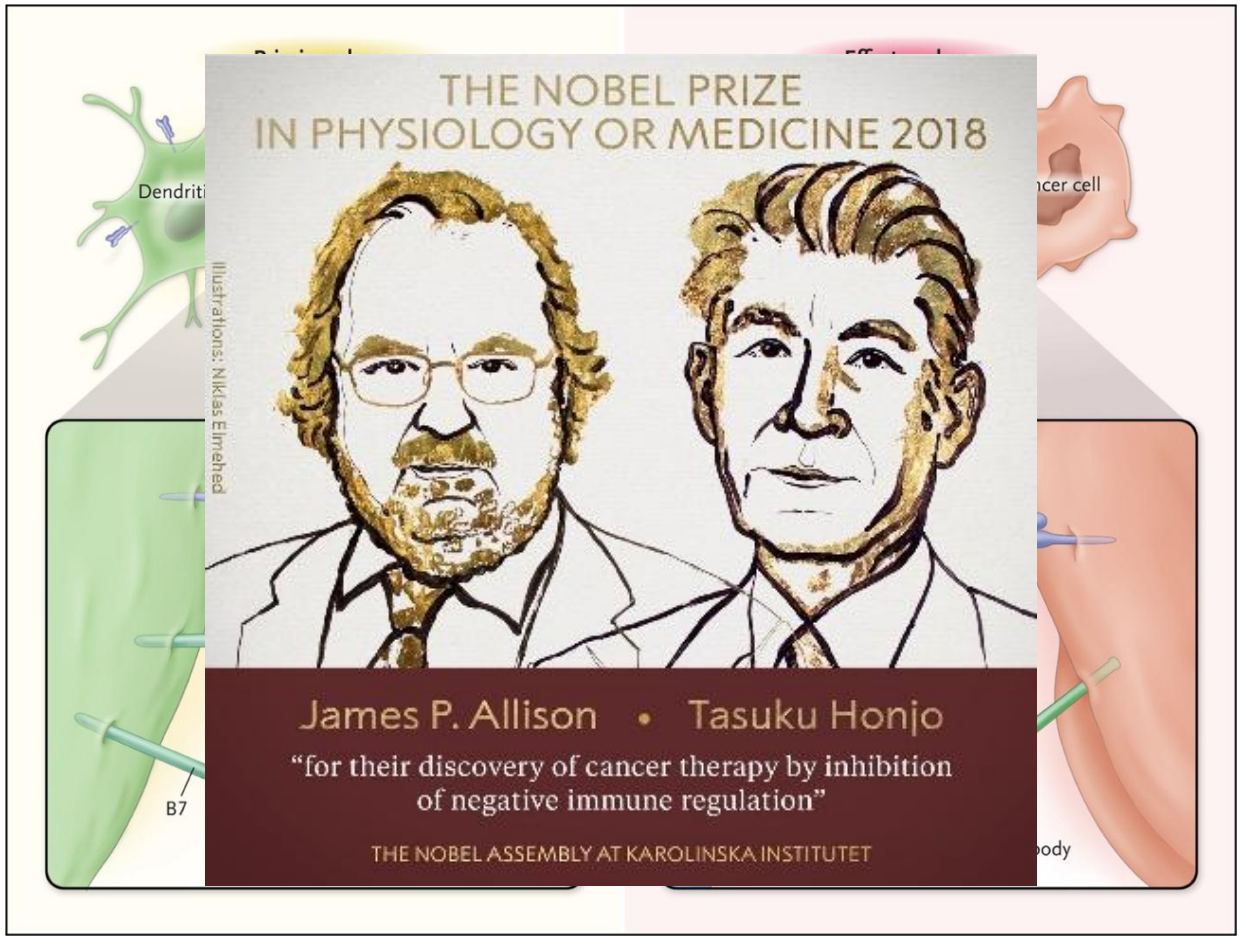
Ontwikkelingen binnnen de IMMUUNTHERAPIE

Sofie Wilgenhof

21 maart 2025

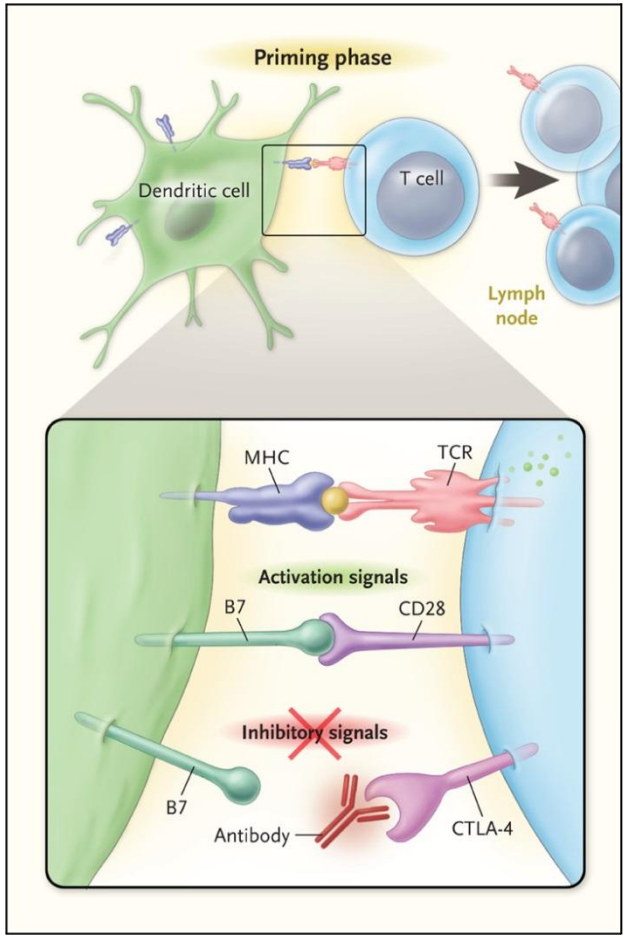
Immuuntherapie met checkpointremmers: CTLA-4 en PD-1/L1



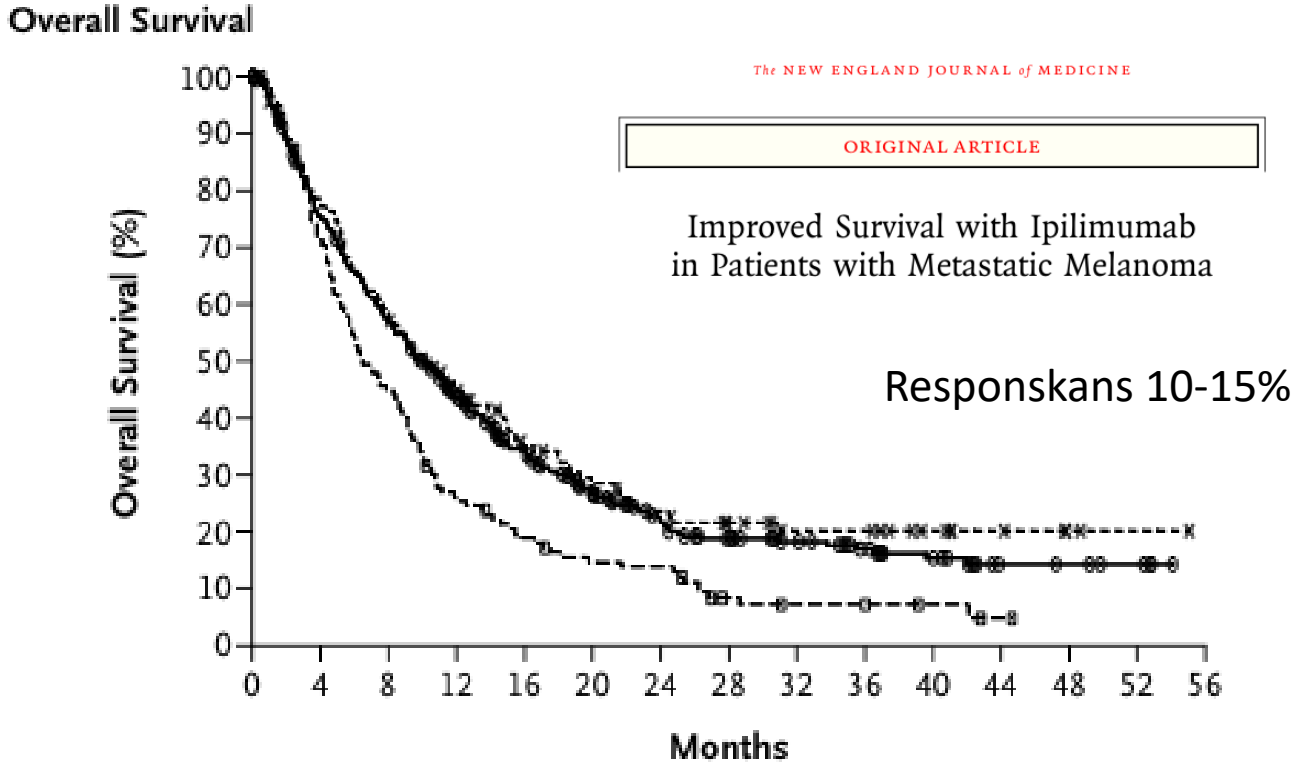
Ribas. NEJM. 2012

Ipilimumab bij gemetastaseerd melanoom

CTLA-4



Ribas. NEJM. 2012



The NEW ENGLAND JOURNAL of MEDICINE

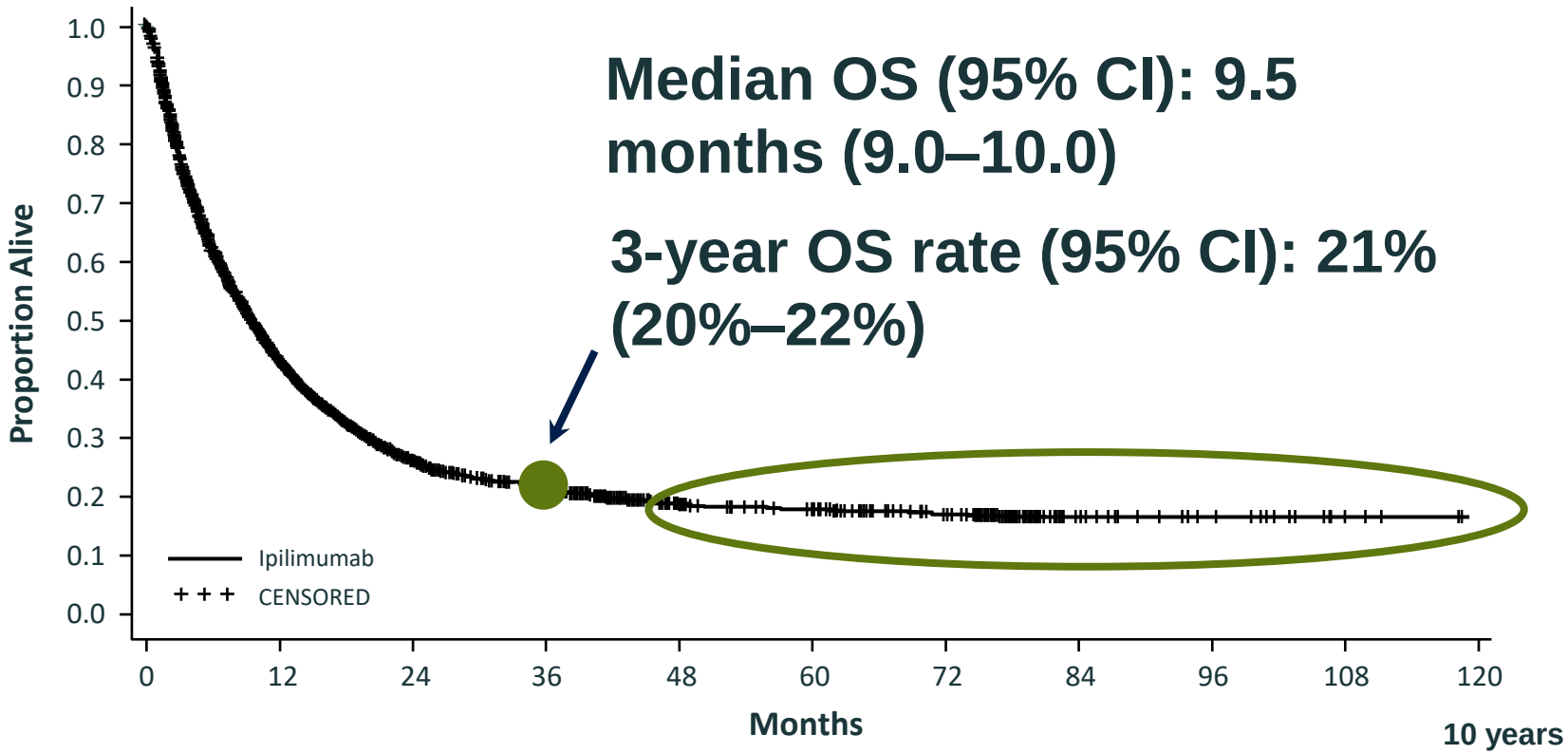
ORIGINAL ARTICLE

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

Responskans 10-15%

Hodi, Haanen, et al. NEJM. 2010

Gepoolde overlevingsanalyse van 4846 met ipilimumab behandelde patiënten



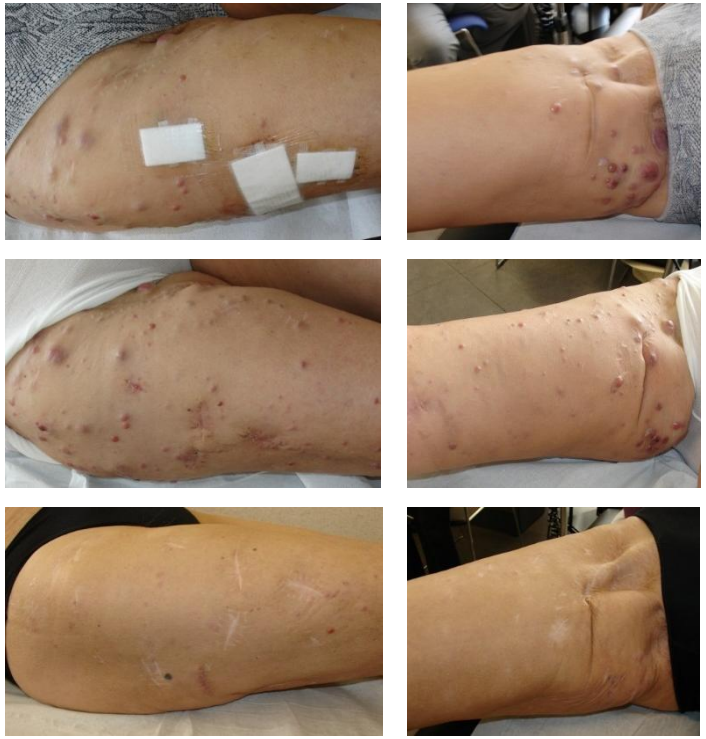
Schadendorf *et al.* ECCO/ESMO 2013
Schadendorf et al. JCO. 2015

ATYPISCHE TUMORRESPONSEN

Pre-treatment

During treatment
(3 weeks)

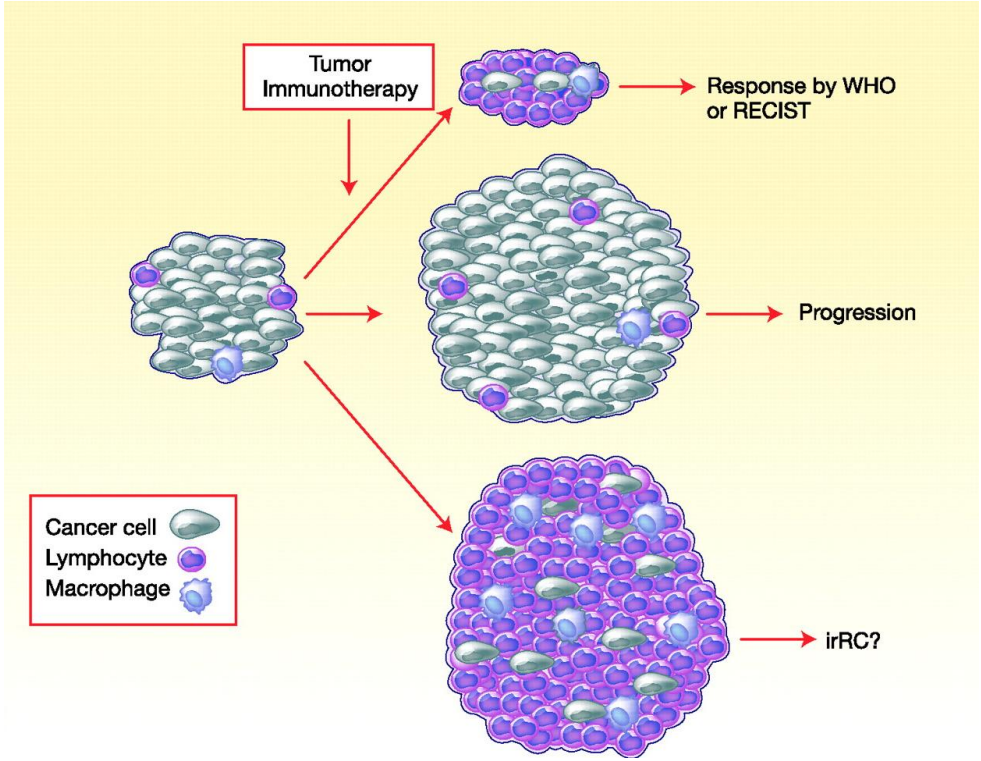
1 year
Post-treatment



Toename van metastasen

Afname van metastasen

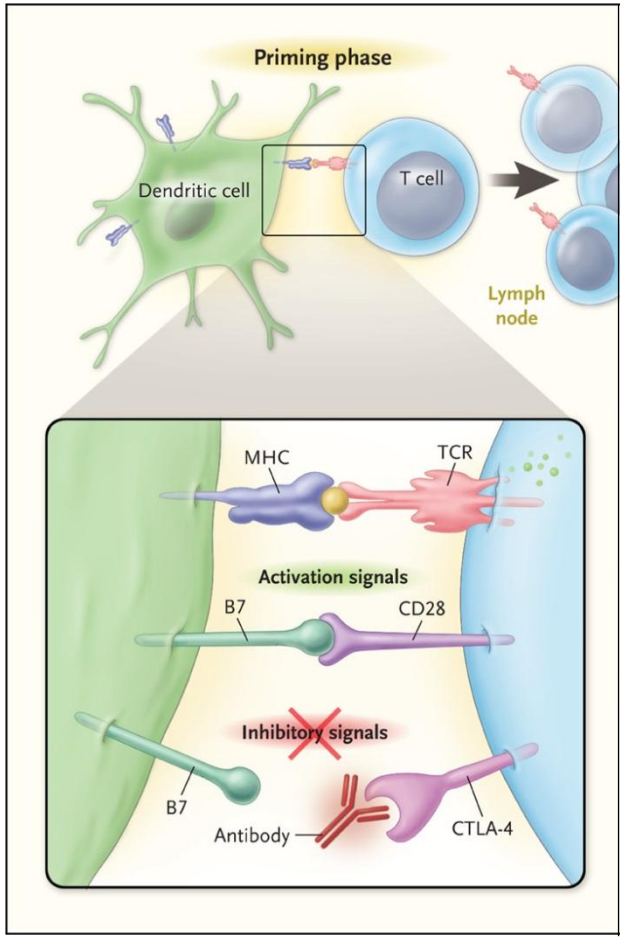
PSEUDOPROGRESSIE



Wolchock et al. CCR. 2009

Immune checkpoint inhibitors

CTLA-4



Ribas. NEJM. 2012

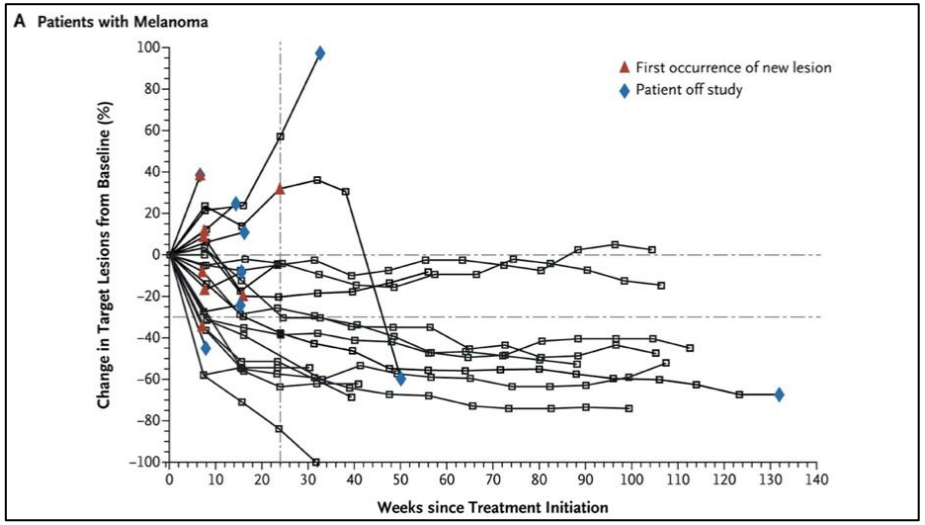
Anti-pd-1 antilichaam

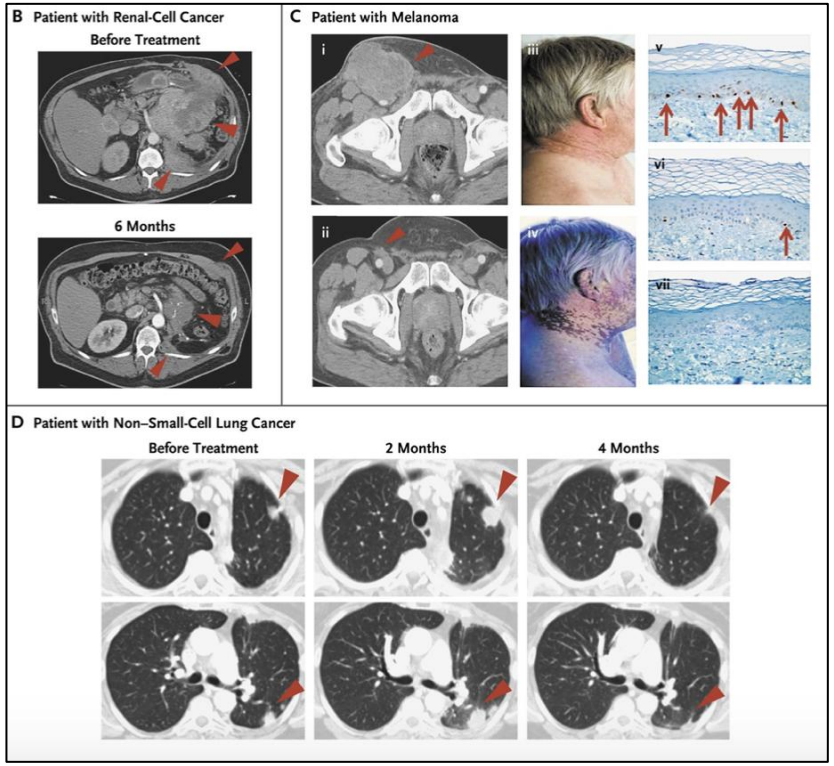
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 28, 2012 VOL. 366 NO. 26

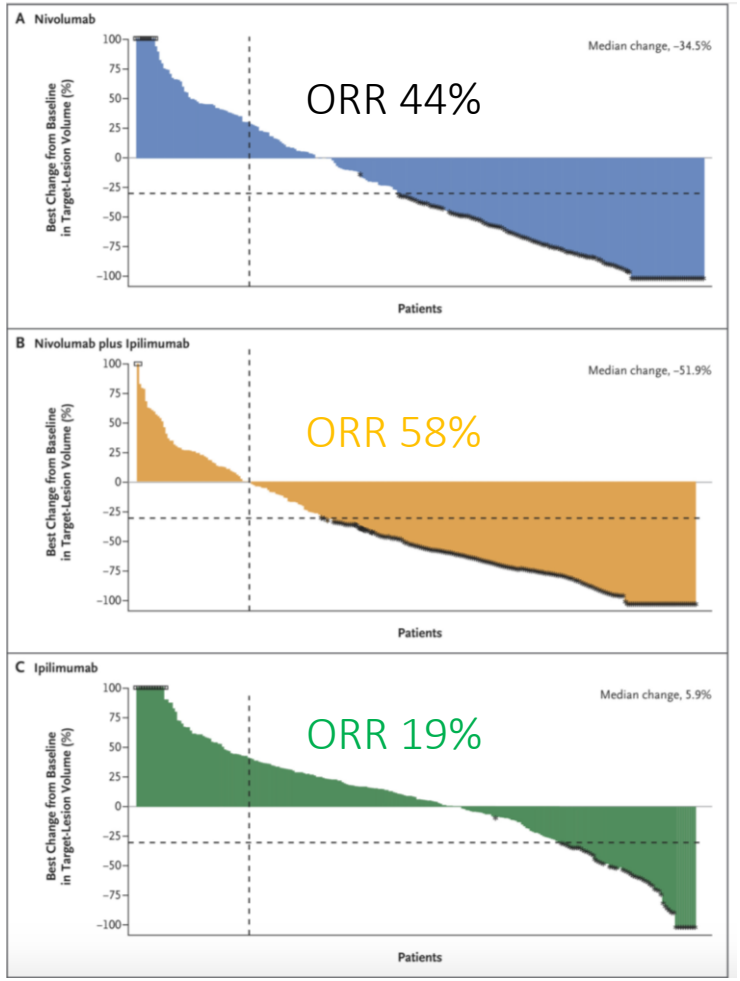
Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.

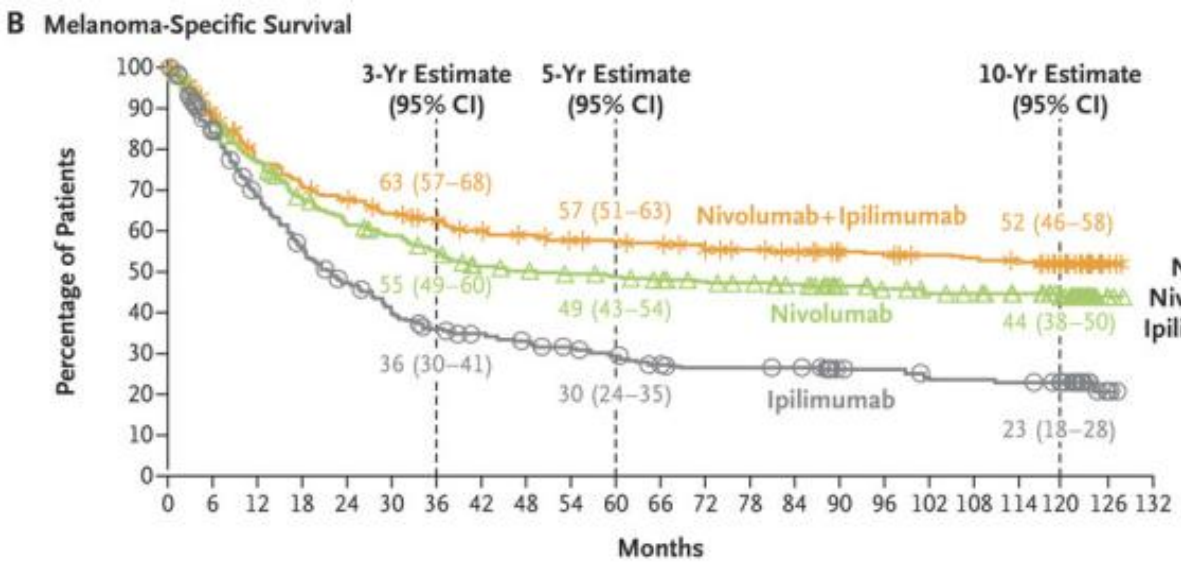




Responskans en 10 jaar-overleving bij gemetastaseerd melanoom



Larkin et al. NEJM. 2015; Larkin et al. NEM 2019



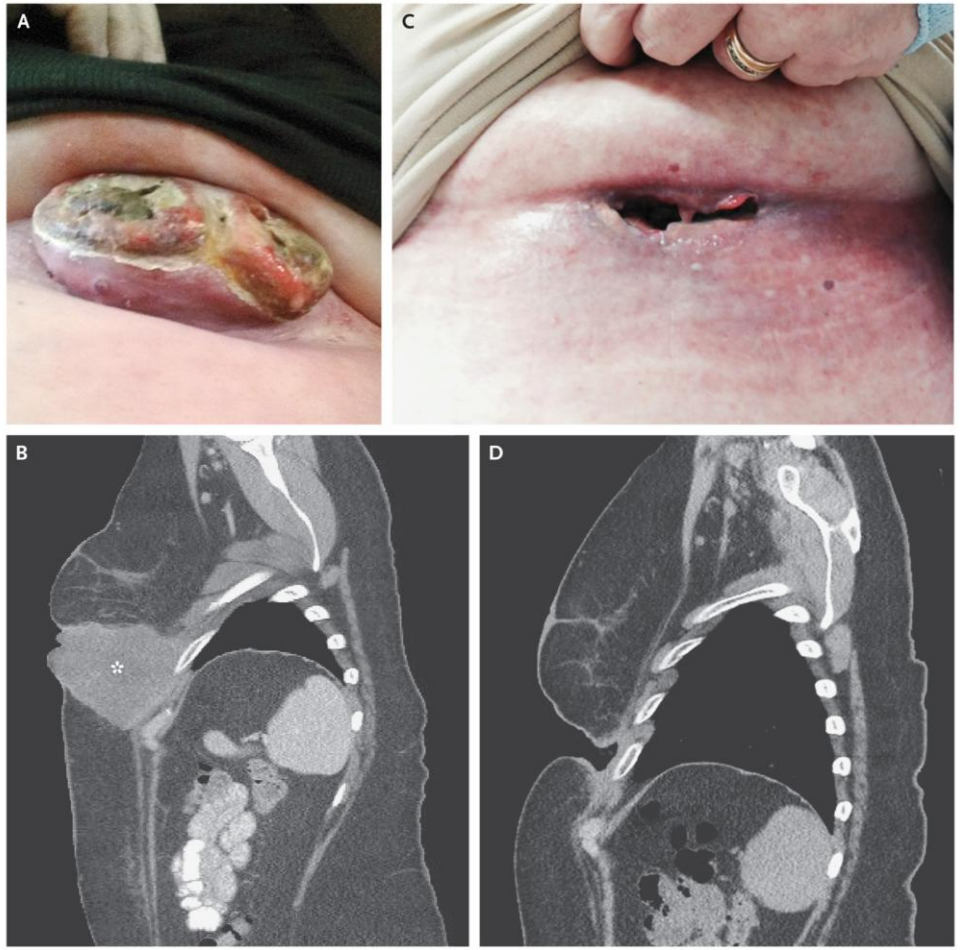
No. at Risk																							
Nivo+ipi	314	265	227	210	199	187	179	169	163	158	156	153	147	144	139	126	124	120	117	115	92	10	0
Nivolumab	316	265	231	201	181	171	158	145	141	137	134	130	126	123	118	107	102	98	96	92	77	4	0
Ipilimumab	315	253	203	163	135	113	100	94	87	81	75	68	64	64	63	50	49	44	43	42	35	3	0

	No. of Patients with Event	Median Melanoma-Specific Survival (95% CI)
		mo
Nivo+Ipi (N=314)	139	NR (71.8–NR)
Nivolumab (N=316)	163	49.4 (35.1–119.4)
Ipilimumab (N=315)	221	21.9 (18.1–27.4)

Hazard ratio for death from melanoma, nivo+ipi vs. ipilimumab, 0.48 (95% CI, 0.39–0.59)
Hazard ratio for death from melanoma, nivolumab vs. ipilimumab, 0.59 (95% CI, 0.49–0.73)
Hazard ratio for death from melanoma, nivo+ipi vs. nivolumab, 0.81 (95% CI, 0.64–1.01)

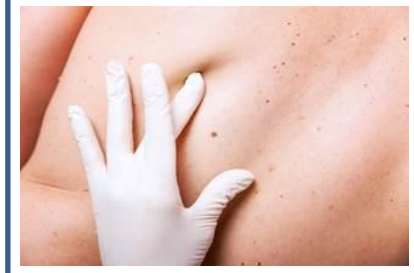
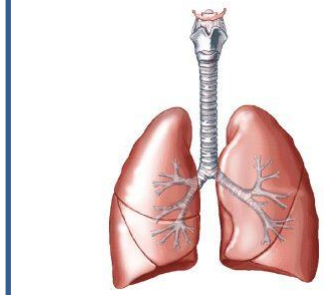
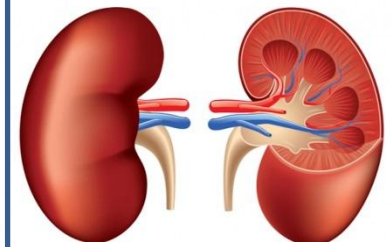
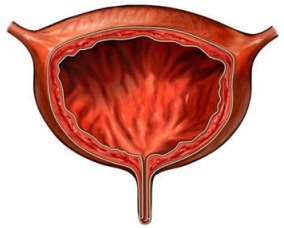
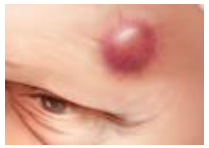
Wolchok JD. et al. NEJM. 2024

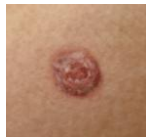
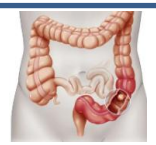
SNELLE TUMORRESPONS NA SLECHTS 1 TOEDIENING IPILIMUMAB + NIVOLUMAB:

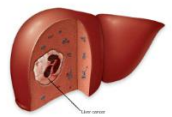
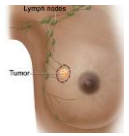
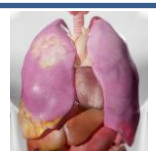
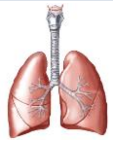


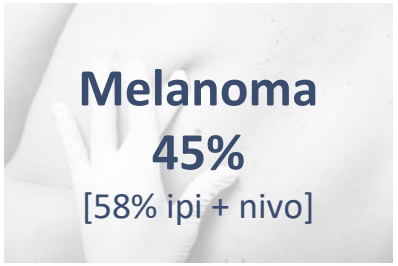
Chapman et al. NEJM. 2015

Indicaties ICI 2025

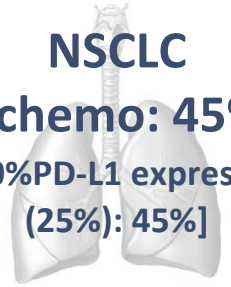






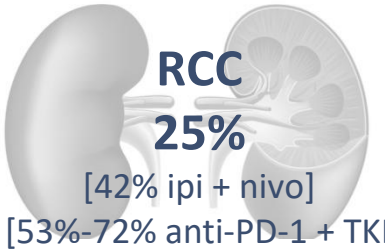





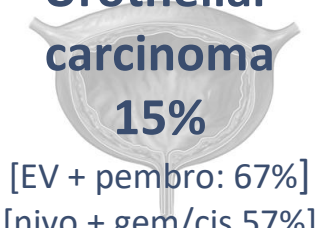
Melanoma
45%
[58% ipi + nivo]



NSCLC
[+chemo: 45%]
[>50%PD-L1 expression (25%): 45%]



RCC
25%
[42% ipi + nivo]
[53%-72% anti-PD-1 + TKI]



Urothelial carcinoma
15%
[EV + pembro: 67%]
[nivo + gem/cis 57%]

Merkel cell carcinoma
30-50%

Hodgkin lymphoma
65-85%

Head and neck carcinoma
15%

Squamous cell carcinoma of the skin
50%

Colorectal cancer
[MSI-H (5%): 50%]

Gastric/oesophageal [PD-L1+]
50-60% (+ chemotherapy)

HCC
30%

TNBC
(PD-L1+ TNBC)
53% (+ chemotherapy)

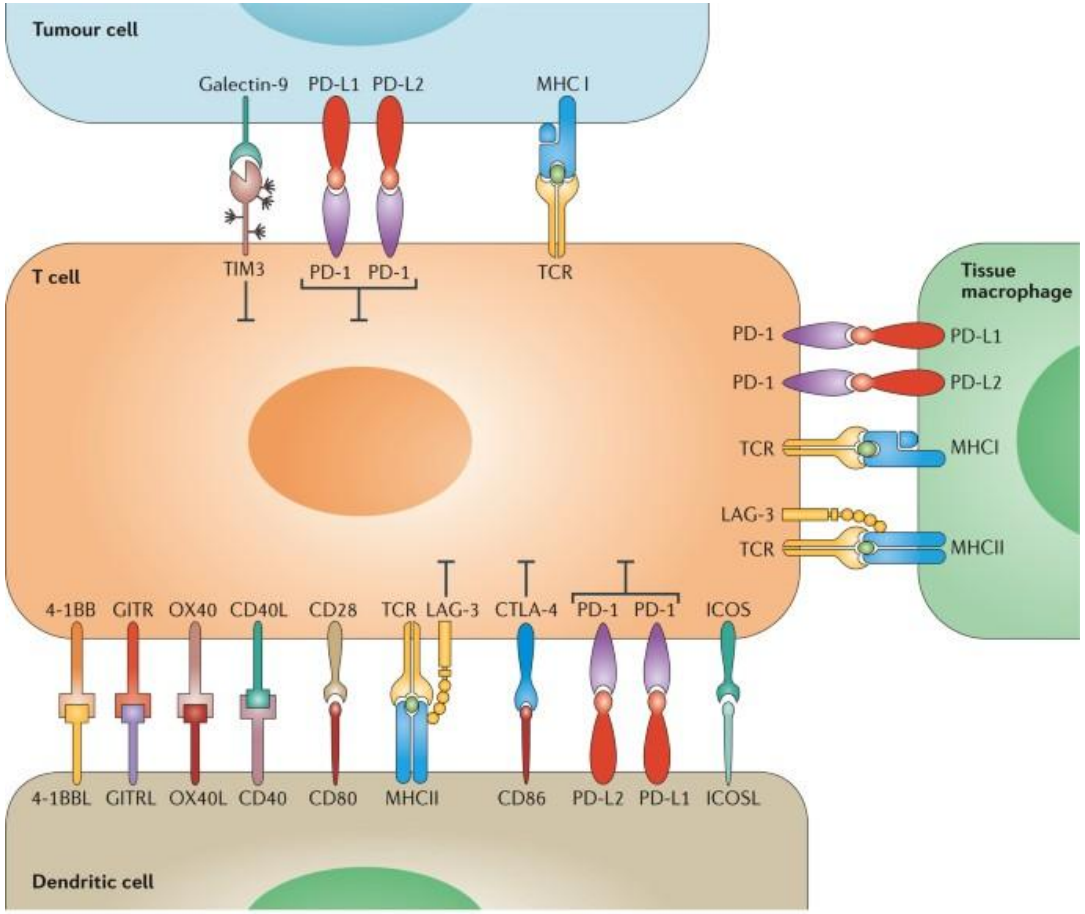
Mesothelioma
40% (ipi + nivo)

SCLC
60% (+ chemotherapy)

Cervical cancer (PD-L1+)
[+ beva + chemo: 68%]
Endometrial carcinoma
[chemo + dostarlimab: 70%]
[lenvatinib + pembrolizumab: 30%]

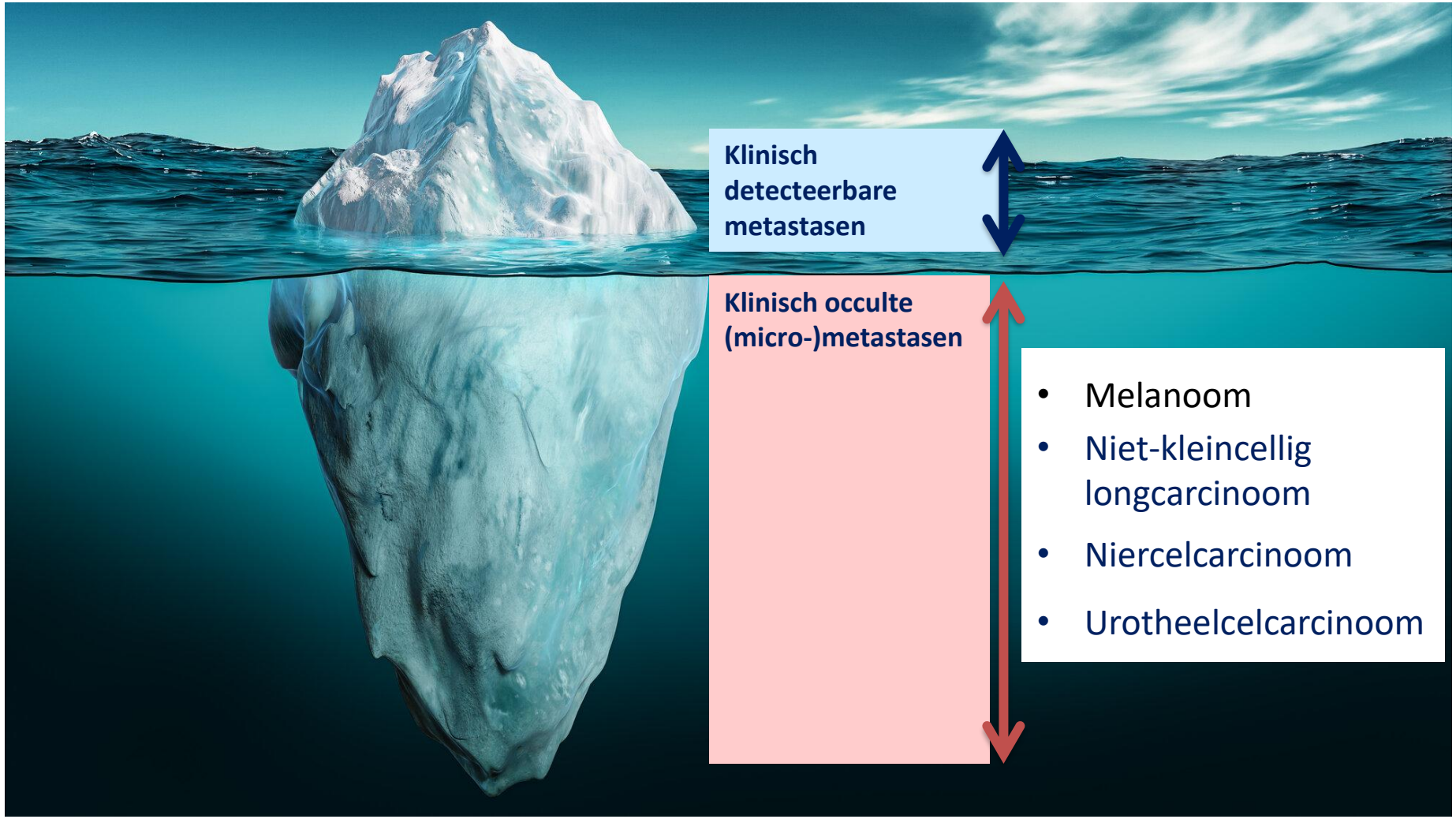
Clinical Trials

Nieuwe checkpoints

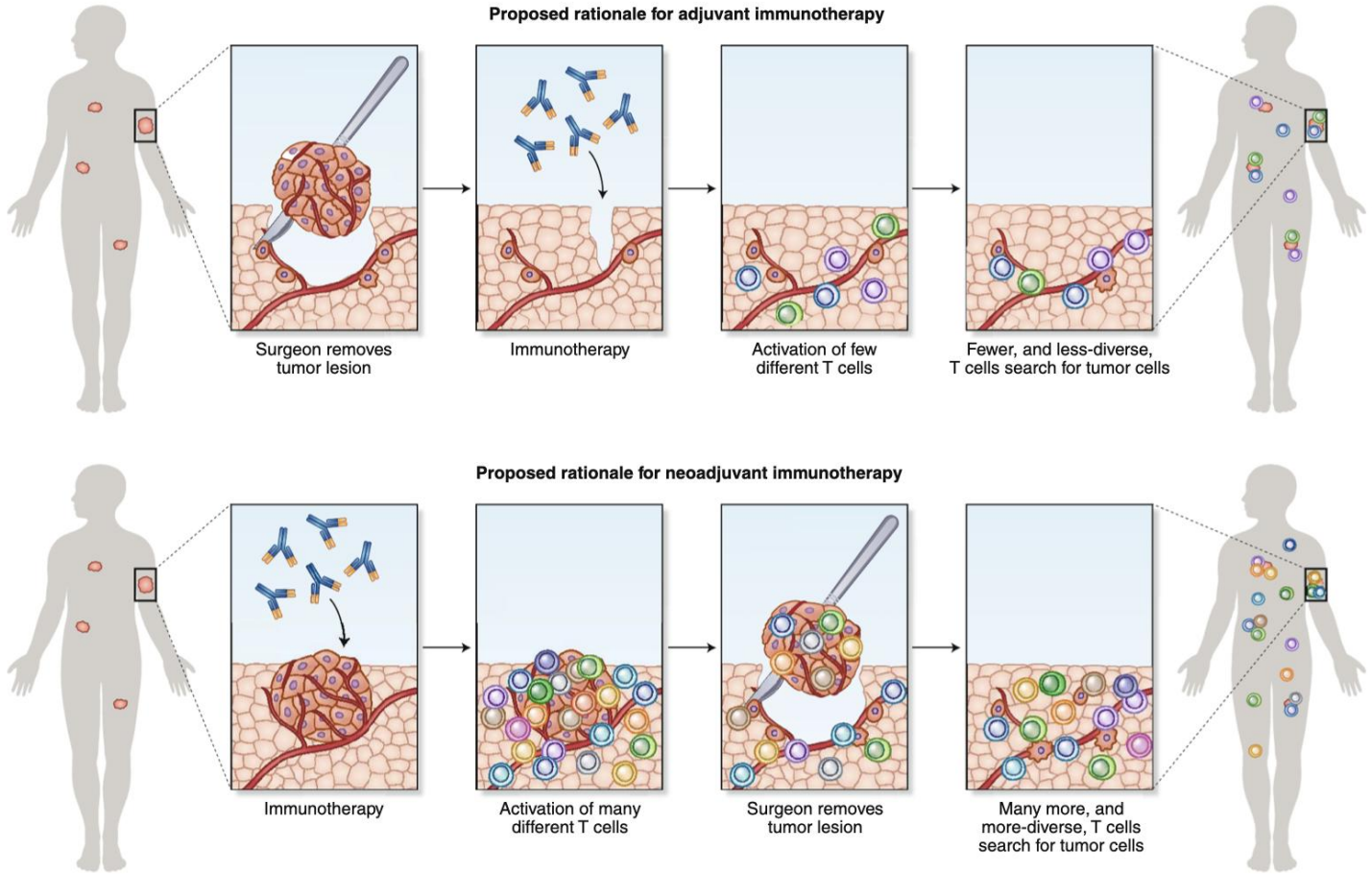


Nishino M. et al. Nature Reviews Clinical Oncology. 2017

ADJUVANTE behandeling



Neo-adjuvante behandeling



Versluis JM, Long GV, Blank CU. Nat Med. 2020

NADINA - Trial Design

- Stage III de novo or recurrent path proven resectable melanoma with at least 1 LN metastasis
- Additional in-transit (≤3) allowed
- Naïve for anti-PD-1, anti-CTLA-4, anti-LAG-3, BRAFi+MEKi
- Stratified for BRAF, continent, and in-transit metastases

A

2 courses IPI 80mg + NIVO 240mg q3w → TLND

- Major pathologic response (MPR; pCR or near pCR; ≤ 10% vital tumor cells): no additional treatment, start FU, CT q12w → FU
- no MPR (pPR or pNR; > 10% vital tumor cells): start no later than week 12 with 11 courses NIVO 480mg q4w (BRAFwt) or 46 weeks DAB 150mg bid + TRAM 2mg qd (BRAFV600E/K) +/- parallel adjuvant RT[#] → FU

B

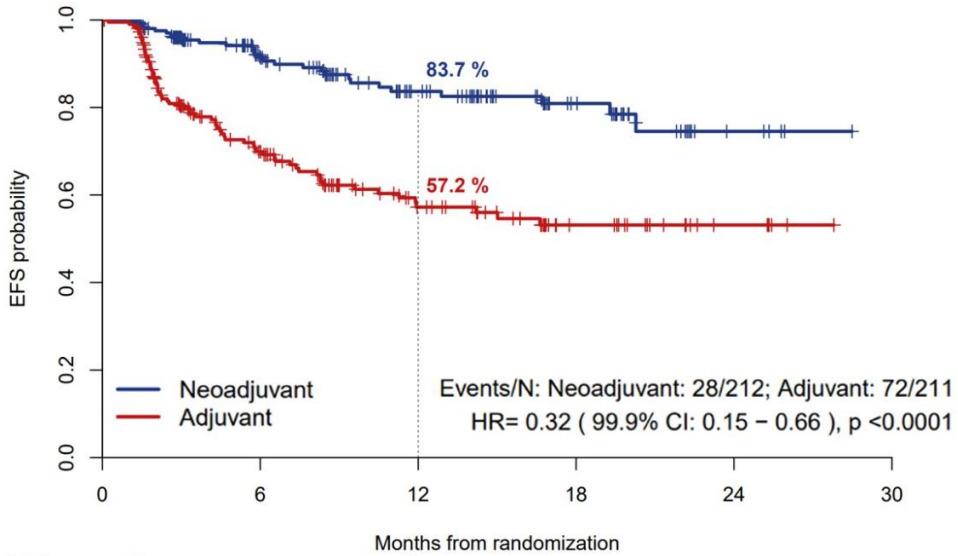
TLND → start no later than week 12 with 12 courses NIVO 480mg q4w +/- adjuvant RT[#] → FU

[#] adjuvant radiotherapy according to patient's and physician's decision allowed

-4	0	3	6	9	12	24	36	48	60	
PET/CT, CT, MR brain, Tumor biopsy, ePRO's, QoL, lab	lab	lab	CT QoL lab	lab	CT QoL lab	CT QoL lab	CT QoL lab	CT QoL lab	CT QoL lab	CT, lab q12w QoL q26w year 2 & 3

PRESENTED BY: Christian U. Blank, MD PhD

NADINA – Primary Endpoint: Event-Free Survival (EFS)

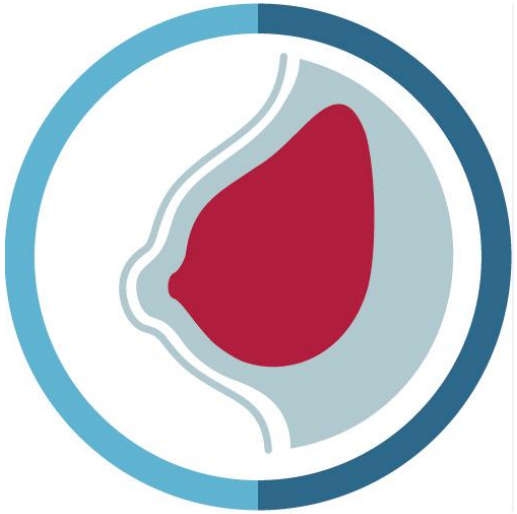


# at risk (censored)										
Neoadjuvant	212	(0)	126	(71)	77	(111)	34	(152)	5	(179)
Adjuvant	211	(0)	100	(57)	53	(89)	23	(116)	6	(133)

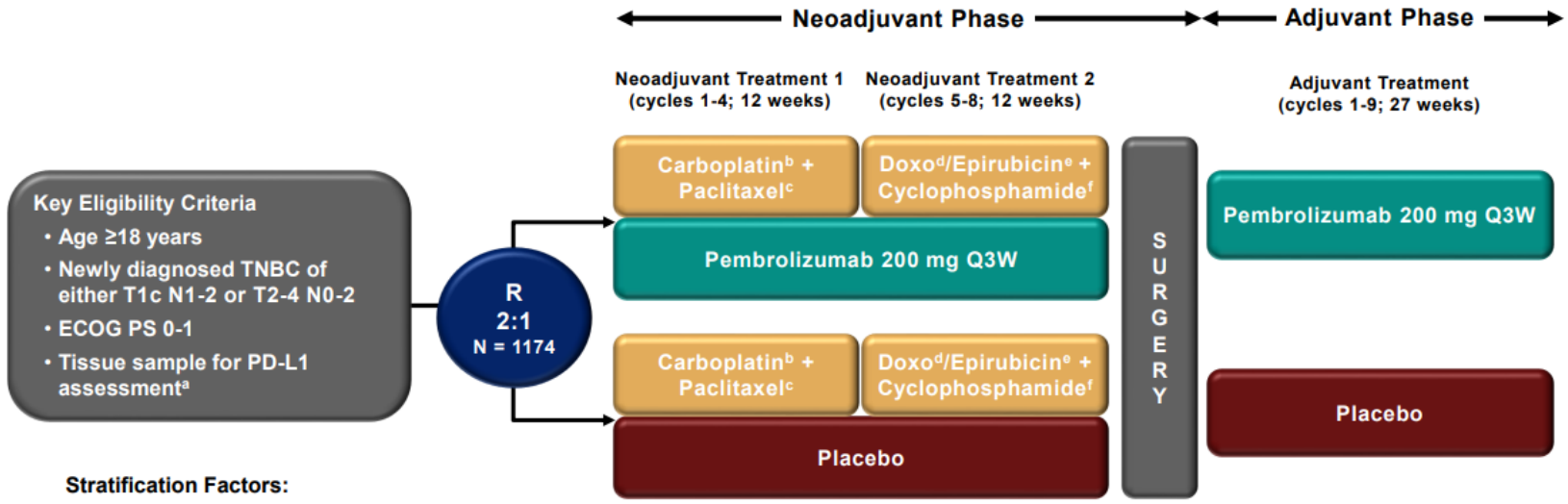
PRESENTED BY: Christian U. Blank, MD PhD

Blank CU et al. NEJM 2024

Peri-operatieve behandeling



KEYNOTE-522 Study Design (NCT03036488)



Stratification Factors:

- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (QW vs Q3W)

Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post-treatment included)

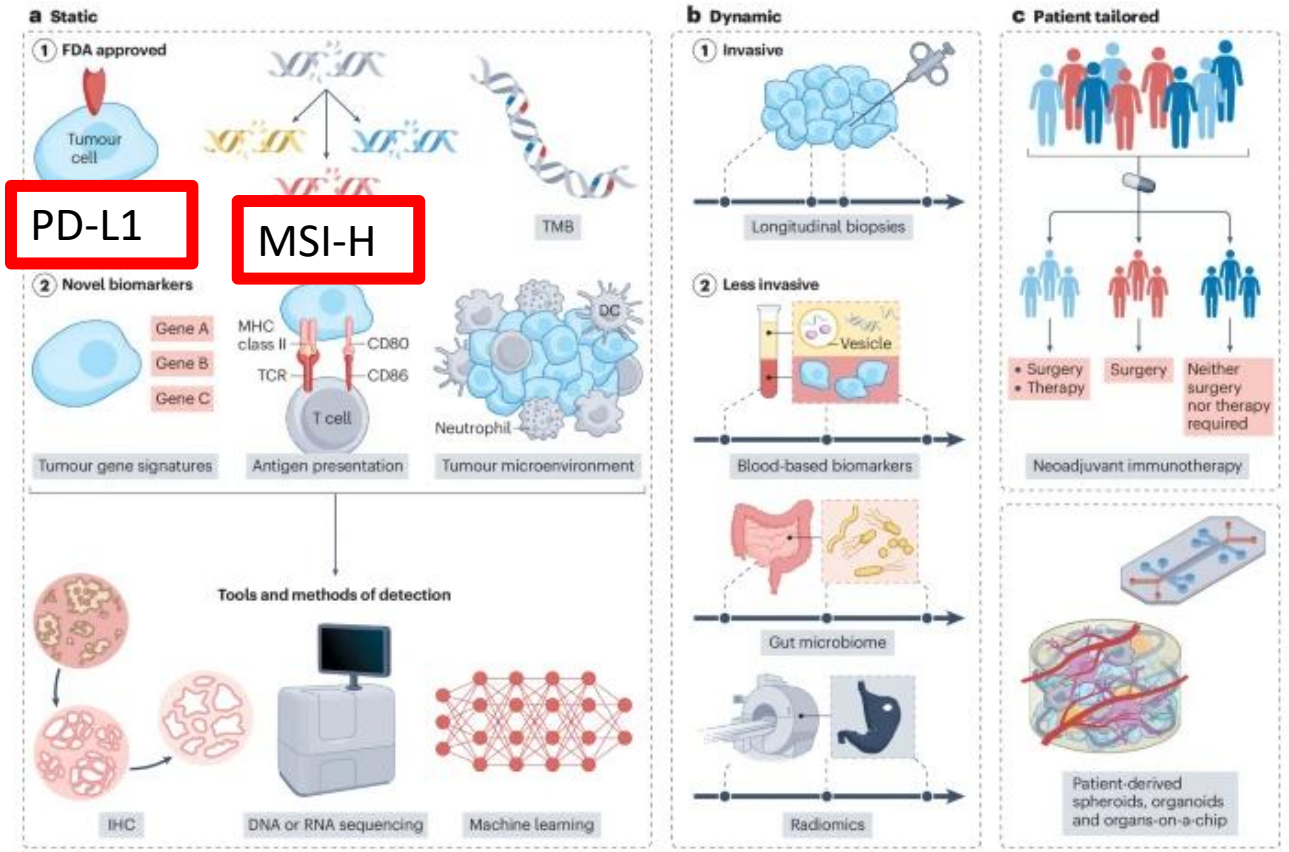
Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post-treatment included)

[a]Must consist of at least 2 separate tumor cores from the primary tumor. [b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW. [c]Paclitaxel dose was 80 mg/m² QW. [d]Doxorubicin dose was 60 mg/m² Q3W. [e]Epirubicin dose was 90 mg/m² Q3W. [f]Cyclophosphamide dose was 600 mg/m² Q3W.

Schmid P. et al NEJM 2024

BIOMARKERS

Fig. 1: Predictive biomarkers of immune checkpoint inhibitors in solid tumours.



Holder A.M. et al. Nat Rev Cancer. 2024

Lokaal gevorderd MSI-H coloncarcinoom

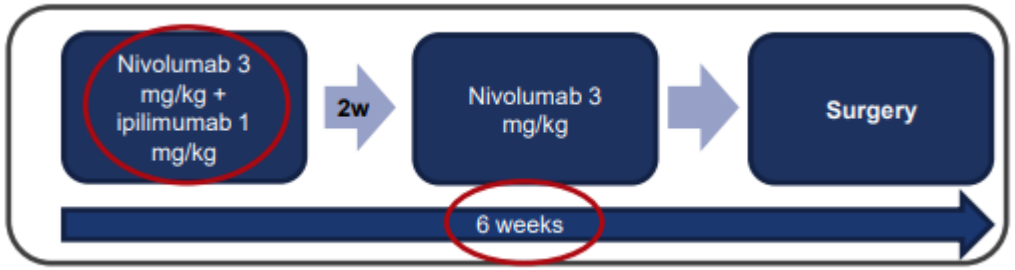
98% pathologische respons
95% MPR

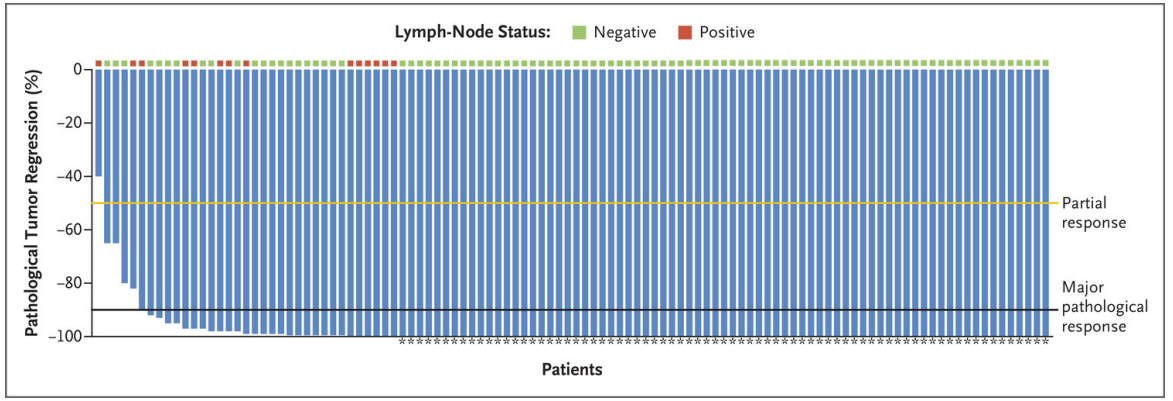
The NEW ENGLAND JOURNAL of MEDICINE

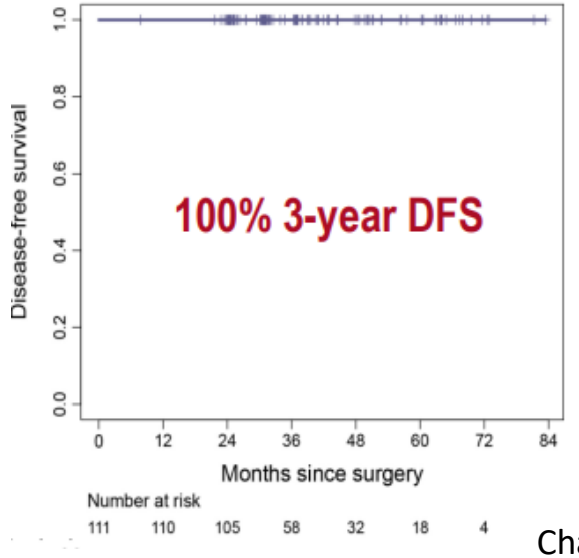
ESTABLISHED IN 1812 JUNE 6, 2024 VOL. 390 NO. 21

Neoadjuvant Immunotherapy in Locally Advanced Mismatch Repair–Deficient Colon Cancer

Myriam Chalabi, M.D., Ph.D., Yara L. Verschoor, M.D., Pedro Batista Tan, M.Sc., Sara Balduzzi, Ph.D., Anja U. Van Lent, M.D., Ph.D., Cecile Grootscholten, M.D., Ph.D., Simone Dokter, M.Sc., Nikė V. Büller, M.D., Ph.D., Brechtje A. Grotenhuis, M.D., Ph.D., Koert Kuhlmann, M.D., Ph.D., Jacobus W. Burger, M.D., Ph.D., Inge L. Huibregtse, M.D., Ph.D., Tjeerd S. Aukema, M.D., Ph.D., Eduard R. Hendriks, M.D., Steven J. Oosterling, M.D., Ph.D., Petur Snaebjornsson, M.D., Ph.D., Emile E. Voest, M.D., Ph.D., Lodewyk F. Wessels, Ph.D., Regina G. Beets-Tan, M.D., Ph.D., Monique E. Van Leerdam, M.D., Ph.D., Ton N. Schumacher, Ph.D., José G. van den Berg, M.D., Ph.D., Geerard L. Beets, M.D., Ph.D., and John B. Haanen, M.D., Ph.D.

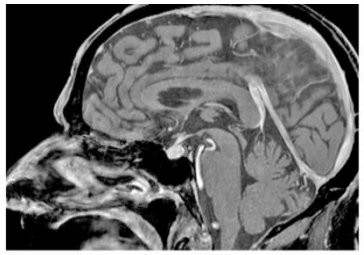


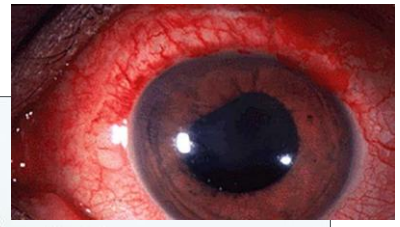


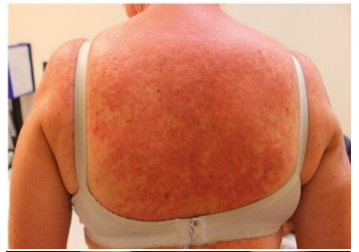


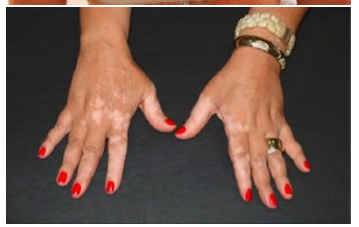
Chalabi M. et al NEJM 2024

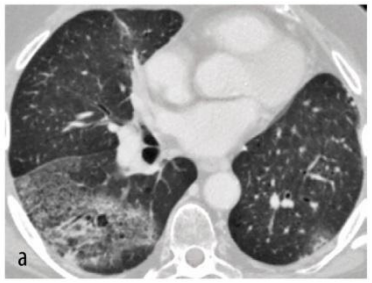
BIJWERKINGEN: auto-immuun reacties

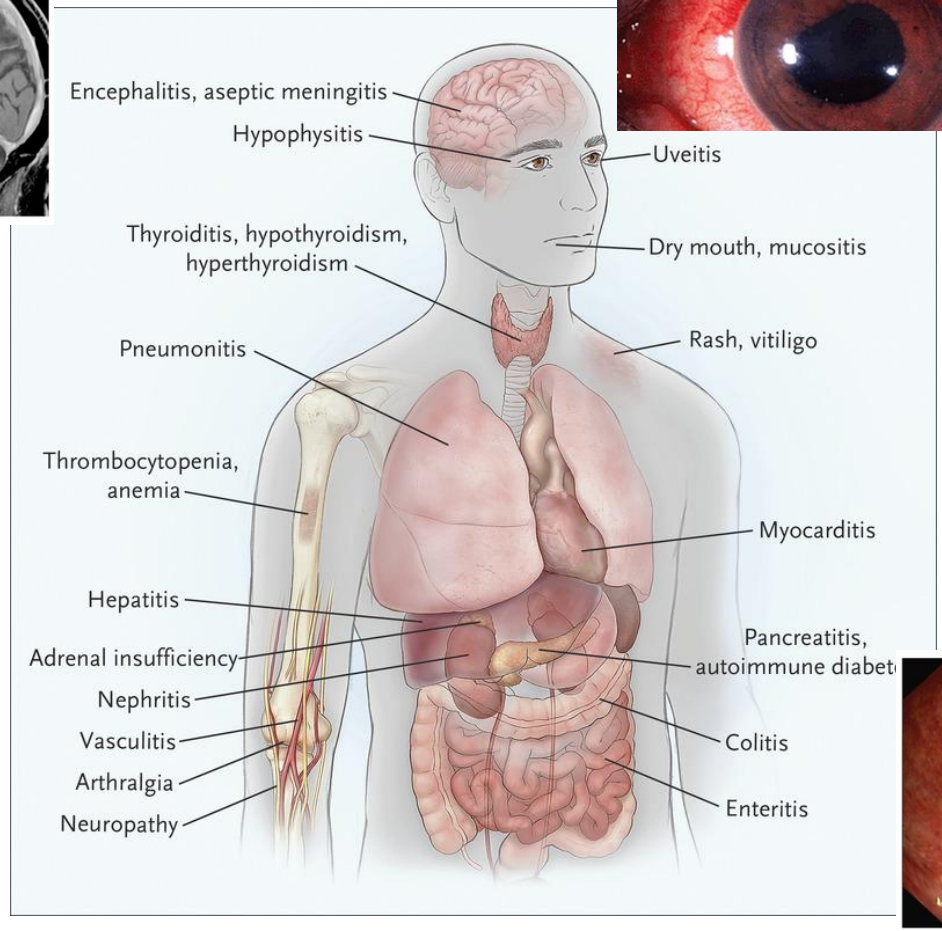


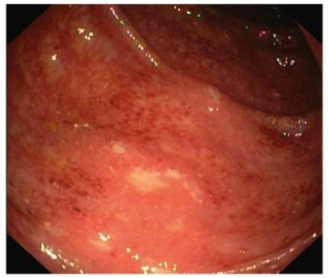






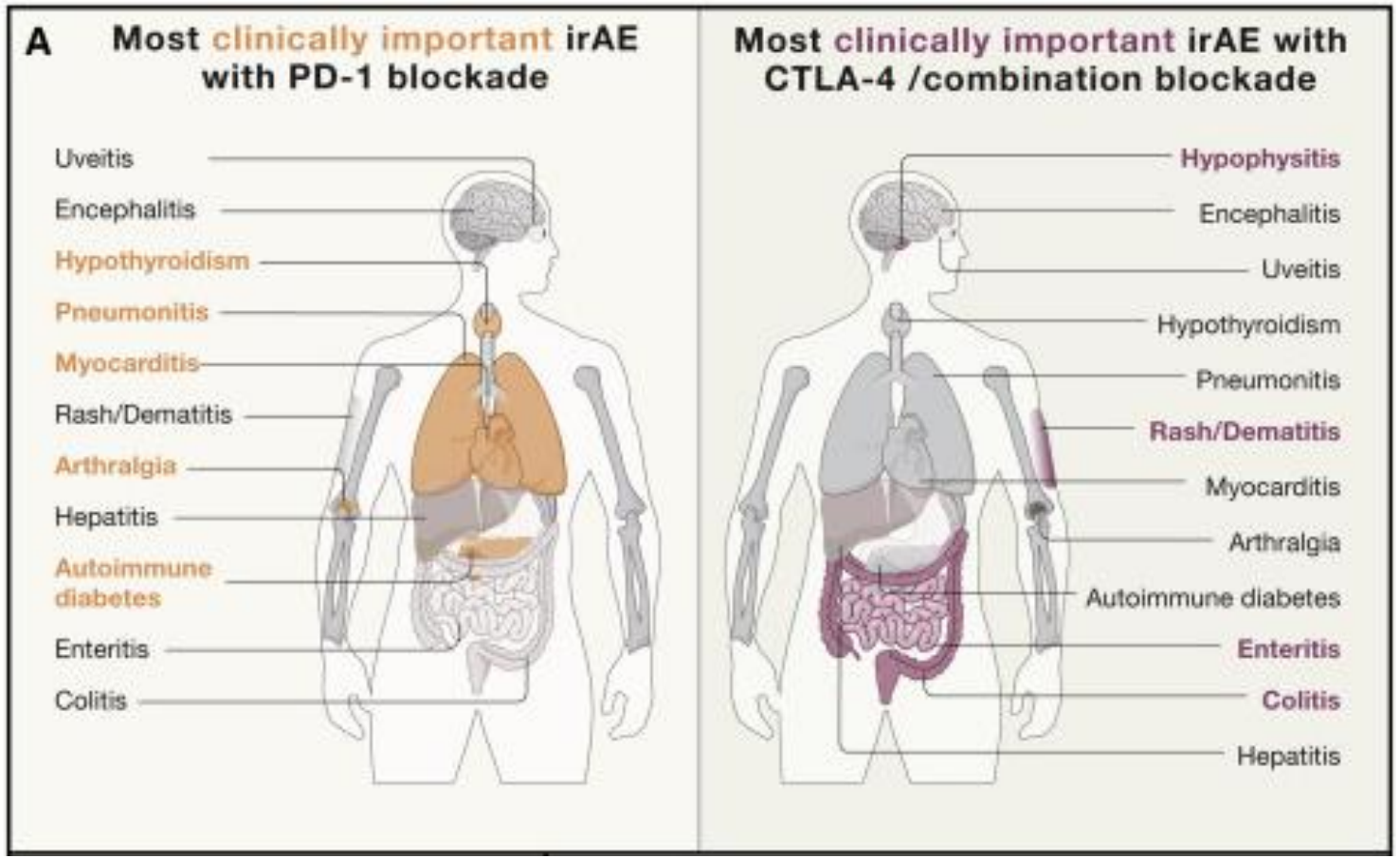






Postow et al. NEJM. 2018; Steebruggen et al. NTvG 2016

BELANGRIJKE BIJWERKINGEN BIJ PD-1/CTLA-4 BLOKKADE

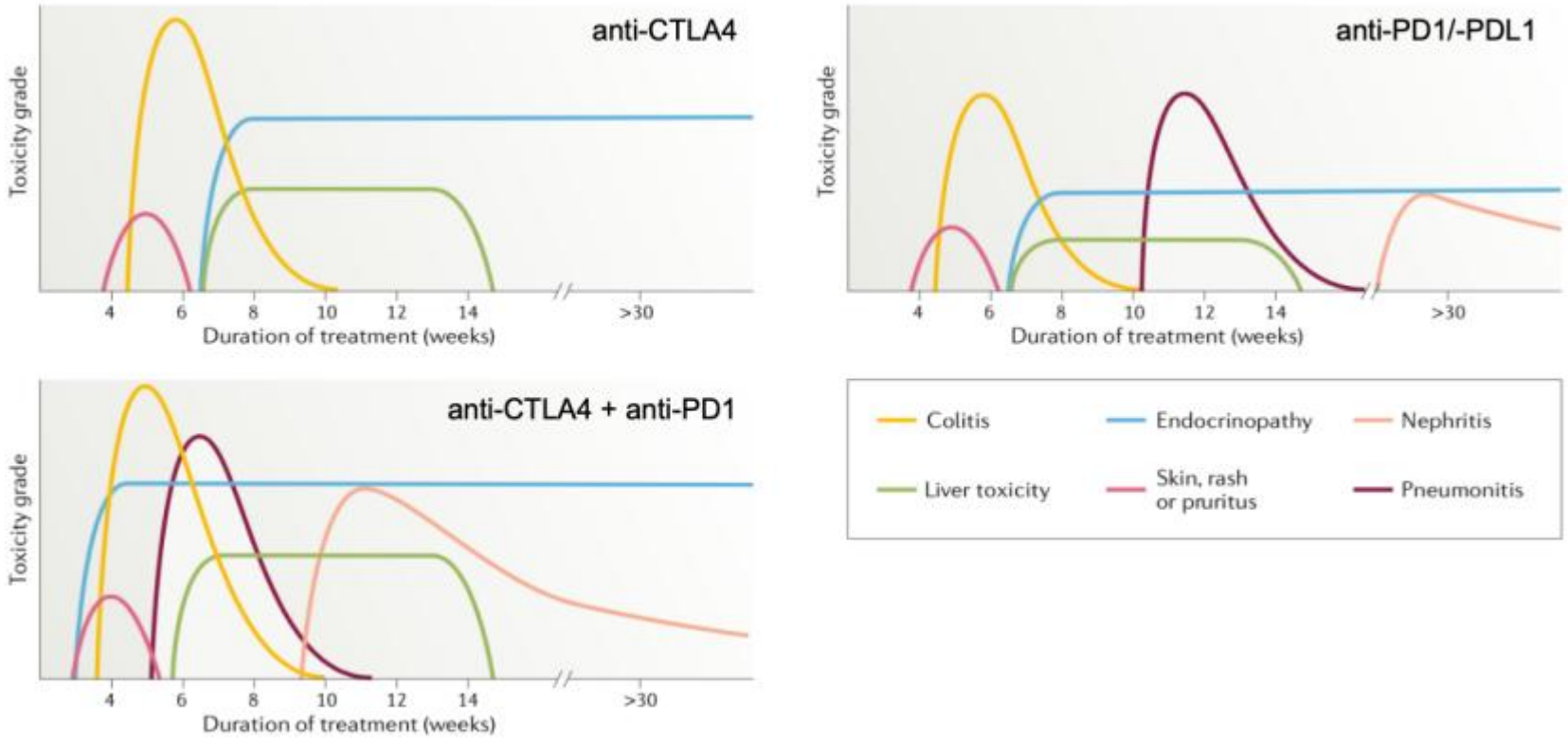


Dougan et al. Cell. 2021

Frequentie van ernstige bijwerkingen

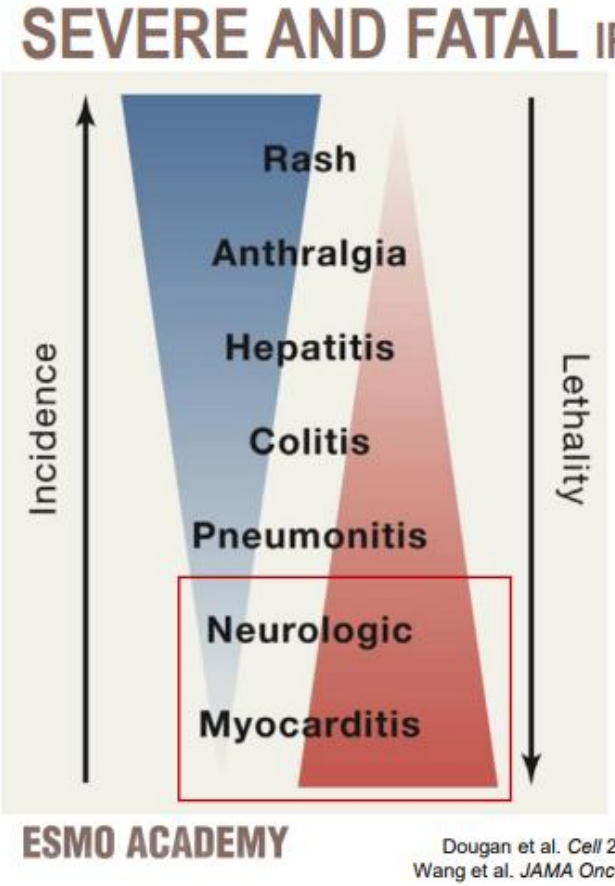
- Anti-PD-1: 10-14%
- Anti-PD-1 + anti-CTLA-4: 48-58%

KINETIEK VAN BIJWERKINGEN

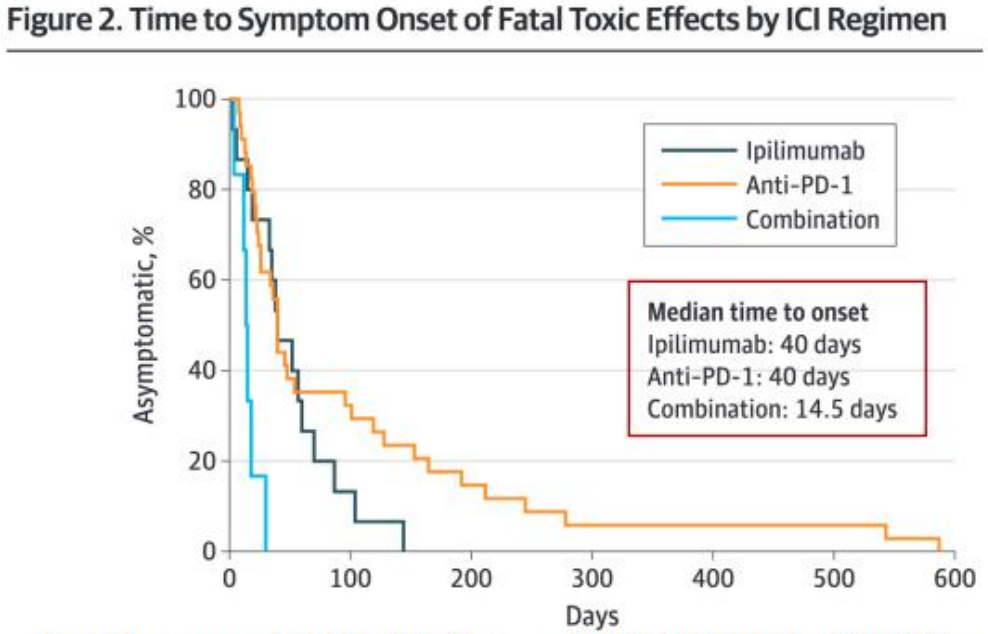


Martins et al. Nat Rev Clin Oncol 2019

Fatale bijwerkingen

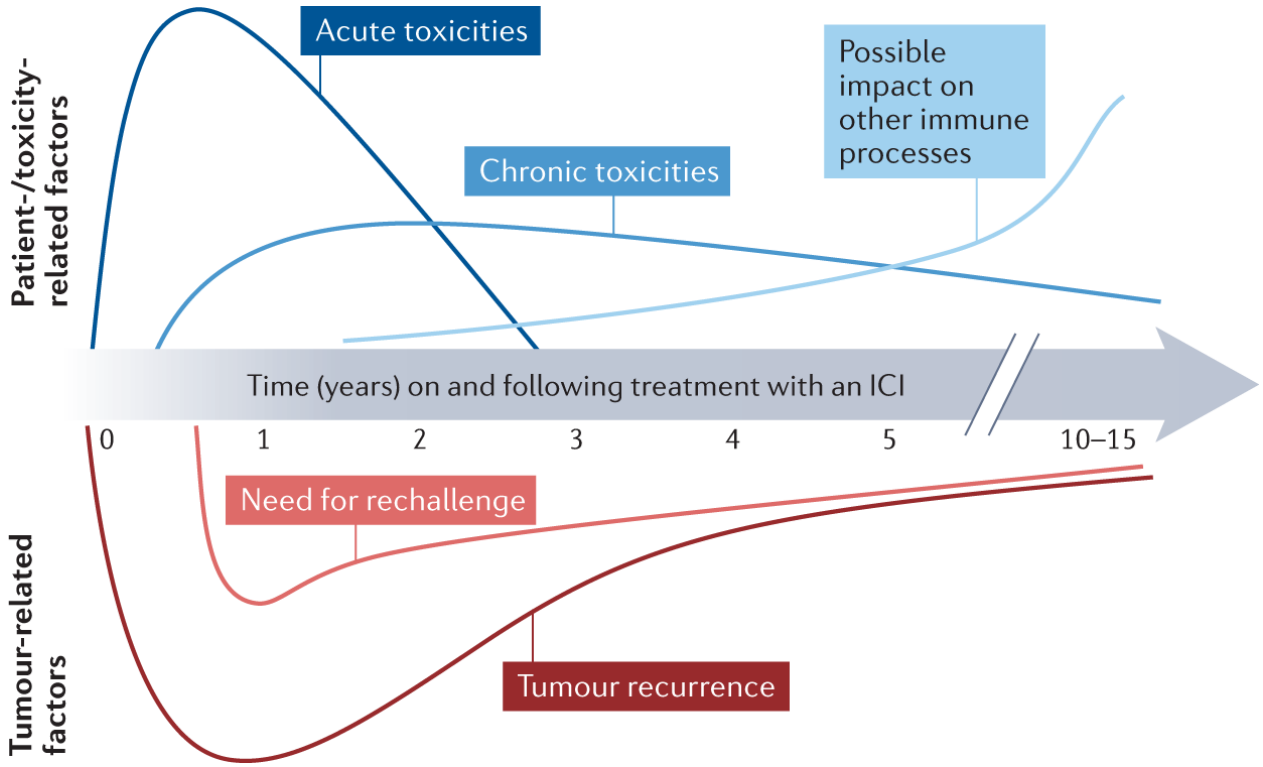


Dougan et al. *Cell* 2021
Wang et al. *JAMA Oncol* 2018



Incidence of lethal irAEs: aPD1/aPDL1: 0.37%
aCTLA4: 1.08%, aCTLA + aPD1/PDL1: 1.23%

Acute en chronische bijwerkingen

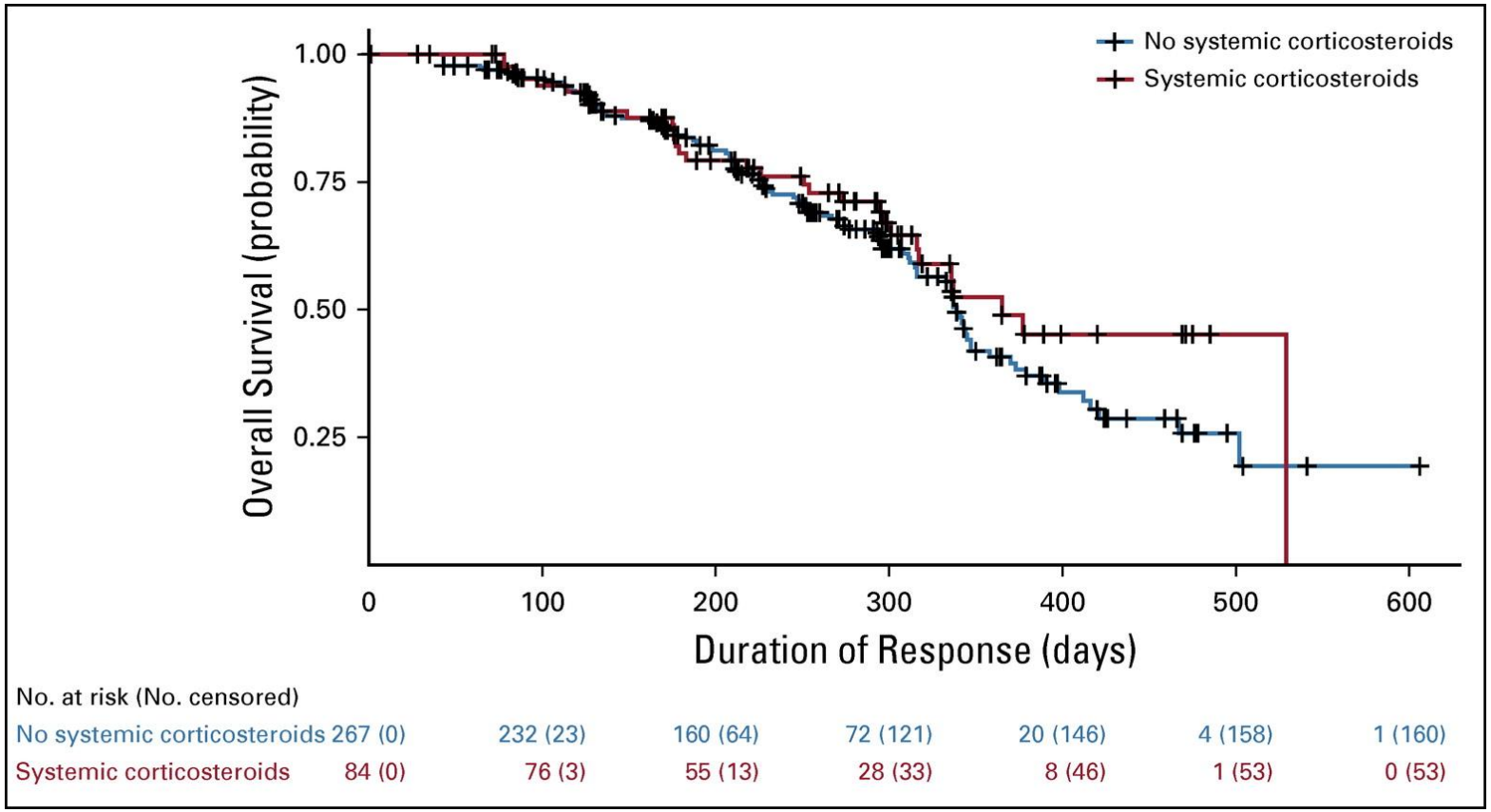


Chronische bijwerkingen in 40% van de patiënten

- Vermoeidheid
- Gewrichtsklachten
- Endocriene bijwerkingen
- Jeuk
- Drogen ogen/mond

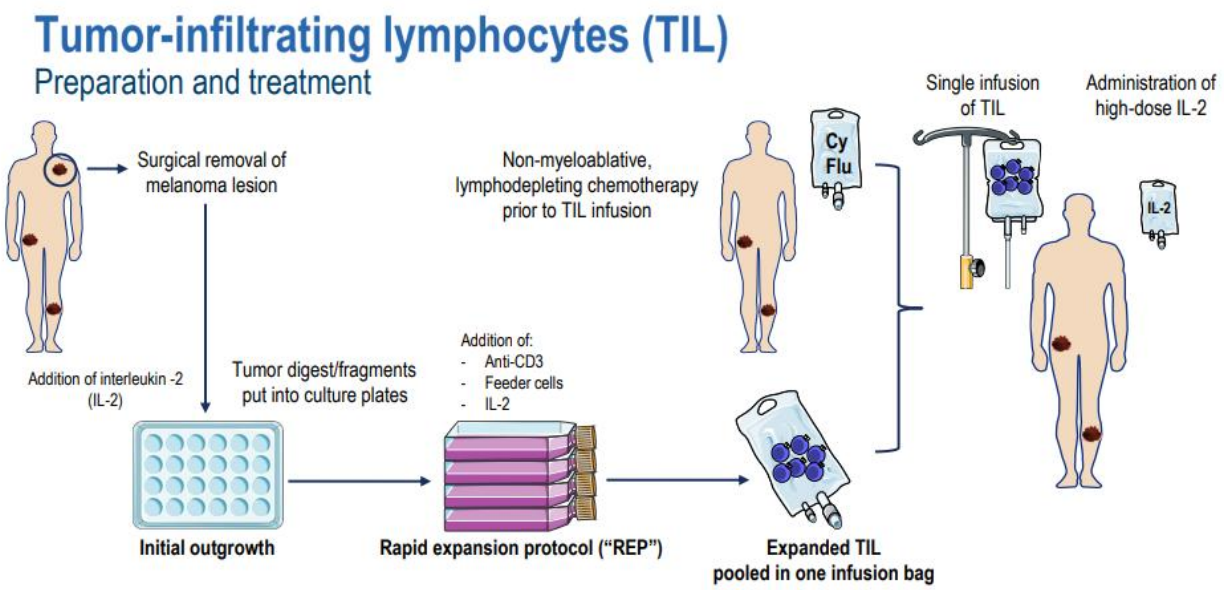
D.B Johnson et al. Nat Rev Clin Oncol. 2023

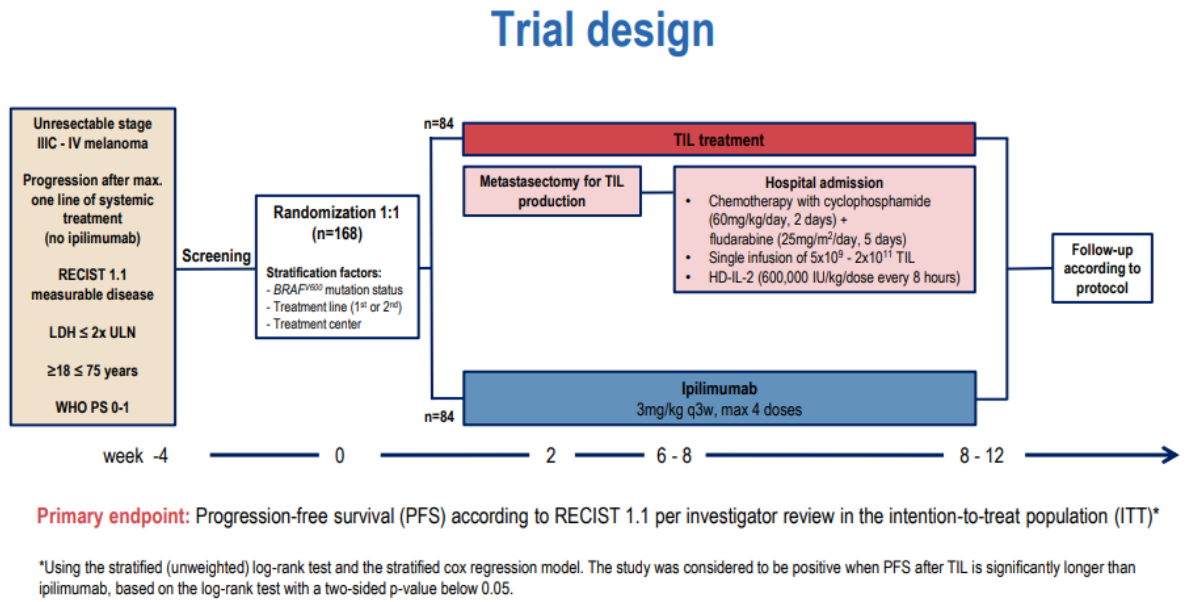
Gebruik van corticosteroïden en uitkomst



Maher et al. JCO 2019

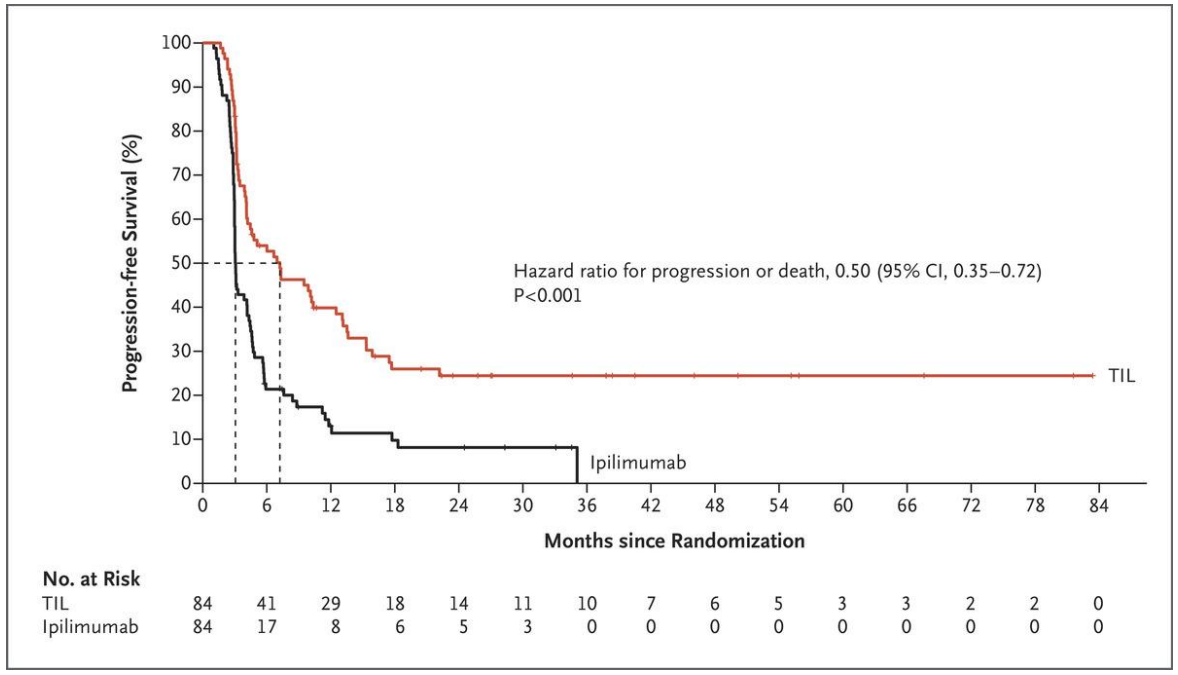
CELTHERAPIE: TIL (tumor-infiltrerende lymfocyten)

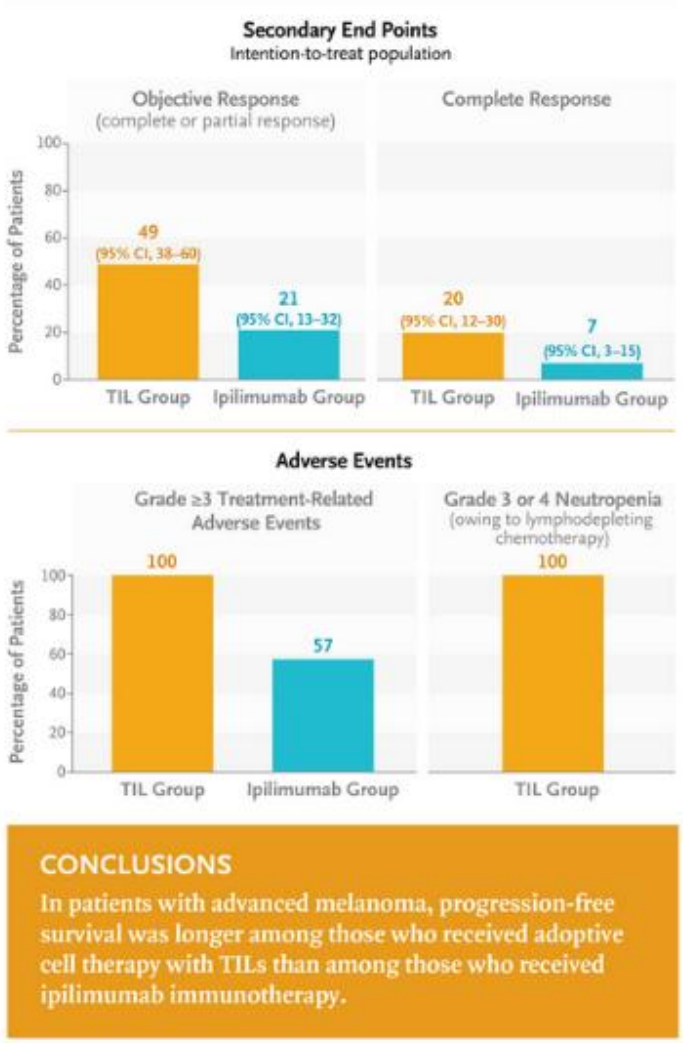




Haanen JBAG. ESMO 2022

CELTHERAPIE: TIL (tumor-infiltrerende lymfocyten)





Rohaan, Svane, Haanen. NEJM. 2022

Kwaliteit van leven

- Voornamelijk onderzocht in studies en tijdens behandeling met immuuntherapie
- Weinig bekend over kwaliteit van leven na behandeling
- Studies hebben aangetoond dat lange termijn overlevers (> 24 months na behandeling) een lager fysiek, emotioneel en cognitief functioneren rapporteren en meer financiële problemen ervaren dan de algemene bevolking.

Boekhout A. et al Acta Oncolgica. 2021; Rogiers A. et al. Supportive Care in Cancer. 2019

Capable project

CAPABLE
CAncer PAtients Better Life Experience

- eHealth applicatie:
  1. Monitoring: Lichamelijke en mentale klachten
  2. Coaching: Werken aan eigen welzijn door middel van interventies (yoga, mindfulness, fysieke activiteit)
  3. Informatievoorziening

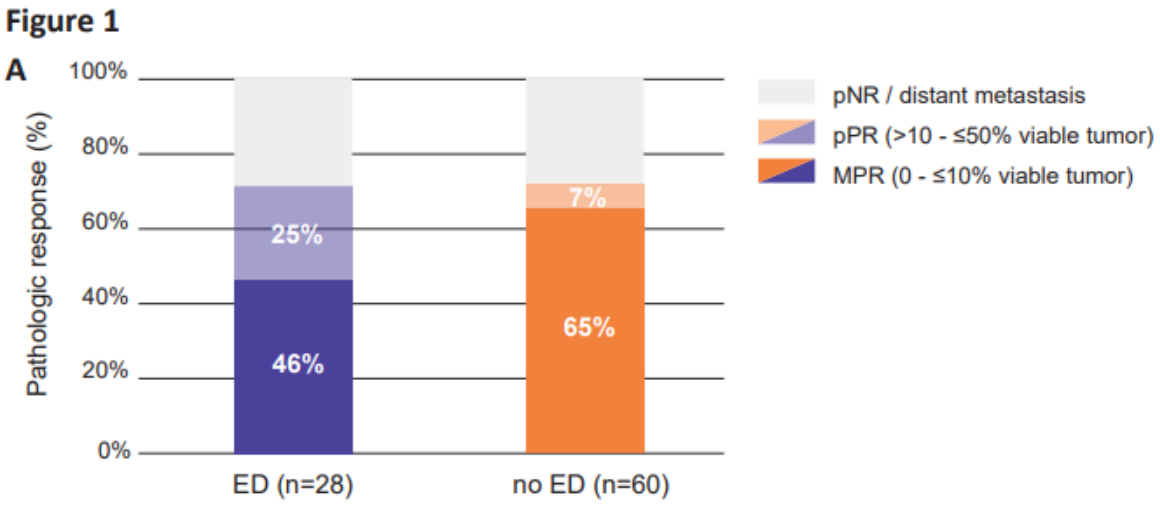
Kleine piloot studie in 31 ptn met melanoom en behandeling met immuuntherapie

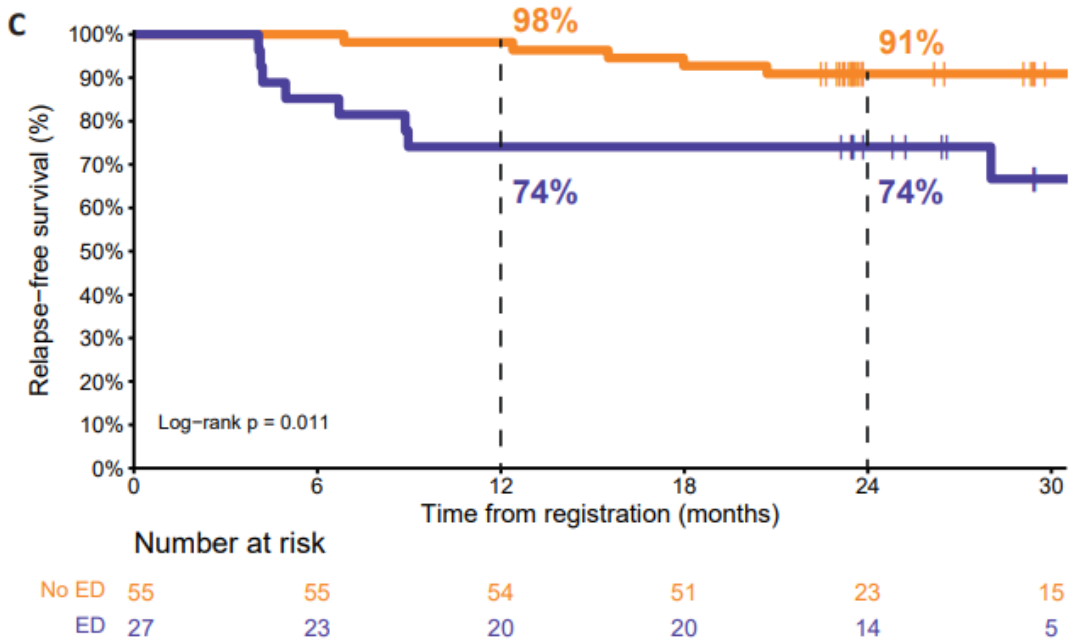
Conclusie:

Interventie resulteerde in verbetering in informatievoorziening en vermindering in vermoeidheid (3m)

Fraterman I. et al. JMIR Cancer. 2025

Associatie tussen emotionele stress en uitkomst op immuuntherapie





Fraterman I. et al. Nature Med. 2023