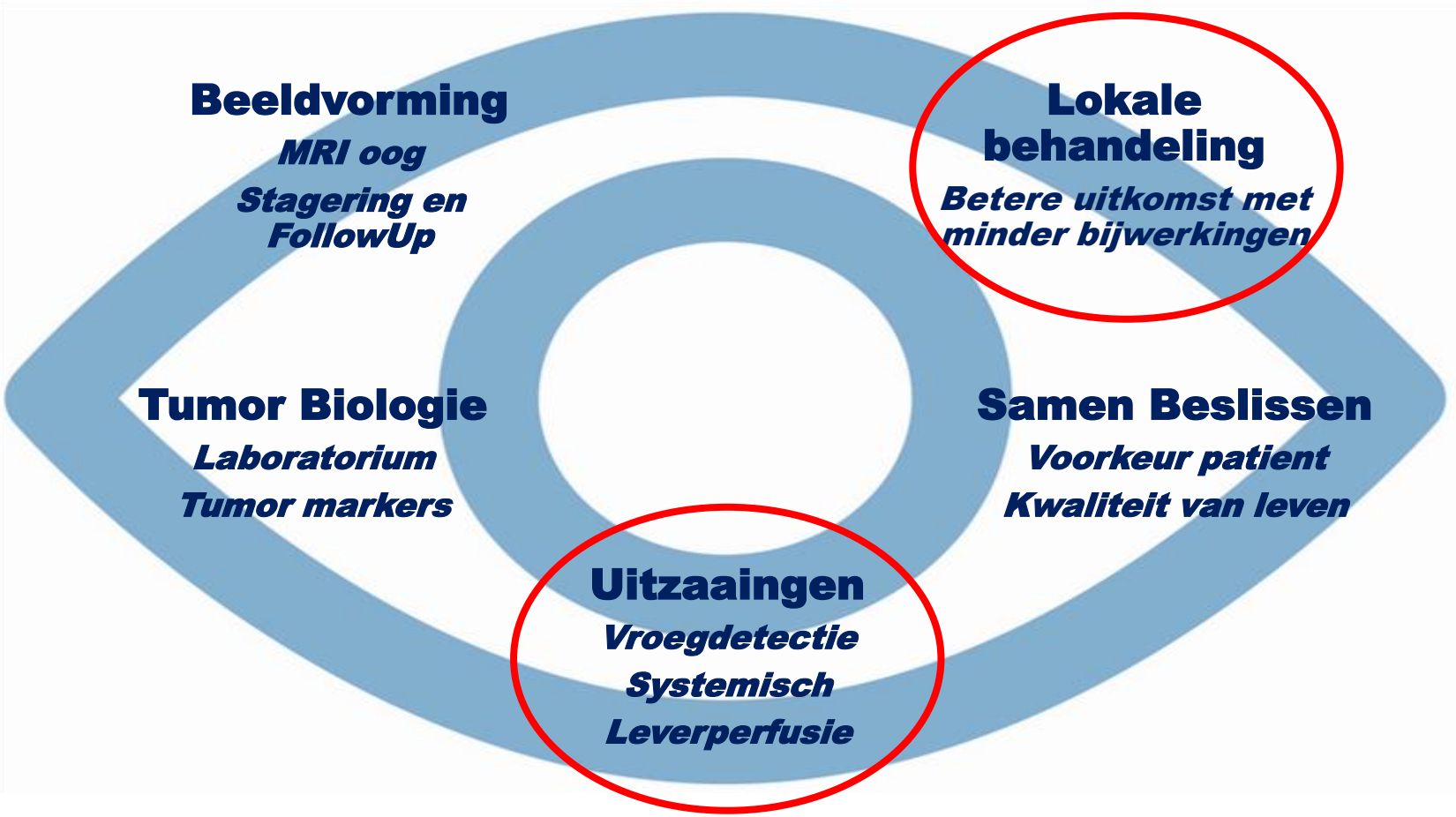
Leiden Ocular Tumor Center

Behandelmogelijkheden van uitgezaaid oogmelanoom en (neo)adjuvante behandeling

Ellen Kapiteijn, internist-oncoloog, LUMC

15 April 2026

Leiden Ocular Tumor Center



Overview

- Achtergrond primair en uitgezaaid oogmelanoom (uveamelanoom)

- Behandelingen

  -Lokale therapie: op de lever gerichte therapie

  -Systemische therapie, immunotherapie: ipilimumab/nivolumab, tebentafusp

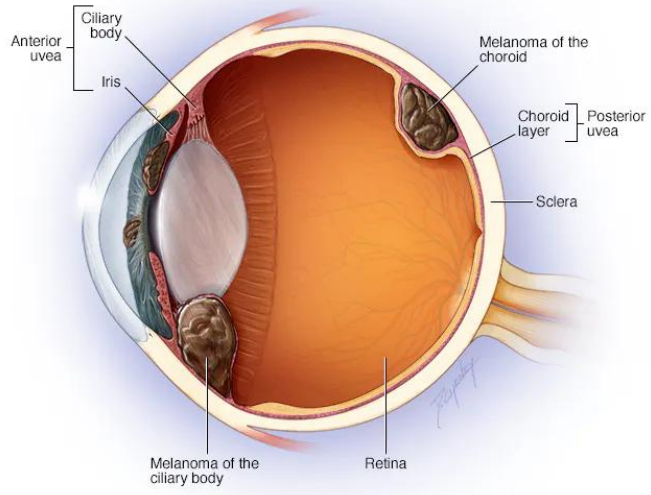
  -Systemische therapie, doelgerichte/targeted therapie: darovasertib/crizotinib

  -(Neo)adjuvante studies bij oogmelanoom zonder uitzaaiingen

- Conclusies

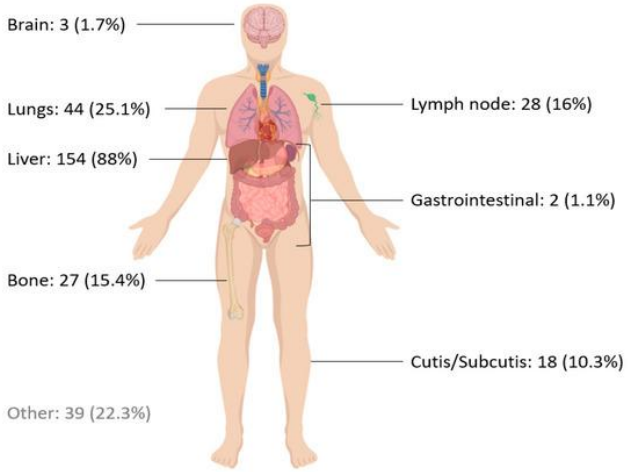
Achtergrond oogmelanoom (uveamelanoom)

- Zeldzame tumor (0.6-0.7 nieuwe ptn/100.000/jr)
- Primaire behandeling van het oogmelanoom is gericht op genezing: radiotherapie (ruthenium), proton bestraling of verwijderen oog
- Verschillen met huidmelanoom: GNA11 of GNAQ mutaties (ongeveer 90% in de uitgezaaide situatie), geen BRAF mutaties, lage mutatie load, lage PDL1-expressie



Achtergrond oogmelanoom (uveamelanoom)

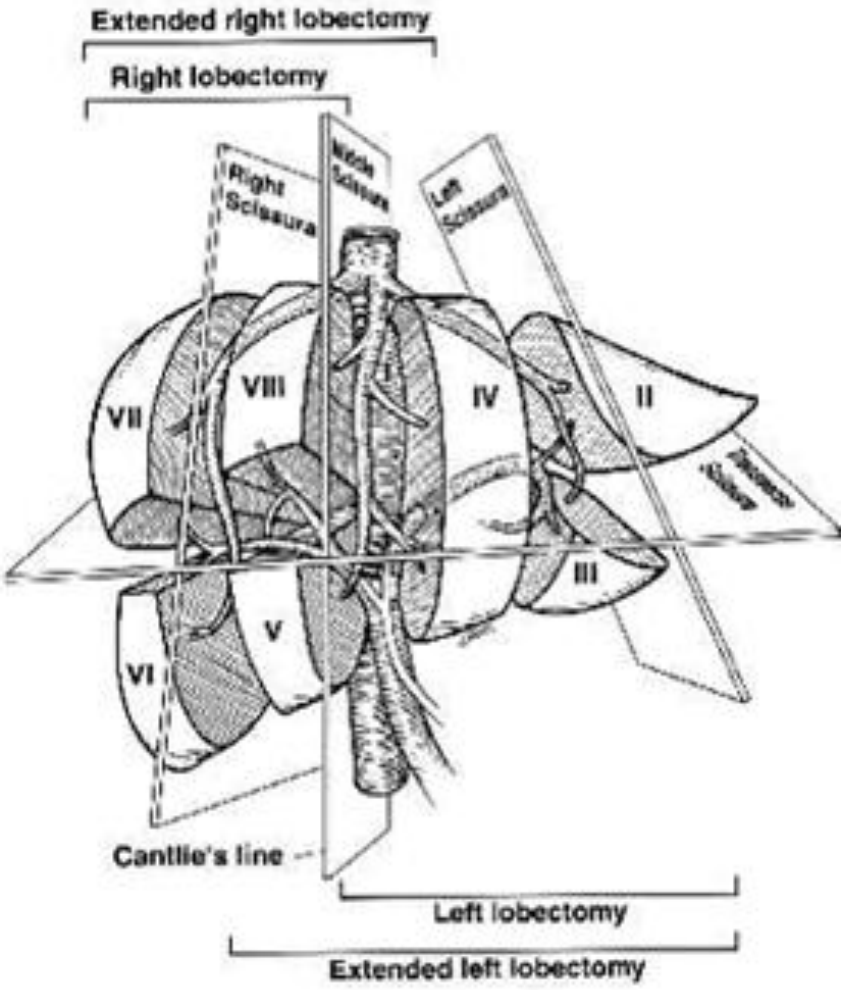
- Uitzaaiingen: < 5 yr: 30% van de ptn
  < 15 jr: 50% van de ptn
- Uitzaaiingen gaan meestal naar de lever (tot 90% van de ptn), longen (25%), botten (15%) en huid/subcutis (10%)
- Beperkte prognose in het geval van uitgezaaide ziekte: 7-8 mnd
- Khoja et al, Ann Oncol 2019: 29 fase II studies (lokale en systemische behandelingen): mediane overleving 10.2 mnd

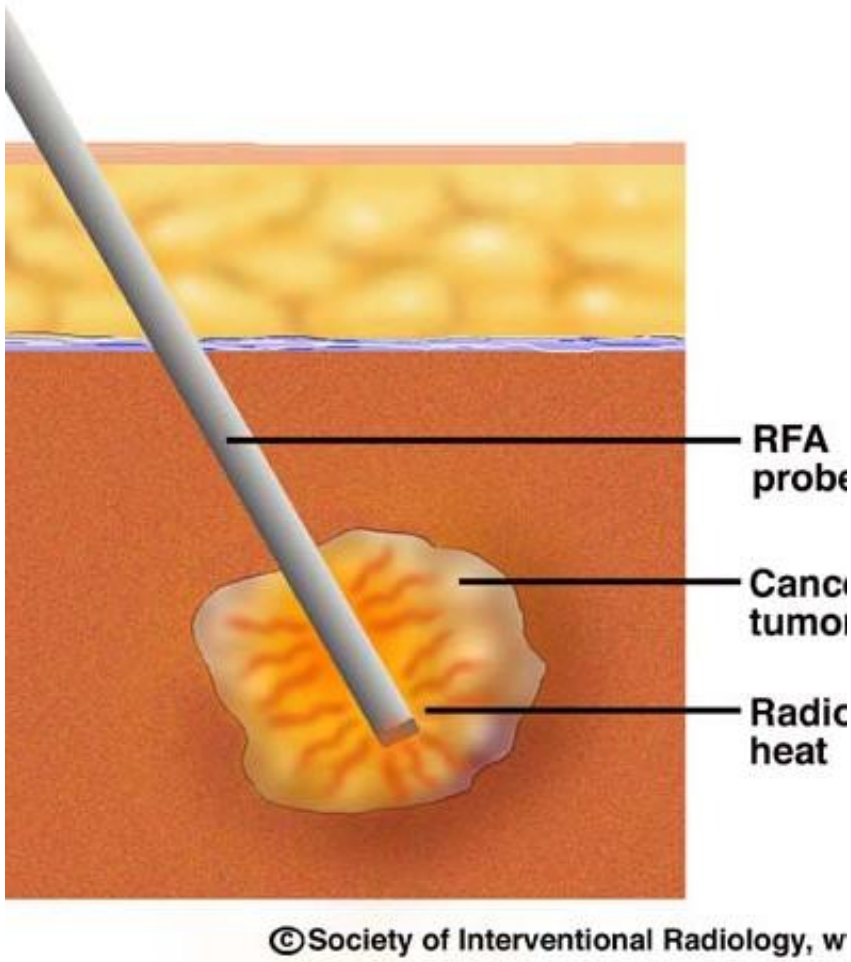


Lokale behandelingen

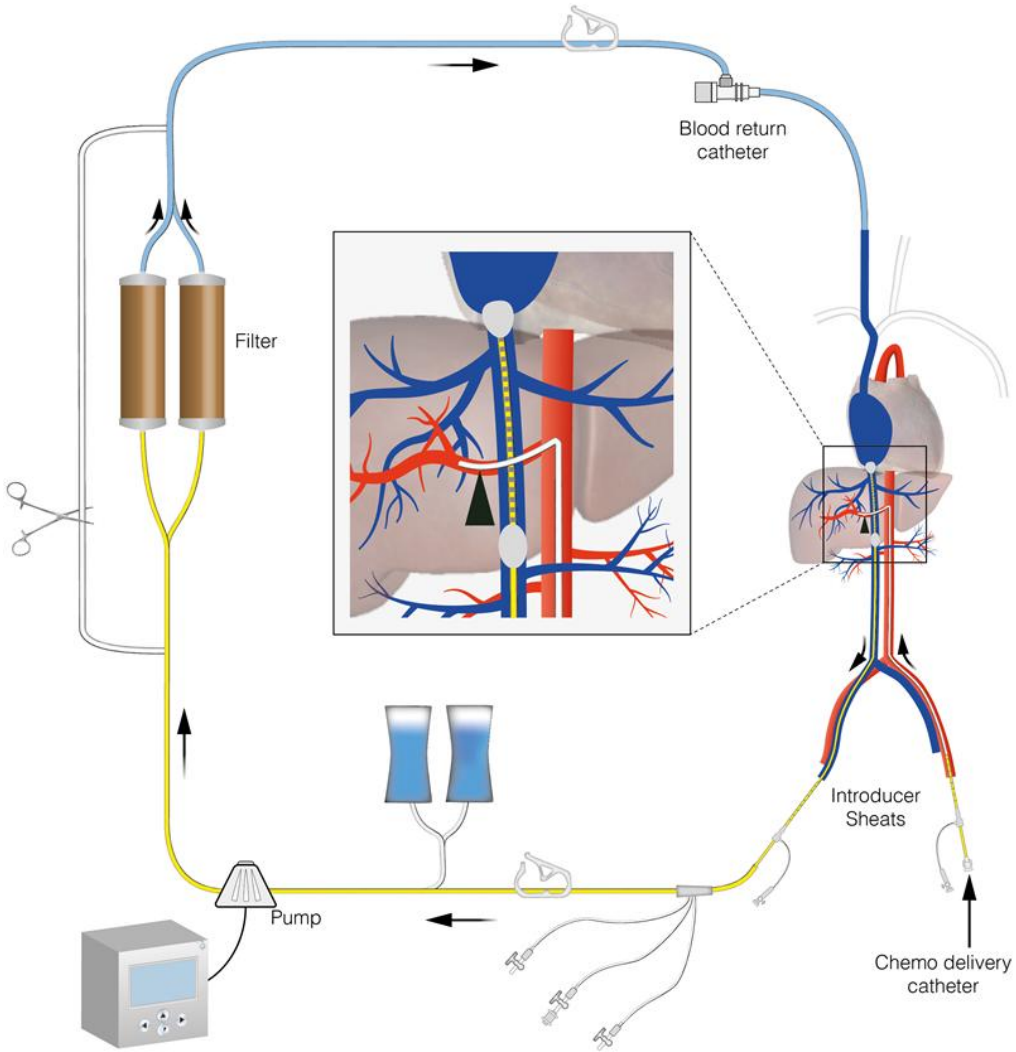
Operatie / radiofrequency ablation (RFA)

NB: maar bij <5% van de ptn mogelijk





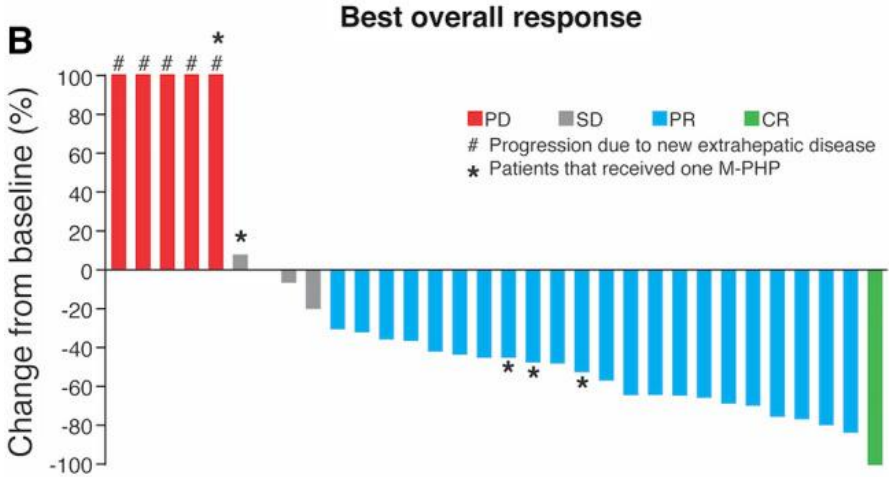
Percutane leverperfusie met melfalan (PHP)
Meijer et al, Ann Surg Oncol, 2020

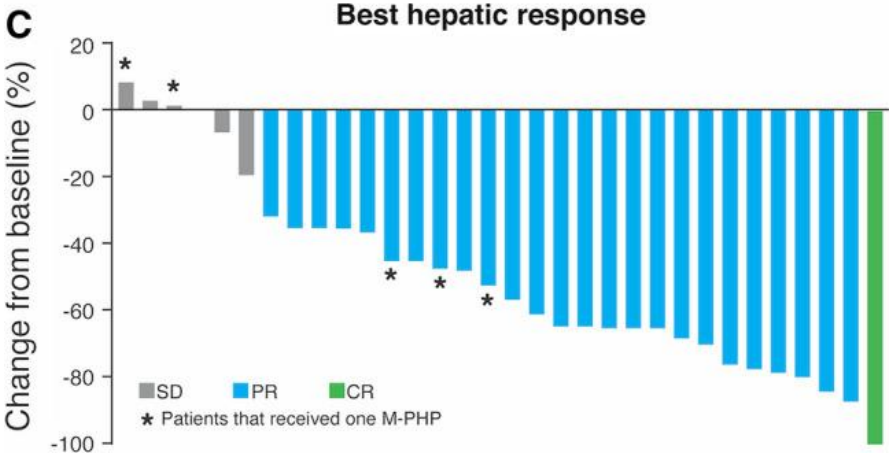


Meijer et al
Ann Surg Oncol 2020

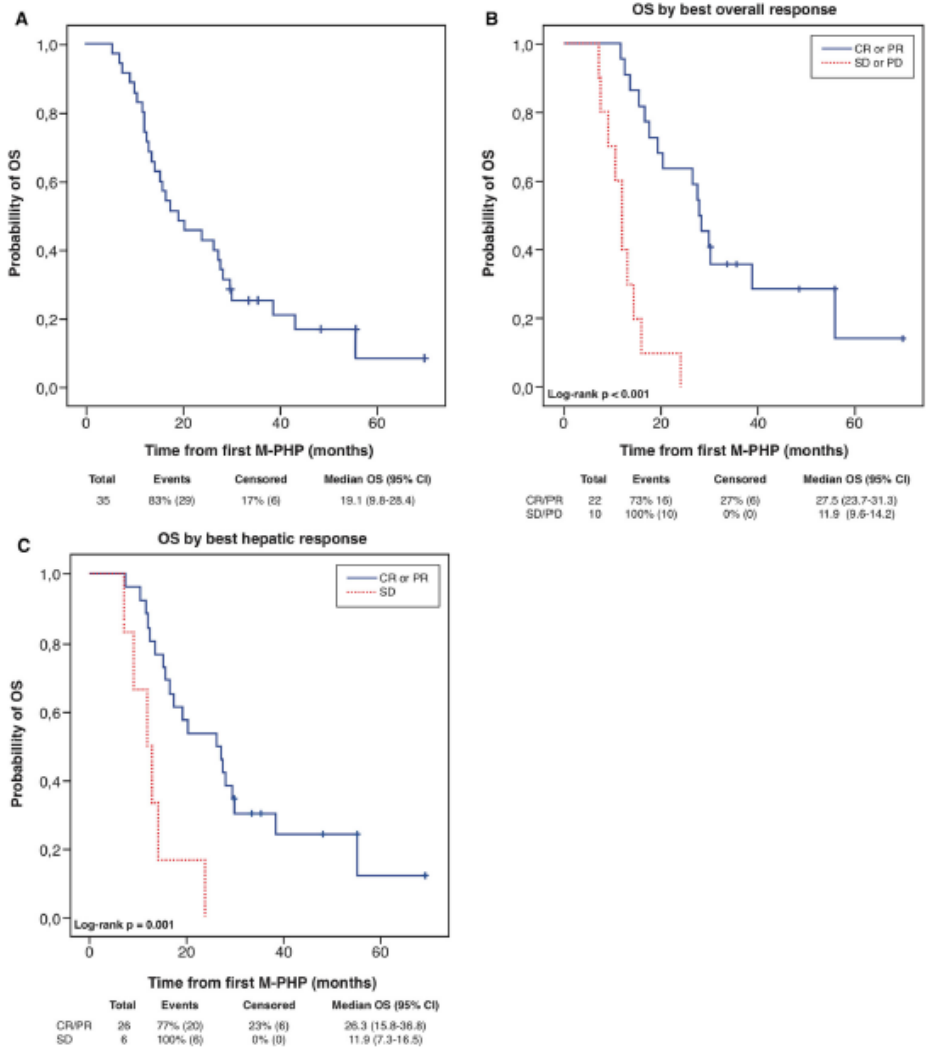
A

	Best overall response				Best hepatic response			
	All evaluable pts		pts with 2 M-PHPs		All evaluable pts		pts with 2 M-PHPs	
	N	%	N	%	N	%	N	%
CR	1	3	1	4	1	3	1	4
PR	22	69	19	70	25	78	22	82
SD	4	13	3	11	6	19	4	15
PD	5	16	4	15	0	0	0	0
Total	32	100	27	100	32	100	27	100





Percutane leverperfusie
Meijer et al, Ann Surg Oncol, 2020



Selectie van “goede” ptn is belangrijk:

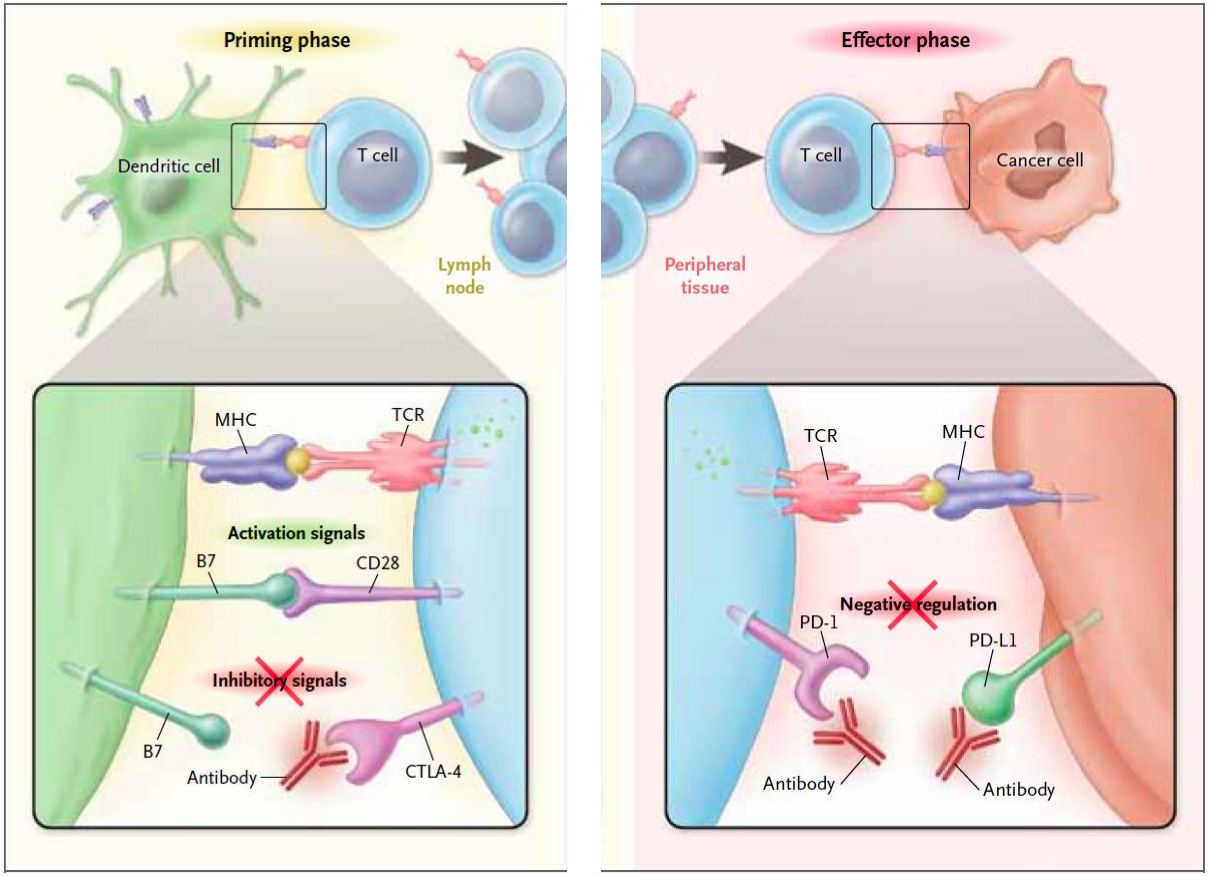
-normaal LDH/leverfuncties

-fit, geen andere ziekten

-< 80 jr

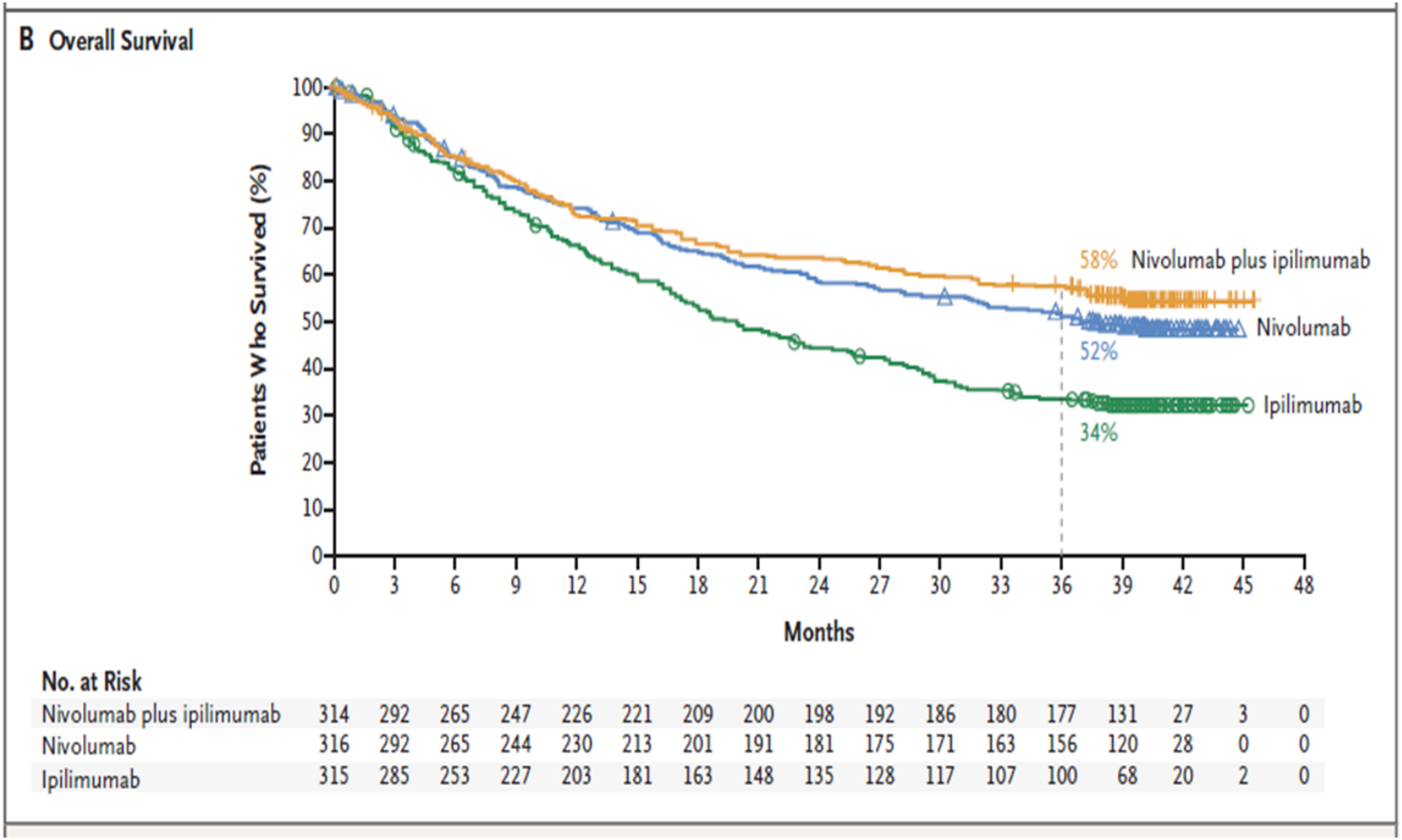
Immunotherapie

Immunotherapie met checkpoint-remmers



Ribas. N Engl J Med

Stadium IV huidmelanoom: Nivolumab /ipilimumab vs Nivolumab vs Ipilimumab, Wolchok et al, *NEJM 2017*



No. at Risk

Nivolumab plus ipilimumab	314	292	265	247	226	221	209	200	198	192	186	180	177	131	27	3	0
Nivolumab	316	292	265	244	230	213	201	191	181	175	171	163	156	120	28	0	0
Ipilimumab	315	285	253	227	203	181	163	148	135	128	117	107	100	68	20	2	0

Tabel 1. Combinatietherapie checkpoint-remmers bij oogmelanoom

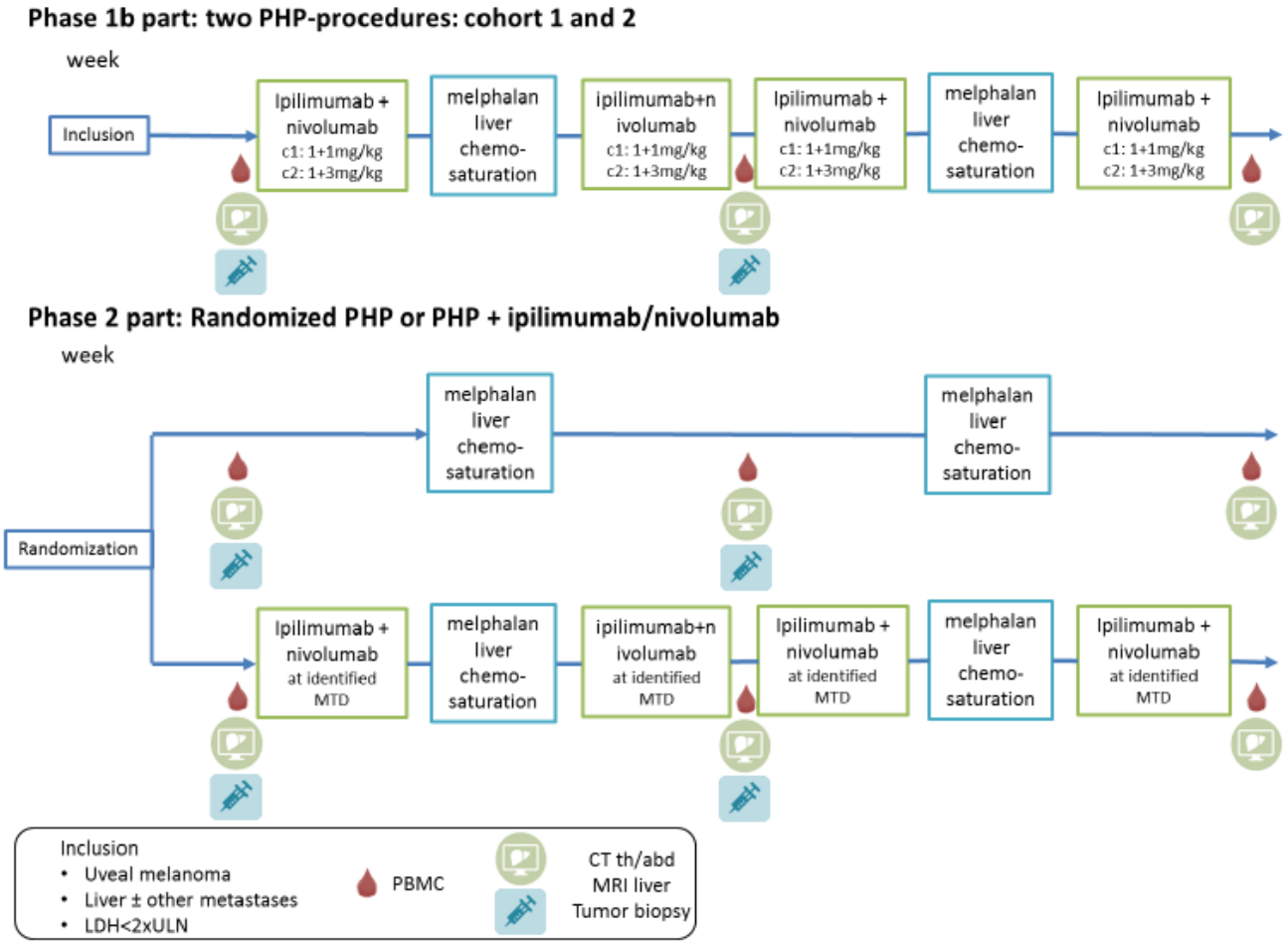
*5 patiënten niet meegenomen in de beoordeling gezien geen beschikbare scan voor evaluatie

Referentie	Aantal ptn	Design	Interventie	Uitkomsten	Locatie
Heppt, 2019	64	Retrospectieve analyse	IPI/NIVO	ORR 15.6% PFS 3.0 mnd OS 16.1 mnd	Duitsland
Bol, 2019	19	Retrospectieve analyse	IPI/NIVO	ORR 21.1% PFS onbekend OS onbekend	Denemarken
Najjar, 2020	89	Retrospectieve analyse	IPI/NIVO	ORR 11.6% PFS 2.7 mnd OS 15 mnd	Verenigde Staten
Pelster, 2021	30*	Fase II studie	IPI/NIVO	ORR 18% PFS 5.5 mnd OS 19.1 mnd	Verenigde Staten
Piulats, 2021	52	Fase II studie	IPI/NIVO	ORR 11.5% PFS 3.0 mnd OS 12.7 mnd	Spanje

Combinatie ipilimumab/nivolumab bij uitgezaaid oogmelanoom

- Ter vergelijking: respons bij uitgezaaid huidmelanoom is 40-50%.
- Veel graad 3-4 bijwerkingen is de keerzijde.
- Selectie van “goede” ptn lijkt belangrijk, met name ptn met alleen uitzaaiingen buiten de lever lijken het beter te doen (uitkomsten volgen uit de Dutch Melanoma Treatment Registry).

Lokale behandeling met immunotherapie: CHOPIN-studie in het LUMC; leverperfusie met of zonder ipilimumab/nivolumab



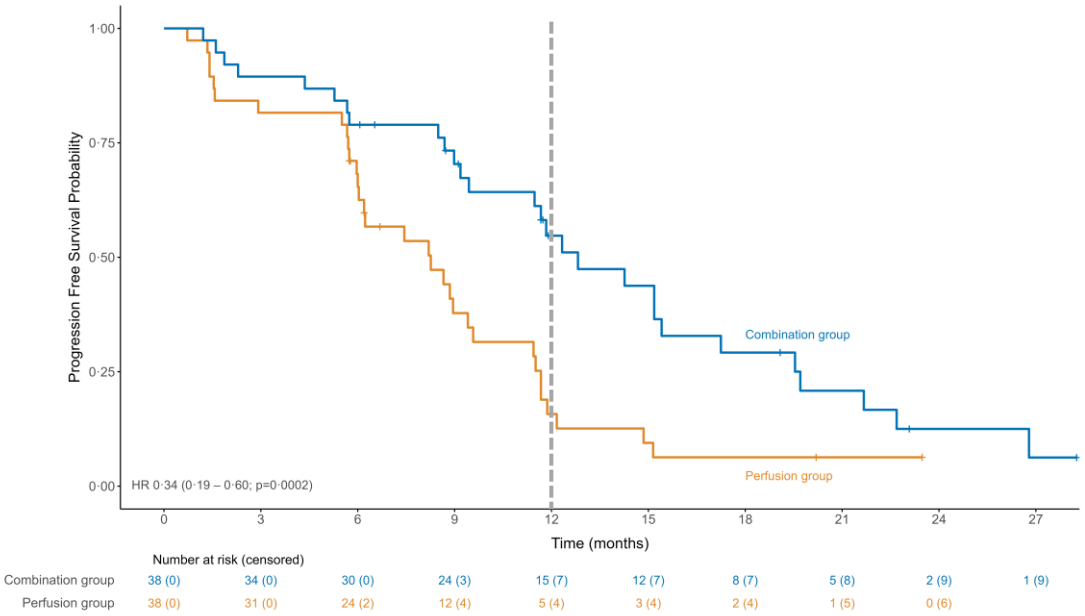
Combined Percutaneous Hepatic Perfusion with Ipilimumab plus Nivolumab in Metastatic Uveal Melanoma (CHOPIN): a single-centre, open-label, randomised, phase 2 trial

Ellen Kapiteijn, L. van den Hoek, F.M. Speetjens, S.M. Zunder, A.R. van Erkel, R.W. van der Meer, C.S.P. van Rijswijk, J. Lutjeboer, T.M.L Tong, M.A. Jonker-Bos, C.F.M. Roozen, S. Kropff, E.L. van Persijn van Meerten, C.H. Martini, R.W.M. Zoethout, M.E. Sitsen, F.G.J. Tijl, C.U. Blank, M.C. Burgmans

October 18th, 2025

Remt de combinatie-behandeling de groei van uitzaaiingen beter? Ja

Progression-free survival



	Combination (n = 38)	Perfusion (n = 38)	P-value
Events (%)	28 (73.7)	32 (84.2)	
1-year PFS, %	54.7	15.8	
[95% CI]	[36.8-69.5]	[5.8-30.1]	
Median PFS, months	12.8	8.3	
[95% CI]	[9.2-15.4]	[6.0-9.6]	
Hazard ratio	0.34		<0.001
[95% CI]	[0.19-0.60]		

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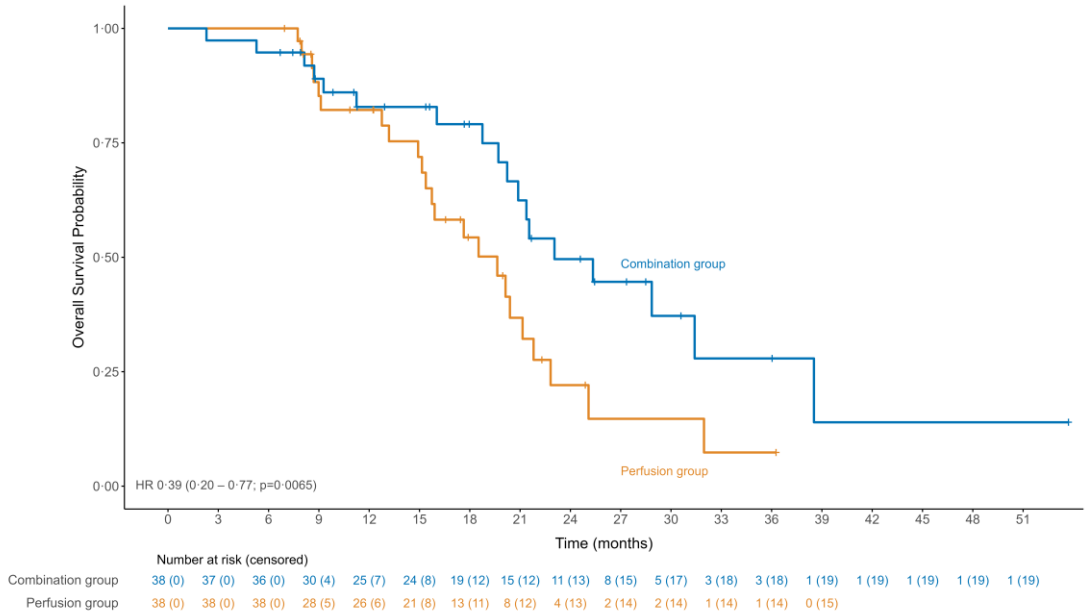
Geeft de combinatiebehandeling een langere algemene overleving? Ja

Overall survival



	Combination (n = 38)	Perfusion (n = 38)	P-value
Events (%)	18 (47.4)	23 (60.5)	
1-year OS, %	82.8	82.2	
[95% CI]	[65.6-91.9]	[64.5-91.6]	
2-year OS, %	49.6	22.1	
[95% CI]	[29.3-67.0]	[7.9-40.6]	
Median OS, months	23.1	19.6	
[95% CI]	[20.2-38.5]	[15.2-21.8]	
Hazard ratio	0.39		0.006
[95% CI]	[0.20-0.77]		

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Maar de combinatiebehandeling geeft wel meer bijwerkingen

Safety

- More high-grade adverse events in the combination group
- ICI seems to enhance toxicity due to PHP (mostly transient)
- More patients discontinued treatment in the combination group
- One ICI-related death (triple M syndrome)

	Combination (n = 38)	Perfusion (n = 37)
	number of patients (%)	
Any treatment-related adverse event	38 (100)	37 (100)
Grade ≥ 3 treatment-related adverse event	**31 (81.6)**	**15 (40.5)**
Serious adverse event	12 (31.6)	3 (8.1)
Any perfusion-related adverse event	36 (94.7)	29 (78.4)
Grade ≥ 3 perfusion-related adverse event	**27 (71.1)**	**12 (32.4)**
Any immunotherapy-related adverse event	30 (78.9)	0
Grade ≥ 3 immunotherapy-related adverse event	**6 (15.8)**	**0**
Any adverse events from either treatment or combination	33 (86.8)	33 (89.2)
Grade ≥ 3 adverse events from either treatment or combination	4 (10.5)	4 (10.8)
Discontinuation of treatment due to adverse event	**13 (34.2)**	**1 (2.7)**
Death due to treatment-related adverse event	**1 (2.6)**	**0**

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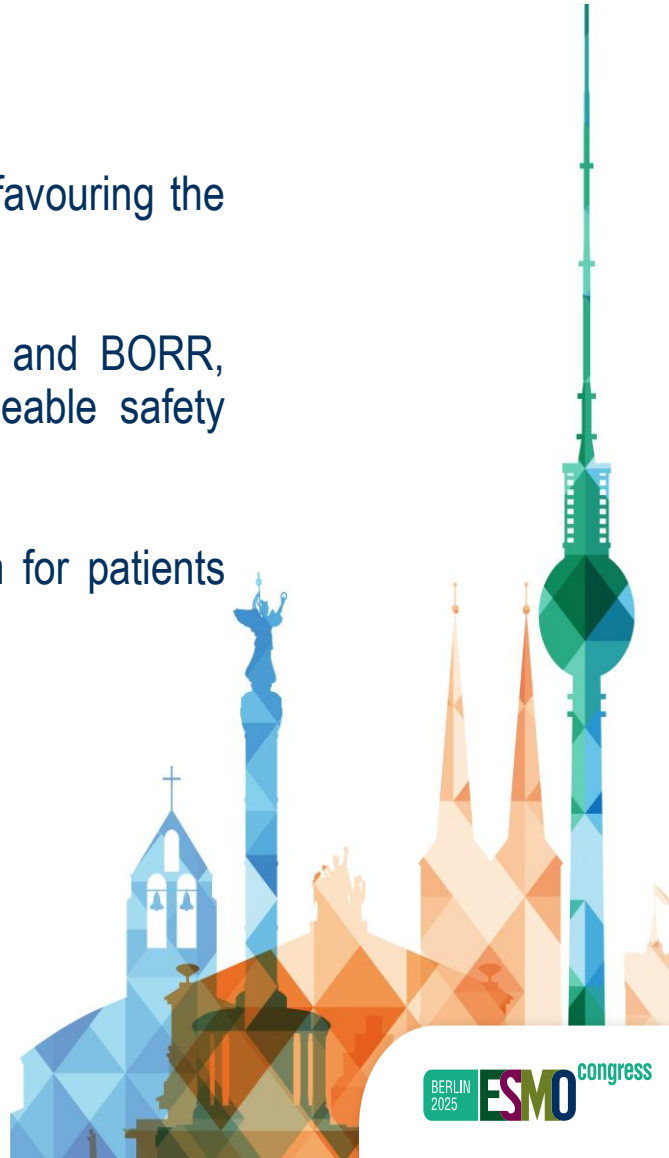
Conclusion

- Primary endpoint analysis showed improved 1-year PFS, favouring the combination group
- Secondary endpoint analysis indicated an improved OS and BORR, favouring the combination group, and showed a manageable safety profile
- ICI plus PHP offers a promising new treatment paradigm for patients with metastatic uveal melanoma



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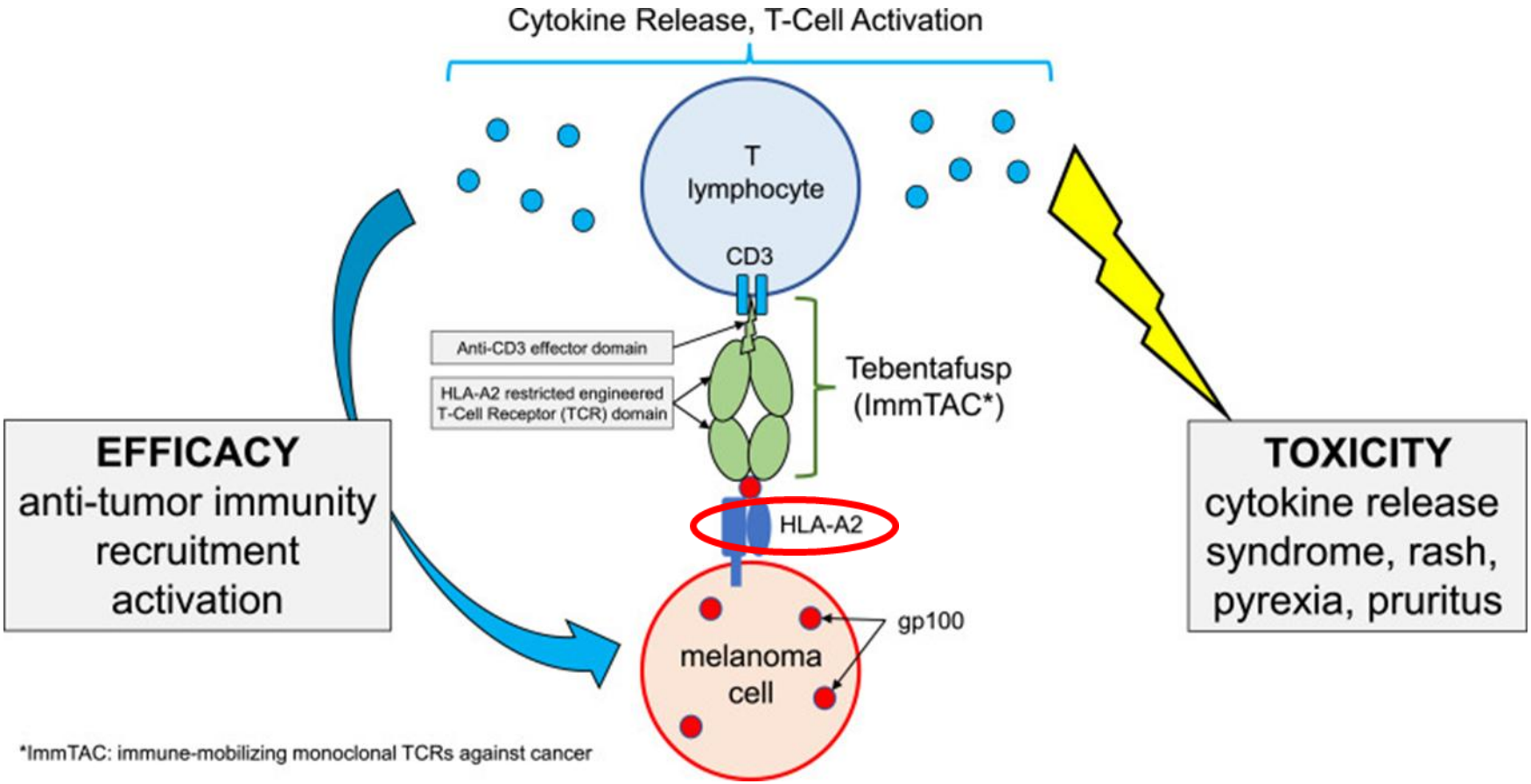
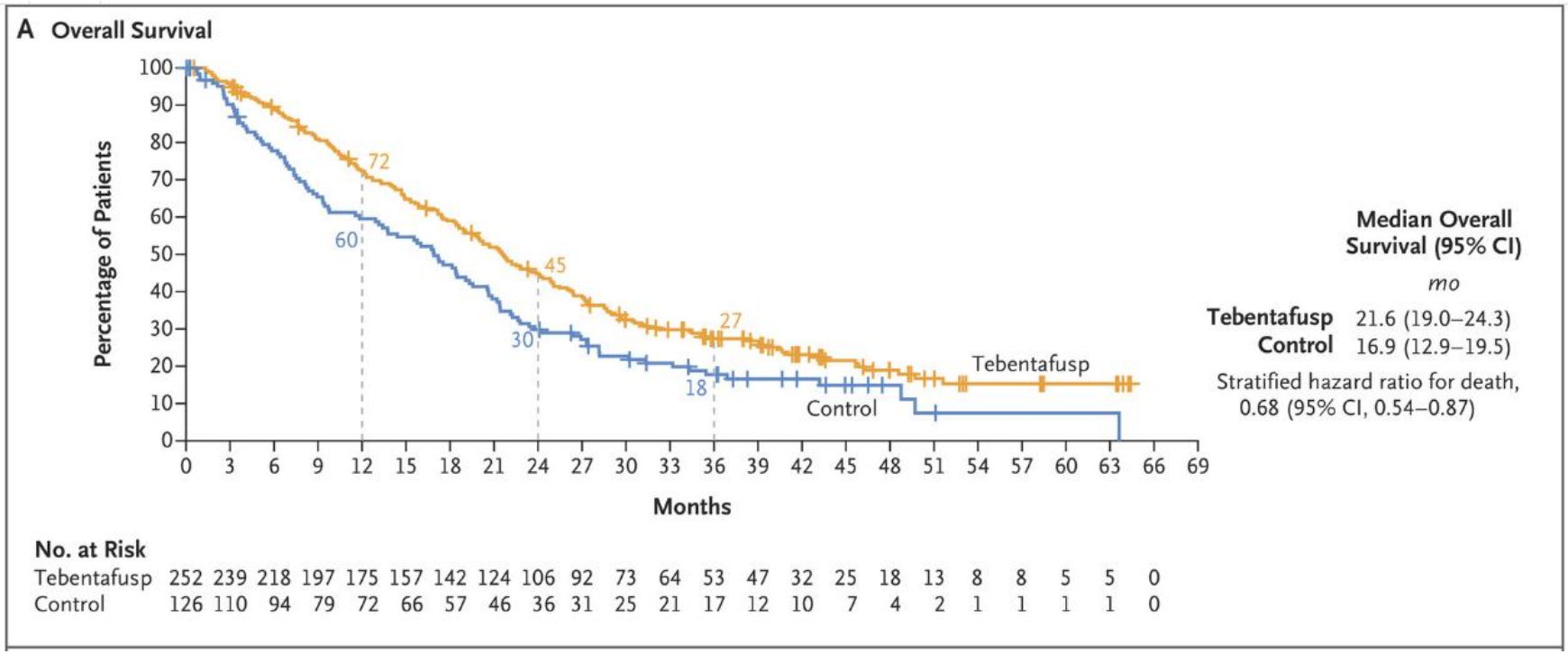
Tebentafusp: bispecifiek antilichaam - immunotherapie



Tebentafusp fase III trial, Hassel et al, *NEJM 2023*



Tebentafusp

- Goedgekeurd per 1 maart 2025
- Ptn met HLA-A201 bloedgroep (40% van de bevolking) kunnen verwezen worden naar het LUMC voor wekelijkse kuren
- Eerste 3 kuren zijn met 1 nacht opname voor observatie van koorts/rillingen/huiduitslag/lage bloeddruk
- Vanaf 4e kuur infusen van 30 minuten

- Gemiddelde overlevingswinst is 6 maanden

Immunotherapie: aanvullend tebentafusp vs observatie in ptn met hoog-risico oogmelanoom (HLA-A201+): ATOM-studie

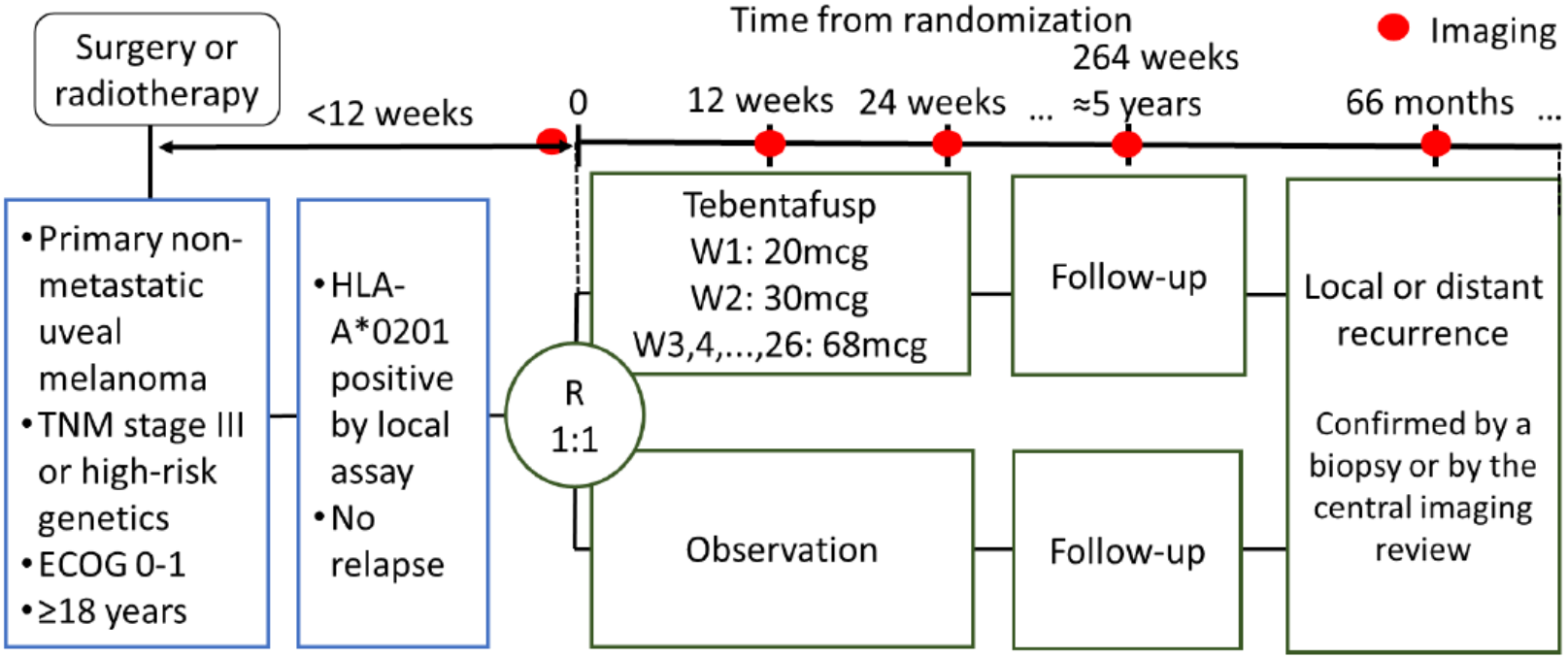
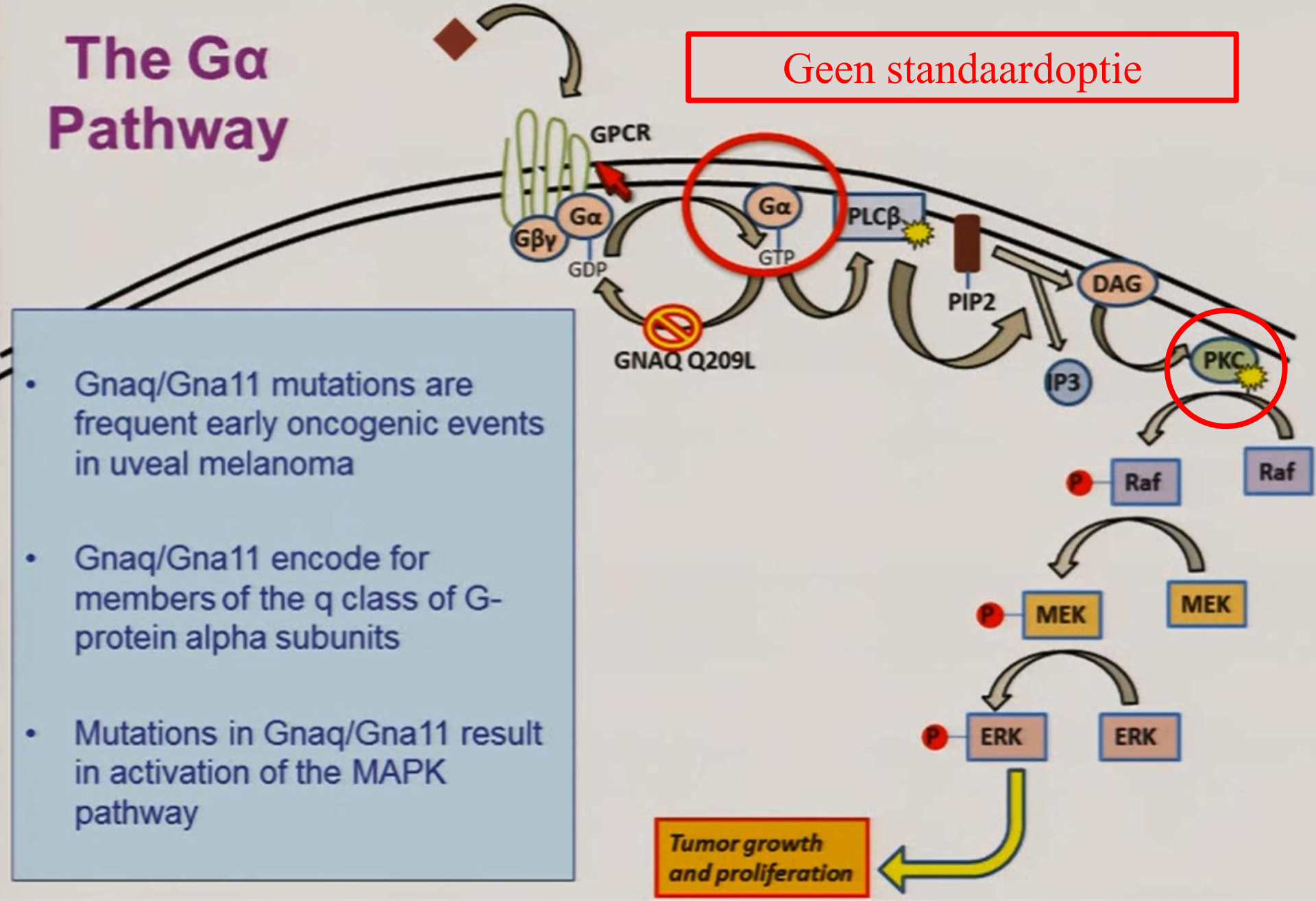


Figure 1: Study scheme

Doelgerichte/targeted therapie

The Gα Pathway

Geen standaardoptie



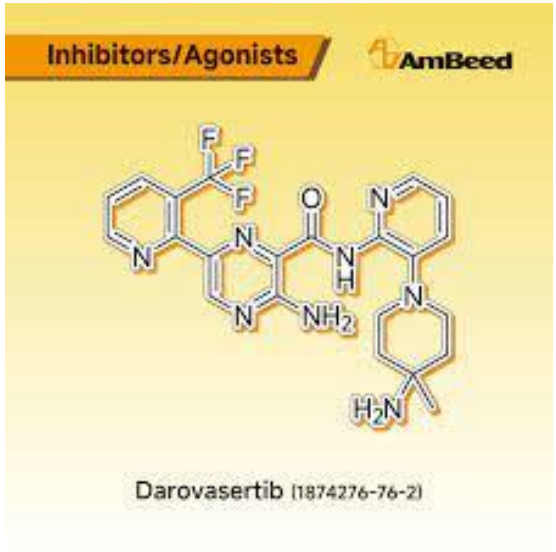
- Gnaq/Gna11 mutations are frequent early oncogenic events in uveal melanoma
- Gnaq/Gna11 encode for members of the q class of G-protein alpha subunits
- Mutations in Gnaq/Gna11 result in activation of the MAPK pathway

Onken et al. *Investigative Ophthalmology and Visual Science*, 2008; Van Raamsdonk *et al. Nature*, 2008; Van Raamsdonk *et al. NEJM*, 2010.

Targeted therapie: darovasertib

- Studie met combinatie darovasertib/crizotinib in ptn met uitzaaiingen

- Studie voor ptn met primair oogmelanoom zonder uitzaaiingen: darovasertib 1-6 mnd voor operatie of bestraling om de tumor kleiner te krijgen

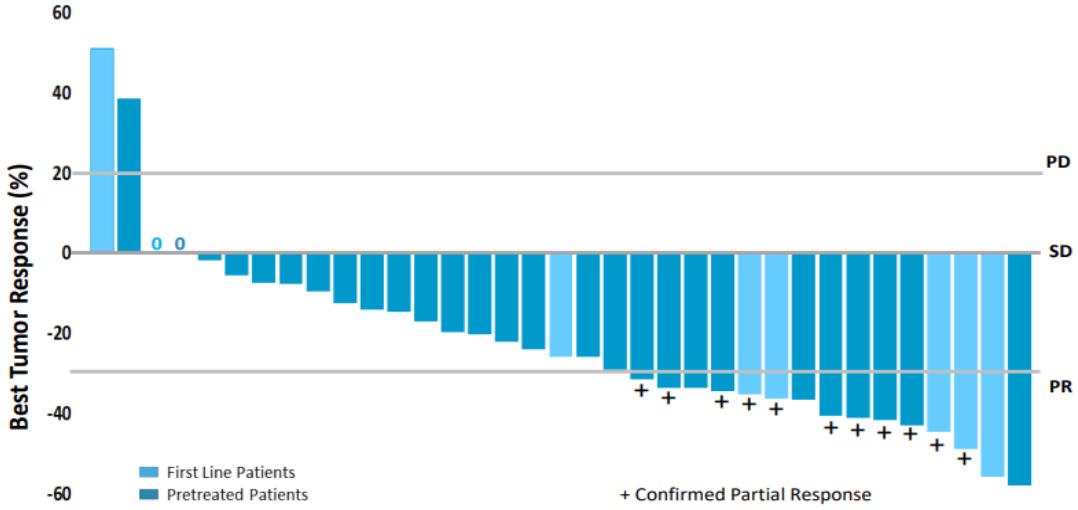


Darovasertib + crizotinib in uitgezaaid oogmelanoom

Daro + Crizo Combo Demonstrates Unprecedented ORR% and DCR% in MUM

Any-Line MUM: 31% ORR by RECIST 1.1

Any-Line Waterfall (n=35 Evaluable)



Response Results

Response by RECIST 1.1 Any-Line MUM	Evaluable (N=35)
ORR(11/35)	31%
Tumor Shrinkage (31/35)	89%
>30% Tumor Shrinkage (15/35)	43%
Best Overall Response	
cPR (11/35)	31%
uPR (2/35)	6%
SD (16/35)	46%
DCR (29/35)	83%

IDEAYA Data: preliminary analysis of unlocked database as of 06/26/2022 by investigator review (n=37); efficacy based on evaluable patients (n=35), including one PR confirmed after cutoff date; two non-evaluable patients, both pretreated, did not progress due to disease: one (1) patient withdrew consent and one (1) patient discontinued early due to fatigue

ORR = Overall Response Rate; DCR = Disease Control Rate; cPR = Confirmed Partial Response; uPR = Unconfirmed Partial Response; SD = Stable Disease

Darovasertib neo-adjuvant in primair oogmelanoom

Preliminary Clinical Proof-of-Concept for Darovasertib in (Neo)Adjuvant UM

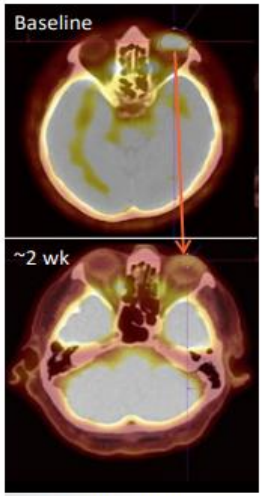
Observed Partial Responses in the Uvea of MUM Patients having Intact Primary Tumor

Darovasertib Monotherapy in MUM with Intact Primary

Observed Partial Response in Uvea Lesion

- 70+ year old pt
- Metastatic disease
- Intact 1° lesion
- Daro monotherapy
- ~74% reduction in ocular lesion at ~ 2 weeks on Darovasertib by PET *
- Improvement in visual symptoms in affected eye
- 32% tumor reduction in target lesions (PR) at Month 2 scan by RECIST 1.1

Patient Remained on Treatment ~ 7 mo



74% Tumor Reduction*

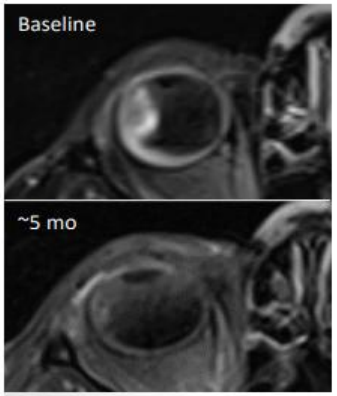
Images (PET) courtesy of Matthew Carlino, MBBS, FRACP, PhD
IDEAYA Data; * PET Standard Uptake Value (SUV)

Daro + Crizo Combination Therapy in MUM with Intact Primary

Observed Partial Response in Uvea Lesion

- 50+ year old pt
- First-Line MUM
- Intact 1° lesion
- Daro + Crizo
- ~67% reduction in ocular lesion
- Visual symptoms improved with treatment
- Confirmed PR

Patient Remains on Treatment at ~ 5 mo ^



67% Tumor Reduction

Images (MRI) courtesy of Marcus Butler, MD
IDEAYA Data ; confirmed PR by RECIST 1.1, ^ Patient remains on treatment as of August 19, 2022

Enucleation prevention and vision preservation in primary uveal melanoma (UM): preliminary results from a phase 2 study of neoadjuvant darovasertib (OptimUM-09)

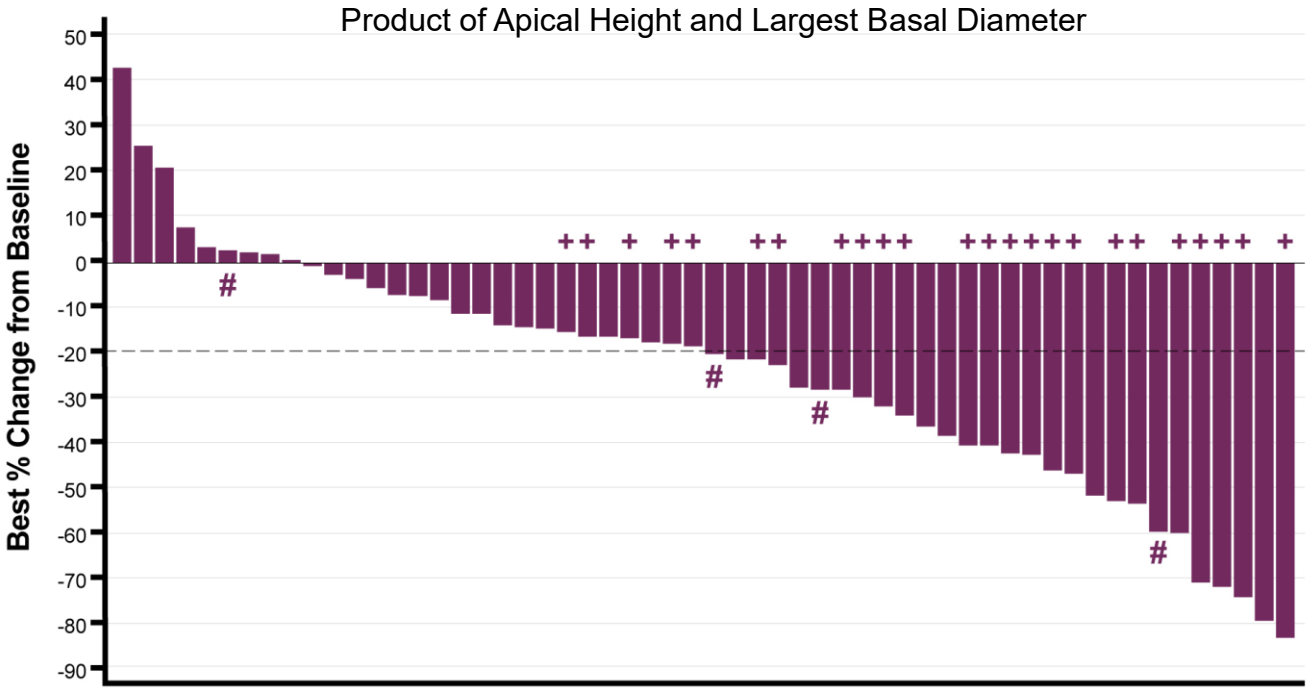
Marcus O. Butler,
David Reichstein, Hatem Krema, Meredith McKean, Anthony M. Joshua, Li Anne Lim, Rod O'Day, Mark Shackleton, Sreenivasa Chandana, Thomas Aaberg, Lauren A. Dalvin, Martina Angi, Ernesto Rossi, Zelia Correa, Jose Lutzky, Mwe Mwe Chao, Jasgit C. Sachdev, Marlana Orloff, Darrin Beaupre, Carol L. Shields

Berlin, Germany
20 October 2025

Oogtumoren krimpen en daardoor kan het oog behouden worden

Primary Efficacy Results for Cohort 1 (Enucleation)

Tumor Shrinkage and Eye Preservation



Tumor Response

	Cohort 1 (N=56)
Tumor Reduction,* n (%)	47 (83.9)
≥20% Reduction	28 (50.0)
≥30% Reduction	21 (37.5)
Tumor Growth, n (%)	9 (16.1)

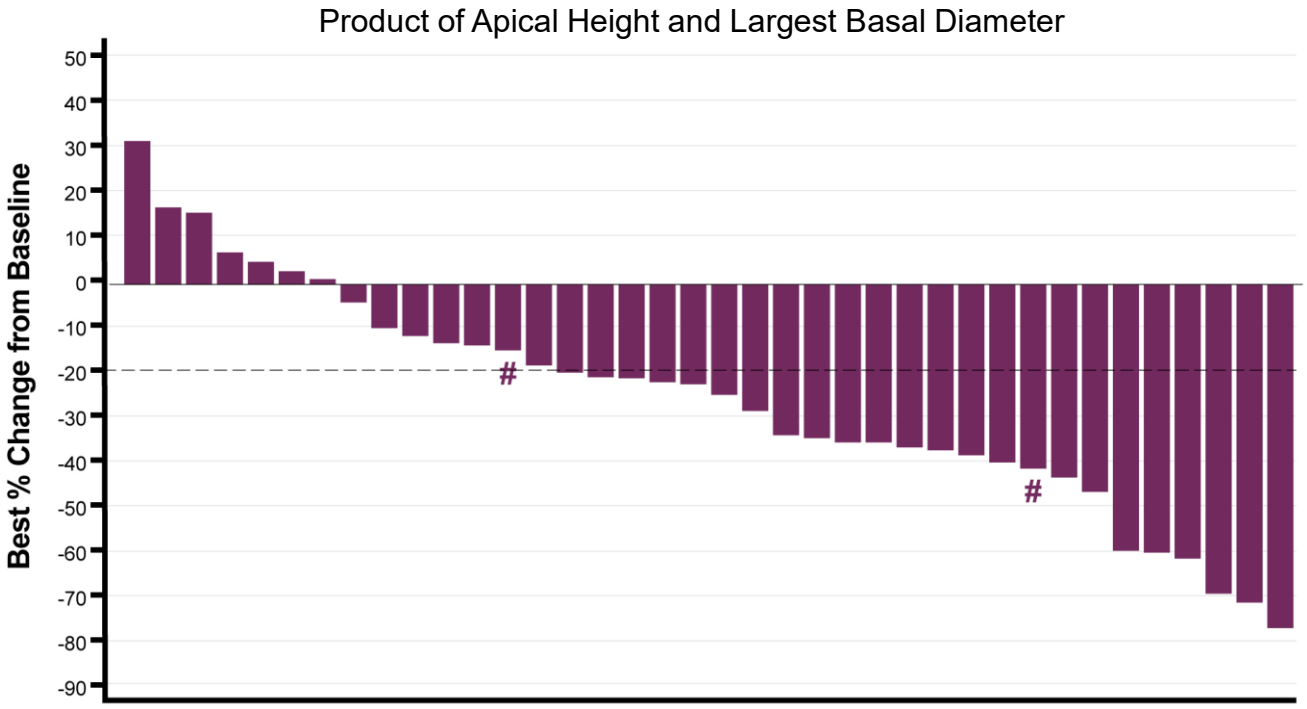
Eye Preservation

	Cohort 1 (N=42)
Eye Preservation Rate, n (%)	24/42 (57.1)**
In patients with 20% reduction	19/20 (95.0)^
Types of Eye Preserving Therapies, n (%)	
Plaque brachytherapy	18/24 (75.0)
External beam radiation	6/24 (25.0)

Oogtumoren krimpen en daardoor kan de bestralingsdosis verlaagd worden

Primary Efficacy for Cohort 2 (Plaque Brachytherapy)

Tumor Shrinkage



Tumor Response

	Cohort 2 (N=38)
% Tumor Reduction, n (%)**	31 (81.6)
≥20% Reduction	23 (60.5)
≥30% Reduction	17 (44.7)
Tumor Growth, n (%)	7 (18.4)

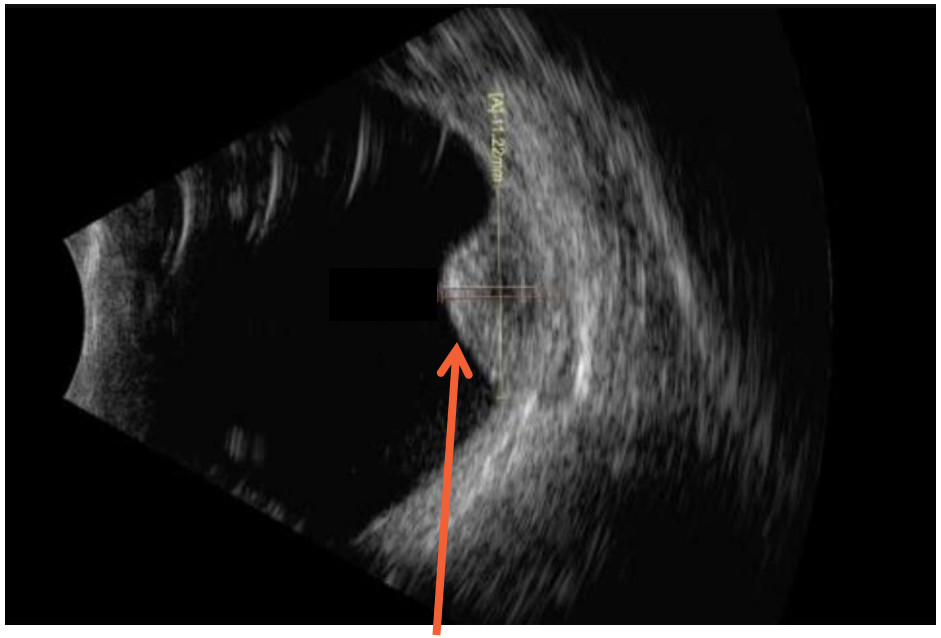
**Product of diameter measurements, >20% tumor shrinkage required for partial response, based on endpoint definition utilized for upcoming OptimUM-10 study.
#Subjects ongoing on neoadjuvant treatment.
Per protocol efficacy evaluable population (N=38) was defined as all subjects who received at least one dose of study drug and have at least one post-baseline tumor assessment.
One patient was not evaluable and therefore not included in the efficacy evaluable population.

Voorbeeld van een patient waarbij de bestralingsdosis verminderd kon worden

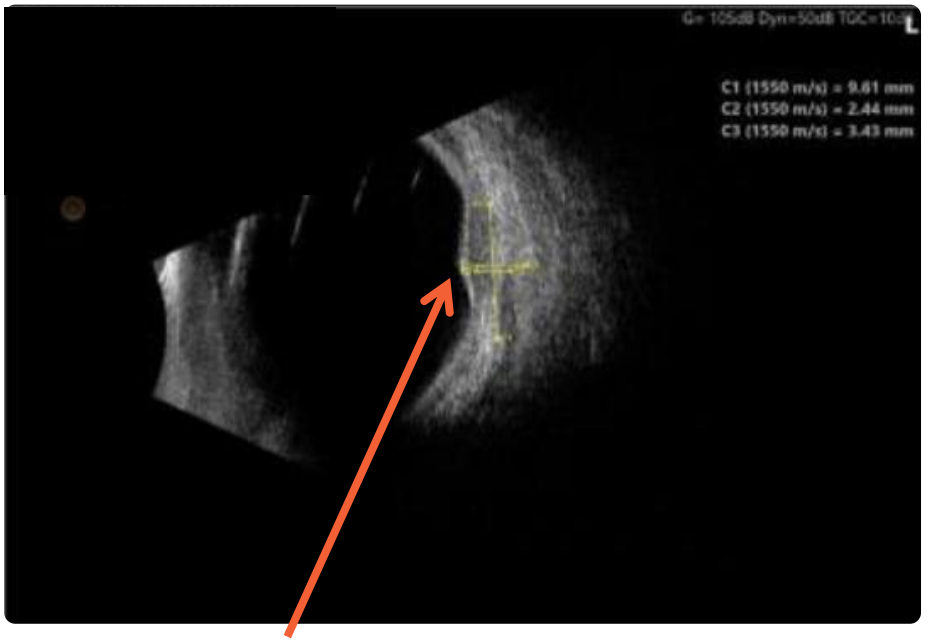
Case: Neoadjuvant Darovasertib for UM Patient Requiring Plaque Brachytherapy

56-Year Old Female Subject Demonstrating Significant Tumor Shrinkage After 10 Cycles of Neoadjuvant Darovasertib

Baseline



End of Neoadjuvant Treatment



77% Reduction in Tumor Product of Diameters, Increased Echo-density

Reduction in tumor size resulted in:

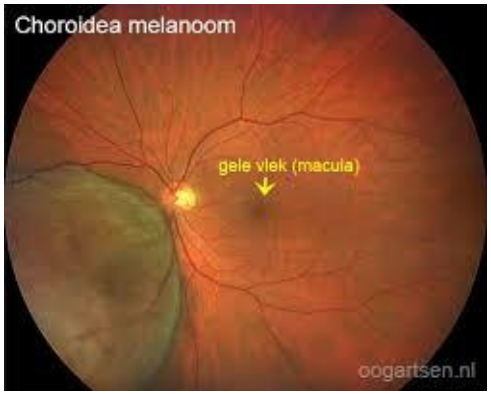
- Radiation dose reduction: -35% to optic disc; -40% to fovea
- Increase in distance of tumor to optic nerve (15%) and fovea (10.2%)
- 3-year risk of <20/200 vision: reduced from 36% to 13% after 3 cycles

Conclusies gemetastaseerd uveamelanoom

- Lokale (lever)behandelingen kunnen succesvol zijn als deze mogelijk zijn (echter, leverperfusie nog niet officieel vergoed).

- Combinatie ipilimumab/nivolumab kan werkzaam zijn in geselecteeerde ptn, maar lagere responskans dan bij huidmelanoom en kan veel bijwerkingen geven
- Combinatie met leverperfusie geeft betere progressie-vrije en algemene overleving: CHOPIN-studie.

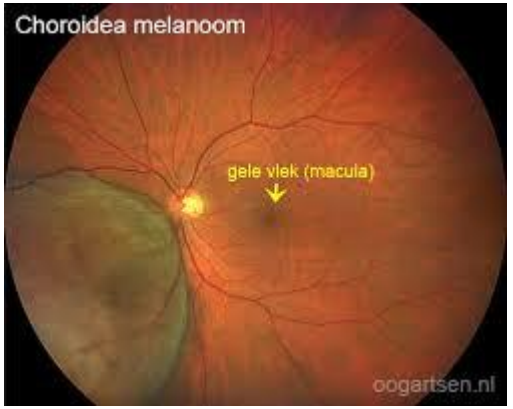
- Tebentafusp (IMCgp100) is bewezen effectief (6 maanden langere overleving); echter, alleen voor HLA-A201 positieve ptn.



Conclusies gemetastaseerd uveamelanoom en (neo)adjuvante behandeling

- Meer inzicht in de moleculaire biologie van oogmelanoom heeft geleid tot studies met specifieke targeted/doelgerichte middelen (PKC-remmers), nog geen standaardoptie – wel beschikbaar in studies.

- Nieuwe indicaties in studies: adjuvant tebentafusp in hoog-risico oogmelanoom en neo-adjuvant darovasertib bij primair oogmelanoom.



Bedankt voor de aandacht!