authors conclusions:</u> **Andtbacka, 2019:** In conclusion, as well as demonstrating a longer-term effect on survival, this analysis confirms that T-VEC resulted in high CR rates,

		Median age, years (range) I: 63 (22 to 94) C: 64 (26 to 91) Male, n (%) I: 173 (59%) C: 77 (55%) ECOG PS: 0 – I: 209 (71%) 0 – C: 97 (69%) 1 – I: 82 (28%) 1 – C: 32 (23%) Unknown: I: 4 (1%) C: 12 (9%) Groups were comparable at baseline.				Immune-related AEs grade 3: n=4 Immune-related AEs grade 4: None reported Treatment-related deaths, n: I: 0 C: 0 For more information on AEs see results section of the article	most notably in patients with early metastatic melanoma (stage IIIB–IVM1a). Once achieved, CRs were durable and associated with prolonged survival. The favorable clinical outcomes observed in some patients treated with T-VEC, along with its good safety profile, support continued efforts to further define its future role in melanoma as a combination partner with immunotherapy. **Andtbacka, 2015:** T-VEC is the first oncolytic immunotherapy to demonstrate

							therapeutic benefit against melanoma in a phase III clinical trial. T-VEC was well tolerated and resulted in a higher DRR (P<0.001) and longer median OS (P=0.051), particularly in untreated patients or those with stage IIIB, IIIC, or IVM1a disease. T-VEC represents a novel potential therapy for patients with metastatic melanoma.
Larkin 2014, **Ascierto 2016,** **Ascierto 2021,** **CoBRIM**	Type of study: multicentre, randomized, controlled, double-blind, phase 3 study. Setting and country: Multicentre, 135	Inclusion criteria: -Histologically confirmed unresectable, locally advanced stage IIIC or stage IV melanoma with a BRAF V600 mutation detected with the use of a	Describe intervention (treatment/procedure/test): Oral administration of vemurafenib (at a dose of 960 mg twice daily) together with cobimetinib (at a dose of 60 mg once daily for 21	Describe control (treatment/procedure/test): Oral administration of vemurafenib (at a dose of 960 mg twice daily) together with placebo (control group)	**Larkin 2014:** Clinical data cutoff July 10, 2014 <u>Median follow-up</u> 7.3 months (range, 0.5 to 16.5).	Outcome measures and effect size (include 95%CI and p-value if available): **Larkin 2014** <u>Median overall survival at 9 months:</u>	*Author's conclusion:* The OS results confirmed the long-term OS benefit in patients treated with cobimetinib plus vemurafenib compared with placebo plus vemurafenib in patients with

	sites in the United States, Canada, Australia, New Zealand, Europe, Russia, Turkey, and Israel. Funding and conflicts of interest: Funded by Bristol-Meyers Squibb. The funder participated in data collection and medical writing support. Detailed declarations of interests are provided in the article.	real-time polymerase-chain-reaction assay (Cobas 4800 BRAF V600 Mutation Test, Roche Molecular Systems) -Aged >= 18 years -Had measurable disease, according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, as assessed by means of computed tomography -ECOG performance status 0 or 1. -Had adequate hematologic, hepatic, renal, and cardiac function Exclusion criteria: ?	days, followed by 7 days off) (combination group).		<u>Loss-to-follow-up</u>: Intervention: 1 *104 discontinued vemurafenib* *107 discontinued cobimetinib* *102 discontinued vemurafenib and cobimetinib* Control: 3 *139 discontinued vemurafenib* *140 discontinued placebo* *138 discontinued vemurafenib and placebo* **Ascierto 2016** Clinical data cutoff Aug 28, 2015 <u>Median follow-up</u>	I: 81% (95% CI, 75 to 87) C: 73% (95% CI, 65 to 80) HR 0.65; 95% CI, 0.42 to 1.00 <u>Median progression-free survival:</u> I: 9.9 months (95% CI, 9.0 - not reached), C: 6.2 months (95% CI, 5.6-7.4) HR 0.51 (95% CI, 0.39 to 0.68 <u>Adverse events:</u> I: 96% C: 96% Treatment related grade 3 and 4: I: 63%	previously untreated, BRAFV600 mutation–positive advanced melanoma. The greatest benefit was observed in patients who achieved a complete response and in those with normal LDHlevels and low tumor burden at baseline.

		N total at baseline: 495 Intervention: 247 Control: 248 Important prognostic factors[2]: Median age (IQR) *I:* 56 (23-88) *C:* 55 (25-85) Sex: *I:* 59% M *C: 56%* M ECOG performance status: *I: 76%* 0 C: 67% 0 BRAF mutation V600E:			18·5 months (IQR 8·5–23·5). Loss-to-follow-up: Intervention: 136 *114 died* *2 lost to follow-up* *17 patient decision to* *withdraw* *3 physician decision* *to withdraw* Control: 164 *141 died* *6 lost to follow-up* *17 patient decision to* *withdraw* **Ascierto 2021**	C: 58% Quality of life: Not reported. **Ascierto 2016** Median overall survival: I: 22·3 months (95% CI 20·3–not estimable) C: 17·4 months (95% CI 15·0–19·8) HR 0·70 [95% CI 0·55–0·90] Median 1 year survival: I: 74·5% (95% CI 68·9–80·2) C: 63·8% (57·6–70·0) Median 2 year survival:	

		I: 69% *C:* 70% Brain metastases: I: <1% C: 1% Increased lactate dehydrogenase levels <ULN: I: 46% C: 43% Groups comparable at baseline? Yes.			Clinical data cutoff July 21, 2019. <u>Median follow-up</u> I: 21.2 months (10.4–59.0) C: 16.6 months (7.3–42.5) <u>Loss-to-follow-up</u>: Intervention: 100 discontinued treatment *167 died* *8 lost to follow-up* *20 patient decision to* *withdraw* *1 physician decision* *4 other*	I: 48·3% (41·4–55·2) C: 38·0% (31·3–44·7) <u>Median progression-free survival:</u> I: 12·3 months (9·5–13·4) C: 7·2 months (5·6–7·5) HR 0·59 (0·47–0·73) <u>Adverse events:</u> I: 99% C: 98% Treatment related grade 3 and 4: I: 75% C: 61% <u>Quality of life:</u>	

					Control: 247 discontinued treatment *157 died* *4 lost to follow-up* *21 patient decision to* *Withdraw* *4 physician decision* *2 other*	Not reported. **Ascierto 2021** <u>Median overall survival</u>: I: 22.5 months (95% CI, 20.3–28.8) C: 17.4 months (95% CI, 15.0–19.8) HR 0·70 [95% CI 0·55–0·90] <u>Median 3 year survival:</u> I: 38% (95% CI, 32–45) C: 31% (95% CI, 25–37) <u>Median 4 year survival:</u> I: 34% (95% CI, 28–40)	

						C: 29% (95% CI, 23–35) <u>Median 5 year survival:</u> I: 31% (95% CI, 25–37) C: 26% (95% CI, 20–32) <u>Median progression-free survival:</u> I: 12.6 months (95% CI, 9.5–14.8) C: 7.2 months (95% CI, 5.6–7.5) <u>Adverse events:</u> I: 99% C: 98% Treatment related grade 3 and 4: I: 78% C: 63%	

						Quality of life: Not reported.	
Robert 2015, **Robert 2016,** **COMBI-v**	Type of study: open-label, randomized, phase 3 study Setting and country: Multicentre, 193 centries. Funding and conflicts of interest: The study was funded by the sponsor, GlaxoSmithKline, and also provided editorial assistance. Detailed declarations of interests are	Inclusion criteria: ->= 18 years -the presence of BRAF V600E or V600K mutations was centrally determined with the investigational use of the THxID BRAF assay (bioMérieux) -measureable disease, according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,15 -An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1	Describe intervention (treatment/procedure/test): A combination of dabrafenib (150 mg orally twice daily) and trametinib (2 mg orally once daily)	Describe control (treatment/procedure/test): Vemurafenib (960 mg orally twice daily).	**Robert 2015** Clinical data cutoff April 17, 2014 <u>Median follow-up</u> 11 (I), 10 (C) months <u>Loss-to-follow-up</u>: I: 16 *4 lost to follow-up* *2 investigator discretion* *10 withdrew consent* C: 28 *9 lost to follow-up*	**Robert 2015** <u>Median overall survival</u>: I: not reached C: 17.2 months <u>Median 1 year survival:</u> I: 72% (95% CI, 67 to 77) C: 65% (95% CI, 59 to 70) <u>Median progression-free survival:</u> I: 11.4 months C: 7.3 months	Author's conclusion: *In conclusion, the combination of dabrafenib plus trametinib was superior to vemurafenib monotherapy with regard to all efficacy end points, including overall survival, with no additional overall toxicity.* *Robert 2016 is only a published conference abstract, limited information available.*

	provided in the article.	-Patients who had undergone treatment for brain metastases with no increase in lesion size for at least 12 weeks were eligible Exclusion criteria: -See supplement. <u>N total at baseline</u>: 703 I: 352 C: 352 <u>Important prognostic factors</u>[2]: Median age (IQR) I: 55 (18–91) C: 54 (18–88)			*1 investigator discretion* *18 withdrew consent* **Robert 2016** Clinical data cutoff July 2016 <u>Median follow-up</u> 27 (I), 26 (C) months <u>Loss-to-follow-up</u>: NR	HR, 0.56; 95% CI, 0.46 to 0.69 <u>Adverse events:</u> I: 343 (98) C: 345 (99) <u>Grade 3-4:</u> I: 167 (48) C: 198 (57) <u>Quality of life:</u> Not reported. **Robert 2016** <u>Median overall survival</u>: NR <u>Median 3 year survival:</u>	

		Sex: I: 208 (59) C: 180 (51) ECOG performance status: I: 248 (71) C: 248 (70) BRAF mutation V600E: I: 312(90) C: 317 (90) Groups comparable at baseline? Yes.				I: 45% [95% CI, 39-50] C: 32% [95% CI, 27-37] <u>Median 3 year progression-free survival:</u> I: 25% [95% CI, 20-30] C: 11% [95% CI, 7-16] <u>Adverse events:</u> Similar to Robert 2015 <u>Quality of life:</u> Not reported.	
Long, 2014 **Long, 2015** **Long, 2017** **Long, 2015**	A double-blind, randomized,	Inclusion criteria: • Histologically confirmed,	A combination of oral dabrafenib (150 mg twice	Oral dabrafenib	**Long 2017:** At data cut-off, 15 Feb 2016, follow-	**Long, 2017:**	• Primary outcome: PFS

Long, 2014 **COMBI-d** **NCT01584648**	phase 3 study without crossover, at 113 centres worldwide. Patient enrolment between: May 2012 through January 2013 <u>Funding and conflicts of interest:</u> • The sponsor, GlaxoSmithKline contributed to: - Study design - Monitoring of data collection - Initial draft of the manuscript - Data analysis - Data interpretation	unresectable stage IIIC or stage IV metastatic melanoma with BRAF V600E or V600K mutations, • Brain metastases that had been definitively treated and stable for at least 12 weeks were eligible to participate. Exclusion criteria: • Previous systemic anticancer therapy (including BRAF or MEK inhibitors). Additional inclusion and exclusion criteria are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.	daily) and oral trametinib (2 mg once daily) n=211	(150 mg twice daily) and placebo. n=212	up among patients who were alive: ≥36 months from time of randomization. Remained on randomized treatment: I: 40 (19%) C: 6 (3%) Median time on treatment: I: 11.8 (range, 0.4–43.7) C: 8.3 (range, 0.1–45.3) months >12 months of treatment: I: 49% C: 38%	3-year OS (95% CI): I: 44% C: 32% HR, 0.75 (95% CI, 0.58–0.96) At data cutoff: 184 progressed - I: 100 (69%) - C: 84 (72%) Median PFS, in months:I: 12.0 (9.3–17.1) C: 10.6 (8.3–12.9) 2-year PFS: I: 30% (24–37) C: 16% (12–22) 3-year PFS: I: 22% C: 12% HR, 0.71 (95% CI, 0.57–0.88) ORR: I: 144 (68%) (61.5–74.5) C: 116 (55%) (47.8–61.5)	• Data cutoff: ○ Long, 2015: Jan 12, 2015 ○ Long, 2017: 15 February 2016 • Notably, 25 (12%) patients in the dabrafenib monotherapy arm crossed over to DþT, of which 6 (24%) had progressed on monotherapy before crossover. Survival outcomes in these crossover patients, all of whom remained on DþT as of data cut-off, continued to be followed up under the monotherapy

	- Writing of the report Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.	Median age, years I: 55.0 (22–89) C: 56.5 (22–86) Male, n (%) I: 111 (53) C: 114 (54) ECOG PS: 0 – I: 155/210 (74) 0 – C: 150/211 (71) 1 – I: 55/210 (26) 1 – C: 61/211 (29) Groups were comparable at baseline.			**Long, 2015:** Median follow-up: I: 20.0 months (range 0–30) C: 16.0 months (range 0–32)	AEs grade 3 or 4: I: 48% C: 50% For more information on AEs see results section of the article. **Long, 2015:** At data cutoff: • 334 deaths - I: 99 (47%) - C: 123 (58%) HR of 0·71 (95% CI 0·55–0·92; p=0·0107 Median OS, months I: 25.1 (95% CI 19·2–not reached) C: 18.7 (15·2–23·7) HR, 0.71; 95% CI, 0.55–0.92	arm. Of combination-arm patients who were progression free (n=31) and alive (n=76) at 3 years, 28 (90%) and 44 (58%) remained on DþT, respectively. <u>Authors conclusions:</u> **Long 2017:** These data demonstrate that durable (3 years) survival is achievable with dabrafenib plus trametinib in patients with BRAF V600-mutant metastatic melanoma and support long-term first-line use of the combination in this setting.

						1-year OS: I: 74% (67–79) C: 68% (61–74) 2-year OS: I: 51% (44–58) C: 42% (35–49) At data cutoff: 301 progressed - I: 139 (66%) - C: 162 (76%) HR 0·67, 95% CI 0·53–0·84, p=0·0004 Median PFS in months I: 11.0 (8·0–13·9) C: 8.8 (5·9–9·3) HR, 0.67; 95% CI, 0.53–0.84	**Long, 2015:** The improvement in overall survival establishes the combination of dabrafenib and trametinib as the standard targeted treatment for BRAF Val600 mutation-positive melanoma. Studies assessing dabrafenib and trametinib in combination with immunotherapies are ongoing. **Long, 2014:** A combination of dabrafenib and trametinib, as compared with dabrafenib alone, improved the rate of progression-free survival in previously untreated patients who had metastatic

						ORR: I: 144 (69%; 62–75) C: 112 (53%; 46–60) Difference: 15% (6–25)§ 0·0014 AEs grade 3: I: 66 (32%) C: 63 (30%)	melanoma with BRAF V600E or V600K mutations.
Dummer 2018, **Dummer 2018-2,** **Ascierto 2020,** **COLUMBUS**	Type of study: multicentre, two-part, randomised, open-label, phase 3 study. Setting and country: Multicentre, 162 hospitals in 28 countriest.	Inclusion criteria: ->= 18 years -A histologically confirmed diagnosis of locally advanced, unresectable, or metastatic cutaneous melanoma or unknown primary melanoma classified as American Joint	Describe intervention (treatment/procedure/test): Oral encorafenib 450 mg once daily plus oral binimetinib 45 mg twice daily (encorafenib plus binimetinib group)	Describe control (treatment/procedure/test): Encorafenib 300 mg once daily orally, or vemurafenib 960 mg twice daily orally	**Dummer 2018** Clinical data cutoff May 19, 2016 Median follow-up 16·6 months (14·8–16·9) <u>Loss to follow-up</u>:	**Dummer 2018** <u>Median progression-free survival:</u> A: 14·9 months (95% CI 11·0–18.5) B: 9·6 months (7·4–14·8) C: 7·3 months (5·6–8.2)	Author's conclusion: *In conclusion, patients treated with encorafenib plus binimetinib had longer PFS and OS than those treated with vemurafenib, with landmark analyses showing consistent improved OS and PFS for COMBO450 vs VEM for each year. Safety*

	Funding and conflicts of interest: Funded by Array BioPharma, Novartis. The sponsors had a role in data collection, analysis, and interpretation. Detailed declarations of interests are provided in the article.	Committee on Cancer (AJCC) stage IIIB, IIIC, or IV -Treatment naive or had progressed on or after previous first-line immunotherapy -Had a BRAFV600E or BRAFV600K mutation or both in tumour tissue as ascertained by central genetic mutation analysis with the bioMérieux THxID BRAF diagnostic test (bioMérieux, Marcy l'Etoile, France) before enrolment -ECOG performance status of 0 or 1 -Adequate bone marrow, organ function, and laboratory parameters -At least one measurable lesion, according to guidelines			A: 124 discontinued treatment *83 had progressive* *disease* *16 had adverse events* *8 physician decision* *7 patient or guardian* *decision* *7 died* *2 protocol deviation* *1 lost to follow-up* B: 146 discontinued *87 had progressive* *disease* *24 had adverse events*	<u>Adverse events:</u> A: 66 (34%) B: 65 (34%) C: 69 (37%) <u>Grade 3-4 adverse events:</u> A: 111 (58%) B: 127 (66%) C: 118 (63%) <u>Quality of life:</u> Not reported. **Dummer 2018-2** <u>Median overall survival</u>: A: 33·6 months (95% CI 24·4–39·2)	*results were consistent with* *the known tolerability profile of COMBO450, and the toxicity burden was reduced over time. These data reinforce encorafenib plus binimetinib as an important treatment option for patients with BRAF-mutant melanoma.*

		based on Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Exclusion criteria: -An untreated CNS lesions; uveal or mucosal melanoma -A history of leptomeningeal metastases -Gilbert's syndrome -history, current evidence, Or risk of retinal vein occlusion -Previous BRAF inhibitor or MEK inhibitor treatment -Previous use of systemic chemotherapy			*19 physician decision* *13 patient or guardian* *decision* *1 died* *1 protocol deviation* *1 lost to follow-up* C: 159 discontinued *101 had progressive* *disease* *26 had adverse events* *13 physician decision* *15 patient or* *guardian decision* *4 died*	B: 23·5 months (19·6–33·6) C: 16·9 months (14·0–24·5) A vs C: HR 0·61 [95% CI 0·47–0·79) A vs B: HR 0·81 [95% CI 0·61–1·06] B vs C: HR 0·76 (95% CI 0·58–0·98) <u>Median 1 year survival:</u> A: 75·5% (95% CI 68·8–81·0) B: 74·6% (67·6–80·3) C: 63·1% (55·7–69·6) <u>Median 2 year survival:</u> A: 57·6% (95% CI 50·3–64·3)	

		-Extensive radiotherapy as evaluated by local investigators, or an investigational agent other than previous immunotherapy for locally advanced, unresectable, or metastatic melanoma (immunotherapy must have ended ≥6 weeks before randomisation). <u>N total at baseline</u>: 577 encorafenib & binimetinib (A): 192 encorafenib (B): 194 vemurafenib (C): 191 <u>Important prognostic factors</u>[2]: Median age (IQR) *A:* 57 (20–89; 48–66)			**Dummer 2018-2** Clinical data cutoff Nov 7, 2017 <u>Median follow-up</u> 36·8 months (95% CI 35·9–37·5) <u>Loss-to-follow-up</u>: A: 149 discontinued *99 progressive disease* *20 adverse events* *9 physician decision* *11 patient or guardian decision* *8 died* *1 protocol deviation* *1 lost to follow-up*	B: 49·1% (41·5–56·2) C: 43·2% (35·9–50·2) <u>Median progression-free survival:</u> A: 14·9 months (95% CI 11·0–20·2) B: 9·6 months (7·4–14·8) C: 7·3 months (5·6–7·9) <u>Adverse events:</u> Similar to Dummer 2018 <u>Quality of life:</u> Not reported. **Ascierto 2020**	

		B: 54 (23–88; 46–63) *C:* 56 (21–82; 45–65) Sex: *A:* 115 (60%) M B: 108 (56%) M *C:* 111 (58%) M ECOG performance status: *A:* 136 (71%) 0 B: 140 (72%) 0 C: 140 (73%) 0 BRAF mutation V600E: *A:* 170 (89%) *B:* 173 (89%) *C:* 168 (88%) Groups comparable at baseline?			B: 168 discontinued *100 progressive disease* *25 adverse events* *24 physician decision* *17 patient or guardian decision* *1 died* *1 protocol deviation* *0 lost to follow-up* C: 173 discontinued *109 progressive disease* *25 adverse events* *17 physician decision* *17 patient or guardian decision* *4 died*	<u>Median overall survival</u>: A: 33.6 months (95% CI, 24.4-39.2), B: 23.5 months (95% CI, 19.6-33.6) C: 16.9 months (95% CI, 14.0-24.5 HR 0.61 (95%CI 0.48-0.79) <u>Median 3 year survival:</u> A: 47% B: 41% C: 31% <u>Median progression-free survival:</u> A: 14.9 months (95% CI, 11.0-20.2)	

		Yes.			*1 new therapy for study indication* *0 protocol deviation* *0 lost to follow-up* **Ascierto 2020** Clinical data cutoff Nov 2018 <u>Median follow-up</u> 48.8 months <u>Loss-to-follow-up</u>: A: 156 discontinued *104 progressive disease* *20 adverse events* *21 physician decision/ patient or guardian decision* *9 died*	B: 9.6 months (95% CI, 7.4-14.8) C: 7.3 months (95% CI, 5.6-7.9) HR (0.51, 95%CI 0.39-0.67) <u>Grade 3/4 adverse events:</u> A: 68% B: 68% C: 66% <u>Quality of life:</u> Not reported.	

					2 other B: 172 discontinued *101 progressive disease* *24 adverse events* *35 physician decision/patient or guardian decision* *1 died* *1 other* C: 177 discontinued *111 progressive disease* *26 adverse events* *35 physician decision/patient or guardian decision* *4 died* *1 other*		

Atkins, 2022 **The DREAMseq Trial** **NCT02224781**.	A two-arm, two-step, open-label, randomized phase 3 trial. Patient enrolment between: July 13, 2015, and July 16, 2021. Funding and conflicts of interest: • Supported by the ECOG-ACRIN Cancer Research Group (Peter J. O'Dwyer, MD and Mitchell D. Schnall, MD, PhD, Group Co-Chairs) and supported by the National Cancer Institute of the National Institutes of Health under	Inclusion criteria Step 1: • Unresectable stage III/IV melanoma with a BRAFV600E/K mutation. • Treatment-naive for metastatic disease. • ECOG PS 0 or 1 • Age ≥ 18 years • Adequate organ and bone marrow function. • Pre-existing brain metastases had to have been treated with either surgery or stereotactic radiosurgery (SRS) • Off steroids for ≥ 10 days before treatment • No evidence of disease progression on a	**Arm A:** nivolumab/ipilimumab n=133 At disease progression patients were enrolled in step 2 to receive the alternate therapy: **Arm C:** dabrafenib/ trametinib n=27 • Nivolumab 1 mg/kg and ipilimumab 3mg/kg once every 3 weeks for four doses followed by nivolumab 240 mg intravenously once every 2 weeks for up to 72 weeks (**arms A and D**) or dabrafenib 150 mg twice a day and trametinib 2 mg orally once daily until progressive disease (**arms B and C**).	**Arm B:** dabrafenib/trametinib n=132 At disease progression patients were enrolled in step 2 to receive the alternate therapy: **Arm D:** nivolumab/ ipilimumab n=46 A: 59.5% (79) B: 53.1% (70) C: 53.8% D: 50.0%	Median follow-up time: 27.7 months (IQR, 41.9-11.9 = 30 months). At the time of the 4th DSMC interim analysis, 176 patients had 2-year follow-up data (arm A=87; arm B=89; 59% information). Median duration of treatment, weeks: A: 8.9 (range, 1-86.9) B: 28.5 (range, 3.7-192.1). **Reasons for ending treatment** Arm A: (n=130)	Death: A: n=38 B: n=62 2-Year OS (95% CI): A: 71.8% (62.5 to 79.1) B: 51.5% (41.7 to 60.4) P = .010, log-rank Deaths at the 4th DSMC interim analysis: Arm A/C = 32 Arm B/D = 42 3-Year OS (95% CI): A: 66.2% (56.0 to 74.6)	• Cutoff date for the 4th interim DSMC analysis: July 16, 2021) • OS and PFS curves exhibited a biphasic pattern with the curves crossing. • Patients not enrolled in step 2 were followed for toxicity resolution and OS. • Study accrual was halted on September 30, 2021, on the basis of the DSMC recommendation: The protocol-specified comparison of 2-year OS rates by the Mantel-Haenszel

	award numbers: U10CA180794, U10CA180821, U10CA180820, U10CA180868, U10CA180888, UG1CA189804, UG1CA189809, UG1CA189822, UG1CA189829, UG1CA189830, UG1CA189863, UG1CA189953, UG1CA189957, UG1CA189997, UG1CA233184, UG1CA233193, UG1CA239769, UG1CA233234, UG1CA233290, UG1CA233320, UG1CA233270, UG1CA233330, UG1CA233331, and UG1CA239758. Authors' disclosures of potential conflicts	repeat brain MRI obtained 4 weeks following radiation or surgery. • From 2019: potential CNS metastases too small for SRS or surgery were permitted, and repeat brain MRI following SRS or surgery was not required if the original MRI was ≤4 weeks of study enrollment. To enroll onto step 2: • Progressive disease and meeting the relevant step 1 eligibility criteria. • Patients crossing over from arm A to arm C were required to have any immune-related adverse	• In 2019, the option was given to use alternate induction doses of nivolumab 3 mg/kg and ipilimumab 1 mg/kg once every 3 weeks for four doses for **arms A and D**.		• Treatment completed (n=33) • Adverse events (n=41) • Disease • Progression (n=32) • Withdrawal (n=1) • Death on study (n=7) • Alternative therapy (n=1) • Other complicating disease (n=1) • Others (n=5) • Missing (n=9) Arm B (n=132): • Treatment completed (NA)	B: 42.8% (32.9 to 52.4) OS in BRAFV600E: A: 71.4 (60.9 to 79.5) B: 43.9 (37.5 to 60.2) P=.020 OS in BRAFV600K A: 80.3 (50.1 to 93.2) B: 53.2 (32.9 to 69.9) P=.075 Median PFS, months (95% CI) A: 11.8 (5.9 to 33.5) B: 8.5 months (6.5 to 11.3)	chi-square test did not cross the efficacy boundary (P = .163); however, 2-year OS rates from a Kaplan-Meier analysis indicated a significant difference and crossed the O'Brien Fleming boundary at 59% information time. Furthermore, the 95% repeated CI around the 2-year OS difference remained positive (95% CI, 2.6% to 37.9%). Therefore, the DSMC deemed this difference in OS to be clinically meaningful and recommended that the study be closed to accrual and patients currently on arm B be given the option to switch to arm D without the need for disease progression.

	of interest are provided with the full text of this article.	events (irAEs) resolve to grade ≤1, but were permitted to be on immunosupp. therapy. Exclusion criteria: • Major surgery or radiation therapy within 14 days of starting study treatment • Autoimmune disease that might recur and affect vital organ function or require immunosupp. treatment • Cardiovascular disease • History of retinal vein occlusion • Use of medications being strong inhibitors or			• Adverse events (n=18) • Disease progression (n=78) • Withdrawal (n=7) • Death on study (n=3) • Alternative therapy (n=1) • Other complicating disease (n=1) • Others (n=8) • Missing (n=16) Arm C (n=26) • Treatment completed (NA) • Adverse events (n=3)	P = .054, log-rank. 2-Year PFS (95% CI): A: 41.9% (31.2 to 52.3) B: 19.2% (12.1 to 27.5) Median PFS for step 2, months (95% CI): C: 9.9 (8.3 to 20.8) D: 2.9 (2.6 to 8.9) ORR (95% CI): Step 1: A (n=113): 46.0% (36.6 to 55.6) B (n=114): 43.0% (33.8 to 52.6) Fisher's exact test P value 5 .690	<u>Authors conclusions:</u> Combination nivolumab/ipilimumab followed by BRAF and MEK inhibitor therapy, if necessary, should be the preferred treatment sequence for a large majority of patients.

		inducers of CYP3A or CYP2C8. Full eligibility criteria and toxicity management guidelines are provided in the Supplements (Table S1) describing the components of each protocol amendment. Median age (range) A: 61 (25-85) B: 61 (30-84) Male, n (%) A: 81 (60.9) B: 86 (65.2) ECOG PS:			• Disease progression (n=16) • Withdrawal (n=1) • Death on study (n=2) • Others (n=2) • Missing (n=2) Arm D (n=46): • Treatment completed (n=7) • Adverse events (n=10) • Disease progression (n=19) • Withdrawal (n=0) • Death on study (n=3) • Others (n=2)	Step 2: C (n=23): 47.8% (26.8 to 69.4) D (n=29): 29.6% (12.7 to 47.2) Grade ≥3 treatment related AEs: A: 59.5% B: 53.1% C: 53.8% D: 50.0% Treatment-related AEs on arms A and D were primarily immune-related and for arms B and C were primarily fevers, leukopenia, and hyponatremia. Treatment related Deaths:	

		0 – A: 90 (67.8) 0 – B: 89 (67.4) 1 – A: 43 (32.2) 1 – B: 43 (32.6) Arm A and B were balanced for most characteristics. More patients on arm B had BRAFV600K-mutant tumors than those on arm A (25.2% v 12.1%)			• Missing (n=5)	A: n=2 (myocarditis and colitis) B: n=1 (cerebral vascular event) C: n=1 (thromboembolic event).	
Ascierto, 2023 **IMspire150** **NCT02908672**.	A multicentre, doubleblind, placebo-controlled, randomised, phase 3 study done in 108 academic and community hospitals in 20 countries. Patient enrolment between: Jan 13, 2017, and April 26, 2018.	Main inclusion criteria • Age ≥18 years • Untreated, histologically confirmed stage IV or unresectable stage IIIc melanoma (defined by the AJCC (7th revised edition) • BRAFV600 mutation-positive tumours by a	Atezolizumab group n= 256 (50%) Cycle 1: All patients received oral cobimetinib 60 mg once daily plus oral vemurafenib 960 mg twice daily for 21 days then vemurafenib 720 mg twice daily (atezolizumab group) or 960 mg twice daily (control group) for 7 days.	Control group n= 258 (50%) Cycle 1: All patients received oral cobimetinib 60 mg once daily plus oral vemurafenib 960 mg twice daily for 21 days then vemurafenib 720 mg twice daily (atezolizumab group) or 960 mg twice daily (control group) for 7 days.	Median follow-up, months: I: 29·1 (IQR 10·1–45·4) C: 22·8 (10·6–44·1) Continued treatment at time of analysis: I: 37 (14%) C: 37 (14%)	Death: n=273 I: n=126 C: n=147 The secondary efficacy endpoint of overall survival was not met. Median OS, months (95% CI): I: 39·0 (29·9–not estimable)	• Data cutoff Sept 8, 2021. • The safety analysis included 511 patients (I: 231; C: 280). • One patient randomly assigned to the control group received atezolizumab and was included in the

	Funding and conflicts of interest: • The study was sponsored by, F Hoffmann-La Roche. The sponsor: ○ Contributed to study design ○ Confirmed accuracy of the data ○ Compiled data for analysis ○ Was involved in data analysis and interpretation and writing and review of the report. ○ The sponsor had no role in data collection; data were collected by investigators and	locally approved test • ECOG PS 0 or 1, • Measurable disease per RECIST version 1.1 criteria • A life expectancy of ≥18 weeks • Patients were permitted to use oral contraceptives, hormone replacement therapy, prophylactic or therapeutic anticoagulation therapy, inactivated influenza vaccinations, megestrol administered as an appetite stimulant, inhaled corticosteroids, mineralocorticoids, low-dose corticosteroids	From cycle 2 onwards atezolizumab was added: Patients received intravenous atezolizumab 840 mg (day 1 and 15), once-daily cobimetinib 60 mg (21 days on and 7 days off), and twice-daily vemurafenib 720 mg.	From cycle 2 onwards placebo was added: Patients received intravenous placebo (day 1 and 15), once-daily cobimetinib 60 mg (21 days on and 7 days off), and twice-daily vemurafenib 960 mg.	Median treatment, months: I: 9·2 (IQR 3·3–23·0) C: 8·9 (4·2–18·8) **Reasons for ending treatment** I: Cycle 1: (256 received allocated intervention): • 22 did not complete cycle one ○ 14 adverse events ○ 4 withdrawal by patient ○ 1 physician decision ○ 1 death	C: 25·8 (22·0–34·6) HR 0·84 (95% CI 0·66–1·060, p=0·14. Post-hoc landmark 12-month OS (95% CI): I: 76% (71–81) C: 76% (71–82) Prespecified landmark OS at 24 months (95% CI): I: 62% (55–68) C: 53% (47–60) With additional follow-up median PFS, months (95% CI): I: 15·1 (11·4–18·4) C: 10·6 (9·3–12·7)	atezolizumab group. • 26 patients randomly assigned to the atezolizumab group never received atezolizumab and were included in the control group. • A higher proportion of patients in the atezolizumab group compared with the control group (difference of ≥2%) had some AEs increased. For more information see the article. • <u>Authors conclusions:</u> In conclusion, additional follow-up of the IMspire150

	their research teams. ○ Medical writing and editorial support for this manuscript was provided by Nishad Parkar (ApotheCom, San Francisco, CA, USA) and was funded by F Hoffmann-La Roche. Authors' declaration of interests are provided at the end of the full text of this article.	administered for orthostatic hypotension or adrenocortical insufficiency and pain medications per standard practice. Main exclusion criteria: • Other active malignancies • Untreated or actively progressing brain metastases • A history of serious autoimmune disease. • Prohibited therapies included concomitant use of approved or experimental cancer treatment, investigational therapy, prophylactic			○ 1 disease progression ○ 1 protocol deviation Cycle 2: (n=230 received allocated intervention) • 4 did not receive allocated intervention ○ 3 adverse events ○ 1 disease progression • 199 discontinued ○ 102 progressive disease ○ 57 adverse event ○ 16 withdrawal by patient	HR 0·79 (95% CI 0·64–0·97), p=0·022. PFS events: I: n=168 C: 198 Median PFS, months (95% CI): I: 15·1 (11·4–18·4) C: 10·6 (9·3–12·7) Post-hoc landmark PFS (95% CI): At 6 months: I: 73% (67–78) C: 74% (69–80); At 12 months: I: 54% (48–60) C: 46% (39–52); At 18 months:	phase 3 study showed that overall survival was not significantly improved in the atezolizumab group versus the control group. Results from the final analysis are awaited to establish whether the atezolizumab, vemurafenib, and cobimetinib triplet combination can significantly improve overall survival in patients with previously untreated BRAFV600 mutation-positive advanced or metastatic melanoma.

		antiemetics, antidiarrhoea medication, haematopoietic growth factors, antiarrhythmic drugs, medications with a risk of torsades de pointes, and acetaminophen. Additional details on in/exclusion criteria are available in the protocol (appendix). Median age (range) A: 54.0 years (44.8-64.0 years) B: 53.5 years (43.0-63.8 years) Male, n (%) A: B:			○ 10 physician's decision ○ 8 death ○ 4 other ○ 1 protocol deviation ○ 1 symptom deterioration C: Cycle 1 (n=255 received allocated intervention): • 3 did not receive allocated placebo ○ 1 withdrawal by patient ○ 2 other • 21 did not complete cycle one	I: 44% (37–50) C: 32% (26–38) ORR : I: 170/255 (67%; 61–72) C: 160/246 (65%; 59–71) Serious AEs: I: 112 (48%)/231 C: 117 (42%)/280 Atezolizumab-associated SAEs: n=57 (25%) Placebo associated SAEs: n=35 (13%) Cobimetinib-associated	

					○ 15 adverse events ○ 2 withdrawal by patient ○ 1 physician decision ○ 1 protocol deviation ○ 2 other Cycle 2 (n=231received allocated intervention): • 3 did not receive allocated intervention ○ 2 withdrawal by patient ○ 2 other • 202 discontinued	SAEs: I: 53 (23%) C: 61 (22%) Vemurafenib-related SAEs: I: 58 (25%) C: 71 (25%) Grade 5 AEs I: n=8 (3%) C: n=6 (2%) For more information on AEs see results section of the article.	

					○ 146 progressive disease ○ 31 adverse event ○ 6 withdrawal by patient ○ 10 physician's decision ○ 4 death ○ 4 other 1 symptom deterioration		

8.3.1.2. Tweedelijnsbehandeling BRAF-V600E/K gemuteerd irresectabel of gemetastaseerd stadium III/IV

Uitgangsvraag

Wat is de plaats van systemische therapie in de tweede lijns-behandeling van patiënten met een BRAF-V600E/K gemuteerd irresectabel of gemetastaseerd stadium III/IV melanoom?

Search and select

The search and selection methods can be found in the main module 8.3 [Link XXX]

Summary of literature

Eight randomized controlled trials that studied clinical outcomes of second line systemic therapy in patients with unresectable or metastatic stadium III/IV melanoma with a BRAF-V600E/K mutation were included in the literature analysis.

Description of studies

The study characteristics of the included trials are summarized in Table 2 in the main module 8.3 [Link XXX].

Revicki (2012), Hodi (2010) - MDX010-20 is a randomized, double-blind phase 3 study that enrolled patients at 125 centres in 13 countries in North America, South America, Europe, and Africa. This trial evaluated the effect of ipilimumab with or without a gp100 peptide vaccine on overall survival compared to gp100 alone in patients with unresectable stage III or IV melanoma who received a previous therapeutic regimen. Patients were randomized to ipilimumab, at a dose of 3 mg/kg of body weight, plus a gp100 peptide vaccine (n=403); ipilimumab (n=137); or gp100 (n=136). The mean age was 55.6 years in the ipilimumab plus gp100 peptide vaccine group, 56.8 years in the ipilimumab group and 57.4 years in the gp100 group. The percentage of males was 61.3 %, 59.1%, and 53.7% for the three groups, respectively. No information was available on the BRAF mutation status of the patients. Hodi (2010) reported on overall survival (OS), progression free survival (PFS), and adverse events (AEs) after a follow up time of 55 months. Revicki (2012) reported health related QoL outcomes during the 12 week treatment induction period. In this literature analysis the median outcomes for OS and PFS are analysed and the last endpoint for OS (2-year OS rates) are described.

Robert (2019), Carlino (2018), Schachter (2017), Robert (2015) - KEYNOTE-006 is an international, randomized, open-label phase 3 study performed in 16 countries. In this trial treatment with pembrolizumab versus ipilimumab was studied, to compare PD-1 inhibition with CTLA-4 blockade in patients with unresectable stage III/IV melanoma. Patients were randomized to pembrolizumab at a dose of 10 mg/kg of body weight

every 2 weeks (n= 279); pembrolizumab at a dose of 10 mg/kg every 3 weeks (n=277); or ipilimumab at a dose of 3 mg/kg every 3 weeks (n=278). The mean age was 61 years in the pembrolizumab every 2 weeks group, 63 years in the pembrolizumab every 3 weeks group and 62 years in the ipilimumab group. The percentage of males was 57.7 %, 62.8%, and 58.3% for the three groups, respectively. Robert (2015) reported on OS, PFS, and AEs after a median follow-up of 7.9 months. Schachter (2017) reported updated results after a median follow-up of 22.9 months. Carlino (2018) reported updated outcomes by line of therapy and programmed death ligand 1 expression after a median follow-up of 33.9 months. Robert (2019) reported updated results of OS, PFS, and AEs after a median follow-up of 57.7 months. In this literature analysis the median outcomes for OS and PFS are analysed and the last endpoints for OS and PFS (2-year OS rates and 2-year PFS rates) are described.

Chesney (2023) - MASTERKEY-265 is a multicenter, double-blind, placebo controlled, randomized phase 3 study in 21 countries. This trial evaluated the efficacy and safety of T-VEC plus pembrolizumab versus placebo plus pembrolizumab in patients with stage IIIB-IV M1c unresectable melanoma. Patients were randomized to a combination of T-VEC plus pembrolizumab 200 mg once every 3 weeks (n=346) or placebo plus pembrolizumab 200 mg once every 3 weeks (n=346). The median age was 64 years in both study groups. The percentage of males was 57.5% in the T-VEC-pembrolizumab group and 63.3% placebo-pembrolizumab group. Chesney (2023) reported OS, PFS, and AES, after a median follow-up of 25.6 months for the primary PFS analysis, 31.0 months for the second OS interim analysis, and 35.6 months for the final analysis. In this literature analysis the median outcomes for OS and PFS are analysed.

Andtbacka (2019), Andtbacka (2015) - OPTiMis a randomized open-label phase 3 trial at 64 sites in the United States, the United Kingdom, Canada, and South Africa. This trial evaluated outcomes with talimogene laherparepvec (T-VEC) compared with granulocyte macrophage colony-stimulating factor (GM-CSF) in patients with unresectable, stage IIIB/C/IV melanoma with ≥1 lesion that was suitable for direct or ultrasound-guided injection. Patients were randomized in 2:1 ratio to T-VEC (at the approved dose) (n=295 (68%)) of subcutaneous recombinant GM-CSF (n=141 (32%)). The median age was 63 years in the T-VEC group and 64 years in the GM-CSF group. The percentage of males was 59% in the T-VEC group and 55% in the GM-CSF group. Of 204 of the 295 (69%) in the T-VEC group, and 95 of the 141 (67%) in the GM-CSF group, the BRAF mutation status was unknown. For 157 of the 295 (53%) patients in the T-VEC group, and 76 of the 141 (54%) in the GM-CSF group, this was a second line therapy or later. OS and AEs were reported after a median follow-up of 49 months in the final analysis of OS. In this literature analysis the median OS is analysed.

Robert (2015), Robert (2016) - COMBI-v described an open-label, randomized, phase 3 study performed at 193 centres worldwide, where they evaluated the efficacy and safety of using combination therapy with dabrafenib plus trametinib versus vemurafenib monotherapy in patients with previously untreated patients with unresectable stage IIIC or IV melanoma with BRAF V600E or V600K mutations. A total of 704 patients were randomized in a 1:1 ratio to receive either a combination of dabrafenib (150 mg orally twice daily) plus trametinib (2 mg orally once daily) or vemurafenib (960 mg orally twice

daily). The median age was 55 (18–91) years in the combination group and 54 (18–88) years in the control group. In the combination group 59% was male, compared to 51% in the control group. The following relevant outcomes were reported, OS, PFS and number of patients with serious AEs. In this literature analysis the median outcomes for OS and PFS are analysed and the last endpoints (3-year OS and 3-year PFS) of the outcomes are described.

Dummer (2018), Dummer (2018-2), Ascierto (2020) - COLUMBUS described a two-part, randomised, open-label, phase 3 study, performed at 162 sites in 28 countries. They evaluated the efficacy and safety of encorafenib plus binimetinib versus encorafenib alone and versus vemurafenib alone in patients with histologically confirmed, locally advanced, unresectable, or metastatic BRAF-V600 mutated cutaneous melanoma, or unknown primary melanoma. In part 1 of the study, 577 patients were randomly assigned (1:1:1) to receive oral encorafenib 450 mg once daily plus oral binimetinib 45 mg twice daily (encorafenib plus binimetinib group), oral encorafenib 300 mg once daily encorafenib group), or oral vemurafenib 960 mg twice daily (vemurafenib group). The median age was 57 (20–89; 48–66) years in the combination group, 54 (23–88; 46–63) years in the encorafenib control group and 56 (21–82; 45–65) years in the vemurafenib control group. In the combination group 60% was male, compared to 60% and 56% in the two control groups, respectively. The following relevant outcomes were reported, OS, PFS and number of patients with serious AEs. In this literature analysis the median outcomes for OS and PFS are analysed and the last endpoint (3-year OS) for the outcome OS is described.

Rohaan (2022) - NCT02278887 is a multicenter, open-label, phase 3, randomized trial with two participating clinical sites. In trial, tumor-infiltrating lymphocytes (TILs) were compared with ipilimumab in patients with unresectable or metastatic stage IIIC or IV cutaneous melanoma, with ≥1 lesions that could be surgically removed for generation of TILs. Patients were randomized to adoptive cell therapy with TILs (n=84) or ipilimumab at a dose of 3 mg/kg every 3 weeks (n=84). The median age was 59 years in both study groups. The percentage of males was 56% in the TILS group and 63% in the ipilimumab group. OS, PFS, AEs, and QoL were reported after a median follow-up of 33 months. In this literature analysis the median outcomes for OS and PFS are analysed and the last endpoints for OS and PFS (2-year OS rates and 6-month PFS rates) are described.

Weber (2015), Larkin (2018) - CHECKMATE-037 described a randomized, controlled, open-label, phase III study, which was conducted in 90 sites in 14 countries with a median follow-up of approximately 2 years. They evaluated the efficacy and safety of second-line nivolumab versus investigator's choice chemotherapy (ICC) in patients with metastatic melanoma who experienced progression after treatment with first-line ipilimumab (plus a BRAF inhibitor, if BRAF-mutation positive). A total of 405 patients were randomized 2:1 to receive nivolumab (n= 272, 3 mg/kg every two weeks) or ICC (n = 133, dacarbazine 1,000 mg/m2 every 3 weeks or carboplatin area under the curve 6 plus paclitaxel 175 mg/m2 every 3 weeks). Of the 272 patients that received nivolumab, 60 (22%) had a BRAF mutation. Of the 133 patients that received ICC, 29 (22%) had a BRAF mutation. The median age was 59 (23-88) years in the nivolumab group and 62

(29-85) years in the ICC group. In the nivolumab group 65% was male, compared to 64% in the ICC group. The following relevant outcomes were reported, OS, PFS, number of patients with serious AEs and quality of life.

Results

Overall survival (OS) - Critical outcome
All eight included studies reported on OS.

MDX010-20 reported the effect of **ipilimumab with a gp100 peptide vaccine** plus **ipilimumab without a gp100 peptide vaccine** compared to **gp100 alone** on OS. The 2-year OS rates were 21.6% in the ipilimumab with a gp100 peptide vaccine group, 23.5% in the ipilimumab group, and 13.7% in the gp100 alone group. Treatment with ipilimumab with or without a gp100 peptide vaccine resulted in a longer median OS compared to treatment with gp100 alone. The absolute difference between treatment with ipilimumab with a gp100 peptide vaccine (10.0 months) and treatment with gp100 alone (6.2 months) was 3.8 months with a HR of 0.68 (95% CI 0.55–0.85). This difference was considered clinically relevant according to the PASKWIL criteria. The absolute difference between treatment with ipilimumab without gp100 (10.1 months) compared to treatment with gp100 peptide vaccine alone was 3.7 months with a HR of 0.66 (0.51–0.87). This difference was considered clinically relevant according to the PASKWIL criteria. Treatment with ipilimumab with a gp100 peptide vaccine resulted in a similar median OS compared to treatment with ipilimumab, with an absolute difference of 0.1 months and HR of 1.04 (95% CI 0.83–1.30). This difference was not considered clinically relevant according to the PASKWIL criteria.

KEYNOTE-006 reported the effect of **pembrolizumab every 2 weeks** or **pembrolizumab every 3 weeks** compared to **ipilimumab every 3 weeks** on OS. The 2-year OS rates were 55% in the pembrolizumab-every-2-weeks group, 55% in the pembrolizumab-every-3-weeks group, and 43% in the ipilimumab-every-3-weeks group. Treatment with pembrolizumab resulted in a longer median OS than treatment with ipilimumab. In patients receiving second-line therapy the absolute difference between the combined pembrolizumab groups (23.5 months) and the ipilimumab group (13.6 months) was 9.9 months with a HR of 0.75 (95% CI 0.55–1.03). This difference was not considered clinically relevant according to the PASKWIL criteria.

MASTERKEY-265 reported the effect of a combination of **T-VEC plus pembrolizumab** versus placebo plus **pembrolizumab** on OS. Treatment with T-VEC-pembrolizumab did not result in a longer OS compared with treatment with placebo-pembrolizumab. The median OS was not estimable in the T-VEC plus pembrolizumab group and 49.2 months (40.57 to not estimable) in the pembrolizumab group with a HR of 0.96 (95% CI 0.76 to 1.22; P =0 .74).

OPTiM reported the effect of **T-VEC** versus **GM-CSF** on OS in first line treatment, without subgroup analyses on BRAF mutation. Treatment with T-VEC resulted in a longer median OS than treatment with GM-CSF. The median follow-up in the final OS analysis was 49

months. Median OS weas 23.3 months (CI, 19.5-29.6) and 18.9 months (95% CI, 16.0-23.7) in the TVEC and GM-CSF arm, respectively (HR, 0.79; 95% CI, 0.62-1.00). This difference was not considered clinically relevant according to the PASKWIL criteria.

COLUMBUS reported the effect of **encorafenib plus binimetinib** versus **encorafenib** versus **vemurafenib** on median OS. Treatment with encorafenib and binimetinib resulted in the longest median OS. The absolute difference between encorafenib and binimetinib (33.6 months) and encorafenib (23.5 months) was 10.1 months with a HR of 0.81 (95% 0.61 to 1.06). This difference was not considered clinically relevant according to the PASKWIL criteria. The absolute difference between encorafenib and binimetinib (33.6 months) and vemurafenib (16.9 months) was 16.7 months with a HR of 0.61 (95% 0.47 to 0.79). This difference was considered clinically relevant according to the PASKWIL criteria. The absolute difference between encorafenib (23.5 months) and vemurafenib (16.9 months) was 6.6 months with a HR of 0.76 (95% 0.58 to 0.98). This difference was not considered clinically relevant according to the PASKWIL criteria.

COMBI-v did not reported the effect of **dabrafenib plus trametinib** versus **vemurafenib** on median OS. However, the absolute difference in median 3-year survival between dabrafenib and trametinib (45%) versus vemurafenib (32%) was 13%, with a higher 3-year survival in the dabrafenib and trametinib group. This difference was considered clinically relevant according to the PASKWIL criteria.

NCT02278887 reported the effect of **tumor-infiltrating lymphocytes (TILs)** versus **ipilimumab** on OS. The 2-year OS rates were 54.3% in the TILs group and 44.1% in the ipilimumab group. Treatment with TILs resulted in a longer median OS compared to treatment with ipilimumab. The absolute difference between the TILs group (25.8 months) and the ipilimumab group (18.9 months) was 6.9 months with a HR of 0.83 (95% CI, 0.54 to 1.27). This difference was not considered clinically relevant according to the PASKWIL criteria.

Checkmate-037 reported the effect of **nivolumab** versus **investigator's choice chemotherapy** (ICC; dacarbazine or carboplatin plus paclitaxel) on OS in patients with a BRAF mutation. The absolute difference in median OS in patients in the nivolumab group (9.07 months) compared to patients in the ICC group (17 months) was 7.93 months with a HR of 1.32 (0.75 to 2.32). This difference was not considered clinically relevant according to the PASKWIL criteria.

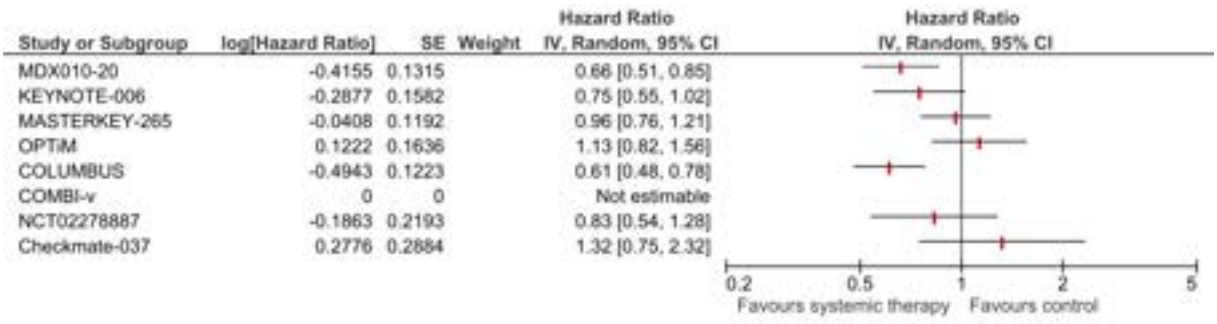

Figure 3. Forest plot of median overall survival for second line systemic therapy versus placebo, other systemic therapy, or best supportive care in patients with a BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma.

[a] For MDX010-20 the HR for ipilumab without gp100 versus gp100 vacine is shown.
[b] For KEYNOTE-066 the HR for combined pembrolizumab versus ipilimumab is shown.
[c] For COLOMBUS the HR for encorafenib and binimetinib versus vemurafenib is shown.
[d] COMBI-v did not report the HR for median OS and is therefore not shown in this figure.

Progression free survival – important outcome measure
Seven of the eight included studies reported on PFS.

MDX010-20 reported the effect of **ipilimumab with a gp100 peptide vaccine** and **ipilimumab without a gp100 peptide vaccine** compared to **gp100 alone** on PFS. Median PFS was comparable between the three study groups. After the first assessment of progression at week 12 there was a separation between the curves. There was a 19% reduction in the risk of progression in the ipilimumab plus gp100 group, as compared with gp100 alone with a HR of 0.81. There was a 36% reduction in risk of progression in the ipilimumab alone group as compared with the gp100 alone group with a HR of 0.64. According to the PASKWIL criteria we could not assess clinical relevance (median OS in the control group was < 12 months).

KEYNOTE-006 reported the effect of **pembrolizumab every 2 weeks** or **pembrolizumab every 3 weeks** compared to **ipilimumab every 3 weeks** on PFS. The 2-year PFS rates were 31% in the pembrolizumab-every-2-weeks group, 28% in the pembrolizumab-every-3-weeks group, and 14% in the ipilimumab-every-3-weeks group. Treatment with pembrolizumab resulted in a longer median PFS than treatment with ipilimumab. The absolute difference between the combined pembrolizumab groups and the ipilimumab group was 5.0 months with a HR of 0.57 (95% CI 0.48–0.67). This difference was considered clinically relevant according to the PASKWIL criteria.

MASTERKEY-265 reported the effect of a combination of **T-VEC plus pembrolizumab** versus placebo plus **pembrolizumab** on PFS. Treatment with T-VEC-pembrolizumab resulted in a longer PFS compared with treatment with placebo-pembrolizumab. The absolute difference between the combined pembrolizumab groups and the ipilimumab group was 5.8 months with a HR of 0.86 (95% CI, 0.71 to 1.04). This difference was not considered clinically relevant according to the PASKWIL criteria.

COLUMBUS reported the effect of **encorafenib plus binimetinib** versus **encorafenib** versus **vemurafenib** on PFS. Treatment with encorafenib and binimetinib resulted in the longest PFS. The absolute difference between encorafenib and binimetinib (14.9 months) and encorafenib (9.6 months) was 5.3 months. According to the PASKWIL criteria we could not assess clinical relevance (HR and 95% CI not provided). The absolute difference between encorafenib and binimetinib (14.9 months) and vemurafenib (7.3 month) was 7.6 months with a HR of 0.51 (95% 0.39 to 0.67). This difference was considered clinically relevant

according to the PASKWIL criteria. The absolute difference between encorafenib (9.6 months) and vemurafenib (7.3 months) was 2.3 months. According to the PASKWIL criteria we could not assess clinical relevance (HR and 95% CI not provided).

COMBI-v reported the effect of **dabrafenib plus trametinib** versus **vemurafenib** on PFS. Treatment with dabrafenib and trametinib resulted in a longer PFS than treatment with vemurafenib. The absolute difference between the dabrafenib and trametinib group (11.4 months) and the vemurafenib group (7.3 months) was 4,1 months with a HR of 0.56 (95% 0.46 to 0.69). This difference was considered clinically relevant according to the PASKWIL criteria.

NCT02278887 reported the effect of **tumor-infiltrating lymphocytes (TILs)** versus **ipilimumab** on PFS. The 6-month PFS rates were 52.7% in the TILs group and 21.4% in the ipilimumab group. Treatment with TILs resulted in a longer median PFS compared to treatment with ipilimumab. The absolute difference between the TILs group and the ipilimumab group was 4.1 months with a HR of 0.50 (95% CI, 0.35 to 0.72). This difference was considered clinically relevant according to the PASKWIL criteria.

Checkmate-037 reported the effect of **nivolumab** versus **investigator's choice chemotherapy** (ICC; dacarbazine or carboplatin plus paclitaxel) on PFS in their total patient population (both BRAF mutant and BRAF wild-type). Treatment with nivolumab resulted in a shorter median PFS compared to treatment with ICC. The absolute difference was 0.6 months with a HR of 1.0 (95.1% CI, 0.78 to 1.44). This difference was not considered clinically relevant according to the PASKWIL criteria.

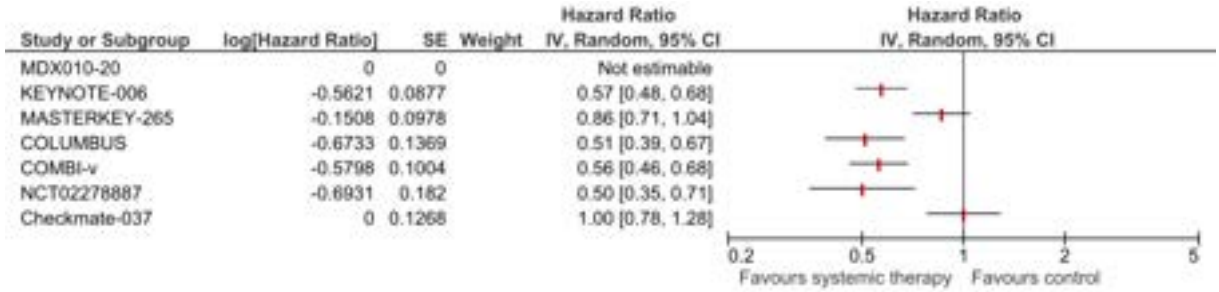

Figure 4. Forest plot of median progression free survival for second line systemic therapy versus placebo, other systemic therapy, or best supportive care in patients with a BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma.

[a] For KEYNOTE-066 the HR for combined pembrolizumab versus ipilimumab is shown.
[b] For COLOMBUS the HR for encorafenib and binimetinib versus vemurafenib is shown.
[c] MDX010-20 did not report the 95% CI of the HR for median PFS and is therefore not shown in this figure.

Treatment related adverse events (AEs) grade ≥ 3 - Important outcome
Eight of the eight studies reported AE.

MDX010-20 reported the effect of **ipilimumab with a gp100 peptide vaccine plus ipilimumab without a gp100 peptide vaccine** compared to **gp100 alone** on AEs. Treatment with ipilimumab with a gp100 peptide vaccine resulted in a higher percentage of treatment related AEs grade ≥3 compared to treatment with gp100 alone. The risk difference between ipilimumab with a gp100 peptide vaccine and gp100 alone is 0.05 (95% CI -0.03, 0.13; NNH= 20) favoring treatment with gp100 alone. This difference is not considered clinically relevant according to the PASKWIL criteria. The risk difference between ipilimumab without a gp100 peptide vaccine and gp100 alone is 0.14 (95% CI 0.03, 0.25; NNH= 7) favoring treatment with gp100 alone. This difference is not considered clinically relevant according to the PASKWIL criteria.

KEYNOTE-006 reported the effect of **pembrolizumab every 2 weeks** or **pembrolizumab every 3 weeks** compared to **ipilimumab every 3 weeks** on AEs. Treatment with pembrolizumab (pooled groups) resulted in a lower percentage of treatment related AEs grade ≥3 compared to treatment with ipilimumab. The risk difference between pembrolizumab (pooled groups) and ipilimumab is -0.01 (95% CI -0.06, 0.05; NNH=100) favoring treatment with pembrolizumab. This difference is not considered clinically relevant according to the PASKWIL criteria.

MASTERKEY-265 reported the effect of a combination of **T-VEC plus pembrolizumab** versus placebo plus **pembrolizumab** on AEs. Treatment with T-VEC-pembrolizumab resulted in a higher percentage of treatment related AEs grade ≥3 compared to treatment with placebo-pembrolizumab. The risk difference between T-VEC plus pembrolizumab and placebo-pembrolizumab is 0.05 (95% CI -0.01, 0.10; NNH=20) favoring treatment with placebo plus pembrolizumab. This difference is not considered clinically relevant according to the PASKWIL criteria.

OPTiM reported the effect of **T-VEC** versus **GM-CSF** on AEs. Treatment with T-VEC resulted in a higher percentage of treatment related AEs grade ≥3 compared to treatment with GM-CSF. The risk difference between T-VEC and GM-CSF is 0.07 (95% CI 0.02, 0.12; NNH=14) favoring treatment with GM-CSF. This difference is not considered clinically relevant according to the PASKWIL criteria.

COLUMBUS reported the effect of **encorafenib and binimetinib** versus **encorafenib** versus **vemurafenib** on AEs. There was no risk difference in the percentage of AEs between encorafenib and binimetinib (68%) and encorafenib (68%). The risk difference in AEs between encorafenib and binimetinib (68%) and vemurafenib (66%) was 2%. This difference was not considered clinically relevant according to the PASKWIL criteria. The risk difference between encorafenib (68%) and vemurafenib (66%) was also 2%. This difference was not considered clinically relevant according to the PASKWIL criteria.

COMBI-v reported the effect of **dabrafenib and trametinib** versus **vemurafenib** on AEs. Treatment with dabrafenib and trametinib resulted in less AEs than treatment with vemurafenib. The risk difference between the dabrafenib and trametinib group (48%) and the vemurafenib group (57%) was 9%. This difference was not considered clinically relevant according to the PASKWIL criteria.

NCT02278887 reported the effect of **tumor-infiltrating lymphocytes (TILs)** versus **ipilimumab** on AEs. Treatment with TILs resulted in a higher percentage of treatment related AEs grade ≥3 compared to treatment with ipilimumab. The risk difference between TILs and ipilimumab is 0.43 (95% CI 0.32, 0.54; NNH=2) favoring treatment with ipilimumab. This difference is considered clinically relevant according to the PASKWIL criteria.

Checkmate-037 reported the effect of **nivolumab** versus **investigator's choice chemotherapy** (ICC; dacarbazine or carboplatin plus paclitaxel) on AES. Treatment with nivolumab resulted in a higher percentage of treatment related AEs grade ≥3 compared to treatment with ICC. The risk difference between nivolumab and ICC is 0.17 (95% CI 0.09, 0.25; NNH=6) favoring treatment with ICC. This difference is not considered clinically relevant according to the PASKWIL criteria.

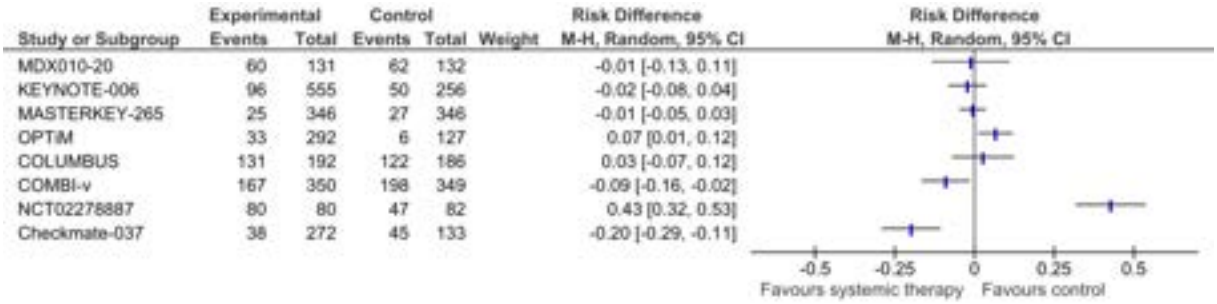

Figure 5. Forest plot of Adverse Events for second line systemic therapy versus placebo, other systemic therapy, or best supportive care in patients with a BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma.

[a] For MDX010-20 the risk difference for ipilumab without gp100 versus gp100 vacine is shown.
[b] For KEYNOTE-066 the risk difference for combined pembrolizumab versus ipilimumab is shown.
[c] For COLOMBUS the risk difference for encorafenib and binimetinib versus vemurafenib is shown.

Quality of life (QoL) - Important outcome
Three of the eight studies reported the effect of second line systemic therapy on QoL.

MDX010-20 analysed the effect of **ipilimumab with or without a gp100 peptide vaccine** compared **to gp100 alone** on health related quality of life (HRQL) with the EORTC QLQ-C30. Mean changes of baseline to week 12 scores for function, global health status, and symptoms were analysed. These were categorized as "no change" (0–5), "a little" (5–10 points), "moderate" (10–20 points), and "very much" (>20). In general, the authors observed "no change" or "a little" impairment in the ipilimumab plus gp100 and ipilimumab alone groups. The study showed significant differences in constipation, favouring ipilimumab ($p<0.05$). This difference is not considered clinically relevant (difference less than 10 points). In the gp100 alone group, moderate to large changes for global health, role function, fatigue, and pain were observed. These differences between the treatment arms are not considered clinically relevant (difference less than 10

points). The authors conclude that ipilimumab with or without gp100 vaccine does not have a significant negative HRQL impact during the treatment induction phase relative to gp100 alone in stage III or IV melanoma patients.

NCT02278887 of **tumor-infiltrating lymphocytes (TILs)** versus **ipilimumab** on QoL. In this study, Health-related quality of life (HRQL) was measured with the EORTC Quality-of-Life Questionnaire Core 15 palliative care. In this questionnaire, higher scores on the global quality-of-life and functioning scales indicate better functioning and higher scores on the symptom scales indicate higher levels of symptom burden. Higher mean scores were observed after treatment among patients in the TIL group on the global health-related quality-of life (difference 7.7), physical functioning (difference 2.9), and emotional functioning (difference 9.7) domains compared to patients in the ipilimumab group. These differences are not considered clinically relevant (differences less than 10 points). Lower symptoms scores were observed after treatment among patients in the TIL group for fatigue, pain, and insomnia compared to patients in the ipilimumab group, with differences still observed at week 60. These differences are not considered clinically relevant (differences less than 10 points). Higher symptom scores of nausea and vomiting were observed among patients in the TIL group compared to patients in the ipilimumab group. This difference was not considered clinically relevant (difference less than 10 points).

Checkmate-037 analysed the effect of **nivolumab** versus **investigator's choice chemotherapy** (ICC; dacarbazine or carboplatin plus paclitaxel) on QoL. HRQL was assessed using the EORTC QLQ-C30 version 3 and EuroQoL EQ-5D summary index and visual analog scale. The study showed that quality of life in patients on nivolumab remained stable for all EORTC QLQ-C30 individual scales during the treatment course. No scores reached the minimal important difference of ≥10 points. The authors stated that no clinically significant improvement was observed for either the EuroQoL EQ-5D utility index or the EuroQoL EQ-5D visual analog scale for nivolumab. In the article the authors mention that at 12 weeks, the ICC group demonstrated a clinically significant decrease in the EuroQoL EQ-5D utility index. These data are not shown in the article or supplementary material.

Level of evidence of the literature

There are four levels of evidence: high, moderate, low, and very low. RCTs start at a high level of evidence.

Ipilimumab with or without a gp100 peptide vaccine compared to gp100 alone
The level of evidence regarding the outcome measure **overall survival** was downgraded by three levels because of study limitations (risk of bias), the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision), and the lack of subgroup analyses (indirectness). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by three levels because of study limitations (risk of bias), because we could not asses clinical relevance according to the PASKWIL criteria (imprecision), and the lack

of subgroup analyses (indirectness). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by three levels because of study limitations (risk of bias), was downgraded by one level because the optimal information size is not met (imprecision) and the lack of subgroup analyses (indirectness). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **quality of life** was downgraded by three levels because of study limitations (risk of bias), was downgraded by one level because the optimal information size is not met (imprecision), and the lack of subgroup analyses (indirectness). Therefore, the level of evidence was graded as very low.

Pembrolizumab every 2 weeks or every 3 weeks compared to ipilimumab

The level of evidence regarding the outcome measure **overall survival** was downgraded by four levels because of study limitations (risk of bias -2); the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision), and the lack of subgroup analyses (indirectness). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by three levels because of study limitations (risk of bias -2) and the lack of subgroup analyses (indirectness). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by four levels because of study limitations (risk of bias -2), because the optimal information size is not met (imprecision), and because of a lack of subgroup analyses (indirectness). Therefore, the level of evidence was graded as very low.

T-VEC plus pembrolizumab versus placebo plus pembrolizumab

The level of evidence regarding the outcome measure **overall survival** was downgraded by four levels because of study limitations (risk of bias -2), the optimal information size is not met (imprecision), and the lack of a subgroup analysis (indirectness). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by four levels because of study limitations (risk of bias -2), the optimal information size is not met (imprecision), and the lack of a subgroup analysis (indirectness). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by four levels because of study limitations (risk of bias -2), the optimal information size is not met (imprecision), and the lack of a subgroup analysis (indirectness). Therefore, the level of evidence was graded as very low.

T-VEC versus GM-CSF

The level of evidence regarding the outcome measure **overall survival** was downgraded by four levels because of study limitations (risk of bias -2); the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision), and the lack of subgroup analyses (indirectness). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by four levels because of study limitations (risk of bias -2), was downgraded by one level because the optimal information size is not met (imprecision), and the lack of subgroup analyses (indirectness). Therefore, the level of evidence was graded as very low.

Dabrafenib and trametinib versus vemurafenib

The level of evidence regarding the outcome measure **overall survival** was downgraded by one level because of study limitations (risk of bias -1). Therefore, the level of evidence was graded as moderate.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by one level because of study limitations (risk of bias -1). Therefore, the level of evidence was graded as moderate.

The level of evidence regarding the outcome measure **adverse events** was downgraded by two level because of study limitations (risk of bias -2). Therefore, the level of evidence was graded as low.

Encorafenib and binimetinib versus encorafenib versus vemurafenib

Encorafenib and binimetinib versus encorafenib

The level of evidence regarding the outcome measure **overall survival** was downgraded by two levels because of study limitations (risk of bias -1) and because the confidence interval encloses the threshold for a clinically relevant effect (imprecision -1). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by two level because of study limitations (risk of bias -1), and no clinically relevant effect could be established (imprecision -1). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by two level because of study limitations (risk of bias -2). Therefore, the level of evidence was graded as low.

Encorafenib and binimetinib versus vemurafenib

The level of evidence regarding the outcome measure **overall survival** was downgraded by two levels because of study limitations (risk of bias -1) and because the confidence interval encloses the threshold for a clinically relevant effect (imprecision -1). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by one level because of study limitations (risk of bias -1). Therefore, the level of evidence was graded as moderate.

The level of evidence regarding the outcome measure **adverse events** was downgraded by two level because of study limitations (risk of bias -2). Therefore, the level of evidence was graded as low.

Encorafenib versus vemurafenib
The level of evidence regarding the outcome measure **overall survival** was downgraded by two levels because of study limitations (risk of bias -1) and because the confidence interval encloses the threshold for a clinically relevant effect (imprecision -1). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by two level because of study limitations (risk of bias -1), and no clinically relevant effect could be established (imprecision -1). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by two level because of study limitations (risk of bias -2). Therefore, the level of evidence was graded as low.

Tumor-infiltrating lymphocytes (TILs) versus ipilimumab
The level of evidence regarding the outcome measure **overall survival** was downgraded by three levels because of study limitations (risk of bias), the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision), and because of the lack of subgroup analyses (indirectness). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by three levels because of study limitations (risk of bias) the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision), and because of the lack of subgroup analyses (indirectness). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by two levels because of study limitations (risk of bias), and because of the lack of subgroup analyses (indirectness). Therefore, the level of evidence was graded as low

The level of evidence regarding the outcome measure **quality of life** was downgraded by two levels because of study limitations (risk of bias), and because of the lack of subgroup analyses (indirectness). Therefore, the level of evidence was graded as low.

Nivolumab versus investigator's choice chemotherapy
(ICC; dacarbazine or carboplatin plus paclitaxel)
The level of evidence regarding the outcome measure **overall survival** was downgraded by three levels because of study limitations (risk of bias -2); was downgraded by one

level because the optimal information size is not met (imprecision). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by four levels because of study limitations (risk of bias -2), the optimal information size is not met (imprecision), and the lack of subgroup analyses (indirectness). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by four levels because of study limitations (risk of bias -2), the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision) , and the lack of subgroup analyses (indirectness). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **quality of life** was downgraded by three levels because of study limitations (risk of bias -2), and the lack of subgroup analyses (indirectness). Therefore, the level of evidence was graded as very low.

Conclusions

Ipilimumab with or without a gp100 peptide vaccine compared to gp100 alone

Overall survival

Very low GRADE	The evidence is very uncertain about the effect of ipilimumab with or without a gp100 peptide vaccine on overall survival when compared with treatment with gp100 alone in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Hodi, 2010*
Very low GRADE	The evidence is very uncertain about the effect of ipilimumab with or without a gp100 peptide vaccine on overall survival when compared with treatment Ipilimumab alone in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Hodi, 2010*

Progression free survival

Very low GRADE	The evidence is very uncertain about the effect of ipilimumab with or without a gp100 peptide vaccine on progression free survival when compared with treatment with gp100 alone in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Hodi, 2010*

Adverse events

Very low GRADE	The evidence is very uncertain about the effect of ipilimumab with or without a gp100 peptide vaccine on adverse events when compared with treatment with gp100 alone in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Hodi, 2010*

Quality of Life

Very low GRADE	The evidence is very uncertain about the effect of ipilimumab with or without a gp100 peptide vaccine on quality of life when compared with treatment with gp100 alone in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Revicki, 2012*

Pembrolizumab every 2 weeks or every 3 weeks compared to ipilimumab

Overall survival

Very low GRADE	The evidence is very uncertain about the effect of pembrolizumab every 2 weeks or every 3 on overall survival when compared with treatment with ipilimumab in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Robert, 2019; Carlino, 2018; Schachter, 2017; Robert, 2015*

Progression free survival

Very low GRADE	The evidence is very uncertain about the effect of pembrolizumab every 2 weeks or every 3 on adverse events when compared with treatment with ipilimumab in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Robert, 2019; Carlino, 2018; Schachter, 2017; Robert, 2015*

Adverse events

Very low GRADE	The evidence is very uncertain about the effect of pembrolizumab every 2 weeks or every 3 on adverse events when compared with treatment with ipilimumab in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Robert, 2019; Carlino, 2018; Schachter, 2017; Robert, 2015*

T-VEC plus pembrolizumab versus placebo plus pembrolizumab

Overall survival

Very low GRADE	The evidence is very uncertain about the effect of treatment with T-VEC plus pembrolizumab on overall survival when compared with placebo plus pembrolizumab in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Chesney, 2023*

Progression free survival

Very low GRADE	The evidence is very uncertain about the effect of treatment with T-VEC plus pembrolizumab on progression free survival when compared with placebo plus pembrolizumab in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Chesney, 2023*

Adverse events

Very low GRADE	The evidence is very uncertain about the effect of treatment with T-VEC plus pembrolizumab on adverse events when compared with placebo plus pembrolizumab in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Chesney, 2023*

T-VEC versus GM-CSF

Overall survival

Very low GRADE	The evidence is very uncertain about the effect of treatment with T-VEC on overall survival when compared with GM-CSF in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Andtbacka, 2019; Andtbacka, 2015*

Adverse events

Very low GRADE	The evidence is very uncertain about the effect of treatment with T-VEC on adverse events when compared with GM-CSF in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Andtbacka, 2019; Andtbacka, 2015*

Dabrafenib plus trametinib versus vemurafenib

Overall survival

Moderate GRADE	Dabrafenib plus trametinib likely result in an increase in overall survival when compared with vemurafenib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Robert (2015), Robert (2016)*

Progression free survival

Moderate GRADE	Dabrafenib plus trametinib likely result in an increase in progression free survival when compared with vemurafenib and placebo in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Robert (2015), Robert (2016)*

Adverse events

Moderate GRADE	Dabrafenib plus trametinib likely result in little to no difference in adverse events when compared with vemurafenib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Robert (2015), Robert (2016)*

Encorafenib and binimetinib versus encorafenib versus vemurafenib

Encorafenib plus binimetinib versus encorafenib

Overall survival

Moderate GRADE	Encorafenib plus binimetinib likely result in little to no difference in overall survival when compared with encorafenib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Dummer (2018), Dummer (2018-2), Ascierto (2020)*

Progression free survival

Low GRADE	Encorafenib plus binimetinib may result in little to no difference in progression free survival when compared with encorafenib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Dummer (2018), Dummer (2018-2), Ascierto (2020)*

Adverse events

Low GRADE	Encorafenib plus binimetinib may result in little to no difference in adverse events when compared with encorafenib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Dummer (2018), Dummer (2018-2), Ascierto (2020)*

Encorafenib plus binimetinib versus vemurafenib
Overall survival

Moderate GRADE	Encorafenib plus binimetinib likely result in an increase in overall survival when compared with vemurafenib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Dummer (2018), Dummer (2018-2), Ascierto (2020)*

Progression free survival

Moderate GRADE	Encorafenib plus binimetinib likely result in an increase in progression free survival when compared with vemurafenib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Dummer (2018), Dummer (2018-2), Ascierto (2020)*

Adverse events

Low GRADE	Encorafenib plus binimetinib may result in little to no difference in adverse events when compared with vemurafenib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Dummer (2018), Dummer (2018-2), Ascierto (2020)*

Encorafenib versus vemurafenib
Overall survival

Moderate GRADE	Encorafenib likely result in little to no difference in overall survival when compared with vemurafenib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Dummer (2018), Dummer (2018-2), Ascierto (2020)*

5

Progression free survival

Low GRADE	Encorafenib may result in little to no difference in overall survival when compared with vemurafenib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Dummer (2018), Dummer (2018-2), Ascierto (2020)*

Adverse events

Low GRADE	Encorafenib may result in little to no difference in adverse events when compared with vemurafenib in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Dummer (2018), Dummer (2018-2), Ascierto (2020)*

10

Tumor-infiltrating lymphocytes (TILs) versus ipilimumab

Overall survival

Very low GRADE	The evidence is very uncertain about the effect of treatment with tumor-infiltrating lymphocytes (TILs) on overall survival when compared with ipilimumab in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Rohaan, 2022*

Progression free survival

Very low GRADE	The evidence is very uncertain about the effect of treatment with tumor-infiltrating lymphocytes (TILs) on overall survival when compared with ipilimumab in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Rohaan, 2022*

5

Adverse events

Low GRADE	Treatment with tumor-infiltrating lymphocytes (TILs) may increase adverse events compared to ipilimumab in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Rohaan, 2022*

Quality of life

Low GRADE	Treatment with tumor-infiltrating lymphocytes (TILs) may result in little to no difference in quality of life compared to ipilimumab in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Rohaan, 2022*

10

Nivolumab versus investigator's choice chemotherapy
(ICC; dacarbazine or carboplatin plus paclitaxel)

Overall survival

Very low GRADE	The evidence is very uncertain about the effect of treatment with nivolumab on overall survival when compared with investigator's choice chemotherapy in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Weber 2015; Larkin 2018*

Progression free survival

Very low GRADE	The evidence is very uncertain about the effect of treatment with nivolumab on progression free survival when compared with investigator's choice chemotherapy in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Weber 2015; Larkin 2018*

Adverse events

Very low GRADE	The evidence is very uncertain about the effect of treatment with nivolumab on adverse events when compared with investigator's choice chemotherapy in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Weber 2015; Larkin 2018*

Quality of life

Very low GRADE	The evidence is very uncertain about the effect of treatment with nivolumab on quality of life when compared with investigator's choice chemotherapy in patients with BRAF-V600E/K mutation with unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Weber 2015; Larkin 2018*

Overwegingen – van bewijs naar aanbeveling

De cruciale uitkomstmaat overall survival in de context van patiënten met irresectabel of gemetastaseerd stadium III/IV melanoom met een BRAF-V600E/K mutatie werd gerapporteerd door 8 RCTs die verschillende systemische behandelingen in de tweede lijn onderzochten.

MDX010-20 rapporteerde het effect van **ipilimumab met een gp100 peptide vaccin** en **ipilimumab zonder een gp100 peptide vaccin** in vergelijking met alleen **gp100** op overall survival bij patiënten met niet-receerbaar of gemetastaseerd stadium III/IV melanoom (Revicki, 2012; Hodi, 2010). Er werd daarbij een klinisch relevant voordeel gevonden voor het gebruik van ipilimumab met een gp100 peptide vaccine en voor ipilimumab zonder een gp100 peptide vaccine in vergelijking met gp100 alleen. Het absolute verschil in mediane overall survival tussen behandeling met ipilimumab met een gp100 peptide vaccine versus behandeling met alleen gp100 was 3.6 maanden met een hazard ratio van 0.68 (95% CI 0.55–0.85). Het absolute verschil in mediane overall survival tussen behandeling met ipilimumab zonder een gp100 peptide vaccine versus behandeling met alleen gp100 was 3.7 maanden met een hazard ratio van 0.66 (0.51–0.87). De bewijskracht van deze studie is laag. Dit heeft te maken met het risico op bias (de rol van de sponsor in deze studie) en door imprecisie omdat de confidence interval de grens voor klinische besluitvorming omvat.

De studie rapporteerde ook het effect op progression free survival, adverse events en kwaliteit van leven. Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor de uitkomsten progression free survival, adverse events en kwaliteit van leven.

KEYNOTE-006 rapporteerde het effect van **pembrolizumab** (iedere 2 of 3 weken) in vergelijking met **ipilimumab** (iedere 3 weken) op overall survival bij patiënten met unresectable of gemetastaseerd stadium III/IV melanoom (Robert, 2019; Carlino, 2018; Schachter, 2017; Robert, 2015). Er werd daarbij geen klinisch relevant voordeel gevonden voor het gebruik van pembrolizumab. Het absolute verschil in mediane overall survival tussen behandeling met pembrolizumab versus behandeling met ipilimumab was 16.8 maanden met een hazard ratio van 0.73 (95% CI 0.61–0.88). De bewijskracht van deze studie is zeer laag. Dit heeft te maken met het risico op bias (open-label studie design; meer patiënten stopten in de controle groep; de rol van de sponsor) en door imprecisie, omdat de confidence interval de grens voor klinische besluitvorming omvat.

De studie rapporteerde ook het effect op progression free survival en adverse events. Voor de uitkomst progression free survival werd een klinisch relevant voordeel gevonden voor behandeling met pembrolizumab. Het absolute verschil in mediane progressievrije overleving was 5.0 maanden (HR 0.57; 95% CI 0.48–0.67). Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor de uitkomst adverse events.

MASTERKEY-265 rapporteerde het effect van **T-VEC plus pembrolizumab** in vergelijking met **placebo plus pembrolizumab** op overall survival bij patiënten met unresectable of gemetastaseerd stadium III/IV melanoom (Chesney, 2023). Er werd daarbij geen klinisch relevant voordeel gevonden voor het gebruik van T-VEC plus pembrolizumab (HR 0.96;

95% CI 0.76 to 1.22). De bewijskracht van deze studie is zeer laag. Dit heeft te maken met het risico op bias (meer patiënten stopten in de controle groep; studie werd vroegtijdig gestopt) en door imprecisie.

De studie rapporteerde ook het effect op progression free survival en adverse events. Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor de uitkomsten progression free survival en adverse events.

OPTiM rapporteerde het effect van **T-VEC** in vergelijking met **GM-CSF** op overall survival bij patiënten met niet-receerbaar of gemetastaseerd stadium III/IV melanoom (Andtbacka, 2019; Andtbacka, 2015). Er werd daarbij geen klinisch relevant voordeel gevonden voor het gebruik van T-VEC. Het absolute verschil in mediane overall survival tussen behandeling met T-VEC versus behandeling met GM-CSF was 4.4 maanden met een hazard ratio 0.79 (95% CI 0.62–1.00). De bewijskracht van deze studie is zeer laag. Dit heeft te maken met het risico op bias (open-label studie design; meer patiënten stopten in de interventie groep; de rol van de sponsor) en door imprecisie, omdat het betrouwbaarheidsinterval de grens voor klinische besluitvorming omvat.

De studie rapporteerde ook het effect op adverse events. Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor de uitkomst adverse events.

COMBI-v rapporteerde niet het effect van dabrafenib en trametinib versus vemurafenib op de mediane OS. Echter, het absolute verschil in mediane 3-jaarsoverleving tussen dabrafenib en trametinib (45%) en vemurafenib (32%) was 13%, met een hogere 3-jaarsoverleving in de dabrafenib en trametinib groep. Dit verschil werd volgens de PASKWIL-criteria als klinisch relevant beschouwd. De bewijskracht hiervan is redelijk, dit heeft te maken met het risico op bias.

De studie rapporteerde ook het effect op progression free survival en adverse events. Voor de uitkomst progression free survival werd een klinisch relevant voordeel gevonden voor behandeling met cobimetinib gecombineerd met vemurafenib. Het absolute verschil in mediane progressievrije overleving was 5.4 maanden (HR 0.51; 95% CI 0.39–0.67). Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor de uitkomst adverse events.

COMBI-v rapporteerde niet het effect van dabrafenib en trametinib versus vemurafenib op de mediane OS. Echter, het absolute verschil in mediane 3-jaarsoverleving tussen dabrafenib en trametinib (45%) en vemurafenib (32%) was 13%, met een hogere 3-jaarsoverleving in de dabrafenib en trametinib groep. Dit verschil werd volgens de PASKWIL-criteria als klinisch relevant beschouwd. De bewijskracht hiervan is redelijk, dit heeft te maken met het risico op bias.

De studie rapporteerde ook het effect op progression free survival en adverse events. Voor de uitkomst progression free survival werd een klinisch relevant voordeel gevonden voor behandeling met cobimetinib gecombineerd met vemurafenib. Het absolute verschil in mediane progressievrije overleving was 5.4 maanden (HR 0.51; 95% CI 0.39–0.67). Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor de uitkomst adverse events.

COLUMBUS rapporteerde het effect van encorafenib en binimetinib versus encorafenib versus vemurafenib op de mediane OS. Behandeling met encorafenib en binimetinib resulteerde in de langste mediane OS. Het absolute verschil tussen encorafenib en binimetinib (33,6 maanden) en encorafenib (23,5 maanden) was 10,1 maanden met een HR van 0,81 (95% BI: 0,61 tot 1,06). Dit verschil werd volgens de PASKWIL-criteria niet als klinisch relevant beschouwd. Het absolute verschil tussen encorafenib en binimetinib (33,6 maanden) en vemurafenib (16,9 maanden) was 16,7 maanden met een HR van 0,61 (95% BI: 0,47 tot 0,79). Dit verschil werd volgens de PASKWIL-criteria als klinisch relevant beschouwd. Het absolute verschil tussen encorafenib (23,5 maanden) en vemurafenib (16,9 maanden) was 6,6 maanden met een HR van 0,76 (95% BI: 0,58 tot 0,98). Dit verschil werd volgens de PASKWIL-criteria niet als klinisch relevant beschouwd. De bewijskracht hiervan is redelijk, dit heeft te maken met de imprecisie, omdat de confidence interval de grens voor klinische besluitvorming omvat.

De studie rapporteerde ook het effect op progression free survival en adverse events. Voor de uitkomst progression free survival werd een klinisch relevant voordeel gevonden voor behandeling met encorafenib end binimetinib vergeleken met vemurafenib. Het absolute verschil in mediane progressievrije overleving was 7.6 maanden (HR en CI niet gegeven). Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor de uitkomst adverse events.

NCT02278887 rapporteerde het effect van **tumor-infiltrating lymphocytes (TILs)** versus **ipilimumab** op overall survival bij patiënten met unresectable of gemetastaseerd stadium III/IV melanoom (Rohaan, 2022). Er werd daarbij geen klinisch relevant voordeel gevonden voor het gebruik van TILs. Het absolute verschil in mediane overall survival was 6.9 maanden met een hazard ratio van 0.83 (95% CI, 0.54 to 1.27). De bewijskracht van deze studie is zeer laag. Dit heeft te maken met het risico op bias (onduidelijke randomisatie, open-label studie design, en doordat meer patiënten in de controle groep de behandeling stopten in vergelijking met de interventie groep) en imprecisie.

De studie rapporteerde ook het effect op progression free survival, adverse events en kwaliteit van leven. Een langere mediane progression free survival werd gevonden voor patiënten in de TILs groep, met een absoluut verschil van 4.1 maanden met patiënten in de ipilimumab groep (HR 0.50; 95% CI 0.35 to 0.72). Behandeling met TILs resulteerde in een hoger percentage patiënten met adverse events (risk difference: 0.43; 95% CI 0.32, 0.54; NNH=2). Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor de uitkomst kwaliteit van leven.

Checkmate-037 rapporteerde het effect van **nivolumab** versus **investigator's choice chemotherapy** (ICC; dacarbazine or carboplatin plus paclitaxel) op overall survival bij patiënten met unresectable of gemetastaseerd stadium III/IV melanoom (Weber 2015, Larkin 2018). Er werd daarbij geen klinisch relevant voordeel gevonden voor het gebruik van nivolumab. Het absolute verschil in mediane overall survival was 1.3 maanden met een hazard ratio van 0.95 (95.54% CI 0.73 to 1.24). De bewijskracht van deze studie is zeer laag. Dit heeft te maken met het risico op bias (open-label studie design; doordat meer patiënten in de interventie groep de behandeling stopten in vergelijking met de controle groep; de rol van de sponsor in deze studie) en imprecisie.

De studie rapporteerde ook het effect op progression free survival, adverse events en kwaliteit van leven. Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor de uitkomsten progression free survival, adverse events en kwaliteit van leven.

Kwaliteit van bewijs

Ipilimumab with or without a gp100 peptide vaccine compared to gp100 alone
De overall kwaliteit van bewijs is zeer laag. Dit betekent dat we zeer onzeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Pembrolizumab every 2 weeks or every 3 weeks compared to ipilimumab
De overall kwaliteit van bewijs is zeer laag. Dit betekent dat we zeer onzeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

T-VEC plus pembrolizumab versus placebo plus pembrolizumab
De overall kwaliteit van bewijs is zeer laag. Dit betekent dat we zeer onzeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

T-VEC versus GM-CSF
De overall kwaliteit van bewijs is zeer laag. Dit betekent dat we zeer onzeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Dabrafenib and trametinib versus vemurafenib
De overall kwaliteit van bewijs is redelijk. Dit betekent dat we redelijk zeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Encorafenib and binimetinib versus encorafenib versus vemurafenib
Encorafenib and binimetinib versus encorafenib
De overall kwaliteit van bewijs is laag. Dit betekent dat we onzeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Encorafenib en binimetinib versus vemurafenib
De overall kwaliteit van bewijs is laag. Dit betekent dat we onzeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Encorafenib versus vemurafenib
De overall kwaliteit van bewijs is laag. Dit betekent dat we onzeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Tumor-infiltrating lymphocytes (TILs) versus ipilimumab
De overall kwaliteit van bewijs is zeer laag. Dit betekent dat we zeer onzeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Nivolumab versus investigator's choice chemotherapy (ICC; dacarbazine or carboplatin plus paclitaxel)
De overall kwaliteit van bewijs is zeer laag. Dit betekent dat we zeer onzeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Overwegingen- van bewijs naar aanbeveling

Ondanks de vooruitgang in de behandeling van irresectabel of gemetastaseerd melanoom, blijven veel vragen onbeantwoord en voor een belangrijke deel van de patiënten blijft de prognose slecht. Inclusie in klinische studies blijft daarom de hoogste prioriteit in alle settings.

Waarden en voorkeuren van patiënten (en eventueel hun naasten/verzorgers)

Bij de behandeling van patiënten met een irresectabel of gemetastaseerd stadium III/IV melanoom dient zorgvuldig rekening te worden gehouden met de waarden en voorkeuren van de patiënt. De keuze voor deelname aan klinische studies of voor tweedelijnsbehandelopties – zoals TIL-therapie, anti-PD-1-blokkade met ipilimumab, of doelgerichte therapie in de vorm van BRAF + MEK-inhibitie bij patiënten met een BRAFV600-mutatie – wordt bij voorkeur afgestemd op individuele patiëntkenmerken en specifieke behandeldoelen.

Professioneel perspectief

Factoren zoals het gewenste behandeldoel (kortetermijn- of langetermijnvoordeel), klinische kenmerken (bijvoorbeeld lactaatdehydrogenase-niveaus, betrokken organen, prestatiestatus, tumorlast en progressiesnelheid), evenals comorbiditeiten spelen een cruciale rol bij deze behandelbeslissing. Door deze aspecten zorgvuldig af te wegen in lijn met de voorkeuren van de patiënt kan een optimaal behandeltraject worden gekozen dat zowel klinische effectiviteit waarborgt als aansluit bij de persoonlijke waarden van de patiënt.

Kostenaspecten

Vanwege geheime prijsafspraken, kan de exacte impact op het geneesmiddelenbudget niet worden vastgesteld, maar het staat vast dat deze impact hoog is. Het huidig prijsniveau wordt echter acceptabel geacht in verhouding tot de effectiviteit van de behandeling. Een lagere prijs van de behandelingen zou desondanks in alle opzichten zeer wenselijk en naar mening van de werkgroep zelfs noodzakelijk zijn, mede met het oog op de komende ontwikkelingen en het betaalbaar houden en borgen van een goede kwaliteit van de zorg in de nabije toekomst.

Haalbaarheid/aanvaardbaarheid

Bij de behandeling van patiënten met een irresectabel of gemetastaseerd stadium III/IV melanoom is het van belang niet alleen te kijken naar klinische effectiviteit en patiëntvoorkeuren, maar ook naar de haalbaarheid en aanvaardbaarheid van de aanbevolen behandelopties. Deelname aan klinische studies kan voor sommige patiënten een haalbare optie zijn, mits er toegang is tot geschikte onderzoeksfaciliteiten en de patiënt bereid is de mogelijk intensieve studieverplichtingen te dragen. Voor patiënten met een BRAFV600-mutatie kunnen tweedelijnsopties zoals TIL-therapie, anti-PD-1-blokkade met ipilimumab, of BRAF + MEK-inhibitie passend zijn, maar de haalbaarheid van deze therapieën wordt mede bepaald door de beschikbaarheid en toegankelijkheid van specialistische zorg en middelen. De aanvaardbaarheid van deze behandelopties hangt bovendien sterk samen met het behandeldoel en de verwachte belasting voor de patiënt: sommige patiënten kunnen de voorkeur geven aan

behandelingen met een potentieel kortetermijnvoordeel en lagere bijwerkingenlast, terwijl anderen bereid zijn intensievere therapieën te overwegen in ruil voor een mogelijke langere overlevingswinst. Zo kunnen haalbaarheid en aanvaardbaarheid per patiënt variëren, wat zorgvuldige overweging van hun persoonlijke en klinische omstandigheden vereist om een passend behandeltraject te waarborgen.

Rationale

De werkgroep is van mening dat deelname aan klinische studies in de behandeling van irresectabel of gemetastaseerd stadium III/IV melanoom de hoogste prioriteit heeft, gezien de sombere prognose voor een groot deel van de patiënten en de noodzaak om effectiviteit en aanvaardbaarheid van behandelingen verder te optimaliseren. Hierbij is het essentieel om patiëntwaarden en individuele klinische kenmerken leidend te laten zijn, zodat behandelbeslissingen aansluiten bij zowel haalbaarheid als de persoonlijke voorkeuren van de patiënt.

Aanbevelingen

Overweeg behandeling in studieverband.

Overweeg als tweedelijnsbehandeloptie voor patiënten met een BRAFV600-gemuteerd irresectabel of gemetastaseerd melanoom volgende behandelopties: TIL- behandeling of anti-PD-1 blokkade met ipilimumab (indien niet gebruikt in de eerstelijns setting) of doelgerichte behandeling in de vorm van BRAF + MEK-inhibitie (indien niet gebruikt in de eerstelijns setting).

Individualiseer deze behandelbeslissing rekening houdend met het behandeldoel (kortetermijnvoordeel versus langetermijnvoordeel) en klinische kenmerken [lactaatdehydrogenase (LDH), betrokken organen, prestatiestatus (PS), tumorlast, snelheid van ziekteprogressie], comorbiditeiten, bijwerkingen van de verschillende therapieën en patiëntvoorkeuren.

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Evidence tabellen

Revicki, 2012 **Hodi, 2010** **MDX010-20** **NCT00094653**	Randomized, double-blind, phase 3 study. Patients at 125 centers in 13 countries in North America, South America, Europe, and Africa. Patient enrolment between: September 2004 and August 2008. <u>Funding and conflicts of interest:</u> • The sponsors, Medarex and Bristol-Myers Squibb contributed to: ▪ Trial design ▪ Data collection ▪ Initial draft of the manuscript • All authors signed a confidentiality disclosure agreement with the sponsor. Disclosure forms provided by the authors are available with the full text of this article.	Inclusion criteria: • Diagnosis of unresectable stage III or IV melanoma who received a previous therapeutic regimen containing one or more of the following: dacarbazine, temozolomide, fotemustine, carboplatin, or interleukin-2.; • Age ≥ 18 years; • Life expectancy ≥ 4 months; • ECOG PS 0 or 1; • Positive status for HLA-A⋆0201; • Normal hematologic, hepatic, and renal function; • No systemic treatment in the previous 28 days. Exclusion criteria: • Any other cancer from which the patient had been disease-free for < 5 years (except treated and cured basal-cell or squamous-cell skin cancer, superficial bladder cancer, or treated carcinoma in situ of the cervix, breast, or bladder); • primary ocular melanoma; • Previous receipt of anti–CTLA-4	I: Ipilimumab, at a dose of 3 mg per kilogram of body weight, plus a gp100 peptide vaccine n= 403	C1: Ipilimumab plus gp100 placebo n=137 C2: gp100 plus ipilimumab placebo. n=136	Patients were followed for up to 55 months. Median follow-up time for survival: I: 21.0 months C1: 27.8 months C2: 17.2 months	Median OS, months (95% CI) I: 10.0 (8.5 to 11.5) C1: 10.1 (8.0 to 13.8) C2: 6.4 (5.5 to 8.7) I vs C2: HR for death: 0.68 (0.55–0.85); P<0.001 C1 vs C2: HR for death: 0.66 (0.51–0.87); P=0.003 I vs C1: HR for death: 1.04 (0.83–1.30). P=0.76 1-Year OS: I: 43.6% C1: 45.6% C2: 25.3% 18-month OS: I: 30.0% C1: 33.2% C2: 16.3% 2-Year OS: I: 21.6% C1: 23.5% C2: 13.7%	• The original primary end point was best overall response rate. The primary end point was amended to overall survival (amendment approved on January 15, 2009) in the ongoing blinded study. • Efficacy analyses were performed on the intention-to-treat population, which included all patients who had undergone randomization (676 patients). • The safety population included all patients who had undergone randomization and who had received any amount of study drug (643 patients). • In the vaccine groups, patients received two modified HLA-A⋆0201–restricted peptides, injected subcutaneously as an emulsion with incomplete Freund's adjuvant (Montanide ISA-51): a gp100:209-217(210M) peptide, 1 mg injected in the right anterior thigh, and a gp100:280-288(288V) peptide, 1 mg injected in the left anterior thigh. <u>Authors conclusions:</u> **Hodi, 2010:** Ipilimumab, with or without a gp100 peptide vaccine, as compared with gp100 alone, improved overall survival in patients with previously treated metastatic melanoma. Adverse events can be severe, long-lasting, or both, but most are reversible with appropriate treatment.

		antibody or cancer vaccine; • Autoimmune disease; • Active, untreated metastases in the central nervous system; • Pregnancy or lactation; • Concomitant treatment with any nonstudy anticancer therapy or immunosuppressive agent; • Long-term use of systemic corticosteroids. Mean age, years I: 55.6 C1: 56.8 C2: 57.4 Male, n (%) I: 247 (61.3%) C1: 81 (59.1%) C2: 73 (53.7%) ECOG PS:				Median PFS, months (95% CI): I: 2.76 (2.73 to 2.79) C1: 2.86 (2.76 to 3.02) C2: 2.76 (2.73 to 2.83) AEs grade 3 or 4: I: 173/374 C1: 60/127 C2: 62/128 Drug-related AEs, Grade 3 or 4/total: I: 66/338 C1: 30/105 C2: 15/104 Immune-related AEs, Grade 3 or 4/total: I: 39/221 C1: 19/80 C2: 4/42	**Revicki, 2012:** Ipilimumab with/without gp100 vaccine does not have a significant negative HRQL impact during the treatment induction phase relative to gp100 alone in stage III or IV melanoma patients.

		0 – I: 232 (57.6%) 0 – C1: 72 (52.6%) 0 – C2: 70 (51.5%) 1 – I: 166 (41.2%) 1 – C1: 64 (46.7%) 1 – C2: 61 (44.9%) 2 – I: 4 (1%) 2 – C1: 1 (0.7%) 2 – C2: 4 (2.9%) 3 – I: 1 (0.2%) 3 – C1: 0 3 – C2: 0 Unknown: I: 0 C1: 0 C2: 1 (0.7%) Groups were comparable at baseline.				Drug-related deaths, n: I: 8 C1: 4 C2: 2 For more information on AEs see results section of the article. EORTC QLQ-C30 symptom scores (improvements are indicated by negative scores): Difference in constipation scores: I: 5.2 C1:1.9 C2:11.8 I vs C2: p<0.05 C1 vs C2: p<0.05 Favouring ipilimumab. None of the other differences in HRQL scores between the	

						three treatments were statistically significant.	
Robert, 2019 Carlino, 2018 Schachter, 2017 Robert, 2015 KEYNOTE-006 NCT01866319	International, randomized, open-label phase 3 study. In 16 countries. Patient enrolment: From September 18, 2013, to March 3, 2014. <u>Funding and conflicts of interest:</u> • The sponsors, Merck Sharp & Dohme, contributed to: • Trial design • Statisticians and a science writer were employed by the sponsor. Disclosure forms provided by the authors are available with the full text of this article.	Inclusion criteria: • Age ≥ 18 years • Histologically confirmed, unresectable stage III or IV melanoma who received no more than one previous systemic therapy for advanced disease • Known BRAF V600 mutational status was required; • previous BRAF inhibitor therapy was not required for patients with normal lactate dehydrogenase levels • no clinically significant tumor-related symptoms or evidence of rapidly progressive disease. • ECOG PS of 0 or 1 • Provision of a tumor sample adequate for assessing PD-L1 expression. Exclusion criteria: • Patients who had received previous	Ia: pembrolizumab at a dose of 10 mg per kilogram of body weight every 2 weeks n= 279 Ib: pembrolizumab at a dose of 10 mg per kilogram of body weight either every 3 weeks n=277	C: Four cycles of ipilimumab at a dose of 3 mg per kilogram every 3 weeks n=278	**Robert, 2019:** Median follow-up for survival: 57.7 months (IQR 56.7–59.2). **Carlino, 2018:** Median follow-up: 33.9 months. **Schachter, 2017:** Median follow-up: 22.9 months Discontinued treatment: Ia: *147 progressive disease* *29 adverse events* *2 deaths* *2 complete responses*	**Robert, 2019:** Median OS: I (pooled groups): 32.7 months (95% CI 24·5–41·6) C: 15.9 months (13.3–22.0) HR: 0.73 (95% CI 0.61–0.88, p=0·00049). Median PFS: I (pooled groups): 8.4 months (95% CI 6.6–11.3) C: 3.4 months (2.9–4.2) HR 0.57, 95% CI 0.48–0.67, p<0.0001. Grade 3–4 treatment-related AEs: I (pooled groups): 96 (17%) C: 50 (20%)	Co-primary endpoints were OS and PFS. **Robert, 2019:** • Data cutoff: Dec 3, 2018. **Carlino, 2018:** • Data cutoff: 03 Nov 2016. • Reported outcomes by line of therapy and PD-L1 expression **Schachter, 2017:** • Data cutoff: Dec 3, 2015. **Robert, 2015:** • Data cutoff 1st interim analysis: Sep 3, 2014 (PFS and AEs) • Data cutoff 2nd interim analysis: Mar 3, 2015 (OS). • OS results for the pembrolizumab groups were superior to those for the ipilimumab group. The independent data and safety monitoring committee recommended stopping the study early.

		therapy with CTLA-4, PD-1, or PD-L1 inhibitors • Ocular melanoma • Active brain metastases • History of serious autoimmune disease. Mean age, years Ia: 61 (18–89) Ib: 63 (22–89) C: 62 (18–88) Male, n (%) Ia: 161 (57.7) Ic: 174 (62.8) C: 162 (58.3) ECOG PS: 0 – Ia: 196 (70.3) 0 – Ib: 189 (68.2) 0 – C: 188 (67.6) 1 – Ia: 83 (29.7) 1 – Ib: 88 (31.8)			*21 other* Ib: *139 progressive disease* *45 adverse events* *1 death* *5 complete responses* *23 other* C: *46 progressive disease* *35 adverse events* *5 deaths* *24 other* Withdrew consent and did not receive treatment: Ia: n=1 C: n=22 **Robert, 2015:**	Treatment-related sepsis. C: n=1 **Schachter, 2017:** Death: n=383 Median OS: Ia: not reached (range 22.1 months–not reached) Ib: not reached (23.5 months–not reached) C: 16.0 months (range 13.5–22.0) HR pembro every 2 weeks vs ipi: 0.68, 95% CI 0·53–0·87; p=0·0009 HR pembro every 3 weeks vs ipi: 0.68, 0·53–0·86; p=0·0008. 2 year OS rate: Ia: 55% (95% CI 49–61) Ib: 55% (95% CI 49–61) C: 43% (95% CI 37–49)	<u>Authors conclusions:</u> **Robert, 2019:** Pembrolizumab continued to show superiority over ipilimumab after almost 5 years of follow-up. These results provide further support for use of pembrolizumab in patients with advanced melanoma. **Carlino, 2018:** Findings support pembrolizumab monotherapy as standard of care in patients with advanced melanoma, regardless of first- or second-line therapy or PD-L1 status. **Schachter, 2017:** Substantiating the results of the interim analyses of KEYNOTE-006, pembrolizumab continued to provide superior overall survival versus ipilimumab, with no difference between pembrolizumab dosing schedules. These conclusions further support the use of pembrolizumab as a standard of care for advanced melanoma.

		1 – C: 90 (32.4) PD-L1-positive tumours: 80.6% Groups were comparable at baseline.			Median follow-up at data cutoff (with 502 events reported), months: 7.9 (range: 6.1 to 11.5) March 3, 2015: Follow-up for OS: Minimum follow-up: 12 months with 289 deaths occurred Mean duration of exposure, days: Ia: 164 Ib: 151 C: 50 Rate discontinuation of a study drug because of treatment related AEs: Ia: 4.0%, Ib: 6.9%,	PFS events: n= 566 I (pooled groups): 364 (65%) C: 202 (35%) Median PFS, months: Ia: 5.6 months (range 3.4–8.2) Ib: 4.1 months (range 2.9–7.2) C: 2.8 months (range 2.8–2.9) HR for both Pembro schedules vs ipi: 0.61; 95% CI 0·50–0·75; p<0·0001 HR for Ia vs Ib: 0.95; 95% CI 0·77–1·17; p=0·62). 2-year PFS rate: Ia: 31% Ib: 28% C: 14%	**Robert, 2015:** The anti–PD-1 antibody pembrolizumab prolonged progression-free survival and overall survival and had less high-grade toxicity than did ipilimumab in patients with advanced melanoma.

					C: 9.4%, Treatment related AEs grade 3 to 5: Ia: 47 (17%) of 278 Ib: 46 (17%) of 277 C: 50 (20%) of 256 **Robert, 2015:** Median overall survival was not reached in any study group. 1-Year OS: Ia: 74.1% Ib: 68.4% C: 58.2% • HR for death for pembrolizumab every 2 weeks versus ipilimumab: 0.63; 95% CI, 0.47 to 0.83; P<0.0005 • HR for death for pembrolizumab every 3 weeks versus ipilimumab: 0.69; 95% CI, 0.52 to 0.90; P = 0.0036	

						Median PFS, months (95% CI): Ia: 5.5 (95% CI, 3.4 to 6.9) Ib: 4.1 (95% CI, 2.9 to 6.9) C: 2.8 (95% CI, 2.8 to 2.9) • HR for progression for pembrolizumab every 2 weeks versus ipilimumab: 0.58 (95% CI, 0.46 to 0.72; P<0.001) • HR for pembrolizumab every 3 weeks versus ipilimumab: 0.58 (95% CI, 0.47 to 0.72; P<0.001). 6-month PFS, months: Ia: 47.3% Ib: 46.4% C: 26.5% Treatment related AEs grade 3 to 5: Ia: 13.3%	

						Ib: 10.1% C: 19.9% Drug-related deaths, n: Ia: 0 Ib: 0 C: 1 For more information on AEs see results section of the article.	
Chesney, 2023 **MASTERKEY-265** **NCT02263508**	A multicenter, double-blind, placebo controlled, randomized phase III study in 21 countries. Patient enrolment between: March 17, 2016, through April 26, 2018. <u>Funding and conflicts of interest:</u> - Supported by Amgen Inc and Merck	Main Inclusion criteria: • Histologically confirmed stage IIIB-IV M1c unresectable melanoma • Age ≥ 18 years • ECOG PS 0 or 1 • At least one visceral or nodal/soft tissue melanoma lesion for which the longest diameter was ≥ 10 mm • In/exclusion criteria with regard to prior therapy for patients with BRAF-mutated melanoma is specified in the article. Exclusion criteria:	I: A combination of T-VEC plus pembrolizumab (T-VEC-pembrolizumab) n=346 T-VEC was administered at ≤ 4 x 106 plaque-forming unit followed by ≤ 4 x 108 PFU 3 weeks later and once every 2 weeks until dose 5 and once every 3 weeks thereafter. Pembrolizumab was administered intravenously 200 mg once every 3 weeks.	C: Placebo plus pembrolizumab (placebo-pembrolizumab n=346 Pembrolizumab was administered intravenously 200 mg once every 3 weeks.	Median follow-up in months: • 25.58 (range, 0.3-45.8) for the PFS primary analysis. • 31.0 (range, 0.3-53.0) for the second OS interim analysis. • 35.56 (range, 0.3-58.4) for the final analysis Discontinued study: I: n = 152 *Death n = 131*	Deaths at planned second interim OS analysis: I: 136 (39.3%) C: 146 (42.2%) Median OS, months (95% CI): I: Not estimable C: 49.2 (40.57 to not estimable) HR of 0.96 (95% CI, 0.76 to 1.22; P = .74)	• The dual primary end points were PFS and OS. • Data cutoff dates: Mar 2, 2020, for the PFS primary analysis; Sep 29, 2020, for the second interim OS analysis; Mar 26, 2021, the final analysis. • On June 12, 2020, the DMC met to review data from the PFS primary analysis and recommended that the study continues as planned. • On December 22, 2020, the DMC reviewed the efficacy and safety data from the second OS interim analysis. The DMC indicated that the futility boundary for OS was crossed and recommended that no further study-related procedures are conducted.

	Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc, Rahway, NJ. The sponsors contributed to: • Medical writing support - Authors' disclosures of potential conflict of interest is provided at the end of the full text article.	• Active untreated brain metastases • Primary uveal or mucosal melanoma • Prior therapy with T-VEC or any other oncolytic viruses • Prior therapy with anti–PD-1/PD-L1/PD-L2 agents • Prior therapy with tumor vaccine in the nonadjuvant setting • History of autoimmune diseases • Evidence of immunosuppression therapy for > 2 weeks or < 7 days prior to the first dose of study • Active herpetic skin lesions • Current treatment with antiherpetic drug. For more information on in-/exclusion see the article. Median age, years (range) I: 64 (26-92) C: 64 (19-94)			*Withdrawal of consent n = 15* *Lost to follow-up n=6* C: n = 170 *Death n = 142* *Withdrawal of consent n = 22* *Lost to follow-up n = 6* April 2020, all patients discontinued study treatments. The final analysis was performed early given the futility noted in the second interim analysis and included an additional follow-up of 6 months.	The primary analysis of PFS was to be performed after 407 PFS events occurred. Median PFS (95% CI) (months): I: 14.3 (10.25 to 22.11) C: 8.5 (5.72 to 13.54) Stratified log-rank: HR, 0.86 (95% CI, 0.71 to 1.04), P=.13 Treatment related AEs grade 3 or 4: I: 70 (20.3%) C: 54 (15.7%) Fatal AEs: I: 45 (13.1%) C: 42 (12.2%) Treatment related fatal AEs, n: I: 4 (1.2%)	• On January 8, 2021, the study was unblinded and proceeded directly to a final analysis conducted in an unblinded manner. • All patients were off study treatment as of April 2020. The last visit date for the final analysis was March 11, 2021. • No improvement in OS was observed in any of the predefined subgroups. • Sensitivity analysis were performed: - which censored patients at the time of subsequent anticancer therapy - excluding patients with stage IVM1c disease - second-line therapies were generally balanced between the arms, and the crossover rate from the placebo arm to receive subsequent T-VEC treatment was<5% <u>Authors conclusions:</u> This randomized, double-blinded, placebo-controlled, multicenter, international phase III trial did not show improved PFS or OS for the combination of T-VEC plus pembrolizumab compared with placebo plus pembrolizumab for immunotherapy- naïve patients with advanced melanoma in the

		Male, n (%) I: 199 (57.5) C: 219 (63.3) ECOG PS: 0 – I: 259 (74.9) 0 – C: 249 (72.0) 1 – I: 87 (25.1) 1 – C: 97 (28.0) Groups were comparable at baseline.				C: 1 (0.3%) Immune-related AEs: I: 27.5% C: 24.8% For more information on AEs see results section of the article At final analysis: - PFS overall stratified HR, 0.87; 95% CI, 0.72 to 1.06 - OS: overall stratified HR, 0.97; 95% CI, 0.77 to 1.21) No new safety signals were observed.	frontline setting. There were no new safety concerns with the addition of T-VEC to pembrolizumab, and the safety profile of the combination was consistent with the known safety profile of each drug.
Robert 2015, Robert 2016, COMBI-v	Type of study: open-label, randomized, phase 3 study Setting and country: Multicentre, 193 centries. Funding and conflicts of interest: The study was funded by the sponsor, GlaxoSmithKline, and	Inclusion criteria: ->= 18 years -the presence of BRAF V600E or V600K mutations was centrally determined with the investigational use of the THxID BRAF assay (bioMérieux) -measureable disease, according to the	Describe intervention (treatment/procedure/test): A combination of dabrafenib (150 mg orally twice daily) and trametinib (2 mg orally once daily)	Describe control (treatment/procedure/test): Vemurafenib (960 mg orally twice daily).	**Robert 2015** Clinical data cutoff April 17, 2014 <u>Median follow-up</u> 11 (I), 10 (C) months <u>Loss-to-follow-up</u>: I: 16 *4 lost to follow-up* *2 investigator discretion* *10 withdrew consent*	**Robert 2015** <u>Median overall survival</u>: I: not reached C: 17.2 months <u>Median 1 year survival:</u> I: 72% (95% CI, 67 to 77) C: 65% (95% CI, 59 to 70) <u>Median progression-free survival:</u> I: 11.4 months	Author's conclusion: *In conclusion, the combination of dabrafenib plus trametinib was superior to vemurafenib monotherapy with regard to all efficacy end points, including overall survival, with no additional overall toxicity.* *Robert 2016 is only a published conference abstract, limited information available.*

	also provided editorial assistance. Detailed declarations of interests are provided in the article.	Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,15 -An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 -Patients who had undergone treatment for brain metastases with no increase in lesion size for at least 12 weeks were eligible Exclusion criteria: -See supplement. <u>N total at baseline</u>: 703 I: 352 C: 352 <u>Important prognostic factors</u>[2]: Median age (IQR) I: 55 (18–91) C: 54 (18–88) Sex: I: 208 (59) C: 180 (51) ECOG performance status: I: 248 (71) C: 248 (70) BRAF mutation V600E:			C: 28 *9 lost to follow-up* *1 investigator discretion* *18 withdrew consent* **Robert 2016** Clinical data cutoff July 2016 <u>Median follow-up</u> 27 (I), 26 (C) months <u>Loss-to-follow-up</u>: NR	C: 7.3 months HR, 0.56; 95% CI, 0.46 to 0.69 <u>Adverse events:</u> I: 343 (98) C: 345 (99) <u>Grade 3-4:</u> I: 167 (48) C: 198 (57) <u>Quality of life:</u> Not reported. **Robert 2016** <u>Median overall survival</u>: NR <u>Median 3 year survival:</u> I: 45% [95% CI, 39-50] C: 32% [95% CI, 27-37] <u>Median 3 year progression-free survival:</u> I: 25% [95% CI, 20-30] C: 11% [95% CI, 7-16] <u>Adverse events:</u> Similar to Robert 2015 <u>Quality of life:</u> Not reported.	

		I: 312(90) C: 317 (90) Groups comparable at baseline? Yes.					
Andtbacka, 2019; Andtbacka, 2015 **OPTiM** **NCT00769704**	A randomized open-label phase III trial at 64 sites in the United States, the United Kingdom, Canada, and South Africa. Patient enrolment between: 2009 and 2011 <u>Funding and conflicts of interest:</u> - Funded by BioVex, who were subsequently acquired by Amgen Inc. during the OPTiM trial. The sponsor contributed to: • Design of the trial • Data collection • Data analysis • Interpretation of data	Main inclusion criteria: • ≥ 18 years • Histologically confirmed, unresectable, bidimensionally measurable stage IIIB/C/IV melanoma with ≥1 cutaneous, subcutaneous or nodal lesions that was suitable for direct or ultrasound-guided injection; • ECOG PS ≤1 • Serum lactate dehydrogenase ≤1.5 × upper limit of normal; • ≤3 visceral lesions (excl. lung or nodal lesions associated with visceral organs) with none > 3 cm; • Adequate organ function. • Patients with history of autoimmune disease, but not use of high-dose steroids. Exclusion criteria: • Requiring intermittent or chronic	I: intratumoral Talimogene laherparepvec (T-VEC) (at the approved dose) n= 295 (68%)	C: subcutaneous recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) n= 141 (32%)	Median follow-up in the final analysis of OS: 49 months. Median duration of treatment in weeks (range): I: 23.1 (0.1–176.7) C: 10.0 (0.6–120.0) **Andtbacka, 2015:** Discontinued T-VEC: n=291 *Disease progression:* *n=191* *PR or CR for ≥ 6 continuous months:* *n=42* *Maximum allowed dose without* *PR/CR: n=26*	**Intent-to treat population (stage IIIB–IVM1c melanoma):** Median OS, months (95% CI): I: 23.3 (19.5–29.6) C: 18.9 (16.0–23.7) unstratified HR for death, 0.79 (95% CI,0.62–1.00); P = 0.0494). Estimated 5-year survival I: 33.4% C: Not estimable **Stage IIIB–IVM1a disease** Effect of T-VEC on OS vs GM-CSF: • Stage IIIB/C: HR, 0.48, P < 0.05	• Primary end point: durable response rate (objective response lasting continuously ≥ 6 months) per independent assessment. Key secondary end points: OS and overall response rate • Data cut-off for this final analysis of OPTiM was 5 September 2014. • 4 patients in the T-VEC arm and 14 in the GM-CSF arm did not receive T-VEC or GM-CSF. • When the 18 patients who did not receive allocated treatment were excluded (T-VEC arm, n =4; GM-CSF arm, n = 14), median OS in the final analysis dataset was 24.5 versus 18.9 months for T-VEC versus GM-CSF (HR, 0.78; P = 0.0439). • Ad-hoc sensitivity analysis for OS accounting for subsequent systemic anti-cancer treatment, there was a 27% reduction in the risk of death for T-VEC versus GM-CSF (unadjusted HR, 0.73; 95% CI, 0.59–0.92; P = 0.0069). <u>Authors conclusions:</u>

	• Development of the manuscript. - A competing interests statement is provided at the end of the full text article.	treatment with an antiviral agent (eg, acyclovir) or high-dose steroids • Primary ocular or mucosal melanoma • Bone metastases • Active cerebral metastases • > 3 visceral metastases • Any visceral metastasis >3 cm • Liver metastases had to be stable for 1 month before random assignment. For more information on in-/exclusion see the article. Median age, years (range) I: 63 (22 to 94) C: 64 (26 to 91) Male, n (%) I: 173 (59%) C: 77 (55%)			*Adverse event: n=11* *Consent withdrawn: n=10* *Physician decision: n=6* *Death: n=5* Discontinued GM-CSF: n=127 *Disease progression: n=95* *PR or CR for ≥ 6 continuous months: n=0* *Maximum allowed dose without* *PR/CR: n=9* *Adverse event: n=3* *Consent withdrawn: n=12* *Physician decision: n=5* *Death: n=3*	Effect of T-VEC on OS vs ITT population including stage IVM1b/c disease: • Stage IIIB–IVM1a: HR, 0.56; 95% CI, 0.40–0.79; P < 0.001 Estimated 5-year survival with T-VEC: • Stage IIIB–IVM1a melanoma: 48.9% (95% CI, 40.6–56.7) • Stage IVM1b/c disease: 15.1% (95% CI, 9.3–22.2). Treatment related AEs grade 3/4: I: 33 (11.3%) C: 6 (4.7%) Immune-related AEs: I: 24/295 C: ? Immune-related AEs grade 3: n=4	**Andtbacka, 2019:** In conclusion, as well as demonstrating a longer-term effect on survival, this analysis confirms that T-VEC resulted in high CR rates, most notably in patients with early metastatic melanoma (stage IIIB–IVM1a). Once achieved, CRs were durable and associated with prolonged survival. The favorable clinical outcomes observed in some patients treated with T-VEC, along with its good safety profile, support continued efforts to further define its future role in melanoma as a combination partner with immunotherapy. **Andtbacka, 2015:** T-VEC is the first oncolytic immunotherapy to demonstrate therapeutic benefit against melanoma in a phase III clinical trial. T-VEC was well tolerated and resulted in a higher DRR (P<0.001) and longer median OS (P=0.051), particularly in untreated patients or those with stage IIIB, IIIC, or IVM1a disease. T-VEC represents a novel potential therapy for

		ECOG PS: 0 – I: 209 (71%) 0 – C: 97 (69%) 1 – I: 82 (28%) 1 – C: 32 (23%) Unknown: I: 4 (1%) C: 12 (9%) Groups were comparable at baseline.				Immune-related AEs grade 4: None reported Treatment-related deaths, n: I: 0 C: 0 For more information on AEs see results section of the article	patients with metastatic melanoma.
Rohaan, 2022 **NCT02278887**	Multicenter, open-label, phase 3, randomized trial, two participating clinical sites (the Netherlands Cancer Institute, Amsterdam and National Center for Cancer Immune Therapy, Copenhagen University Hospital, Herlev, Denmark). Patient enrolment between: September 2014 and March 2022.	Inclusion criteria: • Age 18 to 75 years • Histologically confirmed, unresectable or metastatic stage IIIC or IV cutaneous melanoma • one or more lesions that could be surgically removed for generation of TILs. • Residual measurable disease after resection • WHO performance- status score of 0 or 1	Adoptive cell therapy with tumor-infiltrating lymphocytes (TILs). Patients assigned to receive TILs underwent a metastasectomy for retrieval and expansion of TILs, followed by administration of nonmyeloablative, lymphodepleting chemotherapy, single intravenous adoptive	Ipilimumab: 3 mg/kg intravenously every 3 weeks, for a maximum of 4 doses. n=84	Median follow-up in months: 33 Median duration of hospital admission: 17 days (range, 12 to 38). Median ipilimumab Infusions: 3 (range, 1 to 4)	Median OS, months (95% CI): I: 25.8 (18.2 to not reached) C: 18.9 (13.8 to 32.6) HR for death 0.83 (95% CI, 0.54 to 1.27). 2-year OS (95% CI): I: 54.3% (43.9 to 67.2) C: 44.1% (33.6 to 57.8)	• Data cutoff: June 9, 2022 • At data cutoff 80 patients had received TILs and 82 patients had received at least one infusion of ipilimumab. • For 6-month PFS and ORR the results of assessments according to immune related response criteria are reported. <u>Authors conclusions:</u> In patients with advanced melanoma, progression-free survival was significantly longer

	<u>Funding and conflicts of interest:</u> - Supported by the Dutch Cancer Society, the Netherlands Organization for Health Research and Development, the Dutch Ministry of Health, Stichting Avento, the Antoni van Leeuwenhoek Foundation, Copenhagen University Hospital (Herlev), the Danish Cancer Society, and the Capital Region of Denmark Research Foundation. - Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.	• A serum LDH level that was ≤ 2 times the upper limit of the normal range. • One previous line of systemic treatment for this disease stage, excluding ipilimumab, was allowed. • Patients with vitiligo Exclusion criteria: • Life expectancy <3 mo • Metastatic ocular/ mucosal or other non-cutaneous melanoma • Adjuvant treatment with ipilimumab < 6 mo prior to randomization. • Requirement for immunosuppressive doses of systemic corticosteroids or immunosuppressive drugs < 3 weeks prior to randomization. • >2 CNS metastases • Patients with a symptomatic CNS lesion > 1 cm or that shows significant surrounding edema on MRI scan were not	transfer of 5×109 to 2×1011 TILs, and subsequent high-dose interleukin-2 every 8 hours, for a maximum of 15 doses per protocol. n=84		Treatment discontinuation because of AEs: 26/42 (62%) TIL arm: No patients were lost to follow-up No patients discontinued treatment Ipilimumab arm: No patients were lost to follow-up 42 patients discontinued treatment: • 26 due to adverse events • 14 due to rapid disease progression • 1 patient decision 1 death	Median PFS, in months (95% CI): I: 7.2 (4.2 to 13.1) C: 3.1 (3.0 to 4.3) HR for progression or death, 0.50; 95% CI, 0.35 to 0.72 6-month PFS: I: 52.7% (95% CI, 42.9 to 64.7) C: 21.4% (95% CI, 14.2 to 32.2) Treatment related AEs grade 3 or 4: I: 100% C: 57% In the TIL group, these events were mainly chemotherapy-related myelosuppression.	among those who received TIL therapy than among those who received ipilimumab.

		eligible until they were treated and demonstrated no clinical or radiologic CNS progression for ≥ 2 mo. • Inability to receive high dose interleukin-2 • Toxicities from prior non-systemic treatment that have not recovered to grade ≤1. • Pregnancy or breastfeeding women, • Active systemic infections, coagulation disorders or other active major medical illnesses. • Autoimmune disease For more information on in-/exclusion see the appendix of the article. Median age, years (range) I: 59 (26–74) C: 59 (30–77) Two patients who were older than 75 years of age were included in the trial because these patients were deemed to be in excellent clinical				For more information on AEs see results section of the article. EORTC QLQ-C15 PAL quality-of-life and functioning scales. Mean HRQOL score at 6 months: • Global QoL: I: 77.4 C:69.6 Difference: 7.7 (5.1 to 10.4) • Physical functioning I: 82.0 C: 79.1 Difference: 2.9 (1.4 to 4.5) • Emotional functioning I: 85.4 C: 75.7 Difference: 9.7 (7.5 to 11.9) Scores on the EORTC QLQ-C15 PAL symptom scales: • Fatigue: I: 25.9 C: 33.8	

		condition by the principal investigator. Male, n (%) I: 47 (56) C: 53 (63) WHO PS: 0 – I: 69 (82) 0 – C: 70 (83) 1 – I: 15 (18) 1 – C: 14 (17) Groups were comparable at baseline.				Difference: −7.9 (−11.2 to −4.6) • Nausea and vomiting I: 7.5 C: 5.9 Difference: 1.6 (0.7 to 2.5) • Pain I: 14.3 C: 20.7 Difference: −6.4 (−9.3 to −3.5) • Dyspnea I: 10.0 C: 12.4 Difference: −2.4 (−5.0 to 0.1) • Insomnia I: 23.6 C: 28.1 Difference −4.5 (−7.2 to −1.9) • Appetite loss I: 12.4 C: 13.5 Difference: −1.1 (−2.9 to 0.7) • Constipation I: 6.7 C: 7.1 Difference: −0.4 (−1.3 to 0.5)	
Weber 2015, **Larkin 2018** **Checkmate 037**	Type of study: phase III, randomized, controlled, open-label study	Inclusion criteria: - aged >= 18 years -histologically confirmed, unresectable stage IIIC or IV metastatic melanoma	Describe intervention (treatment/procedure/test): Nivolumab 3 mg/kg intravenously every 2 weeks.	Describe control (treatment/procedure/test): Investigator's choice chemotherapy (ICC), which consisted of dacarbazine	**Larkin 2018** **Clinical data cutoff March 29, 2016** <u>Length of follow-up median (IQR)</u>:	Outcome measures and effect size (include 95%CI and p-value if available):	Original trial Checkmate 037 and updated analysis. ITT and PP analyses performed. Author's conclusion in 2015:

	Setting and country: Multicentre, 90 sites in 14 countries. Funding and conflicts of interest: The study was designed jointly by the funder of the study and the senior investigators (JSW and JL). Data collected by the funder were analysed in collaboration with all authors. The funder of the study funded writing and editorial support. Detailed declarations of interests are provided in the article.	and ECOG performance status 0 or 1. -Patients with BRAF must have experienced progression after treatment with anti-CTLA-4 and BRAF inhibitor. -patients with BRAFV600 mutation must have experienced progression after treatment with anti–CTLA-4 and a BRAF inhibitor. Exclusion criteria: -active brain metastases -prior treatment with anti–PD-1, anti–programmed death ligand 1 (PD-L1), or anti–PD-L2 -grade 4 toxicity or use of infliximab during previous ipilimumab treatment -primary ocular melanoma. More detailed inclusion and exclusion criteria are described in the appendix of Weber et al, 2015.		1,000 mg/m2 every 3 weeks or carboplatin area under the curve 6 plus paclitaxel 175 mg/m2 every 3 weeks intravenously.	Approximately 2 years. <u>Length of duration therapy median:</u> I: 4.7 months (95% CI 3.3-6.0) C: 2.0 months (95% CI 1.6-2.8) <u>Loss-to-follow-up</u>: Intervention: 233 (86%) discontinued treatment. *182 disease progression* *15 study drug toxicity* *6 adverse event* *19 patient request* *3 withdrew consent* *1 maximum clinical benefit* *1 poor/noncompliance* *4 no longer met study criteria*	**Larkin 2018** <u>Median overall survival:</u> I: 15.7 months (95% CI, 12.9 to 19.9) C: 14.4 months (95% CI, 11.7 to 18.2) HR, 0.95; 95% CI, 0.73 to 1.24 <u>Median progression-free survival:</u> I: 3.1 months C: 3.7 months HR, 1.0; 95.1% CI, 0.78 to 1.436 <u>Adverse events:</u> I: 77% C: 82% Treatment related grade 3 and 4: I: 31% C: 14% Further specified in table 3.	*Findings from our study show that nivolumab leads to clinically meaningful improvements in the proportion of patients achieving an objective response and provide a manageable safety profile when compared with chemotherapy.* Authors 'conclusion in 2018: *"Although there were no survival differences between nivolumab and ICC treatments, nivolumab treatment* *after progression on ipilimumab with or without a BRAF inhibitor does provide a higher rate of response and more durable responses. Some situations may still exist that necessitate the use of ipilimumab as first-line therapy and nivolumab provides* *a safer option with a better maintained quality of life for patients who have experienced failure with prior systemic therapies compared with cytotoxic chemotherapy. The OS outcome may* *have been impacted by the increased dropout rate before treatment and increased systemic therapy received after assigned*

		N total at baseline: 405 Intervention: 272 Control: 133 Important prognostic factors[2]: Median age (IQR) *I:* 59 (23-88) *C:* 62 (29-85) Sex: *I:* 65% M *C:* 64% M ECOG performance status: *I:* 60% 0 *C:* 63% 0 BRAF mutant: *I:* 60 (22%)			*2 other* Control: 102 (77%) discontinued treatment. *74 disease progression* *11 study drug toxicity* *3 adverse event* *7 patient request* *2 withdrew consent* *3 maximum clinical benefit* *2 other* **Weber 2015** **Clinical data cutoff not reported?** Range of follow-up: 5.2-16.7 months Loss-to-follow-up: Intervention: 111 (53%) discontinued treatment.	Quality of life: I: no change in EORTC QLQ-C30 no clinically significant improvement for EQ-5D/EQ-5D VAS. C: no change in EORTC QLQ-C30 A clinically significant decrease for EQ-5D at 12 weeks. **Weber 2015** Median overall survival: Not reported. Median progression-free survival: I: 4.7 months (95% CI 2.3–6.5) C: 4.2 months (2.1–6.3) HR, 0.82; 99% CI 0.32–2.05	*therapy in the ICC group, as well as an increased proportion of patients with poor prognostic factors in the nivolumab group.* *Despite the lack of survival advantage, nivolumab remains an effective option for PD-1 inhibitor–naive patients who experienced failure with ipilimumab and a BRAF inhibitor if BRAF mutated."* -Subgroup analysis was performed on the PD-1/PDL1 subgroup: Median overall survival sensitivity analysis PD-1/PD-L1 group Larkin 2018 I: 16.4 months (95% CI, 12.9 to 20.3) C: 11.8 months (95% CI, 9.9 to 14.4) HR, 0.81; 99% CI, 0.59 to 1.1

		C: 29 (22%) Treatment with PD-1/PD-L1: *I:* 11% *C:* 41% Brain metastases: I: 20% C: 14% Increased lactate dehydrogenase levels: I: 52% C: 38% Groups comparable at baseline? Yes, except for brain metastases and lactate dehydrogenase levels.			*96 disease progression* *5 study drug toxicity* *0 death* *2 AE unrelated to study drug* *5 request to discontinue* *2 withdrew consent* *1 max clinical benefit* Control: 129 (92%) discontinued treatment. *175 disease progression* *7 study drug toxicity* *0 death* *3 AE unrelated to study drug* *2 request to continue* *3 withdrew consent* *1 max clinical benefit*	<u>Adverse events:</u> I: 68% C: 79% Treatment related grade 3 and 4: I: 9% C: 31% <u>Quality of life:</u> Not reported.	

					1 other		
Dummer 2018, Dummer 2018-2, Ascierto 2020, COLUMBUS	Type of study: multicentre, two-part, randomised, open-label, phase 3 study. Setting and country: Multicentre, 162 hospitals in 28 countriest. Funding and conflicts of interest: Funded by Array BioPharma, Novartis. The sponsors had a role in data collection, analysis, and interpretation. Detailed declarations of interests are provided in the article.	Inclusion criteria: ->= 18 years -A histologically confirmed diagnosis of locally advanced, unresectable, or metastatic cutaneous melanoma or unknown primary melanoma classified as American Joint Committee on Cancer (AJCC) stage IIIB, IIIC, or IV -Treatment naive or had progressed on or after previous first-line immunotherapy -Had a BRAFV600E or BRAFV600K mutation or both in tumour tissue as ascertained by central genetic mutation analysis with the bioMérieux THxID BRAF diagnostic test (bioMérieux, Marcy l'Etoile, France) before enrolment -ECOG performance status of 0 or 1 -Adequate bone marrow, organ function, and laboratory parameters -At least one measurable lesion, according to	Describe intervention (treatment/procedure/test): Oral encorafenib 450 mg once daily plus oral binimetinib 45 mg twice daily (encorafenib plus binimetinib group)	Describe control (treatment/procedure/test): Encorafenib 300 mg once daily orally, or vemurafenib 960 mg twice daily orally	**Dummer 2018** Clinical data cutoff May 19, 2016 Median follow-up 16·6 months (14·8–16·9) <u>Loss to follow-up</u>: A: 124 discontinued treatment *83 had progressive disease* *16 had adverse events* *8 physician decision* *7 patient or guardian decision* *7 died* *2 protocol deviation* *1 lost to follow-up* B: 146 discontinued *87 had progressive disease* *24 had adverse events* *19 physician decision* *13 patient or guardian decision* *1 died* *1 protocol deviation* *1 lost to follow-up* C: 159 discontinued	**Dummer 2018** <u>Median progression-free survival:</u> A: 14·9 months (95% CI 11·0–18.5) B: 9·6 months (7·4–14·8) C: 7·3 months (5·6–8.2) <u>Adverse events:</u> A: 66 (34%) B: 65 (34%) C: 69 (37%) <u>Grade 3-4 adverse events:</u> A: 111 (58%) B: 127 (66%) C: 118 (63%) <u>Quality of life:</u> Not reported. **Dummer 2018-2** <u>Median overall survival</u>: A: 33·6 months (95% CI 24·4–39·2) B: 23·5 months (19·6–33·6) C: 16·9 months (14·0–24·5) A vs C: HR 0·61 [95% CI 0·47–0·79) A vs B: HR 0·81 [95% CI 0·61–1·06] B vs C: HR 0·76 (95% CI 0·58–0·98)	Author's conclusion: *In conclusion, patients treated with encorafenib plus binimetinib had longer PFS and OS than those treated with vemurafenib, with landmark analyses showing consistent improved OS and PFS for COMBO450 vs VEM for each year. Safety results were consistent with the known tolerability profile of COMBO450, and the toxicity burden was reduced over time. These data reinforce encorafenib plus binimetinib as an important treatment option for patients with BRAF-mutant melanoma.*

		guidelines based on Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Exclusion criteria: -An untreated CNS lesions; uveal or mucosal melanoma -A history of leptomeningeal metastases -Gilbert's syndrome -history, current evidence, Or risk of retinal vein occlusion -Previous BRAF inhibitor or MEK inhibitor treatment -Previous use of systemic chemotherapy -Extensive radiotherapy as evaluated by local investigators, or an investigational agent other than previous immunotherapy for locally advanced, unresectable, or metastatic melanoma (immunotherapy must have ended ≥6 weeks before randomisation). <u>N total at baseline</u>: 577 encorafenib & binimetinib (A): 192 encorafenib (B): 194 vemurafenib (C): 191			*101 had progressive disease* *26 had adverse events* *13 physician decision* *15 patient or guardian decision* *4 died* **Dummer 2018-2** Clinical data cutoff Nov 7, 2017 <u>Median follow-up</u> 36·8 months (95% CI 35·9–37·5) <u>Loss-to-follow-up</u>: A: 149 discontinued *99 progressive disease* *20 adverse events* *9 physician decision* *11 patient or guardian decision* *8 died* *1 protocol deviation* *1 lost to follow-up* B: 168 discontinued *100 progressive disease* *25 adverse events* *24 physician decision* *17 patient or guardian decision* *1 died* *1 protocol deviation* *0 lost to follow-up*	<u>Median 1 year survival:</u> A: 75·5% (95% CI 68·8–81·0) B: 74·6% (67·6–80·3) C: 63·1% (55·7–69·6) <u>Median 2 year survival:</u> A: 57·6% (95% CI 50·3–64·3) B: 49·1% (41·5–56·2) C: 43·2% (35·9–50·2) <u>Median progression-free survival:</u> A: 14·9 months (95% CI 11·0–20·2) B: 9·6 months (7·4–14·8) C: 7·3 months (5·6–7·9) <u>Adverse events:</u> Similar to Dummer 2018 <u>Quality of life:</u> Not reported. **Ascierto 2020** <u>Median overall survival</u>: A: 33.6 months (95% CI, 24.4-39.2), B: 23.5 months (95% CI, 19.6-33.6) C: 16.9 months (95% CI, 14.0-24.5 HR 0.61 (95%CI 0.48-0.79) <u>Median 3 year survival:</u> A: 47%	

		<u>Important prognostic factors</u>[2]: Median age (IQR) *A:* 57 (20–89; 48–66) B: 54 (23–88; 46–63) *C:* 56 (21–82; 45–65) Sex: *A:* 115 (60%) M B: 108 (56%) M *C:* 111 (58%) M ECOG performance status: *A:* 136 (71%) 0 B: 140 (72%) 0 C: 140 (73%) 0 BRAF mutation V600E: *A:* 170 (89%) *B:* 173 (89%) *C:* 168 (88%) Groups comparable at baseline? Yes.			C: 173 discontinued *109 progressive disease* *25 adverse events* *17 physician decision* *17 patient or guardian decision* *4 died* *1 new therapy for study indication* *0 protocol deviation* *0 lost to follow-up* **Ascierto 2020** Clinical data cutoff Nov 2018 <u>Median follow-up</u> 48.8 months <u>Loss-to-follow-up</u>: A: 156 discontinued *104 progressive disease* *20 adverse events* *21 physician decision/ patient or guardian decision* *9 died* *2 other* B: 172 discontinued *101 progressive disease* *24 adverse events* *35 physician decision/patient or guardian decision* *1 died* *1 other*	B: 41% C: 31% <u>Median progression-free survival:</u> A: 14.9 months (95% CI, 11.0- 20.2) B: 9.6 months (95% CI, 7.4-14.8) C: 7.3 months (95% CI, 5.6-7.9) HR (0.51, 95%CI 0.39-0.67) <u>Grade 3/4 adverse events:</u> A: 68% B: 68% C: 66% <u>Quality of life:</u> Not reported.	

					C: 177 discontinued *111 progressive disease* *26 adverse events* *35 physician decision/patient or guardian decision* *4 died* *1 other*		

5

8.3.2.1. Eerstelijnsbehandeling BRAF-wild type gemuteerd irresectabel of gemetastaseerd stadium III/IV

Uitgangsvraag

Wat is de plaats van systemische therapie in de eerste lijns-behandeling van patiënten met een BRAF-wild type gemuteerd irresectabel of gemetastaseerd stadium III/IV melanoom?

Search and select

The search and selection methods can be found in the main module 8.3 [Link XXX]

Summary of literature

Seven randomized controlled trials that studied clinical outcomes of first line systemic therapy in patients with unresectable or metastatic stadium III/IV melanoma with a BRAF-wild type were included in the literature analysis.

Description of studies

The study characteristics of the included trials are summarized in Table 2 in the main module 8.3 [Link XXX].

Robert (2015), Ascierto (2019), Robert (2020) – CHECKMATE-066 described a randomized, controlled, double-blind, phase III study, which was conducted in 80 centres in Europe, Israel, Australia, Canada and South America with a median follow-up of approximately 1.5 years. They evaluated the efficacy and safety of first line nivolumab versus dacarbazine in patients with metastatic melanoma without a BRAF mutation. A total of 418 patients were randomized to receive nivolumab (n = 210) at a dose of 3 mg per kilogram of body weight every 2 weeks and dacarbazine-matched placebo every 3 weeks) or dacarbazine (n = 208 at a dose of 1000 mg per square meter of body-surface area every 3 weeks and nivolumab-matched placebo every 2 weeks). The median age was 64 (18-86) years in the nivolumab group and 66 (26-87) years in the ICC group. In the nivolumab group 58% was male, compared to 60% in the ICC group. The following relevant outcomes were reported, overall survival (OS), progression-free survival (PFS) and number of patients with serious adverse events (AEs). In this literature analysis the median outcomes for OS and PFS are analysed and the last endpoint (5-year OS and 5-year PFS rates) of these outcomes are described.

Tawbi (2022) – RELATIVITY-047 described a phase 2-3 global, double-blind, randomized study, which was conducted in 111 sites in North America, Central America, South America, Europe, Australia, and New Zealand. They evaluated the efficacy and safety of the combination of relatlimab, a LAG-3–blocking antibody, and nivolumab in patients with previously intreated metastatic or unresectable melanoma. A total of 714 patients were randomized to receive a relatlimab and nivolumab combination (160 mg of relatlimab and 480 mg of nivolumab in a fixed-dose combination administered in a single 60-minute intravenous infusion every 4 weeks) versus nivolumab alone (480 mg of

nivolumab administered in a single 60-minute intravenous infusion every 4 weeks). The median age was 63 (20-94) years in the relatlimab + nivolumab group and 62.0 (21–90) years in the control group. In the relatlimab + nivolumab group 59% was male, compared to 57% in the nivolumab alone group. 219 of the 355 (61.7%) patients that were randomized in the relatlimab + nivolumab group, and 220 of the 359 (61.3%) patients that were randomized in the nivolumab alone group, had no BRAF mutation. The following relevant outcomes were reported PFS, AEs and quality of life (QoL). In this literature analysis the median PFS is analysed.

Larkin (2015), Larkin (2019), Wolchock (2017), Wolchok (2022), Hodi (2018) - CHECKMATE 067 is a phase 3, randomized, double-blind study, which is conducted in 137 centres in Australia, Europe, Israel, New Zealand, and North America. They evaluated the efficacy and safety of the use of Nivolumab and Ipilimumab as combination therapy in patients with untreated unresectable stage III or stage IV melanoma. A total of 945 patients were randomized to receive nivolumab 1 mg/kg plus ipilimumab 3 mg/kg once every 3 weeks followed by nivolumab 3 mg/kg once every 2 weeks (n=314, of which 101 patients (32.2%) had a BRAF mutation), or nivolumab 3 mg/kg once every 2 weeks (n=316, of which 100 patients (31.6%) had a BRAF mutation), or ipilimumab 3 mg/kg once every 3 weeks (n=315, of which 97 patients (30.8%) had a BRAF mutation). The median age, of both patients with and without BRAF mutation, was 59 (18-88) years in the combination group, 59 (25-90) in the nivolumab group and 61 (18-89) in the Ipilimumab group. In the combination group, 66% was male, compared to 64% in the nivolumab alone group and 64% in the Ipilimumab group. The following relevant outcomes were reported, PFS, OS and number of patients with serious AEs. The study was not powered for a formal statistical comparison between the nivolumab group and the nivolumab-plus-ipilimumab group. In this literature analysis the median outcomes for OS and PFS are analysed and the last endpoint for OS (6.5-year OS rates) are described.

Robert, 2011 / Maio, 2015 - CA184-024 is a multinational, randomized, double-blind, phase 3 study. This trial compared ipilimumab plus dacarbazine with dacarbazine and placebo in patients with previously untreated stage III (unresectable) or stage IV melanoma with measurable lesions. Patients were randomized to receive ipilimumab at a dose of 10 mg per kg plus dacarbazine at a dose of 850 mg per square meter (n=250) or dacarbazine at a dose of 850 mg per square meter plus placebo (n=252). The mean age was 57.5 years in the intervention group and 56.4 years in the control group. In the intervention group 60.8% and in the control group 59.1% were male. Robert (2011) reported on OS, PFS, and AEs after a follow up time of 54 months between the start of the study (first visit of first patient) and end of the study. Maio (2015) reported updated results after a median survival follow-up of 11 months (range, 0.4 to 71.9 months) for the intervention group and 8.9 months (range, 0.1 to 73.2 months) for the control group. In this literature analysis the median outcomes for OS and PFS are analysed and the last endpoint for OS (5-year OS rates) are described.

Robert, 2019 / Carlino, 2018 / Schachter, 2017 /Robert, 2015 - KEYNOTE-006 is an international, randomized, open-label phase 3 study performed in 16 countries. In this trial treatment with pembrolizumab versus ipilimumab was studied, to compare PD-1 inhibition with CTLA-4 blockade in patients with unresectable stage III/IV melanoma.

Patients were randomized to pembrolizumab at a dose of 10 mg/kg of body weight every 2 weeks (n= 279); pembrolizumab at a dose of 10 mg/kg every 3 weeks (n=277); or ipilimumab at a dose of 3 mg/kg every 3 weeks (n=278). The mean age was 61 years in the pembrolizumab every 2 weeks group, 63 years in the pembrolizumab every 3 weeks group and 62 years in the ipilimumab group. The percentage of males was 57.7 %, 62.8%, and 58.3% for the three groups, respectively. Robert (2015) reported on OS, PFS, and AEs after a median follow-up of 7.9 months. Schachter (2017) reported updated results after a median follow-up of 22.9 months. Carlino (2018) reported updated outcomes by line of therapy and programmed death ligand 1 expression after a median follow-up of 33.9 months. Robert (2019) reported updated results of OS, PFS, and AES after a median follow-up of 57.7 months. In this literature analysis the median outcomes for OS and PFS are analysed and the last endpoints for OS and PFS (2-year OS rates and 2-year PFS rates) are described.

Chesney (2023) - MASTERKEY-265 is a multicenter, double-blind, placebo controlled, randomized phase 3 study in 21 countries. This trial evaluated the efficacy and safety of T-VEC-pembrolizumab versus placebo-pembrolizumab in patients with stage IIIB-IV M1c unresectable melanoma. Patients were randomized to a combination of T-VEC plus pembrolizumab 200 mg once every 3 weeks (n=346) or placebo plus pembrolizumab 200 mg once every 3 weeks (n=346). The median age was 64 years in both study groups. The percentage of males was 57.5% in the T-VEC-pembrolizumab group and 63.3% placebo-pembrolizumab group. Chesney (2023) reported OS, PFS, and AES, after a median follow-up of 25.6 months for the primary PFS analysis, 31.0 months for the second OS interim analysis, and 35.6 months for the final analysis. In this literature analysis the median outcomes for OS and PFS are analysed.

Andtbacka, 2019 /Andtbacka, 2015 - OPTiM is a randomized open-label phase 3 trial at 64 sites in the United States, the United Kingdom, Canada, and South Africa. This trial evaluated outcomes after treatment with talimogene laherparepvec (T-VEC) compared with granulocyte macrophage colony-stimulating factor (GM-CSF) in patients with unresectable, stage IIIB/C/IV melanoma with ≥1 lesion that was suitable for direct or ultrasound-guided injection. Patients were randomized to T-VEC (at the approved dose) (n=295 (68%)) of subcutaneous recombinant GM-CSF (n=141 (32%)). The median age was 63 years in the T-VEC group and 64 years in the GM-CSF group. The percentage of males was 59% in the T-VEC group and 55% in the GM-CSF group. Of 204 of the 295 (69%) in the T-VEC group, and 95 of the 141 (67%) in the GM-CSF group, the BRAF mutation status was unknown. For 138 of the 295 (47%) patients in the T-VEC group, and 65 of the 141 (46%) in the GM-CSF group, this was a first line therapy. OS and AEs were reported after a median follow-up of 49 months in the final analysis of OS. In this literature analysis the median OS is analysed.

Results

Overall survival (OS) – Critical outcome measure

Six of the seven included studies reported on OS.

Checkmate-066 reported the effect of first line **nivolumab** versus **dacarbazine** on OS. The 5-year survival rates were 39% for the nivolumab group compared to 17% for the

dacarbazine group. Treatment with nivolumab resulted in a longer median OS compared to treatment with dacarbazine. The absolute difference in median OS between the intervention (37.3 months) and the control group (11.2 months) is 26.1 months with a hazard ratio (HR) of 0.50 (95% CI 0.40-0.63) favoring treatment with nivolumab. This difference was considered clinically relevant according to the PASKWIL criteria.

Checkmate-067 reported the effect of **nivolumab plus ipilimumab** versus **nivolumab** versus **ipilimumab** on OS in patients with BRAF wild-type tumors. The study was not powered for a formal comparison between the nivolumab plus ipilimumab and the nivolumab treatment groups. The 6.5-year OS rates were 46% for the nivolumab plus ipilimumab group, 42% for the nivolumab group, and 22% for the ipilimumab group. Treatment with nivolumab plus ipilimumab resulted in a longer median OS compared to treatment with nivolumab only or ipilimumab only. The absolute difference in median OS between the group treated with nivolumab plus ipilimumab (39.1 months) versus those treated with nivolumab (34.4 months) was 4.7 months with a HR of 0.92 (95% CI 0.71 to 1.18) favoring treatment with nivolumab plus ipilimumab. This difference was not considered clinically relevant according to the PASKWIL criteria. The absolute difference in median OS between the group treated with nivolumab plus ipilimumab versus those treated with ipilimumab (18.5 months) was 20.6 months with a HR of 0.58 (95% CI 0.45-0.74) favoring treatment with nivolumab plus ipilimumab. This difference was considered clinically relevant according to the PASKWIL criteria. The absolute difference in median OS between the group treated with nivolumab versus those treated with ipilimumab was 15.9 months with a HR of 0.63 (95% CI 0.50 to 0.80) favoring treatment with nivolumab. This difference was considered clinically relevant according to the PASKWIL criteria.

CA184-024 reported the effect of **ipilimumab plus dacarbazine** versus **dacarbazine** plus placebo on OS. The 5-year OS rates were 18.2% for the ipilimumab plus dacarbazine group and 8.8% for the dacarbazine group. Treatment with ipilimumab plus dacarbazine resulted in a longer median OS compared to treatment with dacarbazine only. The absolute difference in median OS between the group treated with ipilimumab plus dacarbazine (11.2 months) versus those treated with dacarbazine (9.1 months) was 2.1 months with a HR of 0.69 (95% CI 0.57 to 0.84) favoring treatment with ipilimumab plus dacarbazine. This difference was not considered clinically relevant according to the PASKWIL criteria.

KEYNOTE-006 reported the effect of **pembrolizumab every 2 weeks** or **pembrolizumab every 3 weeks** compared to **ipilimumab every 3 weeks** on OS. The 2-year OS rates were 55% in the pembrolizumab-every-2-weeks group, 55% in the pembrolizumab-every-3-weeks group, and 43% in the ipilimumab-every-3-weeks group. Treatment with pembrolizumab resulted in a longer median OS than treatment with ipilimumab. The absolute difference between the combined pembrolizumab groups (32.7 months) and the ipilimumab group (15.9 months) was 16.8 months with a HR of 0.73 (95% CI 0.61–0.88). This difference was not considered clinically relevant according to the PASKWIL criteria.

MASTERKEY-265 reported the effect of a combination of **T-VEC plus pembrolizumab** versus placebo plus **pembrolizumab** on OS. Treatment with T-VEC-pembrolizumab did

not result in a longer OS compared with treatment with placebo-pembrolizumab. The median OS was not estimable in the T-VEC plus pembrolizumab group and 49.2 months (40.57 to not estimable) in the pembrolizumab group with a HR of 0.96 (95% CI 0.76 to 1.22; P =0 .74).

OPTiM reported the effect of **T-VEC** versus **GM-CSF** on OS. OPTiM reported the effect of **T-VEC** versus **GM-CSF** on OS in first line treatment, without subgroup analyses on BRAF mutation. Treatment with T-VEC resulted in a longer median OS than treatment with GM-CSF. The absolute difference between the T-VEC group (33.1 months) and the GM-CSF group (17 months) was 16.1 months with a HR of 0.50 (95% CI 0.35-0.73). This difference was considered clinically relevant according to the PASKWIL criteria.

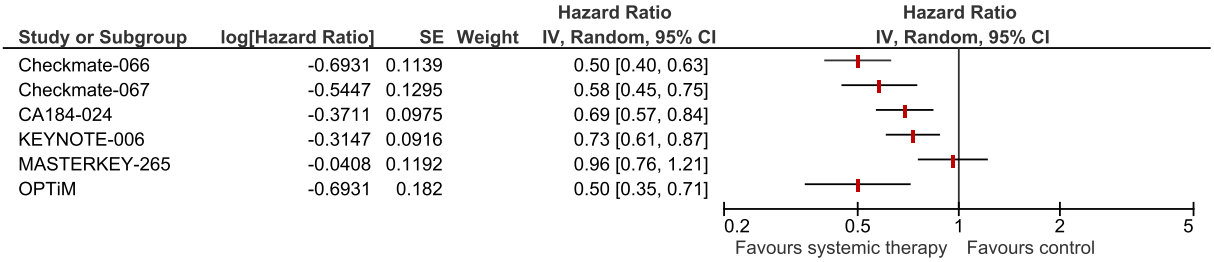

Figure 6. Forest plot of median overall survival for first line systemic therapy versus placebo, other systemic therapy, or best supportive care in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy.
[a] For Checkmate-067 the HR for nivolumab versus ipilimumab is shown.
[b] For KEYNOTE-006 the HR for combined pembrolizumab versus ipilimumab is shown.

Progression free survival – important outcome measure
Six of the seven included studies reported on PFS.

Checkmate-066 reported the effect of first line **nivolumab** versus **dacarbazine** on PFS. The 5-year PFS rates were 28% for the nivolumab group compared to 3% for the dacarbazine group. Treatment with nivolumab resulted in a longer median PFS compared to treatment with dacarbazine. The absolute difference in median PFS between the intervention and the control group is 2.9 months with a hazard ratio (HR) of 0.4 (95%CI 0.33-0.53) favoring treatment with nivolumab. According to the PASKWIL criteria we could not assess clinical relevance (median OS in the control group was < 12 months).

RELATIVITY-047 reported the effect of **relatlimab and nivolumab** versus **nivolumab** on PFS. In the subgroup of patients with wild-type BRAF, the median PFS survival was 10.1 months (95% CI, 5.9 to 17.0) with relatlimab–nivolumab and 4.6 months (95% CI, 2.9 to 6.6) with nivolumab. The absolute difference between the group treated with relatlimab and nivolumab and the group treated with nivolumab was 5.5 months with a HR of 0.76 (95%CI 0.59-0.99) favoring treatment with relatlimab and nivolumab. According to the PASKWIL criteria we could not assess clinical relevance (median OS in the control group not reported).

Checkmate-067 reported the effect of **nivolumab plus ipilimumab** versus **nivolumab** versus **ipilimumab** on PFS in patient with BRAF wild-type. The absolute difference in median PFS between the group treated with nivolumab plus ipilimumab (11.2 months) versus those treated with nivolumab (8.2 months) was 3 months with a HR of 0.88 (0.69 – 1.12) favoring treatment with nivolumab plus ipilimumab. This difference was not considered clinically relevant according to the PASKWIL criteria. The absolute difference in median PFS between the group treated with nivolumab plus ipilimumab versus those treated with ipilimumab (2.8 months) was 8.4 months with a HR of 0.41 (0.33 to 0.52) favoring treatment with nivolumab plus ipilimumab. This difference was considered clinically relevant according to the PASKWIL criteria. The absolute difference in median PFS between the group treated with nivolumab versus those treated with ipilimumab was 5.4 months with a HR of 0.47 (0.38 to 0.59) favoring treatment with nivolumab. This difference was considered clinically relevant according to the PASKWIL criteria.

CA184-024 reported the effect of **ipilimumab plus dacarbazine** versus **dacarbazine** plus placebo on PFS. The median PFS was comparable between the ipilimumab-dacarbazine group and the dacarbazine-only group. After the first assessment of progression at week 12 (after the true median), the Kaplan-Meier curves separated and there was a 24% reduction in the risk of progression in the ipilimumab plus dacarbazine group compared to the dacarbazine only group with a HR of 0.76 (95% CI 0.63–0.93). According to the PASKWIL criteria we could not assess clinical relevance (median OS in the control group was < 12 months).

KEYNOTE-006 reported the effect of **pembrolizumab every 2 weeks** or **pembrolizumab every 3 weeks** compared to **ipilimumab every 3 weeks** on PFS. The 2-year PFS rates were 31% in the pembrolizumab-every-2-weeks group, 28% in the pembrolizumab-every-3-weeks group, and 14% in the ipilimumab-every-3-weeks group. Treatment with pembrolizumab resulted in a longer median PFS than treatment with ipilimumab. The absolute difference between the combined pembrolizumab groups and the ipilimumab group was 5.0 months with a HR of 0.57 (95% CI 0.48–0.67). This difference was considered clinically relevant according to the PASKWIL criteria.

MASTERKEY-265 reported the effect of a combination of **T-VEC plus pembrolizumab** versus placebo plus **pembrolizumab** on PFS. Treatment with T-VEC-pembrolizumab resulted in a longer PFS compared with treatment with placebo-pembrolizumab. The absolute difference between the combined pembrolizumab groups and the ipilimumab group was 5.8 months with a HR of 0.86 (95% CI, 0.71 to 1.04). This difference was not considered clinically relevant according to the PASKWIL criteria.

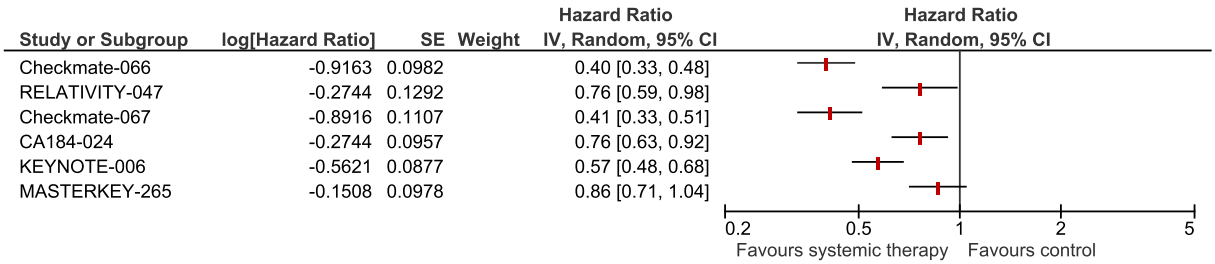

Figure 7. Forest plot of median progression free survival for first line systemic therapy versus placebo, other systemic therapy, or best supportive care in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy.
[a] For Checkmate-067 the HR for nivolumab versus ipilimumab is shown.
[b] For KEYNOTE-006 the HR for combined pembrolizumab versus ipilimumab is shown.

Treatment related adverse events (AEs) grade ≥ 3 - Important outcome
Seven of the seven included studies reported on AEs. The percentages of treatment related AEs grade ≥3 ranged from 4% to 59%.

Checkmate-066 reported the effect of first line **nivolumab** versus **dacarbazine** on AEs without using a subgroup analysis. Treatment with nivolumab resulted in a lower percentage of treatment related AEs grade ≥3 compared to treatment with dacarbazine. The risk difference is -0.02 (95%CI -0.09, 0.06; NNH= 50) favoring treatment with nivolumab. This difference is not considered clinically relevant according to the PASKWIL criteria.

RELATIVITY-047 reported the effect of **relatlimab plus nivolumab** versus **nivolumab** on AEs. Treatment with relatlimab and nivolumab resulted in a higher percentage of treatment related AEs grade ≥3 compared to treatment with nivolumab only. The risk difference is 0.07 (95%CI -0.00, 0.14; NNH= 14) favoring treatment with nivolumab. This difference is not considered clinically relevant according to the PASKWIL criteria.

Checkmate-067 reported the effect of **nivolumab plus ipilimumab** versus **nivolumab** versus **ipilimumab** on AEs. Treatment with nivolumab plus ipilimumab resulted in a higher percentage of treatment related AEs grade ≥3 compared to treatment with nivolumab or ipilimumab only. The risk difference between nivolumab plus ipilimumab and nivolumab is 0.36 (95%CI 0.29, 0.43; NNH= 2.8) favoring treatment with nivolumab. This difference is considered clinically relevant. The risk difference between nivolumab plus ipilimumab and ipilimumab is 0.32 (95% CI 0.25, 0.39; NNH= 3.1) favoring treatment with ipilimumab. This difference is considered clinically relevant. The risk difference between nivolumab and ipilimumab is 0.04 (95% CI -0.03, 0.11; NNH= 25) favoring treatment with nivolumab. This difference is not considered clinically relevant according to the PASKWIL criteria.

CA184-024 reported the effect of **ipilimumab plus dacarbazine** versus **dacarbazine** plus placebo on AEs. Treatment with ipilimumab plus dacarbazine resulted in a higher

percentage of treatment related AEs grade ≥3 compared to treatment with dacarbazine only. The risk difference between ipilimumab plus dacarbazine and dacarbazine is 0.34 (95% CI 0.27, 0.40; NNH= 2.9) favoring treatment with dacarbazine. This difference is considered clinically relevant according to the PASKWIL criteria.

KEYNOTE-006 reported the effect of **pembrolizumab every 2 weeks** or **pembrolizumab every 3 weeks** compared to **ipilimumab every 3 weeks** on AEs. Treatment with pembrolizumab (pooled groups) resulted in a lower percentage of treatment related AEs grade ≥3 compared to treatment with ipilimumab. The risk difference between pembrolizumab (pooled groups) and ipilimumab is -0.01 (95% CI -0.06, 0.05; NNH=100) favoring treatment with pembrolizumab. This difference is not considered clinically relevant according to the PASKWIL criteria.

MASTERKEY-265 reported the effect of a combination of **T-VEC plus pembrolizumab** versus placebo plus **pembrolizumab** on AEs. Treatment with T-VEC-pembrolizumab resulted in a higher percentage of treatment related AEs grade ≥3 compared to treatment with placebo-pembrolizumab. The risk difference between T-VEC plus pembrolizumab and placebo-pembrolizumab is 0.05 (95% CI -0.01, 0.10; NNH=20) favoring treatment with placebo plus pembrolizumab. This difference is not considered clinically relevant according to the PASKWIL criteria.

OPTiM reported the effect of **T-VEC** versus **GM-CSF** on AEs. Treatment with T-VEC resulted in a higher percentage of treatment related AEs grade ≥3 compared to treatment with GM-CSF. The risk difference between T-VEC and GM-CSF is 0.07 (95% CI 0.02, 0.12; NNH=14) favoring treatment with GM-CSF. This difference is not considered clinically relevant according to the PASKWIL criteria.

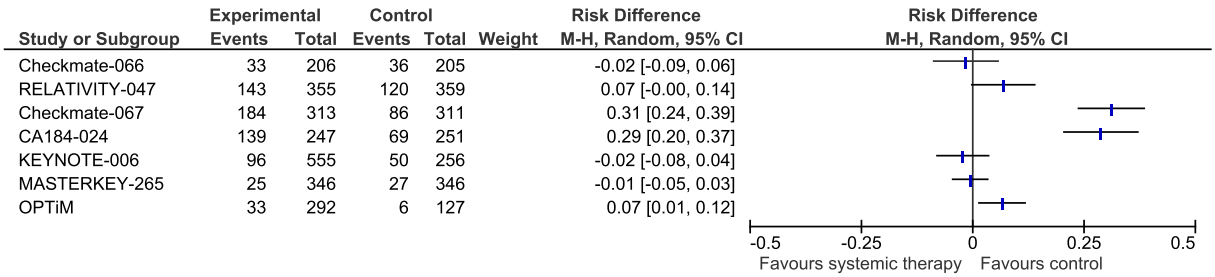

Figure 8. Forest plot of adverse events for first line systemic therapy versus placebo, other systemic therapy, or best supportive care in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy.
[a] For Checkmate-067 the risk difference for nivolumab versus ipilimumab is shown.
[b] For KEYNOTE-006 the risk difference for combined pembrolizumab versus ipilimumab is shown.

Quality of life (QoL) - Important outcome
One study reported the effect of first line systemic therapy on QoL.

RELATIVITY-047 reported the effect of **relatlimab plus nivolumab** versus **nivolumab** on QoL without using a subgroup analysis. In this study, the changes from baseline in FACT-

M total score and EQ-5D-3L health utility index were analysed. The authors considered minimal clinically important differences of 5 in the FACT-M total score and 0.08 in the EQ-5D-3L health utility index to be clinically meaningful. The least-squares mean changes from baseline over time in the FACT-M total score ranged between 1 and -4 and did not exceed the minimal clinically important differences. The least-squares mean changes from baseline over time in the EQ-5D-3L utility index ranged between -0.025 and -0.08 and did not exceed the minimal clinically important differences.

Level of evidence of the literature

There are four levels of evidence: high, moderate, low, and very low. RCTs start at a high level of evidence.

Nivolumab versus dacarbazine

The level of evidence regarding the outcome measure **overall survival** was downgraded by one level because of study limitations (risk of bias). Therefore, the level of evidence was graded as moderate.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by two levels because of study limitations (risk of bias) and because we could not asses clinical relevance according to the PASKWIL criteria (imprecision). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by one level because of study limitations (risk of bias). Therefore, the level of evidence was graded as moderate.

Relatlimab plus nivolumab versus nivolumab

The level of evidence regarding the outcome measure **progression free survival** was downgraded by two levels because of study limitations (risk of bias) and because we could not asses clinical relevance according to the PASKWIL criteria (imprecision). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by one level because of study limitations (risk of bias). Therefore, the level of evidence was graded as moderate.

The level of evidence regarding the outcome measure **quality of life** was downgraded by one level because of study limitations (risk of bias). Therefore, the level of evidence was graded as moderate.

Nivolumab plus ipilimumab versus nivolumab versus ipilimumab

Nivolumab plus ipilimumab versus nivolumab

The level of evidence regarding the outcome measure **overall survival** was downgraded by one level because of study limitations (risk of bias). Therefore, the level of evidence was graded as moderate.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by two levels because of study limitations (risk of bias) and because the

confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by one level because of study limitations (risk of bias). Therefore, the level of evidence was graded as moderate.

Nivolumab plus ipilimumab versus ipilimumab

The level of evidence regarding the outcome measure **overall survival** was downgraded by one level because the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision). Therefore, the level of evidence was graded as moderate.

The level of evidence regarding the outcome measure **progression free survival** the level of evidence was graded as high.

The level of evidence regarding the outcome measure **adverse events** was graded as high.

Nivolumab versus ipilimumab

The level of evidence regarding the outcome measure **overall survival** was downgraded by one level because the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision). Therefore, the level of evidence was graded as moderate.

The level of evidence regarding the outcome measure **progression free survival** was graded as high.

The level of evidence regarding the outcome measure **adverse events** was downgraded by one level because the optimal information size is not met (imprecision). Therefore, the level of evidence was graded as moderate.

Ipilimumab plus dacarbazine versus dacarbazine

The level of evidence regarding the outcome measure **overall survival** was downgraded by three levels because of study limitations (risk of bias -2); the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by three levels because of study limitations (risk of bias -2) and the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by two levels because of study limitations (risk of bias -2). Therefore, the level of evidence was graded as low.

Pembrolizumab every 2 weeks or every 3 weeks versus ipilimumab

The level of evidence regarding the outcome measure **overall survival** was downgraded by three levels because of study limitations (risk of bias -2); the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by two levels because of study limitations (risk of bias -2). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by three levels because of study limitations (risk of bias -2) and was downgraded by one level because the optimal information size is not met (imprecision). Therefore, the level of evidence was graded as very low.

T-VEC plus pembrolizumab versus placebo plus pembrolizumab

The level of evidence regarding the outcome measure **overall survival** was downgraded by three levels because of study limitations (risk of bias -2); and was downgraded by one level because the optimal information size is not met (imprecision). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by three levels because of study limitations (risk of bias -2) and was downgraded by one level because the optimal information size is not met (imprecision). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by three levels because of study limitations (risk of bias -2) and was downgraded by one level because the optimal information size is not met (imprecision). Therefore, the level of evidence was graded as very low.

T-VEC versus GM-CSF

The level of evidence regarding the outcome measure **overall survival** was downgraded by three levels because of study limitations (risk of bias -2); the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by three levels because of study limitations (risk of bias -2) and was downgraded by one level because the optimal information size is not met (imprecision). Therefore, the level of evidence was graded as very low.

Conclusions

Nivolumab versus dacarbazine

Overall survival

Moderate GRADE	Nivolumab likely result in a large increase in overall survival compared to dacarbazine in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Robert, 2015; Ascierto, 2019; Robert, 2020*

Progression free survival

Low GRADE	Nivolumab may result in a small increase in progression free survival compared to dacarbazine in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Robert, 2015; Ascierto, 2019; Robert, 2020*

Adverse events

Moderate GRADE	Nivolumab likely result in little to no difference in adverse events when compared to dacarbazine in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Robert, 2015; Ascierto, 2019; Robert, 2020*

Relatlimab plus nivolumab versus nivolumab

Progression free survival

Low GRADE	Relatlimab plus nivolumab may result in a small increase in progression free survival compared to nivolumab in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Tawbi, 2022*

Adverse events

Moderate GRADE	Relatlimab plus nivolumab likely results in little to no difference in adverse events compared to nivolumab in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Tawbi, 2022*

Quality of Life

Moderate GRADE	Relatlimab plus nivolumab likely results in little to no difference in quality of life compared to nivolumab in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Tawbi, 2022*

Nivolumab plus ipilimumab versus nivolumab versus ipilimumab

Overall survival

Moderate GRADE	Nivolumab plus ipilimumab likely result in little to no difference in overall survival compared to treatment with nivolumab only in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Larkin, 2015; Wolchock, 2017; Hodi, 2018; Larkin, 2019; Wolchok, 2022*
Moderate GRADE	Nivolumab plus ipilimumab likely result in an increase in overall survival compared to treatment with ipilimumab only in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Larkin, 2015; Wolchock, 2017; Hodi, 2018; Larkin, 2019; Wolchok, 2022*
Moderate GRADE	Nivolumab likely resuls in an increase in overall survival compared to treatment with ipilimumab only in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Larkin, 2015; Wolchock, 2017; Hodi, 2018; Larkin, 2019; Wolchok, 2022*

Progression free survival

Low GRADE	Nivolumab plus ipilimumab may result in little to no difference in progression free survival compared to treatment with nivolumab only in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Larkin, 2015; Wolchock, 2017; Hodi, 2018; Larkin, 2019; Wolchok, 2022*
High GRADE	Nivolumab plus ipilimumab result in a large increase in progression free survival compared to treatment with ipilimumab only in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Larkin, 2015; Wolchock, 2017; Hodi, 2018; Larkin, 2019; Wolchok, 2022*
High GRADE	Nivolumab results in an increase in progression free survival compared to treatment with nivolumab only in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Larkin, 2015; Wolchock, 2017; Hodi, 2018; Larkin, 2019; Wolchok, 2022*

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Adverse events

Moderate GRADE	Nivolumab plus ipilimumab likely result in an increase of adverse events compared to treatment with nivolumab only in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Larkin, 2015; Wolchock, 2017; Hodi, 2018; Larkin, 2019; Wolchok, 2022*
High GRADE	Nivolumab plus ipilimumab result in an increase of adverse events compared to treatment with ipilimumab only in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Larkin, 2015; Wolchock, 2017; Hodi, 2018; Larkin, 2019; Wolchok, 2022*
Moderate GRADE	Nivolumab probably result in little to no difference in adverse events compared to treatment with ipilimumab in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Larkin, 2015; Wolchock, 2017; Hodi, 2018; Larkin, 2019; Wolchok, 2022*

Ipilimumab plus dacarbazine versus dacarbazine

Overall survival

Very low GRADE	The evidence is very uncertain about the effect of ipilimumab plus dacarbazine on overall survival compared to treatment with dacarbazine only in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Maio, 2015; Robert, 2011*

Progression free survival

Very low GRADE	The evidence is very uncertain about the effect of ipilimumab plus dacarbazine on progression free survival compared to treatment with dacarbazine only in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Maio, 2015; Robert, 2011*

Adverse events

Low GRADE	Ipilimumab plus dacarbazine may increase adverse events compared to treatment with dacarbazine only in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Maio, 2015; Robert, 2011*

Pembrolizumab every 2 weeks or every 3 weeks compared to ipilimumab

Overall survival

Very low GRADE	The evidence is very uncertain about the effect of pembrolizumab every 2 weeks or every 3 weeks on overall survival compared to treatment with ipilimumab only in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Robert, 2019; Carlino, 2018; Schachter, 2017; Robert, 2015*

Progression free survival

Low GRADE	Pembrolizumab every 2 weeks or every 3 weeks may increase progression free survival compared to treatment with ipilimumab in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Robert, 2019; Carlino, 2018; Schachter, 2017; Robert, 2015*

Adverse events

Very low GRADE	The evidence is very uncertain about the effect of pembrolizumab every 2 weeks or every 3 weeks on adverse events compared to treatment with ipilimumab only in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Robert, 2019; Carlino, 2018; Schachter, 2017; Robert, 2015*

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T-VEC plus pembrolizumab versus placebo plus pembrolizumab

Overall survival

Very low GRADE	The evidence is very uncertain about the effect of T-VEC plus pembrolizumab on overall survival compared to treatment with placebo plus pembrolizumab in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Chesney, 2023*

Progression free survival

Very low GRADE	The evidence is very uncertain about the effect of T-VEC plus pembrolizumab on progression free survival compared to treatment with placebo plus pembrolizumab in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Chesney, 2023*

Adverse events

Very low GRADE	The evidence is very uncertain about the effect of T-VEC plus pembrolizumab on adverse events compared to treatment with placebo plus pembrolizumab in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Chesney, 2023*

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T-VEC versus GM-CSF

Overall survival

Very low GRADE	The evidence is very uncertain about the effect of T-VEC on overall survival compared to treatment with GM-CSF in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Andtbacka, 2019; Andtbacka, 2015*

Adverse events

Very low GRADE	The evidence is very uncertain about the effect of T-VEC on adverse events compared to treatment with GM-CSF in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy. *Source: Andtbacka, 2019; Andtbacka, 2015*

Overwegingen – van bewijs naar aanbeveling

De cruciale uitkomstmaat overall survival in de context van patiënten met irresectabel of gemetastaseerd stadium III/IV melanoom werd gerapporteerd door 6 RCTs die verschillende systemische behandelingen in de eerste lijn onderzochten.

CHECKMATE-066 rapporteerde het effect van **nivolumab** versus **dacarbazine** op overall survival bij patiënten met irresectabel of gemetastaseerd stadium III/IV melanoom (Robert, 2015; Ascierto, 2019; Robert, 2020). Er werd daarbij een klinisch relevant voordeel gevonden voor het gebruik van nivolumab. Het absolute verschil in mediane overall survival was 26.1 maanden met een hazard ratio van 0.50 (95% CI 0.40-0.63). De bewijskracht van deze studie is redelijk. Dit heeft te maken met het risico op bias (doordat meer patiënten in de dacarbazine groep de behandeling stopten in vergelijking met de nivolumab groep.

De studie rapporteerde ook het effect op progression free survival en adverse events. Een langere mediane progression free survival werd gevonden voor patiënten in de nivolumab groep, met een absoluut verschil van 2.9 maanden met patiënten in de dacarbazine groep. De klinische relevantie van dit verschil kan niet worden beoordeeld op basis van de PASKWIL criteria (mediane overall survival in de controle groep < 12 maanden). Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor het ontstaan van adverse events.

CHECKMATE-067 rapporteerde het effect van **nivolumab plus ipilimumab** versus **nivolumab** versus **ipilimumab** op overall survival bij patiënten met irresectabel of gemetastaseerd stadium III/IV melanoom (Larkin 2015, Wolchock 2017, Hodi 2018, Larkin 2019, Wolchok 2022). Er werd daarbij een klinisch relevant voordeel gevonden voor het gebruik van nivolumab plus ipilimumab. Het absolute verschil in mediane overall survival tussen behandeling met nivolumab plus ipilimumab versus behandeling met alleen ipilimumab was 52.2 maanden met een hazard ratio van 0.52 (95% CI 0.43-0.63). De bewijskracht hiervan is hoog. Het absolute verschil in mediane overall survival tussen behandeling met nivolumab plus ipilimumab versus behandeling met alleen

nivolumab was 35.2 maanden met een hazard ratio van 0.84 (95% CI 0.67 to 1.04). De bewijskracht hiervan is redelijk tot laag, dit heeft te maken met imprecisie, omdat de confidence interval de grens voor klinische besluitvorming omvat en het risico op bias (doordat de studie niet gepowered was voor de vergelijking van deze middelen).

De studie rapporteerde ook het effect op progression free survival en adverse events. Een langere mediane progression free survival werd gevonden voor patiënten die behandeld warden met nivolumab plus ipilimumab, met een absoluut verschil van 8.6 maanden (HR 0.42; CI 0.35-0.51) met patiënten die behandeld warden met alleen ipilimumab en een verschil van 4.6 maanden (HR 0.79; CI 0.65 to 0.97) met patiënten die behandeld warden met alleen nivolumab. Behandeling met nivolumab plus ipilimumab resulteerde in een hoger percentage behandelingsgerelateerde adverse events grade ≥3 in vergelijking met behandeling met alleen nivolumab of alleen ipilimumab.

CA184-024 rapporteerde het effect van **ipilimumab plus dacarbazine** versus **dacarbazine** op overall survival bij patiënten met unresectable of gemetastaseerd stadium III/IV melanoom (Maio, 2015; Robert, 2011). Er werd daarbij geen klinisch relevant voordeel gevonden voor het gebruik van ipilimumab plus dacarbazine. Het absolute verschil in mediane overall survival tussen behandeling met ipilimumab plus dacarbazine versus behandeling met alleen dacarbazine was 2.12 maanden met een hazard ratio van 0.69 (95% CI 0.57 to 0.84). De bewijskracht van deze studie is zeer laag. Dit heeft te maken met het risico op bias (onduidelijke behandelings allocatie en doordat meer patiënten in de interventie groep stopten vanwege behandelingsgerelateerde adverse events) en door imprecisie omdat de confidence interval de grens voor klinische besluitvorming omvat.

De studie rapporteerde ook het effect op progression free survival en adverse events. Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor de uitkomst progression free survival. het ontstaan van adverse events. Behandeling ipilimumab plus dacarbazine resulteerde in een hoger percentage behandelingsgerelateerde adverse events grade ≥3 in vergelijking met behandeling met alleen dacarbazine.

KEYNOTE-006 rapporteerde het effect van **pembrolizumab** (iedere 2 of 3 weken) in vergelijking met **ipilimumab** (iedere 3 weken) op overall survival bij patiënten met unresectable of gemetastaseerd stadium III/IV melanoom (Robert, 2019; Carlino, 2018; Schachter, 2017; Robert, 2015). Er werd daarbij geen klinisch relevant voordeel gevonden voor het gebruik van pembrolizumab. Het absolute verschil in mediane overall survival tussen behandeling met pembrolizumab versus behandeling met ipilimumab was 16.8 maanden met een hazard ratio van 0.73 (95% CI 0.61–0.88). De bewijskracht van deze studie is zeer laag. Dit heeft te maken met het risico op bias (open-label studie design; meer patiënten stopten in de controle groep; de rol van de sponsor) en door imprecisie, omdat de confidence interval de grens voor klinische besluitvorming omvat.

De studie rapporteerde ook het effect op progression free survival en adverse events. Voor de uitkomst progression free survival werd een klinisch relevant voordeel gevonden voor behandeling met pembrolizumab. Het absolute verschil in mediane progressievrije overleving was 5.0 maanden (HR 0.57; 95% CI 0.48–0.67). Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor de uitkomst adverse events.

MASTERKEY-265 rapporteerde het effect van **T-VEC plus pembrolizumab** in vergelijking met **placebo plus pembrolizumab** op overall survival bij patiënten met unresectable of gemetastaseerd stadium III/IV melanoom (Chesney, 2023). Er werd daarbij geen klinisch relevant voordeel gevonden voor het gebruik van T-VEC plus pembrolizumab (HR 0.96; 95% CI 0.76 to 1.22). De bewijskracht van deze studie is zeer laag. Dit heeft te maken met het risico op bias (meer patiënten stopten in de controle groep; studie werd vroegtijdig gestopt) en door imprecisie.

De studie rapporteerde ook het effect op progression free survival en adverse events. Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor de uitkomsten progression free survival en adverse events.

OPTiM rapporteerde het effect van **T-VEC** in vergelijking met **GM-CSF** op overall survival bij patiënten met irresectabel of gemetastaseerd stadium III/IV melanoom (Andtbacka, 2019; Andtbacka, 2015). Er werd daarbij geen klinisch relevant voordeel gevonden voor het gebruik van T-VEC. Het absolute verschil in mediane overall survival tussen behandeling met T-VEC versus behandeling met GM-CSF was 4.4 maanden met een hazard ratio 0.79 (95% CI 0.62–1.00). De bewijskracht van deze studie is zeer laag. Dit heeft te maken met het risico op bias (open-label studie design; meer patiënten stopten in de interventie groep; de rol van de sponsor) en door imprecisie, omdat het betrouwbaarheidsinterval de grens voor klinische besluitvorming omvat.

De studie rapporteerde ook het effect op adverse events. Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor de uitkomst adverse events.

RELATIVITY-047 rapporteerde het effect van **relatlimab plus nivolumab** versus **nivolumab** op progression free survival, adverse events en kwaliteit van leven bij patiënten met unresectable of gemetastaseerd stadium III/IV melanoom (Tawbi, 2022). Het absolute verschil in mediane progression free survival was 5.5 maanden met een HR van 0.75 (95% CI 0.62-0.92). De klinische relevantie van dit verschil kan niet worden beoordeeld op basis van de PASKWIL criteria (mediane overall survival in de controle groep < 12 maanden). De bewijskracht van deze studie is laag, dit heeft te maken met het risico op bias (door de rol van de sponsor in deze studie) en door imprecisie.

Relatlimab plus nivolumab resulteert waarschijnlijk niet of nauwelijks in een vermindering of toename van adverse events of kwaliteit van leven vergeleken met nivolumab.

Kwaliteit van bewijs

Nivolumab versus dacarbazine

De overall kwaliteit van bewijs is redelijk. Dit betekent dat we redelijk zeker zijn over het gevonden geschatte effect van cruciale uitkomstmaat overall survival.

Relatlimab plus nivolumab versus nivolumab

De overall kwaliteit van bewijs is laag. Dit betekent dat we onzeker zijn over het gevonden geschatte effect van de belangrijke uitkomstmaten (cruciale uitkomstmaat overall survival werd niet gerapporteerd).

Nivolumab plus ipilimumab versus nivolumab versus ipilimumab

De overall kwaliteit van bewijs is redelijk. Dit betekent dat we redelijk zeker zijn over het gevonden geschatte effect van cruciale uitkomstmaat overall survival.

Ipilimumab plus dacarbazine versus dacarbazine

De overall kwaliteit van bewijs is laag. Dit betekent dat we onzeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Pembrolizumab every 2 weeks or every 3 weeks compared to ipilimumab

De overall kwaliteit van bewijs is zeer laag. Dit betekent dat we zeer onzeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

T-VEC plus pembrolizumab versus placebo plus pembrolizumab

De overall kwaliteit van bewijs is zeer laag. Dit betekent dat we zeer onzeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Ondanks de vooruitgang in de behandeling van irresectabel of gemetastaseerd melanoom, blijven veel vragen onbeantwoord en voor een belangrijke deel van de patiënten blijft de prognose slecht. Inclusie in klinische studies blijft daarom de hoogste prioriteit in alle settings.

Waarden en voorkeuren van patiënten (en eventueel hun naasten/verzorgers)

Bij het kiezen van een behandelstrategie is het van belang om de waarden en voorkeuren van de patiënt centraal te stellen en de beslissing te individualiseren op basis van zowel het gewenste behandeldoel (kortetermijnvoordeel versus langetermijnvoordeel) als klinische kenmerken zoals lactaatdehydrogenase (LDH)-niveau, betrokken organen, performance status, tumorlast, de snelheid van ziekteprogressie en de bijwerkingen van de behandelingen.

Professioneel perspectief

Immunotherapie (PD-1-blokkade of PD-1-blokkade gecombineerd met ipilimumab) heeft de voorkeur , omdat het na het stoppen langdurige ziektecontrole kan bieden.

De keuze tussen monotherapie en combinatiebehandeling wordt mede bepaald door klinische factoren; bijvoorbeeld, patiënten met asymptomatische hersenmetastasen en/of een verhoogd LDH kunnen meer baat hebben bij combinatiebehandeling. In fase 2 studies (ABC studie en Checkmate 204) werd bij patiënten met asymptomatische hersenmetastasen een hogere responskans en betere overleving vastgesteld met ipilimumab + nivolumab (Long, 2019).

Kostenaspecten

Vanwege geheime prijsafspraken, kan de exacte impact op het geneesmiddelenbudget niet worden vastgesteld, maar het staat vast dat deze impact hoog is. Het huidig prijsniveau wordt echter acceptabel geacht in verhouding tot de effectiviteit van de behandeling. Een lagere prijs van de behandelingen zou desondanks in alle opzichten zeer wenselijk en naar mening van de werkgroep zelfs noodzakelijk zijn, mede met het oog op de komende ontwikkelingen en het betaalbaar houden en borgen van een goede kwaliteit van de zorg in de nabije toekomst.

Haalbaarheid/aanvaardbaarheid

Bij de behandeling van patiënten met een irresectabel of gemetastaseerd stadium III/IV melanoom is het van belang niet alleen te kijken naar klinische effectiviteit en patiëntvoorkeuren, maar ook naar de haalbaarheid en aanvaardbaarheid van de aanbevolen behandelopties. Deelname aan klinische studies kan voor sommige patiënten een haalbare optie zijn, mits er toegang is tot geschikte onderzoeksfaciliteiten en de patiënt bereid is de mogelijk intensieve studieverplichtingen te dragen.

Rationale

De werkgroep is van mening dat deelname aan klinische studies in de behandeling van irresectabel of gemetastaseerd stadium III/IV melanoom de hoogste prioriteit heeft, gezien de sombere prognose voor een groot deel van de patiënten en de noodzaak om effectiviteit en aanvaardbaarheid van behandelingen verder te optimaliseren. Hierbij is het essentieel om patiëntwaarden en individuele klinische kenmerken leidend te laten

zijn, zodat behandelbeslissingen aansluiten bij zowel haalbaarheid als de persoonlijke voorkeuren van de patiënt.

5 Aanbevelingen

Overweeg behandeling in studieverband.

Individualiseer de behandelbeslissing rekening houdend met het behandeldoel (kortetermijnvoordeel versus langetermijnvoordeel) en klinische kenmerken [lactaatdehydrogenase (LDH), betrokken organen waaronder de hersenen, algehele conditie (performance status), tumorlast, snelheid van ziekteprogressie], comorbiditeiten, bijwerkingen en patiëntvoorkeuren.

Overweeg immunotherapie bij patiënten die dit in de eerste maanden kunnen verdragen, omdat PD-1 blokkade, eventueel gecombineerd met ipilimumab, langdurige ziektecontrole kan bieden, zelfs na het beëindigen van de behandeling.

Baseer de keuze tussen monotherapie en combinatiebehandeling op klinische parameters. Combinatiebehandeling is meer voorbehouden voor patiënten met hersenmetastasen en/of verhoogd serum LDH.

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Evidence tabellen

Robert, 2015 **Ascierto 2019** **Robert 2020** **Checkmate 066**	Type of study: phase III, randomized, controlled, double blind study Setting and country: Multicentre, 80 centres in Europe, Israel, Australia, Canada and South America. Funding and conflicts of interest: Funded by Bristol-Meyers Squibb. The funder participated in data collection and medical writing support. Detailed declarations of interests are provided in the article.	Inclusion criteria: -Confirmed, unresectable, previously untreated stage III or IV melanoma without a BRAF mutation. -Aged >= 18 years -ECOG performance status 0 or 1. -The availability of tumor tissue from a metastatic or unresectable site for PD-L1 biomarker analysis. Exclusion criteria: -Active brain metastases -Uveal melanoma -A history of serious autoimmune disease. <u>N total at baseline</u>: 418 Intervention: 210 Control: 208 <u>Important prognostic factors[2]</u>: Median age (IQR) *I:* 64 (18-86) *C:* 66 (26-87) Sex: *I:* 57.6% M *C:* 60.1% M ECOG performance status: *I:* 70.5% 0 C: 58.2% 0 No BRAF mutation: *I:* 202 (96.2%) *C:* 204 (98.1%) PD-L1 status positive: *I:* 35.2%	Describe intervention (treatment/procedure/test): Intravenous infusion of 3 mg of nivolumab per kilogram of body weight every 2 weeks, plus a dacarbazine-matched placebo every 3 weeks	Describe control (treatment/procedure/test): Intravenous infusion of 1000 mg of dacarbazine per square meter of body-surface area every 3 weeks, plus a nivolumab-matched placebo every 2 weeks.	**Robert 2015:** Clinical data cutoff June 24, 2014 <u>Range of follow-up:</u> 5.2-16.7 months <u>Loss-to-follow-up</u>: Intervention: 111 (53%) discontinued treatment. *96 disease progression* *5 study drug toxicity* *0 death* *2 AE unrelated to study drug* *5 request to discontinue* *2 withdrew consent* *1 max clinical benefit* Control: 129 (92%) discontinued treatment. *175 disease progression* *7 study drug toxicity* *0 death* *3 AE unrelated to study drug* *2 request to continue* *3 withdrew consent* *1 max clinical benefit* *1 other* **Ascierto 2019:** Clinical data cutoff June 22, 2017 Minimum follow-up 38.4 months (intervention) 38.5 months (control) Loss-to-follow-up: Intervention: 174 (83%) discontinued treatment.	Outcome measures and effect size (include 95%CI and p-value if available): **Robert 2015** <u>Median overall survival:</u> I: not reached C: 10.8 months (95%CI 9.3-12.1) <u>Overall survival rate at 1 year:</u> I: 72.9% (95%CI 65.5-78.9) C: 42.1 % (95%CI 33.0-50.9) HR 0.42, (0.42; 99.79% CI, 0.25 to 0.73; P<0.001 <u>Median progression-free survival:</u> I: 5.1 months (95% CI, 3.5 to 10.8) C: 2.2 months (95% CI, 2.1 to 2.4) HR, 0.43, 95%CI 0.34-0.56, P<0.001 <u>Adverse events:</u> I: 74.35 C: 75.6% Treatment related grade 3 and 4: I: 11.7% C: 17.6% <u>Quality of life:</u> Not reported. **Ascierto 2019**	Authors 'conclusion: *In conclusion, nivolumab was associated with a significant improvement in overall survival and progression-free survival, as compared with dacarbazine. Nivolumab was associated with a low* *risk of high-grade toxic effects.* -Subgroup analysis was performed on the PD-L1 group. <u>Overall survival sensitivity analysis PD-L1 group</u> HR 0.30, 95% CI, 0.15 to 0.60

		C: 35.6% Brain metastases: I: 3.3% C: 3.8% Increased lactate dehydrogenase levels <ULN: I: 37.6% C: 35.6% Groups comparable at baseline? Yes.			*118 disease progression* *18 study drug toxicity* *1 death* *1 poor or noncompliance* *2 AE unrelated to study drug* *18 request to discontinue* *2 withdrew consent* *11 max clinical benefit* *3 other* Control: 197 (95%) discontinued treatment. *167 disease progression* *9 study drug toxicity* *0 death* *6 AE unrelated to study drug* *6 request to continue* *5 withdrew consent* *1 max clinical benefit* *3 other* **Robert 2020:** Clinical data cutoff April 9, 2019 Median follow-up 32 months (intervention) 10.9 months (control) Loss-to-follow-up: Intervention: 189 (92%) discontinued treatment.	Median overall survival: I: 37.5 months (95%CI 25.5-NR) C: 11.2 months (95%CI 9.6-13.0 months) HR 0.46, 95% CI 0.36-0.59) Median progression-free survival: I: 5.1 months (95% CI, 3.5 to 12.2) Rate 32.2% (95%CI 25.6-39.0) C: 2.2 months (95% CI, 2.1 to 2.5) Rate 2.9% (95%CI 0.7-8.1%) HR, 0.42, 95%CI 0.33-0.53, P<0.001 Adverse events: I: 77.7% C: 77.6% Treatment related grade 3 and 4: I: 15% C: 17.6% Quality of life: Not reported. **Robert 2020** Median overall survival: I: 37.3 months (95% CI, 25.4 to 51.6 months)	

					119 disease progression *19 study drug toxicity* *22 request to discontinue* *16 maximum clinical benefit* *5 adverse event unrelated to treatment* *4 other* *2 withdrew consent* *1 poor/non-compliance* *1 death* Control: 204 (98%) discontinued treatment. *174 disease progression* *8 study drug toxicity* *3 request to discontinue* *9 maximum clinical benefit* *6 adverse events unrelated to treatment* *1 other* *3 withdrew consent*	C: 11.2 months (95%CI 9.6-13.0 months) HR 0.50, 95% CI 0.40-0.63) <u>5-year survival rates</u> I: 39% C: 17% <u>Median progression-free survival</u>: I: 5.1 months (95% CI, 3.5 to 12.2) Rate 28% C: 2.2 months (95% CI, 2.1 to 2.5) Rate 3% HR, 0.42, 95%CI 0.33-0.53, P<0.001 <u>Adverse events</u>: I: 77.7% C: 77.6% <u>Treatment related grade 3 and 4</u>: I: 16% C: 18% <u>Quality of life</u>: Not reported.	
Tawbi 2022, RELATIVITY-047	Type of study: phase 2-3, global, double-blind, randomized controlled trial Setting and country: Multicentre, 111 sites in	Inclusion criteria: -Previously untreated, histologically confirmed, unresectable stage III or IV melanoma -Aged >= 12 years	Describe intervention (treatment/procedure/test): 160 mg of relatlimab and 480 mg of nivolumab in a fixed-dose combination administered in a single 60-	Describe control (treatment/procedure/test): 480 mg of nivolumab administered in a single 60-minute intravenous infusion every 4 weeks	<u>Median follow-up:</u> 13.2 months <u>Loss-to-follow-up</u>: Intervention: 237 (66.8%) discontinued treatment.	Outcome measures and effect size (include 95%CI and p-value if available): <u>Overall survival:</u>	Authors' conclusion: *The inhibition of two immune checkpoints, LAG-3 and PD-1, provided a greater benefit with regard to progression-free survival than inhibition of PD-1 alone in patients with previously untreated*

	North America, Central America, South America, Europe, Australia, and New Zealand. Funding and conflicts of interest: Funded by Bristol-Meyers Squibb. The funder participated in data collection and medical writing support. Detailed declarations of interests are provided in the article.	-Measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 -Expression of LAG-3 and programmed death ligand 1 (PD-L1) that could be evaluated in tumor tissue -Patients who had received previous adjuvant or neoadjuvant therapies containing a PD-1, CTLA-4, BRAF, or MEK inhibitor (or a combination of BRAF and MEK inhibitors) were eligible if the therapy was completed at least 6 months before the date of recurrence -Patients who received previous treatment with interferon were eligible if the last dose was received at least 6 weeks before randomization Exclusion criteria: -Active untreated brain or leptomeningeal metastases -Uveal melanoma -A history of serious autoimmune disease. <u>N total at baseline</u>: 714 Intervention: 355 Control: 359	minute intravenous infusion every 4 weeks		*129 disease progression* *63 AE related to study drug* *19 request to discontinue* *12 AE unrelated to study drug* Control: 233 (64.9%) discontinued treatment. *165 disease progression* *32 AE related to study drug* *12 request to discontinue* *14 AE unrelated to study drug*	Not reported. <u>Median progression-free survival:</u> I: 10.1 months (95%CI, 6.4 to 15.7) C: 4.6 months (95%CI 3.4 to 5.6) HR 0.75 (95%CI 0.62-0.92)? <u>Adverse events:</u> I: 345 (97.2%) C: 339 (94.4%) Treatment related grade 3 and 4: I: 143 (40.3%) C: 120 (33.4%) <u>Quality of life:</u> No substantial differences in health-related quality of life were noted between the treatment groups.	*metastatic or unresectable melanoma. Relatlimab and nivolumab in combination showed no new safety signals.* -Outcome overall survival: *At the final analysis of progression-free survival, the data monitoring committee conducted a prespecified interim analysis of overall survival, which at that time point had not reached significance.* Subgroup analysis: the benefit of treatment with relatlimab–nivolumab was observed regardless of patients' BRAF mutation status. In the subgroup of patients with BRAF mutations, the median progression-free survival was 10.1 months (95% CI, 4.6 to 23.1) in the relatlimab–nivolumab group and 4.6 months (95% CI, 3.0 to 6.5) in the nivolumab group (hazard ratio for progression or death, 0.74 [95% CI, 0.54 to 1.03]); in the subgroup of patients with wild-type BRAF, the median progression-free survival was 10.1 months (95% CI, 5.9 to 17.0) with relatlimab–nivolumab and 4.6 months (95% CI, 2.9 to 6.6) with nivolumab (hazard ratio, 0.76 [95% CI, 0.59 to 0.98]).

		Important prognostic factors[2]: Median age (IQR) *I:* 63 (20-94) *C:* 62.0 (21–90) Sex: *I:* 59.2% M *C: 57.4%* M ECOG performance status: *I:* 66.5% 0 C: 67.4% 0 No BRAF mutation: *I:* 219 (61.7) *C:* 220 (61.3) LAG-3 expression >=1% I: 268 (75.5) C: 269 (74.9) PD-L1 expression >=1% I: 146 (41.4) C: 147 (40.9) Groups comparable at baseline? Yes.					
Larkin 2015, Wolchock 2017, Hodi 2018, Larkin 2019, Wolchok 2022 **CheckMate 067**	Type of study: multicentre, randomized, double-blind, phase 3 study. Setting and country: Multicentre, 137 centres in Australia,	Inclusion criteria: -histologically confirmed stage III (unresectable) or stage IV melanoma -no prior systemic treatment for advanced disease. -age >= 18 years	Describe intervention (treatment/procedure/test): Nivo + ipi: 1 mg of nivolumab per kilogram every 3 weeks plus 3 mg of ipilimumab per kilogram every 3 weeks for	Describe control (treatment/procedure/test): Nivo: 3 mg of nivolumab per kilogram of body weight every 2 weeks (plus ipilimumab-matched placebo).	**Larkin 2015** Median follow-up: Clinical data cutoff February 17, 2015. Range 12.2-12.5 months Loss-to-follow-up: Nivo: 3 (0.95%)	Outcome measures and effect size (include 95%CI and p-value if available): **Larkin 2015**	-Subgroup analyses performed on PD-L1 status, BRAF mutation status, and metastasis stage.

	Europe, Israel, New Zealand, and North America. Funding and conflicts of interest: Funded by Bristol-Meyers Squibb. Detailed declarations of interests are provided in the article.	-ECOG performance-status score of 0-1 -measurable disease as assessed by means of computed tomography or magnetic resonance imaging according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 -availability of tissue collected from metastatic or unresectable tumors (archival or recently biopsied samples) for the assessment of PD-L1 status -known BRAF V600 mutation status Exclusion criteria: -ECOG score of 2 or higher -presence of active brain metastases -ocular melanoma -autoimmune disease. <u>N total at baseline</u>: 945 Nivolumab: 316 Nivolumab + ipilimumab: 314 Ipilimumab: 315 <u>Important prognostic factors[2]</u>: Median age (IQR) nivo: 59 (25-90)	4 doses, followed by 3 mg of nivolumab per kilogram every 2 weeks for cycle 3 and beyond. Administered by means of intravenous infusion.	Ipi: 3 mg of ipilimumab per kilogram every 3 weeks for 4 doses (plus nivolumab-matched placebo). Administered by means of intravenous infusion.	*1 no longer met study criteria* *1 withdrew consent* *1 request to discontinue* Nivo + ipi: 1 (0.32%) *1 no longer met study criteria* Ipi: 4 (1.27%) *2 no longer met study criteria* *1 withdrew consent* *1 disease progression* **Wolchok 2017** <u>Median follow-up:</u> Clinical data cutoff May 24, 2017. Nivo: 35.7 months Nivo+ipi: 38.0 months Ipi: 18.6 months <u>Loss-to-follow-up</u>: Nivo: 265 (84.7%) *174 disease progression* *42 study drug toxicity* *1 death* *8 adverse events* *24 patient request* *1 lost to follow-up* *12 maximum clinical benefit* *1 poor/noncompliance* *2 other* Nivo + ipi: 288 (92.0%)	<u>Median progression-free survival:</u> Nivo: 6.9 months (95% CI 4.3-9.5) Nivo + ipi: 11.5 months (95% CI 8.9-16.7) Ipi: 2.9 months (95% CI 2/8-3.4) HR nivo+ipi vs ipi 0.42; 99.5% CI, 0.31 to 0.57 HR nivo+ipi vs nivo 0.74 (95% CI, 0.60 to 0.92) HR nivo vs ipi HR, 0.57; 99.5% CI, 0.43 to 0.76. <u>Adverse events:</u> Nivo: 257 (82.1%) Nivo+ipi: 299 (95.5%) Ipi: 268 (86.2%) Treatment related grade 3 and 4: Nivo: 51 (16.3%) Nivo+ipi: 172 (55.0%) Ipi: 85 (27.3%) <u>Quality of life:</u> Not reported. **Wolchock 2017** <u>Median progression-free survival:</u>	

		nivo+ipi: 59 (18-88) ipi: 61 (18-89) Sex: nivo: 202 (63.9%) M nivo+ipi: 206 (65.6%) M ipi: 202 (64.1%) M ECOG performance status 0: nivo: 238 (75.3%) nivo+ipi: 230 (73.2%) ipi: 224 (71.1%) No BRAF mutation: nivo: 216 (68.4%) nivo+ipi: 213 (67.8%) ipi: 218 (69.2%) Increased serum lactate dehydrogenase <ULN: Nivo: 112 (35.4%) nivo+ipi: 114 (36.3%) ipi: 115 (36.5%) Brain metastases nivo: 8 (2.5%) nivo+ipi: 11 (3.5%) ipi: 15 (4.8%) PD-L1 status positive: nivo: 80 (25.3%) nivo+ipi: 68 (21.7%) ipi: 75 (23.8%) Groups comparable at baseline? Yes			*90 disease progression* *131 study drug toxicity* *4 deaths* *18 adverse events* *24 patient request* *3 withdrew consent* *12 maximum clinical benefit* *1 poor/noncompliance* *1 no longer met study criteria* *4 other* Ipi: 303 (97.4%) *224 disease progression* *52 study drug toxicity* *1 death* *6 adverse events* *13 patient request* *1 withdrew consent* *3 maximum clinical benefit* *1 poor/noncompliance* *2 other* **Hodi 2018** <u>Median follow-up (IQR):</u> Clinical data cutoff May 10, 2018. Nivo: 36.0 months (10.5-51.4 months) Nivo+ipi: 46.9 months (10.9-51.8 months) Ipi: 18.6 months (7.6-49.5 months)	Nivo: 6.9 months (95% CI, 5.1 to 9.7) Nivo + ipi: 11.5 months (95% CI 8.9-19.3) Ipi: 2.9 months (95% CI 2.8-3.2) HR nivo+ipi vs ipi 0.43 (95% CI, 0.35 to 0.52) HR nivo+ipi vs nivo 0.78 (95% CI, 0.64 to 0.96) HR nivo vs ipi HR, 0.55 (95% CI, 0.45 to 0.66) <u>Overall survival at 2 years:</u> Nivo: 59% Nivo+ipi: 64% Ipi: 45% <u>Overall survival at 3 years:</u> Nivo: 52% Nivo+ipi: 58% Ipi: 34% <u>Median overall survival:</u> Nivo: 37.6 months; 95% CI, 29.1 to not reached Nivo+ipi: not reached Ipi: 19.9 months; 95% CI, 16.9 to 24.6 <u>Adverse events:</u>	

					<u>Loss-to-follow-up</u>: Nivo: 280 *177 disease progression* *44 study drug toxicity* *1 death* *8 adverse events* *29 patient request* *1 lost to follow-up* *16 achieved maximum clinical benefit* *1 poor or non-compliance* *3 other* Nivo + ipi: 295 *90 disease progression* *134 study drug toxicity* *4 deaths* *19 adverse events* *27 patient request* *3 withdrew consent* *13 achieved maximum clinical benefit* *1 poor or non-compliance* *1 no longer met study criteria* *3 other* Ipi: 311 *224 disease progression* *52 study drug toxicity* *1 death*	Nivo: 270 (86) Nivo+ipi: 300 (96) Ipi: 268 (86) Treatment related grade 3 and 4: Nivo: 67 (21) Nivo+ipi: 184 (59) Ipi: 86 (28) <u>Quality of life:</u> Not reported. **Hodi 2018:** <u>Median progression-free survival:</u> Nivo: 6.9 months (95% CI, 5.1 to 10.2) Nivo + ipi: 11.5 months (95% CI 8.7–19.3) Ipi: 2.9 months (95% CI 2.8-3.2) HR nivo+ipi vs ipi 0.42 (95% CI, 0.35 to 0.51) HR nivo+ipi vs nivo 0.79 (95% CI, 0.65 to 0.97) HR nivo vs ipi HR, 0.53 (95% CI, 0.44 to 0.64) <u>Median overall survival</u> Nivo: 36·9 months (28·3–not reached) Nivo+ipi: not	

					6 adverse events *13 patient request* *1 withdrew consent* *4 achieved maximum clinical benefit* *1 poor or non-compliance* *6 administrative reason** *3 other* **Larkin 2019** Median follow-up: Clinical data cutoff July 2, 2019. Nivo: 54.6 months Nivo+ipi: 36.0 months Ipi: 18.6 months Loss-to-follow-up: Nivo: 289 (92.3%) *179 disease progression* *45 study drug toxicity* *1 death* *8 adverse events* *33 patient request* *1 lost to follow-up* *18 maximum clinical benefit* *1 poor/non-compliance* *3 other* Nivo + ipi: 301 (96.2%) *90 disease progression* *139 study drug toxicity* *4 death*	reached (95% CI 38·2–not reached) Ipi: 19·9 months (16·9–24·6) Overall survival at 4 years: Nivo: 46% (41−52) Nivo+ipi: 53% (95% CI 47−58) Ipi: 30% (25−35) Adverse events: Nivo: 270 (86) Nivo+ipi: 300 (96) Ipi: 268 (86) Treatment related grade 3 and 4: Nivo: 70 (22%) Nivo+ipi: 185 (59%) Ipi: 86 (28%) Quality of life: Not reported. **Larkin 2019** Median progression-free survival: Nivo: 6.9 months (95% CI, 5.1 to 10.2) Nivo + ipi: 11.5 months (95% CI, 8.7 to 19.3) Ipi: 2.9 months (95% CI 2.8-3.2) Median overall survival	

					18 adverse events *27 patient request* *3 withdrew consent* *15 maximum clinical Benefit* *1 poor/non-compliance* *1 no longer meets study criteria* *3 other* Ipi: 311 (100%) *224 disease progression* *52 study drug toxicity* *1 death* *6 adverse events* *13 patient request* *1 withdrew consent* *4 maximum clinical benefit* *1 poor/non-compliance* *6 administrative reasons* *3 other* **Wolchok 2022** <u>Median follow-up:</u> Clinical data cutoff October 19, 2020. Nivo: 57.5 months Nivo+ipi: 36.0 months Ipi: 18.6 months <u>Loss-to-follow-up</u>: Nivo: 305 (97.4%) *180 disease progression* *49 study drug toxicity*	Nivo: 36.9 months (95% CI, 28.2 to 58.7) Nivo+ipi: 60.0 months (median not reached; 95% confidence interval [CI], 38.2 to not reached) Ipi: 19.9 months (95% CI, 16.8 to 24.6) <u>Overall survival at 5 years:</u> Nivo: 44% Nivo+ipi: 52% Ipi: 26% <u>Adverse events:</u> Nivo: 271 (87) Nivo+ipi: 300 (96) Ipi: 268 (86) Treatment related grade 3 and 4: Nivo: 73 (23%) Nivo+ipi: 186 (59%) Ipi: 86 (28%) <u>Quality of life:</u> Not reported. **Wolchok 2022** <u>Median progression-free survival:</u> Nivo: 6.9 months (95% CI, 5.1 to 10.2)	

					1 death *8 adverse events* *39 patient request* *2 withdrew consent* *1 lost to follow-up* *21 maximum clinical benefit* *1 poor/non-compliance* *3 other* Nivo + ipi: 306 (97.8%) *91 disease progression* *139 study drug toxicity* *4 death* *18 adverse events* *30 patient request* *3 withdrew consent* *16 maximum clinical Benefit* *1 poor/non-compliance* *1 no longer meets study criteria* *3 other* Ipi: 311 (100%) *224 disease progression* *52 study drug toxicity* *1 death* *6 adverse events* *13 patient request* *1 withdrew consent* *4 maximum clinical benefit*	Nivo + ipi: 11.5 months (95% CI, 8.7 to 19.3) Ipi: 2.9 months (95% CI 2.8-3.2) <u>Median overall survival</u> Nivo: 36.9 months (95% CI, 28.2 to 58.7) Nivo+ipi: 72.1 months (38.2 to not reached) Ipi: 19.9 months (95% CI, 16.8 to 24.6) <u>Overall survival at 6.5 years:</u> Nivo: 42% Nivo+ipi: 49% Ipi: 23% <u>Adverse events:</u> Nivo: 271 (87) Nivo+ipi: 300 (96) Ipi: 268 (86) Treatment related grade 3 and 4: Nivo: 73 (23%) Nivo+ipi: 186 (59%) Ipi: 86 (28%) <u>Quality of life:</u> Not reported.	

					1 poor/non-compliance *6 administrative reasons* *3 other*		
Robert, 2019 **Carlino, 2018** **Schachter, 2017** **Robert, 2015** **KEYNOTE-006** **NCT01866319**	International, randomized, open-label phase 3 study. In 16 countries. Patient enrolment: From September 18, 2013, to March 3, 2014. <u>Funding and conflicts of interest:</u> • The sponsors, Merck Sharp & Dohme, contributed to: • Trial design • Statisticians and a science writer were employed by the sponsor. Disclosure forms provided by the authors are available with the full text of this article.	Inclusion criteria: • Age ≥ 18 years • Histologically confirmed, unresectable stage III or IV melanoma who received no more than one previous systemic therapy for advanced disease • Known BRAF V600 mutational status was required; • previous BRAF inhibitor therapy was not required for patients with normal lactate dehydrogenase levels • no clinically significant tumor-related symptoms or evidence of rapidly progressive disease. • ECOG PS of 0 or 1 • Provision of a tumor sample adequate for assessing PD-L1 expression. Exclusion criteria: • Patients who had received previous	Ia: pembrolizumab at a dose of 10 mg per kilogram of body weight every 2 weeks n= 279 Ib: pembrolizumab at a dose of 10 mg per kilogram of body weight either every 3 weeks n=277	C: Four cycles of ipilimumab at a dose of 3 mg per kilogram every 3 weeks n=278	**Robert, 2019:** Median follow-up for survival: 57.7 months (IQR 56.7–59.2). **Carlino, 2018:** Median follow-up: 33.9 months. **Schachter, 2017:** Median follow-up: 22.9 months Discontinued treatment: Ia: *147 progressive disease* *29 adverse events* *2 deaths* *2 complete responses* *21 other*	**Robert, 2019:** Median OS: I (pooled groups): 32.7 months (95% CI 24·5–41·6) C: 15.9 months (13.3–22.0) HR: 0.73 (95% CI 0.61–0.88, p=0·00049). Median PFS: I (pooled groups): 8.4 months (95% CI 6.6–11.3) C: 3.4 months (2.9–4.2) HR 0.57, 95% CI 0.48–0.67, p<0.0001. Grade 3–4 treatment-related AEs: I (pooled groups): 96 (17%)	Co-primary endpoints were OS and PFS. **Robert, 2019:** • Data cutoff: Dec 3, 2018. **Carlino, 2018:** • Data cutoff: 03 Nov 2016. • Reported outcomes by line of therapy and PD-L1 expression **Schachter, 2017:** • Data cutoff: Dec 3, 2015. **Robert, 2015:** • Data cutoff 1st interim analysis: Sep 3, 2014 (PFS and AEs) • Data cutoff 2nd interim analysis: Mar 3, 2015 (OS). • OS results for the pembrolizumab groups were superior to those for the ipilimumab group. The independent data and safety monitoring committee recommended stopping the study early. <u>Authors conclusions:</u>

		therapy with CTLA-4, PD-1, or PD-L1 inhibitors • Ocular melanoma • Active brain metastases • History of serious autoimmune disease. Mean age, years Ia: 61 (18–89) Ib: 63 (22–89) C: 62 (18–88) Male, n (%) Ia: 161 (57.7) Ic: 174 (62.8) C: 162 (58.3) ECOG PS: 0 – Ia: 196 (70.3) 0 – Ib: 189 (68.2) 0 – C: 188 (67.6) 1 – Ia: 83 (29.7) 1 – Ib: 88 (31.8)			Ib: *139 progressive disease* *45 adverse events* *1 death* *5 complete responses* *23 other* C: *46 progressive disease* *35 adverse events* *5 deaths* *24 other* Withdrew consent and did not receive treatment: Ia: n=1 C: n=22 **Robert, 2015:** Median follow-up at data cutoff (with 502 events reported),	C: 50 (20%) Treatment-related sepsis. C: n=1 **Schachter, 2017:** Death: n=383 Median OS: Ia: not reached (range 22.1 months–not reached) Ib: not reached (23.5 months–not reached) C: 16.0 months (range 13.5–22.0) HR pembro every 2 weeks vs ipi: 0.68, 95% CI 0·53–0·87; p=0·0009 HR pembro every 3 weeks vs ipi: 0.68, 0·53–0·86; p=0·0008.	**Robert, 2019:** Pembrolizumab continued to show superiority over ipilimumab after almost 5 years of follow-up. These results provide further support for use of pembrolizumab in patients with advanced melanoma. **Carlino, 2018:** Findings support pembrolizumab monotherapy as standard of care in patients with advanced melanoma, regardless of first- or second-line therapy or PD-L1 status. **Schachter, 2017:** Substantiating the results of the interim analyses of KEYNOTE-006, pembrolizumab continued to provide superior overall survival versus ipilimumab, with no difference between pembrolizumab dosing schedules. These conclusions further support the use of pembrolizumab as a standard of care for advanced melanoma.

		1 – C: 90 (32.4) PD-L1-positive tumours: 80.6% Groups were comparable at baseline.			months: 7.9 (range: 6.1 to 11.5) March 3, 2015: Follow-up for OS: Minimum follow-up: 12 months with 289 deaths occurred Mean duration of exposure, days: Ia: 164 Ib: 151 C: 50 Rate discontinuation of a study drug because of treatment related AEs: Ia: 4.0%, Ib: 6.9%, C: 9.4%,	2 year OS rate: Ia: 55% (95% CI 49–61) Ib: 55% (95% CI 49–61) C: 43% (95% CI 37–49) PFS events: n= 566 I (pooled groups): 364 (65%) C: 202 (35%) Median PFS, months: Ia: 5.6 months (range 3.4–8.2) Ib: 4.1 months (range 2.9–7.2) C: 2.8 months (range 2.8–2.9) HR for both Pembro schedules vs ipi: 0.61; 95% CI 0·50–0·75; p<0·0001	**Robert, 2015:** The anti–PD-1 antibody pembrolizumab prolonged progression-free survival and overall survival and had less high-grade toxicity than did ipilimumab in patients with advanced melanoma.

						HR for Ia vs Ib: 0.95; 95% CI 0·77–1·17; p=0·62). 2-year PFS rate: Ia: 31% Ib: 28% C: 14% Treatment related AEs grade 3 to 5: Ia: 47 (17%) of 278 Ib: 46 (17%) of 277 C: 50 (20%) of 256 **Robert, 2015:** Median overall survival was not reached in any study group. 1-Year OS: Ia: 74.1% Ib: 68.4%	

						C: 58.2% • HR for death for pembrolizumab every 2 weeks versus ipilimumab: 0.63; 95% CI, 0.47 to 0.83; P<0.0005 • HR for death for pembrolizumab every 3 weeks versus ipilimumab: 0.69; 95% CI, 0.52 to 0.90; P = 0.0036 Median PFS, months (95% CI): Ia: 5.5 (95% CI, 3.4 to 6.9) Ib: 4.1 (95% CI, 2.9 to 6.9) C: 2.8 (95% CI, 2.8 to 2.9) • HR for progression for pembrolizumab every 2 weeks versus ipilimumab: 0.58 (95% CI, 0.46 to 0.72; P<0.001) • HR for pembrolizumab every 3 weeks versus ipilimumab:	

						0.58 (95% CI, 0.47 to 0.72; P<0.001). 6-month PFS, months: Ia: 47.3% Ib: 46.4% C: 26.5% Treatment related AEs grade 3 to 5: Ia: 13.3% Ib: 10.1% C: 19.9% Drug-related deaths, n: Ia: 0 Ib: 0 C: 1 For more information on AEs see results section of the article.	

Chesney, 2023 **MASTERKEY-265** **NCT02263508**	A multicenter, double-blind, placebo controlled, randomized phase III study in 21 countries. Patient enrolment between: March 17, 2016, through April 26, 2018. <u>Funding and conflicts of interest:</u> - Supported by Amgen Inc and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc, Rahway, NJ. The sponsors contributed to: • Medical writing support - Authors' disclosures of potential conflict of interest is provided at the end of the full text article.	Main Inclusion criteria: • Histologically confirmed stage IIIB-IV M1c unresectable melanoma • Age ≥ 18 years • ECOG PS 0 or 1 • At least one visceral or nodal/soft tissue melanoma lesion for which the longest diameter was ≥ 10 mm • In/exclusion criteria with regard to prior therapy for patients with BRAF-mutated melanoma is specified in the article. Exclusion criteria: • Active untreated brain metastases • Primary uveal or mucosal melanoma • Prior therapy with T-VEC or any other oncolytic viruses • Prior therapy with anti–PD-1/PD-L1/PD-L2 agents • Prior therapy with tumor vaccine in the nonadjuvant setting • History of autoimmune diseases • Evidence of immunosuppression	I: A combination of T-VEC plus pembrolizumab (T-VEC-pembrolizumab) n=346 T-VEC was administered at ≤ 4 x 106 plaque-forming unit followed by ≤ 4 x 108 PFU 3 weeks later and once every 2 weeks until dose 5 and once every 3 weeks thereafter. Pembrolizumab was administered intravenously 200 mg once every 3 weeks.	C: Placebo plus pembrolizumab (placebo-pembrolizumab n=346 Pembrolizumab was administered intravenously 200 mg once every 3 weeks.	Median follow-up in months: • 25.58 (range, 0.3-45.8) for the PFS primary analysis. • 31.0 (range, 0.3-53.0) for the second OS interim analysis. • 35.56 (range, 0.3-58.4) for the final analysis Discontinued study: I: n = 152 *Death n = 131* *Withdrawal of consent n = 15* *Lost to follow-up n=6* C: n = 170 *Death n = 142* *Withdrawal of consent n = 22* *Lost to follow-up n = 6*	Deaths at planned second interim OS analysis: I: 136 (39.3%) C: 146 (42.2%) Median OS, months (95% CI): I: Not estimable C: 49.2 (40.57 to not estimable) HR of 0.96 (95% CI, 0.76 to 1.22; P = .74) The primary analysis of PFS was to be performed after 407 PFS events occurred. Median PFS (95% CI) (months): I: 14.3 (10.25 to 22.11) C: 8.5 (5.72 to 13.54)	• The dual primary end points were PFS and OS. • Data cutoff dates: Mar 2, 2020, for the PFS primary analysis; Sep 29, 2020, for the second interim OS analysis; Mar 26, 2021, the final analysis. • On June 12, 2020, the DMC met to review data from the PFS primary analysis and recommended that the study continues as planned. • On December 22, 2020, the DMC reviewed the efficacy and safety data from the second OS interim analysis. The DMC indicated that the futility boundary for OS was crossed and recommended that no further study-related procedures are conducted. • On January 8, 2021, the study was unblinded and proceeded directly to a final analysis conducted in an unblinded manner. • All patients were off study treatment as of April 2020. The last visit date for the final analysis was March 11, 2021. • No improvement in OS was observed in any of the predefined subgroups. • Sensitivity analysis were performed: - which censored patients at the time of subsequent anticancer therapy

		therapy for > 2 weeks or < 7 days prior to the first dose of study • Active herpetic skin lesions • Current treatment with antiherpetic drug. For more information on in-/exclusion see the article. Median age, years (range) I: 64 (26-92) C: 64 (19-94) Male, n (%) I: 199 (57.5) C: 219 (63.3) ECOG PS: 0 – I: 259 (74.9) 0 – C: 249 (72.0) 1 – I: 87 (25.1) 1 – C: 97 (28.0)			April 2020, all patients discontinued study treatments. The final analysis was performed early given the futility noted in the second interim analysis and included an additional follow-up of 6 months.	Stratified log-rank: HR, 0.86 (95% CI, 0.71 to 1.04), P=.13 Treatment related AEs grade 3 or 4: I: 70 (20.3%) C: 54 (15.7%) Fatal AEs: I: 45 (13.1%) C: 42 (12.2%) Treatment related fatal AEs, n: I: 4 (1.2%) C: 1 (0.3%) Immune-related AEs: I: 27.5% C: 24.8% For more information on AEs	- excluding patients with stage IVM1c disease - second-line therapies were generally balanced between the arms, and the crossover rate from the placebo arm to receive subsequent T-VEC treatment was<5% <u>Authors conclusions:</u> This randomized, double-blinded, placebo-controlled, multicenter, international phase III trial did not show improved PFS or OS for the combination of T-VEC plus pembrolizumab compared with placebo plus pembrolizumab for immunotherapy- naïve patients with advanced melanoma in the frontline setting. There were no new safety concerns with the addition of T-VEC to pembrolizumab, and the safety profile of the combination was consistent with the known safety profile of each drug.

		Groups were comparable at baseline.				see results section of the article At final analysis: - PFS overall stratified HR, 0.87; 95% CI, 0.72 to 1.06 - OS: overall stratified HR, 0.97; 95% CI, 0.77 to 1.21) No new safety signals were observed.	
Andtbacka, 2019 **Andtbacka, 2015** **OPTiM** **NCT00769704**	A randomized open-label phase III trial at 64 sites in the United States, the United Kingdom, Canada, and South Africa. Patient enrolment between: 2009 and 2011 <u>Funding and conflicts of interest:</u> - Funded by BioVex, who were subsequently acquired by Amgen Inc. during the OPTiM trial.	Main inclusion criteria: • ≥ 18 years • Histologically confirmed, unresectable, bidimensionally measurable stage IIIB/C/IV melanoma with ≥1 cutaneous, subcutaneous or nodal lesions that was suitable for direct or ultrasound-guided injection; • ECOG PS ≤1 • Serum lactate dehydrogenase ≤1.5 × upper limit of normal; • ≤3 visceral lesions (excl. lung or nodal lesions associated with visceral organs) with none > 3 cm;	I: intratumoral Talimogene laherparepvec (T-VEC) (at the approved dose) n= 295 (68%)	C: subcutaneous recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) n= 141 (32%)	Median follow-up in the final analysis of OS: 49 months. Median duration of treatment in weeks (range): I: 23.1 (0.1–176.7) C: 10.0 (0.6–120.0) **Andtbacka, 2015:** Discontinued T-VEC: n=291 *Disease progression:*	**Intent-to treat population (stage IIIB–IVM1c melanoma):** Median OS, months (95% CI): I: 23.3 (19.5–29.6) C: 18.9 (16.0–23.7) unstratified HR for death, 0.79 (95% CI,0.62–1.00); P = 0.0494). Estimated 5-year survival I: 33.4%	• Primary end point: durable response rate (objective response lasting continuously ≥ 6 months) per independent assessment. Key secondary end points: OS and overall response rate • Data cut-off for this final analysis of OPTiM was 5 September 2014. • 4 patients in the T-VEC arm and 14 in the GM-CSF arm did not receive T-VEC or GM-CSF. • When the 18 patients who did not receive allocated treatment were excluded (T-VEC arm, n =4; GM-CSF arm, n = 14), median OS in the final analysis dataset was 24.5 versus 18.9 months for T-VEC versus GM-CSF (HR, 0.78; P = 0.0439).

	The sponsor contributed to: • Design of the trial • Data collection • Data analysis • Interpretation of data • Development of the manuscript. - A competing interests statement is provided at the end of the full text article.	• Adequate organ function. • Patients with history of autoimmune disease, but not use of high-dose steroids. Exclusion criteria: • Requiring intermittent or chronic treatment with an antiviral agent (eg, acyclovir) or high-dose steroids • Primary ocular or mucosal melanoma • Bone metastases • Active cerebral metastases • > 3 visceral metastases • Any visceral metastasis >3 cm • Liver metastases had to be stable for 1 month before random assignment. For more information on in-/exclusion see the article. Median age, years (range) I: 63 (22 to 94)			*n=191* *PR or CR for ≥ 6 continuous months:* *n=42* *Maximum allowed dose without* *PR/CR: n=26* *Adverse event: n=11* *Consent withdrawn: n=10* *Physician decision: n=6* *Death: n=5* Discontinued GM-CSF: n=127 *Disease progression: n=95* *PR or CR for ≥ 6 continuous months: n=0* *Maximum allowed dose without* *PR/CR: n=9* *Adverse event: n=3*	C: Not estimable **Stage IIIB–IVM1a disease** Effect of T-VEC on OS vs GM-CSF: • Stage IIIB/C: HR, 0.48, P < 0.05 Effect of T-VEC on OS vs ITT population including stage IVM1b/c disease: • Stage IIIB–IVM1a: HR, 0.56; 95% CI, 0.40–0.79; P < 0.001 Estimated 5-year survival with T-VEC: • Stage IIIB–IVM1a melanoma: 48.9% (95% CI, 40.6–56.7) • Stage IVM1b/c disease: 15.1% (95% CI, 9.3–22.2). Treatment related AEs grade 3/4: I: 33 (11.3%)	• Ad-hoc sensitivity analysis for OS accounting for subsequent systemic anti-cancer treatment, there was a 27% reduction in the risk of death for T-VEC versus GM-CSF (unadjusted HR, 0.73; 95% CI, 0.59–0.92; P = 0.0069). <u>Authors conclusions:</u> **Andtbacka, 2019:** In conclusion, as well as demonstrating a longer-term effect on survival, this analysis confirms that T-VEC resulted in high CR rates, most notably in patients with early metastatic melanoma (stage IIIB–IVM1a). Once achieved, CRs were durable and associated with prolonged survival. The favorable clinical outcomes observed in some patients treated with T-VEC, along with its good safety profile, support continued efforts to further define its future role in melanoma as a combination partner with immunotherapy. **Andtbacka, 2015:** T-VEC is the first oncolytic immunotherapy to demonstrate

		C: 64 (26 to 91) Male, n (%) I: 173 (59%) C: 77 (55%) ECOG PS: 0 – I: 209 (71%) 0 – C: 97 (69%) 1 – I: 82 (28%) 1 – C: 32 (23%) Unknown: I: 4 (1%) C: 12 (9%) Groups were comparable at baseline.			*Consent withdrawn: n=12* *Physician decision: n=5* *Death: n=3*	C: 6 (4.7%) Immune-related AEs: I: 24/295 C: ? Immune-related AEs grade 3: n=4 Immune-related AEs grade 4: None reported Treatment-related deaths, n: I: 0 C: 0 For more information on AEs see results section of the article	therapeutic benefit against melanoma in a phase III clinical trial. T-VEC was well tolerated and resulted in a higher DRR (P<0.001) and longer median OS (P=0.051), particularly in untreated patients or those with stage IIIB, IIIC, or IVM1a disease. T-VEC represents a novel potential therapy for patients with metastatic melanoma.

8.3.2.2. Tweedelijnsbehandeling BRAF-wild type gemuteerd irresectabel of gemetastaseerd stadium III/IV

Uitgangsvraag

Wat is de plaats van systemische therapie in de tweede lijns-behandeling van patiënten met een BRAF-wild type gemuteerd irresectabel of gemetastaseerd stadium III/IV melanoom?

Search and select

The search and selection methods can be found in the main module 8.3 [Link XXX]

Summary of literature

Five randomized controlled trials that studied clinical outcomes of second line systemic therapy in patients with unresectable or metastatic stadium III/IV melanoma with a BRAF-wild type were included in the literature analysis.

Description of studies

The study characteristics of the included trials are summarized in Table 2 in the main module 8.3 [Link XXX].

Andtbacka, 2019 /Andtbacka, 2015 - OPTiM is a randomized open-label phase 3 trial at 64 sites in the United States, the United Kingdom, Canada, and South Africa. This trial evaluated outcomes after treatment with talimogene laherparepvec (T-VEC) compared with granulocyte macrophage colony-stimulating factor (GM-CSF) in patients with unresectable, stage IIIB/C/IV melanoma with ≥1 lesion that was suitable for direct or ultrasound-guided injection. Patients were randomized to T-VEC (at the approved dose) (n=295 (68%)) of subcutaneous recombinant GM-CSF (n=141 (32%)). The median age was 63 years in the T-VEC group and 64 years in the GM-CSF group. The percentage of males was 59% in the T-VEC group and 55% in the GM-CSF group. Of 204 of the 295 (69%) in the T-VEC group, and 95 of the 141 (67%) in the GM-CSF group, the BRAF mutation status was unknown. For 157 of the 295 (53%) patients in the T-VEC group, and 76 of the 141 (54%) in the GM-CSF group, this was a second line therapy or later. OS and AEs were reported after a median follow-up of 49 months in the final analysis of OS. In this literature analysis the median OS is analysed.

Robert, 2019 / Carlino, 2018 / Schachter, 2017 /Robert, 2015 - KEYNOTE-006 is an international, randomized, open-label phase 3 study performed in 16 countries. In this trial treatment with pembrolizumab versus ipilimumab was studied, to compare PD-1 inhibition with CTLA-4 blockade in patients with unresectable stage III/IV melanoma.Patients were randomized to pembrolizumab at a dose of 10 mg/kg of body weight every 2 weeks (n= 279); pembrolizumab at a dose of 10 mg/kg every 3 weeks (n=277); or ipilimumab at a dose of 3 mg/kg every 3 weeks (n=278). The mean age was 61 years in the pembrolizumab every 2 weeks group, 63 years in the pembrolizumab every 3 weeks group and 62 years in the ipilimumab group. The percentage of males was 57.7 %, 62.8%, and 58.3% for the three groups, respectively. Robert (2015) reported on OS, PFS, and AEs after a median follow-up of 7.9 months. Schachter (2017) reported updated results after a median follow-up of 22.9 months. Carlino (2018) reported updated outcomes by line of therapy and programmed death ligand 1 expression after a median follow-up of 33.9 months. Robert (2019) reported

updated results of OS, PFS, and AES after a median follow-up of 57.7 months. In this literature analysis the median outcomes for OS and PFS are analysed and the last endpoints for OS and PFS (2-year OS rates and 2-year PFS rates) are described.

Revicki, 2012 / Hodi, 2010 - MDX010-20 is a randomized, double-blind phase 3 study that enrolled patients at 125 centres in 13 countries in North America, South America, Europe, and Africa. This trial evaluated the effect of ipilimumab with or without a gp100 peptide vaccine on overall survival compared to gp100 alone in patients with unresectable stage III or IV melanoma who received a previous therapeutic regimen containing one or more of the following: dacarbazine, temozolomide, fotemustine, carboplatin, or interleukin-2. Patients were randomized to ipilimumab, at a dose of 3 mg/kg of body weight, plus a gp100 peptide vaccine (n=403); ipilimumab plus gp100 placebo (n=137); or gp100 plus ipilimumab placebo (n=136). The mean age was 55.6 years in the ipilimumab plus gp100 peptide vaccine group, 56.8 years in the ipilimumab group and 57.4 years in the gp100 group. The percentage of males was 61.3 %, 59.1%, and 53.7% for the three groups, respectively. Hodi (2010) reported on OS, PFS, and AEs after a follow up time of 55 months. Revicki (2012) reported health related QoL outcomes during the 12 week treatment induction period. In this literature analysis the median outcomes for OS and PFS are analysed and the last endpoint for OS (2-year OS rates) are described.

Rohaan (2022) - NCT02278887 is a multicenter, open-label, phase 3, randomized trial with two participating clinical sites. In trial, tumor-infiltrating lymphocytes (TILs) were compared with ipilimumab in patients with unresectable or metastatic stage IIIC or IV cutaneous melanoma, with ≥1 lesions that could be surgically removed for generation of TILs. Patients were randomized to adoptive cell therapy with TILs (n=84) or ipilimumab at a dose of 3 mg/kg every 3 weeks (n=84). The median age was 59 years in both study groups. The percentage of males was 56% in the TILS group and 63% in the ipilimumab group. OS, PFS, AEs, and QoL were reported after a median follow-up of 33 months. In this literature analysis the median outcomes for OS and PFS are analysed and the last endpoints for OS and PFS (2-year OS rates and 6-month PFS rates) are described.

Weber (2015) / Larkin (2018) - CHECKMATE-037 described a randomized, controlled, open-label, phase III study, which was conducted in 90 sites in 14 countries with a median follow-up of approximately 2 years. They evaluated the efficacy and safety of second-line nivolumab versus investigator's choice chemotherapy (ICC) in patients with metastatic melanoma who experienced progression after treatment with first-line ipilimumab (plus a BRAF inhibitor, if BRAF-mutation positive). A total of 405 patients were randomized 2:1 to receive nivolumab (n= 272, 3 mg/kg every two weeks) or ICC (n = 133, dacarbazine 1,000 mg/m2 every 3 weeks or carboplatin area under the curve 6 plus paclitaxel 175 mg/m2 every 3 weeks).. The median age was 59 (23-88) years in the nivolumab group and 62 (29-85) years in the ICC group. In the nivolumab group 65% was male, compared to 64% in the ICC group. Of the 272 patients that received nivolumab, 212 (78%) had BRAF wild type. Of the 133 patients that received ICC, 104 (78%) had BRAF wild type. The following relevant outcomes were reported, OS, PFS, number of patients with serious AEs and QoL. For OS, the researchers performed a subgroup analysis on BRAF status.

<u>Results</u>

Overall survival (OS) – Critical outcome measure

Five of the five included studies reported on OS.

OPTiM reported the effect of **T-VEC** versus **GM-CSF** on OS in the second-line or greater treatment without analyzing subgroups based on BRAF mutation status. The absolute difference between the T-VEC group (17.1 months) and the GM-CSF group (23.2 months) was 6.1 months in favor of the GM-CSF group with a HR of 1.13 (95% CI 0.82–1.57). This difference was not considered clinically relevant according to the PASKWIL criteria.

KEYNOTE-006 reported the effect of **pembrolizumab every 2 weeks** or **pembrolizumab every 3 weeks** compared to **ipilimumab every 3 weeks** on OS. The 2-year OS rates were 55% in the pembrolizumab-every-2-weeks group, 55% in the pembrolizumab-every-3-weeks group, and 43% in the ipilimumab-every-3-weeks group. Treatment with pembrolizumab resulted in a longer median OS than treatment with ipilimumab. In patients receiving second-line therapy the absolute difference between the combined pembrolizumab groups (23.5 months) and the ipilimumab group (13.6 months) was 9.9 months with a HR of 0.75 (95% CI 0.55–1.03). This difference was not considered clinically relevant according to the PASKWIL criteria.

MDX010-20 reported the effect of **ipilimumab with a gp100 peptide vaccine** and **ipilimumab without a gp100 peptide vaccine** compared to **gp100 alone** on OS. The 2-year OS rates were 21.6% in the ipilimumab with a gp100 peptide vaccine group, 23.5% in the ipilimumab group, and 13.7% in the gp100 alone group. Treatment with ipilimumab with or without a gp100 peptide vaccine resulted in a longer median OS compared to treatment with gp100 alone. The absolute difference between treatment with ipilimumab with a gp100 peptide vaccine (10.0 months) and treatment with gp100 alone (6.2 months) was 3.8 months with a HR of 0.68 (95% CI 0.55–0.85). This difference was considered clinically relevant according to the PASKWIL criteria. The absolute difference between treatment with ipilimumab without gp100 (10.1 months) compared to treatment with gp100 peptide vaccine alone was 3.7 months with a HR of 0.66 (0.51–0.87). This difference was considered clinically relevant according to the PASKWIL criteria. Treatment with ipilimumab with a gp100 peptide vaccine resulted in a similar median OS compared to treatment with ipilimumab plus placebo, with an absolute difference of 0.1 months and HR of 1.04 (95% CI 0.83–1.30). This difference was not considered clinically relevant according to the PASKWIL criteria.

NCT02278887 reported the effect of **tumor-infiltrating lymphocytes (TILs)** versus **ipilimumab** on OS. The 2-year OS rates were 54.3% in the TILs group and 44.1% in the ipilimumab group. Treatment with TILs resulted in a longer median OS compared to treatment with ipilimumab. The absolute difference between the TILs group and the ipilimumab group was 6.9 months with a HR of 0.83 (95% CI, 0.54 to 1.27). This difference was not considered clinically relevant according to the PASKWIL criteria.

Checkmate-037 reported the effect of **nivolumab** versus **investigator's choice chemotherapy** (ICC; dacarbazine or carboplatin plus paclitaxel) on OS in patients with BRAF wild type. The absolute difference in median OS between the nivolumab group (17.97 months) compared to the ICC group (14.32 months) was 3,65 with a HR of 0.83 (0.62 to 1.11). This difference was not considered clinically relevant according to the PASKWIL criteria.

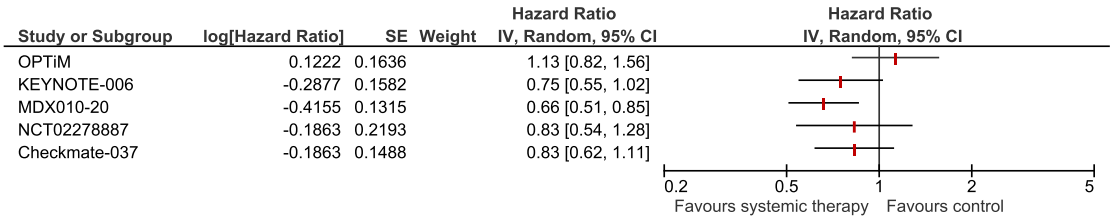

Figure 9. Forest plot of median overall survival for second line systemic therapy versus placebo, other systemic therapy, or best supportive care in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy.

[a] For KEYNOTE-006 the HR for combined pembrolizumab versus ipilimumab is shown.

[b] For MDX010-20 the HR for ipilimumab without gp100 versus gp100 vaccine alone is shown.

Progression free survival – important outcome measure

Four of the five included studies reported on PFS.

KEYNOTE-006 reported the effect of **pembrolizumab every 2 weeks** or **pembrolizumab every 3 weeks** compared to **ipilimumab every 3 weeks** on PFS. The 2-year PFS rates were 31% in the pembrolizumab-every-2-weeks group, 28% in the pembrolizumab-every-3-weeks group, and 14% in the ipilimumab-every-3-weeks group. Treatment with pembrolizumab resulted in a longer median PFS than treatment with ipilimumab. The absolute difference between the combined pembrolizumab groups and the ipilimumab group was 5.0 months with a HR of 0.57 (95% CI 0.48–0.67). This difference was considered clinically relevant according to the PASKWIL criteria.

MDX010-20 reported the effect of **ipilimumab with a gp100 peptide vaccine** plus **ipilimumab without a gp100 peptide vaccine** compared to **gp100 alone** on PFS. Median PFS was comparable between the three study groups. After the first assessment of progression at week 12 there was a separation between the curves. There was a 19% reduction in the risk of progression in the ipilimumab plus gp100 group, as compared with gp100 alone with a HR of 0.81. There was a 36% reduction in risk of progression in the ipilimumab alone group as compared with the gp100 alone group with a HR of 0.64. According to the PASKWIL criteria we could not assess clinical relevance (median OS in the control group was < 12 months).

NCT02278887 reported the effect of **tumor-infiltrating lymphocytes (TILs)** versus **ipilimumab** on PFS. The 6-month PFS rates were 52.7% in the TILs group and 21.4% in the ipilimumab group. Treatment with TILs resulted in a longer median PFS compared to treatment with ipilimumab. The absolute difference between the TILs group and the ipilimumab group was 4.1 months with a HR of 0.50 (95% CI, 0.35 to 0.72). This difference was considered clinically relevant according to the PASKWIL criteria.

Checkmate-037 reported the effect of **nivolumab** versus **investigator's choice chemotherapy** (ICC; dacarbazine or carboplatin plus paclitaxel) on PFS. Treatment with nivolumab resulted in a shorter median PFS compared to treatment with ICC. The absolute difference was 0.6 months with a HR of 1.0 (95.1% CI, 0.78 to 1.44). This difference was not considered clinically relevant according to the PASKWIL criteria.

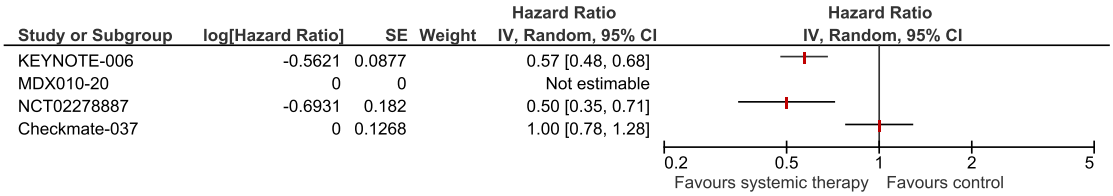

Figure 10. Forest plot of median progression free survival for second line systemic therapy versus placebo, other systemic therapy, or best supportive care in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy.

[a] For KEYNOTE-006 the HR for combined pembrolizumab versus ipilimumab is shown.

[b] MDX010-20 did not report the 95% CI of the HR and therefore the HR is not shown.

Treatment related adverse events (AEs) grade ≥ 3 - Important outcome

Five of the five included studies reported on AEs. The percentages of treatment related AEs grade ≥3 ranged from 14% to 100%.

OPTiM reported the effect of **T-VEC** versus **GM-CSF** on AEs. Treatment with T-VEC resulted in a higher percentage of treatment related AEs grade ≥3 compared to treatment with GM-CSF. The risk difference between T-VEC and GM-CSF is 0.07 (95% CI 0.02, 0.12; NNH=14) favoring treatment with GM-CSF. This difference is not considered clinically relevant according to the PASKWIL criteria.

KEYNOTE-006 reported the effect of **pembrolizumab every 2 weeks** or **pembrolizumab every 3 weeks** compared to **ipilimumab every 3 weeks** on AEs. Treatment with pembrolizumab (pooled groups) resulted in a lower percentage of treatment related AEs grade ≥3 compared to treatment with ipilimumab. The risk difference between pembrolizumab (pooled groups) and ipilimumab is -0.01 (95% CI -0.06, 0.05; NNH=100) favoring treatment with pembrolizumab. This difference is not considered clinically relevant according to the PASKWIL criteria.

MDX010-20 reported the effect of **ipilimumab with a gp100 peptide vaccine** plus **ipilimumab without a gp100 peptide vaccine** compared to **gp100 alone** on AEs. Treatment with ipilimumab with a gp100 peptide vaccine resulted in a higher percentage of treatment related AEs grade ≥3 compared to treatment with gp100 alone. The risk difference between ipilimumab with a gp100 peptide vaccine and gp100 alone is 0.05 (95% CI -0.03, 0.13; NNH= 20) favoring treatment with gp100 alone. This difference is not considered clinically relevant according to the PASKWIL criteria. The risk difference between ipilimumab without a gp100 peptide vaccine and gp100 alone is 0.14 (95% CI 0.03, 0.25; NNH= 7) favoring treatment with gp100 alone. This difference is not considered clinically relevant according to the PASKWIL criteria.

NCT02278887 reported the effect of **tumor-infiltrating lymphocytes (TILs)** versus **ipilimumab** on AEs. Treatment with TILs resulted in a higher percentage of treatment related AEs grade ≥3 compared to treatment with ipilimumab. The risk difference between TILs and ipilimumab is 0.43 (95% CI 0.32, 0.54; NNH=2) favoring treatment with ipilimumab. This difference is considered clinically relevant according to the PASKWIL criteria.

Checkmate-037 reported the effect of **nivolumab** versus **investigator's choice chemotherapy** (ICC; dacarbazine or carboplatin plus paclitaxel) on AES. Treatment with nivolumab resulted in a higher percentage of treatment related AEs grade ≥3 compared to treatment with ICC.

The risk difference between nivolumab and ICC is 0.17 (95% CI 0.09, 0.25; NNH=6) favoring treatment with ICC. This difference is not considered clinically relevant according to the PASKWIL criteria.

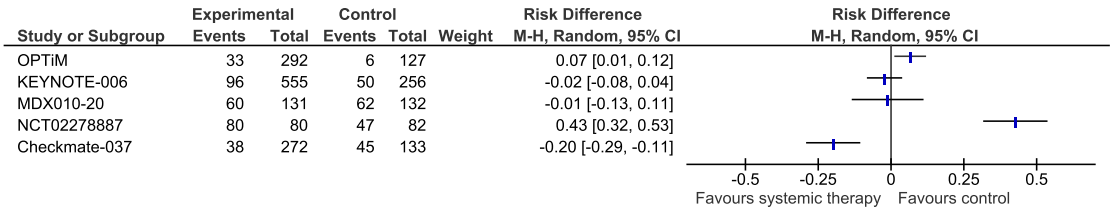

Figure 11. Forest plot of adverse events for second line systemic therapy versus placebo, other systemic therapy, or best supportive care in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving first line systemic therapy.
[a] For KEYNOTE-006 the risk difference for combined pembrolizumab versus ipilimumab is shown.
[b] For MDX010-20 the risk difference for ipilimumab without gp100 versus gp100 vaccine alone is shown.

Quality of life (QoL) - Important outcome

Three studies reported the effect of second line systemic therapy on QoL.

MDX010-20 analysed the effect of **ipilimumab with or without a gp100 peptide vaccine** compared **to gp100 alone** on health-related quality of life (HRQL) with the EORTC QLQ-C30. Mean changes of baseline to week 12 scores for function, global health status, and symptoms were analysed. These were categorized as “no change” (0–5), “a little” (5–10 points), “moderate” (10–20 points), and “very much” (>20). In general, the authors observed “no change” or “a little” impairment in the ipilimumab plus gp100 and ipilimumab alone groups. The study showed significant differences in constipation, favouring ipilimumab ($p<0.05$). This difference is not considered clinically relevant (difference less than 10 points). In the gp100 alone group, moderate to large changes for global health, role function, fatigue, and pain were observed. These differences between the treatment arms are not considered clinically relevant (difference less than 10 points). The authors conclude that ipilimumab with or without gp100 vaccine does not have a significant negative HRQL impact during the treatment induction phase relative to gp100 alone in stage III or IV melanoma patients.

NCT02278887 of **tumor-infiltrating lymphocytes (TILs)** versus **ipilimumab** on QoL. In this study, Health-related quality of life (HRQL) was measured with the EORTC Quality-of- Life Questionnaire Core 15 palliative care. In this questionnaire, higher scores on the global quality-of-life and functioning scales indicate better functioning and higher scores on the symptom scales indicate higher levels of symptom burden. Higher mean scores were observed after treatment among patients in the TIL group on the global health-related quality-of life (difference 7.7), physical functioning (difference 2.9), and emotional functioning (difference 9.7) domains compared to patients in the ipilimumab group. These differences are not considered clinically relevant (differences less than 10 points). Lower symptoms scores were observed after treatment among patients in the TIL group for fatigue, pain, and insomnia compared to patients in the ipilimumab group, with differences still observed at week 60. These differences are not considered clinically relevant (differences less than 10 points). Higher symptom scores of nausea and vomiting were observed among patients in the TIL group compared to patients in the ipilimumab group. This difference was not considered clinically relevant (difference less than 10 points).

Checkmate-037 analysed the effect of **nivolumab** versus **investigator's choice chemotherapy** (ICC; dacarbazine or carboplatin plus paclitaxel) on QoL. HRQL was assessed using the EORTC QLQ-C30 version 3 and EuroQoL EQ-5D summary index and visual analog scale. The study showed that quality of life in patients on nivolumab remained stable for all EORTC QLQ-C30 individual scales during the treatment course. No scores reached the minimal important difference of ≥10 points. The authors stated that no clinically significant improvement was observed for either the EuroQoL EQ-5D utility index or the EuroQoL EQ-5D visual analog scale for nivolumab. In the article the authors mention that at 12 weeks, the ICC group demonstrated a clinically significant decrease in the EuroQoL EQ-5D utility index. These data are not shown in the article or supplementary material.

Level of evidence of the literature

There are four levels of evidence: high, moderate, low, and very low. RCTs start at a high level of evidence.

T-VEC versus GM-CSF

The level of evidence regarding the outcome measure **overall survival** was downgraded by three levels because of study limitations (risk of bias -2); the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by three levels because of study limitations (risk of bias -2) and was downgraded by one level because the optimal information size is not met (imprecision). Therefore, the level of evidence was graded as very low.

Pembrolizumab every 2 weeks or every 3 weeks compared to ipilimumab

The level of evidence regarding the outcome measure **overall survival** was downgraded by three levels because of study limitations (risk of bias -2); the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by two levels because of study limitations (risk of bias -2). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by three levels because of study limitations (risk of bias -2) and was downgraded by one level because the optimal information size is not met (imprecision). Therefore, the level of evidence was graded as very low.

Ipilimumab with or without a gp100 peptide vaccine compared to gp100 alone

The level of evidence regarding the outcome measure **overall survival** was downgraded by two levels because of study limitations (risk of bias) and the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by two levels because of study limitations (risk of bias) and because we could not asses clinical relevance according to the PASKWIL criteria (imprecision). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by two levels because of study limitations (risk of bias) and was downgraded by one level because the optimal information size is not met (imprecision). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **quality of life** was downgraded by two levels because of study limitations (risk of bias) and was downgraded by one level because the optimal information size is not met (imprecision). Therefore, the level of evidence was graded as low.

Tumor-infiltrating lymphocytes (TILs) versus ipilimumab

The level of evidence regarding the outcome measure **overall survival** was downgraded by two levels because of study limitations (risk of bias) and because the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by two levels because of study limitations (risk of bias) and because the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision). Therefore, the level of evidence was graded as low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by one level because of study limitations (risk of bias). Therefore, the level of evidence was graded as moderate.

The level of evidence regarding the outcome measure **quality of life** was downgraded by one level because of study limitations (risk of bias). Therefore, the level of evidence was graded as moderate.

Nivolumab versus investigator's choice chemotherapy (ICC; dacarbazine or carboplatin plus paclitaxel)

The level of evidence regarding the outcome measure **overall survival** was downgraded by four levels because of study limitations (risk of bias -2), and because the optimal information size is not met and the confidence interval encloses the threshold for a clinically relevant effect and no clinically relevant effect (imprecision -2). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **progression free survival** was downgraded by three levels because of study limitations (risk of bias -2); was downgraded by one level because the optimal information size is not met (imprecision). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **adverse events** was downgraded by three levels because of study limitations (risk of bias -2) and the confidence interval encloses

the threshold for a clinically relevant effect and no clinically relevant effect (imprecision). Therefore, the level of evidence was graded as very low.

The level of evidence regarding the outcome measure **quality of life** was downgraded by three levels because of study limitations (risk of bias -2). Therefore, the level of evidence was graded as low.

Conclusions

T-VEC versus GM-CSF

Overall survival

Very low GRADE	The evidence is very uncertain about the effect of T-VEC on overall survival compared to treatment with GM-CSF in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Andtbacka, 2019; Andtbacka, 2015*

Adverse events

Very low GRADE	The evidence is very uncertain about the effect of T-VEC on adverse events compared to treatment with GM-CSF in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Andtbacka, 2019; Andtbacka, 2015*

Pembrolizumab every 2 weeks or every 3 weeks compared to ipilimumab

Overall survival

Very low GRADE	The evidence is very uncertain about the effect of pembrolizumab every 2 weeks or every 3 weeks on overall survival compared to treatment with ipilimumab in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Robert, 2019; Carlino, 2018; Schachter, 2017; Robert, 2015*

Progression free survival

Low GRADE	Pembrolizumab every 2 weeks or every 3 weeks may increase progression free survival compared to treatment with ipilimumab in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Robert, 2019; Carlino, 2018; Schachter, 2017; Robert, 2015*

Adverse events

Very low GRADE	The evidence is very uncertain about the effect of pembrolizumab every 2 weeks or every 3 weeks on adverse events compared to treatment with ipilimumab in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Robert, 2019; Carlino, 2018; Schachter, 2017; Robert, 2015*

Ipilimumab with or without a gp100 peptide vaccine compared to gp100 alone

Overall survival

Low GRADE	Ipilimumab with or without a gp100 peptide vaccine may increase overall survival compared to treatment with gp100 alone in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma but the evidence is very uncertain receiving second line systemic therapy. *Source: Hodi, 2010*
Low GRADE	Ipilimumab with a gp100 peptide vaccine may have little to no effect on overall survival compared to treatment Ipilimumab alone in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma but the evidence is very uncertain receiving second line systemic therapy. *Source: Hodi, 2010*

Progression free survival

Low GRADE	Ipilimumab with or without a gp100 peptide vaccine may increase progression free survival compared to treatment with gp100 alone in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Hodi, 2010*

Adverse events

Low GRADE	Ipilimumab with or without a gp100 peptide vaccine may increase adverse events slightly compared to treatment with gp100 alone in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Hodi, 2010*

Quality of Life

Low GRADE	Ipilimumab with or without a gp100 peptide vaccine may may result in little to no difference compared to treatment with gp100 alone in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Revicki, 2012*

Tumor-infiltrating lymphocytes (TILs) versus ipilimumab

5 *Overall survival*

Low GRADE	Treatment with tumor-infiltrating lymphocytes (TILs) may result in little to no difference in overall survival compared to ipilimumab in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Rohaan, 2022*

Progression free survival

Low GRADE	Treatment with tumor-infiltrating lymphocytes (TILs) may increase progression free survival compared to ipilimumab in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Rohaan, 2022*

Adverse events

Moderate GRADE	Treatment with tumor-infiltrating lymphocytes (TILs) likely increases adverse events compared to ipilimumab in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Rohaan, 2022*

Quality of life

Moderate GRADE	Treatment with tumor-infiltrating lymphocytes (TILs) likely results in little to no difference in quality of life compared to ipilimumab in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Rohaan, 2022*

10

Nivolumab versus investigator's choice chemotherapy
(ICC; dacarbazine or carboplatin plus paclitaxel)

Overall survival

Very low GRADE	The evidence is very uncertain about the effect of treatment with nivolumab on overall survival compared to treatment with investigator's choice chemotherapy in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Weber 2015; Larkin 2018*

Progression free survival

Very low GRADE	The evidence is very uncertain about the effect of treatment with nivolumab on progression free survival compared to treatment with investigator's choice chemotherapy in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Weber 2015; Larkin 2018*

Adverse events

Very low GRADE	The evidence is very uncertain about the effect of treatment with nivolumab on adverse events compared to treatment with investigator's choice chemotherapy in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Weber 2015; Larkin 2018*

Quality of life

Low GRADE	Treatment with nivolumab may have little to no effect on quality of life compared to investigator's choice chemotherapy in patients with BRAF-wild type unresectable or metastatic stadium III/IV melanoma receiving second line systemic therapy. *Source: Weber 2015; Larkin 2018*

Overwegingen – van bewijs naar aanbeveling

De cruciale uitkomstmaat overall survival in de context van patiënten met unresectable of gemetastaseerd stadium III/IV melanoom werd gerapporteerd door 5 RCTs die verschillende systemische behandelingen in de tweede lijn onderzochten.

OPTiM rapporteerde het effect van **T-VEC** in vergelijking met **GM-CSF** op overall survival bij patiënten met niet-receerbaar of gemetastaseerd stadium III/IV melanoom (Andtbacka, 2019; Andtbacka, 2015). Er werd daarbij geen klinisch relevant voordeel gevonden voor het gebruik van T-VEC. Het absolute verschil in mediane overall survival tussen behandeling met T-VEC versus behandeling met GM-CSF was 4.4 maanden met een hazard ratio 0.79 (95% CI 0.62–1.00). De bewijskracht van deze studie is zeer laag. Dit heeft te maken met het risico op bias (open-label studie design; meer patiënten stopten in de interventie groep; de rol van de sponsor) en door imprecisie, omdat het betrouwbaarheidsinterval de grens voor klinische besluitvorming omvat.

De studie rapporteerde ook het effect op adverse events. Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor de uitkomst adverse events.

KEYNOTE-006 rapporteerde het effect van **pembrolizumab** (iedere 2 of 3 weken) in vergelijking met **ipilimumab** (iedere 3 weken) op overall survival bij patiënten met unresectable of gemetastaseerd stadium III/IV melanoom (Robert, 2019; Carlino, 2018; Schachter, 2017; Robert, 2015). Er werd daarbij geen klinisch relevant voordeel gevonden voor het gebruik van pembrolizumab. Het absolute verschil in mediane overall survival tussen behandeling met pembrolizumab versus behandeling met ipilimumab was 16.8 maanden met een hazard ratio van 0.73 (95% CI 0.61–0.88). De bewijskracht van deze studie is zeer laag. Dit heeft te maken met het risico op bias (open-label studie design; meer patiënten stopten in de controle groep; de rol van de sponsor) en door imprecisie, omdat de confidence interval de grens voor klinische besluitvorming omvat.

De studie rapporteerde ook het effect op progression free survival en adverse events. Voor de uitkomst progression free survival werd een klinisch relevant voordeel gevonden voor behandeling met pembrolizumab. Het absolute verschil in mediane progressievrije overleving was 5.0 maanden (HR 0.57; 95% CI 0.48–0.67). Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor de uitkomst adverse events.

MDX010-20 rapporteerde het effect van **ipilimumab met een gp100 peptide vaccine** en **ipilimumab zonder een gp100 peptide vaccine** in vergelijking met alleen **gp100** op overall survival bij patiënten met niet-receerbaar of gemetastaseerd stadium III/IV melanoom (Revicki, 2012; Hodi, 2010). Er werd daarbij een klinisch relevant voordeel gevonden voor het gebruik van ipilimumab met een gp100 peptide vaccine en voor ipilimumab zonder een gp100 peptide vaccine in vergelijking met gp100 alleen. Het absolute verschil in mediane overall survival tussen behandeling met ipilimumab met een gp100 peptide vaccine versus behandeling met alleen gp100 was 3.6 maanden met een hazard ratio van 0.68 (95% CI 0.55–0.85). Het absolute verschil in mediane overall survival tussen behandeling met ipilimumab zonder een gp100 peptide vaccine versus behandeling met alleen gp100 was 3.7 maanden met een hazard ratio van 0.66 (0.51–0.87). De bewijskracht van deze studie is laag. Dit heeft te maken met het risico op bias (de rol van de sponsor in deze studie) en door imprecisie omdat de confidence interval de grens voor klinische besluitvorming omvat.

De studie rapporteerde ook het effect op progression free survival, adverse events en kwaliteit van leven. Er werd geen klinisch relevant verschil gevonden tussen de

studiegroepen voor de uitkomsten progression free survival, adverse events en kwaliteit van leven.

NCT02278887 rapporteerde het effect van **tumor-infiltrating lymphocytes (TILs)** versus **ipilimumab** op overall survival bij patiënten met unresectable of gemetastaseerd stadium III/IV melanoom (Rohaan, 2022). Er werd daarbij geen klinisch relevant voordeel gevonden voor het gebruik van TILs. Het absolute verschil in mediane overall survival was 6.9 maanden met een hazard ratio van 0.83 (95% CI, 0.54 to 1.27). De bewijskracht van deze studie is zeer laag. Dit heeft te maken met het risico op bias (onduidelijke randomisatie, open-label studie design, en doordat meer patiënten in de controle groep de behandeling stopten in vergelijking met de interventie groep) en imprecisie.

De studie rapporteerde ook het effect op progression free survival, adverse events en kwaliteit van leven. Een langere mediane progression free survival werd gevonden voor patiënten in de TILs groep, met een absoluut verschil van 4.1 maanden met patiënten in de ipilimumab groep (HR 0.50; 95% CI 0.35 to 0.72). Behandeling met TILs resulteerde in een hoger percentage patiënten met adverse events (risk difference: 0.43; 95% CI 0.32, 0.54; NNH=2). Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor de uitkomst kwaliteit van leven.

Checkmate-037 rapporteerde het effect van **nivolumab** versus **investigator's choice chemotherapy** (ICC; dacarbazine or carboplatin plus paclitaxel) op overall survival bij patiënten met unresectable of gemetastaseerd stadium III/IV melanoom (Weber 2015, Larkin 2018). Er werd daarbij geen klinisch relevant voordeel gevonden voor het gebruik van nivolumab. Het absolute verschil in mediane overall survival was 1.3 maanden met een hazard ratio van 0.95 (95.54% CI 0.73 to 1.24). De bewijskracht van deze studie is zeer laag. Dit heeft te maken met het risico op bias (open-label studie design; doordat meer patiënten in de interventie groep de behandeling stopten in vergelijking met de controle groep; de rol van de sponsor in deze studie) en imprecisie.

De studie rapporteerde ook het effect op progression free survival, adverse events en kwaliteit van leven. Er werd geen klinisch relevant verschil gevonden tussen de studiegroepen voor de uitkomsten progression free survival, adverse events en kwaliteit van leven.

<u>Kwaliteit van bewijs</u>

T-VEC versus GM-CSF

De overall kwaliteit van bewijs is zeer laag. Dit betekent dat we zeer onzeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Pembrolizumab every 2 weeks or every 3 weeks vergeleken met ipilimumab

De overall kwaliteit van bewijs is zeer laag. Dit betekent dat we zeer onzeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Ipilimumab with or without a gp100 peptide vaccine vergeleken met gp100 alone

De overall kwaliteit van bewijs is laag. Dit betekent dat we onzeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Tumor-infiltrating lymphocytes (TILs) versus ipilimumab
De overall kwaliteit van bewijs is laag. Dit betekent dat we onzeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Nivolumab versus investigator's choice chemotherapy
(ICC; dacarbazine of carboplatin plus paclitaxel)

De overall kwaliteit van bewijs is zeer laag. Dit betekent dat we zeer onzeker zijn over het gevonden geschatte effect van de cruciale uitkomstmaat overall survival.

Overwegingen- van bewijs naar aanbeveling
Ondanks de vooruitgang in de behandeling van irresectabel of gemetastaseerd melanoom, blijven veel vragen onbeantwoord en voor een belangrijke deel van de patiënten blijft de prognose slecht. Inclusie in klinische studies blijft daarom de hoogste prioriteit in alle settings.

Waarden en voorkeuren van patiënten (en eventueel hun naasten/verzorgers)
Bij de behandeling van patiënten met een irresectabel of gemetastaseerd stadium III/IV melanoom dient zorgvuldig rekening te worden gehouden met de waarden en voorkeuren van de patiënt. De keuze voor deelname aan klinische studies of voor tweedelijnsbehandelopties – zoals TIL-therapie, anti-PD-1-blokkade met ipilimumab wordt bij voorkeur afgestemd op individuele patiëntkenmerken en specifieke behandeldoelen.

Professioneel perspectief
Factoren zoals het gewenste behandeldoel (kortetermijn- of langetermijnvoordeel), klinische kenmerken (bijvoorbeeld lactaatdehydrogenase-niveaus, betrokken organen, prestatiestatus, tumorlast en progressiesnelheid), evenals comorbiditeiten spelen een cruciale rol bij deze behandelbeslissing. Door deze aspecten zorgvuldig af te wegen in lijn met de voorkeuren van de patiënt kan een optimaal behandeltraject worden gekozen dat zowel klinische effectiviteit waarborgt als aansluit bij de persoonlijke waarden van de patiënt.

Kostenaspecten
Vanwege geheime prijsafspraken, kan de exacte impact op het geneesmiddelenbudget niet worden vastgesteld, maar het staat vast dat deze impact hoog is. Het huidig prijsniveau wordt echter acceptabel geacht in verhouding tot de effectiviteit van de behandeling. Een lagere prijs van de behandelingen zou desondanks in alle opzichten zeer wenselijk en naar mening van de werkgroep zelfs noodzakelijk zijn, mede met het oog op de komende ontwikkelingen en het betaalbaar houden en borgen van een goede kwaliteit van de zorg in de nabije toekomst.

Haalbaarheid/aanvaardbaarheid
Bij de behandeling van patiënten met een irresectabel of gemetastaseerd stadium III/IV melanoom is het van belang niet alleen te kijken naar klinische effectiviteit en patiëntvoorkeuren, maar ook naar de haalbaarheid en aanvaardbaarheid van de aanbevolen behandelopties. Deelname aan klinische studies kan voor sommige patiënten een haalbare optie zijn, mits er toegang is tot geschikte onderzoeksfaciliteiten en de patiënt bereid is de mogelijk intensieve studieverplichtingen te dragen. Voor patiënten met een BRAF wildtype melanoom kunnen tweedelijnsopties zoals TIL-therapie of anti-PD-1-blokkade met ipilimumab passend zijn, maar de haalbaarheid van deze therapieën wordt mede bepaald

door de beschikbaarheid en toegankelijkheid van specialistische zorg en middelen. De aanvaardbaarheid van deze behandelopties hangt bovendien sterk samen met het behandeldoel en de verwachte belasting voor de patiënt: sommige patiënten kunnen de voorkeur geven aan behandelingen met een potentieel kortetermijnvoordeel en lagere bijwerkingenlast, terwijl anderen bereid zijn intensievere therapieën te overwegen in ruil voor een mogelijke langere overlevingswinst. Zo kunnen haalbaarheid en aanvaardbaarheid per patiënt variëren, wat zorgvuldige overweging van hun persoonlijke en klinische omstandigheden vereist om een passend behandeltraject te waarborgen.

Rationale

De werkgroep is van mening dat deelname aan klinische studies in de behandeling van irresectabel of gemetastaseerd stadium III/IV melanoom de hoogste prioriteit heeft, gezien de sombere prognose voor een groot deel van de patiënten en de noodzaak om effectiviteit en aanvaardbaarheid van behandelingen verder te optimaliseren. Hierbij is het essentieel om patiëntwaarden en individuele klinische kenmerken leidend te laten zijn, zodat behandelbeslissingen aansluiten bij zowel haalbaarheid als de persoonlijke voorkeuren van de patiënt.

Aanbevelingen

Overweeg behandeling in studieverband.

Overweeg als tweedelijnsbehandeloptie voor patiënten met een BRAF wildtype irresectabel of gemetastaseerd melanoom volgende behandelopties: TIL- behandeling of anti-PD-1 blokkade met ipilimumab (indien niet gebruikt in de eerstelijns setting).

Individualiseer deze behandelbeslissing rekening houdend met het behandeldoel (kortetermijnvoordeel versus langetermijnvoordeel) en klinische kenmerken (lactaatdehydrogenase (LDH), betrokken organen, prestatiestatus (PS), tumorlast, snelheid van ziekteprogressie), comorbiditeiten, bijwerkingen van de verschillende therapieën en patiëntvoorkeuren.

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Revicki, 2012 **Hodi, 2010** **MDX010-20** **NCT00094653**	Randomized, double-blind, phase 3 study. Patients at 125 centers in 13 countries in North America, South America, Europe, and Africa. Patient enrolment between: September 2004 and August 2008. <u>Funding and conflicts of interest:</u> • The sponsors, Medarex and Bristol-Myers Squibb contributed to: ▪ Trial design ▪ Data collection ▪ Initial draft of the manuscript • All authors signed a confidentiality disclosure agreement with the sponsor. Disclosure forms provided by the authors are available with the full text of this article.	Inclusion criteria: • Diagnosis of unresectable stage III or IV melanoma who received a previous therapeutic regimen containing one or more of the following: dacarbazine, temozolomide, fotemustine, carboplatin, or interleukin-2.; • Age ≥ 18 years; • Life expectancy ≥ 4 months; • ECOG PS 0 or 1; • Positive status for HLA-A⋆0201; • Normal hematologic, hepatic, and renal function; • No systemic treatment in the previous 28 days. Exclusion criteria: • Any other cancer from which the patient had been disease-free for < 5 years (except treated and cured basal-cell or squamous-cell skin cancer, superficial	I: Ipilimumab, at a dose of 3 mg per kilogram of body weight, plus a gp100 peptide vaccine n= 403	C1: Ipilimumab plus gp100 placebo n=137 C2: gp100 plus ipilimumab placebo. n=136	Patients were followed for up to 55 months. Median follow-up time for survival: I: 21.0 months C1: 27.8 months C2: 17.2 months	Median OS, months (95% CI) I: 10.0 (8.5 to 11.5) C1: 10.1 (8.0 to 13.8) C2: 6.4 (5.5 to 8.7) I vs C2: HR for death: 0.68 (0.55–0.85); P<0.001 C1 vs C2: HR for death: 0.66 (0.51–0.87); P=0.003 I vs C1: HR for death: 1.04 (0.83–1.30). P=0.76 1-Year OS: I: 43.6% C1: 45.6% C2: 25.3% 18-month OS: I: 30.0% C1: 33.2% C2: 16.3%	• The original primary end point was best overall response rate. The primary end point was amended to overall survival (amendment approved on January 15, 2009) in the ongoing blinded study. • Efficacy analyses were performed on the intention-to-treat population, which included all patients who had undergone randomization (676 patients). • The safety population included all patients who had undergone randomization and who had received any amount of study drug (643 patients). • In the vaccine groups, patients received two modified HLA-A⋆0201–restricted peptides, injected subcutaneously as an emulsion with incomplete Freund's adjuvant (Montanide ISA-51): a gp100:209-217(210M) peptide, 1

		bladder cancer, or treated carcinoma in situ of the cervix, breast, or bladder); • primary ocular melanoma; • Previous receipt of anti–CTLA-4 antibody or cancer vaccine; • Autoimmune disease; • Active, untreated metastases in the central nervous system; • Pregnancy or lactation; • Concomitant treatment with any nonstudy anticancer therapy or immunosuppressive agent; • Long-term use of systemic corticosteroids. Mean age, years I: 55.6 C1: 56.8 C2: 57.4 Male, n (%)				2-Year OS: I: 21.6% C1: 23.5% C2: 13.7% Median PFS, months (95% CI): I: 2.76 (2.73 to 2.79) C1: 2.86 (2.76 to 3.02) C2: 2.76 (2.73 to 2.83) AEs grade 3 or 4: I: 173/374 C1: 60/127 C2: 62/128 Drug-related AEs, Grade 3 or 4/total: I: 66/338 C1: 30/105 C2: 15/104	mg injected in the right anterior thigh, and a gp100:280-288(288V) peptide, 1 mg injected in the left anterior thigh. <u>Authors conclusions:</u> **Hodi, 2010:** Ipilimumab, with or without a gp100 peptide vaccine, as compared with gp100 alone, improved overall survival in patients with previously treated metastatic melanoma. Adverse events can be severe, long-lasting, or both, but most are reversible with appropriate treatment. **Revicki, 2012:** Ipilimumab with/without gp100 vaccine does not have a significant negative HRQL impact during the treatment induction phase relative to gp100 alone

		I: 247 (61.3%) C1: 81 (59.1%) C2: 73 (53.7%) ECOG PS: 0 – I: 232 (57.6%) 0 – C1: 72 (52.6%) 0 – C2: 70 (51.5%) 1 – I: 166 (41.2%) 1 – C1: 64 (46.7%) 1 – C2: 61 (44.9%) 2 – I: 4 (1%) 2 – C1: 1 (0.7%) 2 – C2: 4 (2.9%) 3 – I: 1 (0.2%) 3 – C1: 0 3 – C2: 0 Unknown: I: 0 C1: 0 C2: 1 (0.7%)				Immune-related AEs, Grade 3 or 4/total: I: 39/221 C1: 19/80 C2: 4/42 Drug-related deaths, n: I: 8 C1: 4 C2: 2 For more information on AEs see results section of the article. EORTC QLQ-C30 symptom scores (improvements are indicated by negative scores): Difference in constipation scores: I: 5.2 C1:1.9 C2:11.8	in stage III or IV melanoma patients.

		Groups were comparable at baseline.				I vs C2: p<0.05 C1 vs C2: p<0.05 Favouring ipilimumab. None of the other differences in HRQL scores between the three treatments were statistically significant.	
Robert, 2019 **Carlino, 2018** **Schachter, 2017** **Robert, 2015** **KEYNOTE-006** **NCT01866319**	International, randomized, open-label phase 3 study. In 16 countries. Patient enrolment: From September 18, 2013, to March 3, 2014. <u>Funding and conflicts of interest:</u> • The sponsors, Merck Sharp & Dohme,	Inclusion criteria: • Age ≥ 18 years • Histologically confirmed, unresectable stage III or IV melanoma who received no more than one previous systemic therapy for advanced disease • Known BRAF V600 mutational status was required; • previous BRAF inhibitor therapy was not required for patients with normal lactate dehydrogenase levels • no clinically significant tumor-	Ia: pembrolizumab at a dose of 10 mg per kilogram of body weight every 2 weeks n= 279 Ib: pembrolizumab at a dose of 10 mg per kilogram of body weight either every 3 weeks n=277	C: Four cycles of ipilimumab at a dose of 3 mg per kilogram every 3 weeks n=278	**Robert, 2019:** Median follow-up for survival: 57.7 months (IQR 56.7–59.2). **Carlino, 2018:** Median follow-up: 33.9 months. **Schachter, 2017:** Median follow-up: 22.9 months	**Robert, 2019:** Median OS: I (pooled groups): 32.7 months (95% CI 24·5–41·6) C: 15.9 months (13.3–22.0) HR: 0.73 (95% CI 0.61–0.88, p=0·00049). Median PFS: I (pooled groups): 8.4 months (95% CI 6.6–11.3) C: 3.4 months (2.9–4.2) HR 0.57, 95% CI 0.48–0.67,	Co-primary endpoints were OS and PFS. **Robert, 2019:** • Data cutoff: Dec 3, 2018. **Carlino, 2018:** • Data cutoff: 03 Nov 2016. • Reported outcomes by line of therapy and PD-L1 expression **Schachter, 2017:** • Data cutoff: Dec 3, 2015. **Robert, 2015:** • Data cutoff 1st interim analysis:

	contributed to: • Trial design • Statisticians and a science writer were employed by the sponsor. Disclosure forms provided by the authors are available with the full text of this article.	related symptoms or evidence of rapidly progressive disease. • ECOG PS of 0 or 1 • Provision of a tumor sample adequate for assessing PD-L1 expression. Exclusion criteria: • Patients who had received previous therapy with CTLA-4, PD-1, or PD-L1 inhibitors • Ocular melanoma • Active brain metastases • History of serious autoimmune disease. Mean age, years Ia: 61 (18–89) Ib: 63 (22–89) C: 62 (18–88) Male, n (%) Ia: 161 (57.7) Ic: 174 (62.8)			Discontinued treatment: Ia: *147 progressive disease* *29 adverse events* *2 deaths* *2 complete responses* *21 other* Ib: *139 progressive disease* *45 adverse events* *1 death* *5 complete responses* *23 other* C: *46 progressive disease* *35 adverse events* *5 deaths* *24 other*	p<0.0001. Grade 3–4 treatment-related AEs: I (pooled groups): 96 (17%) C: 50 (20%) Treatment-related sepsis. C: n=1 **Schachter, 2017:** Death: n=383 Median OS: Ia: not reached (range 22.1 months–not reached) Ib: not reached (23.5 months–not reached) C: 16.0 months (range 13.5–22.0) HR pembro every 2 weeks vs ipi: 0.68, 95% CI 0·53–0·87; p=0·0009	Sep 3, 2014 (PFS and AEs) • Data cutoff 2nd interim analysis: Mar 3, 2015 (OS). • OS results for the pembrolizumab groups were superior to those for the ipilimumab group. The independent data and safety monitoring committee recommended stopping the study early. <u>Authors conclusions:</u> **Robert, 2019:** Pembrolizumab continued to show superiority over ipilimumab after almost 5 years of follow-up. These results provide further support for use of pembrolizumab in patients with advanced melanoma. **Carlino, 2018:** Findings support pembrolizumab monotherapy as

		C: 162 (58.3) ECOG PS: 0 – Ia: 196 (70.3) 0 – Ib: 189 (68.2) 0 – C: 188 (67.6) 1 – Ia: 83 (29.7) 1 – Ib: 88 (31.8) 1 – C: 90 (32.4) PD-L1-positive tumours: 80.6% Groups were comparable at baseline.			Withdrew consent and did not receive treatment: Ia: n=1 C: n=22 **Robert, 2015:** Median follow-up at data cutoff (with 502 events reported), months: 7.9 (range: 6.1 to 11.5) March 3, 2015: Follow-up for OS: Minimum follow-up: 12 months with 289 deaths occurred Mean duration of exposure, days: Ia: 164 Ib: 151 C: 50	HR pembro every 3 weeks vs ipi: 0.68, 0·53–0·86; p=0·0008. 2 year OS rate: Ia: 55% (95% CI 49–61) Ib: 55% (95% CI 49–61) C: 43% (95% CI 37–49) PFS events: n= 566 I (pooled groups): 364 (65%) C: 202 (35%) Median PFS, months: Ia: 5.6 months (range 3.4–8.2) Ib: 4.1 months (range 2.9–7.2) C: 2.8 months (range 2.8–2.9) HR for both Pembro schedules vs ipi: 0.61; 95% CI 0·50–0·75; p<0·0001	standard of care in patients with advanced melanoma, regardless of first- or second-line therapy or PD-L1 status. **Schachter, 2017:** Substantiating the results of the interim analyses of KEYNOTE-006, pembrolizumab continued to provide superior overall survival versus ipilimumab, with no difference between pembrolizumab dosing schedules. These conclusions further support the use of pembrolizumab as a standard of care for advanced melanoma. **Robert, 2015:** The anti–PD-1 antibody pembrolizumab prolonged progression-free survival and overall survival and had less high-grade toxicity

					Rate discontinuation of a study drug because of treatment related AEs: Ia: 4.0%, Ib: 6.9%, C: 9.4%,	HR for Ia vs Ib: 0.95; 95% CI 0·77–1·17; p=0·62). 2-year PFS rate: Ia: 31% Ib: 28% C: 14% Treatment related AEs grade 3 to 5: Ia: 47 (17%) of 278 Ib: 46 (17%) of 277 C: 50 (20%) of 256 **Robert, 2015:** Median overall survival was not reached in any study group. 1-Year OS: Ia: 74.1% Ib: 68.4%	than did ipilimumab in patients with advanced melanoma. •

						C: 58.2% • HR for death for pembrolizumab every 2 weeks versus ipilimumab: 0.63; 95% CI, 0.47 to 0.83; P<0.0005 • HR for death for pembrolizumab every 3 weeks versus ipilimumab: 0.69; 95% CI, 0.52 to 0.90; P = 0.0036 Median PFS, months (95% CI): Ia: 5.5 (95% CI, 3.4 to 6.9) Ib: 4.1 (95% CI, 2.9 to 6.9) C: 2.8 (95% CI, 2.8 to 2.9) • HR for progression for pembrolizumab every 2 weeks versus ipilimumab: 0.58 (95% CI, 0.46 to 0.72; P<0.001) • HR for pembrolizumab every 3 weeks versus ipilimumab: 0.58 (95% CI, 0.47 to 0.72; P<0.001).	

						6-month PFS, months: Ia: 47.3% Ib: 46.4% C: 26.5% Treatment related AEs grade 3 to 5: Ia: 13.3% Ib: 10.1% C: 19.9% Drug-related deaths, n: Ia: 0 Ib: 0 C: 1 For more information on AEs see results section of the article.	
Andtbacka, 2019 **Andtbacka, 2015** **OPTiM**	A randomized open-label phase III trial at 64 sites in the United States, the United	Main inclusion criteria: • ≥ 18 years • Histologically confirmed, unresectable,	I: intratumoral Talimogene laherparepvec (T-VEC) (at the approved dose) n= 295 (68%)	C: subcutaneous recombinant granulocyte-macrophage colony-stimulating	Median follow-up in the final analysis of OS: 49 months.	**Intent-to treat population (stage IIIB–IVM1c melanoma):**	• Primary end point: durable response rate (objective response lasting continuously ≥ 6

NCT00769704	Kingdom, Canada, and South Africa. Patient enrolment between: 2009 and 2011 <u>Funding and conflicts of interest:</u> - Funded by BioVex, who were subsequently acquired by Amgen Inc. during the OPTiM trial. The sponsor contributed to: • Design of the trial • Data collection • Data analysis • Interpretation of data • Development of the manuscript. - A competing interests statement is provided at the end of the full text article.	bidimensionally measurable stage IIIB/C/IV melanoma with ≥1 cutaneous, subcutaneous or nodal lesions that was suitable for direct or ultrasound-guided injection; • ECOG PS ≤1 • Serum lactate dehydrogenase ≤1.5 × upper limit of normal; • ≤3 visceral lesions (excl. lung or nodal lesions associated with visceral organs) with none > 3 cm; • Adequate organ function. • Patients with history of autoimmune disease, but not use of high-dose steroids. Exclusion criteria: • Requiring intermittent or chronic treatment with an antiviral agent (eg, acyclovir) or high-dose steroids • Primary ocular or mucosal melanoma • Bone metastases		factor (GM-CSF) n= 141 (32%)	Median duration of treatment in weeks (range): I: 23.1 (0.1–176.7) C: 10.0 (0.6–120.0) **Andtbacka, 2015:** Discontinued T-VEC: n=291 *Disease progression:* *n=191* *PR or CR for ≥ 6 continuous months:* *n=42* *Maximum allowed dose without* *PR/CR: n=26* *Adverse event: n=11* *Consent withdrawn: n=10* *Physician decision: n=6* *Death: n=5*	Median OS, months (95% CI): I: 23.3 (19.5–29.6) C: 18.9 (16.0–23.7) unstratified HR for death, 0.79 (95% CI,0.62–1.00); P = 0.0494). Estimated 5-year survival I: 33.4% C: Not estimable **Stage IIIB–IVM1a disease** Effect of T-VEC on OS vs GM-CSF: • Stage IIIB/C: HR, 0.48, P < 0.05 Effect of T-VEC on OS vs ITT population including stage IVM1b/c disease: • Stage IIIB–IVM1a: HR, 0.56; 95% CI, 0.40–0.79; P < 0.001 Estimated 5-year survival with T-VEC:	months) per independent assessment. Key secondary end points: OS and overall response rate • Data cut-off for this final analysis of OPTiM was 5 September 2014. • 4 patients in the T-VEC arm and 14 in the GM-CSF arm did not receive T-VEC or GM-CSF. • When the 18 patients who did not receive allocated treatment were excluded (T-VEC arm, n =4; GM-CSF arm, n = 14), median OS in the final analysis dataset was 24.5 versus 18.9 months for T-VEC versus GM-CSF (HR, 0.78; P = 0.0439). • Ad-hoc sensitivity analysis for OS accounting for subsequent systemic anti-cancer treatment, there was a 27% reduction in the risk of death for T-VEC versus GM-CSF (unadjusted HR, 0.73; 95% CI, 0.59–0.92; P = 0.0069).

		• Active cerebral metastases • > 3 visceral metastases • Any visceral metastasis >3 cm • Liver metastases had to be stable for 1 month before random assignment. For more information on in-/exclusion see the article. Median age, years (range) I: 63 (22 to 94) C: 64 (26 to 91) Male, n (%) I: 173 (59%) C: 77 (55%) ECOG PS: 0 – I: 209 (71%) 0 – C: 97 (69%) 1 – I: 82 (28%) 1 – C: 32 (23%)			Discontinued GM-CSF: n=127 *Disease progression: n=95* *PR or CR for ≥ 6 continuous months: n=0* *Maximum allowed dose without* *PR/CR: n=9* *Adverse event: n=3* *Consent withdrawn: n=12* *Physician decision: n=5* *Death: n=3*	• Stage IIIB–IVM1a melanoma: 48.9% (95% CI, 40.6–56.7) • Stage IVM1b/c disease: 15.1% (95% CI, 9.3–22.2). Treatment related AEs grade 3/4: I: 33 (11.3%) C: 6 (4.7%) Immune-related AEs: I: 24/295 C: ? Immune-related AEs grade 3: n=4 Immune-related AEs grade 4: None reported Treatment-related deaths, n: I: 0 C: 0	<u>Authors conclusions:</u> **Andtbacka, 2019:** In conclusion, as well as demonstrating a longer-term effect on survival, this analysis confirms that T-VEC resulted in high CR rates, most notably in patients with early metastatic melanoma (stage IIIB–IVM1a). Once achieved, CRs were durable and associated with prolonged survival. The favorable clinical outcomes observed in some patients treated with T-VEC, along with its good safety profile, support continued efforts to further define its future role in melanoma as a combination partner with immunotherapy. **Andtbacka, 2015:** T-VEC is the first oncolytic immunotherapy to demonstrate

		Unknown: I: 4 (1%) C: 12 (9%) Groups were comparable at baseline.				For more information on AEs see results section of the article	therapeutic benefit against melanoma in a phase III clinical trial. T-VEC was well tolerated and resulted in a higher DRR (P<0.001) and • longer median OS (P=0.051), particularly in untreated patients or those with stage IIIB, IIIC, or IVM1a disease. T-VEC represents a novel potential therapy for patients with metastatic melanoma.
Rohaan, 2022 **NCT02278887**	Multicenter, open-label, phase 3, randomized trial, two participating clinical sites (the Netherlands Cancer Institute, Amsterdam and National Center for Cancer Immune Therapy, Copenhagen University Hospital, Herlev, Denmark). Patient enrolment between: September 2014 and March 2022.	Inclusion criteria: • Age 18 to 75 years • Histologically confirmed, unresectable or metastatic stage IIIC or IV cutaneous melanoma • one or more lesions that could be surgically removed for generation of TILs. • Residual measurable disease after resection • WHO performance- status score of 0 or 1 • A serum LDH level that was ≤ 2 times	Adoptive cell therapy with tumor-infiltrating lymphocytes (TILs). Patients assigned to receive TILs underwent a metastasectomy for retrieval and expansion of TILs, followed by administration of nonmyeloablative, lymphodepleting chemotherapy, single intravenous adoptive transfer of 5×109 to 2×1011 TILs, and subsequent high-	Ipilimumab: 3 mg/kg intravenously every 3 weeks, for a maximum of 4 doses. n=84	Median follow-up in months: 33 Median duration of hospital admission: 17 days (range, 12 to 38). Median ipilimumab Infusions: 3 (range, 1 to 4)	Median OS, months (95% CI): I: 25.8 (18.2 to not reached) C: 18.9 (13.8 to 32.6) HR for death 0.83 (95% CI, 0.54 to 1.27). 2-year OS (95% CI): I: 54.3% (43.9 to 67.2) C: 44.1% (33.6 to 57.8)	• Data cutoff: June 9, 2022 • At data cutoff 80 patients had received TILs and 82 patients had received at least one infusion of ipilimumab. • For 6-month PFS and ORR the results of assessments according to immune related response criteria are reported. <u>Authors conclusions:</u> In patients with advanced melanoma, progression-free

	Funding and conflicts of interest: - Supported by the Dutch Cancer Society, the Netherlands Organization for Health Research and Development, the Dutch Ministry of Health, Stichting Avento, the Antoni van Leeuwenhoek Foundation, Copenhagen University Hospital (Herlev), the Danish Cancer Society, and the Capital Region of Denmark Research Foundation. - Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.	the upper limit of the normal range. • One previous line of systemic treatment for this disease stage, excluding ipilimumab, was allowed. • Patients with vitiligo Exclusion criteria: • Life expectancy <3 mo • Metastatic ocular/ mucosal or other non-cutaneous melanoma • Adjuvant treatment with ipilimumab < 6 mo prior to randomization. • Requirement for immunosuppressive doses of systemic corticosteroids or immunosuppressive drugs < 3 weeks prior to randomization. • >2 CNS metastases • Patients with a symptomatic CNS lesion > 1 cm or that shows significant surrounding edema on MRI scan were not eligible until they were treated and	dose interleukin-2 every 8 hours, for a maximum of 15 doses per protocol. n=84		Treatment discontinuation because of AEs: 26/42 (62%) TIL arm: No patients were lost to follow-up No patients discontinued treatment Ipilimumab arm: No patients were lost to follow-up 42 patients discontinued treatment: • 26 due to adverse events • 14 due to rapid disease progression • 1 patient decision 1 death	Median PFS, in months (95% CI): I: 7.2 (4.2 to 13.1) C: 3.1 (3.0 to 4.3) HR for progression or death, 0.50; 95% CI, 0.35 to 0.72 6-month PFS: I: 52.7% (95% CI, 42.9 to 64.7) C: 21.4% (95% CI, 14.2 to 32.2) Treatment related AEs grade 3 or 4: I: 100% C: 57% In the TIL group, these events were mainly chemotherapy-related myelosuppression.	survival was significantly longer • among those who received TIL therapy than among those who received ipilimumab.

		demonstrated no clinical or radiologic CNS progression for ≥ 2 mo. • Inability to receive high dose interleukin-2 • Toxicities from prior non-systemic treatment that have not recovered to grade ≤1. • Pregnancy or breastfeeding women, • Active systemic infections, coagulation disorders or other active major medical illnesses. • Autoimmune disease For more information on in-/exclusion see the appendix of the article. Median age, years (range) I: 59 (26–74) C: 59 (30–77) Two patients who were older than 75 years of age were included in the trial because these patients were deemed to be in excellent				For more information on AEs see results section of the article. EORTC QLQ-C15 PAL quality-of-life and functioning scales. Mean HRQOL score at 6 months: • Global QoL: I: 77.4 C:69.6 Difference: 7.7 (5.1 to 10.4) • Physical functioning I: 82.0 C: 79.1 Difference: 2.9 (1.4 to 4.5) • Emotional functioning I: 85.4 C: 75.7 Difference: 9.7 (7.5 to 11.9) Scores on the EORTC QLQ-C15 PAL symptom scales: • Fatigue: I: 25.9 C: 33.8	

		clinical condition by the principal investigator. Male, n (%) I: 47 (56) C: 53 (63) WHO PS: 0 – I: 69 (82) 0 – C: 70 (83) 1 – I: 15 (18) 1 – C: 14 (17) Groups were comparable at baseline.				Difference: −7.9 (−11.2 to −4.6) • Nausea and vomiting I: 7.5 C: 5.9 Difference: 1.6 (0.7 to 2.5) • Pain I: 14.3 C: 20.7 Difference: −6.4 (−9.3 to −3.5) • Dyspnea I: 10.0 C: 12.4 Difference: −2.4 (−5.0 to 0.1) • Insomnia I: 23.6 C: 28.1 Difference −4.5 (−7.2 to −1.9) • Appetite loss I: 12.4 C: 13.5 Difference: −1.1 (−2.9 to 0.7) • Constipation I: 6.7 C: 7.1 Difference: −0.4 (−1.3 to 0.5)	
Weber 2015, **Larkin 2018** **Checkmate 037**	Type of study: phase III, randomized, controlled, open-label study	Inclusion criteria: - aged >= 18 years -histologically confirmed, unresectable stage IIIC or IV metastatic melanoma and ECOG	Describe intervention (treatment/procedure/test):	Describe control (treatment/procedure/test): Investigator's choice chemotherapy (ICC), which	**Larkin 2018** **Clinical data cutoff March 29, 2016**	Outcome measures and effect size (include 95%CI and p-value if available):	Original trial Checkmate 037 and updated analysis. ITT and PP analyses performed.

	Setting and country: Multicentre, 90 sites in 14 countries. Funding and conflicts of interest: The study was designed jointly by the funder of the study and the senior investigators (JSW and JL). Data collected by the funder were analysed in collaboration with all authors. The funder of the study funded writing and editorial support. Detailed declarations of interests are provided in the article.	performance status 0 or 1. -Patients with BRAF must have experienced progression after treatment with anti-CTLA-4 and BRAF inhibitor. -patients with BRAFV600 mutation must have experienced progression after treatment with anti–CTLA-4 and a BRAF inhibitor. Exclusion criteria: -active brain metastases -prior treatment with anti–PD-1, anti–programmed death ligand 1 (PD-L1), or anti–PD-L2 -grade 4 toxicity or use of infliximab during previous ipilimumab treatment -primary ocular melanoma. More detailed inclusion and exclusion criteria are described in the appendix of Weber et al, 2015.	Nivolumab 3 mg/kg intravenously every 2 weeks.	consisted of dacarbazine 1,000 mg/m2 every 3 weeks or carboplatin area under the curve 6 plus paclitaxel 175 mg/m2 every 3 weeks intravenously.	<u>Length of follow-up median (IQR)</u>: Approximately 2 years. <u>Length of duration therapy median:</u> I: 4.7 months (95% CI 3.3-6.0) C: 2.0 months (95% CI 1.6-2.8) <u>Loss-to-follow-up</u>: Intervention: 233 (86%) discontinued treatment. *182 disease progression* *15 study drug toxicity* *6 adverse event* *19 patient request* *3 withdrew consent* *1 maximum clinical benefit* *1 poor/noncompliance*	**Larkin 2018** <u>Median overall survival:</u> I: 15.7 months (95% CI, 12.9 to 19.9) C: 14.4 months (95% CI, 11.7 to 18.2) HR, 0.95; 95% CI, 0.73 to 1.24 <u>Median progression-free survival:</u> I: 3.1 months C: 3.7 months HR, 1.0; 95.1% CI, 0.78 to 1.436 <u>Adverse events:</u> I: 77% C: 82% Treatment related grade 3 and 4: I: 31% C: 14% Further specified in table 3.	Author's conclusion in 2015: *Findings from our study show that nivolumab leads to clinically meaningful improvements in the proportion of patients achieving an objective response and provide a manageable safety profile when compared with chemotherapy.* Authors 'conclusion in 2018: *"Although there were no survival differences between nivolumab and ICC treatments, nivolumab treatment* *after progression on ipilimumab with or without a BRAF inhibitor does provide a higher rate of response and more durable responses. Some situations may still exist that necessitate the use of ipilimumab as first-*

		N total at baseline: 405 Intervention: 272 Control: 133 Important prognostic factors[2]: Median age (IQR) *I:* 59 (23-88) *C:* 62 (29-85) Sex: *I:* 65% M *C:* 64% M ECOG performance status: *I:* 60% 0 *C:* 63% 0 BRAF mutant:			*4 no longer met study criteria* *2 other* Control: 102 (77%) discontinued treatment. *74 disease progression* *11 study drug toxicity* *3 adverse event* *7 patient request* *2 withdrew consent* *3 maximum clinical benefit* *2 other* **Weber 2015** **Clinical data cutoff not reported?** Range of follow-up: 5.2-16.7 months Loss-to-follow-up:	Quality of life: I: no change in EORTC QLQ-C30 no clinically significant improvement for EQ-5D/EQ-5D VAS. C: no change in EORTC QLQ-C30 A clinically significant decrease for EQ-5D at 12 weeks. **Weber 2015** Median overall survival: Not reported. Median progression-free survival: I: 4.7 months (95% CI 2.3–6.5) C: 4.2 months (2.1–6.3) HR, 0.82; 99% CI 0.32–2.05	*line therapy and nivolumab provides* *a safer option with a better maintained quality of life for patients who have experienced failure with prior systemic therapies compared with cytotoxic chemotherapy. The OS outcome may* *have been impacted by the increased dropout rate before treatment and increased systemic therapy received after assigned therapy in the ICC group, as well as an increased proportion of patients with poor prognostic factors in the nivolumab group.* *Despite the lack of survival advantage, nivolumab remains an effective option for PD-1 inhibitor–naive patients who experienced failure with ipilimumab and a BRAF inhibitor if BRAF mutated."*

		I: 60 (22%) *C:* 29 (22%) Treatment with PD-1/PD-L1: *I:* 11% *C:* 41% Brain metastases: I: 20% C: 14% Increased lactate dehydrogenase levels: I: 52% C: 38% Groups comparable at baseline? Yes, except for brain metastases and lactate dehydrogenase levels.			Intervention: 111 (53%) discontinued treatment. *96 disease progression* *5 study drug toxicity* *0 death* *2 AE unrelated to study drug* *5 request to discontinue* *2 withdrew consent* *1 max clinical benefit* Control: 129 (92%) discontinued treatment. *175 disease progression* *7 study drug toxicity* *0 death* *3 AE unrelated to study drug* *2 request to continue*	<u>Adverse events:</u> I: 68% C: 79% Treatment related grade 3 and 4: I: 9% C: 31% <u>Quality of life:</u> Not reported.	-Subgroup analysis was performed on the PD-1/PDL1 subgroup: <u>Median overall survival sensitivity analysis PD-1/PD-L1 group</u> Larkin 2018 I: 16.4 months (95% CI, 12.9 to 20.3) C: 11.8 months (95% CI, 9.9 to 14.4) HR, 0.81; 99% CI, 0.59 to 1.1

					3 withdrew consent *1 max clinical benefit* *1 other*		

8.3.3. Doelmatig voorschrijven systemische therapieën

Uitgangsvragen

Hoe worden systemische therapieën doelmatig voorgeschreven voor patiënten met irresectabel melanoom?

Inleiding

De afgelopen jaren zijn er steeds meer systemische therapieën beschikbaar gekomen voor patiënten met melanoom. Het doelmatig voorschrijven van deze therapieën is van groot belang voor de betaalbaarheid en toegankelijkheid van de zorg. Om die reden richt deze module zich op de doelmatigheid van systemische therapieën voor patiënten met een irresectabel melanoom.

Disclaimer: Deze module heeft alleen betrekking op patiënten met gunstige en intermediaire karakteristieken (zie 'Overwegingen' voor de definities) en houdt rekening met de volgende systemische therapieën: pembrolizumab, nivolumab, nivolumab plus ipilimumab, dabrafenib plus trametinib, vemurafenib plus cobimetinib en encorafenib plus binimetinib. Patiënten met ongunstige karakteristieken en andere systemische therapieën worden buiten beschouwing gelaten. Bij het gebruik van deze module wordt geadviseerd om tevens Module 8.3 'Systemische behandeling' te raadplegen.

Overwegingen

Ziektemodel voor patiënten met irresectabel melanoom

Voor deze module is gebruikt gemaakt van een ziektemodel voor patiënten met irresectabel melanoom, dat is ontwikkeld door de Erasmus Universiteit Rotterdam (institute for Medical Technology Assessment en Erasmus School of Health Policy & Management) in samenwerking met het Dutch Institute for Clinical Auditing. Het ziektemodel biedt de mogelijkheid om de effectiviteit en kosteneffectiviteit van verschillende behandelingen en behandelsequenties voor deze patiëntpopulatie te evalueren. In het ziektemodel wordt zowel gebruik gemaakt van de resultaten van een netwerk meta-analyse van fase 3 RCTs (Franken, 2019) als *real-world* data uit de Dutch Melanoma Treatment Registry (DMTR). Aanvullende informatie met betrekking tot de ontwikkeling van het ziektemodel is elders beschikbaar.

Binnen deze module wordt onderscheid gemaakt tussen patiënten met gunstige en intermediaire karakteristieken:

- patiënten met gunstige karakteristieken hebben een normaal serum LDH, een ECOG performances status van 0 of 1 én geen hersenmetastasen;
- patiënten met intermediaire karakteristieken hebben 1) een éénmaal verhoogd serum LDH, een ECOG performance status van 0 of 1 én geen of asymptomatische hersenmetastasen OF 2) een normaal serum LDH, een ECOG performance status van 0 of 1 én asymptomatische hersenmetastasen.

Patiënten met ongunstige karakteristieken zijn in het ziektemodel buiten beschouwing gelaten, omdat zij veelal geëxcludeerd worden in RCTs. Dit betreft patiënten met een tweemaal verhoogd serum LDH, een ECOG performance status van 2 of hoger en/of symptomatische hersenmetastasen.

Resultaten van het ziektemodel

De resultaten waarop deze module is gebaseerd, zijn terug te vinden in een rapport op de website van Zorginstituut Nederland. De initiële resultaten van het ziektemodel zijn beschreven in twee wetenschappelijke publicaties.

Belangrijkste overwegingen voor het interpreteren van de resultaten waarop deze module gebaseerd is:

- het ziektemodel is ontwikkeld voor patiënten met gunstige of intermediaire prognostische factoren;
- de resultaten zijn alleen van toepassing op patiënten met irresectabel melanoom die geen (neo)adjuvante therapie ontvangen hebben;
- de effectiviteit van de geïncludeerde behandelingen is gebaseerd op een netwerk meta-analyse van fase 3 RCTs (Franken, 2019) (beperkt tot RCTs met nieuw gediagnosticeerde patiënten);
- de effectiviteit van encorafenib plus binimetinib is, in overleg met klinische experts, gebaseerd op de effectiviteit van dabrafenib plus trametinib, omdat er geen RCT-data beschikbaar is voor uitsluitend nieuwe gediagnosticeerde patiënten;
- het relatieve behandeleffect is gelijk tussen nieuw gediagnosticeerde en eerder behandelde patiënten;
- de behandelduur van de geïncludeerde behandelingen is gebaseerd op DMTR data;
- indien de behandelduur in de DMTR data afwijkt van de behandelduur in de fase 3 RCTs heeft dat geen invloed op de effectiviteit van de behandeling;
- voor het berekenen van de geneesmiddelkosten is gebruik gemaakt van declaratieprijzen.

Voorschrijven van immuuntherapie

De resultaten van het ziektemodel tonen beperkte verschillen in kosten en effecten (in termen van ‘quality-adjusted life years’) tussen behandelsequenties die starten met een anti-PD-1 of nivolumab plus ipilimumab. Om die reden is er vanuit doelmatigheidsperspectief geen duidelijke voorkeur voor starten met een anti-PD-1 of nivolumab plus ipilimumab. Zie ook module 8.3 voor de andere overwegingen die hierbij van belang zijn. Aangezien nivolumab plus ipilimumab meer toxisch is, kan overwogen worden te starten met een anti-PD-1. Bij onvoldoende respons kan vervolgens nivolumab plus ipilimumab voorgeschreven worden.

Aanbevelingen

Overweeg de volgende criteria voor het doelmatig voorschrijven van systemische therapieën voor patiënten met irresectabel melanoom:

- effectiviteit;
- toxiciteit;
- patiëntkarakteristieken;
- patiëntvoorkeuren;
- kosten.

Overweeg patiënten in te delen op basis van de volgende karakteristieken:

- BRAF mutatie;
- serum LDH;
- ECOG performance status;
- hersenmetastasen.

Patiënten met gunstige karakteristieken (definitie: een normaal serum LDH, een ECOG performances status van 0 of 1 én geen hersenmetastasen)

Vanuit doelmatigheidsperspectief wordt aanbevolen om bij patiënten met gunstige karakteristieken te starten met immuuntherapie in plaats van doelgerichte therapie, ongeacht de aanwezigheid van een BRAF mutatie.

Bij het voorschrijven van immuuntherapie is er vanuit doelmatigheidsperspectief geen duidelijke voorkeur voor starten met anti-PD-1 monotherapie of de combinatie van nivolumab en ipilimumab. Overweeg te starten met een anti-PD-1 monotherapie, zodat de combinatie van nivolumab en ipilimumab kan worden voorgeschreven bij onvoldoende response.*

Schrijf doelgerichte therapie voor bij patiënten met een contra-indicatie voor immuuntherapie, mits een BRAF mutatie aanwezig is.

**Zie voor overwegingen ook Module 8.3*

Patiënten met intermediaire karakteristieken (definitie: een éénmaal verhoogd serum LDH, een ECOG performance status van 0 of 1 én geen of asymptomatische hersenmetastasen OF een normaal serum LDH, een ECOG performance status van 0 of 1 én asymptomatische hersenmetastasen)

Vanuit doelmatigheidsperspectief wordt aanbevolen om bij patiënten met intermediaire karakteristieken te starten met immuuntherapie in plaats van doelgerichte therapie, ongeacht de aanwezigheid van een BRAF mutatie.

Bij het voorschrijven van immuuntherapie is er vanuit doelmatigheidsperspectief geen duidelijke voorkeur voor starten met anti-PD-1 monotherapie of de combinatie van nivolumab en ipilimumab. Overweeg te starten met een anti-PD-1 monotherapie, zodat

de combinatie van nivolumab en ipilimumab kan worden voorgeschreven bij onvoldoende response.*

Schrijf doelgerichte therapie voor bij patiënten met snelle progressie van ziekte of een contra-indicatie voor immunotherapie, mits een BRAF mutatie aanwezig is.

**zie voor overwegingen ook module 8.3*

Literatuur (overige referenties volgen na publicatie)

Franken MG, Leeneman B, Gheorghe M, Uyl-de Groot CA, Haanen JBAG, van Baal PHM. A systematic literature review and network meta-analysis of effectiveness and safety outcomes in advanced melanoma. Eur J Cancer. 2019 Dec;123:58-71. doi: 10.1016/j.ejca.2019.08.032. Epub 2019 Oct 25. PMID: 31670077.

9.3. Onbekende primaire tumor melanoom

Uitgangsvragen

- Welke diagnostische strategie is het meest effectief bij patiënten met een onbekende primaire tumorlokalisatie?
- Welke behandelstrategie is het meest effectief bij patiënten met een onbekende primaire tumorlokalisatie?
- Welke informatie wordt aanbevolen te geven aan de patiënt met een onbekende primaire tumorlokalisatie?

Inleiding

Patiënten met melanoom presenteren zich in ongeveer 3% van de gevallen met een metastase als eerste uiting van de ziekte (Kamposioras, 2011; Bae, 2015). De anamnese levert in een dergelijk geval soms een waarschijnlijkheidsdiagnose op. Er kan sprake zijn geweest van een huidtumor die na verloop van tijd spontaan is verdwenen. Waarschijnlijk is het primaire melanoom dan in regressie gegaan. Het kan ook zijn dat er in het verleden een huidtumor was verwijderd zonder dat de werkelijke diagnose was gesteld. Bij een ander deel van de patiënten wordt anamnestisch geen bijbehorende primaire tumor gevonden. Het betreft hier dan ook geen primaire tumor onbekend, maar een primaire tumorlokalisatie onbekend.

Zoeken en selecteren

De werkgroep heeft besloten om geen systematisch literatuuronderzoek (PICO) uit te voeren voor deze vraag. De huidige uitgangsvraag wordt beantwoord met bestaande literatuur die bekend is bij de werkgroep en expert opinion.

Overwegingen– van bewijs naar aanbeveling

<u>Voor- en nadelen van de interventie en de kwaliteit van het bewijs</u>

Inspectie van de totale huid en biopsie van suspecte laesies zijn aangewezen. Overweeg pathologische revisie van eerder verwijderde huidlaesies. Kennis van de lymfedrainage is daarbij een leidraad. Het behaarde hoofd en de anus zijn bekende plekken waar zich nog wel eens een primaire tumor bevindt. Aanvullend onderzoek, zoals oftalmoscopie en endoscopie, levert zelden iets op en is niet nodig. De helft van de metastasen bevindt zich in een lymfeklier, meestal in de oksel. Ongeveer 40% bevindt zich in de subcutis, de rest in de huid en in inwendige organen. Bij een melanoommetastase in een lymfeklier in de hals moet tevens worden gedacht aan een primair mucosaal melanoom van de bovenste lucht- en voedselweg. Specifiek onderzoek door een KNO-arts of MKA chirurg-oncoloog kan dan overwogen worden als de klinische presentatie hier aanleiding toe geeft, echter met in acht neming van onderstaande. (Song 2018)

Aanvullend moleculair pathologisch onderzoek middels next-generation sequencing (NGS) naar genetische afwijkingen in de metastase kan behulpzaam zijn bij het nader bepalen van een eventuele primaire locatie en behulpzaam zijn bij het richting geven aan verder klinisch/beeldvormend.

Melanomen van verschillende primaire lokalisaties hebben namelijk veelal verschillende genetische driver mutaties of fusies, dan wel verschil in frequentie van voorkomen van driver afwijkingen die een specifieke primaire locatie meer of minder waarschijnlijk maken (Bastian, 2014; Yeh, 2021). *GNAQ* en *GNA11* mutaties worden bijvoorbeeld vooral in primair uvea / oogmelanoom gezien en de meeste huidmelanomen hebben een *BRAF* of *NRAS* mutatie. *BRAF* mutaties zijn zelden tot niet aanwezig in primaire mucosale melanomen.

In tegenstelling tot wat vaak wordt aangenomen, is de prognose van patiënten met een onbekende primaire tumorlokalisatie niet slechter dan die van patiënten met vergelijkbare metastasen van een bekende primaire tumor. In opzet curatieve behandeling is aangewezen en identiek aan de behandeling van stadium III of IV melanoom (Song 2018).

De prognose van patiënten van solitaire (sub)cutane metastasen lijkt aanzienlijk beter te zijn dan van patiënten met gemetastaseerde ziekte (OS 73-83%) (Bowen 2000, Lee 2009)

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Het is van waarde dat patiënt goed geïnformeerd worden over het feit dat de prognose van patiënten met een onbekende primaire tumorlokalisatie niet slechter is dan die van patiënten met vergelijkbare metastasen van een bekende primaire tumorlokalisatie. Patiënten moeten toegang hebben tot het gehele palet van behandeling en derhalve laagdrempelig in een melanoom centrum worden besproken.

Kosten (middelenbeslag)

De kosten zijn gelijk aan die van patiënten met stadium III of IV melanoom.

Aanvaardbaarheid, haalbaarheid en implementatie

De werkgroep verwacht geen barrières.

Aanbeveling(en)

Verricht bij een onbekende primair tumor melanoom een totale huidinspectie en diagnostische excisie van suspecte laesies.

Overweeg aanvullend moleculair pathologisch onderzoek met next-generation sequencing (NGS) van de metastase om de primaire locatie en verdere diagnostiek te bepalen.

Bied [18F]FDG-PET/CT aan ten behoeve van het detecteren van de primaire lokalisatie en de stadiëring.

Zet de behandeling in zoals bij stadium III bij lymfogene en subcutane laesies en zoals bij bij stadium IV bij orgaan laesies.

Informeer de patiënt over het feit dat de prognose van patiënten met een onbekende primaire tumorlokalisatie niet slechter is dan die van patiënten met vergelijkbare metastasen

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10. Palliatieve zorg

Uitgangsvraag

Wat wordt geadviseerd ten aanzien van de zorg aan patiënten met melanoom in de palliatieve fase?

Inleiding

In het verschenen 'Kwaliteitskader palliatieve zorg Nederland' (mei 2020), dat is opgesteld voor zorgverleners, worden er kaders gegeven voor het bieden van goede palliatieve zorg. Hierin wordt aangegeven dat palliatieve zorg gebaseerd moet zijn op de waarden, wensen en behoefte van de patiënt en zijn naasten, en niet alleen op lichamelijke zorg, maar ook op psychische en sociale zorg op het gebied van zingeving.

Overwegingen

Palliatieve zorg voor patiënten met melanoom wordt verleend door een multidisciplinair team, waarbij de patiënt centraal staat. Ieder lid van het team heeft zijn specifieke deskundigheid. Zorg voor voldoende afstemming en communicatie tussen huisarts en medisch specialist en doe dit zo vroeg mogelijk in het behandeltraject. Zorg voor duidelijkheid over de taakverdeling en voor goede afstemming en overdracht tussen alle betrokken zorgverleners. Het is belangrijk dat de patiënt altijd weet wie de hoofdbehandelaar is.

In de palliatieve fase kan het detecteren van behoefte aan psychosociale zorg en het zo nodig verlenen van psychosociale zorg de kwaliteit van leven (ook doen) verbeteren. In de richtlijn Detecteren behoefte psychosociale zorg (Nederlandse Vereniging Psychosociale Oncologie (NVPO, 2017) wordt een signaleringsinstrument (de Lastmeter) aanbevolen. Signalering van klachten dient bij voorkeur eens in de drie maanden plaats te vinden. Zie verder richtlijn Detecteren behoefte psychosociale zorg.
Om te bepalen of oncologische revalidatie een geschikte interventie is voor de patiënt met klachten kan de Lastmeter aangevuld worden met de Visual Analogue Scale (VAS) vermoeidheidlijst en de Patiënt Specifieke Klachtenlijst (PSK).

Er zijn speciale oncologische revalidatieprogramma's die gericht zijn op de ziektegerichte en symptoomgerichte fasen van palliatie. In het revalidatieprogramma staan de persoonlijke doelen en voorkeuren van de patiënt (en zijn naasten) centraal.
Er kan gestreefd worden naar preventie en behandeling van symptomen enerzijds en optimaliseren van de kwaliteit van leven anderzijds. Het streven naar behoud van fysieke functies zoals traplopen kan hierin essentieel zijn.

Zie verder de richtlijn Medisch specialistische revalidatie bij oncologie (VRA, 2018). Voor de richtlijnen palliatieve zorg zie www.pallialine.nl.

Aanbeveling

Zorg voor duidelijkheid over de taakverdeling en voor goede afstemming en overdracht tussen alle betrokken zorgverleners.

Zorg voor voldoende afstemming en communicatie tussen huisarts en medisch specialist en doe dit zo vroeg mogelijk in het behandeltraject. Zorg dat het voor de patiënt op ieder moment duidelijk is wie de hoofdbehandelaar is.

Detecteer de behoefte aan psychosociale middels een signaleringsinstrument bij voorkeur elke drie maanden.

Bepaal of de patiënt geschikt is voor oncologische revalidatie.

Streef naar preventie en behandeling van symptomen en het optimaliseren van de kwaliteit van leven.

Stimuleer de zelfredzaamheid en eigen regie van de patiënt.

11. Ondersteunende zorg

Uitgangsvraag

Welke ondersteunende zorg kan worden ingezet voor de lichamelijke, psychosociale en praktische problemen die op kunnen treden in het zorgtraject (van diagnostiek tot nazorg) bij patiënten met een melanoom?

Inleiding

Ondersteunende zorg omvat alle zorg in aanvulling op de medische zorg, die ten goede komt aan de patiënt met een melanoom. Ondersteunende zorg is niet gebonden aan een bepaalde fase in het behandeltraject. Derhalve dient iedere betrokken professional gedurende het gehele zorgtraject alert te zijn op een hulpvraag met betrekking tot ondersteunende zorg.

Overwegingen

Ondersteunende zorg omvat alle zorg in aanvulling op de medische zorg, die ten goede komt aan de patiënt met een melanoom. Ondersteunende zorg is niet gebonden aan een bepaalde fase in het behandeltraject. Derhalve dient iedere betrokken professional gedurende het gehele zorgtraject alert te zijn op een hulpvraag met betrekking tot ondersteunende zorg. Hiervoor kunnen de Last-meter, of andere melanoom specifieke PROM metingen, gebruikt worden, bij kwetsbare (veelal oudere) patiënten aangevuld met gerichte navraag naar functionele, fysieke, psychische, cognitieve en sociale problemen verbonden met kanker.

<u>Online informatiebronnen</u>

De Verwijsgids Kanker (www.verwijsgidskanker.nl), ontwikkeld en onderhouden door de IKNL, kan gebruikt worden door hulpverleners, patiënten en diens naasten om verwijsmogelijkheden te verkennen. Het gaat daarbij om zorgmogelijkheden op zowel landelijk als regionaal niveau, zoals fysiotherapie, psychosociale zorg, ergotherapeuten, diëtisten, et cetera. De website is vrij toegankelijk.

Thuisarts.nl (www.thuisarts.nl) is een initiatief van het Nederlands Huisartsen Genootschap (NHG) en is bedoeld voor mensen die informatie zoeken over gezondheid en ziekten en kan gebruikt worden als ondersteuning bij voorlichting aan patiënten voor, tijdens en na het consult. De website is vrij toegankelijk.

Het Oncokompas (www.oncokompas.nl) is een onlineprogramma bedoeld voor patiënten, waarin eerst een totaalbeeld gevormd wordt van de ervaren kwaliteit van leven door te kijken naar leefstijl, fysiek, psychisch en sociaal functioneren en levensvragen. Dit wordt vervolgens gekoppeld aan concrete stappen die de patiënt kan nemen om kwaliteit van leven te verbeteren. Op basis van deze gegevens, de gezondheidstoestand, persoonlijkheid en motivatie van de patiënt adviseert het Oncokompas vervolgens specifieke zelfhulpprogramma's of doorverwijzing naar gespecialiseerde zorg. Om gebruik te maken van het Oncokompas dient de patiënt aangemeld te worden via zijn oncologisch behandelaar of verpleegkundig specialist.

Patiëntenorganisaties
Patiëntenorganisaties bieden actuele patiënteninformatie, lotgenotencontact en belangenbehartiging aan voor patiënten met een melanoom. Het is daarom zinvol patiënten tijdig te wijzen op deze bron van informatie en ondersteuning.

Professionele ondersteunende zorg
Voor ondersteunende zorg op psychosociale, paramedisch en medisch vlak is een uitgebreid palet aan professionele zorgverleners inzetbaar. Te denken valt bijvoorbeeld aan psychologie, maatschappelijk werk, diëtetiek, ergotherapie, fysiotherapie, revalidatiegeneeskunde, en bij kwetsbare (oudere) patiënten ook de specialist ouderengeneeskunde/geriatrie/ interne ouderengeneeskunde.
Een consult bij een specialist integratieve geneeskunde kan behulpzaam zijn om de juiste keuze van verwijzing en ondersteuning te maken.

De Verwijsgids Kanker geeft een overzicht van paramedische zorgverleners met specialisatie in de problematiek van oncologische patiënten. In het deskundigenbestand van de Nederlandse Vereniging voor Psychosociale Oncologie (https://nvpo.nl/deskundigenbestand) staan psychosociale zorgverleners geregistreerd die voldoen aan de criteria van hun beroepsvereniging voor het verlenen van psychosociale zorg in de Oncologie.

De bedrijfsarts speelt een belangrijke rol in de terugkeer naar werk. Raadpleeg de *Richtlijn Kanker en Werk (NAVB 2019)* voor uitgebreide informatie over hun werkwijze en interventiemogelijkheden.

Voor ondersteunende zorg in de palliatieve setting kan het palliatief team geconsulteerd worden [zie module Palliatieve zorg].

Aanbeveling

Informeer patiënten over beschikbare informatiebronnen zoals patiëntenorganisaties, Thuisarts.nl, verwijsgids kanker en Oncokompas.

Informeer de patiënt over de mogelijkheden van ondersteunende zorg en stem eventuele verwijzing goed af, zodat de patiënt goed geïnformeerd kan beslissen en gemotiveerd is voor de gekozen zorg. Controleer of de informatie door de patiënt begrepen wordt, met name bij patiënten met cognitieve problemen.

Verwijs voor ondersteunende zorg bij voorkeur naar een psychosociale en/of (para)medische zorgverlener met ervaring in oncologie. Overweeg bij re-integratie problematiek na kanker een verwijzing naar een gespecialiseerde bedrijfsarts: de bedrijfsartsconsulent oncologie (BACO).

Zorg voor regelmatige interdisciplinaire overdracht van informatie ten aanzien van de al dan niet ingezette behandeling en voortgang, ook naar de huisarts.

12. Organisatie van zorg

Uitgangsvraag

Aan welke voorwaarden dient de organisatie van het **behandeltraject** van een patiënt met melanoom te voldoen?

Deelvragen:

1. Wie is er primair verantwoordelijk voor de behandeling bij welk stadium?
2. Welke patiënten dienen behandeld te worden in een melanoomcentrum?
3. Welke patiënten dienen in een MDO besproken te worden?
4. In welk MDO, met welke vertegenwoordiging van disciplines en met welke frequentie dienen patiënten besproken te worden voor het formuleren van een behandeladvies?
5. Wat is de optimale informatievoorziening rondom de behandeling van een patiënt met een melanoom?

Introductie

Bij de organisatie van het behandeltraject van een patiënt met een melanoom, vooral in de stadia III en IV, is het van cruciaal belang dat er voldaan wordt aan specifieke voorwaarden om de best mogelijke zorg te garanderen. Het multidisciplinaire overleg (MDO) speelt hierbij een centrale rol, waarbij deskundigheid vanuit verschillende medische disciplines nauw wordt afgestemd volgens de richtlijnen van het SONCOS normeringsdocument. Dit overleg zorgt ervoor dat alle aspecten van de diagnostiek en behandeling optimaal worden afgestemd, waarbij specialisten zoals dermatologen, chirurgen, internist-oncologen, radiologen, radiotherapeuten, pathologen en gespecialiseerde verpleegkundigen betrokken zijn. Door deze structuur kan een geïntegreerde en patiëntgerichte benadering worden gegarandeerd.

Overwegingen

Primair verantwoordelijke

De behandeling van melanoom vereist een gestructureerde aanpak waarbij de verantwoordelijke zorgverlener varieert afhankelijk van het ziektestadium. Een goede informatievoorziening is cruciaal om patiënten te helpen weloverwogen keuzes te maken. Deze gecombineerde strategie zorgt voor effectieve en gepersonaliseerde zorg voor melanoompatiënten.

Behandeling in melanoomcentrum

Complexe gevallen worden idealiter behandeld in een gespecialiseerd melanoomcentrum. Daarnaast dienen alle patiënten die in aanmerking komen voor systemische behandeling behandeld te worden in een melanoomcentrum.

MDO

Complexe casuïstiek en alle patiënten met een stadium III/IV melanoom dienen in een aangewezen melanoomcentrum besproken te worden in een multidisciplinair overleg (MDO) met diverse specialisten.

Invulling MDO

Houd wekelijks een multidisciplinair overleg (MDO) voor de afstemming van diagnostiek en behandeling van patiënten met stadium III/IV melanoom, waarbij deskundigheid

volgens het SONCOS normeringsdocument aanwezig is. Dit overleg dient vertegenwoordigd te worden door een chirurg, internist-oncoloog, radioloog/nucleair geneeskundige, radiotherapeut-oncoloog, patholoog, case manager en/of oncologieverpleegkundige en/of verpleegkundig specialist/physician assistant oncologie. Indien nodig kan een vertegenwoordiger van het melanoomcentrum wekelijks geconsulteerd worden

Optimale informatievoorziening

Voorlichting is een essentieel onderdeel van de behandeling. Voorlichting binnen een multidisciplinaire setting moet eenduidig worden gegeven, zodat iedere professional weet wanneer welke informatie aan de patiënt gegeven wordt en wie hiervoor verantwoordelijk is. Het verhoogde risico bij een belaste familieanamnese moet, indien van toepassing, met de patiënt besproken worden. Bij een belaste familieanamnese wordt met patiënt besproken dat er wellicht sprake is van een familiaire aanleg en wordt een consult klinische genetica aangeboden. Het is van belang patiënten te wijzen op gezond beweeg- en voedingsgedrag, maar ook op risicofactoren die gezondheidsproblemen kunnen veroorzaken of verergeren.

Samen beslissen over de behandelmogelijkheden of behandeling speelt een belangrijke rol. Goede voorlichting en informatievoorziening is hierbij essentieel voor de patiënt om een goede keuze te maken. De werkgroep adviseert daarom ook om voorlichting over de voor- en nadelen van een behandeling herhaaldelijk te bespreken en eventueel te ondersteunen met schriftelijke informatie. Ook moet aan de patiënt duidelijk worden gemaakt hoe de contactmomenten zijn ingericht. Dit kan opgenomen worden in een zorgpad.

Aanbevelingen

Primaire verantwoordelijkheid voor de behandeling

Stem de primaire verantwoordelijkheid af binnen het multidisciplinaire team.

Behandeling in melanoomcentrum

Behandel alle patiënten die in aanmerking komen voor systemische therapie in een daarvoor aangewezen melanoomcentrum. Met betrekking tot chirurgische behandeling kan eveneens afgestemd worden met een melanoom centrum.

Bespreken van patiënten in een MDO

Alle patiënten met een stadium III/IV melanoom dienen in een aangewezen melanoomcentrum besproken te worden. Verwijs deze patiënten voor behandeling door naar één van deze centra. Overleg symptomatische patiënten met (verdenking op) hersenmetastasen dezelfde werkdag (en bij ernstige klachten ook in het weekend) met een neuroloog ten aanzien van de snelheid van verwijzing naar de neurologie (SEH of poli), de snelheid van het verrichten van het aanvullend onderzoek, het eventueel starten van dexamethason en

bespreking in het (neuro)oncologisch MDO (aanbeveling conform Richtlijn Hersenmetastasen).

Invulling van MDO

Houd wekelijks een multidisciplinair overleg.

Stem de diagnostiek en behandeling voor een patiënt met een stadium III/IV melanoom af in een multidisciplinair overleg (MD). Bij dit MDO dient deskundigheid voor diagnostiek en behandeling aanwezig te zijn, zoals in SONCOS normeringsdocument.
Hierbij dienen de volgende disciplines aanwezig te zijn:

- (Plastisch) chirurg
- Dermatoloog
- Internist-oncoloog
- Radioloog/nucleair geneeskundige,
- Radiotherapeut-oncoloog
- Patholoog,
- Verpleegkundig specialist
- Case manager en/of oncologieverpleegkundige/physician assistant en eventueel andere verpleegkundigen.

Maak, indien nodig, bij dit overleg gebruik van de wekelijkse consultatie van een vertegenwoordiger van het melanoomcentrum.

Optimale informatievoorziening

Bespreek de voor- en nadelen van de behandelmogelijkheid of -mogelijkheden met de patiënt en richt daarbij de informatievoorziening op de volgende manier in zodat:

- Adequaat mondeling voorlichting gegeven wordt.
- Voorlichting gegeven wordt die op de fase van behandeling en de patiënt (en eventuele familie en naasten) toegesneden is.
- De (mondelinge) voorlichting met schriftelijke informatie of een website wordt ondersteund.
- Controleer bij de patiënt of de informatie is begrepen.

Kennisvragen

Kennisvragen behorend bij module 3.1. Familiare risicofactoren

- In de afgelopen jaren verschijnen er steeds meer wetenschappelijke studies over de rol van polygene overerving van laagrisicovarianten bij zowel sporadisch als familiair melanoom. Bij een deel van de genetisch onverklaarde melanoomfamilies lijkt het hoge melanoomrisico verklaard te kunnen worden door een hoge polygenetische risicoscore (PRS) bij de aangedane individuen. Meer onderzoek is echter nodig, vooral om de vertaalslag naar de klinische praktijk mogelijk te maken. Hoe kan een melanoomspecifieke PRS diagnostisch worden ingezet voor individuele risicostratificatie en het opstellen van passende surveillance-adviezen binnen melanoomfamilies?
- Bij ongeveer de helft van de patiënten met familiair of multipel melanoom is de oorzaak onbekend. Er kan geen oorzakelijk gendefect worden aangetoond, polygeen bepaald risico lijkt geen verklaring te bieden en blootstelling aan UV straling is niet bovengemiddeld. Deze 'missing heritability' belemmert het vinden van personen met hoog risico op melanoom in families en met hoog risico op ontwikkelen van multipel melanoom na de eerste diagnose. Dit staat weer effectieve surveillance als preventie van metastatisch melanoom in de weg.

Kennisvragen behorende bij module 7.2.1 Neoadjuvante behandeling stadium III

- Het is nog onbekend of afzien van adjuvante behandeling veilig en effectief is voor patiënten die een major pathologische respons hebben na neoadjuvante behandeling met pembrolizumab.
- Het is nog onbekend wat de beste timing en modaliteit is voor responsevaluatie/restadiering (en responsvoorspelling) bij neoadjuvante therapie.
- Bij een radiologische en/of klinische respons kan een dilemma ontstaan als de geplande chirurgie technisch lastig is of tot forse morbiditeit leidt. In de SWOG studie was de-escalatie van chirurgie geen optie hoewel er geen data zijn die dat bevestigen. Meerdere proof-of-concept studies laten zien dat resectie van een 'indexklier' geen slechtere resultaten geeft dan een regionale klierdissectie, maar dat is nog niet bevestigd in grotere studies.

Kennisvraag behorend bij module 8.2.2. Behandeling van oligometastase(n) bij stadium IV

- Er is een duidelijke behoefte aan goed opgezette prospectieve studies over de waarde van lokale behandeling bij patiënten met een uitgezaaid melanoom die ook systeembehandeling krijgen of hebben gehad.