



Neo-adjuvante behandeling van melanoom

Louter belofte of ook resultaat?

Studiedag Melanoompunt 2025

25 januari 2025

Crowne Plaza Hotel Antwerpen

Ewout Landeloos, MD PhD

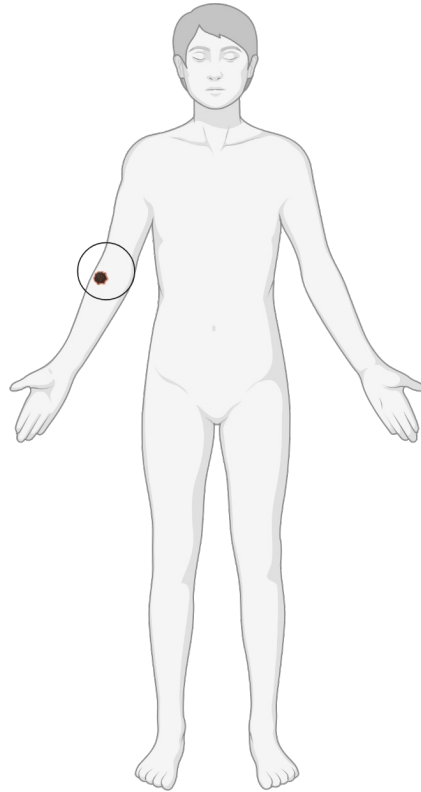
Disclosures

- Farmaceutische industrie:
 - Speaker fees: BMS
 - Travel fees: Teva Belgium, Pfizer, Pierre-Fabre
- Studiebeurzen:
 - Kom op Tegen Kanker, Melanoma Research Alliance

Behandeling van lokaal gevorderd melanoom

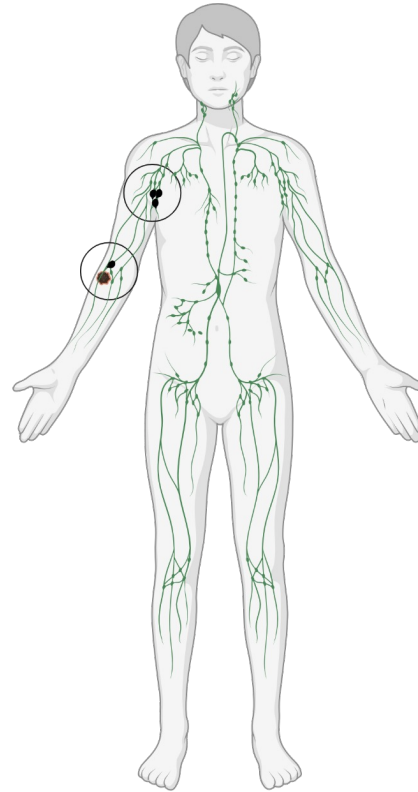


'Lokaal'



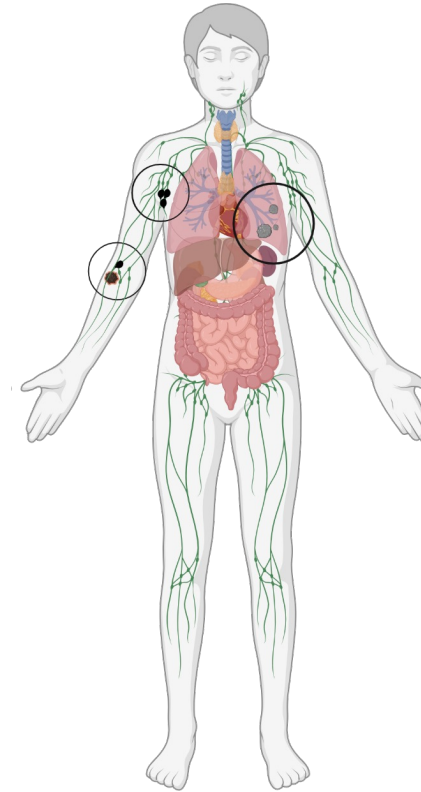
Stadium I: Breslow dikte < 2 mm
Stadium II: Breslow dikte ≥ 2 mm
OF ≥ 1 mm met ulceratie

'Regionaal of
Lokaal gevorderd'



Stadium III: Regionale lymfeklieren
OF 'MSI-letsels'

'Gevorderd'

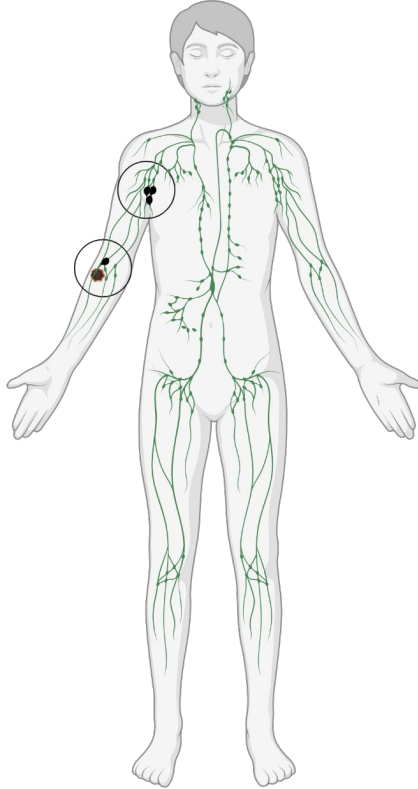


Stadium IV: Letsels op afstand
in organen en/of
in klieren



Behandeling van lokaal gevorderd melanoom

‘Regionaal of
Lokaal gevorderd’

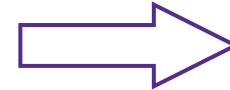


Stadium III: Regionale lymfeklieren
OF ‘MSI-letsels’

Heelkunde



“Primaire” of
hoofdbehandeling



Doelgerichte therapie



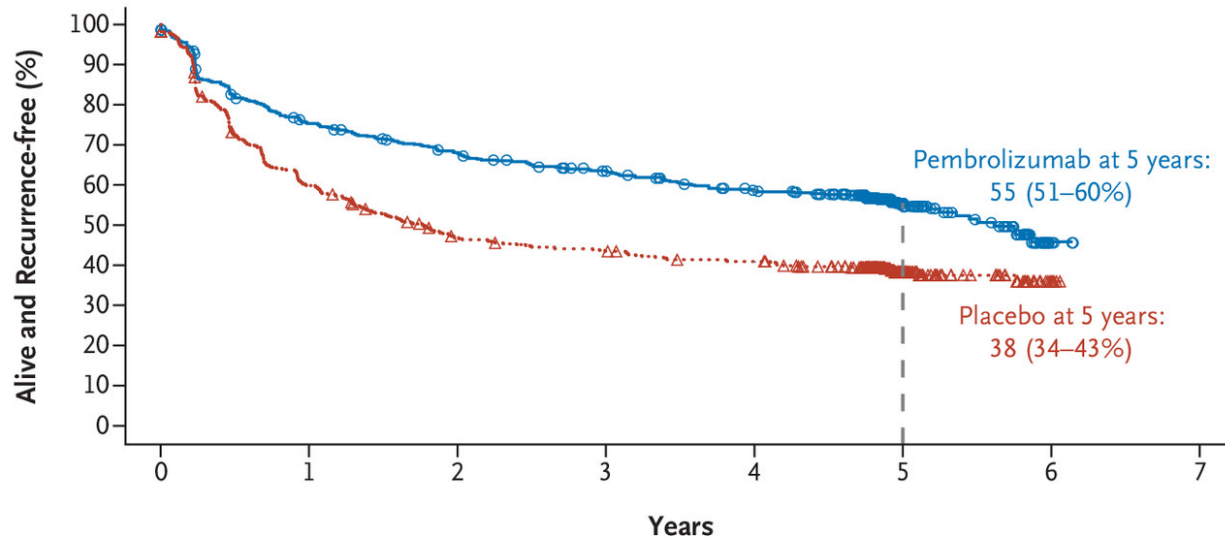
“Adjuvante” of nabehandeling



Immunotherapie

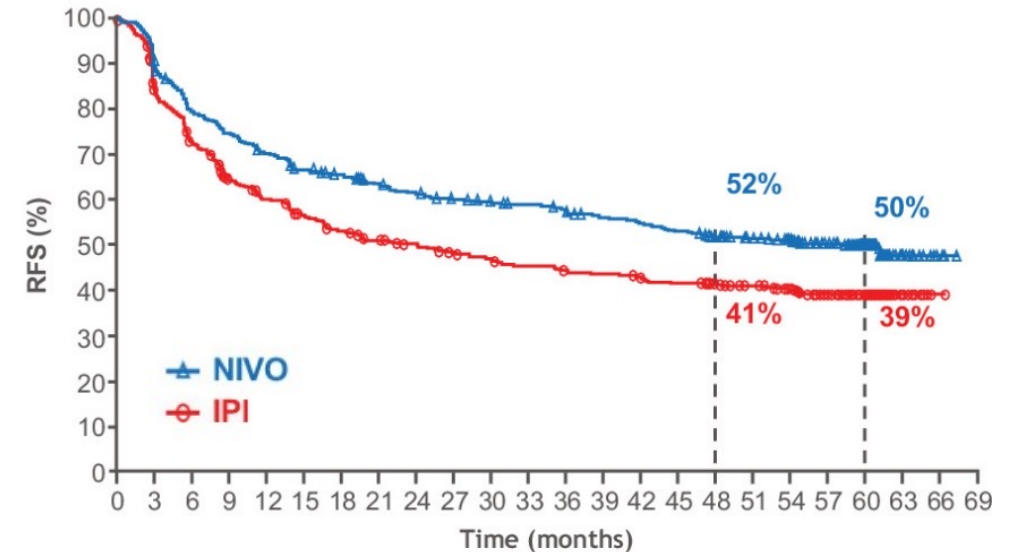
Behandeling van lokaal gevorderd melanoom

KEYNOTE-054



Treatment arm	Event	Total	Hazard ratio (95% CI)
Pembrolizumab	228	514	0.61 (0.51–0.72)
Placebo	304	505	Reference

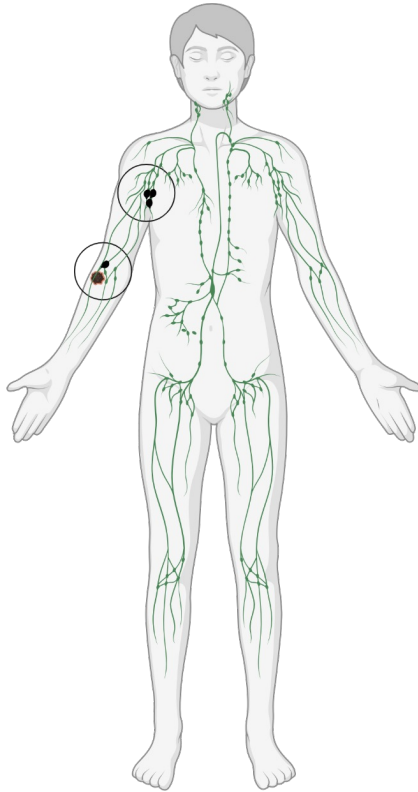
CheckMate 238



	NIVO (n = 453)	IPI (n = 453)
Events, n	218	257
Median, mo (95% CI)	61.0 (42.5–NR)	24.1 (16.6–35.1)
HR (95% CI)	0.72 (0.60–0.86)	

Neo-adjuvante behandeling

‘Regionaal of
Lokaal gevorderd’



Stadium III: Regionale lymfeklieren
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Heelkunde



“Primaire” of
hoofdbehandeling



Doelgerichte therapie



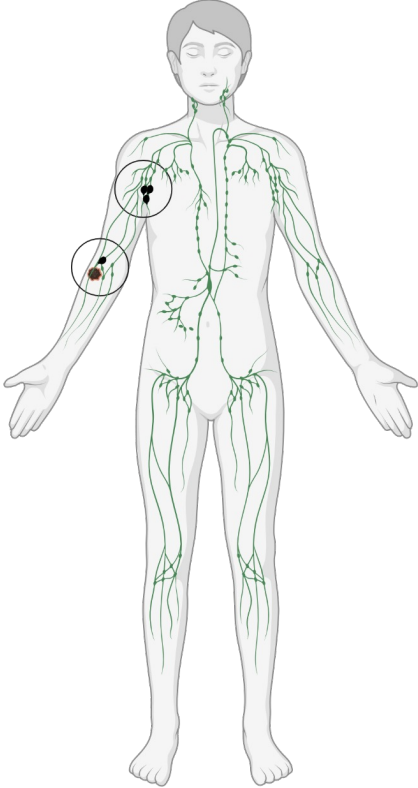
“Adjuvante” of nabehandeling



Immuuntherapie

Neo-adjuvante behandeling

‘Regionaal of
Lokaal gevorderd’



Stadium III: Regionale lymfeklieren
OF ‘MSI-letsels’

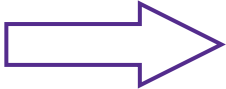
Doelgerichte therapie



“Neo-adjuvante” behandeling



Immuuntherapie



Heelkunde



“Primaire” of
hoofdbehandeling

Neo-adjuvante behandeling

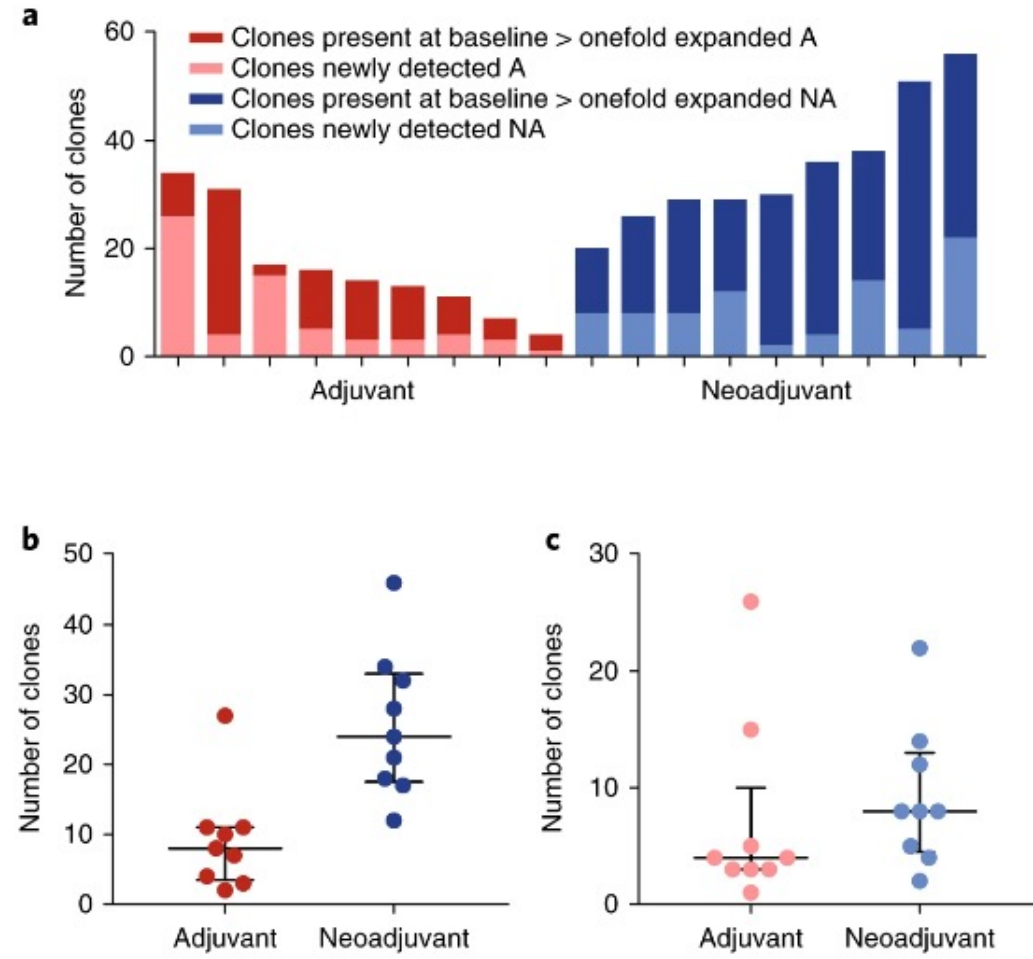
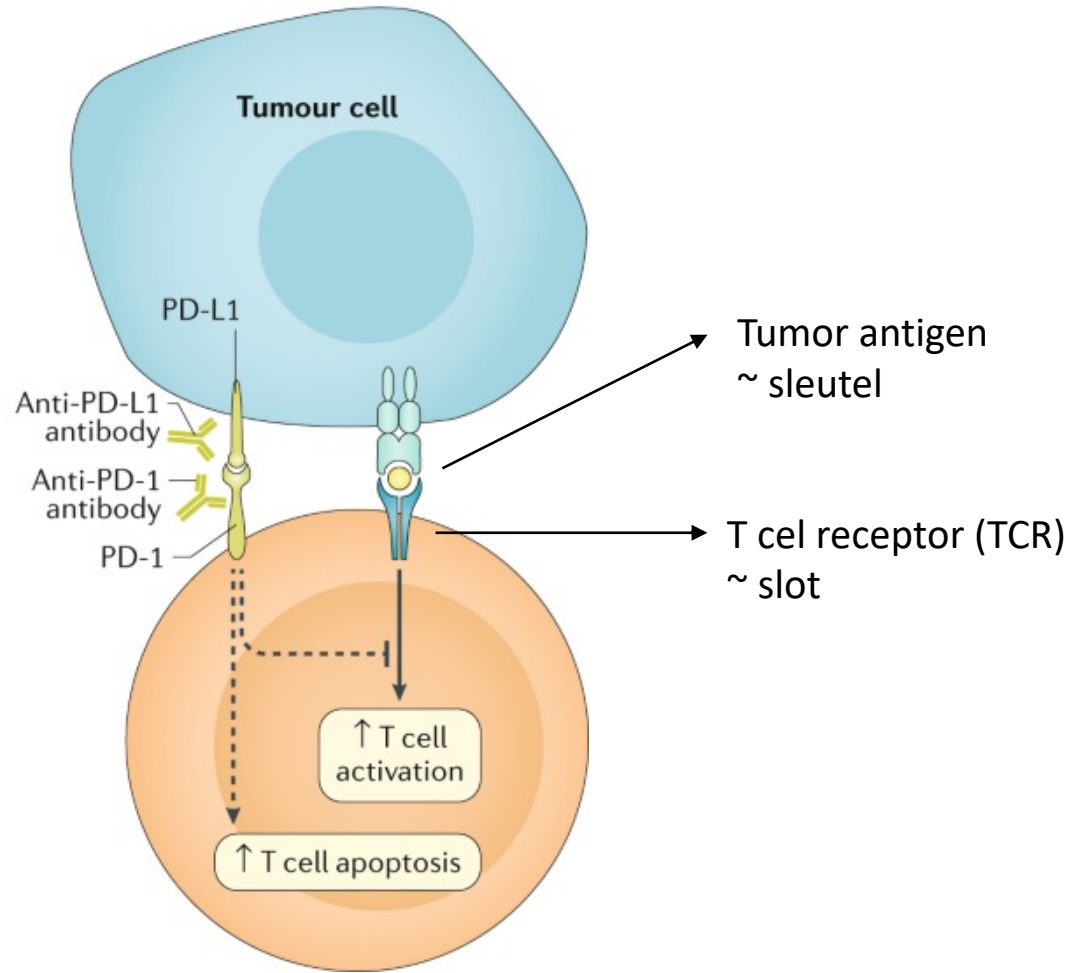
De beloften van een neo-adjuvante behandeling bij melanoom:

- 1) Verbeterde activatie van het immuunsysteem om melanoom aan te vallen
- 2) Voorspellen van de behandelingsuitkomst
- 3) Betere behandelingsuitkomsten
- 4) Behandeling aangepast aan het hervalrisico
 - Afbouw van behandeling bij “responders”
 - Minder uitgebreide chirurgie, en dus minder verwikkelingen
 - Minder lange/intense of zelfs helemaal geen nabehandeling
 - Intensifiëren van behandeling bij “non-responders”



Verbeterde activatie van het
immuunsysteem

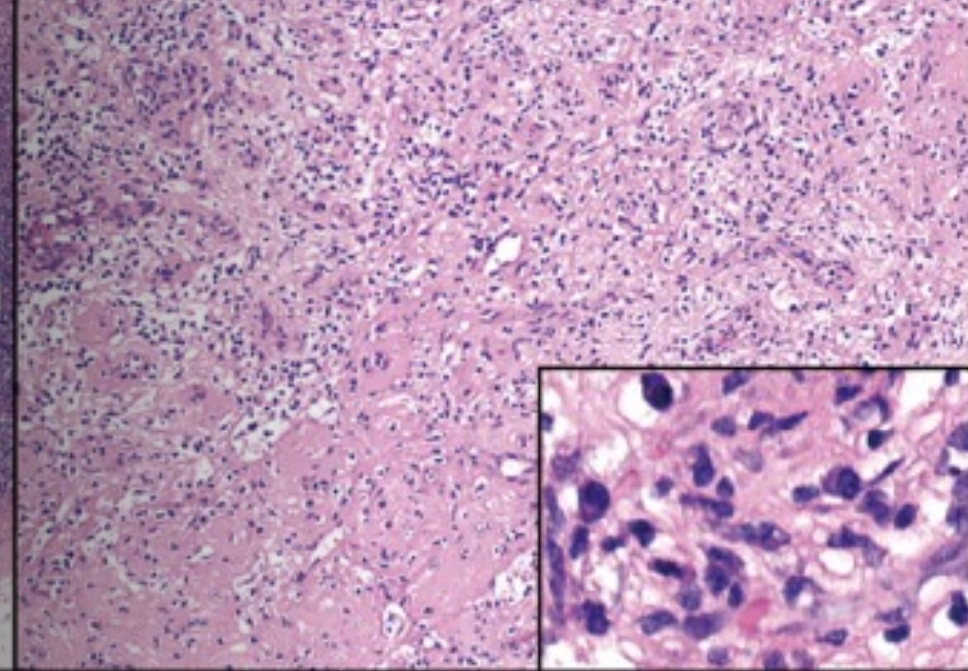
Verbeterde activatie van het immuunsysteem



Voorspellen van de behandelings- uitkomst

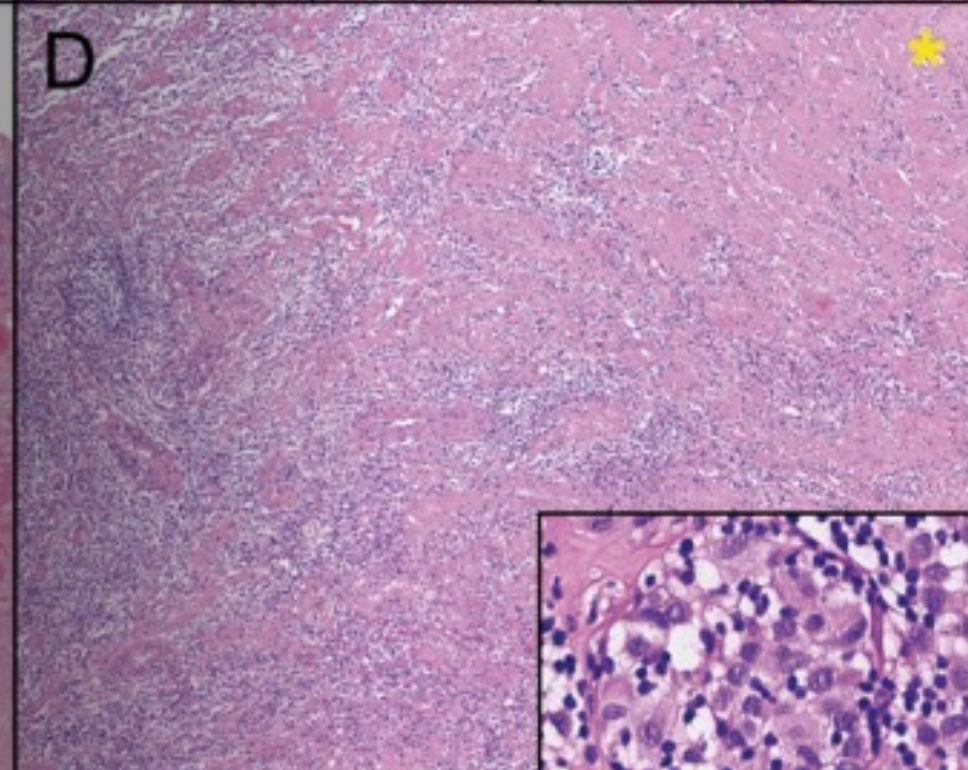
Regression

Normal
LN

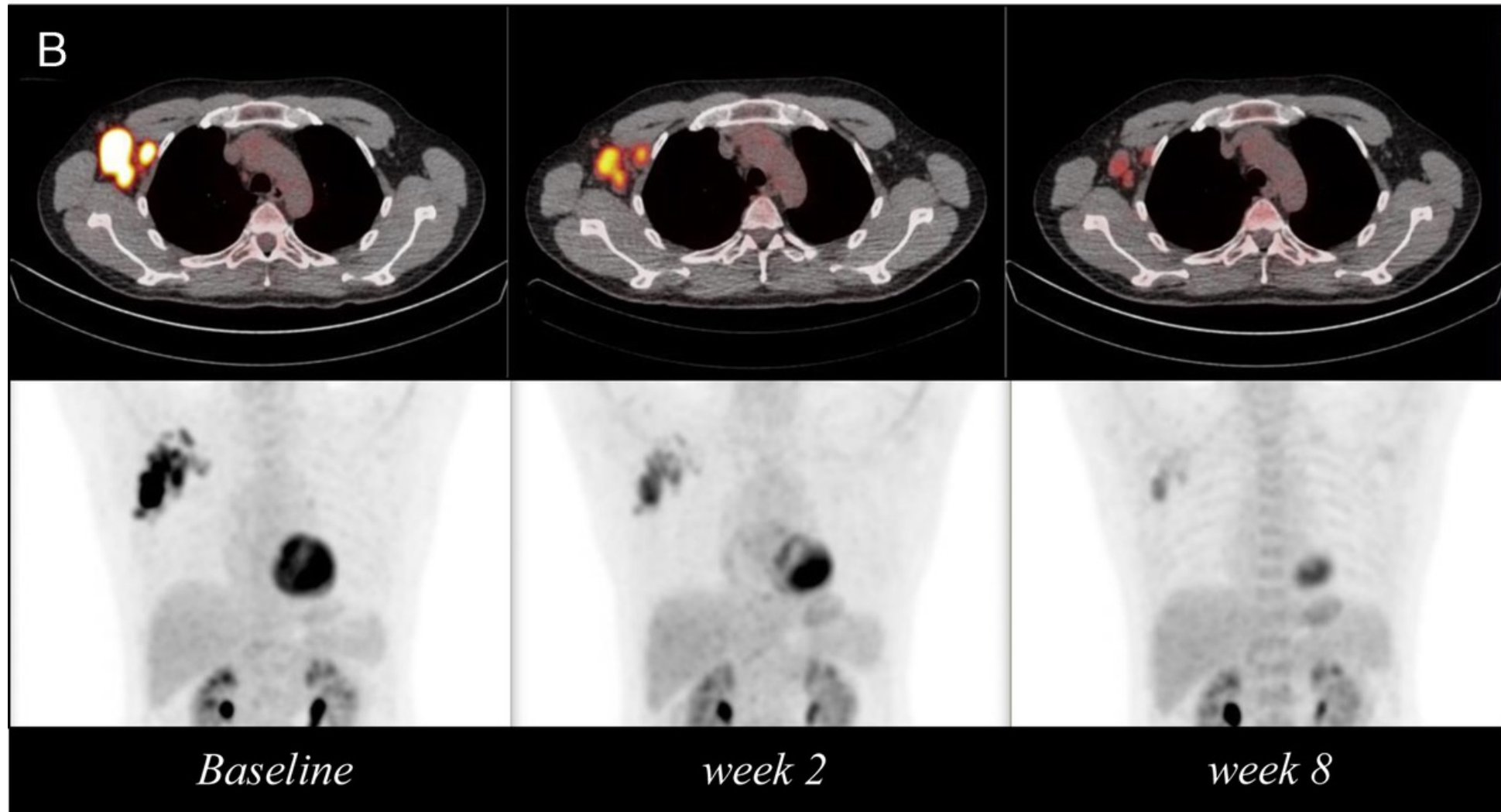


Regression

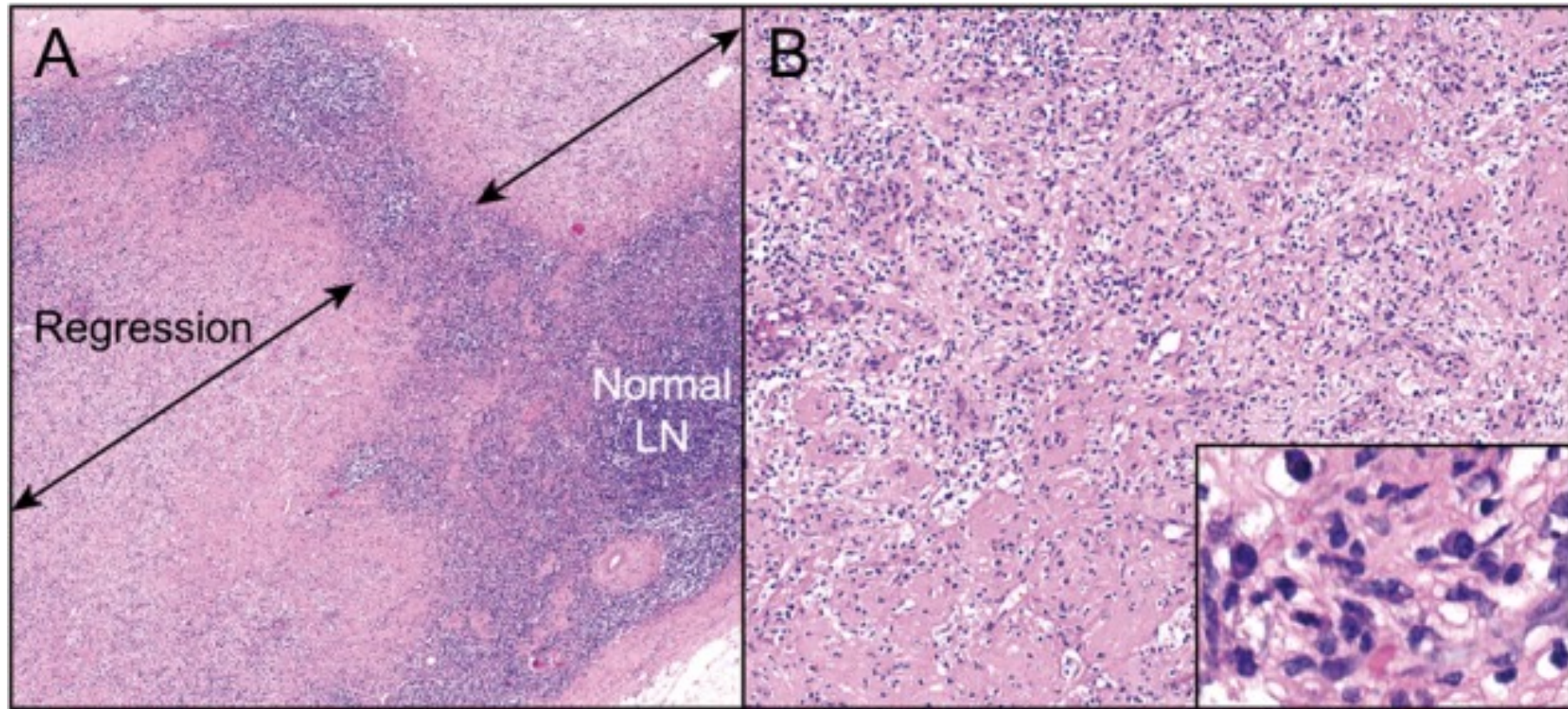
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Voorspellen van de behandelingsuitkomst



Voorspellen van de behandelingsuitkomst



Voorspellen van de behandelingsuitkomst

$$\% \text{ viabele (levende) resttumor} = \frac{\text{oppervlakte viabele resttumor}}{\text{totale oppervlakte van het geanalyseerde tumorbed}}$$

pCR	0 % viabele resttumor in het tumorbed	} Majeure pathologische respons MPR	} Pathologische respons rate pRR
pnCR	<10 % viabele resttumor in het tumorbed		
pPR	<50 % viabele resttumor in het tumorbed		
pNR	≥50 % viabele resttumor in het tumorbed		

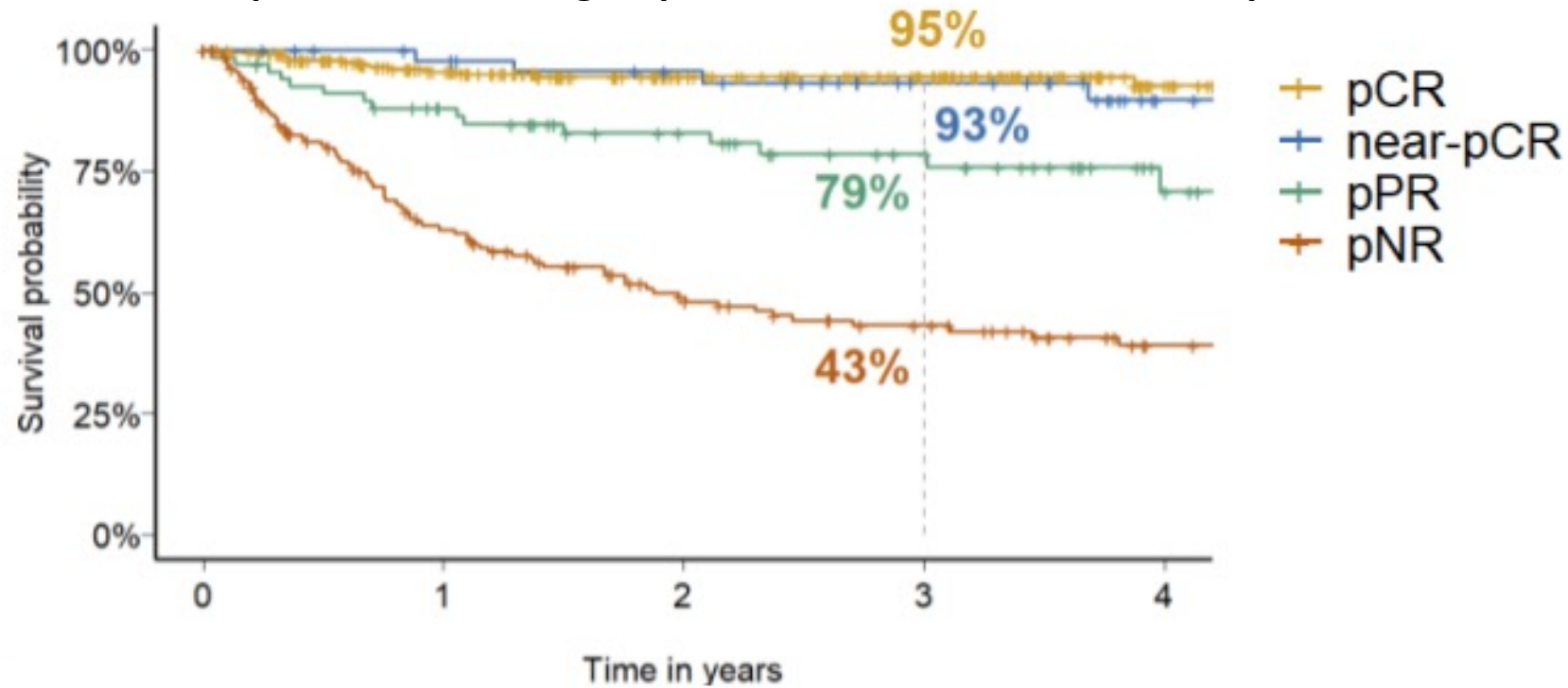
Voorspellen van de behandelingsuitkomst

Gepoolde INMC analyse bij lokaal gevorderd operabel melanoom

818 patiënten, waarvan 610 behandeld met immuuntherapie

173 patiënten kregen monotherapie

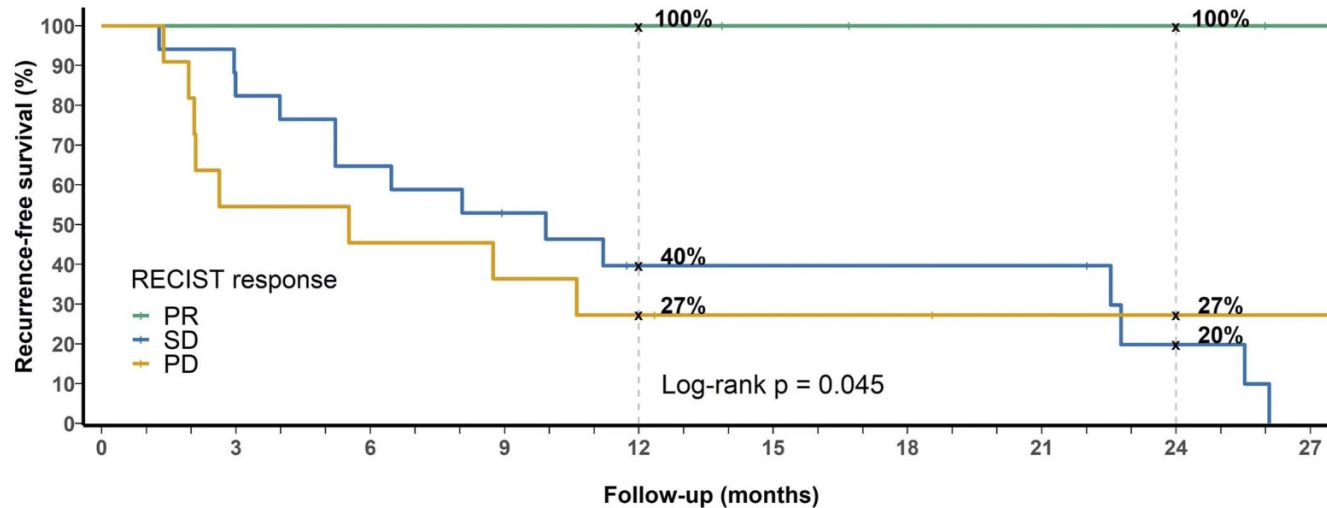
INMC 2024 update - Patientengroep behandeld met immuuntherapie



	ICI mono	ICI combi
pCR	38%	51%
MPR	46%	62%
pNR	38%	27%

Radiologische respons

INMC - Patiëntengroep behandeld met immuuntherapie



Patiënten met een radiologische (complete of partiële) respons hebben een betere prognose...

... **onafgezien** de pathologische respons!

PET-CT **onderschat** de kans op (majeure) pathologische respons (MPR) en de pathologische response rate (pRR)

Radiologische respons	Kans op MPR
Complete respons (CR)	100 %
Partiële respons (PR)	83 %
Stabiele ziekte (SD)	38 %
Ziekteprogressie (PD)	8 %



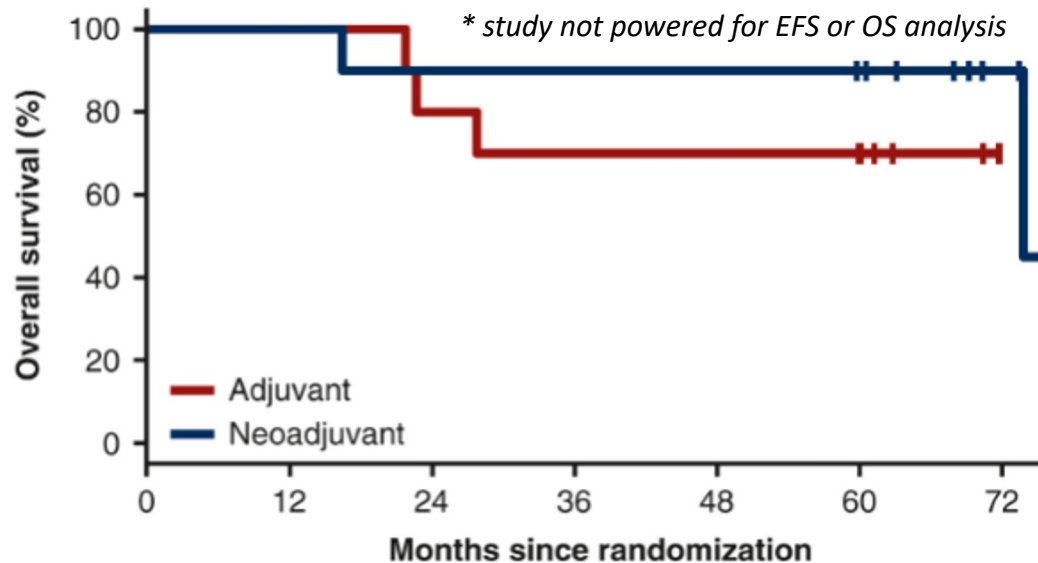
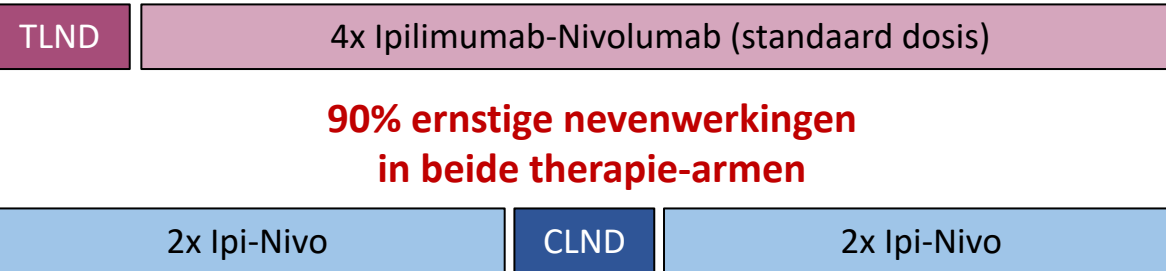
Betere behandelingsuitkomsten

Betere behandelingsuitkomsten

OpACIN

Fase Ib studie (n = 20)
Operabel st. IIIB-IIIC

1:1

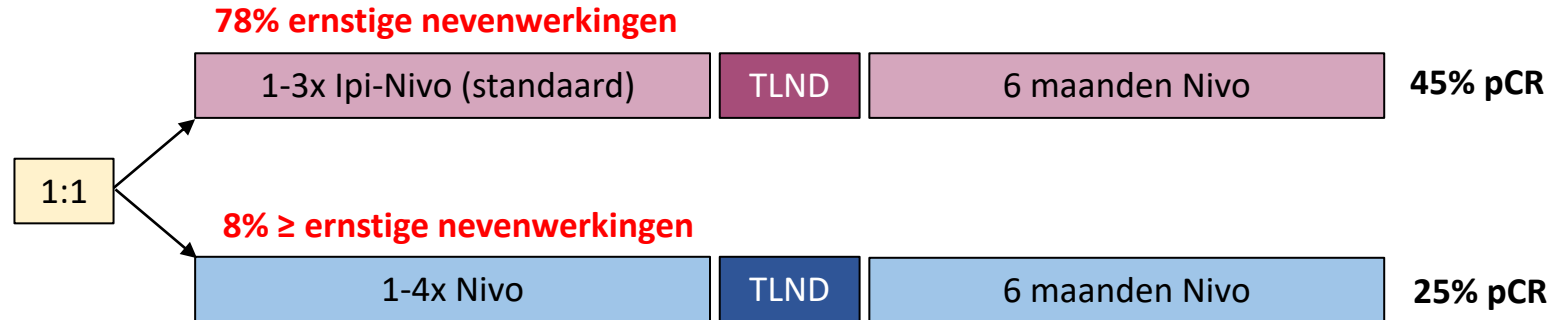


pCR	33%
MPR	66%
pNR	22%

Nevenwerkingen

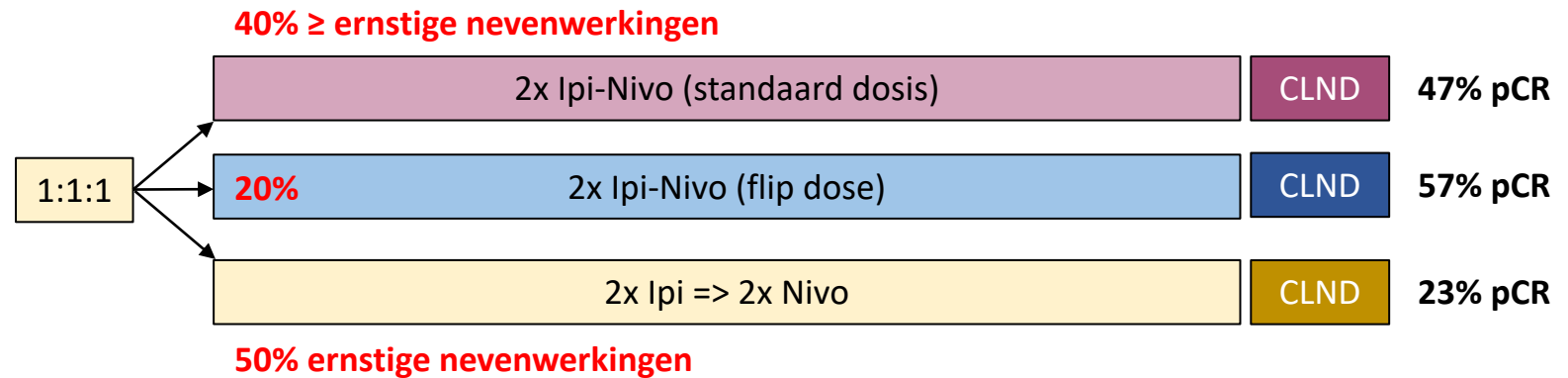
Amaria. Nat Med. 2018.

Fase II studie (n = 23)
Operabel st. III-IV



OpACIN-neo

Fase II studie (n = 86)
Operabel st. IIIB-IIIC



Amaria. Nature. 2022.

Fase II studie (n = 30)
Operabel st. III-IV



Nevenwerkingen

Amaria. Nat Med. 2018.

Fase II studie (n = 23)
Operabel st. III-IV

OpACIN-neo

Fase II studie (n = 86)
Operabel st. IIIB-IIIC

Amaria. Nature. 2022.

Fase II studie (n = 30)
Operabel st. III-IV

Nevenwerkingen

Amaria. Nat Med. 2018.

Fase II studie (n = 23)
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OpACIN-neo

Fase II studie (n = 86)
Operabel st. IIIB-IIIC

Amaria. Nature. 2022.

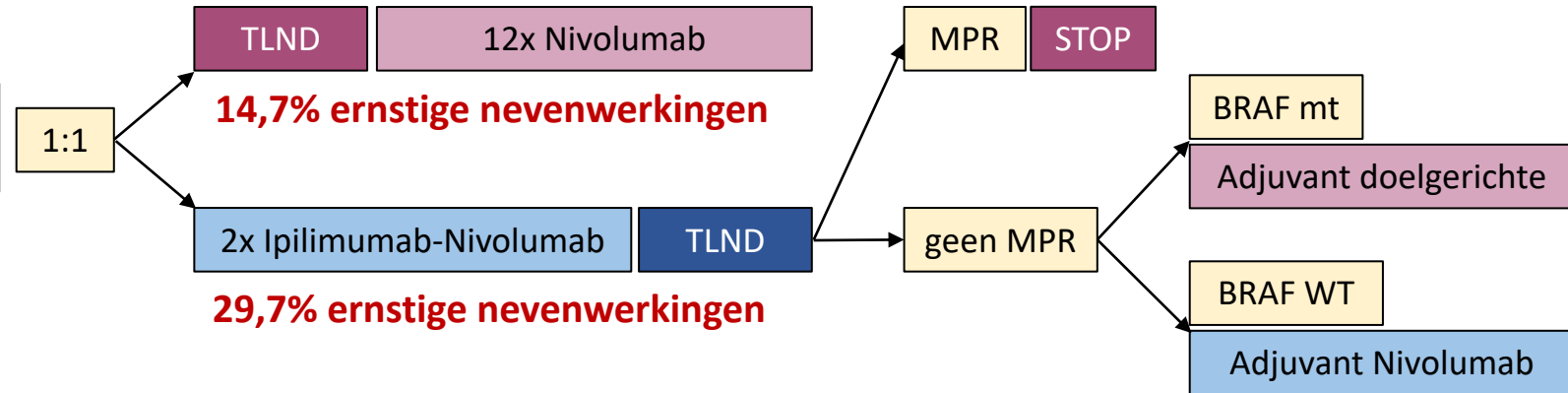
Fase II studie (n = 30)
Operabel st. III-IV

Studie	Neo-adjuvante strategie	Ernstige nevenwerkingen	Patiënten met pCR
Amaria 2018	Ipi-Nivo flip dose	78%	45%
	Nivo mono	8%	25%
OpACIN-neo	Ipi-Nivo standard dose	40%	47%
	Ipi-Nivo flip dose	20%	57%
	Ipi-Nivo sequential	50%	23%
Amaria 2022	Nivo-Rela	26%	57%

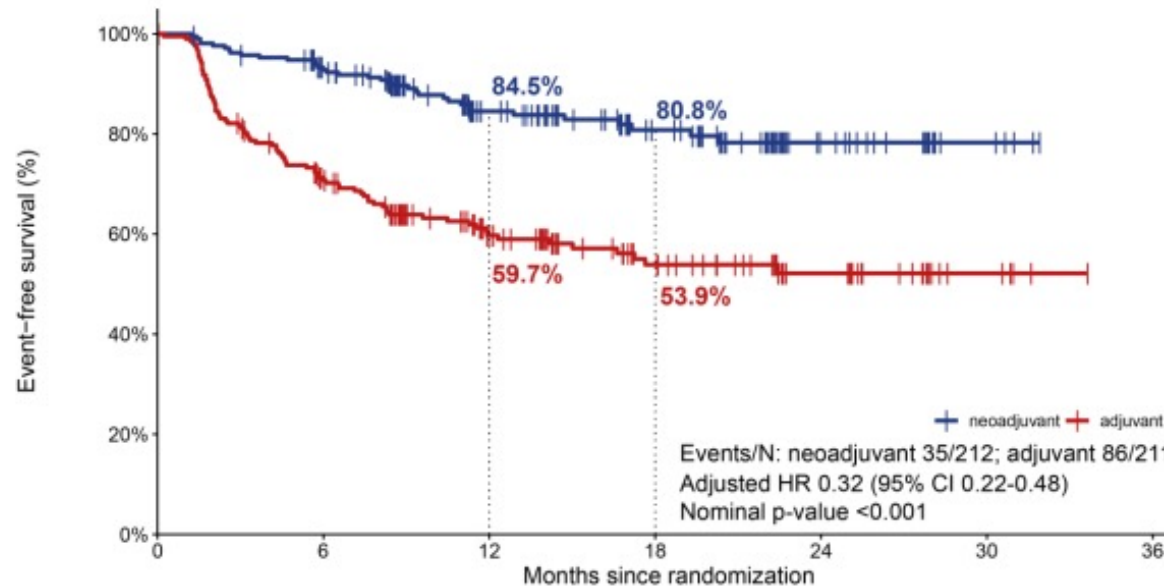
Betere behandelingsuitkomsten

NADINA

Fase III studie (n = 423)
Operabel st. III



pCR	49%
MPR	59%
pNR	26.4%



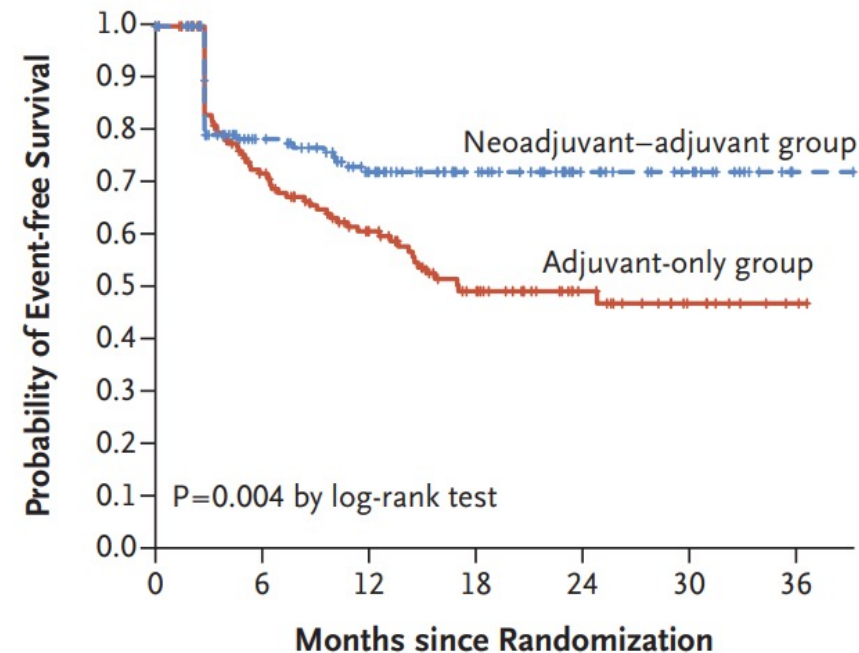
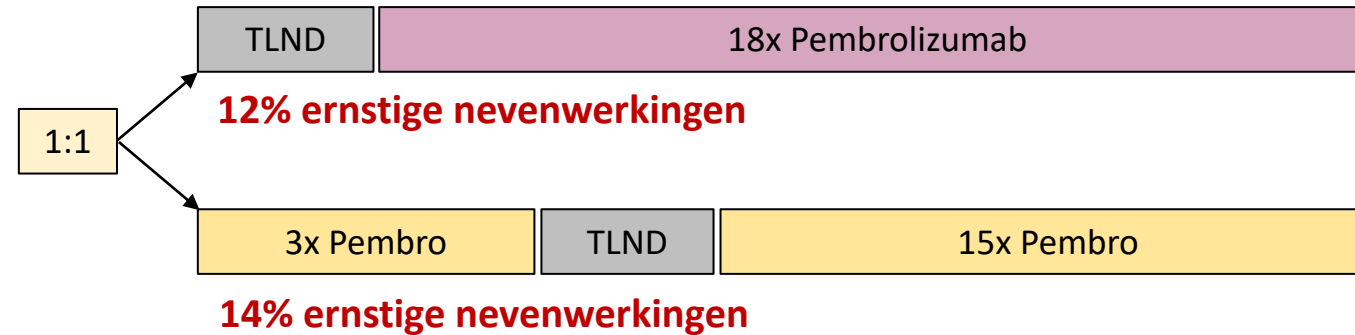
Op termijn van 1,5 jaar
~30% minder kans op
herval, ziekteprogressie,
of overlijden

Betere behandelingsuitkomsten

SWOG 1801

Fase II studie (n = 313)
Operabel st. IIIB-IV

pCR	38%
MPR	53%
pNR	21%



Op termijn van 2 jaar ~30% minder kans op herval, ziekteprogressie, of overlijden



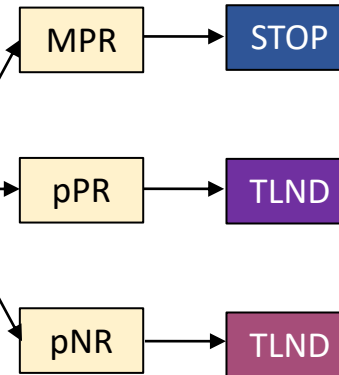
Behandeling aangepast
aan het hervalrisico

Behandeling aangepast aan hervalrisico

PRADO

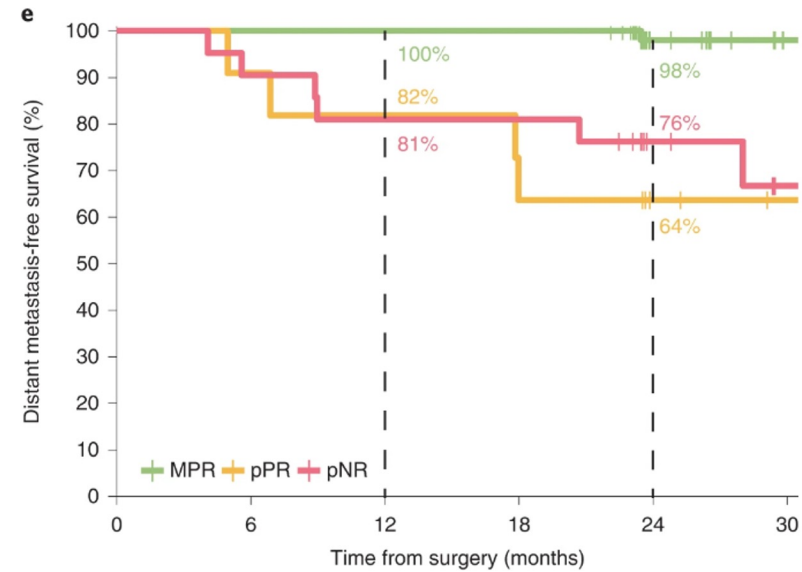
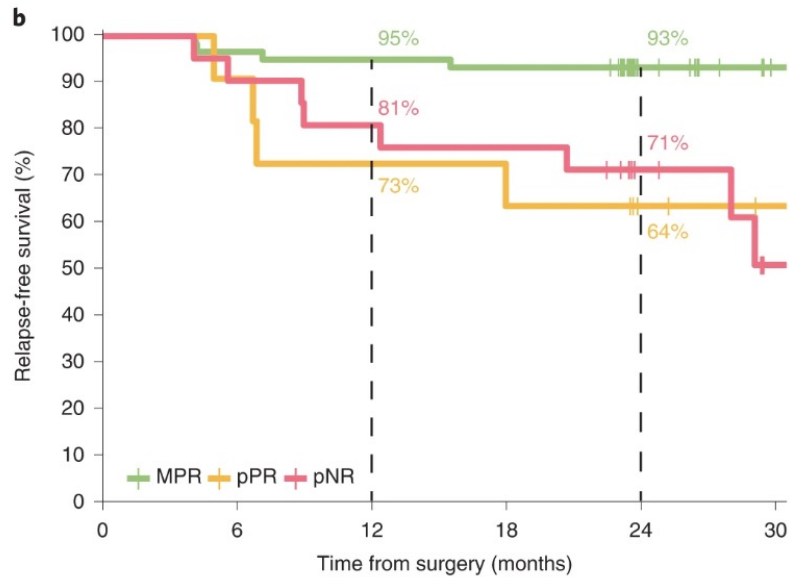
Fase II studie (n = 99)
Operabel st. IIIB-IIID

2x Ipi-Nivo (flip dose) ILN
22% ernstige nevenwerkingen

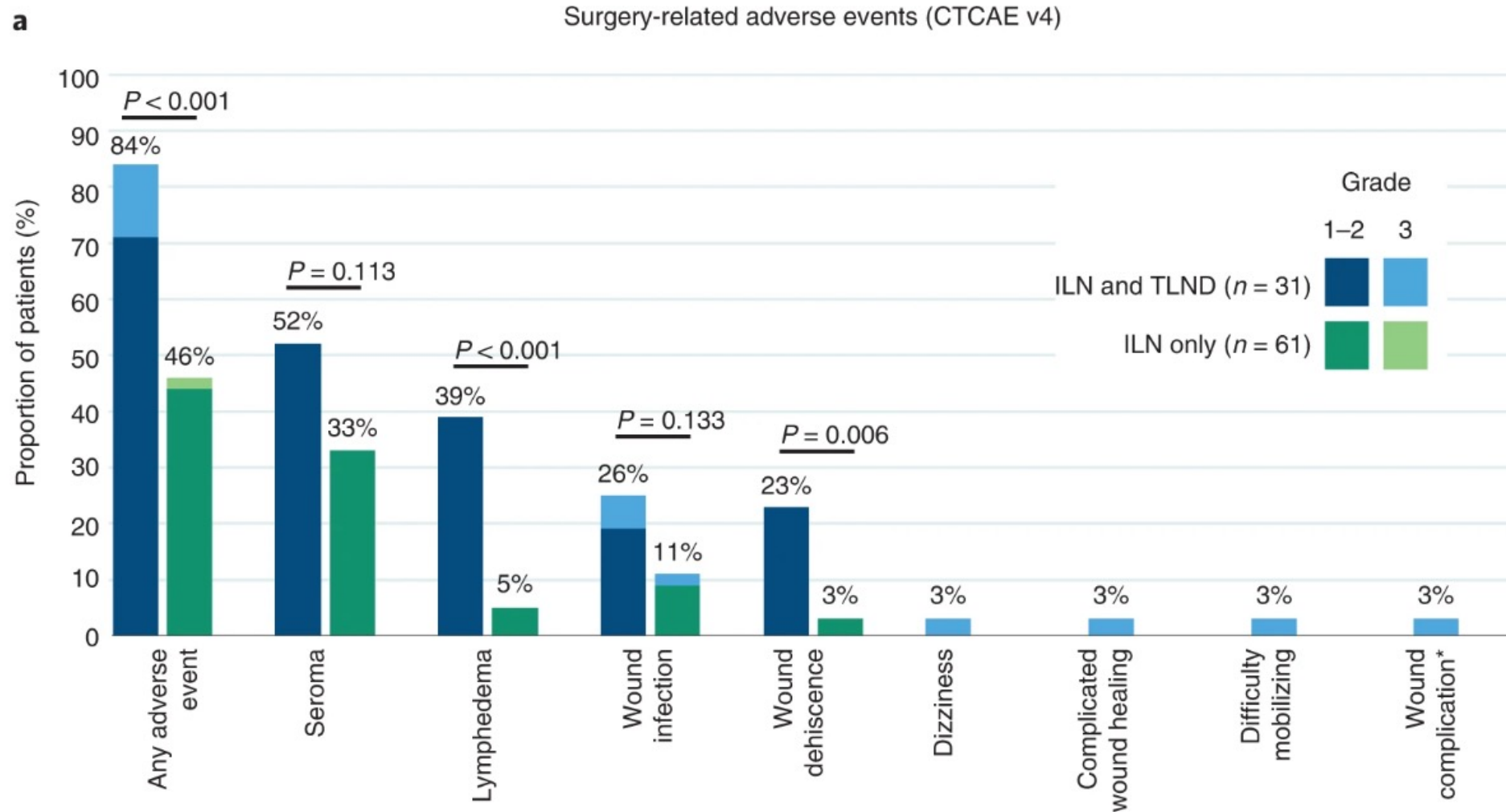


Adjuvante therapie

- 3x Nivolumab
- BRAFi/MEKi
- Radiotherapie



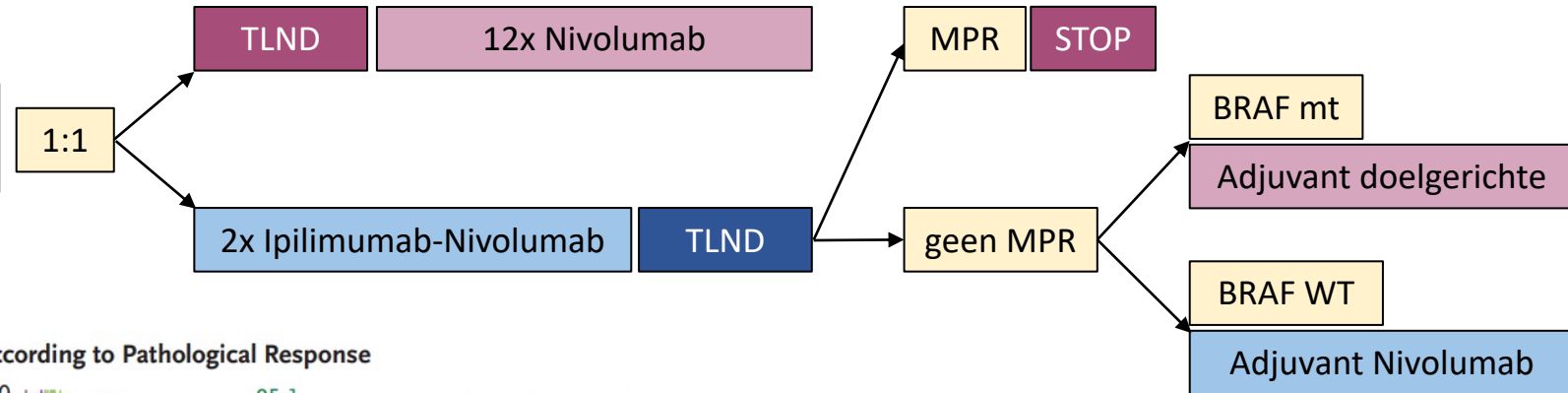
Behandeling aangepast aan hervalrisico



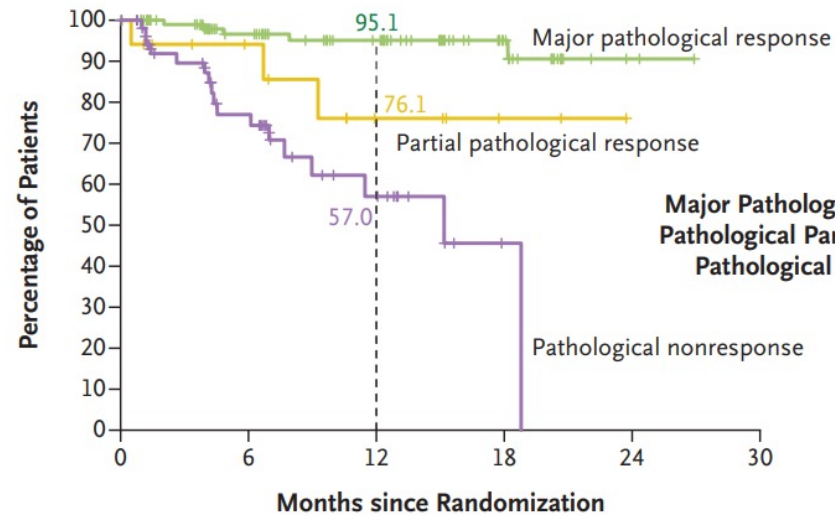
Risk-adapted treatment

NADINA

Fase III studie (n = 423)
Operabel st. III



Recurrence-free Survival According to Pathological Response



No. of Events/
Total No.
of Patients

Major Pathological Response 5/125
Pathological Partial Response 3/17
Pathological Nonresponse 17/56

No. at Risk (no. censored)

	0	6	12	18	24	30
Major pathological response	125 (0)	76 (46)	55 (66)	22 (99)	2 (118)	
Pathological partial response	17 (0)	11 (5)	5 (9)	2 (12)		
Pathological nonresponse	56 (0)	29 (17)	11 (30)	1 (39)		



Discussion

Neo-adjuvante behandeling

De beloften van een neo-adjuvante behandeling bij melanoom:

- 1) Verbeterde activatie van het immuunsysteem om melanoom aan te vallen **JA**
- 2) Voorspellen van de behandelingsuitkomst **JA**
- 3) Betere behandelingsuitkomsten **JA**
- 4) Behandeling aangepast aan het hervalrisico
 - Afbouw van behandeling bij “responders” **MISSCHIEN**
 - Minder uitgebreide chirurgie, en dus minder complicaties
 - Minder lange/intense of zelfs helemaal geen nabehandeling
 - Intensifiëren van behandeling bij “non-responders” **HANGT ER VAN AF**

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