INTRODUCTIE “CANCER” IMMUNOTHERAPIE
UPDATE MELANOOM + CELTHERAPIE

Kishan Naipal, internist-Oncoloog, Antoni van Leeuwenhoek ziekenhuis

27 September 2022

ANTONI
VAN
LEEUWENHOEK
NEDERLANDS KANKER INSTITUUT

DISCLOSURES

(potentiële) belangenverstrengeling	Geen

INHOUD

- Geschiedenis van immunotherapie
  - Vormen van immunotherapie
    - Checkpoint remmers
- Huidige systemische behandelingen bij melanoom
  - Gemetastaseerd
  - Gelokaliseerd
- Upcoming behandelingen
  - Neo-adjuvant
  - Nieuwe checkpoint remmers
  - Celtherapie

GESCHIEDENIS VAN IMMUNOTHERAPIE BIJ KANKER

1891: injectie van Str. Pyogenes om immuunactivatie en anti-kanker response te bewerkstelligen

William Coley and the birth of cancer immunotherapy

New York Times - July 20, 1908

ERYSIPELAS GERMS AS CURE FOR CANCER

Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

Physician Has Used the Cure for 15 Years and Treated 430 Cases— Probably 150 Sure Cures.

Following news from St. Louis that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York, it came out yester-

Decker W.K. et al. Front. Immunol. 2017 8:829;1-13

ANTONI VAN LEEUWENHOEK
NEDERLANDS KANKER INSTITUUT

RAPIE BIJ KANKER

ne 2016114:125-133

ANTONI VAN LEEUWENHOEK
NEDERLANDS KANKER INSTITUUT

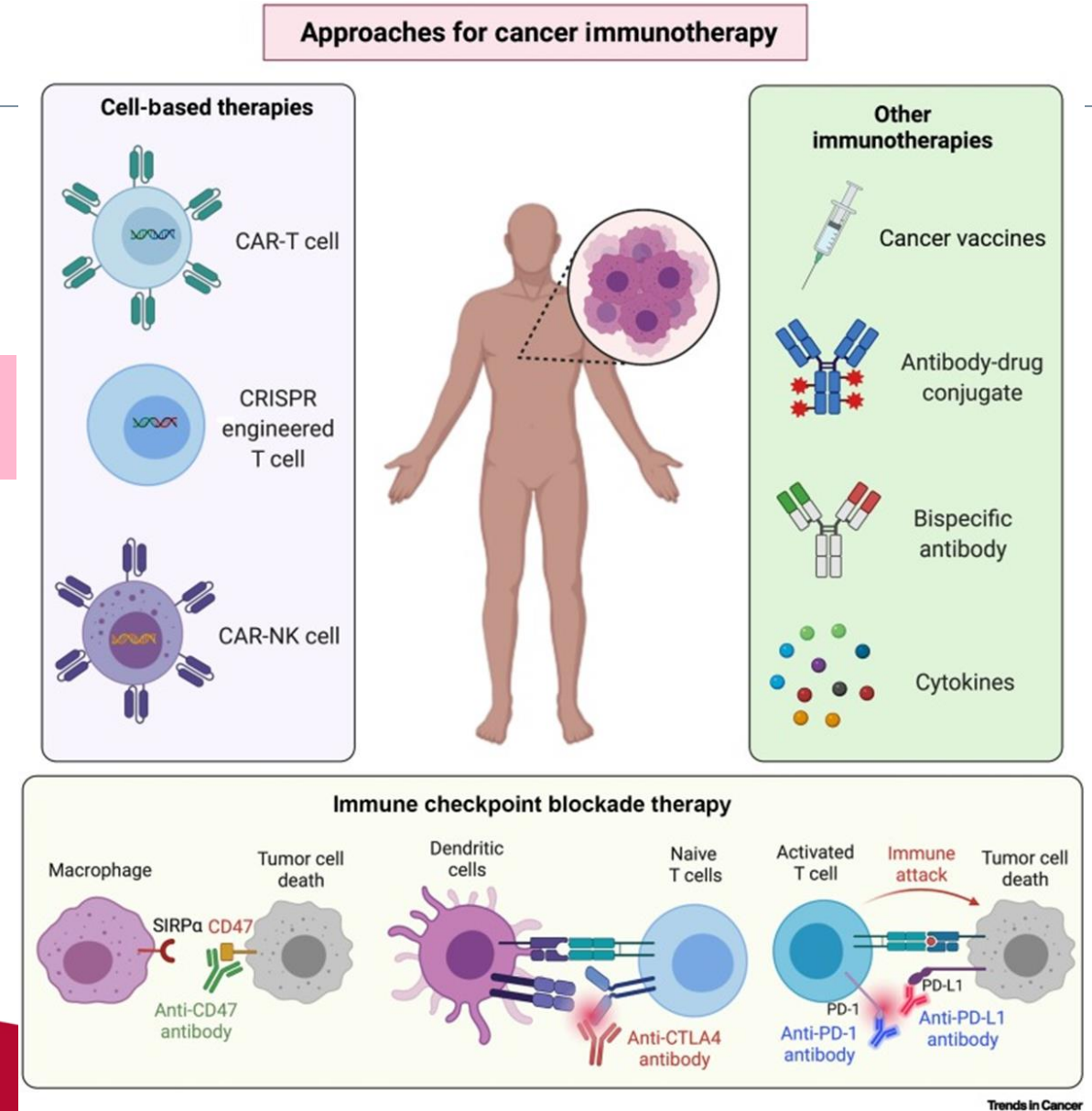
WAT IS IMMUNOTHERAPIE EIGENLIJK?

- “Cancer immunotherapy”

  Gebruikmaken van de intrinsieke kracht van het immuunsysteem om maligne celmateriaal te eradiceren.

WAARUIT KAN IMMUNOTHERAPIE BESTAAN?

TIL-therapie



T-VEC,
BCG

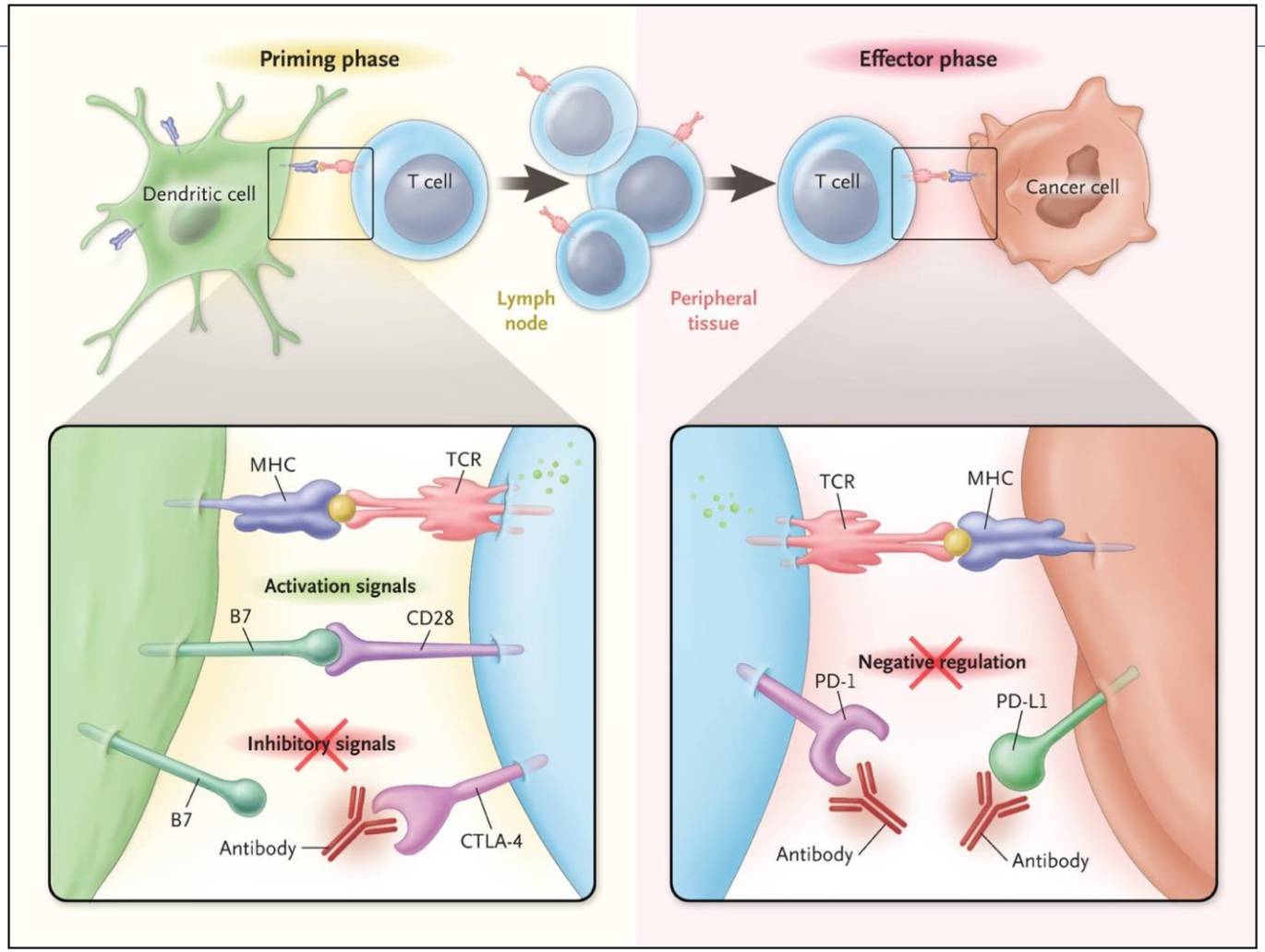
bv trastuzumab-deruxtecan,
enfortumab-vedotin

bv Blinatumomab
(anti CD3 + anti CD19)

INFα, TNF, IL-2

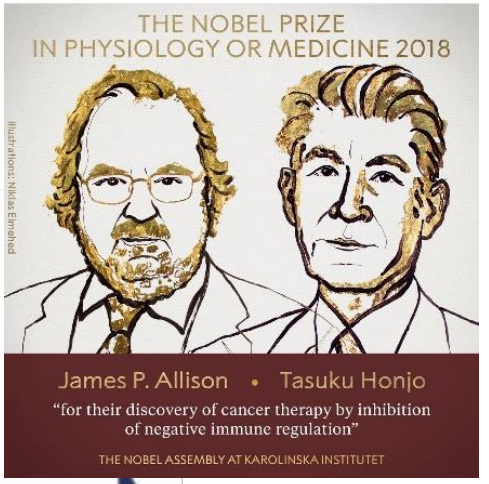
ANTONI VAN LEEUWENHOEK
NEDERLANDS KANKER INSTITUUT

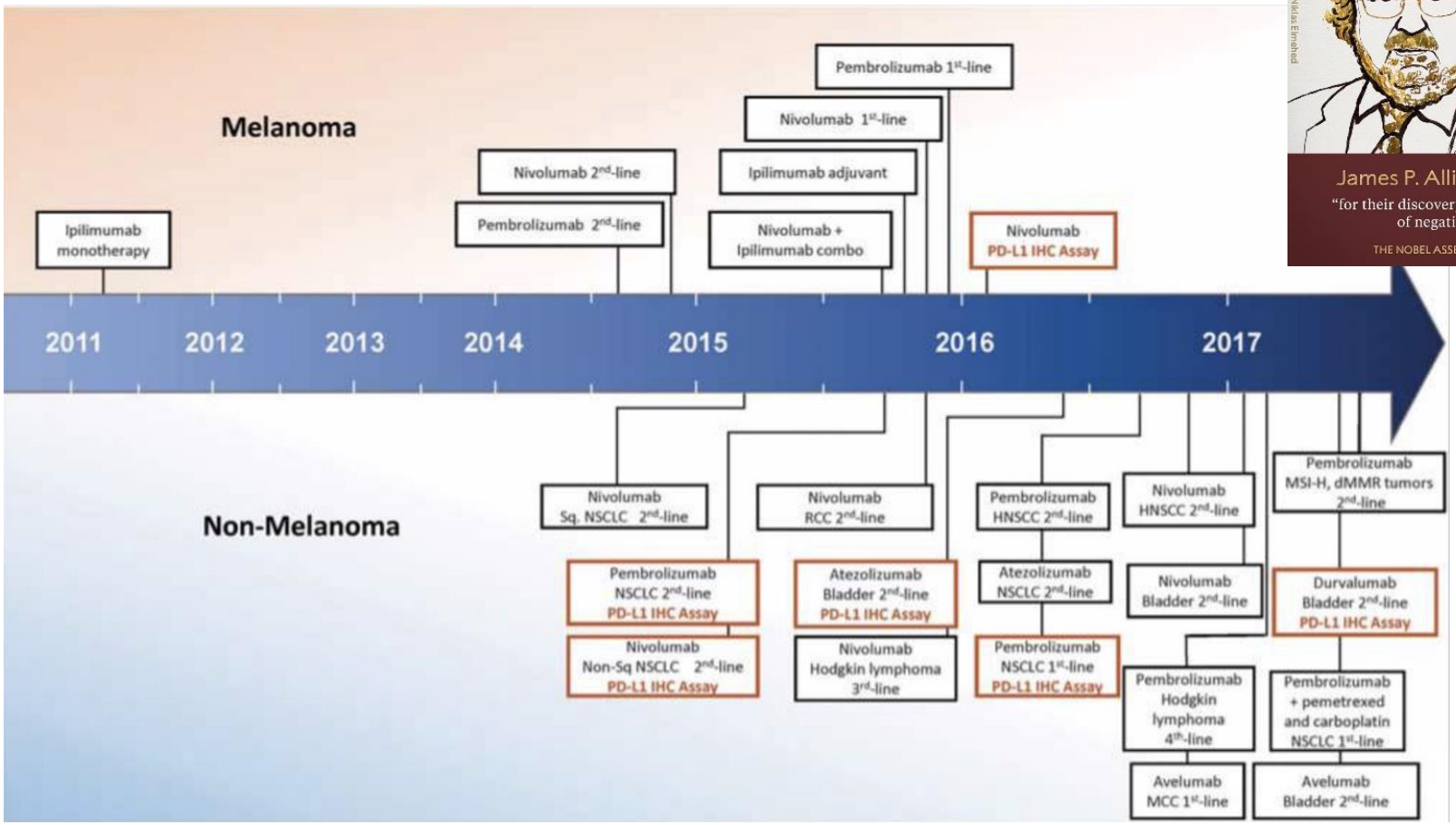
CHECKPOINT INHIBITORS: ANTI-CTLA-4 EN ANTI-PD-1/L1



Ribas. NEJM. 2012

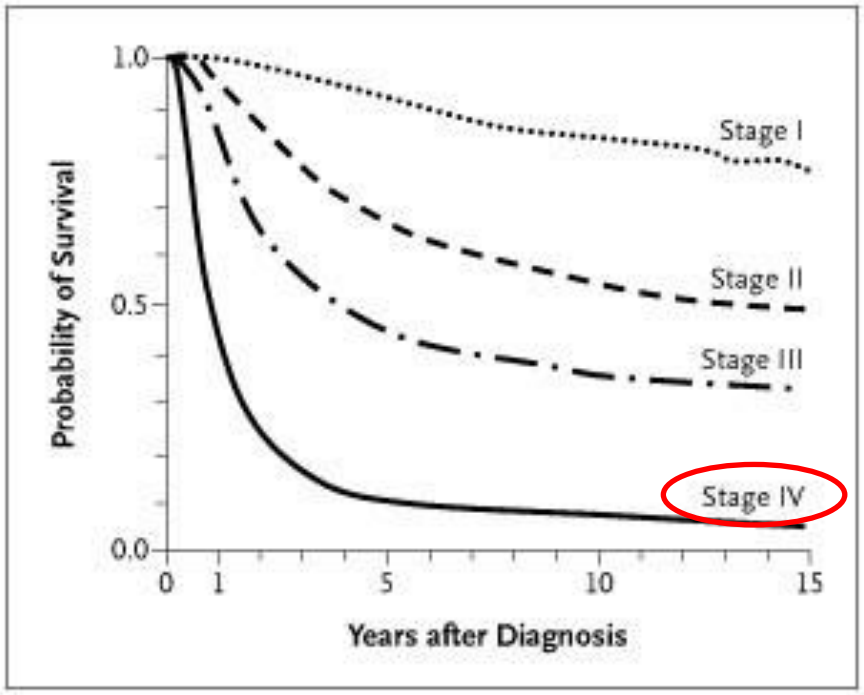
FDA APPROVAL CHECKPOINT INHIBITORS





Taube et al. Mod Pathol. 2018

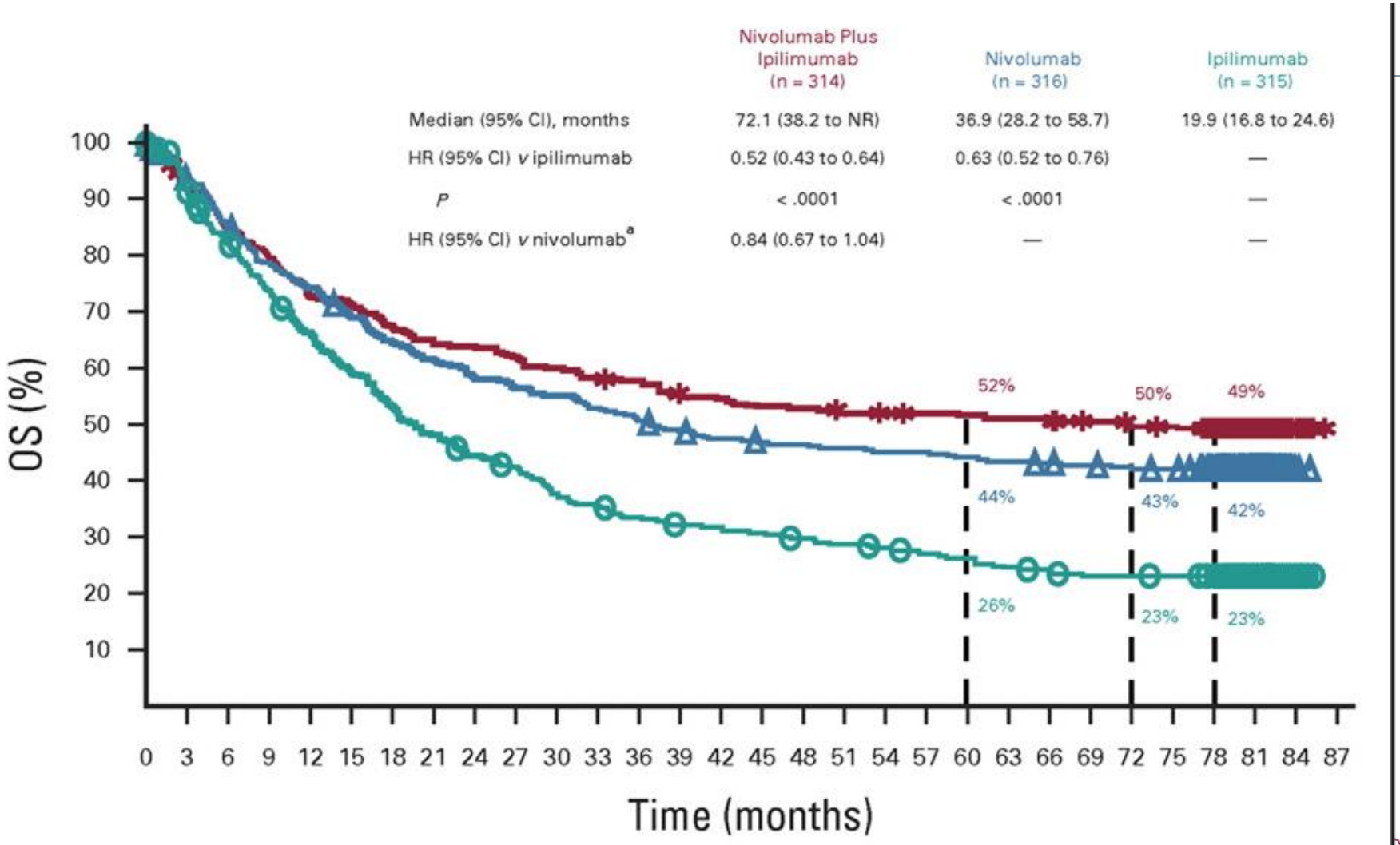
STAGE IV MELANOMA: BEFORE 2010



- Median overall survival 6-10 months
- 5j OS < 5%

Tsao et al. NEJM 2004

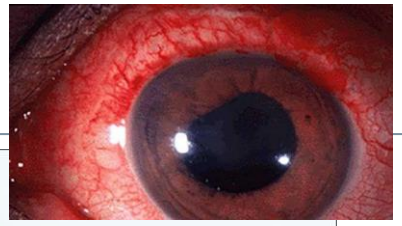
CURRENT LONGTERM SURVIVAL MELANOMA

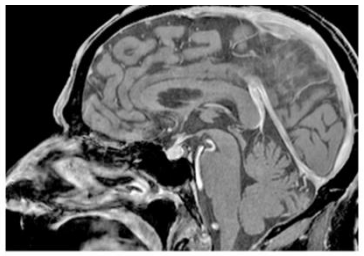


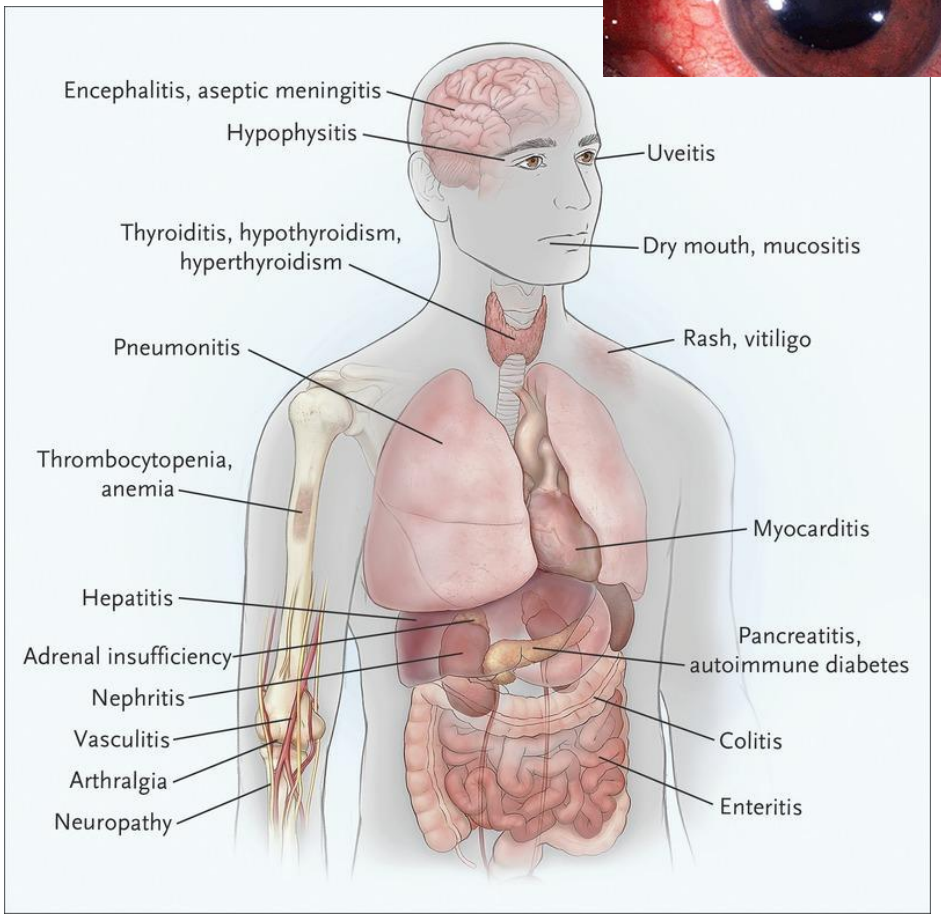
Larkin et al. NEJM. 2015; Hodi et al. Lancet Oncol. 2018; WOLCHOK ET AL JCO 2022

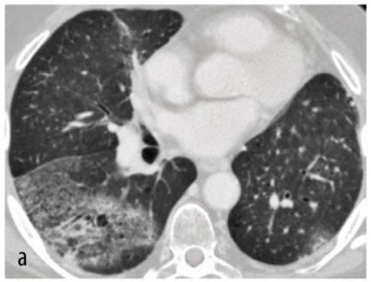
ANTONI VAN LEEUWENHOEK
NEDERLANDS KANKER INSTITUUT

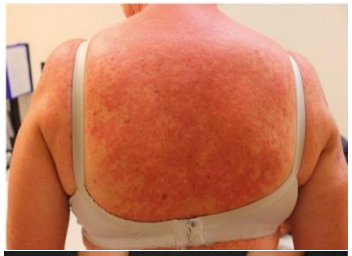
ADVERSE EVENTS

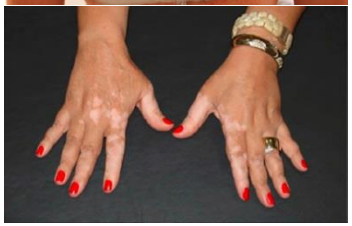


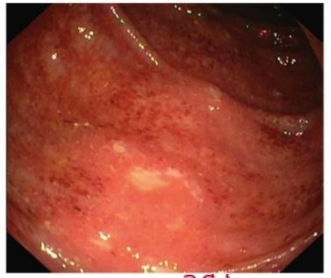












Postow et al. NEJM. 2018; Steebruggen et al. NTvG 2016

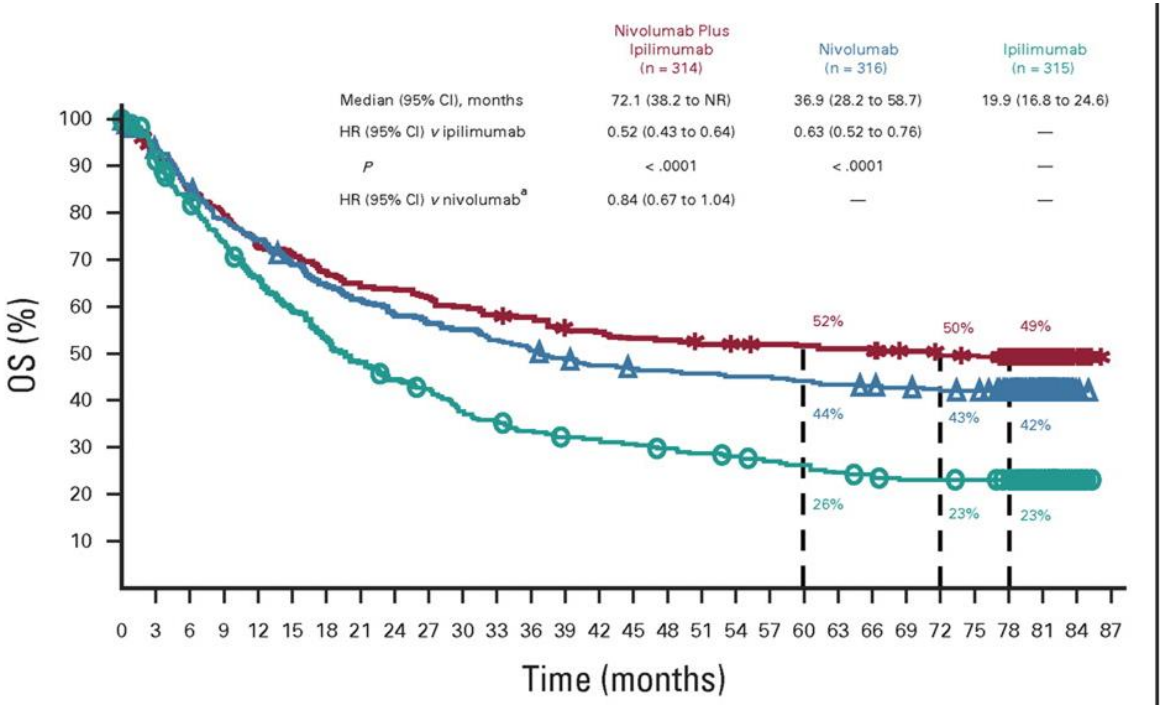
ANTONI VAN LEEUWENHOEK
NEDERLANDS KANKER INSTITUUT

BEHANDELING VAN GEMETASTASEERD MELANOOM ANNO 2022

ANTONI VAN LEEUWENHOEK
NEDERLANDS KANKER INSTITUUT

BEHANDELING VAN GEMETASTASEERD MELANOOM ANNO 2022

- Gemetastaseerd
  - Lage tumorload, normaal LDH, geen hersenmetastasen anti-PD1 monotherapie
  - Hoog risico metastasen, hoog LDH combinatie anti-PD1 + anti-CTLA4



Wolchok et al JCO 2022

ANTONI VAN LEEUWENHOEK
NEDERLANDS KANKER INSTITUUT

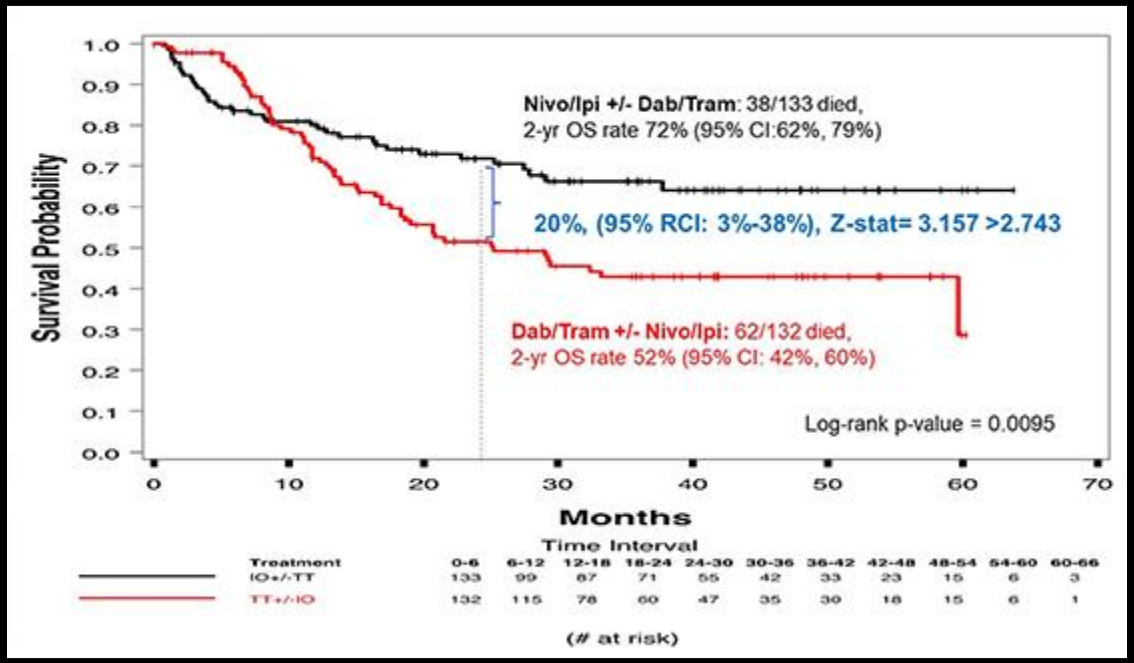
EN BRAF GEMUTEERDE TUMOREN DAN???

DREAMseq (D
Melanoma Sequ

AIM: to compare the
the converse sequenc
PATINETS: treatment-

1:1
265 pts

Median follow-up:
27.7 months



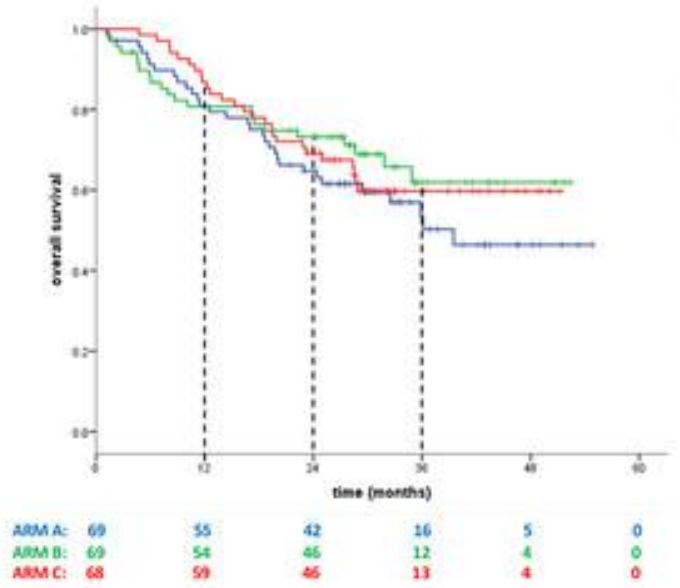
CONCLUSION:
- **the treatment**
- **The difference became evident at 10 months**

ASCO 2021 abstract, Atkins et al

ANTONI VAN LEEUWENHOEK
NEDERLANDS KANKER INSTITUUT

EN BRAF GEMUTEERDE TUMOREN DAN???

Sequential Combo Immuno And Target Therapy (Secombit) Study: Overall Survival



	Arm A	Arm B	Arm C
1y tot OS (95% CI)	81 (72-90)	81 (72-90)	87 (69-95)
2y tot OS (95% CI)	65 (54-76)	73 (62-84)	69 (58-80)
3y tot OS (95% CI)	54 (41-67)	62 (48-76)	60 (58-72)
HR (95% CI) vs Arm B Exploratory analysis	0.73 (0.42-1.26)	-	-
HR (95% CI) vs Arm C Exploratory analysis	0.81 (0.48-1.37)	-	-

ARM A: Enco/Bini PD → Ipi/Nivo
ARM B: Ipi/Nivo PD → Enco/Bini
ARM C: Enco/Bini (8 weeks) → Ipi/Nivo PD → Enco/Bini

Ascierto et al 2021 ESMO abstract

ANTONI VAN LEEUWENHOEK
NEDERLANDS KANKER INSTITUUT

BEHANDELING VAN GEMETASTASEERD MELANOOM ANNO 2022

- Gemetastaseerd
  - Lage tumorload, normaal LDH, geen hersenmetastasen anti-PD1 monotherapie
  - Hoog risico metastasen, hoog LDH combinatie anti-PD1 + anti-CTLA4

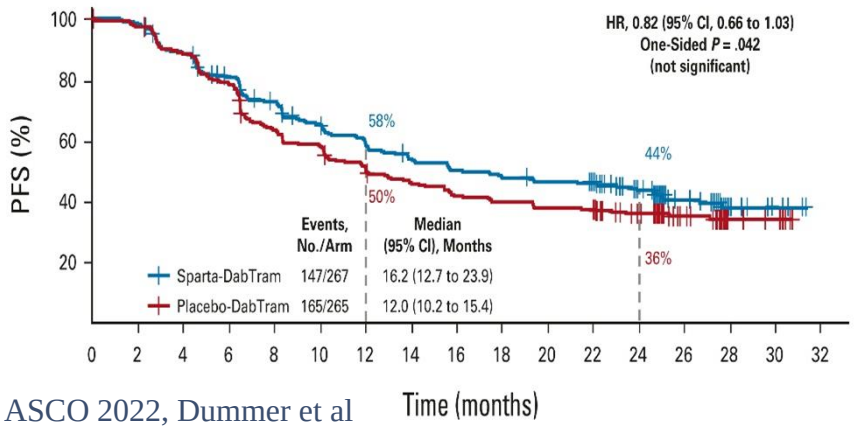
  - BRAF gemuteerde tumoren voorkeur voor immunotherapie in 1e lijn tenzij snelle response noodzakelijk (bv hersenmetastasen/ dexamethasongebruik/ viscerale crisis)

Wolchok et al JCO 2022

EN COMBINATIEBEHANDELING IMMUNOTHERAPIE + BRAF/MEK REMMERS DAN?

COMBI-i : Spartalizumab + DABTRAM vs DABTRAM only

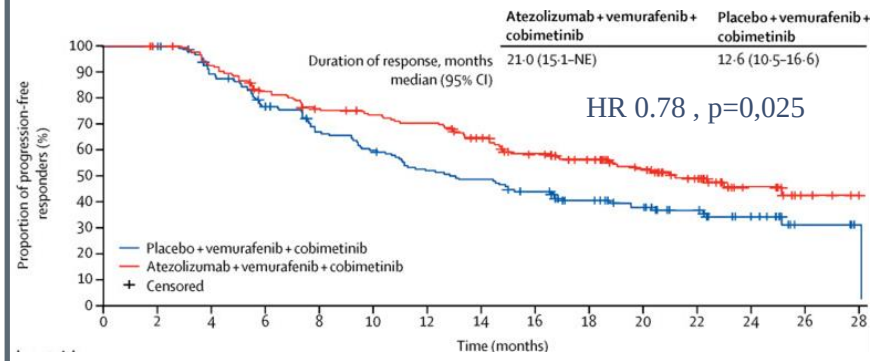
≥ grade 3 tox: 70% vs 57%



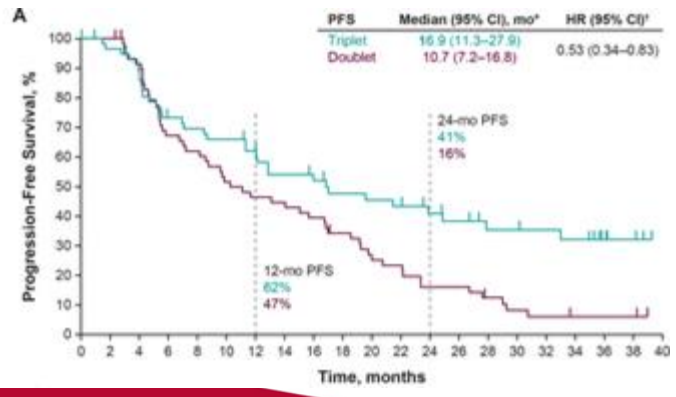
ASCO 2022, Dummer et al

IMspire150: Atezoluzimab + Vemu/Cobi vs Vemu/Cobi only

≥ grade 3 tox: 79% vs 73%



Gutzmer et al 2020, The Lancet



Keynote 022: Pembro + DABTRAM vs DABTRAM only

≥ grade 3 tox: 70% vs 45%

Ferruci et al 2020, BMJ

ANTONI VAN LEEUWENHOEK
NEDERLANDS KANKER INSTITUUT

BEHANDELING VAN GEMETASTASEERD MELANOOM ANNO 2022

- Gemetastaseerd
  - Lage tumorload, normaal LDH, geen hersenmetastasen anti-PD1 monotherapie
  - Hoog risico metastasen, hoog LDH combinatie anti-PD1 + anti-CTLA4

  - BRAF gemuteerde tumoren
    - voorkeur voor immunotherapie in 1e lijn tenzij snelle response noodzakelijk (bv hersenmetastasen/ dexamethasongebruik/ viscerale crisis)
    - Combinatie BRAF/MEKremmer + immunotherapie erg toxisch en levert geen/weinig overlevingsvoordeel op. Onbekend wat voordeel is ten opzichte van immunotherapie alleen of sequentieel BRAF/MEKi + immunotherapie.

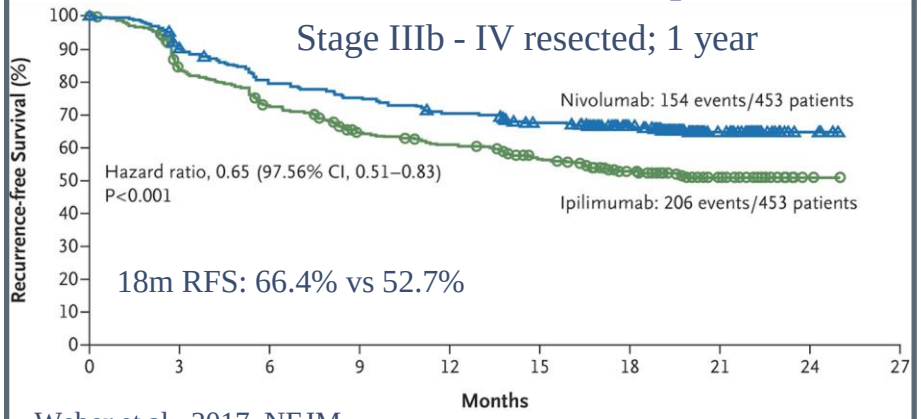
Wolchok et al JCO 2022

BEHANDELING VAN GELOKALISEERD MELANOOM ANNO 2022 – SYSTEMISCHE THERAPIE ADJUVANT

- Voorkeur voor chirurgie en in hoog risico gevallen adjuvant systemische therapie

Checkmate 238: nivolumab vs ipilimumab

Stage IIIb - IV resected; 1 year

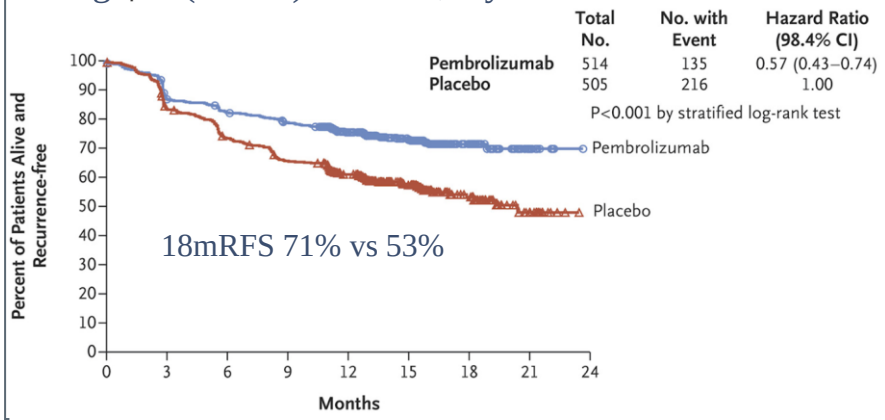


18m RFS: 66.4% vs 52.7%

Weber et al , 2017, NEJM
Ascierto et al 2020: 4yrRFS: 51% vs 41%; 4yrOS: 77% vs 76%

Keynote-054: pembrolizumab vs placebo

Stage III (>1mm) resected; 1 year



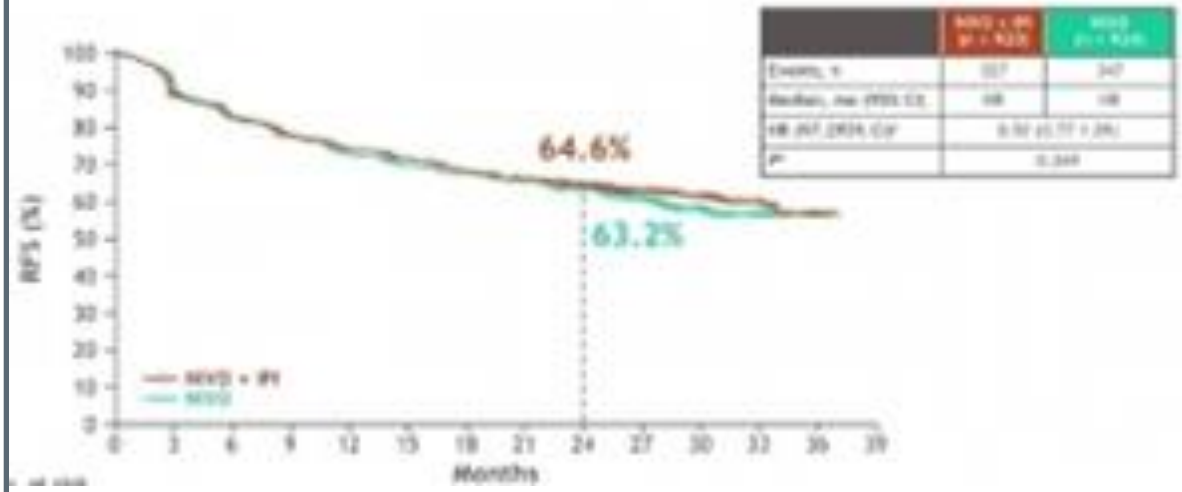
18mRFS 71% vs 53%

Eggermont et al , 2018, NEJM
Eggermont et al 2022: 5yrRFS: 55,4% vs 38.3%; 5yrOS: not reported !!!

ANTONI VAN LEEUWENHOEK
NEDERLANDS KANKER INSTITUUT

Checkmate 915: ipilimumab+nivolumab vs nivolumab

Stage IIIb - IV resected; 1 year

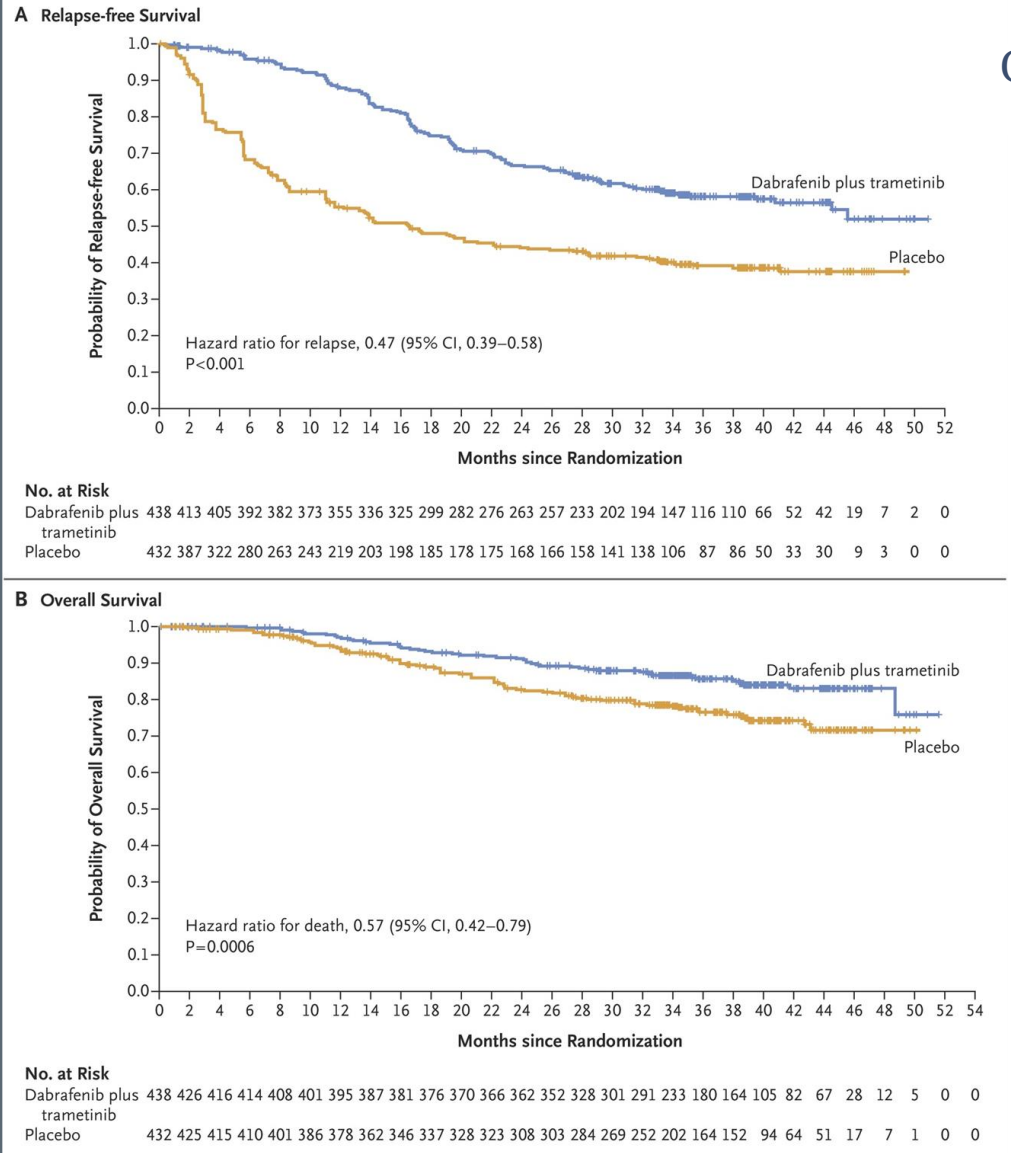


Long et al AACR, 2021

BEHANDELING VAN GELOKALISEERD MELANOOM ANNO 2022 – SYSTEMISCHE THERAPIE ADJUVANT

- Stadium IIIb-IV resected:
  - Nivolumab Q4w max 1 year
- Stadium III, >1mm:
  - Pembrolizumab max 1 year

EN BRAF GEMUTEERDE TUMOREN DAN???



COMBI-AD: DABTRAM vs placebo

BRAF-V600E/K,
Stage IIIb - IIIc resected;
1 year

3yrRFS: 58% vs 39%
3yr OS: 86% vs 77%

Dummer et al 2020:
5yr RFS: 52% vs 36%
OS not reported

Long et al 2017, NEJM

ANTONI VAN LEEUWENHOEK
NEDERLANDS KANKER INSTITUUT

BEHANDELING VAN GELOKALISEERD MELANOOM ANNO 2022 – SYSTEMISCHE THERAPIE ADJUVANT

- Stadium IIIb-IV resected:
  - Nivolumab Q4w max 1 year
- Stadium III, >1mm, resected:
  - Pembrolizumab max 1 year
- Stadium IIIb-IIIc, resected, BRAF-V600E/K:
  - Dabrafenib + trametinib max 1 year of immunotherapie (nivo of pembro)

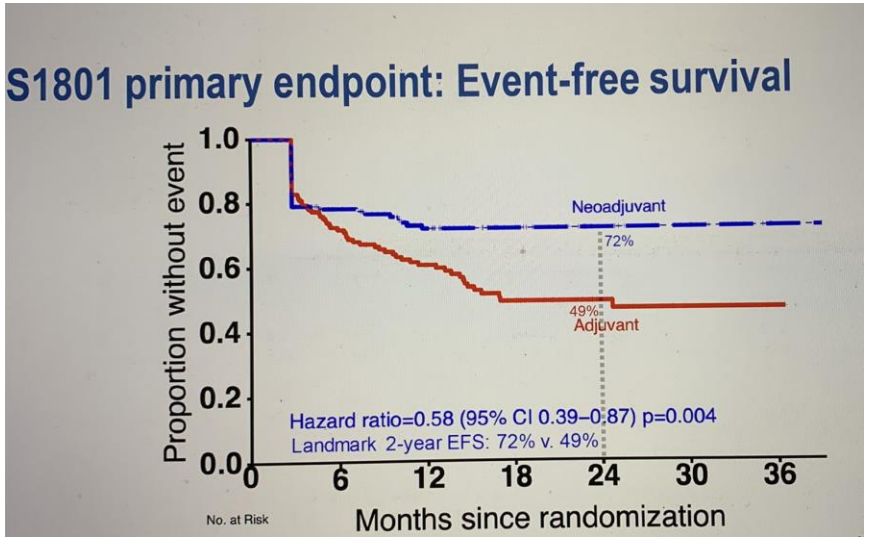
NIEUWE BEHANDELINGEN MELANOOM

- Neo-adjuvant
- Nieuwe checkpoint remmers
- Celtherapie

NEO-ADJUVANTE BEHANDELING MELANOOM – PHASE 3 STUDIES

SWOG S1801: neoadjuvant 3x pembrolizumab vs adjuvant pembrolizumab

Stage IIIb - IV resected; max 1 year



21% pCR

Patel et al ESMO, 2022

Ongoing:

- NADINA: 2x neo-adj ipi/nivo vs adj nivo of DAB/TRAM. No adjuvant treatment in pMPR (According to PRADO trial)

NIEUWE CHECKPOINT REMMERS

Atezolizumab,
Avelumab, Durvalumab

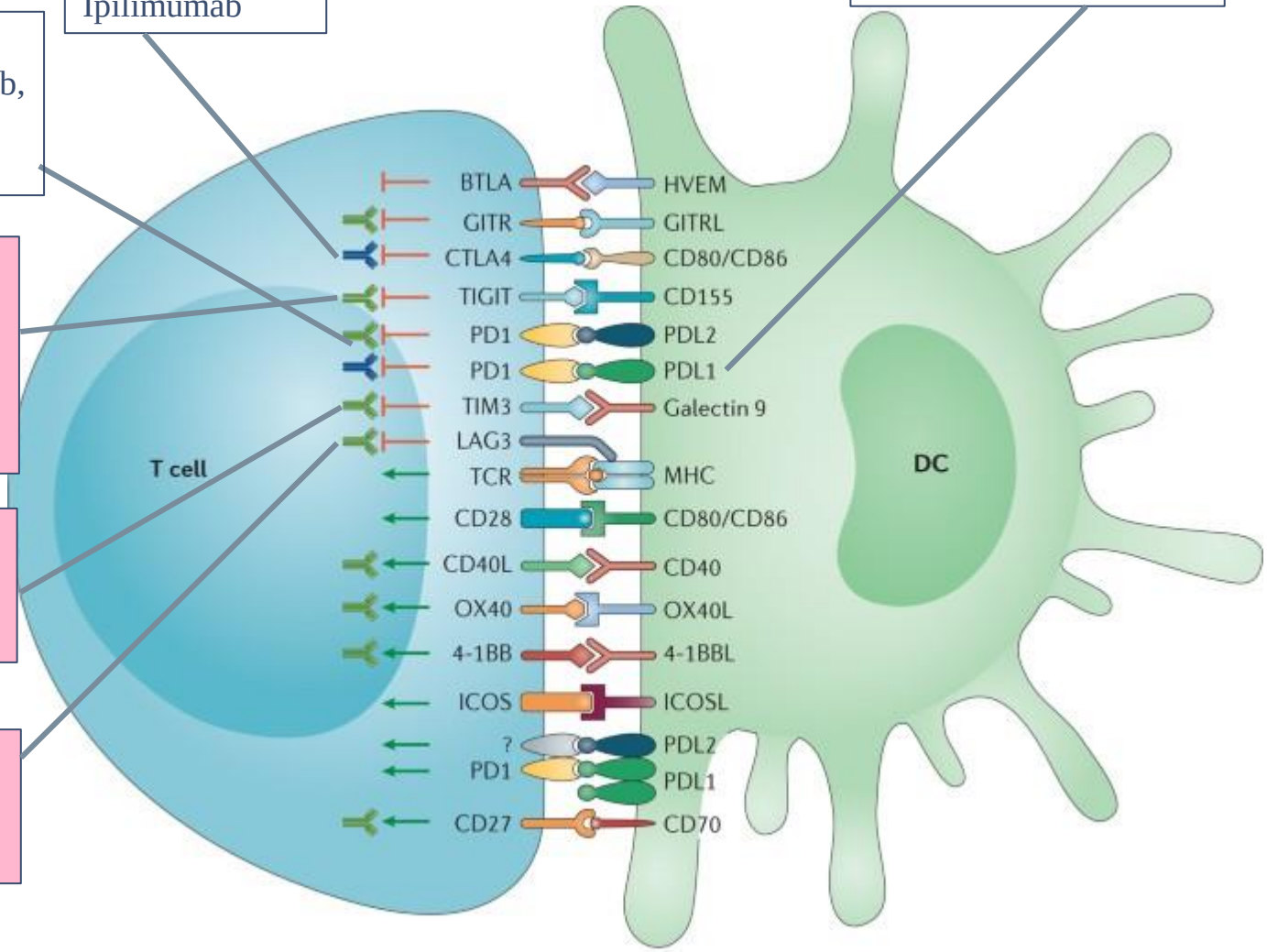
Ipilimumab

Nivolumab,
Pembrolizumab,
Cemiplimab,
Dostarlimab

Anti-TIGIT:
- Tiragolumab – phase III – NSCL +SCLC
- N=9 – phase I-II inclusief melanoma

Anti-TIM3:
N=8 – phase I-II inclusief melanoom

Anti-LAG3:
Relatlimab – phase III
N=10 – phase I-II

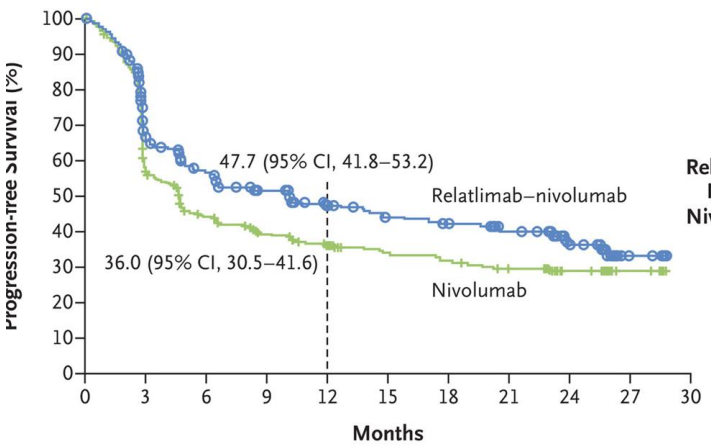


Wykes et al 2018 Nat Rev Immunology

NIEUWE CHECKPOINT REMMERS - RELATLIMAB

Relativity-047: Relatlimab + nivolumab vs nivolumab alone

Stage III irresectable -IV; untreated melanoma



	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Relatlimab–Nivolumab	355	10.12 (6.37–15.74)
Nivolumab	359	4.63 (3.38–5.62)

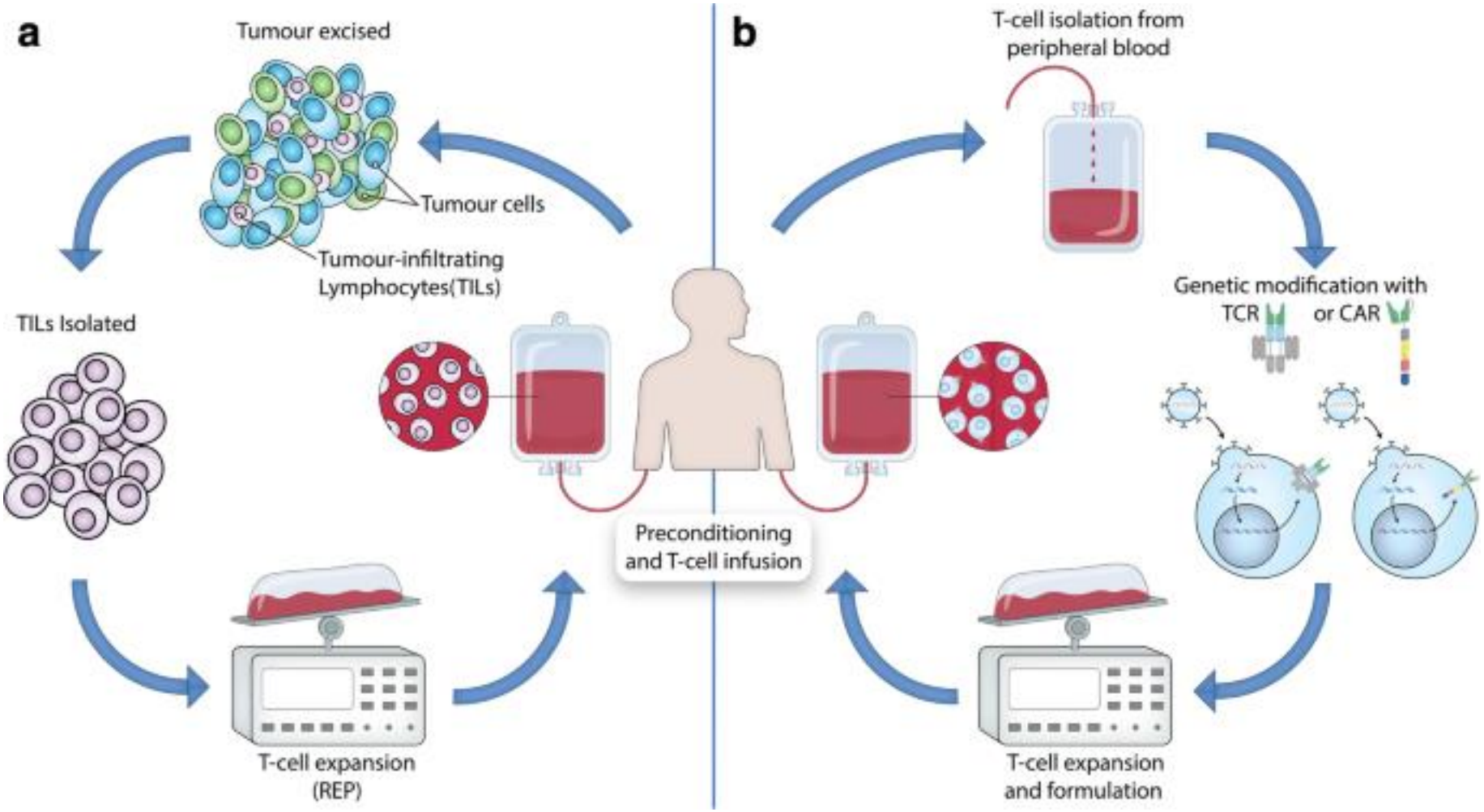
Hazard ratio for progression or death, 0.75 (95% CI, 0.62–0.92)
P=0.006

mPFS: 10.1m vs 4.6m

≥ grade 3 tox: 18.9% vs 9.7%

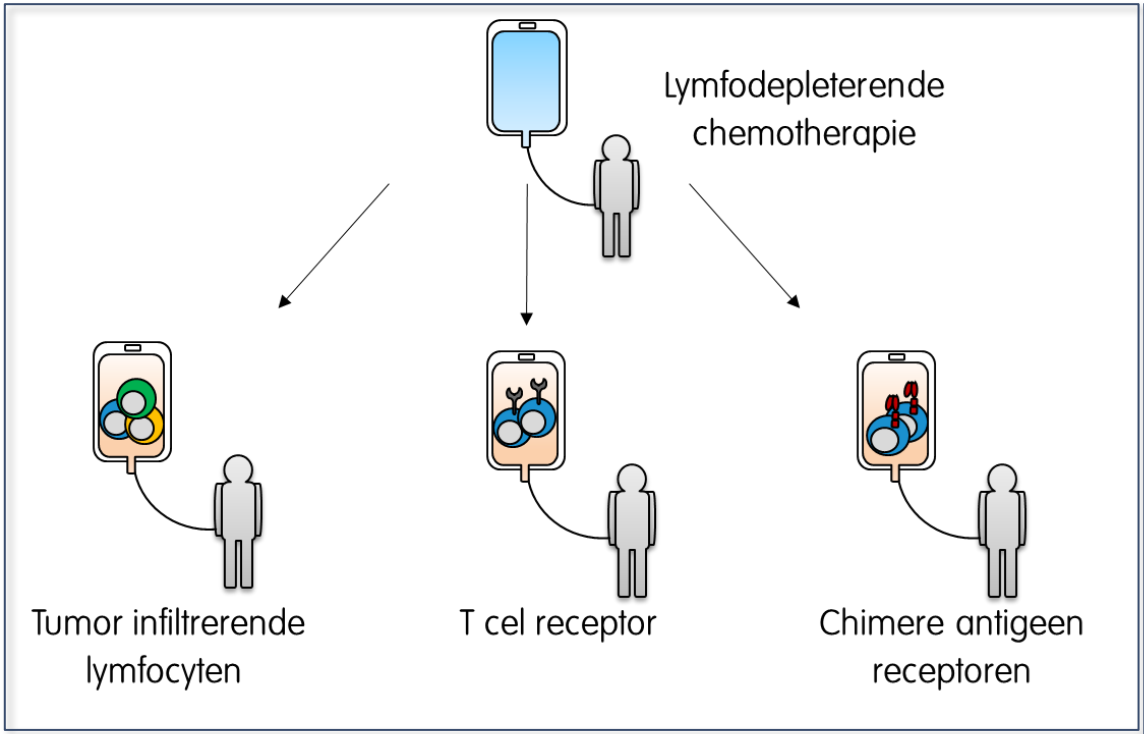
Tawbi et al 2022, NEJM

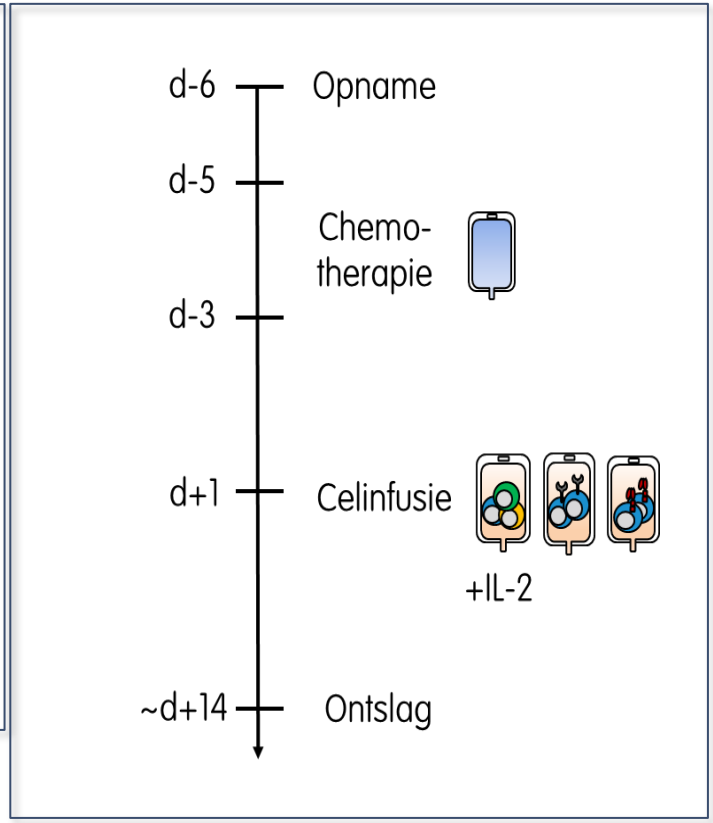
CELTHERAPIE



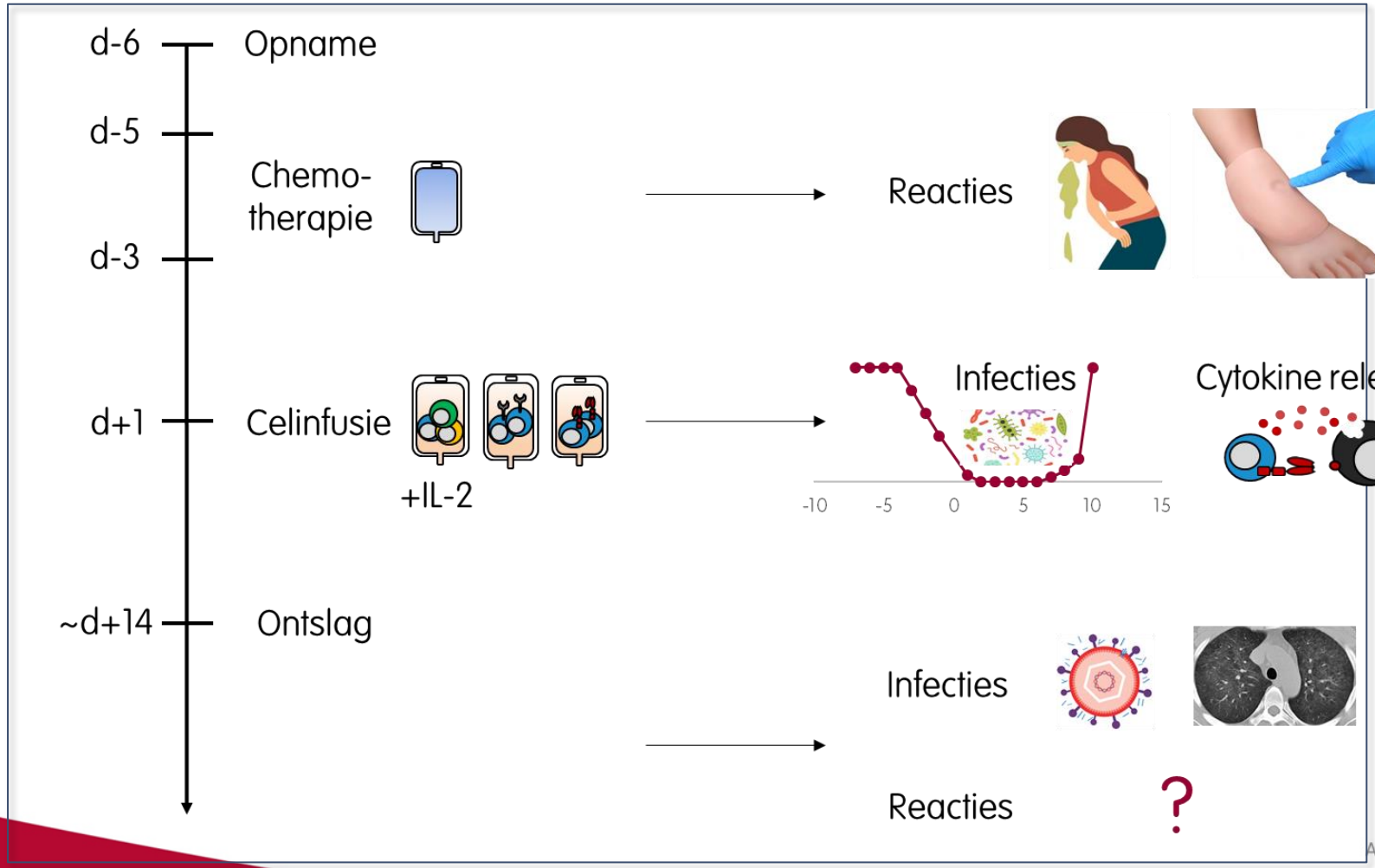
Met et al 2019, Sem. In Immunopathol.

IMMUNE EFFECTOR CELLTHERAPY



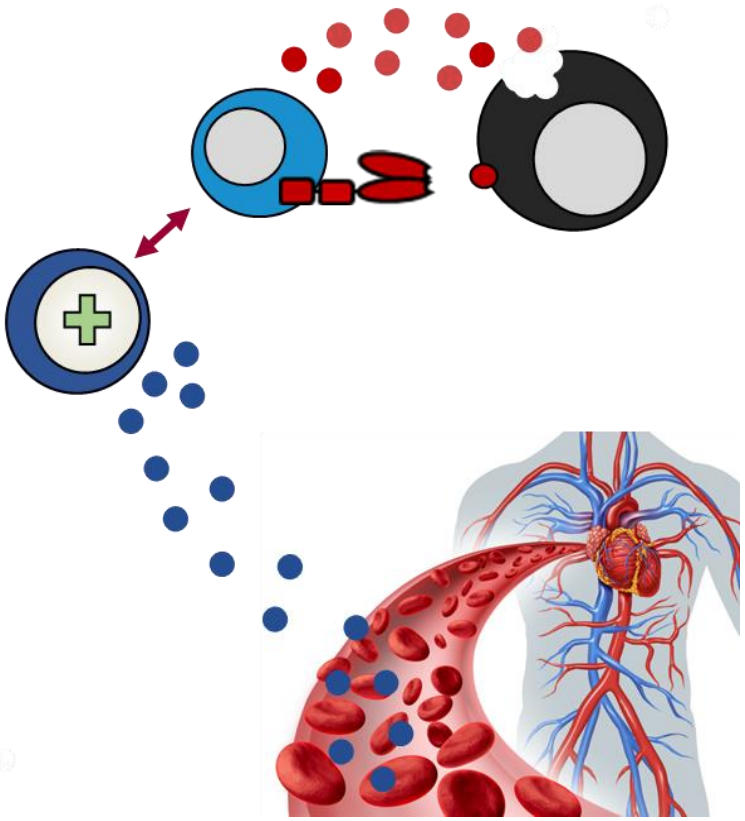


BIJWERKINGEN VAN IMMUNE EFFECTOR CELTHERAPIE

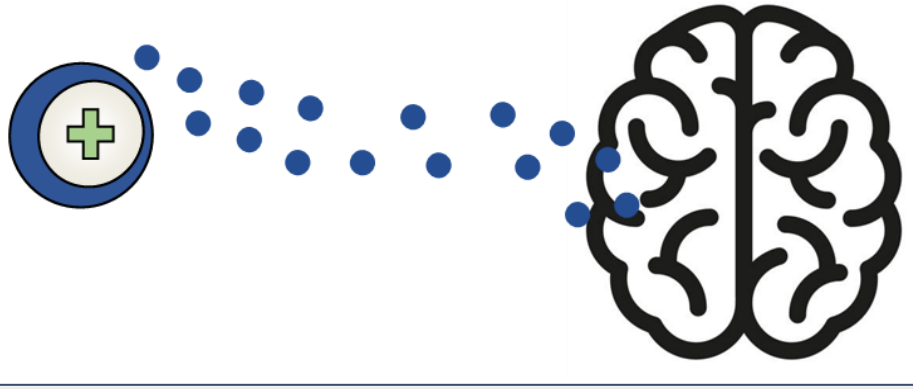


BIJWERKINGEN

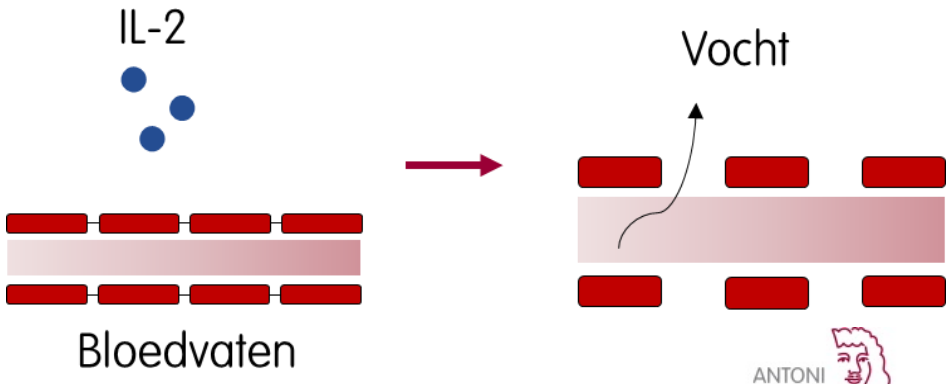
Cytokine release syndroom



Immune effector cell-associated neurotoxicity syndroom



Capillary leak syndroom



BEHANDELING

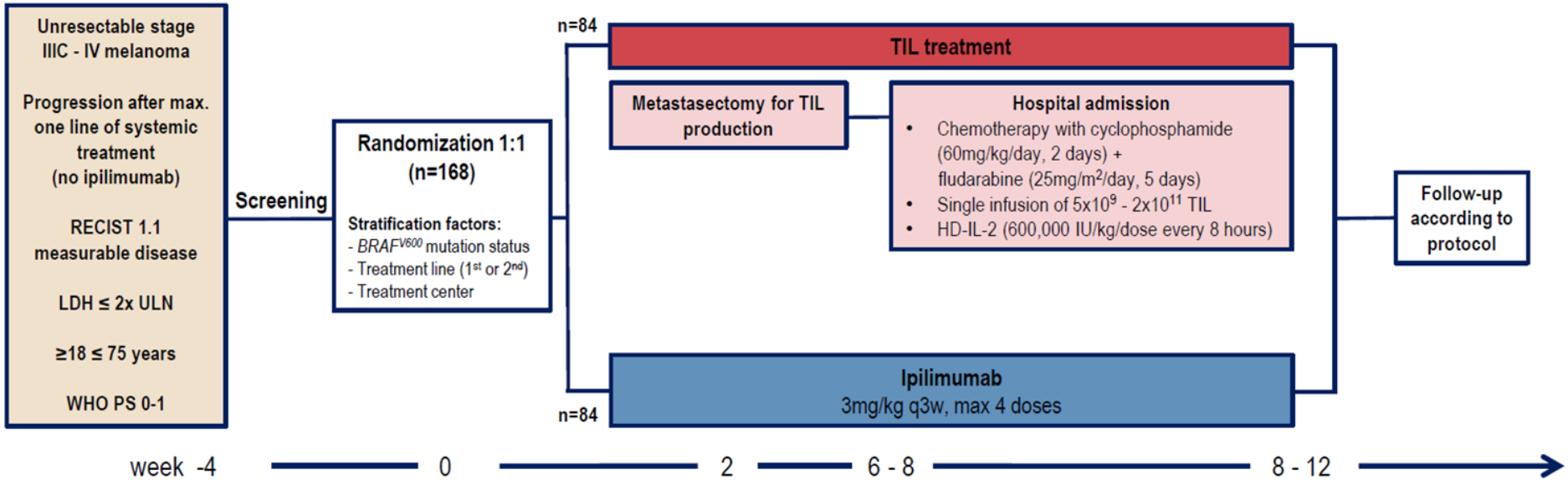
	Graad 1	Graad 2	Graad 3	Graad 4
Koorts[1]	≥38°C	≥38°C	≥38°C	≥38°C
			Met	
Hypotensie[2]	Geen	Vulling (max 2L in bolussen van 500mL), geen ondersteunende medicatie nodig	Ondersteunende medicatie nodig	Ondersteunende medicatie werkt onvoldoende
			En/of[4]	
Hypoxie[3]	Geen	≤5L/min O_2 (neusbril)	>5L/min (mond-neusmasker, non-rebreating masker, of Venturi masker)	(Dreigende) respiratoire insufficiëntie

→ Anti-IL-6

→ Anti-IL-1 (Anakinra)

ANTONI VAN LEEUWENHOEK
NEDERLANDS KANKER INSTITUUT

1E FASE III STUDIE – CELTHERAPIE MELANOOM TIL



Primary endpoint: Progression-free survival (PFS) according to RECIST 1.1 per investigator review in the intention-to-treat population (ITT)*

*Using the stratified (unweighted) log-rank test and the stratified cox regression model. The study was considered to be positive when PFS after TIL is significantly longer than ipilimumab, based on the log-rank test with a two-sided p-value below 0.05.

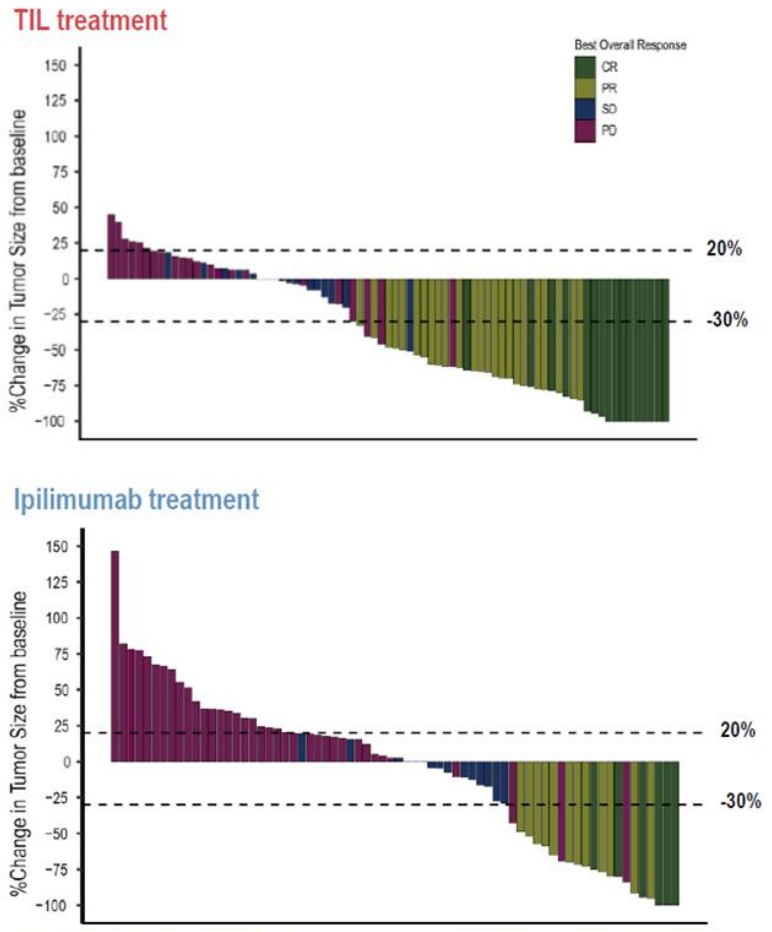
1E FASE III STUDIE – CELTHERAPIE MELANOOM

Results (3)

Best overall response according to RECIST 1.1*

	TIL (n=84)	Ipilimumab (n=84)
Best overall response	**n (%)**	**n (%)**
Complete response	17 (20.2)	6 (7.1)
Partial response	24 (28.6)	12 (14.3)
Stable disease	16 (19.1)	15 (17.9)
Progressive disease	24 (28.6)	40 (47.6)
Not evaluable/done#	3 (3.6)	11 (13.1)
Overall response†	41 (48.8)	18 (21.4)
Clinical benefit‡	57 (67.9)	33 (39.3)

*In the intention-to-treat population. #In 3 (3.6%) and 11 (13.1%) of TIL and ipilimumab treated patients, respectively, best radiologic response could not be evaluated or was not done due to an event (death or need to start subsequent anticancer therapy) before the moment of first response evaluation or due to unevaluable target lesions in follow-up. †Defined as CR plus PR and ‡CR, PR plus SD according to RECIST 1.1.



TOXICITEIT

Safety with grade ≥ 3 treatment-related adverse events according to CTCAEv4.03*

TIL (n=80)				Ipilimumab (n=82)	
Chemotherapy		TIL plus IL-2			
Adverse event	**n (%)**	**Adverse event**	**n (%)**	**Adverse event**	**n (%)**
Total	**80 (100)**	**Total**	**77 (96.3)**	**Total**	**47 (57.3)**
Neutropenia	80 (100)	Febrile neutropenia	58 (72.5)	Colitis	16 (19.5)
Thrombocytopenia	71 (88.8)	Hypophosphatemia	48 (60.0)	Diarrhea	12 (14.6)
Febrile neutropenia	67 (83.8)	Fever	36 (45.0)	Elevated ALT	8 (9.8)
Lymphopenia	57 (71.3)	Dyspnea	15 (18.8)	Elevated AST	7 (8.5)
Hypophosphatemia	20 (25.0)	Hypertension	11 (13.8)	GGT increased	7 (8.5)
Anemia	16 (20.0)	CPK increased	9 (11.3)		
Elevated ALT	7 (8.8)	Rash	9 (11.3)		
GGT increased	6 (7.5)	Elevated ALT	8 (10.0)		
Elevated AST	4 (5.0)	Elevated AST	8 (10.0)		
Fatigue	4 (5.0)	Fatigue	7 (8.8)		
		Chills	6 (7.5)		
		GGT increased	6 (7.5)		
		Hypotension	6 (7.5)		
		Hypoxia	5 (6.3)		

*Most common grade ≥ 3 treatment-related adverse according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03 that occurred in ≥5% of patients receiving at least one dose of treatment (safety analysis set), per treatment arm. More than one adverse event could occur in the same patient.

CONCLUSIE - TIL

- 1e fase 3 studie betreffende celtherapie bij melanoom
- 20% complete remissie
- Eenmalige behandeling

- Echter:
  - Veel toxiciteit
  - Geen significante OS data
  - Waar komt de plek van TIL in de behandeling van melanoom
    - 1e lijn??? 2e lijn na ipi/nivo?

- Dessalniettemin:
  - We zullen nog meer horen over celtherapie bij melanoom in de toekomst.

WAAR HEB IK HET NOU ALLEMAAL OVER GEHAD?

- Geschiedenis van immunotherapie – William Coley naar nu
  - Vormen van immunotherapie
    - Checkpoint remmers
- Huidige systemische behandelingen bij melanoom
  - Gemetastaseerd
  - Gelokaliseerd
- Upcoming behandelingen
  - Neo-adjuvant
  - Nieuwe checkpoint remmers – bv Relatlimab
  - Celtherapie – bv TIL

DANK VOOR UW AANDACHT!!!
QUESTIONS?