Behandelingen van het melanoom: van de sprint naar de marathon

dr. Marika Ransschaert, UZ Antwerpen

MELANOOM STUDIEDAG 2024

10 JAAR HOOP

Melanoompunt is een volledig onafhankelijke patiëntenvereniging voor en door melanoompatiënten en hun naastbetrokkenen. Met de gewaardeerde steun van :

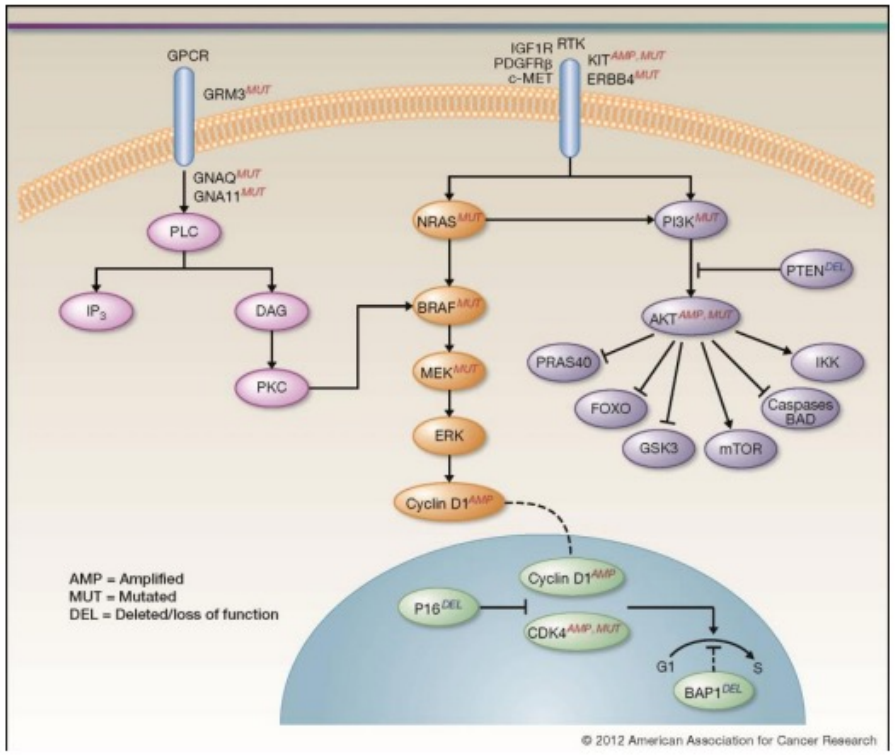
Met steun van Kom op tegen Kanker · ichting tegen Kanker · Pierre Fabre · MSD · Bristol Myers Squibb · NOVARTIS · Eau Thermale Avène Laboratoire Dermatologique · sanofi

Behandelingen van het melanoom: van de sprint naar de marathon

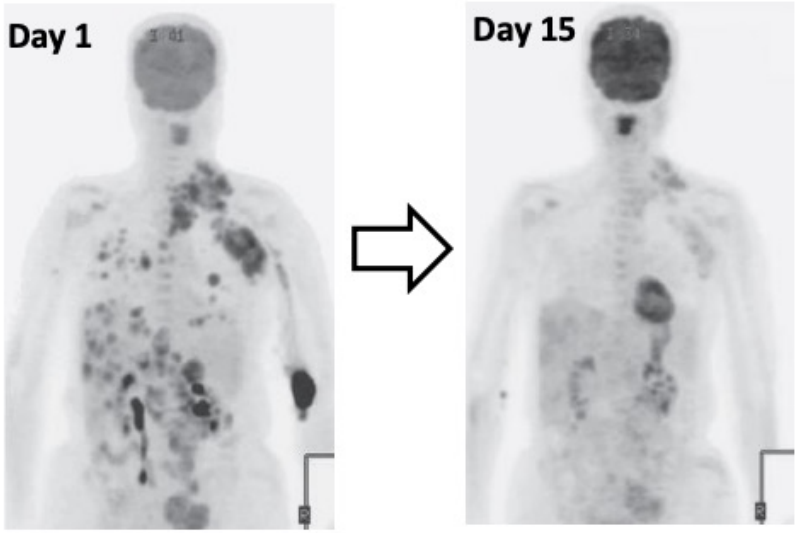
Zaterdag 27 januari 2024

Marika Rasschaert, MD, PhD

UZA



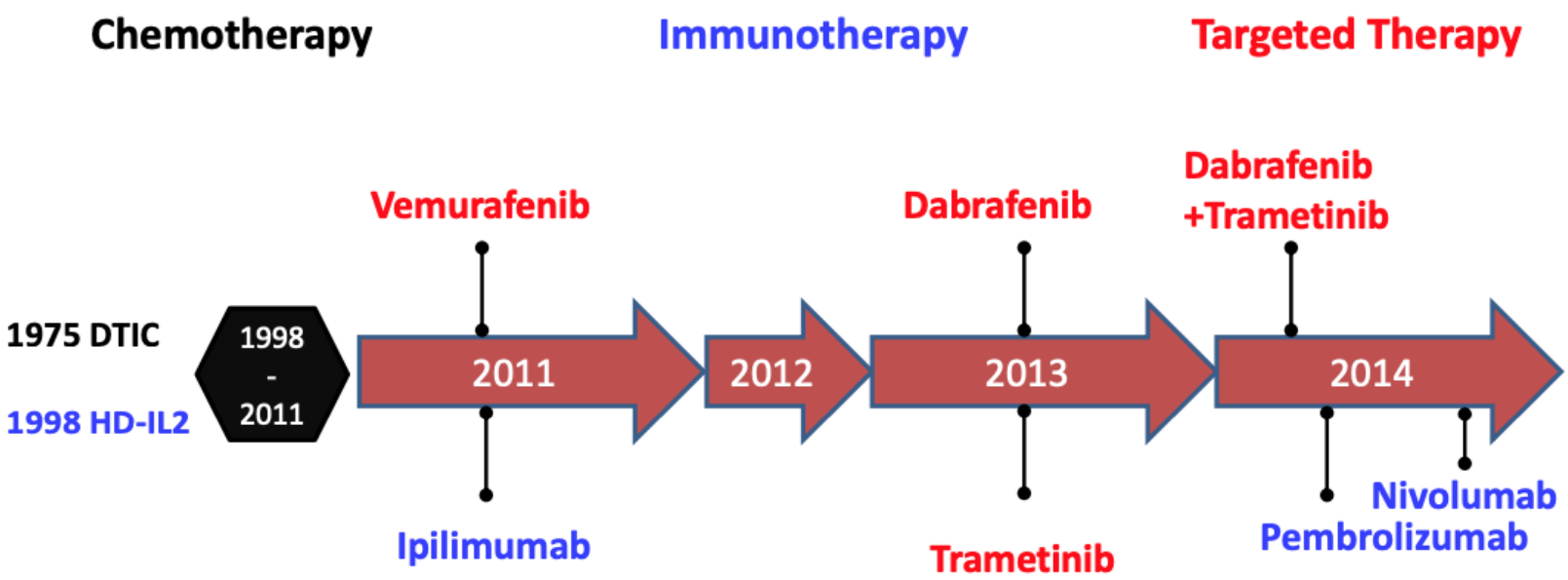
CCR, 2012



Flaherty *NEJM*, 2010

Nieuwe medicijnen voor het gemetastaseerd melanoma

2011-2014 7 new regimens approved



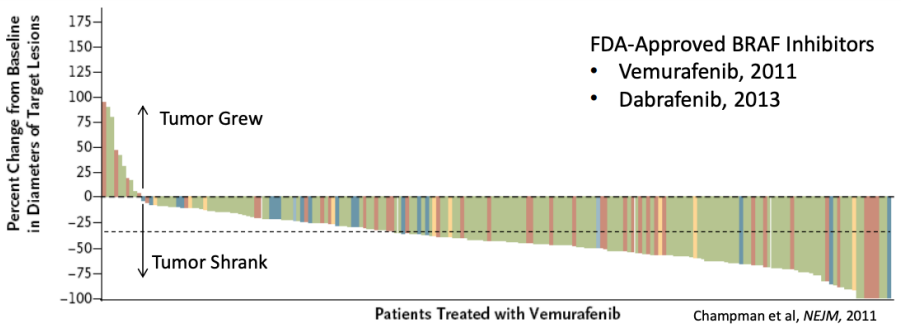
Wat is “targeted” therapy – gerichte behandeling

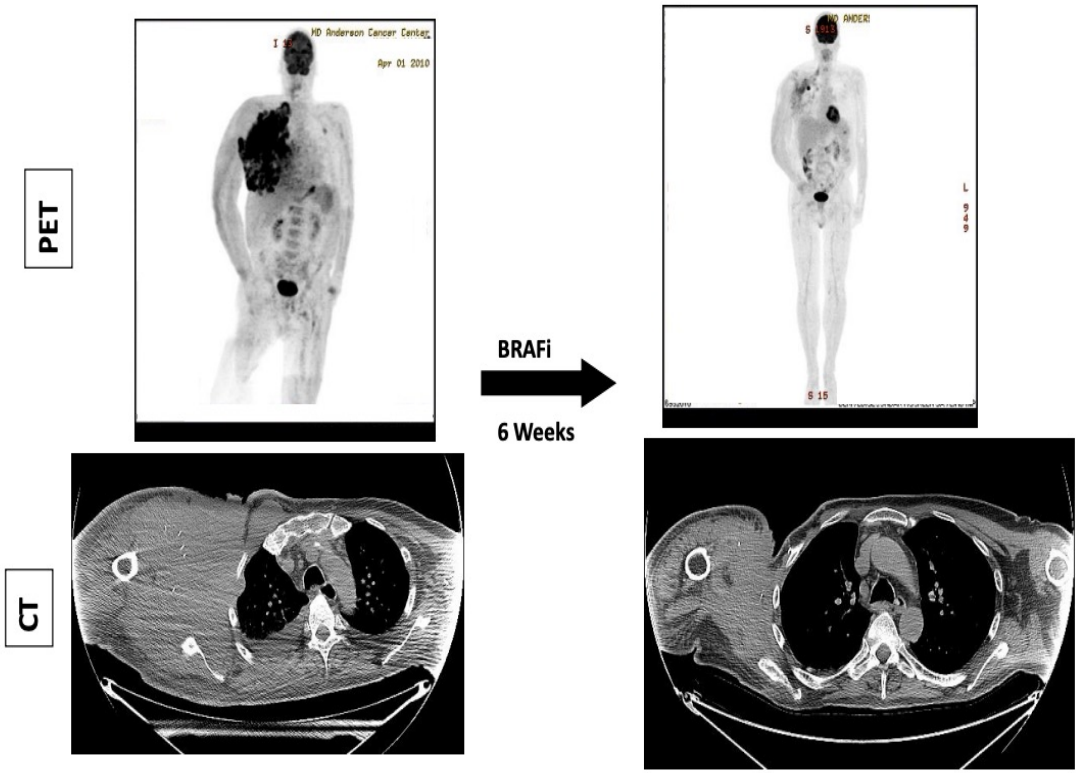
- Behandelt de kanker door zich te richten op de genetische fout of mutatie die zich in de tumor bevindt.

- Het melanoom is gekend met veel mutaties
- Specifieke mutaties kunnen teruggevonden worden in 70% vd cutane melanomen

DE belofte van Braf

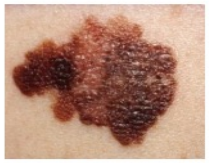
- Braf V600E mutatie is een activerende mutatie
- Bij blokkade – grote effecten op de tumor load
- Maar …
- Snelle resistentie



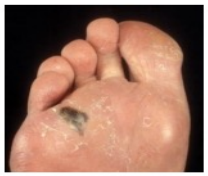


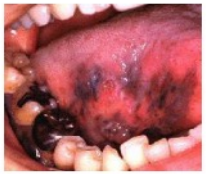
Verschillende klinische vormen – verschillende mutaties

Different Types of Melanomas Have Different Mutations

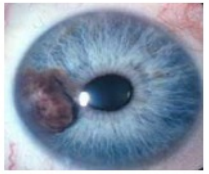


Cutaneous w/o Chronic Sun Damage (C.S.D)





Acral Melanoma
Mucosal Melanoma



Uveal

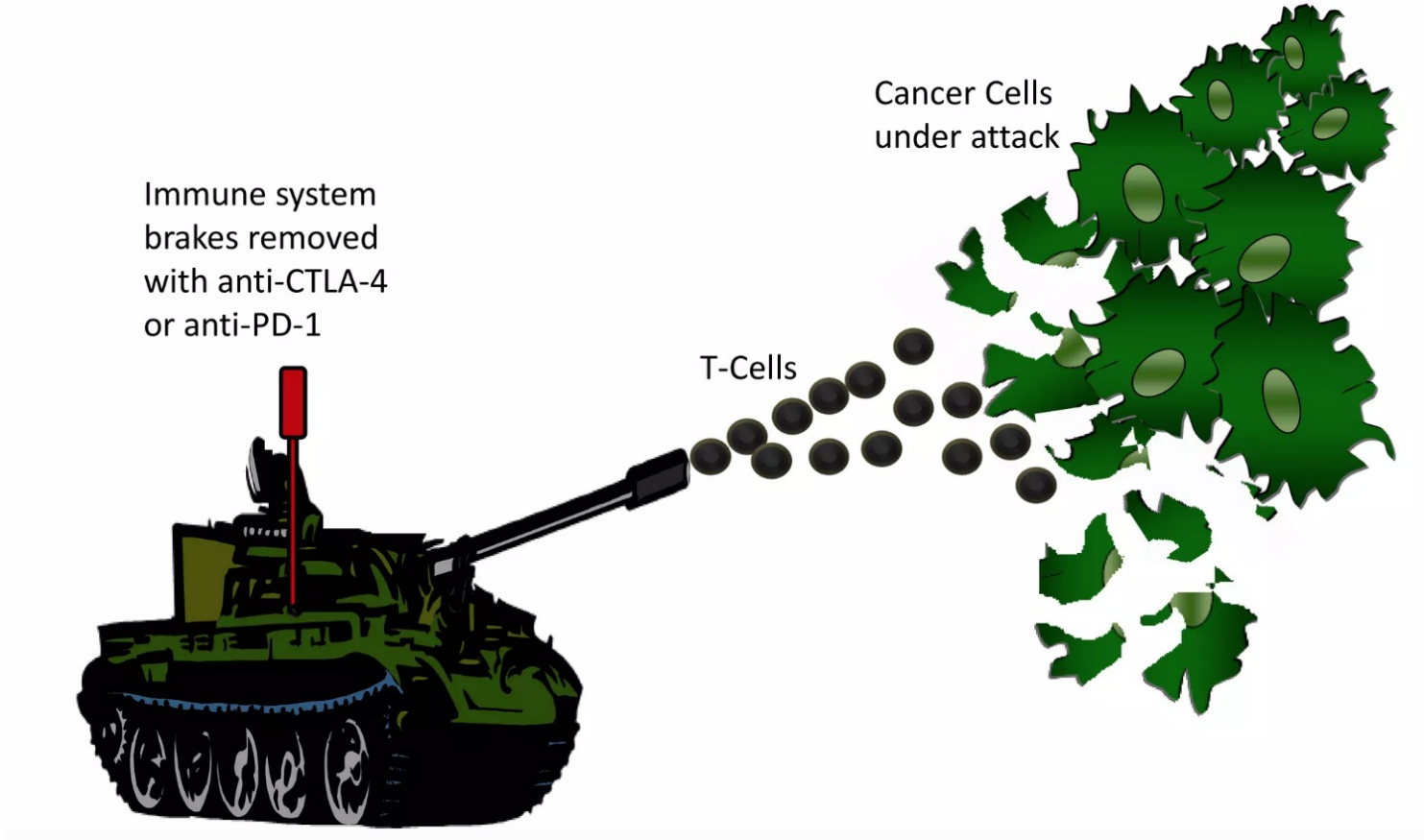
45% BRAF Mutations **20%** NRAS Mutations	**Acral:** 20% BRAF 10% NRAS **Mucosal:** 3% BRAF 5% NRAS	Virtually No BRAF/NRAS
	20-30% mutations in c-KIT	***~80% mutations in GNAQ/GNA11***

Immunotherapie

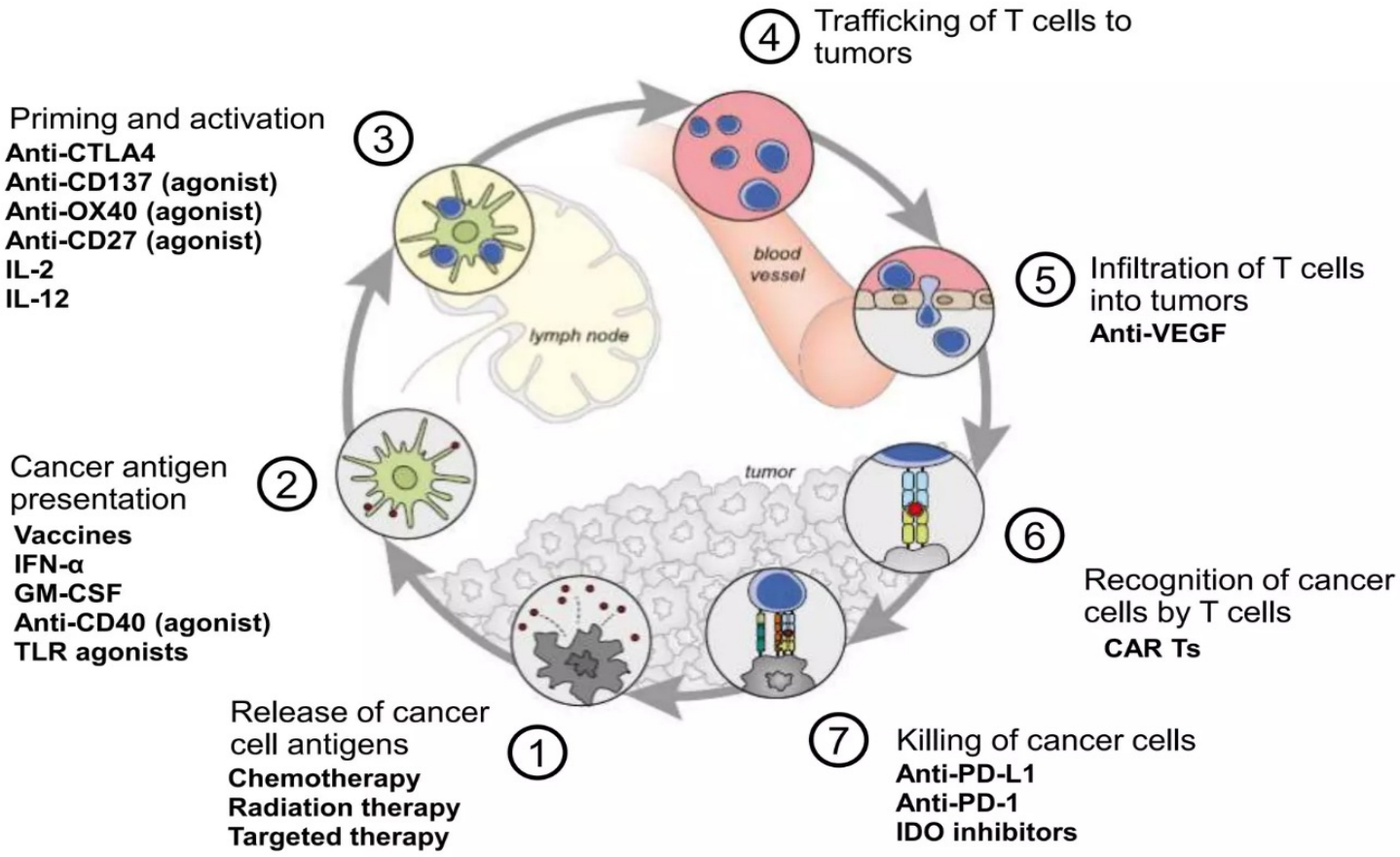
Immune
system
brakes on

Cancer Cells
Growing

Immunotherapie



Mogelijkheden om in te grijpen op het immuunsysteem



Met opties komen mogelijkheden

Opties > verschillende moleculen

- Afhankelijk van tumor eigen afwijkingen

Mogelijkheden

- Zijn afhankelijk van stadium :
  - neo–adjuverend
  - adjuverend
  - gevorderd (niet curatief)
- Specifieke omstandigheden (bv heelkunde/radiotherapie voor metastatishe localisaties)
- patiënten voorkeur

Opties bij het behandelen van een Melanoma

BRAF-WT or mutant

BRAF-mutant only

Adjuvant

- Anti-PD-1
- DAB + TRAM
- IPI (US only)

METASTATIC DISEASE

First-line

- NIVO + IPI
- NIVO + RELA[b]
- Anti-PD-1
- Combo targeted therapy (BRAF + MEK)
- Triplet therapy (TT + I-O; US and Switzerland only[c])

Second-line +

- Anti-PD-1
- NIVO + IPI
- NIVO + RELA (US only)
- IPI
- Combo targeted therapy (BRAF + MEK)
- Clinical trial

Useful in certain circumstances: intralesional T-VEC, cytotoxic agents, imatinib (KIT mutations)

Best supportive care

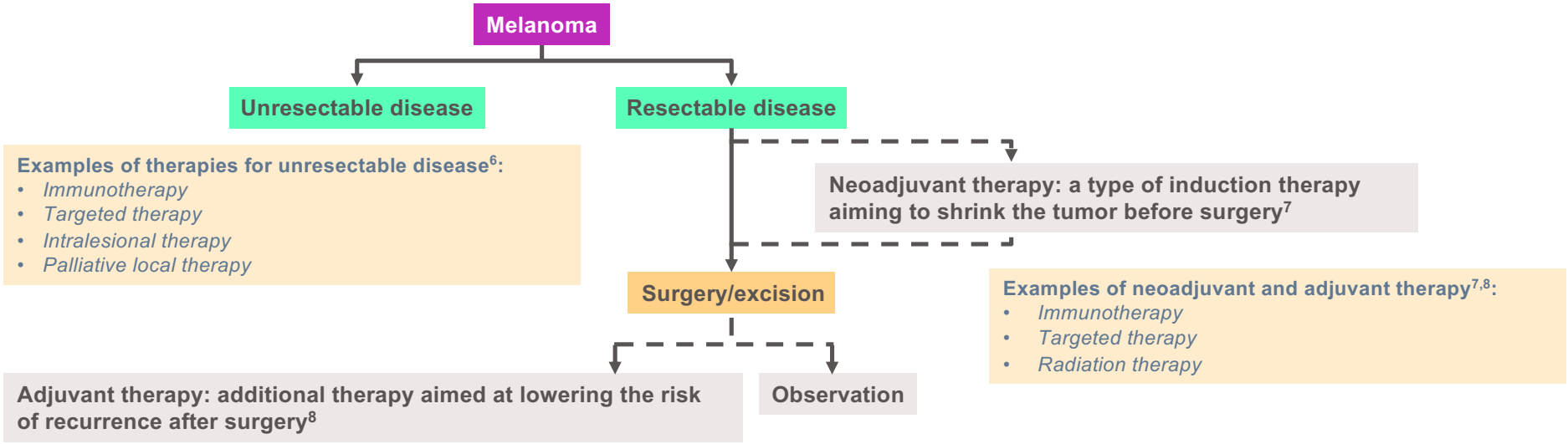
[a]Based on the experience of the speaker; frequently used, systemic options only are shown. [b]With tumor-cell PD-L1 expression < 1% in EU.[1] [c]Atezolizumab + vemurafenib + cobimetinib.[2,3]
BRAF, proto-oncogene B-Raf; DAB, dabrafenib; IL-2, interleukin-2; I-O, immuno-oncology; IPI, ipilimumab; MEK, mitogen-activated protein kinase kinase; NIVO, nivolumab; PD-1, programmed death-1; PD-L1, programmed death ligand 1; RELA, relatlimab; TRAM, trametinib; TT, targeted therapy; T-VEC, talimogene laherparepvec; US, United States; WT, wild-type.

1. OPDUALAG® (nivolumab and relatlimab-rmbw) [summary of product characteristics]. Uxbridge, UK: Bristol Myers Squibb; Accessed July 31, 2023. 2. Targeted Oncology. Accessed August 22, 2023. https://www.targetedonc.com/view/fda-approves-atezolizumab-triplet-regimen-for-treatment-of-advanced-braf-mutant-melanoma 3. Interpharma. Accessed September 26, 2023. https://www.interpharma.ch/blog/news/18842/

Treatment overview

Treatment options for melanoma[1–3]

- Treatment recommendations depend on a variety of factors, such as disease characteristics/stage, risk of recurrence, risk of treatment toxicity, and patient preference[1,2]
  - Defining surgical resectability can be very subjective[4,5]



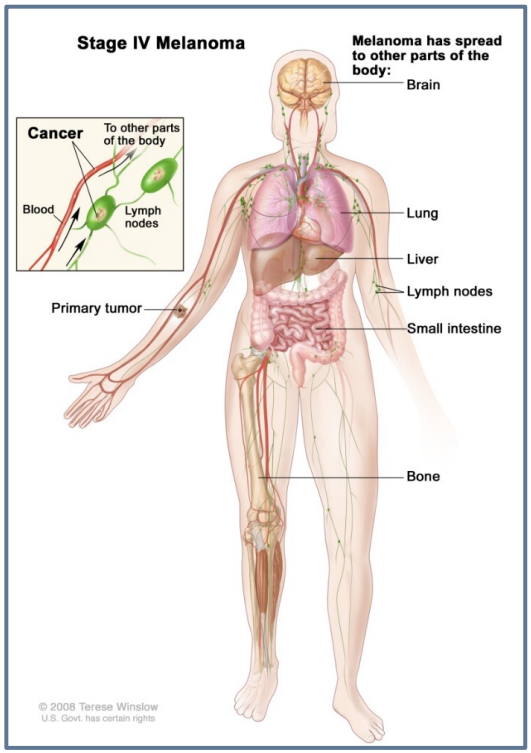
Treatment options shown here are not listed in any preferential order/category. Dashed lines represent potential treatment options that may be considered for certain patients.

NCCN, National Comprehensive Cancer Network® (NCCN®).
1. Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Cutaneous Melanoma V.2.2023. © 2023 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 2. Michielin O et al. *Ann Oncol*. 2020;31:1449-1461. 3. Garbe C et al. *Eur J Cancer*. 2022;170:256-284. 4. Sarver M et al. *Hum Vaccin Immunother*. 2022;18:1943987. 5. Jakub JW et al. *J Surg Oncol*. 2018;117:1164-1169. 6. National Cancer Institute. Melanoma treatment (PDQ)-health professional version. https://www.cancer.gov/types/skin/hp/melanoma-treatment-pdq#section/_885. Accessed June 2, 2023. 7. Neoadjuvant therapy. NCI Dictionary of Cancer Terms. National Cancer Institute website. https://www.cancer.gov/publications/dictionaries/cancer-terms. Accessed June 2, 2023. 8. Adjuvant therapy. NCI Dictionary of Cancer Terms. National Cancer Institute website. https://www.cancer.gov/publications/dictionaries/cancer-terms. Accessed June 2, 2023.

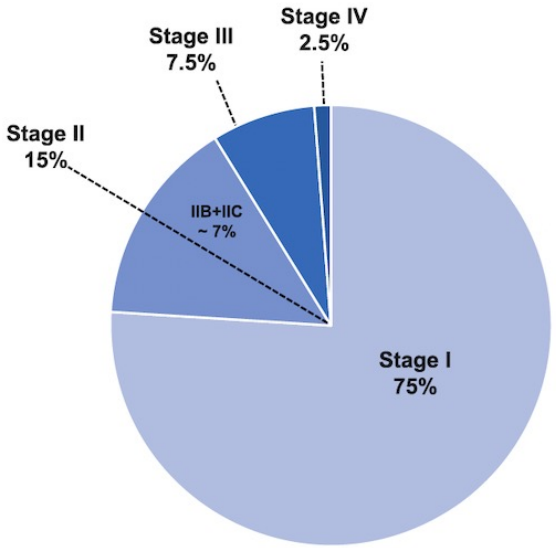
De adjuverende behandeling bij een te reseceren melanoma Stage II-IV Melanoma

Stagering melanoom

TNM



Verdeling stadia bij diagnose



Poklepovic el al.Cancer 2019, DOI: 10.1002/cncr.32585

Global: Epidemiology (1 of 2)

De overleving is afhankelijk van stadium bij diagnose

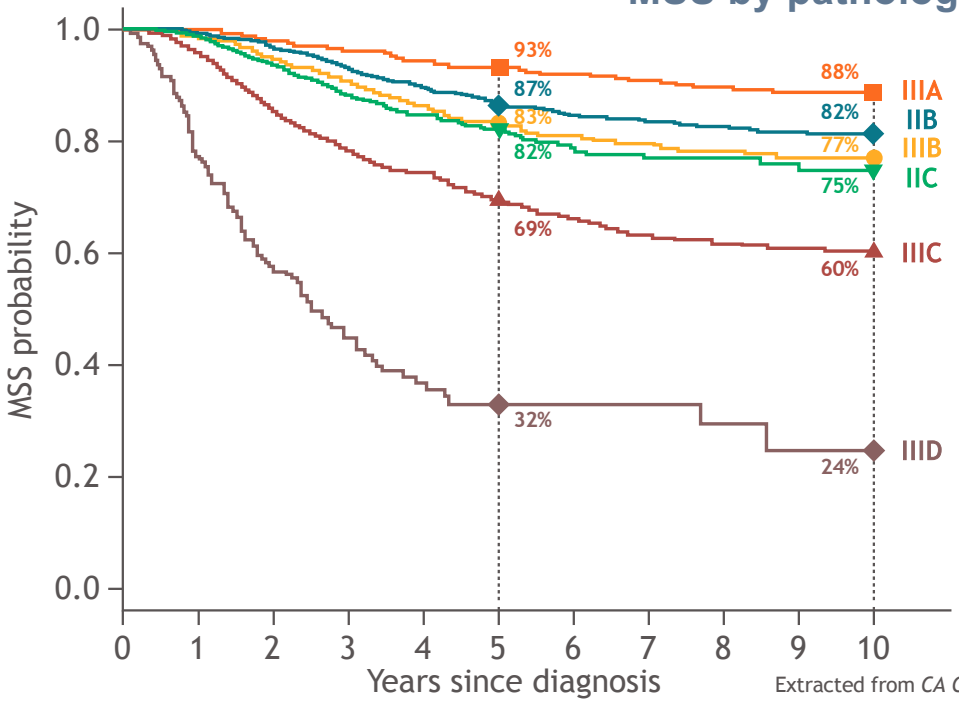
International 5-year and 10-year Melanoma-specific Survival Rates for Melanoma, by Skin Cancer Stage

Adjuvante therapie mogelijk

Gershenwald JE, et al. *CA Cancer J Clin*. 2017;67(6):472-492.

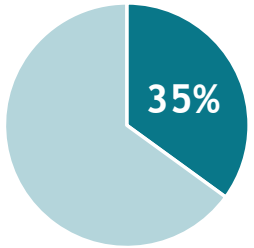
Unmet needs for patients with stage II-III melanoma

MSS by pathological stage[1,2,a,b]

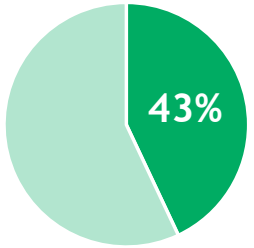


Extracted from *CA Cancer J Clin.*[1]

5-year risk of disease recurrence[3,b,c]



Stage IIB



Stage IIC

[a]MSS was calculated from the date of initial melanoma diagnosis. MSS survival rates represent the percentage of patients who have not died from melanoma in a defined time period.
[b]Based on AJCC 8th edition. [c]Confirmatory cohort data.
AJCC, American Joint Committee on Cancer, Cancer Staging Manual; MSS, melanoma-specific survival; RFS, recurrence-free survival.

1. Gershenwald JE et al. *CA Cancer J Clin*. 2017;67:472-492. 2. NCI Dictionary. Disease-specific survival rate. Accessed February 1, 2023. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/disease-specific-survival-rate 3. Garbe C et al. *J Clin Oncol*. 2022;40:3741-3749.

Adjuvante therapie mogelijk bij

(Dikke) primaire melanomen zonder klieraantasting (IIb en IIc)

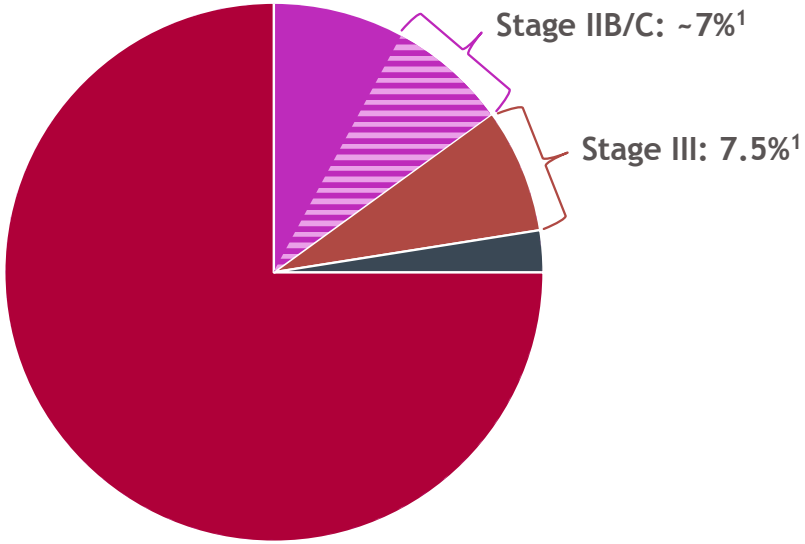
- 2,1mm met ulceratie (pT3b) of
- >4mm ongeacht ulceratie (pT4a en pT4b)
- Geen kliermeta's

Primaire melanomen (ongeacht Breslow) met kliermeta's (III)

- Alle T stadia
- N+

(Gemetastaseerde ziekte na complete resectie)

Incidence of stage IIB/C melanoma



An estimated 7% of patients diagnosed with melanoma will have stage IIB/C disease[1,a]

- Similar incidence as stage III melanoma[1,a]

Stage IIB/C melanoma is primarily treated with surgery; however, these patients have a high risk of recurrence following complete resection[1–6]

[a]US data.1. Poklepovic AS, Luke JJ. *Cancer*. 2020;126:1166–1174. 2. Michielin O et al. *Ann Oncol*. 2019;30:1884–1901. 3. American Cancer Society. Treatment of melanoma skin cancer, by stage. Accessed February 1, 2023. https://www.cancer.org/cancer/melanoma-skin-cancer/treating/by-stage.html 4. Gershenwald JE et al. *CA Cancer J Clin*. 2017;67:472-492. 5. Podlipnik S et al. *J Am Acad Dermatol*. 2016;75:516-524. 6. Bleicher J et al. *J Surg Oncol*. 2020;122:1770-1777.

Het doel bij een adjuvante behandeling: Risico reductie op *herval* na heelkundige resectie

PATIENT OUTCOME

TOXICITY

Primaire doel :
RFS

Secondaire doel:
DMFS en OS

Tertiaire doel:
toxiciteit, quality of life

Slide developed based on the clinical expertise of the speaker.
DMFS, distant metastasis-free survival; OS, overall survival; RFS, recurrence-free survival.

KEYNOTE-716: Adjuvant Pembrolizumab vs Placebo in High-risk, Resected, Stage II Melanoma

Patients aged ≥12 yr with newly diagnosed, resected, high-risk stage IIB/C melanoma; negative sentinel LN biopsy; ECOG PS 0 or 1 (N = 976)

Pembrolizumab
200 mg (or 2 mg/kg pediatric) IV Q3W for 17 cycles (n = 487)

Placebo
IV Q3W for 17 cycles (n = 489)

Recurrence

Part 2: Rechallenge/Crossover

Pembrolizumab
200 mg (or 2 mg/kg pediatric) IV Q3W until progression or recurrence, up to 2 yr

Long. Lancet Oncol. 2022;23:1378.

Benefits of pembrolizumab adjuvant

Stadium IIb/IIc

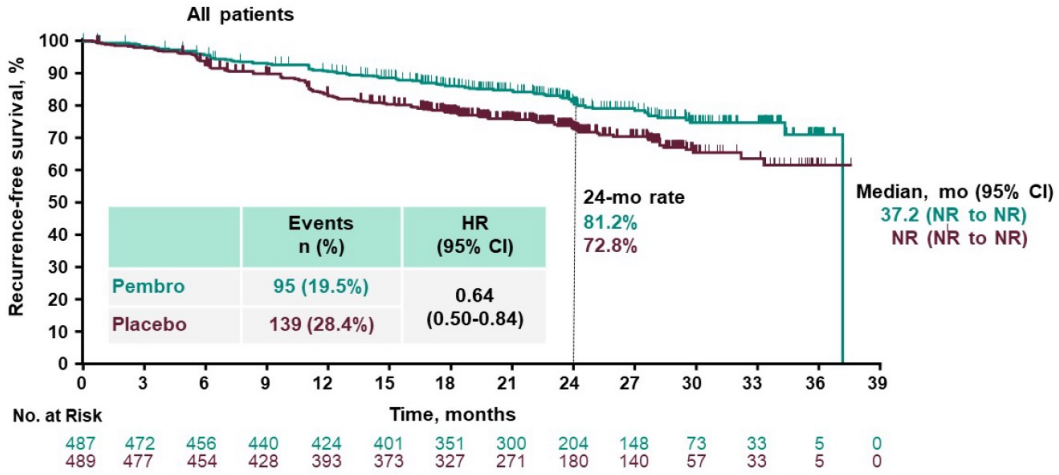
Recidief-vrije overleving - winst van 8,4% na 2 jaar

Public

ADJUVANT THERAPY | KEYNOTE-716

Abbreviations

IA3: RFS (Primary End Point)



Median follow-up of 27.4 months (range 14.0-39.4 months). Data cutoff: January 4, 2022.
Long GV, et al. Presented at ASCO 2022.

MSD

UZA

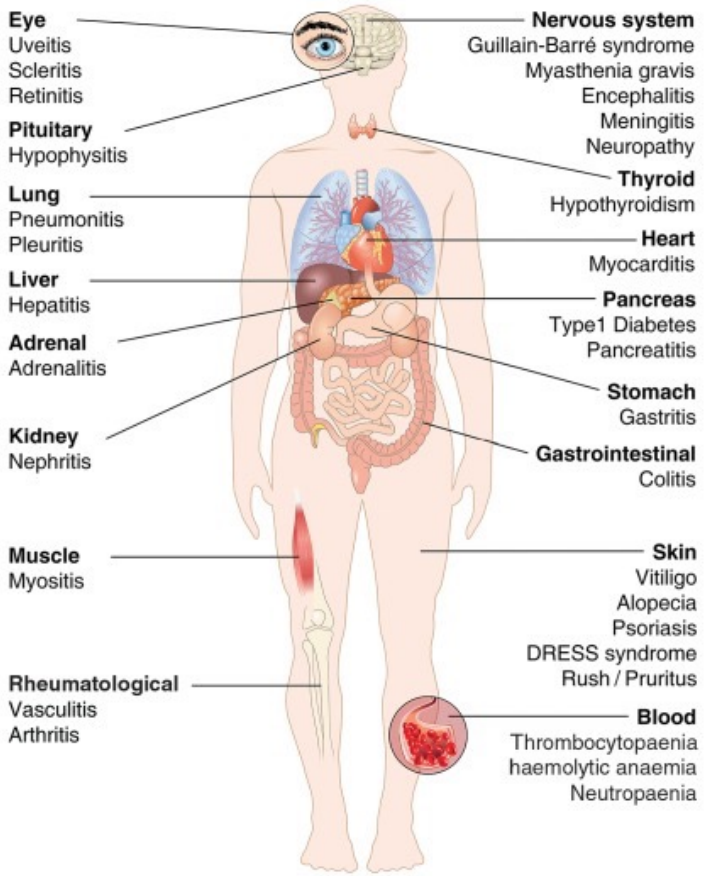
Knelpunt van een adjuverende therapie

- 72% hervalt niet (nutteloos risico op tox)
- 19% hervalt ondanks (primaire resistentie)
- WINST 8%

- Cijfers zijn afh vh stadium

Bijwerkingen

Immune related adverse events (irAE's)



Varrichi ey al. ESMO Open 2017

Bijwerkingen

Public

ADJUVANT THERAPY | KEYNOTE-716

Abbreviations

IA3: Adverse Events in the Treated Population[a]

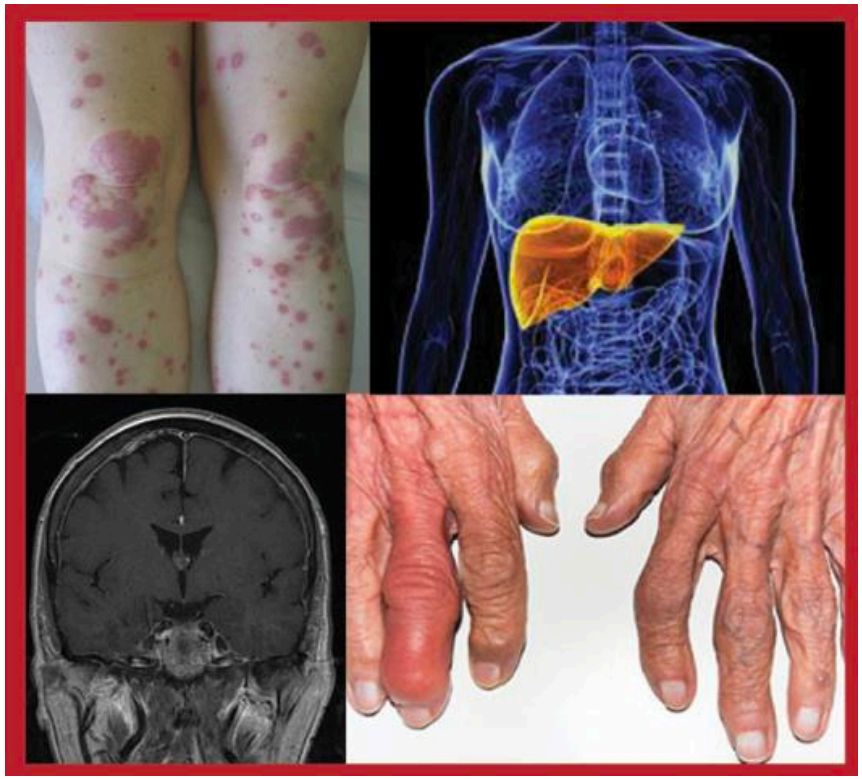
	Pembrolizumab (n=483)		Placebo (n=486)	
	Any, n (%)	Grade ≥3, n (%)	Any, n (%)	Grade ≥3, n (%)
Any cause adverse event	462 (96)	–	445 (92)	–
Any treatment-related event	400 (83)	83 (17)	309 (64)	24 (5)
Discontinued	77 (16)	–	12 (2)	–
Died	0	–	0	–
Immune-mediated events and infusion reactions	182 (38)	–	45 (9)	–
Treatment-related events occurring in ≥15% of patients in each group				
Fatigue	103 (21)	1 (<1)	92 (19)	1 (<1)
Hypothyroidism	77 (16)	0	13 (3)	0
Arthralgia	81 (17)	2 (<1)	39 (8)	0
Pruritus	119 (25)	3 (1)	52 (11)	0
Rash	78 (16)	7 (1)	34 (7)	1 (<1)
Diarrhea	90 (19)	5 (1)	56 (12)	1 (<1)

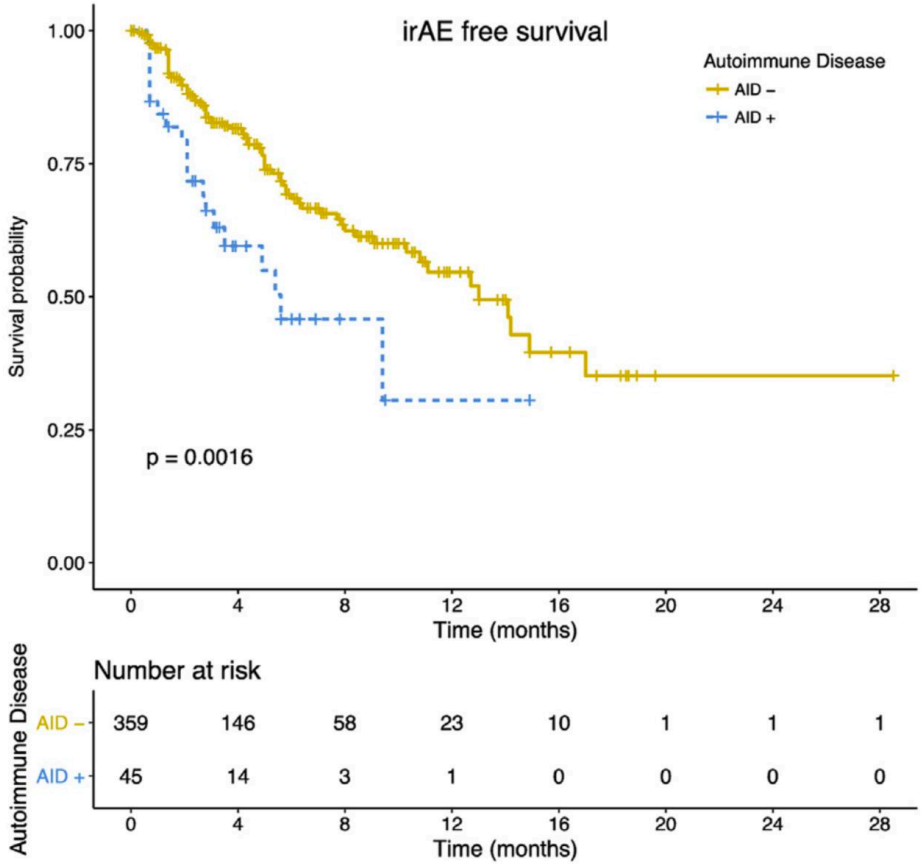
Median follow-up of 27.4 months (range 14.0-39.4 months). Data cutoff: January 4, 2022.
Long GV, et al. Presented at ASCO 2022.

MSD

UZA

Patients with preexisting autoimmune disease

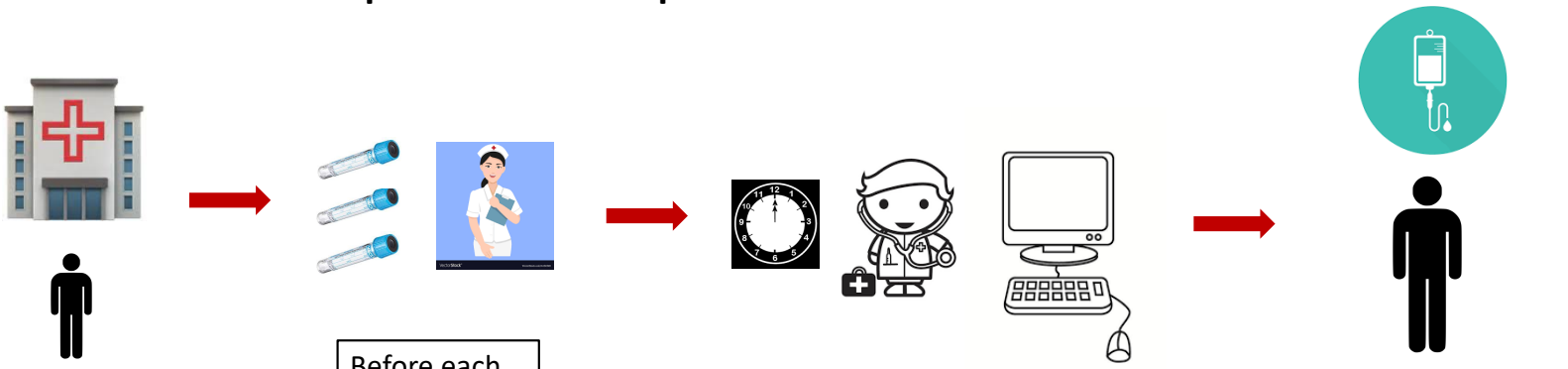




Danlos et al. Eur. J. Cancer 2018;91:21–29

Behandeling op het dagziekenhuis

Treatment schedule – pembrolizumab q3 or 6 w



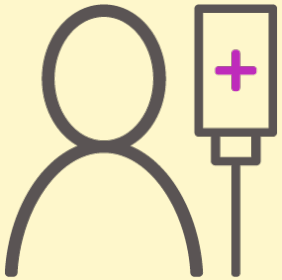
Before each cycle an extensive blood test is done (d -1 or d0)

Before each cycle a consultation with a physician takes place

The administration of pembrolizumab +/- 30 min

Therapieduur : 1 jaar

How can we improve the treatment of patients with resectable melanoma?



Optimize patient management and the patient journey

Identify biomarkers to tailor treatment to specific patients

"Precision adjuvant treatment"

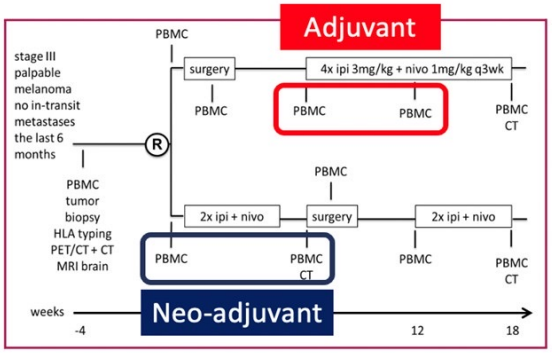
Develop new, more effective agents and combinations

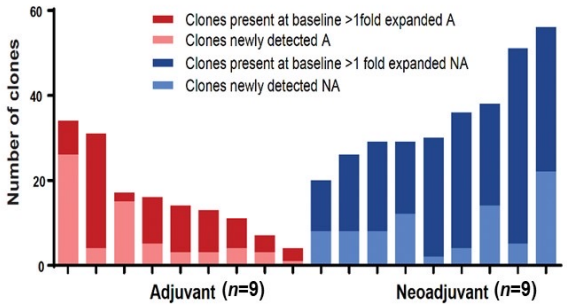
Hoe toxiciteit voorkomen?

- Door mensen die geen immuuntherapie nodig hebben niet te behandelen!
- Door minder immuuntherapie te geven
- Door andere immuuntherapie te geven

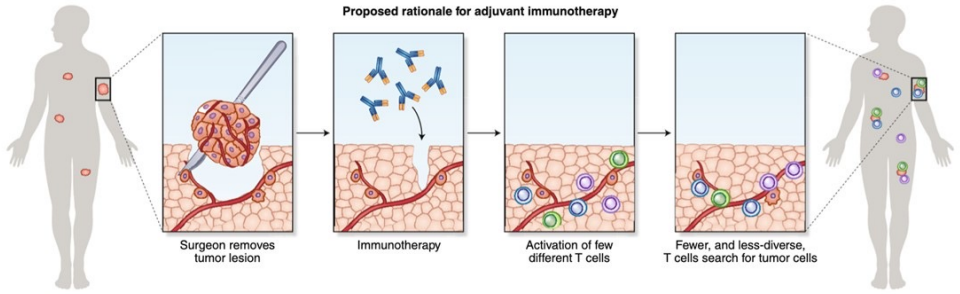
Niet of minder behandelen

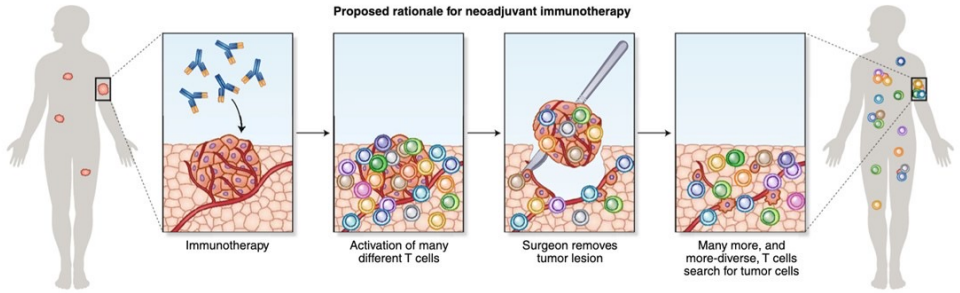
Neoadjuvant checkpoint inhibition is thought to be superior to adjuvant due to induction of a larger and broader immune repertoire





Blank et al, Nature Medicine 2018

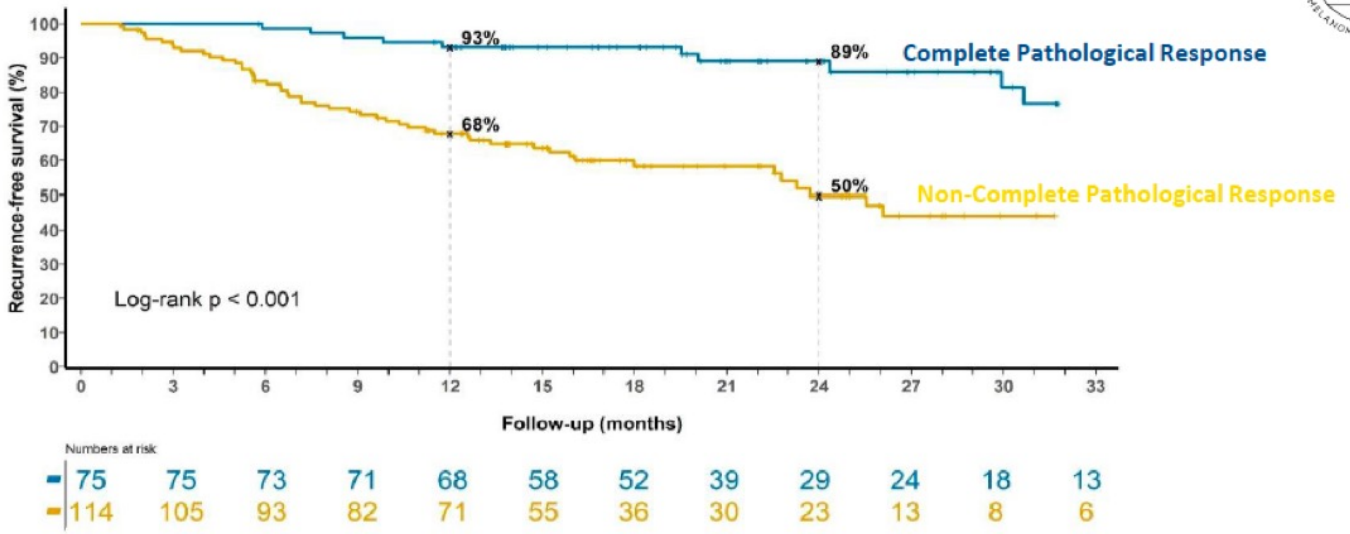




Versluis et al, Nature Medicine 2020

Niet of minder behandelen

Pooled Analysis: Neoadjuvant Therapy in Stage III Melanoma
RFS by Pathological Response Checkpoint Inhibitors or BRAF Targeted Therapy



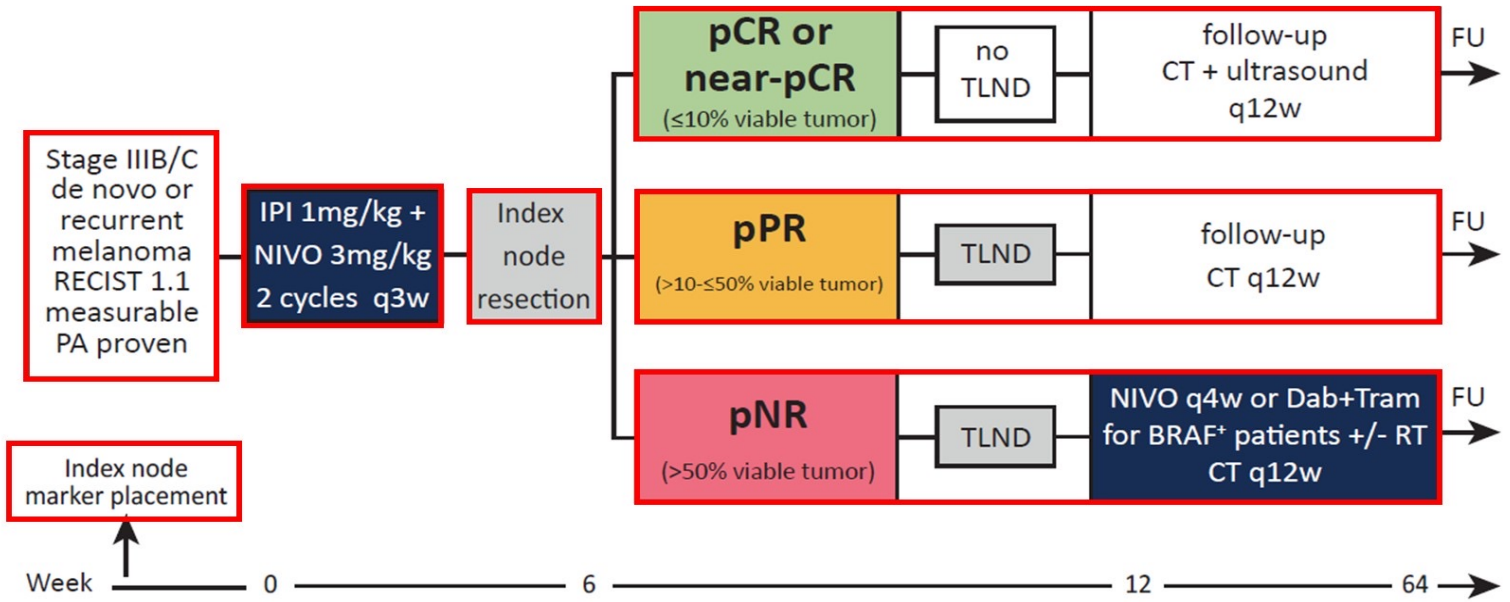
Med f/u 20.9 mo

Menzies et al Nat Med 2020 ms accepted

Presented by Georgina V Long @ProfGLongMIA

Neo-adjuverende immunotherapie

PRADO study design



Minder therapie – voor de patienten met goede of complete respons na 2 cycli

Patients with major pathologic response (MPR) had high RFS/DMFS rates

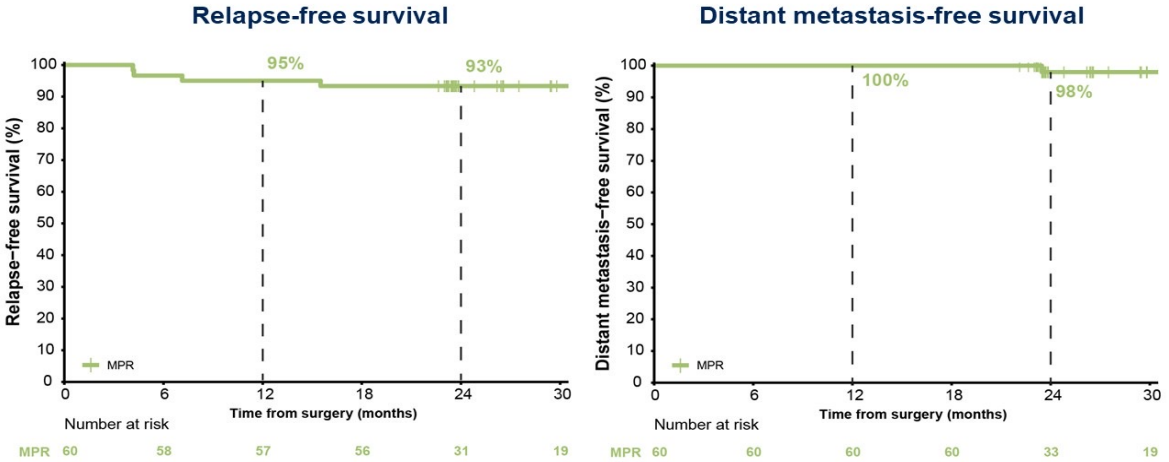
MPR patients

At 2 years, 4/60 MPR patients had developed a recurrence
- 3 only regional metastasis
- 1 also M1a disease (23.5mo)

These 4 patients had ≥2 positive nodes on baseline PET-scan.
- Total 28 patients with ≥2 positive nodes (4/28 = 14% recurrences)

Primary endpoint was not met (null hypothesis not rejected in case of >1 recurrence)

TLND omission might be safe



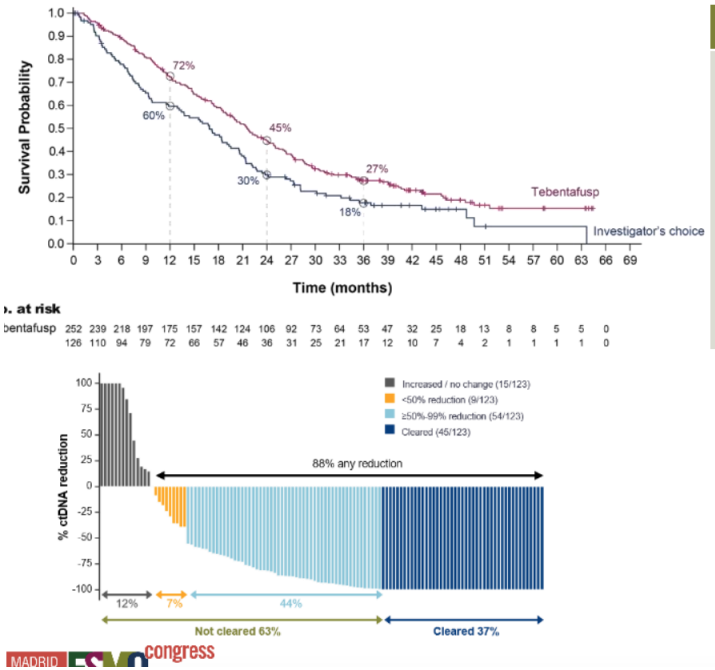
OpACIN-neo: 2-year RFS MPR cohort: 96%

PRESENTED BY: Christian U Blank

Minder behandelen / durven stoppen?

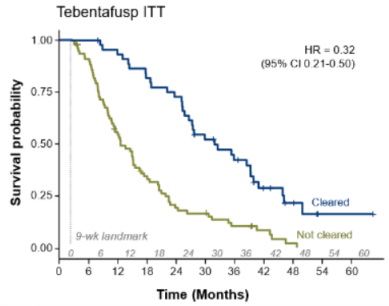
- Wanneer er *geen ziekte te zien is* en zelfs dan behandelen we nog even door
- Wanneer er *geen tumoraal dna* (ctDNA) in het serum terug te vinden is cfr de gegevens over Tebentafusp

LBA50 - Three-year survival with tebentafusp in previously untreated metastatic uveal melanoma in a phase 3 trial. **Sophie Piperno-Neumann et al.**



THE WAY THEY DO IT & MAIN FINDINGS

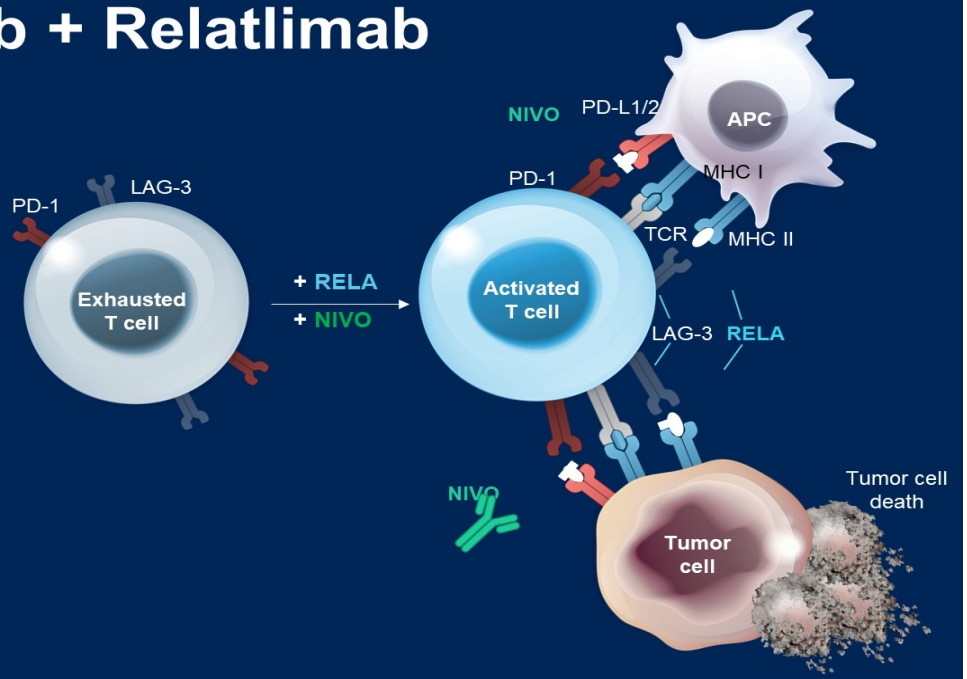
- Long term analysis of ph3 clinical trial at 3y
- 27% of patients treated with tebentafusp are still alive at 3y (9% of increment vs control)
- This benefit is seen even for patients with PD as BOR, highlighting that classic response evaluation fail to predict the benefit in this setting
- ctDNA clearance (>50%) is associated with OS



Andere immuuntherapie / minder tox

Rationale for Nivolumab + Relatlimab

- LAG-3 and PD-1 are distinct and often co-expressed on tumor-infiltrating lymphocytes and contribute to tumor-mediated T-cell exhaustion[1,2]
- Relatlimab (RELA) is a human LAG-3-blocking antibody that restores effector function of exhausted T cells
- In preclinical models, LAG-3 and PD-1 blockade demonstrated synergistic antitumor activity[1]
- RELA + NIVO demonstrated clinically meaningful antitumor activity including durable objective responses and was well tolerated in patients with melanoma that was relapsed/refractory to anti–PD-1 therapy[3,4]

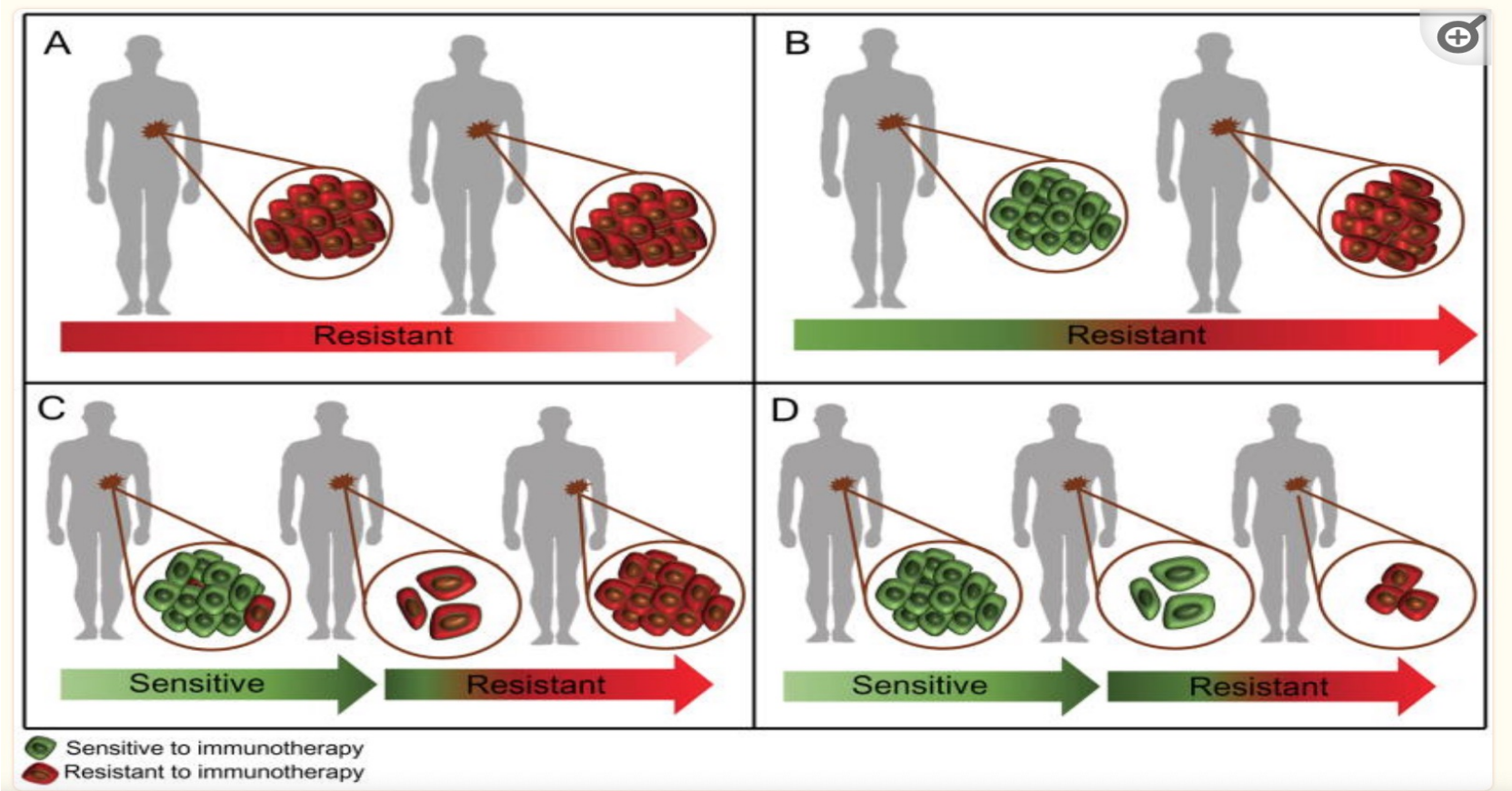


NIVO, nivolumab; PD-L1/2, programmed death ligand 1/2; APC, antigen-presenting cell; TCR, T-cell receptor; MHC, major histocompatibility complex.1. Woo S-R, et al. *Cancer Res* 2012;72:917–927; 2. Anderson AC, et al. *Immunity* 2016;44:989–1004. 3. Ascierto PA, et al. Oral presentation at ASCO Annual Meeting; June 2–6, 2017; Chicago, IL. Abstract 9520; 4. Ascierto PA, et al. Oral presentation at ESMO Congress; September 8–12, 2017; Madrid, Spain. Abstract LBA18.

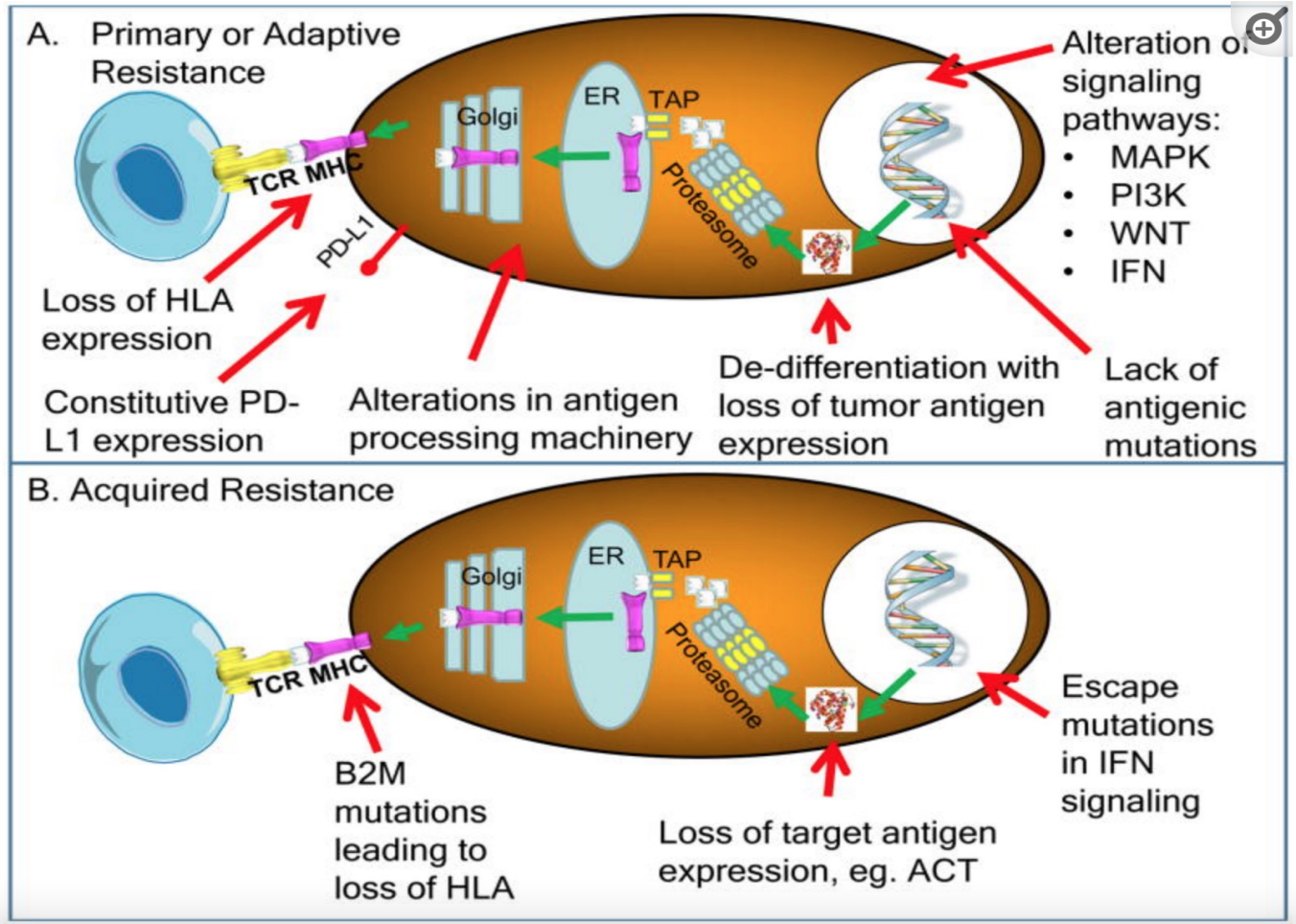
Presented By: R. N. Amaria

2021 ASCO ANNUAL MEETING

Primaire resistentie vs secundaire resistentie



Primaire resistentie vs secundaire resistentie



Wat bij primaire of secundaire resistente

Deze lijst is niet exhaustief en dient enkel als voorstelling van verschillende concepten :

- Aanbieden van tumor eiwit (vaccinaties)
- Aanbieden van actieve witte bloedcellen (TIL's)
- Nieuwe manieren om de rem op witte bloedcellen op te heffen
- Combinatie van gekende molecules
- Blokkeren van vooropgestelde resistentie mechanismen
- Avastine bij BM – bias (mogelijks ook effect op ss door resorptie oedeem)

Van sprint tot Marathon

Melanoompunt

MELANOOM STUDIEDAG 2024

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informeren, ontmoeten, ondersteunen

Melanoompunt is een volledig onafhankelijke patiëntenvereniging voor en door melanoompatiënten en hun naastbetrokkenen. Met de gewaardeerde steun van :

Met steun van Kom op tegen Kanker

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MSD

Bristol Myers Squibb

NOVARTIS

Eau Thermale Avène Laboratoire Dermatologique

sanofi