Bijlagen bij
Cluster Neuro-oncologie
Conceptrichtlijnmodules
2e cyclus

Inhoudsopgave

Bijlagen richtlijnmodules Gliomen

Bijlagen bij Module 3.3. Verwijscriteria klinische genetica

Search and select

An exploratory literature search was conducted to map the available evidence. The search question was: "Which pathogenic germline variants are associated with glioma in adults?" Given the nature of the review question, the findings were not subjected to a formal GRADE assessment. The purpose of the search was primarily to gain an overview rather than to evaluate the certainty of the evidence. Therefore, no GRADE ratings were applied to the results. The studies deemed relevant have been described in the Considerations section.

The literature search was performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline. Both databases were searched from 2015 to December 1st 2025 for systematic reviews and observational studies. Systematic searches were completed using a combination of controlled vocabulary and natural language keywords. The overall search strategy was derived from the following primary search concepts: (1) glioma; (2) germline/ hereditary; (3) DNA analysis. Duplicates were removed using EndNote software. After deduplication a total of 1618 records were imported for title/abstract screening.
Eligible studies were required to include a minimum of 20 participants. Titles and abstracts were screened using the ASReview software. The settings *ELAS u4 (TF-IDF* and *SVM)* were used. Van Opijnen (2025) and McDonald (2023) were used as prior knowledge for inclusion. The first 20% of hits were screened by the working group and the guideline methodologist. The remaining articles were subsequently screened by the guideline methodologist, using the following stopping rule: stop after 50 subsequent exclusions.
Initially, 9 studies were selected based on title and abstract screening. After reading the full text, 5 studies were excluded (see the exclusion table under the tab 'Evidence tabellen'), and four studies were included.

Summary of literature

The studies deemed relevant are described in the Considerations section.

Verkeerslichtanalyse

Kruis aan		
	ROOD	Sterke aanbeveling tegen, geldend voor de gehele populatie, en waar passend bewijs voor is [1]
X	**ORANJE**	Aanbeveling waar geen passend bewijs is voor gehele populatie • Sterke aanbeveling tegen (geen passend bewijs voor gehele populatie en subpopulaties/ condities) • Conditionele aanbeveling (geen passend bewijs voor gehele populatie, maar wel passend bewijs voor een subgroep/-conditie (overweging))
	GROEN	Sterke aanbeveling voor, geldend voor de gehele populatie, en waar passend bewijs voor is [1,2]

Agenderen-tabel

Vraag	***Antwoord*** *Kruis aan*	*Vul in*
A1. Is onderzoek wenselijk om de <u>uitgangsvraag of zoekvraag</u> (met meer/voldoende		
	x	Ja

zekerheid) te kunnen beantwoorden?		
A2. Wat is de kennisvraag?	Kennis-vraag	Wat is de opbrengst van de genetische diagnostiek bij patiënten met een glioom die worden verwezen op basis van deze nieuwe module?
	P	Patiënten met glioom die voldoen aan de verwijscriteria
	I	DNA onderzoek gericht op erfelijke aanlegfactoren voor glioom
	C	Opbrengst van genetische diagnostiek bij gliomen op basis van de literatuur (10%).
	O	Percentage patiënten met een erfelijk tumorsyndroom
A3. Waarom is dit een belangrijke kennisvraag?	Toelichting	Het is belangrijk om te weten of de opgestelde criteria adequaat zijn voor het identificeren van de erfelijke gevallen van glioom [b)]
A4. Welk onderzoeksdesign is passend om deze kennisvraag te beantwoorden?		RCT
	x	Observationeel onderzoek
		Kwaliteitsregistratie
		Anders, namelijk
	Toelichting	[tekst]
A5. Zijn er een andere kennisvragen naar voren gekomen die passen bij het <u>onderwerp van de module</u>, maar niet hetzelfde zijn als de uitgangs- of zoekvraag en waar *geen* passend bewijs voor is?	x	Nee
		Ja

Implementeren-tabel

Vraag	*Antwoord:* *Kruis aan en licht toe/ beschrijf*		*Toelichting keuze:*
I1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?		**Ongewenste praktijkvariatie**	
		Nieuwe evidentie	
	X	**Anders**	Er was nog geen module over erfelijkheid. Wel behoefte aan informatie bij de behandelaar wanneer aan erfelijke belasting en in welke gevallen doorverwezen dient te worden
I2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	**X**	**< 1000** [wat betreft daadwerkelijke verwijzing]	
		< 5000	
		5000-40.000	
		> 40.000	
I3. Is de aanbeveling onderdeel van een bredere set interventies of verwant aan andere richtlijnen of modules? Zo ja, hoe verhoudt zij zich daartoe en moet hiermee rekening worden gehouden bij de implementatie, of kan de aanbeveling als losstaand worden beschouwd?		**Ja**	
	X	**Nee**	
I4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:		**Belemmerende factoren**	**Bevorderende factoren/ kansen**
Richtlijn/ klinisch traject (innovatie)	**X**		
Zorgverleners (artsen en verpleegkundigen)			
Patiënt/ cliënt (naasten)			
Sociale context			
Organisatorische context			
Financiële en juridische context			
I5. A) Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk? (kruis aan) **B) Wat is er nodig van deze personen/partijen om de aanbeveling in de praktijk te kunnen brengen?** *Denk aan aanpassingen in gedrag, werkwijzen, beleid, samenwerking of andere randvoorwaarden.*		**A**	**B**
		Patiënt/ cliënt (naaste)	
	X	Professional	
		Beroepsvereniging, nl	
		Ziekenhuis (raad van bestuur/UMCNL (voorheen NFU)/NVZ)	
		Zorgverzekeraars/ NZa	
		Zorginstituut [duiding nodig]	
		Anders	

Met opmerkingen [JB1]: @Tessa en Edward: voorzet gedaan, graag jullie blik. Bij het invullen ben ik uitgegaan dat er géén implementatie-issues worden verwacht. Klopt dat?

I6. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	**X**	< 1 jaar	
		binnen 2-3 jaar	
I7. Conclusie: is er extra actie en/of ondersteuning nodig voor implementatie van de aanbeveling? *De reguliere implementatieroutes (publicatie en disseminatie via officiele kanalen, opname in professionele standaarden, scholing en nascholing, gebruik van bestaande ICT systemen, audits en visitaties) van de richtlijnmodule alleen is onvoldoende.*		Ja	
	X	Nee	
I8. Plaatsing op de Landelijke Implementatieagenda Medisch Specialistische zorg is gewenst. *Het gaat om zorg die (grotendeels) wordt uitgevoerd binnen de ziekenhuismuren. Succesvolle implementatie vraagt om actieve betrokkenheid en samenwerking van meerdere relevante partijen binnen de zorgpraktijk.*		Ja *	
	X	Nee	

Table of excluded studies

Reference	Reason for exclusion
Bainbridge, M. N., Armstrong, G. N., Gramatges, M. M., Bertuch, A. A., Jhangiani, S. N., Doddapaneni, H., ... & Gliogene Consortium. (2015). Germline mutations in shelterin complex genes are associated with familial glioma. *Journal of the National Cancer Institute*, *107*(1), dju384.	Too specific (POT 1)
Ahmed, K. I., Govardhan, H. B., Roy, M., Naveen, T., Siddanna, P., Sridhar, P., ... & Nelson, N. (2019). Cell-free circulating tumor DNA in patients with high-grade glioma as diagnostic biomarker–A guide to future directive. *Indian Journal of Cancer*, *56*(1), 65-69.	Not specified germline mutations
Nikiforova, M. N., Wald, A. I., Melan, M. A., Roy, S., Zhong, S., Hamilton, R. L., ... & Horbinski, C. (2015). Targeted next-generation sequencing panel (GlioSeq) provides comprehensive genetic profiling of central nervous system tumors. *Neuro-oncology*, *18*(3), 379-387.	Not specified germline mutations
Eckel-Passow, J. E., Decker, P. A., Kosel, M. L., Kollmeyer, T. M., Molinaro, A. M., Rice, T., ... & Jenkins, R. B. (2019). Using germline variants to estimate glioma and subtype risks. *Neuro-oncology*, *21*(4), 451-461.	Not according PICO (polyporfism)
Cho, Y. A., Kim, D., Lee, B., Shim, J. H., & Suh, Y. L. (2021). Incidence, clinicopathologic, and genetic characteristics of mismatch repair gene-mutated glioblastomas. *Journal of neuro-oncology*, *153*(1), 43-53.	Too small panel

Literature search strategy

Embase.com

No.	Query	Results
#1	'glioma'/exp/mj OR 'gliomatosis cerebri'/exp/mj OR glioma*:ti,ab,kw OR astrocytoma*:ti,ab,kw OR oligoastrocytoma*:ti,ab,kw OR xanthoastrocytoma*:ti,ab,kw OR glioblastoma*:ti,ab,kw OR oligodendroglioma*:ti,ab,kw OR ganglioglioma*:ti,ab,kw OR (((glia OR glial) NEAR/3 (tumor* OR tumour*)):ti,ab,kw)	207410
#2	'germ line'/exp OR 'inheritance'/exp OR 'familial incidence'/exp OR 'family assessment'/exp OR 'familial predisposition'/exp OR 'family history'/exp OR 'genetic susceptibility'/exp OR 'genetic predisposition'/exp OR 'genetics'/de OR 'cancer genetics'/exp OR 'hereditary tumor syndrome'/exp OR famil*:ti,ab,kw OR heritab*:ti,ab,kw OR heredit*:ti,ab,kw OR inherit*:ti,ab,kw OR genetic*:ti,ab,kw OR oncogenetic*:ti,ab,kw OR germline*:ti,ab,kw OR 'germ line*':ti,ab,kw OR 'tumor syndrome*':ti,ab,kw OR 'tumour syndrome*':ti,ab,kw	4643756
#3	'germline testing'/exp OR 'whole genome sequencing'/exp OR 'whole exome sequencing'/exp OR 'pathogenic variant'/exp OR 'genetic analysis'/exp OR 'genetic screening'/exp OR (((panel OR dna) NEAR/3 (analys* OR test* OR screen*)):ti,ab,kw) OR (((genetic OR gene* OR 'germ line' OR germline) NEAR/3 (analys* OR test* OR screen* OR panel)):ti,ab,kw) OR ((pathogenic NEAR/3 variant*):ti,ab,kw) OR 'mutation analys*':ti,ab,kw OR 'exome sequencing':ti,ab,kw OR ((('whole exome*' OR 'whole genome*' OR 'complete genome*' OR 'full genome*' OR 'entire genome*' OR 'next generation' OR 'high throughput' OR germline OR 'germ line') NEAR/3 sequenc*):ti,ab,kw) OR wes:ti,ab,kw OR wgs:ti,ab,kw OR ngs:ti,ab,kw	1390633
#4	#1 AND #2 AND #3 NOT ('conference abstract'/it OR 'clinical trial':dtype) NOT (('editorial'/it OR 'letter'/it OR 'note'/it) NOT 'evidence based medicine'/exp) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	3758
#5	#4 AND [2015-2026]/py	2487
#6	'meta analysis'/exp OR 'systematic review'/exp OR 'scoping review'/exp OR 'rapid review'/exp OR 'umbrella review'/exp OR 'cochrane database of systematic reviews'/jt OR 'network meta-analysis'/exp OR 'networkmeta analy*':ti,ab,kw OR 'networkmetaanaly*':ti,ab,kw OR metaanaly*:ti,ab,kw OR 'meta analy*':kw OR metanaly*:ti,ab,kw OR prisma:ti,ab,kw OR prospero:ti,ab,kw OR metaanali*:ti,ab,kw OR 'meta anali*':ti,ab,kw OR metanali*:ti,ab,kw OR ((meta NEAR/1 analy*):ab,ti) OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab,kw) OR (((structured OR systemic*) NEAR/3 (review* OR overview* OR synth*) NEAR/3 literature):ti,ab,kw) OR ((systemic* NEAR/1 review*):ti,ab,kw) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab,kw) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab,kw) OR (((literature NEAR/3 (review* OR overview*)):ti,ab,kw) AND (search*:ti,ab,kw OR database*:ti,ab,kw OR 'data base*':ti,ab,kw)) OR (('data extraction*':ti,ab,kw OR 'data source*':ti,ab,kw) AND ('study selection*':ti,ab,kw OR 'studies selection*':ti,ab,kw)) OR ('search strateg*':ti,ab,kw AND 'selection criteria*':ti,ab,kw) OR ('data source*':ti,ab,kw AND 'data synth*':ti,ab,kw) OR medline*:ab OR pubmed*:ab OR 'pub med*':ab OR embase:ab OR cochrane*:ab,jt OR (((critical* OR rapid*) NEAR/2 (review* OR overview* OR synth*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synth*)):ab) AND (search*:ab OR	1215173

	database*:ab OR 'data base*':ab)) OR metasynth*:ti,ab,kw OR 'meta synth*':ti,ab,kw OR 'review* of review*':ti,ab,kw OR psycinfo:ab OR 'data extraction':ab OR cinahl:ab	
#7	'major clinical study'/de OR 'clinical study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'cohort analysis'/de OR '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 ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti) 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 OR controls) 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* 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 quadruple 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 (('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))) OR (((pretest OR 'pre test') NEAR/2 (posttest OR 'post test')):ti,ab,kw)	19337281
#8	#5 AND #6	102
#9	#5 AND #7 NOT #8	1413
#10	#8 OR #9	1515

Ovid/Medline

#	Searches	Results
1	exp Glioma/ or glioma*.ti,ab,kf. or astrocytoma*.ti,ab,kf. or oligoastrocytoma*.ti,ab,kf. or xanthoastrocytoma*.ti,ab,kf. or glioblastoma*.ti,ab,kf. or oligodendroglioma*.ti,ab,kf. or ganglioglioma*.ti,ab,kf. or ((glia or glial) adj3 (tumor* or tumour*)).ti,ab,kf.	155305

2	exp Inheritance Patterns/ or exp "Genetic Predisposition to Disease"/ or Genetics/ or exp Genetics, Medical/ or exp Germ-Line Mutation/ or exp Neoplastic Syndromes, Hereditary/ or famil*.ti,ab,kf. or heritab*.ti,ab,kf. or heredit*.ti,ab,kf. or inherit*.ti,ab,kf. or genetic*.ti,ab,kf. or oncogenetic*.ti,ab,kf. or germline*.ti,ab,kf. or 'germ line*'.ti,ab,kf. or 'tumor syndrome*'.ti,ab,kf. or 'tumour syndrome*'.ti,ab,kf.	3005623
3	exp Genetic Testing/ or exp Whole Genome Sequencing/ or Sequence Analysis, DNA/ or ((panel or dna) adj3 (analys* or test* or screen*)).ti,ab,kf. or ((genetic or gene* or 'germ line' or germline) adj3 (analys* or test* or screen* or panel)).ti,ab,kf. or (pathogenic adj3 variant*).ti,ab,kf. or 'mutation analys*'.ti,ab,kf. or 'exome sequencing'.ti,ab,kf. or (('whole exome*' or 'whole genome*' or 'complete genome*' or 'full genome*' or 'entire genome*' or 'next generation' or 'high throughput' or germline or 'germ line') adj3 sequenc*).ti,ab,kf. or wes.ti,ab,kf. or wgs.ti,ab,kf. or ngs.ti,ab,kf.	917373
4	(1 and 2 and 3) not ((exp animals/ or exp models, animal/) not humans/) not ((letter/ or comment/ or editorial/) not (exp Clinical Trial/ or exp Meta-Analysis/ or exp Scoping Review/ or exp Systematic Review/))	2508
5	limit 4 to yr="2015 -Current"	1710
6	exp Meta-Analysis/ or exp Network Meta-Analysis/ or exp Systematic Review/ or networkmeta analy*.ti,ab,kf. or networkmetaanaly*.ti,ab,kf. or metaanaly*.ti,ab,kf. or meta analy*.kf. or metanaly*.ti,ab,kf. or prisma.ti,ab,kf. or prospero.ti,ab,kf. or metaanali*.ti,ab,kf. or meta anali*.ti,ab,kf. or metanali*.ti,ab,kf. or (meta adj1 analy*).ab,ti. or ((systemati* or scoping or umbrella or structured literature) adj3 (review* or overview*)).ti,ab,kf. or ((structured or systemic*) adj3 (review* or overview* or synth*) adj3 literature).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* or overview*)) and (search* or database* or data base*)).ti,ab,kf. or ((data extraction* or data source*) and (study selection* or studies selection*)).ti,ab,kf. or (search strateg* and selection criteria*).ti,ab,kf. or (data source* and data synth*).ti,ab,kf. or medline*.ab. or pubmed*.ab. or pub med*.ab. or embase.ab. or cochrane*.ab. or ((critical* or rapid*) adj2 (review* or overview* or synth*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synth*)) and (search* or database* or data base*)).ab. or metasynth*.ti,ab,kf. or meta synth*.ti,ab,kf. or psycinfo.ab. or data extraction.ab. or cinahl.ab. or cochrane.jw.	914228
7	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 or controls) 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 quadruple 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	8275917

	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.)) or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ or ((pretest or pre test) adj2 (posttest or post test)).ti,ab,kf.	
8	5 and 6	61
9	(5 and 7) not 8	477
10	8 or 9	538

Bijlagen bij Module 10.2 Signalering en verwijzing voor psychosociale, neuropsychologische en neuropsychiatrische zorg bij gliomen

Zoeken en selecteren

Er is geen systematisch literatuuronderzoek uitgevoerd voor deze uitgangsvraag, omdat werd ingeschat dat er onvoldoende directe evidentie beschikbaar zou zijn. De module is dan ook gebaseerd op expertopinie, de kennis en ervaring van de werkgroepleden, en bestaande afspraken over zorgorganisatie in Nederland.

Verkeerslichtanalyse

Kruis aan		
	ROOD	Sterke aanbeveling tegen, geldend voor de gehele populatie, en waar passend bewijs voor is [1]
	ORANJE	Aanbeveling waar geen passend bewijs is voor gehele populatie • Sterke aanbeveling tegen (geen passend bewijs voor gehele populatie en subpopulaties/ condities) • Conditionele aanbeveling (geen passend bewijs voor gehele populatie, maar wel passend bewijs voor een subgroep/-conditie (overweging))
X	**GROEN**	Sterke aanbeveling voor, geldend voor de gehele populatie, en waar passend bewijs voor is [1,2]

Agenderen-tabel

Vraag	***Antwoord*** *Kruis aan*	*Vul in*
A1. Is onderzoek wenselijk om de <u>uitgangsvraag of zoekvraag</u> (met meer/voldoende zekerheid) te kunnen beantwoorden?		Nee. *Tijdens de ontwikkeling van deze module is gebleken dat er volgens het cluster sprake is van passend bewijs voor de uitgangsvraag en zoekvraag.*
	x	Ja
A2. Wat is de kennisvraag?	Kennis-vraag	Wat is de impact van tijdige diagnostiek en behandeling van neurocognitieve en neuropsychiatrische symptomen op de kwaliteit van leven en het ziektebeloop bij patiënten met een glioom?
	P	Patiënten met een glioom
	I	Tijdige diagnostiek en behandeling van neurocognitieve en neuropsychiatrische symptomen
	C	Geen of latere diagnostiek en behandeling/ gebruikelijke zorg zonder gestructureerde vroege screening
	O	Kwaliteit van leven en ziektebeloop (bijv. functionele status, progressie, overleving)
A3. Waarom is dit een belangrijke kennisvraag?	Toelichting	Zie overwegingen “Belang van neurocognitieve en neuropsychiatrische zorg”
		RCT
	x	Observationeel onderzoek

A4. Welk onderzoeksdesign is passend om deze kennisvraag te beantwoorden?		Kwaliteitsregistratie
		Anders, namelijk
	Toelichting	Niet van toepassing
A5. Zijn er een andere kennisvragen naar voren gekomen die passen bij het <u>onderwerp van de module</u>, maar niet hetzelfde zijn als de uitgangs- of zoekvraag en waar *geen* passend bewijs voor is?		Nee
	x	Ja
A6. Wat is de kennisvraag?	Kennis-vraag	Wat is de kosten-batenverhouding van tijdige medebehandeling door een (klinisch) neuropsycholoog en/of psychiater bij patiënten met een glioom en neurocognitieve en neuropsychiatrische symptomen?
	P	Patiënten met een glioom en neurocognitieve en/of neuropsychiatrische symptomen
	I	Tijdige medebehandeling door een (klinisch) neuropsycholoog en/of psychiater
	C	Gebruikelijke zorg zonder (of met latere) inzet van gespecialiseerde neuropsychologische/psychiatrische medebehandeling
	O	Kosten-batenverhouding (bijv. zorgkosten, zorggebruik, kwaliteit van leven, functionele uitkomsten)
A7. Waarom is dit een belangrijke kennisvraag?	Toelichting	Zie overwegingen “Belang van neurocognitieve en neuropsychiatrische zorg”
A8. Welk onderzoeksdesign is passend om deze kennisvraag te beantwoorden?		RCT
	x	Observationeel onderzoek
		Kwaliteitsregistratie
		Anders, namelijk:
	Toelichting	Niet van toepassing
A9. Is onderzoek wenselijk om de <u>uitgangsvraag of zoekvraag</u> (met meer/voldoende zekerheid) te kunnen beantwoorden?		Nee. *Tijdens de ontwikkeling van deze module is gebleken dat er volgens het cluster sprake is van passend bewijs voor de uitgangsvraag en zoekvraag.*
	x	Ja
A10. Wat is de kennisvraag?	Kennis-vraag	Valideren van de Nederlandse Neuropsychiatric Inventory (NPI) voor populatie glioompatiënten
	P	Patiënten met een glioom
	I	Afname van de Nederlandse Neuropsychiatric Inventory (NPI)
	C	Standaard klinische beoordeling en/of andere gevalideerde neuropsychiatrische meetinstrumenten
	O	Validiteit van de NPI in deze populatie (bijv. betrouwbaarheid, constructvaliditeit,

		sensitiviteit/specificiteit, klinische bruikbaarheid)
A11. Waarom is dit een belangrijke kennisvraag?	Toelichting	Zie overwegingen “Belang van neurocognitieve en neuropsychiatrische zorg”
A12. Welk onderzoeksdesign is passend om deze kennisvraag te beantwoorden?		RCT
	x	Observationeel onderzoek
		Kwaliteitsregistratie
		Anders, namelijk:
	Toelichting	Niet van toepassing

5

Implementatie-tabel

Vraag	*Antwoord:* *Kruis aan en licht toe/ beschrijf*		*Toelichting keuze:*
I1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	**X**	**Ongewenste praktijkvariatie**	
		Nieuwe evidentie	
		Anders	
I2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?		**< 1000**	
	X	**< 5000**	
		5000-40.000	
		> 40.000	
I3. Is de aanbeveling onderdeel van een bredere set interventies of verwant aan andere richtlijnen of modules? Zo ja, hoe verhoudt zij zich daartoe en moet hiermee rekening worden gehouden bij de implementatie, of kan de aanbeveling als losstaand worden beschouwd?	**X**	**Ja**	**Deze module gaat om signalering en verwijzing van de patiënt, behandelaanbevelingen verwijzen naar de behandelmodules.**
		Nee	
I4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:		**Belemmerende factoren**	**Bevorderende factoren/ kansen**
Richtlijn/ klinisch traject (innovatie)		Niet van toepassing	Niet van toepassing
Zorgverleners (artsen en verpleegkundigen)		- Extra belasting op werkzaamheden door te screenen op symptomen	- Intercollegiale kennisoverdracht - Ontlasting door behandeling psychische, neurocognitieve en neuropsychiatrische symptomen te delegeren aan gespecialiseerd hulpverlener
Patiënt/ cliënt (naasten)		- betrekken extra hulpverlener en toename zorgafspraken kan belastend zijn voor patiënt en/of naasten.	- Tijdige signalering en verwijzing kan ziektelast snel verbeteren en kwaliteit van leven bevorderen - Uitputting van steunsysteem/mantelzorgers voorkomen
Sociale context		Stigma op psychische stoornissen	Bewustwording van psychische klachten bij hersentumoren
Organisatorische context		- Onvoldoende beschikbaarheid van psychologische en psychiatrische verwijsmogelijkheden binnen oncologisch centrum - Lange wachtlijsten sGGZ	- Opzetten van gespecialiseerde samenwerking/ketenzorg
Financiële en juridische context		- Extra zorgkosten op de korte termijn bij het	Tijdige behandeling en voorkomen van verergeren

		bieden van extra behandeltraject. De exacte kosten hiervan zijn moeilijk in te schatten. Dit is ook afhankelijk van hoe psychologische en psychiatrische zorg per ziekenhuis is georganiseerd en bekostigd (ZPM vs DOT-DBC). Dit zal waarschijnlijk geen miljoenen bedragen zijn daar het verlenen van psychosociale zorg in de somatische DBC wordt geregistreerd en niet tot verzwaring, en dus hoger tarief, van deze DBC leidt. - Er is binnen de DOT-DBC geen apart tarief/bekostiging voor het verlenen van psychosociale zorg (zie tevens kwaliteitsstandaard Psychosociale zorg bij somatische aandoeningen).	psychische klachten kan op langere termijn hogere zorgkosten besparen (bv door voorkomen van spoedzorg/klinische opnames)
I5. A) Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk? (kruis aan) **B) Wat is er nodig van deze personen/partijen om de aanbeveling in de praktijk te kunnen brengen?** *Denk aan aanpassingen in gedrag, werkwijzen, beleid, samenwerking of andere randvoorwaarden.*		**A**	**B**
	X	Patiënt/ cliënt (naaste)	
	X	Professional	Interprofessionele samenwerking, tussen vakgroep neurologie en (medische) psychologie/psychiatrie, of externe GGZ-aanbieder wanneer deze zorg niet binnen het ziekenhuis georganiseerd is.
		Beroepsvereniging, nl	
	x	Ziekenhuis (raad van bestuur/UMCNL (voorheen NFU)/NVZ)	Faciliteren van tijdige psychologische en psychiatrische behandeling binnen het ziekenhuis, danwel het opstellen van passende ketenzorgafspraken waarmee tijdige verwijzing mogelijk wordt gemaakt als dit nodig is.
	x	Zorgverzekeraars/ NZa	Passende financiering voor psychosociale, (neuro-)psychologische en psychiatrische zorg binnen het ziekenhuis.
		Zorginstituut [duiding nodig]	

Met opmerkingen [Jd2]: Esther Baptist: Ja ik vond dit in de vergadering een ingewikkelde opmerking. Het gebrek aan kennis over neuropsychiatrische symptomen bij de neurologen/neurochirurgen zou er dan mi ook bij horen.
Het is wat mij betreft geen gebrek aan scholing. Het gaat immers over een zeldzaam ziektebeeld.
Ik vind het dus de opmerking dat dit een hiaat is in de opleiding niet terecht en zou ik de beroepsverenigingen hier niet noemen.
Dit probleem ligt voornamelijk bij de organisatie van psychologische/psychiatrische zorg van het ziekenhuizen en de samenwerkingen tussen verschillende specialismen/vakgroepen. Hier gaan de beroepsverenigingen niet over, maar primair het ziekenhuisbestuur. Vaak wordt er in ziekenhuizen bezuinigd op de psychologische en psychiatrische zorg, daar hier geen passende financiële vergoeding tegenover staat (zie ook de kwaliteitsstandaard psychosociale zorg).
Ik zou dit dus graag er uit halen en het onderbrengen in de organisatie van zorg in de ziekenhuizen, evt aangevuld met GGZ NL als het gaat om de wachtlijstproblematiek in de GGZ.

Ik heb dit even naar mijn visie aangepast.
Mocht het nodig zijn kan ik dit altijd nog een keer uitgebreider toelichten of over overleggen.

		Anders	
I6. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	**X**	< 1 jaar	
		binnen 2-3 jaar	
I7. Conclusie: is er extra actie en/of ondersteuning nodig voor implementatie van de aanbeveling? *De reguliere implementatieroutes (publicatie en disseminatie via officiële kanalen, opname in professionele standaarden, scholing en nascholing, gebruik van bestaande ICT systemen, audits en visitaties) van de richtlijnmodule alleen is onvoldoende.*	**X**	Ja	
		Nee	
I8. Plaatsing op de Landelijke Implementatieagenda Medisch Specialistische zorg is gewenst. *Het gaat om zorg die (grotendeels) wordt uitgevoerd binnen de ziekenhuismuren. Succesvolle implementatie vraagt om actieve betrokkenheid en samenwerking van meerdere relevante partijen binnen de zorgpraktijk.*	**X**	Ja *	
		Nee	

Bijlagen richtlijnmodules Hersenmetastasen

Bijlagen bij Module 3.7 Frequentie neurologische en radiologische follow-up

Search and select
A systematic review of the literature was performed to answer the following question(s):
What is the most effective duration and frequency to detect recurrence after treatment for brain metastases?

Table 1. PICO

Patients	People treated for brain metastases
Intervention	Follow-up protocol including duration, and frequency of tests (MRI scans)
Control	• Any other follow-up protocol • No follow up (wait until patient reports symptoms of recurrence)
Outcomes	Critical: • Change/initiation of treatment • symptomatic versus asymptomatic presentation Important: o overall survival. o cognition o health-related quality of life o neurological outcomes o seizures
Other selection criteria	Study design: systematic reviews and randomized controlled trials *Search from 2017 on (NICE searched in september 2017, no literature was found).*

Relevant outcome measures
The guideline panel considered change/initiation of treatment, symptomatic versus asymptomatic presentation as **critical** outcome measurements for decision making; and overall survival, cognition, health-related quality of life, neurological outcomes, and seizures as **important** outcome measurements for decision making.

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

The guideline panel did not define hard thresholds as a minimal clinically (patient) important difference.

Search and select (Methods)
A systematic literature search was performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline. Both databases were searched until 28 Augustus 2025 for systematic reviews, RCTs and observational studies. Systematic searches were completed using a combination of controlled vocabulary/subject headings (e.g., Emtree-terms, MeSH) wherever they were available and natural language keywords. The overall search strategy was derived from three primary search concepts: (1) brain metastases; (2) MRI; (3) Follow-up. Duplicates were removed using EndNote software. After deduplication a total of 810 records were imported for title/abstract screening. After the screening based on title and abstract screening, no study met the PICO criteria.

Summary of literature
Not applicable.

Met opmerkingen [Jd3]: Speelt neurologische follow-up geen rol meer?

Met opmerkingen [IB4R3]: Dit vind ik een lastige. De MRI scans worden niet standaard door een neuroloog aangevraagd en vervolgd. Er kans dan dus geen sprake zijn van een neurologische FU. Laagdrempelig kan de neuroloog gevraagd worden. Om deze reden wilde ik de neurologische FU eruit hebben omdat dat een neurologische anamnese en neurologisch onderzoek suggereert

Met opmerkingen [MS5]: Dit is mogelijk standaard tekst, maar voor mij leest dit alsof alleen studies vanaf dat moment zijn meegenomen…

Met opmerkingen [NT6R5]: eens

Met opmerkingen [IB7R5]: Jing, dit was al tekst van jullie en niet iets aan gewijzigd. Suggestie?

Met opmerkingen [NT8]: Wow, wel opmerkelijk dat er zoveel literatuur is maar niet specifiek naar de vraag van de PICO, verbaast me eigenlijk!

Verkeerslichtanalyse

Kruis aan		
	ROOD	Sterke aanbeveling tegen, geldend voor de gehele populatie, en waar passend bewijs voor is [1]
X	**ORANJE**	Aanbeveling waar geen passend bewijs is voor gehele populatie • Sterke aanbeveling tegen (geen passend bewijs voor gehele populatie en subpopulaties/ condities) • Conditionele aanbeveling (geen passend bewijs voor gehele populatie, maar wel passend bewijs voor een subgroep/-conditie (overweging))
	GROEN	Sterke aanbeveling voor, geldend voor de gehele populatie, en waar passend bewijs voor is [1,2]

Agenderen-tabel

Vraag	***Antwoord*** *Kruis aan*	*Vul in*
A1. Is onderzoek wenselijk om de <u>uitgangsvraag of zoekvraag</u> (met meer/voldoende zekerheid) te kunnen beantwoorden?		Nee. *Tijdens de ontwikkeling van deze module is gebleken dat er volgens het cluster sprake is van passend bewijs voor de uitgangsvraag en zoekvraag.*
	x	Ja
A2. Wat is de kennisvraag?	Kennis-vraag	*What is the most effective duration and frequency to detect recurrence after treatment for brain metastases?*
	P	People treated for brain metastases with a chronic response lasting longer than 2 years
	I	Perform a follow-up MRI scan every 12 months and stop surveillance after 5 years
	C	Perform follow-up MRI scans every 6 months and continue surveillance indefinitely
	O	Critical: • Change/initiation of treatment • symptomatic versus asymptomatic presentation Important: o overall survival. o neuro cognitive function o health-related quality of life o neurological outcomes o seizures
A3. Waarom is dit een belangrijke kennisvraag?	Toelichting	Door de toenemende druk op de klinische en radiologische capaciteit en een toenemend aantal patiënten die langdurig leven met hersenmetastasen is het noodzakelijk kritisch te kijken naar huidige follow-uppraktijken bij patiënten met hersenmetastasen. Er zijn signalen dat follow-upintervallen enigszins worden opgerekt om het aantal scans te beperken.

		Een systematische literatuursearch laat zien dat er geen studies beschikbaar zijn die voldoen aan de betreffende PICO. Dit wordt bevestigd door de recente richtlijnen: de NICE-guideline (2018, geüpdatet) en de ESMO-guideline (2021, geüpdatet) noemen geen relevante studies. Patiënten willen geen MRI-scans ondergaan die onnodig zijn aangezien deze elke keer ook stress kan geven. Een dergelijk onderzoek kan zowel zorgverleners als patiënten informeren over de optimale balans tussen medische noodzaak en beschikbare capaciteit. Het tekort aan klinische en radiologische capaciteit beperkt niet alleen de zorg voor patiënten met hersenmetastasen, maar ook voor andere patiëntengroepen. Dit onderzoek kan daarom inzicht geven in de mogelijke bredere impact van follow-upintervallen.
A4. Welk onderzoeksdesign is passend om deze kennisvraag te beantwoorden?		RCT
	x	Observationeel onderzoek
		Kwaliteitsregistratie
		Anders, namelijk
	Toelichting	Prospectief cohort studie
A5. Zijn er een andere kennisvragen naar voren gekomen die passen bij het <u>onderwerp van de module</u>, maar niet hetzelfde zijn als de uitgangs- of zoekvraag en waar *geen* passend bewijs voor is?	x	Nee
		Ja

Implementeren-tabel

Vraag	*Antwoord:* *Kruis aan en licht toe/ beschrijf*		*Toelichting keuze:*
I1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	**X**	**Ongewenste praktijkvariatie**	**Beperkte MRI capaciteit**
		Nieuwe evidentie	
		Anders	
I2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	**X**	**< 1000**	
		< 5000	
		5000-40.000	
		> 40.000	
I3. Is de aanbeveling onderdeel van een bredere set interventies of verwant aan andere richtlijnen of modules? Zo ja, hoe verhoudt zij zich daartoe en moet hiermee rekening worden gehouden bij de implementatie, of kan de aanbeveling als losstaand worden beschouwd?		**Ja**	
	X	**Nee, kan als losstaande aanbeveling beschouwd worden.**	
I4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:		**Belemmerende factoren**	**Bevorderende factoren/ kansen**
Richtlijn/ klinisch traject (innovatie)		Niet van toepassing	Niet van toepassing
Zorgverleners (artsen en verpleegkundigen)		Niet van toepassing	Verwacht wordt dat het aantal scans in de follow-up licht zal afnemen, kan dit een positief effect hebben op de capaciteit van radiologen.
Patiënt/ cliënt (naasten)		Belangrijk is om duidelijk uit te leggen dat minder frequente follow-up niet betekent dat de patiënt wordt “losgelaten”, maar dat de behoefte aan follow-up wordt besproken en de wens van de patiënt wordt meegenomen.	Bij sommige patiënten is minder frequente follow-up wenselijk.
Sociale context		Niet van toepassing	Niet van toepassing
Organisatorische context		Niet van toepassing	Niet van toepassing
Financiële en juridische context			Naar verwachting wordt er minder onnodige MRI scans verricht, wat leidt tot later kosten.
I5. A) Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk? (kruis aan)		**A**	**B**
		Patiënt/ cliënt (naaste)	
	X	Professional	Afdeling radiologie
	X	Beroepsvereniging, nl	Hoofdbehandelaar: na twee jaar follow-up afwegen of elke

B) Wat is er nodig van deze personen/partijen om de aanbeveling in de praktijk te kunnen brengen? *Denk aan aanpassingen in gedrag, werkwijzen, beleid, samenwerking of andere randvoorwaarden.*			radiologische follow-up zinvol is.
		Ziekenhuis (raad van bestuur/UMCNL (voorheen NFU)/NVZ)	
		Zorgverzekeraars/ NZa	
		Zorginstituut [duiding nodig]	
		Anders	
I6. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	**X**	< 1 jaar	
		binnen 2-3 jaar	
I7. Conclusie: is er extra actie en/of ondersteuning nodig voor implementatie van de aanbeveling? *De reguliere implementatieroutes (publicatie en disseminatie via officiele kanalen, opname in professionele standaarden, scholing en nascholing, gebruik van bestaande ICT systemen, audits en visitaties) van de richtlijnmodule alleen is onvoldoende.*		Ja	
	X	Nee	
I8. Plaatsing op de Landelijke Implementatieagenda Medisch Specialistische zorg is gewenst. *Het gaat om zorg die (grotendeels) wordt uitgevoerd binnen de ziekenhuismuren. Succesvolle implementatie vraagt om actieve betrokkenheid en samenwerking van meerdere relevante partijen binnen de zorgpraktijk.*		Ja *	
	X	Nee	

Literature search strategy
Embase.com

No.	Query	Results
#1	'brain metastasis'/exp OR (((brain OR cerebr* OR intracerebr* OR intracrani* OR mening* OR brainstem*) NEAR/3 (metasta* OR micromet* OR macromet* OR oligomet* OR spread* OR carcinomatosis OR carcinosis OR secondar* OR seeding OR seeded OR disseminat* OR migrat*)):ti,ab,kw)	90506
#2	'neuroimaging'/exp/mj OR 'nuclear magnetic resonance imaging'/exp OR 'mri scanner'/exp OR ('magnetic resonance':ab,ti AND (image:ab,ti OR images:ab,ti OR imaging:ab,ti)) OR mri:ab,ti OR mris:ab,ti OR nmr:ab,ti OR mra:ab,ti OR mras:ab,ti OR zeugmatograph*:ab,ti OR 'mr tomography':ab,ti OR 'mr tomographies':ab,ti OR 'mr tomographic':ab,ti OR 'mr imag*':ti,ab,kw OR 'proton spin':ab,ti OR ((magneti*:ab,ti OR 'chemical shift':ab,ti) AND imaging:ab,ti) OR fmri:ti,ab,kw OR fmris:ti,ab,kw OR rsfmri:ti,ab,kw OR 'neuro imag*':ti,ab,kw OR neuroimag*:ti,ab,kw	1856611
#3	'aftercare'/exp/mj OR 'follow up'/exp/mj OR 'disease surveillance'/exp OR 'periodic medical examination'/exp OR 'medical record review'/exp OR 'patient monitoring'/exp/mj OR aftercare:ti,ab,kw OR 'after care':ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR surveillance:ti,ab,kw OR 'after treatment':ti,ab,kw OR 'post treatment':ti,ab,kw OR posttreatment:ti,ab,kw OR 'post therap*':ti,ab,kw OR posttherap*:ti,ab,kw OR ((('post surg*' OR 'post operat*' OR postoperat*) NEAR/2 (evaluat* OR monitor* OR care)):ti,ab,kw) OR 'post hospital*':ti,ab,kw OR posthospital*:ti,ab,kw OR 'after hospital*':ti,ab,kw OR 'follow* hopital*':ti,ab,kw OR 're examin*':ti,ab,kw OR reexamin*:ti,ab,kw OR monitor*:ti,ab,kw OR 'periodic	5180423

	examin*':ti,ab,kw OR 'regular examin*':ti,ab,kw OR checkup*:ti,ab,kw OR 'check up*':ti,ab,kw OR follow*:ti	
#4	#1 AND #2 AND #3 AND [2017-2025]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT (('adolescent'/exp OR 'child'/exp OR adolescent*:ti,ab,kw OR child*:ti,ab,kw OR schoolchild*:ti,ab,kw OR infant*:ti,ab,kw OR girl*:ti,ab,kw OR boy*:ti,ab,kw OR teen:ti,ab,kw OR teens:ti,ab,kw OR teenager*:ti,ab,kw OR youth*:ti,ab,kw OR pediatr*:ti,ab,kw OR paediatr*:ti,ab,kw OR puber*:ti,ab,kw) NOT ('adult'/exp OR 'aged'/exp OR 'middle aged'/exp OR adult*:ti,ab,kw OR man:ti,ab,kw OR men:ti,ab,kw OR woman:ti,ab,kw OR women:ti,ab,kw))	2395
#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	1179937
#6	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	4090488
#7	'major clinical study'/de OR 'clinical study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'cohort analysis'/de OR '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 ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti) 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* 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 (('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)))	18961858
#8	#4 AND #5 - SR	106
#9	#4 AND #6 NOT #8 - RCT	513
#10	#4 AND #7 NOT (#8 OR #9) - observationeel	983

#11	#8 OR #9 OR #10	1602

Ovid/Medline

#	Searches	Results
1	(Neoplasm Metastasis/ and Brain Neoplasms/) or ((brain or cerebr* or intracerebr* or intracrani* or mening* or brainstem*) adj3 (metasta* or micromet* or macromet* or oligomet* or spread* or carcinomatosis or carcinosis or secondar* or seeding or seeded or disseminat* or migrat* or tumor* or tumour* or cancer* or carcinoma*)).ti,ab,kf. or 'intracranial activity'.ti,ab,kf.	130491
2	exp *Neuroimaging/ or exp magnetic resonance imaging/ or ("magnetic resonance" and (image or images or imaging)).ti,ab,kf. or mri.ti,ab,kf. or mris.ti,ab,kf. or nmr.ti,ab,kf. or mra.ti,ab,kf. or mras.ti,ab,kf. or zeugmatograph*.ti,ab,kf. or "mr tomography".ti,ab,kf. or "mr tomographies".ti,ab,kf. or "mr tomographic".ti,ab,kf. or 'mr imag*'.ti,ab,kf. or "proton spin".ti,ab,kf. or ((magneti* or "chemical shift") and imaging).ti,ab,kf. or fmri.ti,ab,kf. or fmris.ti,ab,kf. or rsfmri.ti,ab,kf. or neuro-imag*.ti,ab,kf. or neuroimag*.ti,ab,kf.	1136505
3	exp Aftercare/ or exp *Follow-Up Studies/ or aftercare.ti,ab,kf. or 'after care'.ti,ab,kf. or 'follow up'.ti,ab,kf. or followup.ti,ab,kf. or surveillance.ti,ab,kf. or 'after treatment'.ti,ab,kf. or 'post treatment'.ti,ab,kf. or posttreatment.ti,ab,kf. or 'post therap*'.ti,ab,kf. or posttherap*.ti,ab,kf. or (('post surg*' or 'post operat*' or postoperat*) adj2 (evaluat* or monitor* or care)).ti,ab,kf. or 'post hospital*'.ti,ab,kf. or posthospital*.ti,ab,kf. or 'after hospital*'.ti,ab,kf. or 'follow* hopital*'.ti,ab,kf. or 're examin*'.ti,ab,kf. or reexamin*.ti,ab,kf. or monitor*.ti,ab,kf. or 'periodic examin*'.ti,ab,kf. or 'regular examin*'.ti,ab,kf. or checkup*.ti,ab,kf. or 'check up*'.ti,ab,kf. or follow*.ti.	3549163
4	(1 and 2 and 3) not (comment/ or editorial/ or letter/) not ((exp animals/ or exp models, animal/) not humans/) not ((Adolescent/ or Child/ or Infant/ or adolescen*.ti,ab,kf. or child*.ti,ab,kf. or schoolchild*.ti,ab,kf. or infant*.ti,ab,kf. or girl*.ti,ab,kf. or boy*.ti,ab,kf. or teen.ti,ab,kf. or teens.ti,ab,kf. or teenager*.ti,ab,kf. or youth*.ti,ab,kf. or pediatr*.ti,ab,kf. or paediatr*.ti,ab,kf. or puber*.ti,ab,kf.) not (Adult/ or adult*.ti,ab,kf. or man.ti,ab,kf. or men.ti,ab,kf. or woman.ti,ab,kf. or women.ti,ab,kf.))	4752
5	limit 4 to yr="2017 -Current"	2413
6	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.	856608
7	exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.	2933212
7	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4801407
8	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	8143707

	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.))	
9	5 and 6 - SR	101
10	(5 and 7) not 9 - RCT	264
11	(5 and 8) not (9 or 10) - observationeel	963
12	9 or 10 or 11	1328

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Bijlagen bij Module 4.8 Systemische therapie bij hersenmetastasen melanoom

Search and select
A systematic review of the literature was performed to answer the following question(s):

Table 1. PICOs

Patients	1. and 4. Patients with brain metastases from melanoma, not previously treated locally 2. Patients with brain metastases from melanoma and BRAF-mutation, not previously treated locally 3. Patients with brain metastases from melanoma, previously treated locally (radiotherapy and/or resection)
Intervention	1.and 3. Systemic therapy (combinations of) 2. Systematic therapy followed by local treatment 4. Systemic therapy with concurrent radiotherapy
Control	1.Other (combinations of) systemic therapy, radiotherapy and/or resection 2.Local treatment followed by systematic therapy 3.No treatment/best supportive care 4. Radiotherapy followed by systemic therapy, only systemic therapy, only radiotherapy
Outcomes	(Melanoma specific) overall survival (OS), time to response, progression-free survival (PFS), quality of Life (QoL)
Other selection criteria	Systematic reviews/meta-analyses, RCT's

Relevant outcome measures
The guideline panel considered (melanoma specific) overall survival (OS), time to response as a critical outcome measure for decision making; and progression-free survival (PFS), quality of Life and (QoL) as an important outcome measure(s) for decision making.

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

The guideline panel defined a difference in overall survival and/or progression-free survival of > 12 weeks and or HR < 0.7 / > 1.4 or an increase 2-year overall survival gain ≥ 10% (provided that > 20% of patients in the intervention group are still alive after 2 years) as a minimal clinically (patient) important difference, based on the PASKWIL criteria (2023).

Search and select (Methods)
A systematic literature search was performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline all. Both databases were searched from August 6th 2018 to December 5th 2025 for systematic reviews, RCTs and observational studies. Systematic searches were completed using a combination of controlled vocabulary and natural language keywords. The overall search strategy was derived from the following primary search concepts: (1) brain metastasis of melanoma; (2) systemic therapy. Duplicates were removed using EndNote software.
For the systematic literature summary, we focused on systematic review and RCTs. After deduplication a total of 523 records of systematic reviews and RCTs were imported for title/abstract screening.
Studies were included conform the PICOs. Eligible studies were required to include a minimum of 15 participants per study arm. Titles and abstracts were screened using the ASReview software. The settings *ELAS u4 (TF-IDF* and *SVM)* were used. Long (2025) and di Giacomo (2021) were used as prior

knowledge for inclusion. The first 20% of hits were screened by the working group and the guideline methodologist. The remaining articles were subsequently screened by the guideline methodologist, using the following stopping rule: stop after 50 subsequent exclusions.

Initially, 30 articles were selected based on title and abstract screening. After reading the full text, 26 articles were excluded (see the exclusion table under the tab 'Evidence tabellen'), and 4 articles (2 unique studies) were included

Summary of literature

Description of studies

A total of two studies were included in the analysis of the literature. Important study characteristics and results are summarized in table 1. The assessment of the risk of bias is summarized in the risk of bias table. For both trials, extended follow-up publications were identified and used to supplement long-term survival and additional outcome data.

1.1 Systemic therapy for untreated brain metastases from melanoma

Long (2018) performed a randomized, open-label phase II trial ('ABC-trial) to assess the efficacy of nivolumab alone versus nivolumab plus ipilimumab in patients with melanoma brain metastases (n=79). Eligible patients were aged ≥18 years with histologically confirmed melanoma and at least one measurable brain metastasis (≥5 mm) according to modified RECIST criteria. Patients had an ECOG performance status of 0 or 1 and could not have received prior systemic therapy for metastatic melanoma (adjuvant therapy was permitted under specific conditions).
Patients with asymptomatic, untreated brain metastases were randomized to nivolumab monotherapy or nivolumab plus ipilimumab. Patients with leptomeningeal disease were excluded. Brain MRI was required at baseline and regular intervals for intracranial response assessment. **Long (2025)** reports extended follow-up of the ABC trial population. This publication provides longer-term overall survival data (approximately 7-year follow-up), updated intracranial and extracranial response durability data, and additional subgroup analyses, including outcomes according to BRAF mutation status. No new patients were included and no additional treatment arms were introduced.

Di Giacomo (2021) reported the long-term results of the randomized phase II NIBIT-M2 trial, which evaluated immunotherapy versus chemotherapy in patients brain metastases from melanoma (n=80). Eligible patients were aged ≥18 years with histologically confirmed melanoma and at least one measurable brain metastasis. Patients were required to have an ECOG performance status of 0 or 1 and adequate organ function. Prior systemic treatment for metastatic disease was permitted in some cases, depending on cohort allocation.
Patients were randomized to receive fotemustine alone, fotemustine plus ipilimumab, or nivolumab plus ipilimumab. Both asymptomatic patients and selected patients with controlled or minimally symptomatic brain metastases were eligible. Patients requiring high-dose corticosteroids or with leptomeningeal disease were excluded. Brain imaging (MRI) was performed at baseline and during follow-up for intracranial response assessment according to RECIST criteria. **Di Giacomo (2024)** reports extended follow-up of the NIBIT-M2 trial with approximately 7 years of follow-up. This publication provides updated overall survival data, additional long-term intracranial and extracranial outcome data, and reports patient-reported quality-of-life outcomes. No additional randomization or new treatment arms were introduced.

1.2 Optimal sequence for symptomatic BRAF-mutated brain metastases from melanoma

1.3 First-line systemic therapy on previously treated (resection/radiotherapy) brain metastases from melanoma

1.4 Systemic therapy with concurrent radiotherapy for brain metastases from melanoma

No studies met the selection criteria.

Table 2. Characteristics and methodological quality assessment of included studies

Study	Participants	Inclusion criteria brain metastases	Comparison	Follow-up	Outcome measures	Comments	Risk of bias
Systemic therapy for untreated brain metastases from melanoma							
Long 2018 (ABC trial)	N at baseline: Cohort A: 36 Cohort B: 27 Non-randomized cohort: Cohort C: 16 (not further elaborated in this table) Age at randomisation, years Cohort A: 59 (53–68) Cohort B: 63 (52–74)	stage IV melanoma brain metastases ECOG 0–2 Symptomatic/asymptomatic brain metastases: asymptomatic (Cohort A and B) Prior treatment for brain metastases: no previous local brain therapy Size brain metastases: 5–40 mm Corticosteroid use: N.S.	Intervention: Cohort A: nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses then nivolumab 3 mg/kg every 2 weeks Cohort B: nivolumab 3 mg/kg every 2 weeks	14 months (8–22) for cohort A, 17 months (13–22) for cohort B	Intracranial response rate from week 12: Complete response Partial response Best extracranial Response: Complete response Partial response Intracranial and Extracranial progression-free survival Overall survival, Overall progression-free survival, Safety (grade ≥3 AEs)	Funding by industry (Melanoma Institute Australia and Bristol-Myers Squibb)	Some concerns (overall survival, progression-free survival)

Di Giacomo 2021 (NIBIT-M2 primary analysis)	N at baseline: 80 Age: Fotemustine 57 (20–80) Ipilimumab plus fotemustine 60 (31–74) Ipilimumab plus nivolumab 56 (25–79)	stage IV melanoma BRAF wild-type or mutant ECOG 0–1 Symptomatic/asymptomatic brain metastases: asymptomatic Prior treatment for brain metastases: untreated Size brain metastases: diameter, 5–20 mm Corticosteroid use: N.S.	Arm A: fotemustine 100 mg/m2 over 60 minutes, once every week for three doses (weeks 1, 2 and 3; induction phase), and once every 3 weeks from week 9 for six doses (maintenance phase). Arm B: fotemustine+ ipilimumab 10 mg/kg over 90 minutes given as induction every 3 weeks for four doses (weeks 1, 4, 7, and 10), and then as maintenance every 12 weeks from week 24 Arm C: ipilimumab 3 mg/kg over 90 minutes + nivolumab 1 mg/kg over 60 minutes every 3 weeks for four doses (weeks 1, 4, 7, and 10;	median follow-up of 52 months (IQR, 38–62)	Overall survival objective response rate (ORR) Global progression-free survival (PFS) Intracranial response Duration of response intracranial and extracranial PFS quality of life Safety	Funding: Fondazione AIRC under 5 per Mille 2018—ID 21073 program (M. Maio), and from an unrestricted grant from Bristol Myers Squibb to the NIBIT Foundation.	Some concerns (overall survival, progression-free survival)

			induction phase), and from week 12 received maintenance treatment with nivolumab 3 mg/kg over 60 minutes every 2 weeks				

Results

Summary of Findings table: 1.1 Systemic therapy for untreated brain metastases from melanoma

Population: Patients with brain metastases from melanoma, not previously treated locally

Intervention: ipilimumab +nivolumab

Comparator: nivolumab

Outcomes	Study results and measurements	Absolute effect estimates		Certainty of the Evidence	Conclusions
		Control (nivolumab)	Intervention (nivolumab + ipilimumab)		
Overall survival (OS) (critical)	Median OS months (95% CI) A: NR (11·9–NR) B: NR (6·9–NR) At 6 months (95% CI) A: 80% (65–98) B: 73% (56–96) Median OS at 7 years, months (95% CI) A: NR (32·9–NR) B: 37·2 (9·6–NR) OS At 7 years (95% CI) A: 51% (35–74) B: 29% (14–60)	73 per 100 alive at 6 months	80 per 100 alive at 6 months	Moderate[1]	Nivolumab + ipilimumab probably result in little to no difference in short-term overall survival, but probably increase long-term overall survival compared with nivolumab alone in patients with untreated melanoma brain metastases.
Progression-free survival (PFS) (important)	Intracranial PFS Number of patients with disease Progression, 7-year A: 14 (52%) B: 16 (84%)	21 per 100 progression-free at 6 months	60 per 100 progression-free at 6 months	Low[2]	Nivolumab + ipilimumab may improve progression-free survival largely compared with nivolumab alone in patients with untreated melanoma brain metastases.

	Median intracranial progression-free survival, months (95% CI), 7-year A: 47% (32–71) B: 14% (4–46) Median duration, months (95% CI) A: NR (4·7–NR) B: 2·6 (1·8–NR) At 6 months (95% CI) A: 60% (44–83) B: 21% (9–50) HR not reported				
Time to response (critical)	Not reported	Not reported	Not reported	-	No evidence
Quality of life (important)	Not reported	Not reported	Not reported	-	No evidence
Safety (grade ≥3 AEs)	<u>At median follow up of 17 months</u> A grade 3: 19 (54%) grade 4: 3 (9%) B grade 3: 4 (16%) <u>At median follow-up was 7·6 years</u>				

	A: unchanged B: 1 additional				

NR: Not reached

[1] **Imprecision**: **serious.** Low number of patients, optimal information size not achieved.

[2] **Risk of bias: serious.** Allocation concealment questionable, role of the funderand open-label design . **Imprecision: serious.** Low number of patients, optimal information size not achieved.

5

Population: Patients with brain metastases from melanoma, not previously treated locally
Intervention: ipilimumab +nivolumab / ipilimumab + fotemustine
Comparator: fotemustine

Outcomes	**Study results and measurements**	**Absolute effect estimates**			**Certainty of the Evidence**	**Conclusions**
		Control (fotemustine)	**Intervention (Ipilimumab + Fotemustine)**	**Intervention (nivolumab + ipilimumab)**		
Overall survival (OS) (critical)	Deaths A:20 (87.0%) B: 23 (88.5%) C: 15 (55.6%) Median OS, mo (95% CI) A: 8.5 (4.8–12.2) B:8.2 (2.2–14.3) C:29.2 (0–65.1) B: HR (95% CI) vs. fotemustine, 1.09 (0.59–1.99) C: HR (95% CI) vs. fotemustine, 0.44 (0.22–0.87) 7-year OS rate (95% CI) A: 10.0% (0–22.5)	87 deaths per 100 patients	8 more deaths (36 fewer to 86 more)	49 fewer deaths (68–11 fewer)	Moderate[1]	Nivolumab + ipilimumab probably lead to a large increase in overall survival compared with fotemustine in patients with untreated melanoma brain metastases.

	B: 10.3% (0–22.6) C: 42.8% (23.4–62.2)					
Progression-free survival (PFS) (important)	Intracranial PFS Patients with disease progression A: 22 (95.7%) B: 23 (88.5%) C: 17 (63.0%) Median PFS, mo (95% CI) A: 3.0 (2.3–3.6) B: 3.3 (1.2–5.4) C: 8.7 (0.0–19.9) 6-mo PFS rated A: 4.3% (0–12.7) B: 34.6% (16.4–52.8) C: 63.0% (44.8–81.2) 7-year intracranial PFS rate (95% CI) A: 4.3% (0–12.7) B:11.5% (0–23.8) C: 43.5% (24.5–62.5)	96 progressions per 100 patients	31 fewer progressions (12–49 fewer)	59 fewer progressions (41–77 fewer)	Low[2]	Nivolumab + ipilimumab may lead to a large improvement in progression-free survival compared with fotemustine in patients with untreated melanoma brain metastases.
Time to response (critical)	Median time to global response, months (IQR) A: NA B: 3.4 (2.9–4.7) C: 3.0 (2.7–4.8)	-	-	-	Low[2]	Nivolumab + ipilimumab results in little to no difference in time to response compared with fotemustine in patients with untreated melanoma brain metastases.
Quality of life (important)	Mean baseline GhS (SD) A: 73.0 (18.4) B: 65.7 (27.8)	-	-	-	Very low[3]	The evidence is very uncertain about the effect of nivolumab

	C: 78.3 (16.1) HRQoL deterioration ≥10-point at 12 Weeks A: 44% B: 44% C: 29%					plus ipilimumab or ipilimumab plus fotemustine on quality of life compared with fotemustine in patients with untreated melanoma brain metastases.
Safety	Treatment-relatedadverseevents grade 3 + 4 A: 11(48%) B: 18(69%) C: 8(30%)					

GhS: Global Health Status ; NA: Not applicable

[1] **Imprecision**: **serious.** Low number of patients, optimal information size not achieved.

[2] **Risk of bias: serious.** Allocation concealment questionable, role of the funder and open-label design . **Imprecision: serious.** Low number of patients, optimal information size not achieved.

5 [2] **Risk of bias: serious.** Allocation concealment questionable, role of the funder and open-label design . **Imprecision: serious.** Low number of patients, optimal information size not achieved. Indirectness: **serious**. HRQoL was not pre-specified and was assessed only at short-term follow-up (12 weeks).

Verkeerslichtanalyse

Kruis aan		
	ROOD	Sterke aanbeveling tegen, geldend voor de gehele populatie, en waar passend bewijs voor is [1]
X	**ORANJE**	Aanbeveling waar geen passend bewijs is voor gehele populatie • Sterke aanbeveling tegen (geen passend bewijs voor gehele populatie en subpopulaties/ condities) • Conditionele aanbeveling (geen passend bewijs voor gehele populatie, maar wel passend bewijs voor een subgroep/-conditie (overweging))
	GROEN	Sterke aanbeveling voor, geldend voor de gehele populatie, en waar passend bewijs voor is [1,2]

Implementatietabel

Vraag	***Antwoord:*** *Kruis aan en licht toe/ beschrijf*		***Toelichting keuze:***
I1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?		**Ongewenste praktijkvariatie**	
	X	**Nieuwe evidentie**	
		Anders	
I2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	**X**	**< 1000**	
		< 5000	
		5000-40.000	
		> 40.000	
I3. Is de aanbeveling onderdeel van een bredere set interventies of verwant aan andere richtlijnen of modules? Zo ja, hoe verhoudt zij zich daartoe en moet hiermee rekening worden gehouden bij de implementatie, of kan de aanbeveling als losstaand worden beschouwd?		**Ja**	
	X	**Nee**	
I4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:		**Belemmerende factoren**	**Bevorderende factoren/ kansen**
Richtlijn/ klinisch traject (innovatie)			Aanbeveling voor deze groep (patienten met hersenmetastasen) in lijn met aanbeveling voor patienten met gevorderde melanoom, en dus in lijn met RL melanoom
Zorgverleners (artsen en verpleegkundigen)			
Patiënt/ cliënt (naasten)			
Sociale context			
Organisatorische context			

Financiële en juridische context			
I5. A) Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk? (kruis aan) **B) Wat is er nodig van deze personen/partijen om de aanbeveling in de praktijk te kunnen brengen?** *Denk aan aanpassingen in gedrag, werkwijzen, beleid, samenwerking of andere randvoorwaarden.*		**A**	**B**
		Patiënt/ cliënt (naaste)	
	X	Professional	
		Beroepsvereniging, nl	
		Ziekenhuis (raad van bestuur/UMCNL (voorheen NFU)/NVZ)	
		Zorgverzekeraars/ NZa	
		Zorginstituut [duiding nodig]	
		Anders	
I6. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	**X**	< 1 jaar	
		binnen 2-3 jaar	
I7. Conclusie: is er extra actie en/of ondersteuning nodig voor implementatie van de aanbeveling? *De reguliere implementatieroutes (publicatie en disseminatie via officiele kanalen, opname in professionele standaarden, scholing en nascholing, gebruik van bestaande ICT systemen, audits en visitaties) van de richtlijnmodule alleen is onvoldoende.*		Ja	
	X	Nee	
I8. Plaatsing op de Landelijke Implementatieagenda Medisch Specialistische zorg is gewenst. *Het gaat om zorg die (grotendeels) wordt uitgevoerd binnen de ziekenhuismuren. Succesvolle implementatie vraagt om actieve betrokkenheid en samenwerking van meerdere relevante partijen binnen de zorgpraktijk.*		Ja *	
	X	Nee	

**Deze aanbeveling komt mogelijk in aanmerking voor plaatsing op de Landelijke Implementatieagenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG), waarin alle betrokken partijen in de medisch-specialistische zorg samenwerken aan de implementatie van bewezen beste zorg. De Federatie levert namens het veld goed onderbouwde aanbevelingen aan, die zijn getoetst op de behoefte aan een implementatie-impuls. De onderwerpen op de Implementatieagenda zijn onderdeel van landelijke zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders. Voor de beoordeling van aanbevelingen uit richtlijnen wordt gebruikgemaakt van de implementatietabel. Op basis hiervan kunnen we de andere partijen goed informeren en gezamenlijk besluiten of plaatsing op de Implementatieagenda passend is.*

Agenderen-tabel

Vraag	***Antwoord*** *Kruis aan*	*Vul in*
A1. Is onderzoek wenselijk om de <u>uitgangsvraag of zoekvraag</u>	x	Nee. *Tijdens de ontwikkeling van deze module is gebleken dat er volgens het cluster sprake is van*

Met opmerkingen [JB9]: @Maureen/Fons/Filip:
Welke kennisvragen relevant?

Bijv.
Iets over volgorderlijkheid van behandelingen?

Mag breder dan de module zijn.

(met meer/voldoende zekerheid) te kunnen beantwoorden?		*passend bewijs voor de uitgangsvraag en zoekvraag.*
		Ja
A2. Wat is de kennisvraag?	Kennis-vraag	[tekst] [a)]
	P	[tekst]
	I	[tekst]
	C	[tekst]
	O	[tekst]
A3. Waarom is dit een belangrijke kennisvraag?	Toelichting	[tekst] [b)]
A4. Welk onderzoeksdesign is passend om deze kennisvraag te beantwoorden?		RCT
		Observationeel onderzoek
		Kwaliteitsregistratie
		Anders, namelijk
	Toelichting	[tekst]
A5. Zijn er een andere kennisvragen naar voren gekomen die passen bij het <u>onderwerp van de module</u>, maar niet hetzelfde zijn als de uitgangs- of zoekvraag en waar *geen* passend bewijs voor is?	x	Nee
		Ja
A6. Wat is de kennisvraag?	Kennis-vraag	[tekst] [a)]
	P	[tekst]
	I	[tekst]
	C	[tekst]
	O	[tekst]
A7. Waarom is dit een belangrijke kennisvraag?	Toelichting	[tekst] [b)]
A8. Welk onderzoeksdesign is passend om deze kennisvraag te beantwoorden?		RCT
		Observationeel onderzoek
		Kwaliteitsregistratie
		Anders, namelijk:
	Toelichting	[tekst]

Risk of Bias tables

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?** Definitely yes / Probably yes / Probably no / Definitely no	**Was the allocation adequately concealed?** Definitely yes / Probably yes / Probably no / Definitely no	**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?** Definitely yes / Probably yes / Probably no / Definitely no	**Are reports of the study free of selective outcome reporting?** Definitely yes / Probably yes / Probably no / Definitely no	**Was the study apparently free of other problems that could put it at a risk of bias?** Definitely yes / Probably yes / Probably no / Definitely no	**Overall risk of bias If applicable/necessary, per outcome measure** **LOW** **Some concerns** **HIGH**
Long, 2018	Definitely yes; Reason: Central computer-generated randomization	Probably yes; Reason: Allocation performed centrally, but detailed	Definitely no; Reason: Open-label trial; patients and healthcar	Probably yes; Reason: Loss to follow-up limited and balance	Probably yes; Reason: Prespecified outcomes (intracranial	Probably yes; Reason: Phase II study with small sample size;	**Some concerns** (progression-free survival)

	reported in a multicentre randomized phase II design.	concealment procedure not fully described.	e providers not blinded. Outcome assessors likely not blinded; blinding of data collectors and analysts not reported.	d between groups; most patients included in analyses.	response, PFS, OS) reported; no clear evidence of selective reporting.	industry funding present but no major baseline imbalances or early stopping reported.	
Di Giacomo, 2021	Definitely yes; Reason: Randomized phase II design with computer-generated allocation sequence described in trial methodology.	Probably yes; Reason: Central randomization reported; exact concealment method not fully detailed.	Definitely no; Reason: Open-label trial; patients and healthcare providers not blinded. Blinding of outcome assessors, data collectors and analysts not reported.	Probably yes; Reason: Long-term follow-up available for most randomized patients; missing outcome data limited.	Definitely yes; Reason: All predefined outcomes (intracranial response, PFS, OS) reported in long-term follow-up publication.	Probably yes; Reason: No major baseline imbalances or early termination reported; phase III sample size relatively small.	**Some concerns** (progression-free survival)

Literature search strategy
Embase.com

No.	Query	Results
#1	('brain metastasis'/exp OR (((brain OR cerebr* OR intracerebr* OR intracrani* OR cerebellar OR mening* OR brainstem* OR 'central nervous system' OR cns) NEAR/3 (metasta* OR micromet* OR macromet* OR oligomet* OR spread* OR carcinomatosis OR carcinosis OR secondar* OR seeding OR seeded OR disseminat* OR migrat* OR tumor* OR tumour* OR cancer* OR carcinoma*)):ti,ab,kw) OR 'posterior cranial fossa tumor'/exp OR 'posterior fossa':ti,ab,kw OR 'posterior cranial fossa':ti,ab,kw OR 'intracranial activity':ti,ab,kw OR 'intracranial cohort*':ti,ab,kw) AND ('melanoma'/exp OR melanoma*:ti,ab,kw OR nevocarcinoma*:ti,ab,kw OR naevocarcinoma:ti,ab,kw OR 'pigmentary cancer':ti,ab,kw)	13096
#2	'systemic therapy'/exp OR ((systemic NEAR/3 (therap* OR treatment*)):ti,ab,kw) OR 'immunotherapy'/de OR 'cancer immunotherapy'/exp OR 'chemoimmunotherapy'/exp OR	1119910

	immunotherap*:ti,ab,kw OR 'immuno* therap*':ti,ab,kw OR immunetherap*:ti,ab,kw OR 'immune therap*':ti,ab,kw OR chemoimmunotherap*:ti,ab,kw OR 'immune checkpoint inhibitor'/exp OR (((checkpoint OR 'check point*' OR immunocheckpoint*) NEAR/3 (inhibit* OR block* OR therap*)):ti,ab,kw) OR ((('pd 1' OR pd1 OR 'pd l1' OR pdl1 OR 'programmed death 1' OR 'programmed cell death 1' OR 'programmed cell death protein 1' OR 'programmed death ligand 1' OR ctla4 OR 'ctla 4' OR 'cytotoxic t lymphocyte antigen 4') NEAR/2 (anti* OR inhibit* OR block*)):ti,ab,kw) OR 'ipilimumab'/exp OR ipilimumab:ti,ab,kw OR yervoy:ti,ab,kw OR 'pembrolizumab'/exp OR 'pembrolizumab':ti,ab,kw OR 'nivolumab'/exp OR 'nivolumab':ti,ab,kw OR 'vemurafenib'/exp OR 'vemurafenib':ti,ab,kw OR 'til therapy'/exp OR til:ti,ab,kw OR ((('tumor infiltrating lymphocyt*' OR 'tumour infiltrating lymphocyt*' OR til) NEAR/3 therap*):ti,ab,kw) OR 'targeted therapy'/exp OR 'personalized medicine'/exp OR (((targeted OR tailored OR personalize* OR personalise* OR individualize* OR individualise* OR precision) NEAR/3 (therap* OR oncotherap* OR medicine OR oncomedicine OR treatment* OR oncolog*)):ti,ab,kw) OR 'dabrafenib'/exp OR 'dabrafenib':ti,ab,kw OR 'cobimetinib'/exp OR 'cobimetinib':ti,ab,kw OR 'gdc 0973':ti,ab,kw OR 'gdc0973':ti,ab,kw OR 'trametinib'/exp OR 'trametinib':ti,ab,kw OR 'braf inhibitor'/exp OR 'b raf kinase inhibitor'/exp OR (((braf OR 'b raf') NEAR/3 (inhibit* OR block*)):ti,ab,kw) OR 'encorafenib'/exp OR 'encorafenib':ti,ab,kw OR 'lgx 818':ti,ab,kw OR 'lgx818':ti,ab,kw OR 'binimetinib'/exp OR 'binimetinib':ti,ab,kw OR mektovi:ti,ab,kw	
#3	#1 AND #2 NOT ('conference abstract'/it OR 'clinical trial':dtype) NOT (('editorial'/it OR 'letter'/it OR 'note'/it) NOT 'evidence based medicine'/exp) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	3234
#4	#3 AND [06-08-2018]/sd	2053
#5	'meta analysis'/exp OR 'systematic review'/exp OR 'scoping review'/exp OR 'rapid review'/exp OR 'umbrella review'/exp OR 'cochrane database of systematic reviews'/jt OR 'network meta-analysis'/exp OR 'networkmeta analy*':ti,ab,kw OR 'networkmetaanaly*':ti,ab,kw OR metaanaly*:ti,ab,kw OR 'meta analy*':kw OR metanaly*:ti,ab,kw OR prisma:ti,ab,kw OR prospero:ti,ab,kw OR metaanali*:ti,ab,kw OR 'meta anali*':ti,ab,kw OR metanali*:ti,ab,kw OR ((meta NEAR/1 analy*):ab,ti) OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab,kw) OR (((structured OR systemic*) NEAR/3 (review* OR overview* OR synth*) NEAR/3 literature):ti,ab,kw) OR ((systemic* NEAR/1 review*):ti,ab,kw) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab,kw) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab,kw) OR (((literature NEAR/3 (review* OR overview*)):ti,ab,kw) AND (search*:ti,ab,kw OR database*:ti,ab,kw OR 'data base*':ti,ab,kw)) OR (('data extraction*':ti,ab,kw OR 'data source*':ti,ab,kw) AND ('study selection*':ti,ab,kw OR 'studies selection*':ti,ab,kw)) OR ('search strateg*':ti,ab,kw AND 'selection criteria*':ti,ab,kw) OR ('data source*':ti,ab,kw AND 'data synth*':ti,ab,kw) OR medline*:ab OR pubmed*:ab OR 'pub med*':ab OR embase:ab OR cochrane*:ab,jt OR (((critical* OR rapid*) NEAR/2 (review* OR overview* OR synth*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synth*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynth*:ti,ab,kw OR 'meta synth*':ti,ab,kw OR 'review* of review*':ti,ab,kw OR psycinfo:ab OR 'data extraction':ab OR cinahl:ab	1217979
#6	'randomized controlled trial'/exp OR 'clinical trial'/exp OR 'randomization'/de OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'triple blind procedure'/exp OR 'crossover	4603672

	procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR ((random* NEAR/2 (trial OR study)):ti,ab) OR ((random* NEAR/10 (trial OR trail OR 'clinical trial' OR 'clinical trail' OR 'clinical study' OR 'multicenter study' OR crossover OR 'cross over')):ti) OR ((('single blind*' OR 'double blind*' OR 'triple blind*' OR 'quadruple blind*') NEAR/4 (study OR trial OR trail OR design)):ti,ab) OR ((random* NEAR/3 distribut* NEAR/7 group*):ti,ab) OR (((pragmatic OR practical) NEAR/1 ('clinical trial' OR 'clinical trail')):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 (trial OR trail)):ti,ab) OR ((random* NEAR/4 ('cross over*' OR crossover*)):ti,ab) OR ((phase NEAR/5 ('clinical trial' OR 'clinical trail')):ti) OR ((random* NEAR/3 phase NEAR/3 (trial OR trail OR study)):ti,ab) OR randomi*:ti,ab OR rct:ti,ab OR 'random* control*':ti,ab OR placebo*:ti,ab OR randomly*:ti,ab	
#7	'major clinical study'/de OR 'clinical study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'cohort analysis'/de OR '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 ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti) 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 OR controls) 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* 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 quadruple 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 (('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))) OR (((pretest OR 'pre test') NEAR/2 (posttest OR 'post test')):ti,ab,kw)	19363082
#8	#4 AND #5	160
#9	#4 AND #6 NOT #8	345
#10	#4 AND #7 NOT (#8 OR #9)	768

#11	#8 OR #9 OR #10	1273

Ovid/Medline

#	Searches	Results
1	((Neoplasm Metastasis/ and Brain Neoplasms/) or ((brain or cerebr* or intracerebr* or intracrani* or cerebellar or mening* or brainstem* or 'central nervous system' or cns) adj3 (metasta* or micromet* or macromet* or oligomet* or spread* or carcinomatosis or carcinosis or secondar* or seeding or seeded or disseminat* or migrat* or tumor* or tumour* or cancer* or carcinoma*)).ti,ab,kf. or exp Cranial Fossa, Posterior/ or 'posterior fossa'.ti,ab,kw. or 'posterior cranial fossa'.ti,ab,kw. or 'intracranial activity'.ti,ab,kf. or 'intracranial cohort*'.ti,ab,kf.) and (exp Melanoma/ or melanoma*.ti,ab,kf. or nevocarcinoma*.ti,ab,kf. or naevocarcinoma*.ti,ab,kf. or 'pigmentary cancer*'.ti,ab,kf.)	5538
2	(systemic adj3 (therap* or treatment*)).ti,ab,kf. or exp Immunotherapy/ or immunotherap*.ti,ab,kf. or 'immuno* therap*'.ti,ab,kf. or immunetherap*.ti,ab,kf. or 'immune therap*'.ti,ab,kf. or chemoimmunotherap*.ti,ab,kf. or exp Immune Checkpoint Inhibitors/ or exp CTLA-4 Antigen/ or ((checkpoint or 'check point*' or immunocheckpoint*) adj3 (inhibit* or block* or therap*)).ti,ab,kf. or (('PD 1' or pd1 or 'PD L1' or pdl1 or 'programmed death 1' or 'programmed cell death 1' or 'programmed cell death protein 1' or 'programmed death ligand 1' or CTLA4 or 'CTLA 4' or 'cytotoxic T lymphocyte antigen 4') adj2 (anti* or inhibit* or block*)).ti,ab,kf. or exp Ipilimumab/ or ipilimumab.ti,ab,kf. or yervoy.ti,ab,kf. or 'pembrolizumab'.ti,ab,kf. or exp Nivolumab/ or 'nivolumab'.ti,ab,kf. or exp Vemurafenib/ or 'vemurafenib'.ti,ab,kf. or til.ti,ab,kf. or (('tumor infiltrating lymphocyt*' or 'tumour infiltrating lymphocyt*' or til) adj3 therap*).ti,ab,kf. or exp Molecular Targeted Therapy/ or Precision Medicine/ or ((targeted or tailored or personalize* or personalise* or individualize* or individualise* or precision) adj3 (therap* or oncotherap* or medicine or oncomedicine or treatment* or oncolog*)).ti,ab,kf. or 'dabrafenib'.ti,ab,kf. or 'cobimetinib'.ti,ab,kf. or 'gdc 0973'.ti,ab,kf. or 'gdc0973'.ti,ab,kf. or 'trametinib'.ti,ab,kf. or Proto-Oncogene Proteins B-raf/ai or ((braf or 'b raf') adj3 (inhibit* or block*)).ti,ab,kf. or 'encorafenib'.ti,ab,kf. or 'lgx 818'.ti,ab,kf. or 'lgx818'.ti,ab,kf. or 'binimetinib'.ti,ab,kf. or mektovi.ti,ab,kf.	926565
3	(1 and 2) not ((exp animals/ or exp models, animal/) not humans/) not ((letter/ or comment/ or editorial/) not (exp Clinical Trial/ or exp Meta-Analysis/ or exp Scoping Review/ or exp Systematic Review/))	1654
4	limit 3 to dt="20180806-20251231"	997
5	exp Meta-Analysis/ or exp Network Meta-Analysis/ or exp Systematic Review/ or networkmeta analy*.ti,ab,kf. or networkmetaanaly*.ti,ab,kf. or metaanaly*.ti,ab,kf. or meta analy*.kf. or metanaly*.ti,ab,kf. or prisma.ti,ab,kf. or prospero.ti,ab,kf. or metaanali*.ti,ab,kf. or meta anali*.ti,ab,kf. or metanali*.ti,ab,kf. or (meta adj1 analy*).ab,ti. or ((systemati* or scoping or umbrella or structured literature) adj3 (review* or overview*)).ti,ab,kf. or ((structured or systemic*) adj3 (review* or overview* or synth*) adj3 literature).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* or overview*)) and (search* or database* or data base*)).ti,ab,kf. or ((data extraction* or data source*) and (study selection* or studies selection*)).ti,ab,kf. or (search strateg* and selection criteria*).ti,ab,kf. or (data source* and data synth*).ti,ab,kf. or medline*.ab. or pubmed*.ab. or pub med*.ab. or embase.ab. or cochrane*.ab. or ((critical* or rapid*) adj2 (review* or	917386

	overview* or synth*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synth*)) and (search* or database* or data base*)).ab. or metasynth*.ti,ab,kf. or meta synth*.ti,ab,kf. or psycinfo.ab. or data extraction.ab. or cinahl.ab. or cochrane.jw.	
6	exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (random* adj2 (trial or study)).ti,ab. or (random* adj10 (trial or trail or clinical trial or clinical trail or clinical study or multicenter study or crossover or cross over)).ti,ab,kf. or ((single blind* or double blind* or triple blind* or quadruple blind*) adj4 (study or trial or trail or design)).ti,ab. or (random* adj3 distribut* adj7 group*).ti,ab. or ((pragmatic or practical) adj1 (clinical trial or clinical trail)).ti,ab. or ((non inferiority or noninferiority or superiority or equivalence) adj3 (trial or trail)).ti,ab. or (random* adj4 (cross over* or crossover*)).ti,ab. or (phase adj5 (clinical trial or clinical trail)).ti. or (random* adj3 phase adj3 (trial or trail or study)).ti,ab. or randomi*.ti,ab. or rct.ti,ab. or random* control* clinical trial.ti,ab. or random* control* clinical trail.ti,ab. or random* control*.ti,ab. or placebo*.ti,ab. or randomly*.ti,ab.	2163019
7	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 or controls) 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 quadruple 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.)) or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ or ((pretest or pre test) adj2 (posttest or post test)).ti,ab,kf.	8289547
8	4 and 5	84
9	(4 and 6) not 8	81
10	(4 and 7) not (8 or 9)	373
11	8 or 9 or 10	538

Bijlage bij Module 4.10 Veiligheid continueren systemische therapie tijdens radiotherapie voor hersenmetastasen

Search and select

A systematic review of the literature was performed to answer the following question(s):
Which combinations of systemic therapy with intracranial radiotherapy are not safe?

Table 1. PICO

Patients	patients with brain metastases who are eligible for systemic therapy with concurrent radiotherapy;
Intervention	systemic therapy with concurrent intracraniële radiotherapy;
Control	as stated in the study
Outcomes	Critical: Safety (neuro)toxicity or symptomatic radionecrosis (at least grade 3)
Other selection criteria	Study design: systematic reviews and randomized controlled trials

Relevant outcome measures

The guideline panel considered Safety and (neuro)toxicity or symptomatic radionecrosis (at least grade 3) as **critical outcome measurements** for decision making; and no important outcome measurements was considered for decision making.

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

Search and select (Methods)

A systematic literature search was performed, which resulted in a large body of literature across different drug classes. Among these, a series of publications developed by the European Society for Medical Oncology (ESMO) and the European Society for Radiotherapy and Oncology (ESTRO) was identified. This series provides joint clinical safety statements regarding the combination of radiotherapy with targeted cancer therapies (excluding antibody–drug conjugates) and immunotherapy (with a focus on immune checkpoint inhibitors), covering both clinical toxicity data and biological interaction mechanisms (van Aken, 2025). The working group decided to adopt this series of ESMO–ESTRO consensus statements as the guiding framework for this module.

Summary of literature

In the series of ESMO–ESTRO consensus statements, based on the expected risk, safety recommendations were defined a priori in four scenarios: not combining both treatments, major treatment adaptation, or minor/no treatment adaptation. The definitions of the safety measures per scenario are presented in **Figure 1**.

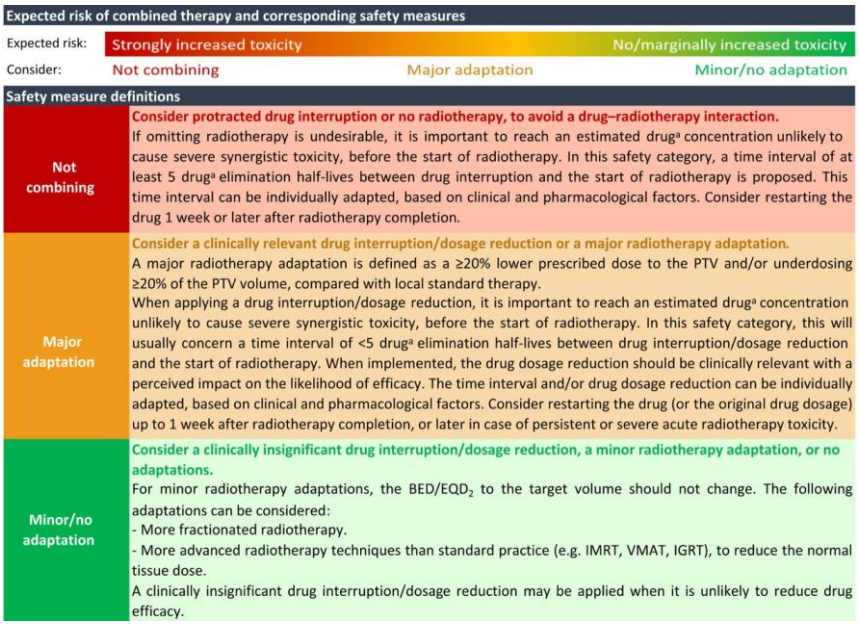

Figure 1. Predefined safety measure definitions for combining targeted agents with radiotherapy, based on the expected risk.
BED, biologically equivalent dose; EQD 2 , equivalent dose in 2 Gy fractions; IGRT , image-guided radiotherapy; IMRT, intensity-modulated radiotherapy; PTV, planning target volume; VMAT , volumetric-modulated arc therapy.
a Drug or active drug metabolites.
***Resource**: ESMO-ESTRO consensus statements (van Aken, 2025)*

In the next step, a systematic review was performed for each included drug class to evaluate the toxicity associated with combining RT with different targeted therapies and immunotherapies. Only studies in which RT and immunotherapy or targeted therapy were administered concurrently were included. Concurrent treatment was defined as a maximum interval of 5 drug half-lives before RT or up to 2 weeks after RT between drug administration and RT.

Thereafter, a modified Delphi process was conducted among a total of 20 experts, equally divided between ESMO and ESTRO representatives. During this process, panel members were required to use the provided literature database and to consider any additional evidence known to them when voting on whether they agreed or disagreed with each proposed safety statement for the different drug–RT combinations. The agreement rates for each statement are presented in **Table 1**. Agreement rates ≥90% were considered strongly recommended.

To generate drug-specific and irradiated area–specific safety recommendations, each drug target–specific systematic literature review was subdivided into six irradiated area–specific reviews: skin, brain, head and neck, thorax, abdomen/pelvis, and musculoskeletal tissues. In this module, only data related to irradiation of the brain were extracted and used.

All reviewed drug classes, including detailed recommendations and agreement rates from the modified Delphi process, are presented in **Table 1** below.

Table 1. Consensus statements on the safety of combining immunotherapy, targeted therapy with radiotherapy

	Drug examples	Radiotherapy scenario*	Recommendation	Agreement rate	Level of evidence
PD-(L)1 inhibitors	nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab	Low-dose palliative High-dose conventionally fractionated High-dose stereotactic	Minor/no adaptation Minor/no adaptation Minor/no adaptation	100% 100% 100%	III IV III
CTLA-4 inhibitors	ipilimumab, tremelimumab	Low-dose palliative High-dose conventionally fractionated High-dose stereotactic	Minor/no adaptation Minor/no adaptation Minor/no adaptation	100% 95% 95%	III IV III
VEGF(R) inhibitors	bevacizumab, ramucirumab, aflibercept	Low-dose palliative High-dose conventionally fractionated High-dose stereotactic	Major adaptation (no consensus) Major adaptation Major adaptation	60% 95% 95%	I I IV
Multitargeted TKI	cabozantinib, lapatinib, pazopanib, sorafenib, sunitinib, vandetanib	Low-dose palliative High-dose conventionally fractionated High-dose stereotactic	Major adaptation Major adaptation Major adaptation	75% 80% 85%	III III V
CDK 4/6 inhibitors	palbociclib, abemaciclib, ribociclib	Low-dose palliative High-dose conventionally fractionated High-dose stereotactic	Major adaptation Major adaptation Major adaptation	100% 100% 100%	**V** **V** **V**
PARP inhibitors	olaparib, niraparib, veliparib, talazoparib, rucaparib	Low-dose palliative High-dose conventionally fractionated High-dose stereotactic	Major adaptation Major adaptation Major adaptation	94% 94% 94%	**II** **II** **V**
mTOR inhibitors	sirolimus, temsirolimus, everolimus	Low-dose palliative High-dose conventionally fractionated High-dose stereotactic	Minor/no adaptation Major adaptation Major adaptation	100% 100% 100%	**II**[a] **II** **III**
anti-HER2 monoclonal antibodies	trastuzumab pertuzumab	Low-dose palliative High-dose conventionally fractionated High-dose stereotactic	Minor/no adaptation Minor/no adaptation Minor/no adaptation	100% 94% 94%	**II** **V** **IV**
EGFR inhibitors	Gefitinib Erlotinib Cetuximab	Low-dose palliative High-dose conventionally fractionated High-dose stereotactic	Minor/no adaptation Major adaptation Major adaptation	89% 95% 100%	**II** **III** **II**
ALK inhibitors	alectinib brigatinib ceritinib crizotinib lorlatinib	Low-dose palliative High-dose conventionally fractionated High-dose stereotactic	Major adaptation Major adaptation Major adaptation	100% 100% **95%**	**V** **V** **IV**
BRAF/MEK inhibitors	vemurafenib dabrafenib trametinib	Low-dose palliative High-dose conventionally fractionated High-dose stereotactic	Major adaptation Major adaptation Major adaptation	100% 100% 100%	**IV** **IV** **IV**

Abbreviations:
***** Examples of these three scenarios are provided in the original ESMO–ESTRO consensus article. As these scenarios are not applied in clinical practice in the Netherlands for intracranial metastases, they are not presented here.
PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T lymphocyte antigen 4; VEGF(R), vascular endothelial growth factor (receptor)
[a]Level of evidence based on data from high radiotherapy dose scenarios.

Table 2 Summary and details of the systematic reviews among patients with brain metastasis in the ESMO-ESTRO consensus statement*

Drug	Summary	Details from the systematic review in ESMO-statement
PD-(L)1 inhibitors	The combination of brain RT concurrently with ICIs appears generally safe. However, some studies report an (often not statistically significant) increased risk of radionecrosis.	A monocentric analysis of a **phase I/II study** combined durvalumab (10 mg/kg every 2 weeks) with RT in 10 patients, including brain SRT for 3 lesions. For these brain lesions, no toxicity was observed [14]. In a large **retrospective study**, use of PD-1 inhibitors only (n=48) was compared with PD-1 inhibitors + RT (n=153). 51 patients received brain RT, but were not seperately analyzed. In the group receiving no RT, only 2 patients had brain metastases. Both factors limit the interpretability of this study for brain RT. Overall, G3-4 toxicity was manageble in the RT group, with fatigue in 4.9%, vertigo in 1.4% and headache in 1.4% [15]. In a **retrospective study** analyzing nivolumab + ablative/palliative RT in 20 patients with metastases from lung or kidney cancer, no intracranial G3-4 toxicity was observed in patients receiving ablative RT (n=4) or palliative RT (n=4) for brain metastases [16].
CTLA-4 inhibitors		A **phase I study** combined ipilimumab concurrently with WBRT (n=5) or 2 days after SRS (n=11) in patients with melanoma brain metastases. No G4-5 toxicity was observed. One G3 headache after SRS, before start of immunotherapy, one G3 hypophysitis (WBRT) one G3 fatigue (WBRT) were the only possibly RT-related G3 toxicities. Subclinical intracranial hemorrhage occurred in 4 SRS patients, but not in WBRT patients. For SRS, this resulted in a recommended ipilimumab dose of 10 mg/kg every 3 weeks. No radionecrosis was observed, but the median follow-up in the SRS arm was only 10.5 months. Due to slow accrual, safety was not demonstrated for ipilimumab doses higher than 3 mg/kg every 3 weeks for WBRT [17]. In a small **retrospective cohort study** (n=13) combining WBRT and ipilimumab (most patients 3 mg/kg) within 30 days for melanoma brain metastases, only one patient developed G3 toxicity (cognitive changes). Intratumoral hemorrhage occurred in all 10 patients with post-treatment imaging. 8 patients already had this at baseline, but all increased. Most were asymptomatic, but 4 patients developed new or worsening symptoms possibly related to the hemorrhage [18]. Intratumoral hemorrhage is common in melanoma brain metastases [19], but it is not clear if the use of ipilimumab has led to this exceptionally high rate. Moreover, the number of patients in this study is small.
PD-(L)1 and/or CTLA-4		In a **meta-analysis** comparing hypofractionated RT with vs. without ICIs for brain metastases, the risk of radionecrosis was higher with ICIs, but the difference was not significant (OR 1.35, p=0.361). There was also no significant difference in the risk of haemorrhage (OR 1.15, p=0.738) [20]. Another **meta-analysis** also showed a slightly, but not significantly increased radionecrosis risk for the combination of SRS with ICIs (OR 1.27, p=0.55) [21]. In another **meta-analysis**, two analysis types were performed. Odds ratio analysis of 10 studies revealed a significantly increased risk of radionecrosis for the combination of RT with ICIs vs. RT alone (OR 1.75, p=0.041). However, incidence rate analysis on 23 studies revealed a non-significant increase of radionecrosis: 9% vs. 6% (p=0.37). No clear differences were observed regarding the timing of ICIs in relation to RT [22]. A **retrospective study** compared stereotactic RT + ICIs (n=36) with stereotactic RT alone (n=179) for brain metastases from various primary tumor types. The 1-year radionecrosis risk was 7% for RT alone and 4% for RT + ICIs (p=0.25). On univariate and multivariate analysis, ICI use did not influence the radionecrosis risk. On multivariate analysis, only tumor size ≤2 cm did significantly reduce the risk of radionecrosis [23]. In a **retrospective study** (n=271) analyzing SRS for brain metastases from lung cancer and melanoma, 101 patients received immunotherapy, but only 13 concurrently. Among patients receiving ICIs, 1-year neurologic mortality was 9% in ICI-treated patients compared to 23% in ICI-

		naive individuals (p=0.01), but there were significant differences between the different SRS timings. Overall, 33% experienced neurologic toxicity requiring intervention. In patients receiving ICI treatment, G3-4 CNS toxicity occurred in 21%, but was not further specified [24]. In another **retrospective trial**, 57 patients received SRS and 21 received whole-brain RT combined with ICIs (within 30 days) for brain metastases. No G≥3 neurological toxicity was observed in the whole-brain RT group. In the SRS group, one G5 seizure (resulting in a ruptured aneurysm), one G3 nausea and one G3 paresthesia/weakness were observed. The risk of overall acute neurological toxicity was significantly higher with whole-brain RT, compared to SRS (OR 3.98, p=0.013) [25]. In a **retrospective trial** assessing the combination of RT with several different systemic treatments for melanoma metastases, 5 patients received brain RT concomitantly with immunotherapy (ipilimumab or nivolumab), without infield acute toxicity [26].
VEGF(R) inhibitors	Most prospective data are available for high-grade gliomas (HGGs). The most common toxicities of combined therapy are hematologic or extracranial, indicating that there is no absolute contraindication to combining VEGF inhibition with brain RT. However, radiation necrosis/pseudoprogression data are conflicting, as a large retrospective study shows higher radiation necrosis rates when combining VEGF TKIs with SRS for brain metastases, while in GBM patients, VEGF inhibitor use may decrease the radiation necrosis risk. Also, intracranial and extracranial bleeding risk may increase upon use of VEGF inhibitors. Furthermore, data regarding cognitive function and late toxicity are often limited.	In another **phase I study,** concurrent BEV and whole-brain radiation therapy for the treatment of brain metastasis from solid tumors appeared to be a tolerable treatment. Patients received 30 Gy in 15 fractions over 3 weeks for dose levels 0 (BEV 5 mg/kg/2 weeks), DL1 (10 mg/kg) and DL2 (15 mg/kg) and later 30 Gy in 10 fractions over 2 weeks for DL3 (15 mg/kg). In this study, 13/19 patients had breast cancer. DL3 of BEV with 30 Gy/10 fractions appeared to be the most suitable dose for phase II evaluation. No patients had G3-4 toxicity. Overall, 11/19 patients developed grade G1-2 treatment-related toxicity. Grade 2 arterial hypertension was observed in 3/9 patients. Grade 2 nausea, vomiting and lymphopenia were seen in 1 patient each at DL3 [25]. In a **retrospective analysis**, 376 renal cell carcinoma patients (on treatment with VEGF TKI or mTOR inhibitors) with brain metastasis were treated with either whole brain RT (39/164 with VEGF TKI), SRS (119/231 with VEGF TKI) or surgery (22/77 with VEGF TKI). Use of VEGF TKIs within a month of the SRS was associated with a significantly higher incidence of radiation necrosis (10.9% vs 6.4%; p=0.04). The increased risk of radiation necrosis with VEGF TKI use in the overall cohort was also seen in multivariate analysis (HR 1.29; 95% CI 1.04-2.10; p=0.045) [28].
Multitargeted TKI	Most studies do not report increased radiation-induced toxicity rates. Hematologic toxicities are common. However, late toxicity data are not always available, which warrants caution.	Lapatinib: Brain metastases: WBRT A **phase I (n=35) and a phase II (n=81) study** describe the combination with WBRT for brain metastases [20, 21]. In the **phase I trial**, an MTD of 1250 mg q.d. was determined. Most of the commonly occurring high-grade toxicities were not related to RT: G4 pulmonary embolism (n=2), G≥3 rash (n=4) and G3 diarrhea (n=6). Fatigue was observed in 1 (G4) and 2 (G3) patients [20]. In the **phase II trial**, lapatinib 1250 mg daily during RT and 1500 mg daily after RT was considered relatively safe, although 8 patients died during treatment, 4 possibly due to the study drug. Most common *treatment-related* G3-4 toxicities were diarrhea (7%), rash (5%), elevated Gamma-Glutamyl Transferase (GGT) (4%)

		and infection (4%) [21]. In both studies, specific late toxicity data and neurocognitive tests are missing, but the rate and nature of the mentioned toxicities do not suggest a substantial increase of RT-related toxicity. Lapatinib: Brain metastases: SRS **Two retrospectiv**e, probably largely overlapping studies about SRS for brain metastases show no increased radionecrosis rates [66, 67]. The largest study shows even lower rates of radionecrosis after 12 months in patients receiving lapatinib (n=24) (1.3% vs. 6.3%, p=0.001) [66]. Also in larger lesions (>1.5 cm), concurrent lapatinib was not associated with increased G≥2 radionecrosis risks [67]. Sorafenib In **one phase I trial** (n=23), the combination of sorafenib with single fraction or fractionated SRS for brain metastases was examined. No unexpected toxicities were observed. The RP2D was 400 mg b.i.d. [42]. In a retrospective study, sorafenib (400 mg b.i.d.) or sunitinib were combined with SRS for cerebral (29 sorafenib, 22 sunitinib) or spinal renal cell carcinoma metastases [31]. No unexpected toxicity rates or radionecrosis were observed [31]. A case report shows a good response after irradiation of a brain metastasis, combined with (temporarily paused) sorafenib, but also unexpected radiological, probably asymptomatic radionecrosis [70]. Sunitinib In **a phase II trial**, the addition of sunitinib (37.5 mg daily, paused from 2 days before until 2 days after RT) to profylactic cranial irradiation in 21 small-cell lung cancer patients did not increase intracranial toxicity [71]. In a phase Ib trial with 15 patients having a primary or metastatic CNS malignancy, partial brain or WBRT combined with sunitinib possibly caused a higher rate of G≥3 toxicities in the WBRT group (n=9) compared to WBRT alone in other studies, but the patient number was low. Two patients developed G5 toxicity (status epilepticus and pulmonary embolism), deemed unrelated to study therapy [51]. **In the retrospective study** mentioned earlier, sorafenib or sunitinib (50 mg daily) were combined with SRS for cerebral (29 sorafenib, 22 sunitinib) or spinal renal cell carcinoma metastases. No unexpected toxicity rates or radionecrosis were observed, but one patient developed G5 cerebral bleeding, considered related to disease progression [31]. A prospective study in metastatic renal cell carcinoma patients combing sunitinib (50 mg daily) with hypofractionated RT included 3 patients receiving brain RT and did not report increased intracranial toxicity [49]. Vandetanib In **a phase II trial**, vandetanib (100 mg q.d.) was combined with WBRT in 16 patients with melanoma brain metastases. Combined treatment was considered tolerable. Grade 3 confusion was the most common serious adverse event, with 19% (vandetanib) vs. 0% (placebo) [60].
CDK 4/6 inhibitors	Limited data are available regarding brain RT.	One retrospective study does not report increased toxicity for the concurrent (n=6) or sequential (n=18) combination of whole brain RT or stereotactic brain RT with CDK4/6 inhibitors. Neutropenia (83%) was the most common adverse event [14]. In several other studies, RT to the brain is combined with CDK4/6 inhibitors, without notable neurological toxicities [6-8, 11, 15-17]. However, low patient numbers, the inclusion of patients receiving RT to other tissues and inclusion of non-concurrently treated patients limit the possibility to draw brain-RT-specific conclusions from these studies.
PARP inhibitors	Combining PARP inhibitors with brain radiotherapy appears feasible up to	In a randomized, placebo-controlled **phase II trial**, WBRT was combined with veliparib (50 mg b.i.d. (n=103) or 200 mg b.i.d. (n=102)) in NSCLC patients with brain metastases. Unexpectedly, the total rate of G3-4 toxicity was even lower in the veliparib-treated groups, compared to

	certain PARP inhibitor doses, although long-term safety data, as well as possible effects on cognitive functioning are lacking. Also, no studies regarding the combination with stereotactic brain RT were identified. The most common (increased) toxicities are hematologic.	placebo (28% (50 mg) and 25% (200 mg), vs. 43% (placebo), p<0.05) [15]. A **phase I study** examining the combination of WBRT with veliparib in 81 patients with brain metastases, reported no unexpected toxicity rates, as long as the veliparib dose did not exceed 200 mg b.i.d. The most-occurring all-grade toxicities were fatigue (56%), nausea (40%), headache (36%) and alopecia (27%). The most-occurring G3-4 toxicities were fatigue (7%), hyponatremia (6%), lymphopenia (5%) and dehydration (5%) [16].
mTOR inhibitors	Hematological toxicity and infection risk may be most concerning when (chemo-)RT to the brain is combined with mTOR inhibitors. For stereotactic RT and radionecrosis risk, data are very limited.	One large retrospective study included the combination of mTOR inhibitors with WBRT/SRS for renal cell carcinoma brain metastases. Most patients used mTOR inhibitors combined with VEGFR TKIs. VEGFR TKI use, but not mTOR inhibitor use was significantly associated with increased radionecrosis risk in the multivariate analysis [26].
anti-HER2 monoclonal antibodies	The data considering brain RT combined with anti-HER2 monoclonal antibodies are limited, but do not indicate increased toxicity.	In one randomized phase III trial, 51 patients using trastuzumab were randomized between prophylactic cranial irradiation (PCI) and no PCI. G3 toxicity was seen in 3/24 patients receiving PCI: one G3 nausea and two G3 fatigue. Hospital Anxiety and Depression Scale, Quality of Life and Addenbrookes Cognitive Examination Questionnaire were not significantly different between PCI and no PCI [20]. In a retrospective trial concerning WBRT combined with trastuzumab (n=31), no WBRT-related G≥2 toxicity was observed [10]. For brain SRS, a retrospective trial shows no differences in the rate of radiation necrosis when combined with anti-HER2 monoclonal antibodies (combined therapy for 374 lesions) [21].
EGFR inhibitors	Most studies describe the addition of EGFR TKIs (and not monoclonal antibodies) to brain RT. Several studies suggest an increased risk of toxicities when EGFR inhibitors are combined with RT, but most RTrelated toxicities are moderately or insignificantly increased. The most relevant clinical data are summarized below.	In a meta-analysis comparing whole brain RT + erlotinib/gefitinib with whole brain RT alone, the rates of G3-4 dyspnea (OR 1.09), fatigue (OR 0.69), diarrhea (OR 1.37) and nausea/vomiting (OR 1.37) were not significantly different. However, there was a significantly lower risk of G3-4 myelosuppression in patients receiving combined therapy (OR 0.19, p=0.001) [19]. In a meta-analysis analyzing whole brain RT/stereotactic RT +/- EGFR TKIs for NSCLC brain metastases, the overall adverse event risk was higher in the RT+EGFR TKI group (20% vs. 12%, p=0.003), but the only significantly increased non-dermatological toxicity was G≥3 diarrhea (20% vs. 8%, p=0.02). Possibly RT-related toxicities, including G≥3 fatigue (21% vs. 13%), dizziness (26% vs. 19%) and nausea/vomiting (26% vs. 17%), occurred more often in the RT+EGFR TKI group, but the differences were not statistically significant [20]. In another meta-analysis in the same patient category, no significant differences were seen in non-dermatological adverse events of any grade [21]. A **phase III** trial comparing whole brain RT + SRS +/- erlotinib (150 mg q.d.) for NSCLC brain metastases showed a significantly higher risk of G≥3 toxicity in the erlotinib arm (n=41): 49% vs. 11% (p<0.001). The G≥3 toxicity rate in a third arm (n=40), with temozolomide instead of erlotinib, was 41%. Grade 4-5 toxicities were only observed in the erlotinib and temozolomide arms. In the erlotinib arm, G4 myocardial ischemia, G4 brain necrosis and G5 hemorrhagic stroke (all n=1) were reported. In the temozolomide arm, G4 cytopenia, G4 hypokalemia and G5 thrombocytopenia (all n=1). The frequency of specific G3 toxicities was not reported [22].

		A **randomized phase II** study adding gefitinib (250 mg q.d., n=16) or temozolomide (n=43) to whole brain RT for NSCLC brain metastases showed the following G3-4 toxicities in the gefitinib arm: G4 fatigue (n=1), G3 fatigue (n=2), G3 diarrhea, G3 mucositis and G3 dyspnea (all n=1). In the gefitinib arm, 3 patients discontinued therapy due to toxicity (asthenia, mucositis and diarrhea). Quality of life and cognitive function were analyzed, but not compared between the two treatment arms [25]. A placebo-controlled, **randomized phase II** trial adding erlotinib (100 mg q.d.) to whole brain RT in patients with multiple NSCLC brain metastases, did not show increased non-dermatological G3-4 toxicity in the erlotinib arm (n=40), compared to placebo (n=40) and an even lower rate of G3-4 fatigue (17.5% vs. 35%). Quality of life scores at 1 and 2 months after RT were comparable between the two arms [29]. A **phase I** study evaluating the addition of icotinib (125-625 mg t.i.d.) to whole brain RT in 15 patients with NSCLC brain metastases, showed a recommended dose of 375 mg t.i.d. Only at 500 mg t.i.d., G3 toxicity was observed (nausea in 2/6 and alanine aminotransferase elevation in 1/6 patients). Within the short follow-up of 20 weeks, no deterioration of neurocognitive function (MMSE) was observed. Whole brain RT did not increase the blood-brain barrier penetration of icotinib [30]. A large **prospective** study did not show significant toxicity differences between patients with lung adenocarcinoma brain metastases receiving Gamma Knife radiosurgery with (n=238) or without (n=370) EGFR TKI concurrently or after SRS. In both groups together, SRS-related G3-4 toxicity was observed in only 2%, but a non-significant trend was seen towards more SRS-related (all-grade) toxicity in the EGFR TKI group (HR 1.72, p=0.097) [31]. Some small, **retrospective** studies did not report increased toxicity when combining EGFR TKIs with intracranial RT [32-35].
ALK inhibitors	*In general, no high rates of ≥G3 toxicity are reported. Most data concern crizotinib use during radiotherapy, which has a limited blood brain barrier penetration [6, 9]. These results should therefore not be extrapolated to newer TKIs with a higher brain penetration rate. Furthermore, some relatively larger studies combine data from patients using ALK and EGFR inhibitors [10-14], which complicates interpretation of the ALK-specific results.*	One **retrospective study** in 29 patients concludes that gammaknife radiotherapy can be safely administered during crizotinib use [15]. Another **retrospective study** describes a higher rate of radionecrosis after SRS (stereotactic radiosurgery) (18% vs. 4% at 12 months, multivariable analysis, p<0.001) in ALK+ patients, but no significant association with concurrent ALK inhibitor use within 30 days of SRS, which took place in 15 patients [12]. **Nakashima et al.** show G3 otitis media in both patients who received whole brain radiotherapy (WBRT) with concurrent ALK inhibition (crizotinib and alectinib) and tinnitus complaints in one patient 33 months after WBRT [13]. One small **retrospective study** of 24 patients with mainly cerebral, bone and lung metastases describes G3 fatigue within 6 months after WBRT in 2/6 patients, but no unexpected side effects. However, they do not describe whether these patients received either crizotinib (ALK inhibitor) or erlotinib (EGFR inhibitor) [14]. **Borghetti et al.** do not report unexpected toxicities when SRS and non-SRS radiotherapy are combined with ALK (primarily crizotinib) or EGFR inhibitors within 30 days [10, 11]. Furthermore, the **case reports** do not clearly show extra toxicity of concurrent or sequential ALK TKI use [16-20]. Although it is not the scope of this review, it is noteworthy to mention that three **case-reports** describe severe radionecrosis after administration of alectinib or lorlatinib within 4 months up to 7 years after stereotactic radiotherapy [21-23]. It is unknown whether these findings are incidental or if ALK inhibitors may lead to an interaction with late normal tissue reactions to radiotherapy.
BRAF/MEK inhibitors	*A number of retrospective studies and case reports have been published with various methodologies, toxicity analyses*	In the study of **Hecht et al.** (2018), in both the concomitant vemurafenib (24 WBRT, 14 brain SRT) and dabrafenib (7 WBRT, 9 brain SRT) group, one patient was identified with a hemorrhagic brain metastasis. This toxicity did not occur in the (smaller) interrupted groups (vemurafenib 23 WBRT, 9 brain SRT; dabrafenib 5 WBRT, 7 brain SRT) [28]. One case with a hemorrhagic brain metastasis was mentioned in

	and time intervals between BRAFi ± MEKi and RT. In many studies, BRAFi/MEKi are temporarily paused. Although some studies show higher neurological toxicity rates when BRAFi/MEKi are combined with RT (concurrently or within a certain time interval), several other studies do not report increased toxicity. Combined therapy is therefore not an absolute contra-indication with regard to neurological toxicity, but due to the low quality and heterogeneity of the data, increased neurological toxicity cannot be ruled out. We found no studies investigating brain RT combined with a MEKi without a BRAFi.	**their earlier study** [27]. However, melanoma brain metastasis hemorrhage also regularly occurs without treatment [40, 41]. **Kroeze et al.** (2021) report more all-grade early (p=0.014) and late (p=0.009) toxicity when BRAFi/MEKi are continued during (multi-site) SRT, compared to interrupted SRT, but G≥3 toxicity is not increased. All toxicity in the BRAFi/MEKi group was CNS-related, but the toxicity details are not specified per treatment group [29]. Several small **retrospective studies** with often <30 patients receiving brain RT combined with BRAFi ± MEKi at different time intervals and with different RT techniques, do not show increased rates of radionecrosis, brain metastasis hemorrhage or other (high-grade) toxicities [26, 30-33, 42-45]. However, **Ly et al.** (2015) show a higher risk of brain metastasis hemorrhage in 17 patients treated with SRS and BRAFi with a median washout period of 7 days. The 1-year freedom from hemorrhage rate was 39.3% in patients with BRAFi and 77.0% in patients without BRAFi (p=0.0003). The 1-year local control rate with BRAFi was better (85.0% vs. 51.5%, p=0.0077) [46]. **Patel et al.** (2016) show a significantly higher risk of radiographic (HR=3.38, p=0.011) and symptomatic (HR=6.10, p≤0.001) radiation necrosis after SRS in patients treated with BRAFi vs. no BRAFi, although the majority (10/15) in the BRAFi group started BRAFi after SRS (median interval between SRS and BRAFi was 40 days) [47]. Other even **smaller studies and case reports** concerning brain SRT or WBRT show mixed results: some with severe neurological toxicity [16, 48, 49] and others with acceptable or no neurological toxicity [17, 19, 34, 50].

*The numbers in [ ] are the number of the reference in the original article. For the details of these cited studies please see the original article.

Agenderen-tabel

Vraag	***Antwoord*** *Kruis aan*	*Vul in*
A1. Is onderzoek wenselijk om de <u>uitgangsvraag of zoekvraag</u> (met meer/voldoende zekerheid) te kunnen beantwoorden?		Nee. *Tijdens de ontwikkeling van deze module is gebleken dat er volgens het cluster sprake is van passend bewijs voor de uitgangsvraag en zoekvraag.*
	x	Ja
A2. Wat is de kennisvraag?	Kennis-vraag	Wat is de veiligheid van radiotherapie voor hersenmetastasen in combinatie met systemische therapie, vergeleken met radiotherapie zonder systemische behandeling?
	P	Patiënten met hersenmetastasen
	I	Radiotherapie voor hersenmetastasen met systemisch therapie (zoals BRAF/MEK-, EGFR- en ALK-remmers bij longcarcinoom of melanoom)
	C	Radiotherapie voor hersenmetastasen zonder systemisch behandeling
	O	Veiligheid
A3. Waarom is dit een belangrijke kennisvraag?	Toelichting	Tijdens de ontwikkeling van deze module is gebleken dat er weinig bewijs van hoge kwaliteit beschikbaar is over de veiligheid van systemische therapie tijdens radiotherapie. Dit onderwerp is zeer breed, maar tegelijkertijd ook zeer relevant voor de klinische praktijk. Besluitvorming hierover vindt vaak plaats in een MDO, op basis van klinische ervaring en beperkt hoogwaardig bewijs. Daarom is het zeer wenselijk dat hiernaar onderzoek wordt gedaan. De werkgroep geeft aan dat de meest voorkomende situaties betrekking hebben op behandelingen met BRAF/MEK-, EGFR- en ALK-remmers bij longcarcinoom of melanoom.
A4. Welk onderzoeksdesign is passend om deze kennisvraag te beantwoorden?		RCT
	x	Observationeel onderzoek
		Kwaliteitsregistratie
		Anders, namelijk
	Toelichting	Prospectief cohort studie
A5. Zijn er een andere kennisvragen naar voren gekomen die passen bij het <u>onderwerp van de module</u>, maar niet hetzelfde zijn als de uitgangs- of zoekvraag en waar *geen* passend bewijs voor is?	x	Nee
		Ja

Implementeren-tabel

Vraag	*Antwoord:* *Kruis aan en licht toe/ beschrijf*		*Toelichting keuze:*
I1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?		**Ongewenste praktijkvariatie**	
	X	**Nieuwe evidentie**	Er komen steeds meer systemische therapieën beschikbaar voor patiënten met gemetastaseerde maligniteiten.
		Anders	
I2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?		**< 1000**	
	x	**< 5000** Toelichting: Inschatting gebaseerd op ca 3500ptn met hersenmetastasen per jaar	
		5000-40.000	
		> 40.000	
I3. Is de aanbeveling onderdeel van een bredere set interventies of verwant aan andere richtlijnen of modules? Zo ja, hoe verhoudt zij zich daartoe en moet hiermee rekening worden gehouden bij de implementatie, of kan de aanbeveling als losstaand worden beschouwd?		**Ja**	
	X	**Nee**	
I4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:		**Belemmerende factoren**	**Bevorderende factoren/ kansen**
Richtlijn/ klinisch traject (innovatie)		- Gebrek aan eenduidig bewijs voor veiligheid bij combinatie van specifieke systemische therapieën en radiotherapie. - Variatie in bestaande protocollen tussen centra (verschillende dosisaanpassingen, timing).	- Richtlijn biedt uniforme, evidence-based kaders waardoor variatie wordt verminderd. - Mogelijkheid om nieuwe klinische workflows te integreren (zoals monitoring bij combinatietherapie).
Zorgverleners (artsen en verpleegkundigen)		- Onzekerheid of angst voor verhoogde toxiciteit bij voortzetten van systemische therapie. - Wisselende kennis over interacties tussen radiotherapie en nieuwe doelgerichte	Richtlijn biedt duidelijkere handvaten en vergemakkelijkt gedeelde besluitvorming

		middelen of immunotherapie. - Extra coördinatie vereist tussen medische oncologie, radiotherapie en verpleegkundigen.	
Patiënt/ cliënt (naasten)		Onvoldoende inzicht in risico's van het combineren van therapieën, angst voor bijwerkingen.	Betere patiëntvoorlichting verhoogt therapietrouw
Sociale context		nvt	nvt
Organisatorische context		- Verschillen tussen ziekenhuizen in beschikbaarheid van radiotherapie, dagbehandeling, monitoringfaciliteiten. - Beperkte tijd en personeel voor intensievere coördinatie van gecombineerde behandelingen.	Standaardisatie van processen tussen afdelingen en centra
Financiële en juridische context		nvt	Nvt
I5. A) Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk? (kruis aan) **B) Wat is er nodig van deze personen/partijen om de aanbeveling in de praktijk te kunnen brengen?** *Denk aan aanpassingen in gedrag, werkwijzen, beleid, samenwerking of andere randvoorwaarden.*		**A**	**B**
	x	Patiënt/ cliënt (naaste)	
	x	Professional	Inclusief NVMO
	x	Beroepsvereniging, nl	alle bij deze module betrokken beroepsverenigingen (NIV, NVRO, NVALT)
		Ziekenhuis (raad van bestuur/UMCNL (voorheen NFU)/NVZ)	
		Zorgverzekeraars/ NZa	
		Zorginstituut [duiding nodig]	
		Anders	
I6. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	**x**	< 1 jaar	
		binnen 2-3 jaar	
I7. Conclusie: is er extra actie en/of ondersteuning nodig voor implementatie van de aanbeveling? *De reguliere implementatieroutes (publicatie en*		Ja	
	x	Nee	

disseminatie via officiele kanalen, opname in professionele standaarden, scholing en nascholing, gebruik van bestaande ICT systemen, audits en visitaties) van de richtlijnmodule alleen is onvoldoende.			
I8. Plaatsing op de Landelijke Implementatieagenda Medisch Specialistische zorg is gewenst. *Het gaat om zorg die (grotendeels) wordt uitgevoerd binnen de ziekenhuismuren. Succesvolle implementatie vraagt om actieve betrokkenheid en samenwerking van meerdere relevante partijen binnen de zorgpraktijk.*		Ja *	
	x	Nee	

**Deze aanbeveling komt mogelijk in aanmerking voor plaatsing op de Landelijke Implementatieagenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG), waarin alle betrokken partijen in de medisch-specialistische zorg samenwerken aan de implementatie van bewezen beste zorg. De Federatie levert namens het veld goed onderbouwde aanbevelingen aan, die zijn getoetst op de behoefte aan een implementatie-impuls. De onderwerpen op de Implementatieagenda zijn onderdeel van landelijke zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders. Voor de beoordeling van aanbevelingen uit richtlijnen wordt gebruikgemaakt van de implementatietabel. Op basis hiervan kunnen we de andere partijen goed informeren en gezamenlijk besluiten of plaatsing op de Implementatieagenda passend is.*