Vibeke KRUSE MD PhD / Dienst Medische Oncologie

Wat zijn de potentiële gevaren van immunotherapie

Kan immunotherapie de ziekteverzekering ondermijnen?

ALUMNI GENEESKUNDE UGENT VZW

19 Februari 2020

UZ GENT

UNIVERSITEIT GENT

DE TIJD

Nieuws Markten Netto

Koning start driedaagse consultatieronde

Geens: 'Wij zijn niet de dweil van de Wetstraat'

Johnson zegt BBC de wacht aan

NIEUWS > POLITIEK & ECONOMIE > BELGIË > FEDERAAL

Nieuwe kankertherapie jaagt ziekteverzekering op kosten

TWITTER
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WHATSAPP
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BEWAREN
SCHENK DIT ARTIKEL
4 REAGEER

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WIM DE PRETER | 26 augustus 2019 07:33

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Ontdek Video Audio Zoek Net binnen

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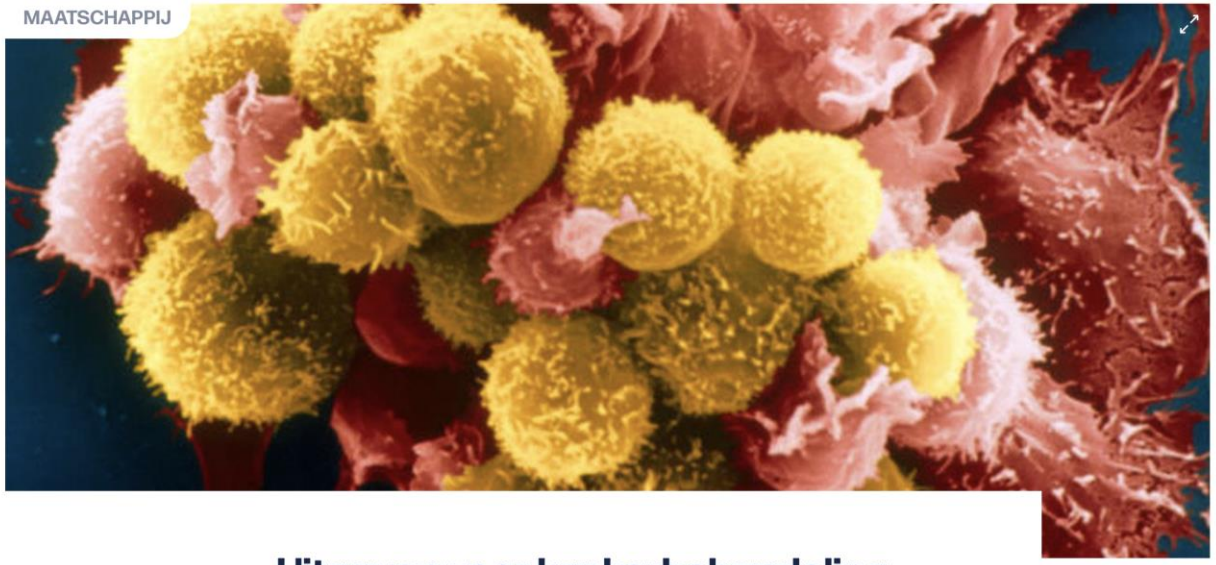


Uitgaven voor kankerbehandeling lopen op tot meer dan 1 miljard euro, immuuntherapie zit in de lift

Tobias Santens
ma 26 aug 2019 13:36

Medscape Sunday, February 16, 2020

NEWS & PERSPECTIVE DRUGS & DISEASES CME & EDUCATION ACADEMY VIDEO

News > Medscape Medical News > Oncology News

Immunotherapy Combos: Will Cost Put Them out of Reach?

Kerry Dooley Young
October 18, 2018

Hoeveel is uw leven waard?

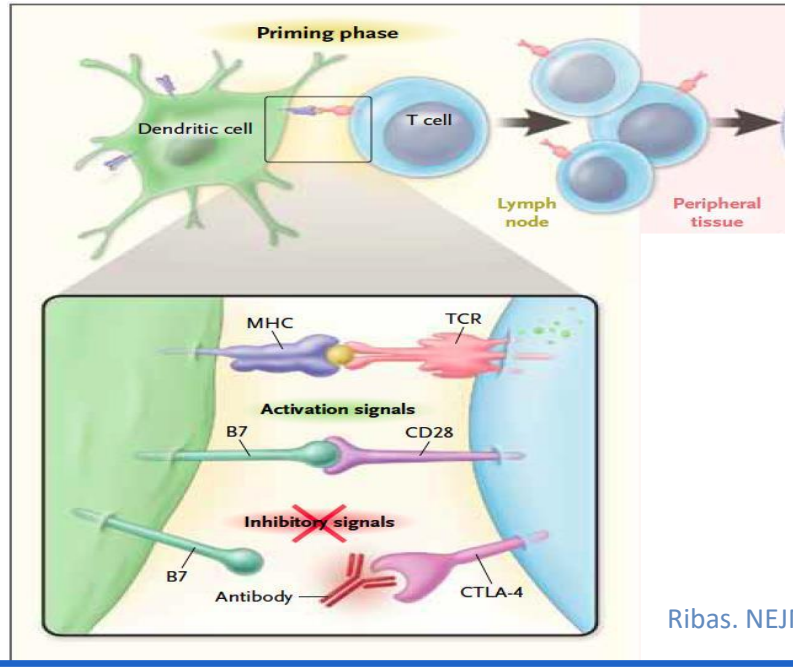
De strijd tegen kanker botst op economische en ethische dilemma's

Zou u uw huis verkopen om een kankerbehandeling te betalen? De vraag is niet zo vreemd als ze lijkt. De innovatieve behandelingen waar we van mogen dromen, zijn op grote schaal onbetaalbaar. De grenzen liggen niet meer in de labo's, maar in onze portefeuille. Het laatste taboe in de strijd tegen kanker: 'Als we deze koers blijven varen, gaat onze sociale zekerheid failliet.'

Door Ine Renson, Saar Sinnaeve en Jasper D'hoore
Foto's: Kristof Vadino, Shutterstock - Video: Dirk Selleslagh - Techniek: Raphael Cockx - Grafieken: Maarten Lambrechts

Checkpoint inhibitoren

CTLA4 blockade renders T cells in an active state



Ribas. NEJM 20

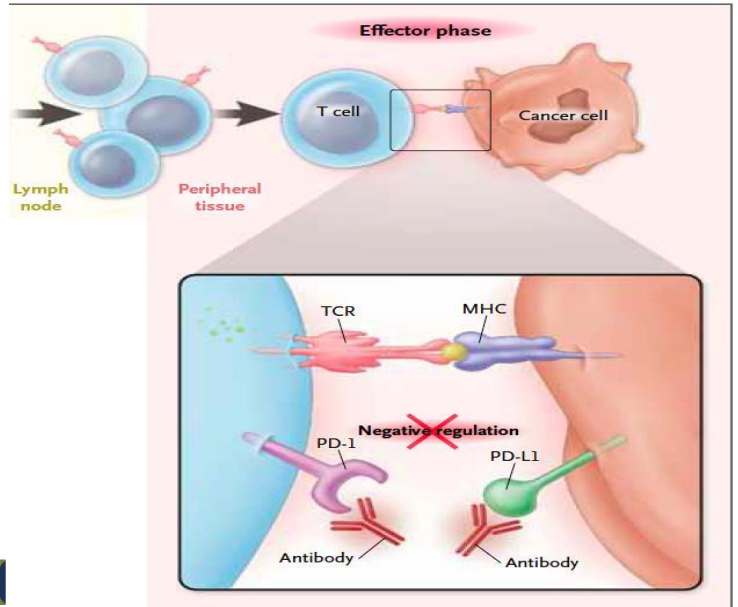
Anti-CTLA4: ipilimumab

Anti-PD1 : nivolumab, pembrolizumab

Anti-PDL1: atezolizumab, avelumab

…

PD1/PDL1 blockade reinvigorates inactivated T cells at the tumor site



Ribas. NEJM 2012

Terugbetaalde indicaties


Melanoom


Long

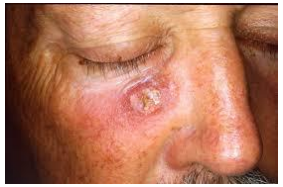

Nier

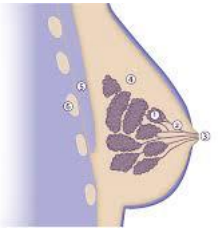

Lymfoom



Hoofd&Hals Blaas

Merckelcel carcinoma


Gemetastaseerd spinocellulair carcinoom van de huid


TNBC

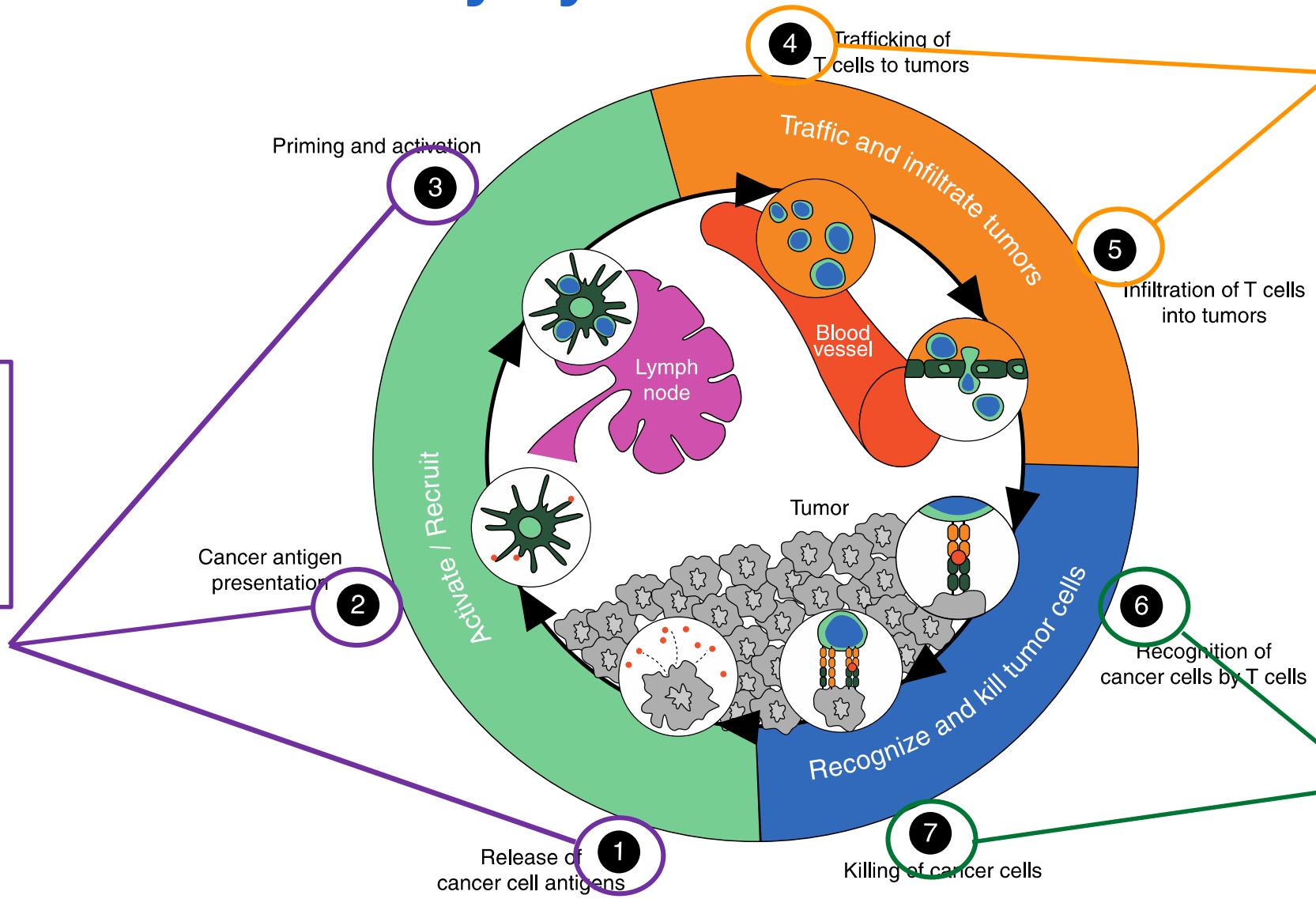
GROUP	INDICATION	ORR (%)	Agents approved	Main driver of response
High response rate	Hodgkin's disease	87	Nivolumab Pembrolizumab	PDJ amplicon
	Desmoplastic Melanoma	70	Nivolumab Pembrolizumab	Mutations from chronic sun exposure
	Merkel cell	56	Avelumab Pembrolizumab	Merkel cell virus
	MSI-h cancers	53	Nivolumab Pembrolizumab	Mutations from mismatch-repair deficiency
Intermediate response rate	Skin Melanoma	35-40	Nivolumab Pembrolizumab	Mutations from intermittent sun exposure
	Renal cell carcinoma	25	Nivolumab Pembrolizumab	Insertions and deletions (indels)
	NSCLC	20	Nivolumab Pembrolizumab Atezolizumab	Mutations from cigarette smoking
	Hepatocellular carcinoma	20	Nivolumab	Hepatitis virus
	Head and neck	15	Nivolumab Pembrolizumab	Mutations from cigarette smoking
	Bladder and Urinary tract	15	Nivolumab Pembrolizumab Atezolizumab Avelumab Durvalumab	Mutations from cigarette smoking

Adpated from Ribas et al. Science 2018

Very promising results, but…

Up to 85% of the patients will not respond to anti-PD1 / anti-PDL1 treatment!

The Cancer Immunity cycle



Infiltration of T-cells into tumors

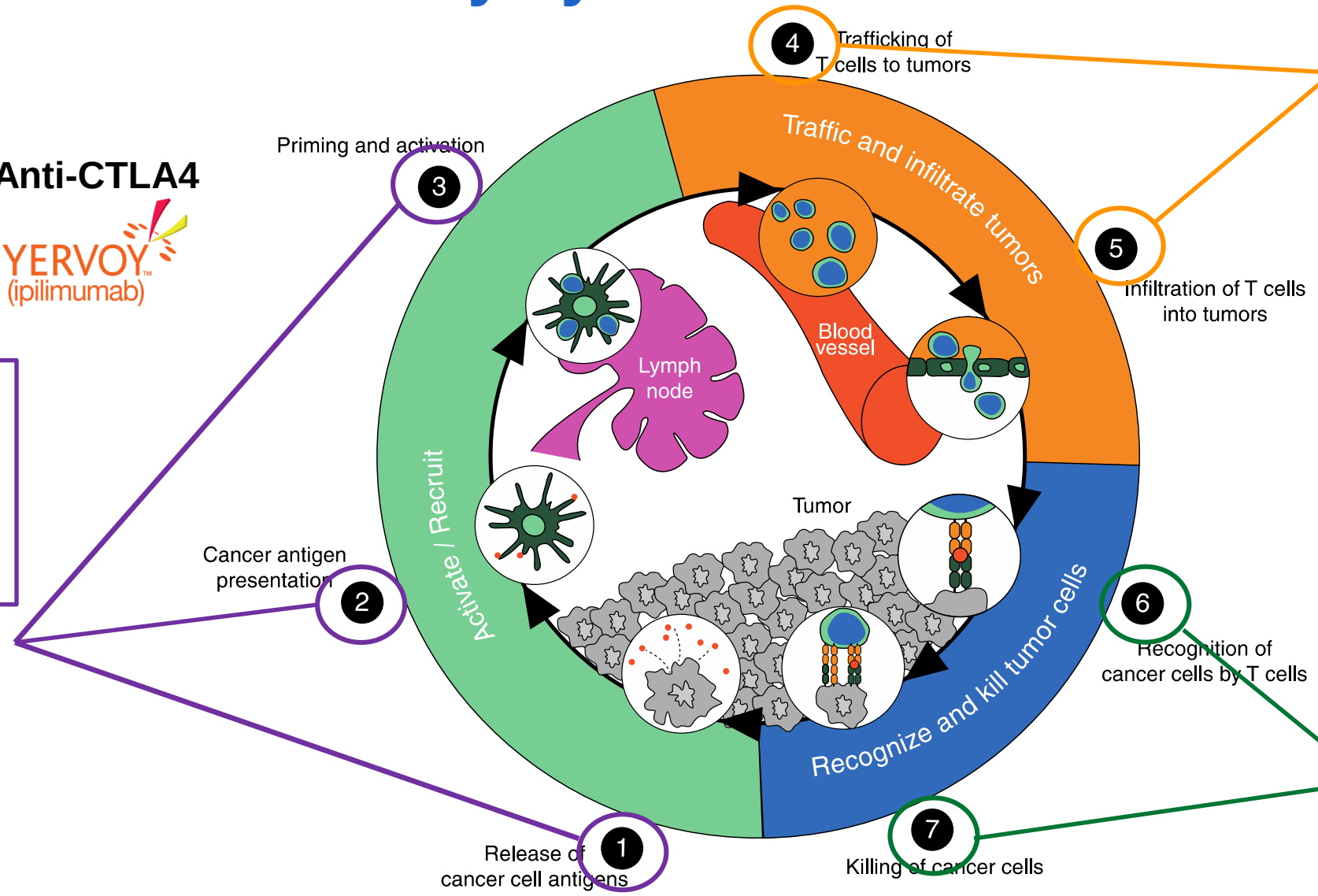
Early stages of T-cell priming and activation

Recognition and killing of the cancer cells

Figure 1. The cancer-immunity cycle. Figure modified from Chen and Mellman [1], with permission from Elsevier.

Kim et al. Annal Oncol 2016

The Cancer Immunity cycle



Infiltration of T-cells into tumors

Anti-CTLA4

YERVOY (ipilimumab)

Early stages of T-cell priming and activation

Anti-PD1

OPDIVO (nivolumab)

KEYTRUDA (pembrolizumab)

Recognition and killing of the cancer cells

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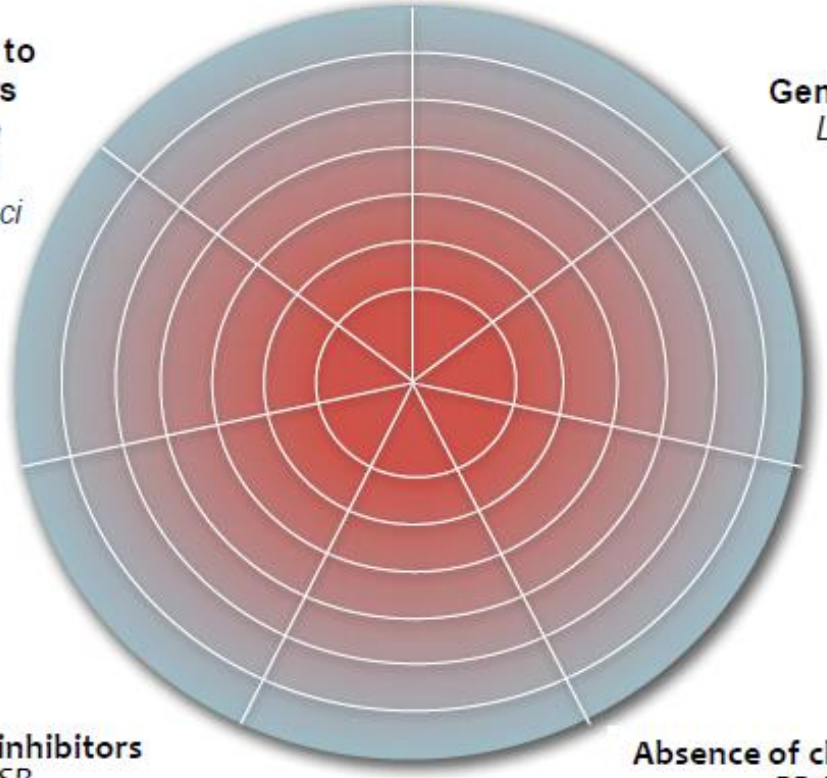
Can we identify responders?

An evolving immunogram : a complexity to acknowledge



Tumor foreignness
Mutational load
Neoantigen load

Tumor sensitivity to immune effectors
MHC expression
IFN-γ sensitivity
Heterozygocity at all MHC loci

General immune status
Lymphocyte count, LAG3, TIGIT, CD27
Ki67 PD1+ CD8

Microbiome
Low bacteroides
High faecalibacterium prausnitzii

Absence of inhibitory tumor metabolism
LDH, glucose utilization
IDO1, tumor acidity

Immune cell infiltration
Intratumoral T cells
Shared T cell clones
B7-H3/CD276 macrophages
CCL5 attracting T cells
CCR5 expressing BATF3 DC
LAG3, TIM3, TIGIT, CTLA4

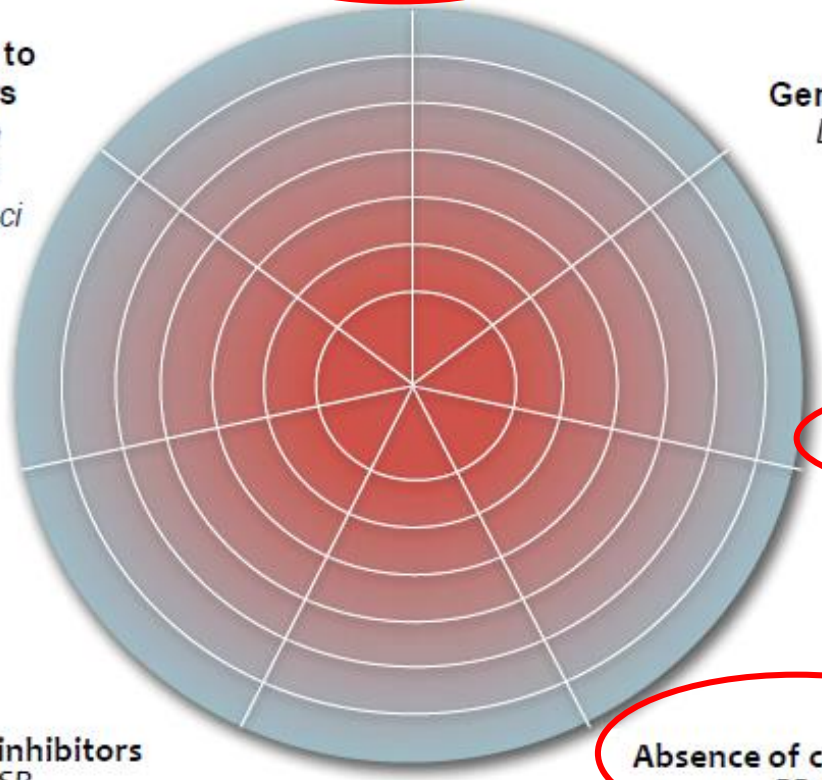
Absence of soluble inhibitors
IL-6 → CRP/ESR
CD73 → adenosine

Absence of checkpoints
PD-L1

MUNICH 2018 ESMO congress

Adapted from Blank Science 2016

An evolving immunogram : a complexity to acknowledge



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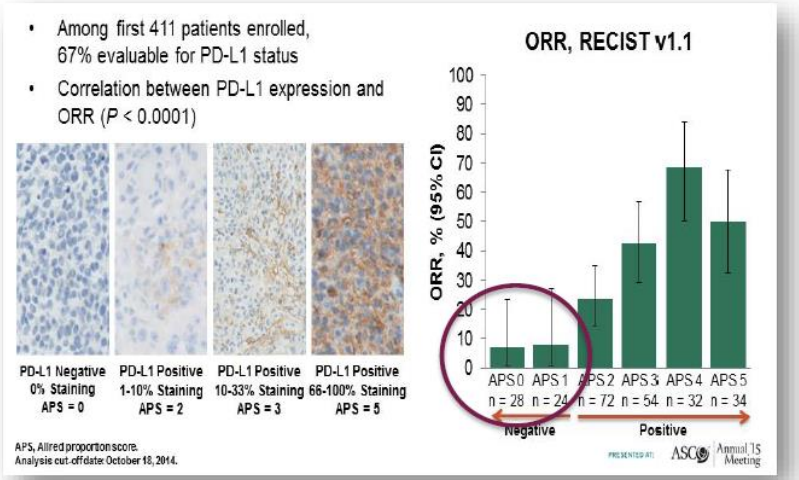
Adapted from Blank Science 2016

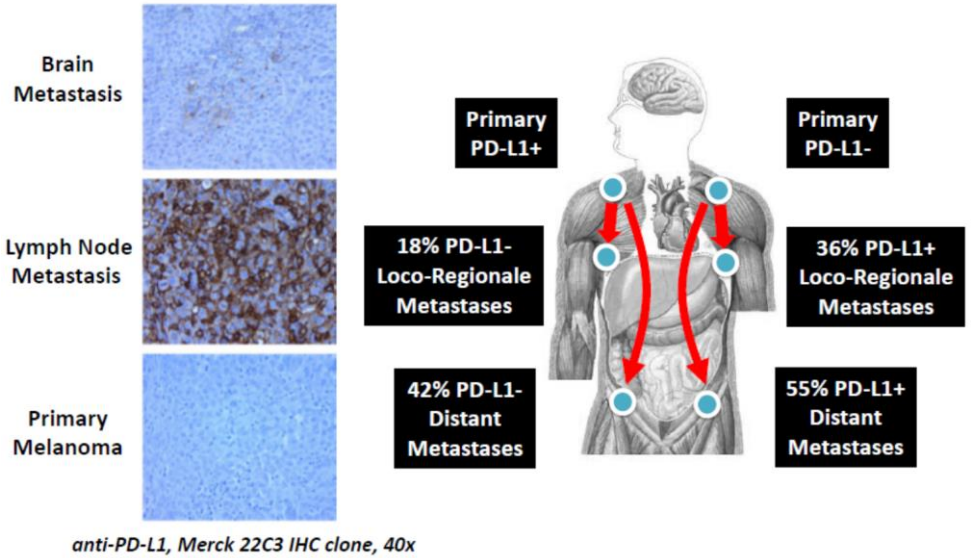
PD-L1 expression

PD-L1 expression and relationship with response to anti-PD-1 in melanoma



Daud et al., J Clin Oncol 2016

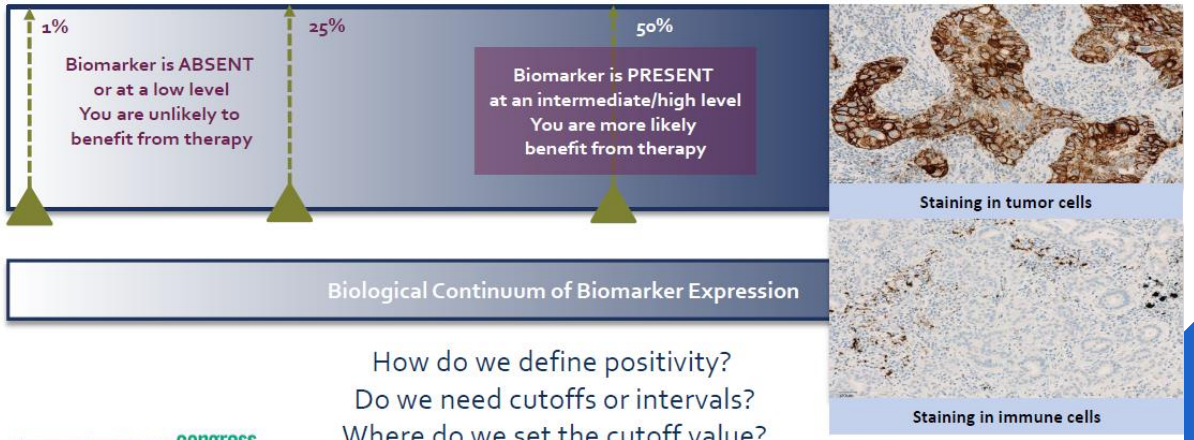
Intrapatient PD-L1 Discordance



anti-PD-L1, Merck 22C3 IHC clone, 40x

Adapted from Madore J, et al. Pigment Cell Melanoma Res 2015

Biomarker "Positivity": Present, Absent, or Graduated?

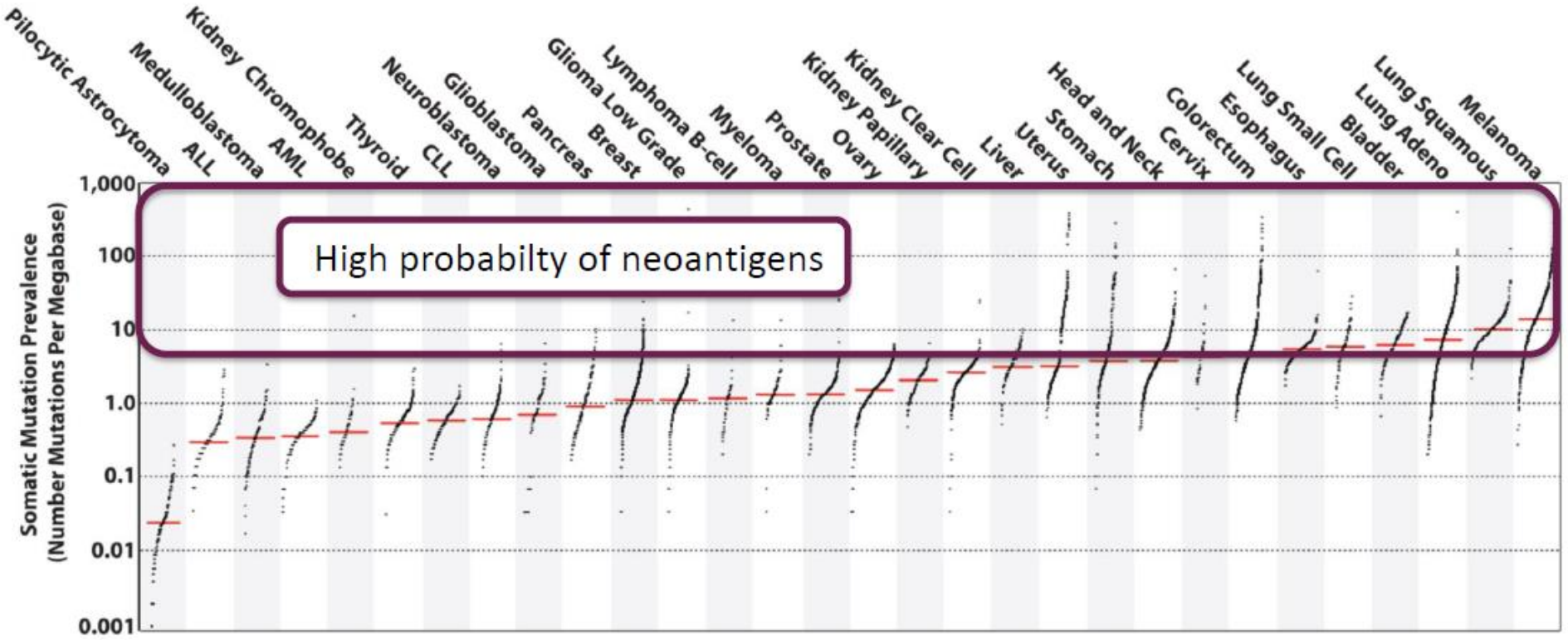


How do we define positivity?
Do we need cutoffs or intervals?
Where do we set the cutoff value?

Courtesy S Peters

Tumor mutational burden

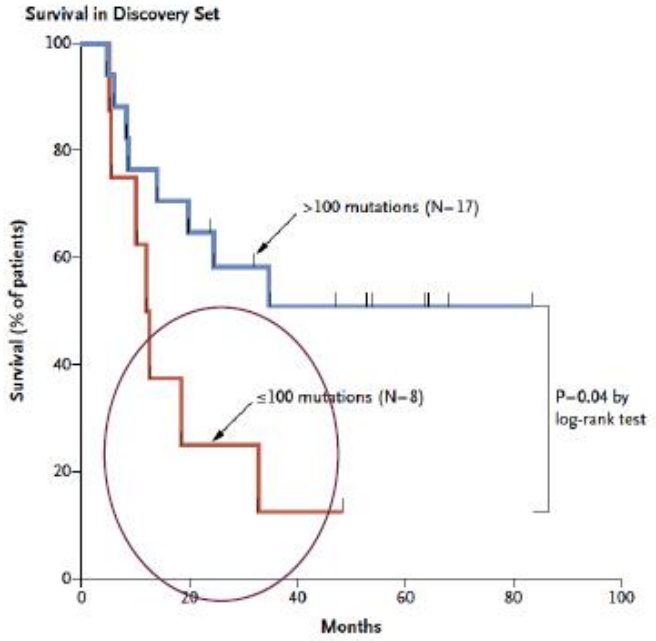
TMB is an independant biomarker, increasing the likelihood a tumour will be recognized as foreign

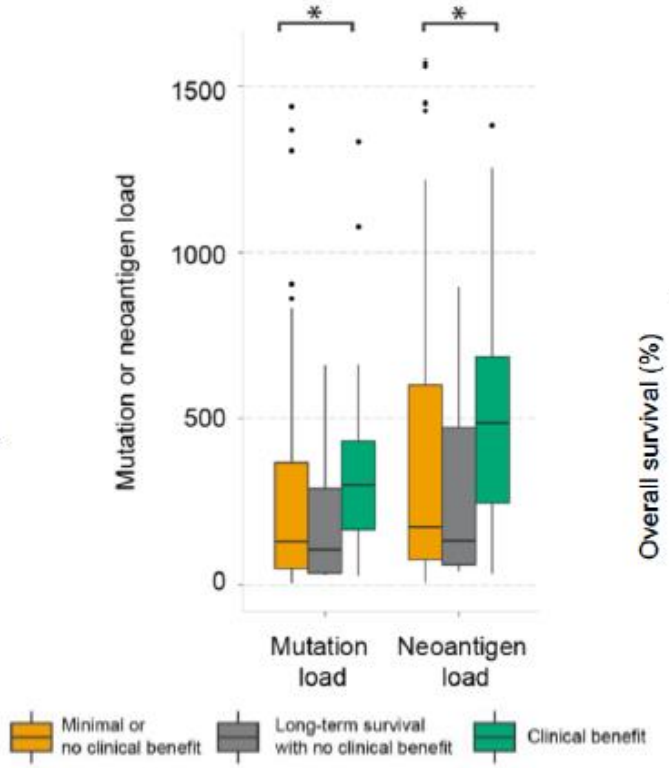


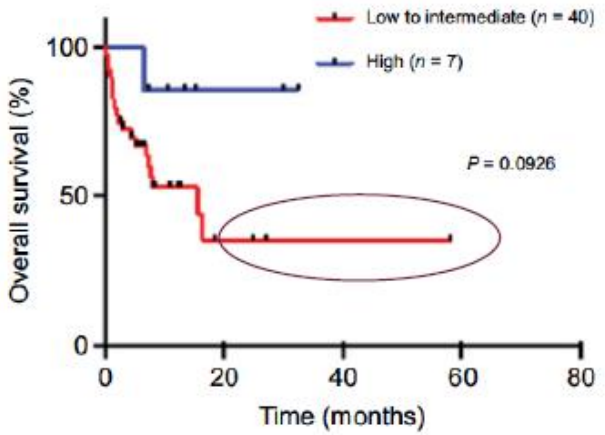
Lawrence, Nature 2015; Alexandrov, Nature 2013; Schumacher & Schreiber Science 2016

Tumor mutational burden

Low mutational load correlates with little clinical benefit from CTLA-4 or PD-1 blockade in melanoma







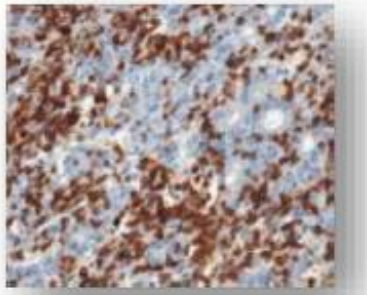
MUNICH 2018 ESMO congress

Snyder et al., N Engl J Med 2014; Van Allen et al., Science 2015; Goodman et al., Mol Canc Ther 2017

Immune cell infiltration

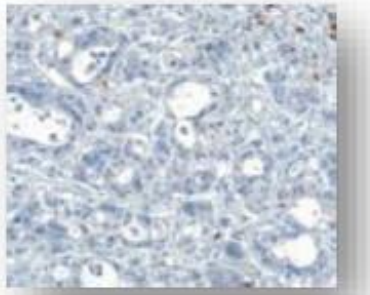
‘Inflamed’ (hot) vs ‘non-inflamed’ (cold) tumors and response to immune checkpoint inhibition

Inflamed

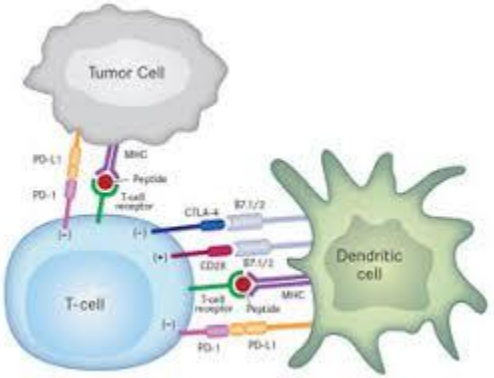


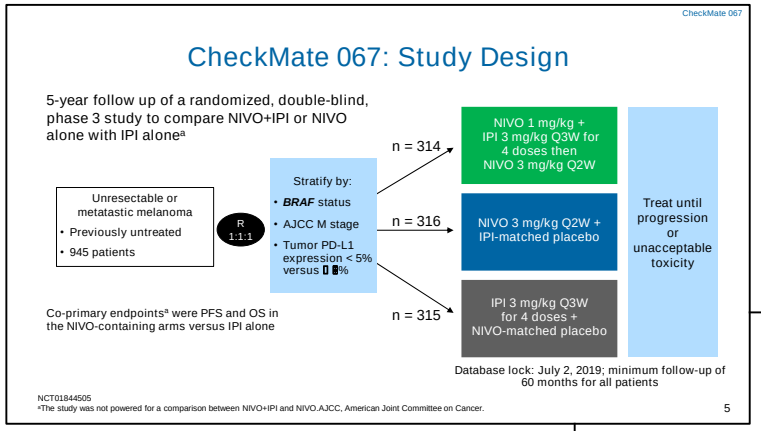
TILs
CD8+ T cells
IFN-γ gene signature
PDL1 expression
Pre-existing immunity

Non-inflamed



- How do we increase response rates?





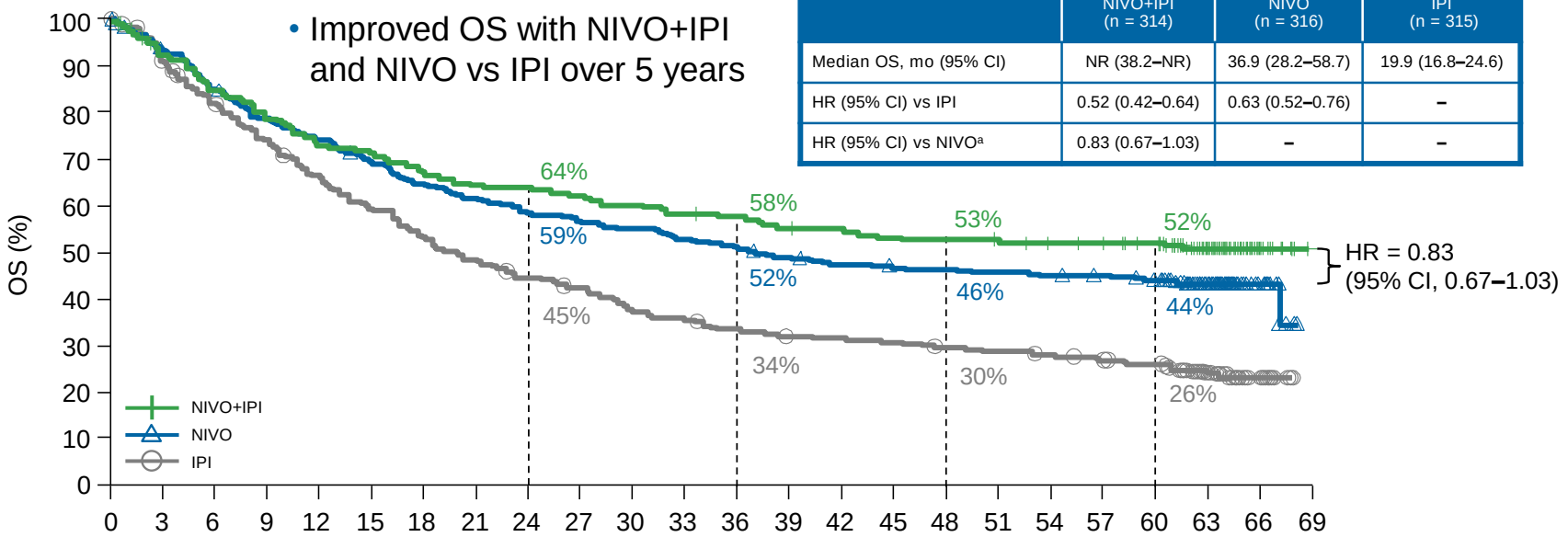
YERVOY (ipilimumab) + OPDIVO (nivolumab)

In gemetastaseerd melanoom

Overall Survival

- Improved OS with NIVO+IPI and NIVO vs IPI over 5 years

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.42–0.64)	0.63 (0.52–0.76)	–
HR (95% CI) vs NIVO[a]	0.83 (0.67–1.03)	–	–



No. at risk

NIVO+IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

[a]Descriptive analysis. 1. Larkin J, et al. Oral presentation at the AACR Annual Meeting; April 1–5, 2017; Washington DC, USA. Abstract CT075; 2. Wolchok JD, et al. *N Engl J Med* 2017;377:1345–1356; 2. Hodi FS, et al. *Lancet Oncol* 2018;19:1480–1492.

Safety Summary

- No new safety signals were observed with the additional follow-up
- No additional deaths due to study drug toxicity were reported since the prior analysis[a]

Patients reporting event	NIVO+IPI (n = 313)		NIVO (n = 313)		IPI (n = 311)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related AE, %	96	59	87	23	86	28
Treatment-related AE leading to discontinuation, %	42	31	13	8	15	14
Treatment-related death, n (%)	2 (1)		1 (< 1)		1 (< 1)	

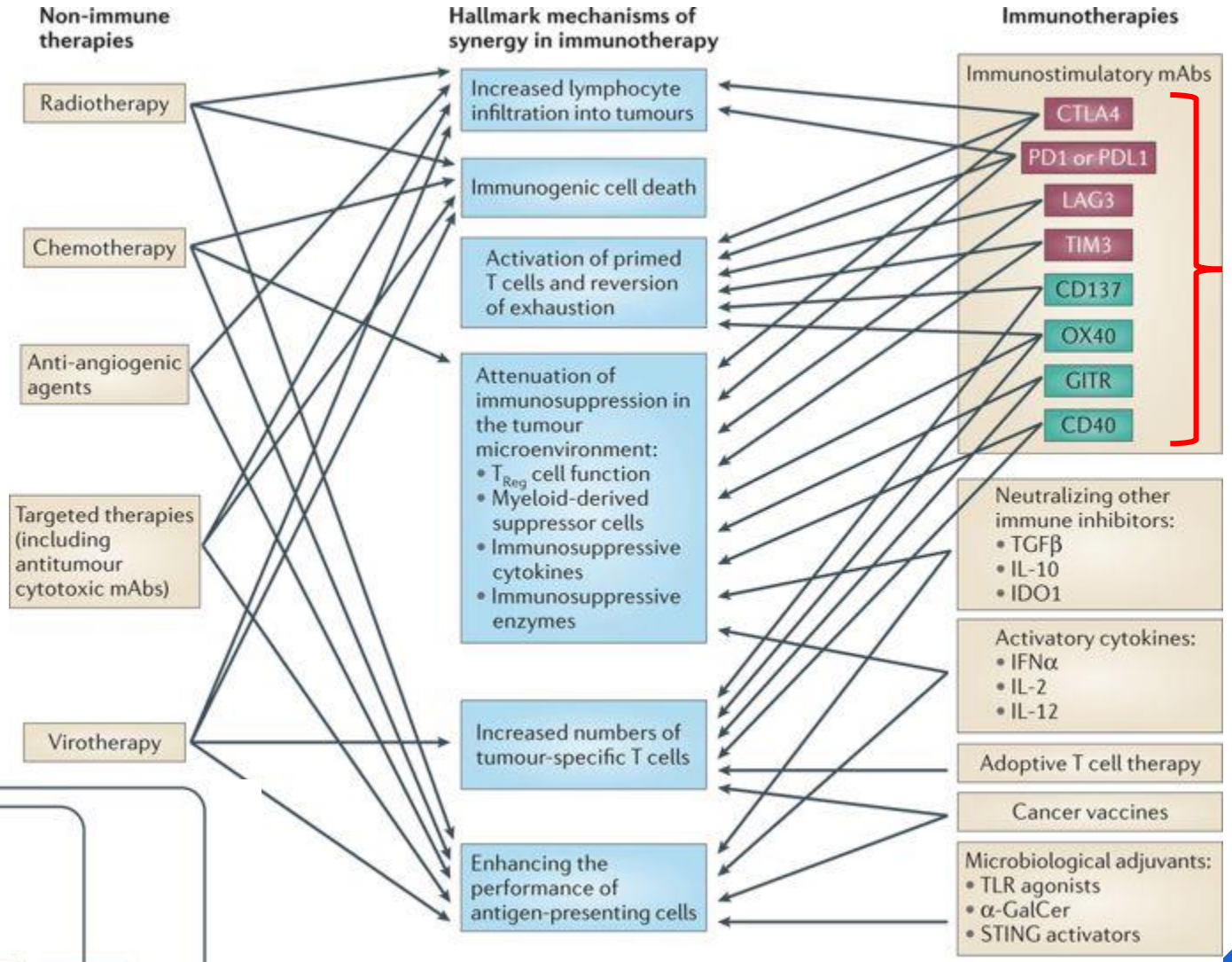
- Survival outcomes were not impacted by discontinuing NIVO+IPI early due to a TRAE[b]
  - Patients who discontinued NIVO+IPI during induction due to a TRAE had 5-year PFS (35%) and OS rates (51%) similar to patients in the overall population (36% and 52%, respectively)

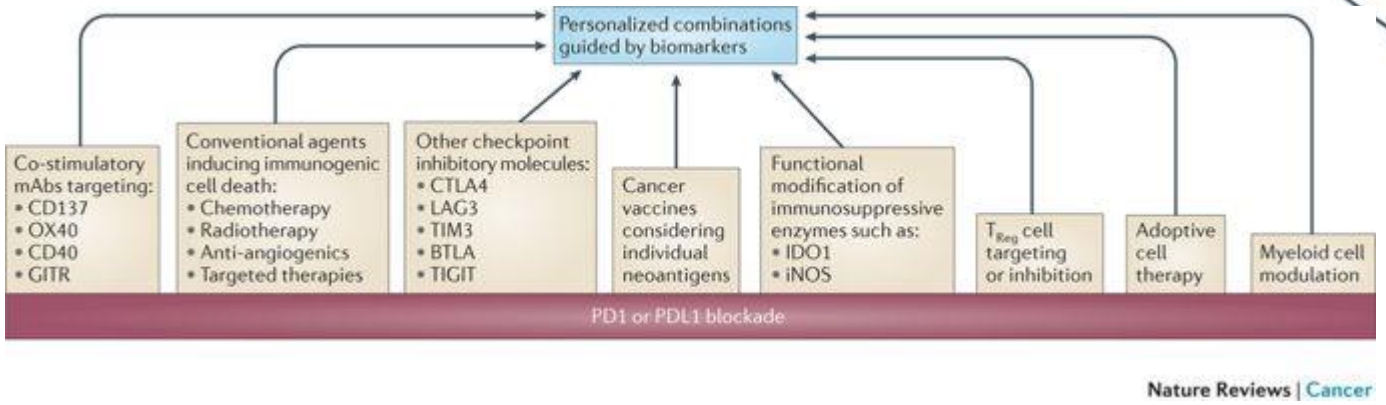
[a]Previously reported treatment-related deaths were cardiomyopathy and liver necrosis for NIVO+IPI (n = 1 each; both occurred > 100 days after last treatment), neutropenia for NIVO (n = 1), and colonic perforation for IPI (n = 1); [b]Post-hoc analysis. TRAE, treatment-related adverse event.

Combination strategies

- Using anti-PD1/PDL1 as backbone

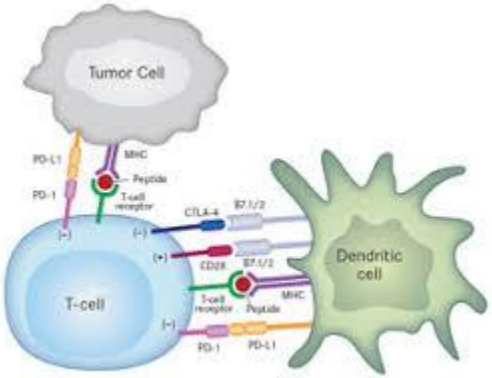
- Today, a solid scientific rational & strong activity signals are required for new combinations to be tested





Melero, Haanen Nat Rev Canc 2015;

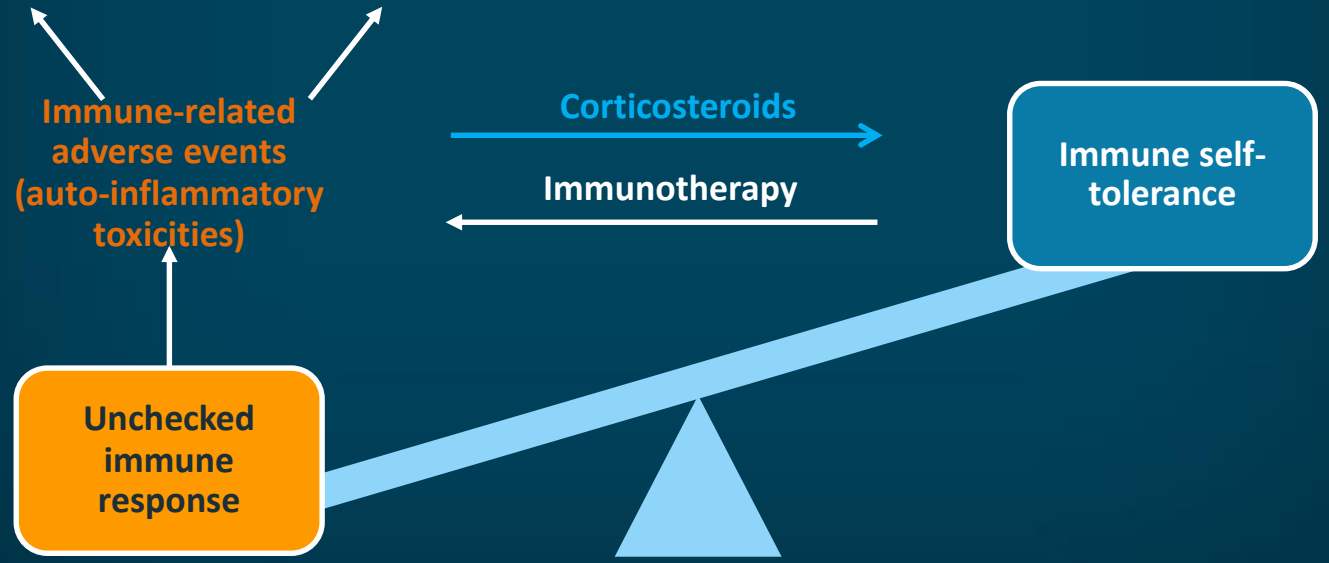
- What are the risks?



Toxicities with Checkpoint Protein Inhibitors

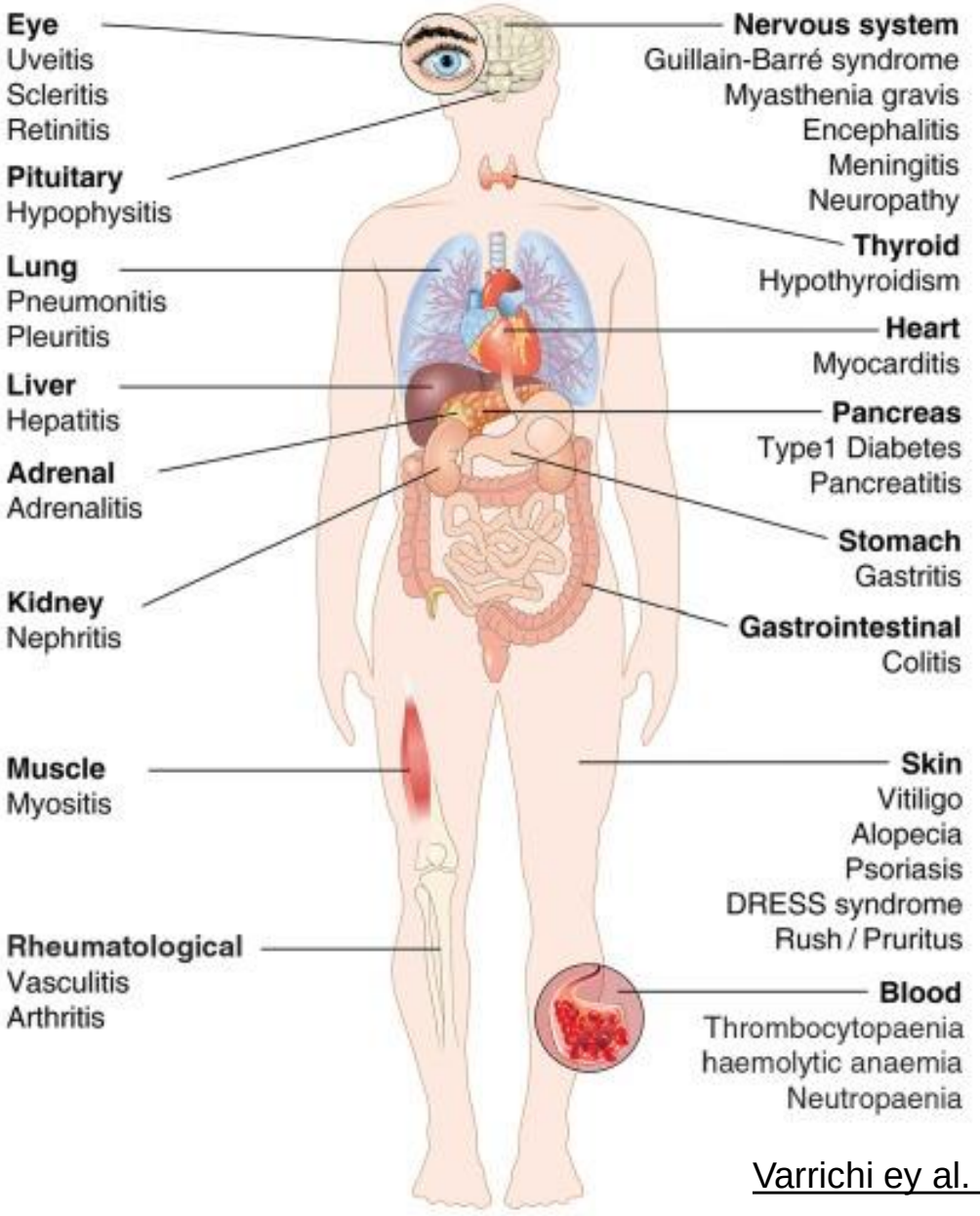
Organ-specific events
- Skin
- Gastrointestinal
- Liver
- Pulmonary
- Endocrine system
- Cardiovascular

General events
- Fatigue
- Pyrexia, chills
- Infusion reactions



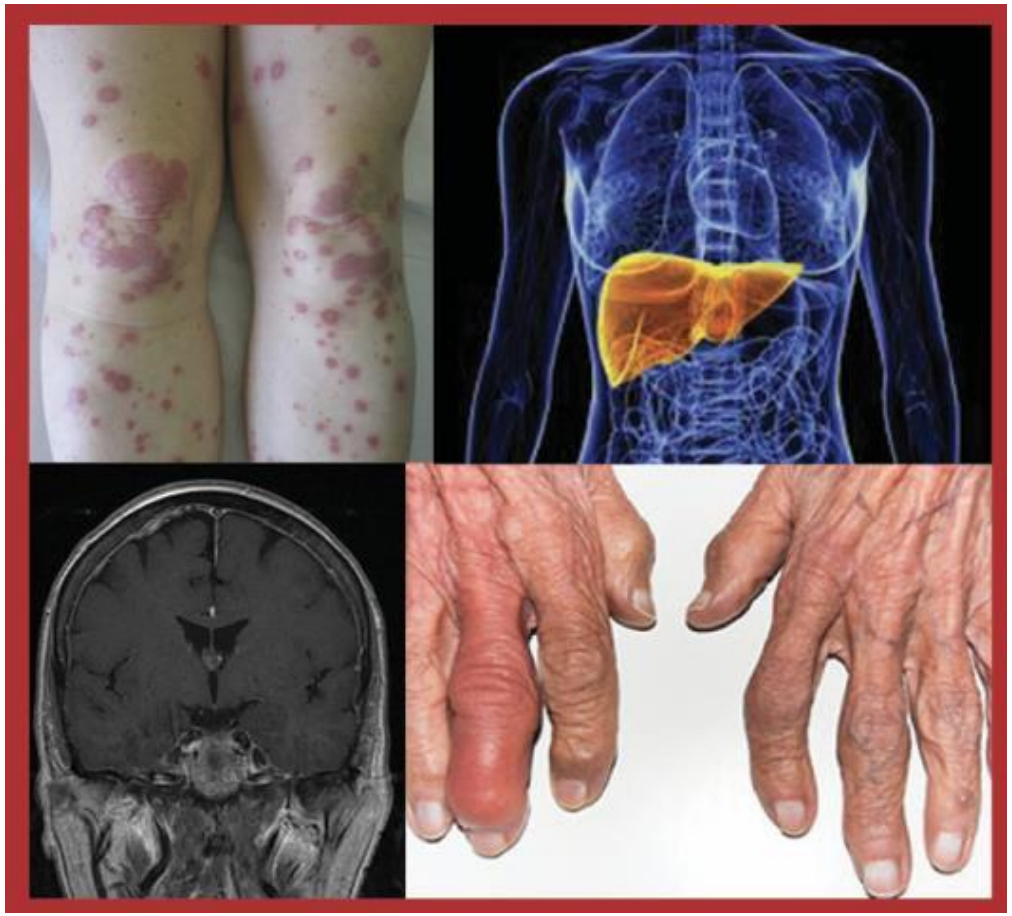
J. Weber, ESMO Immuno-Oncology 2017

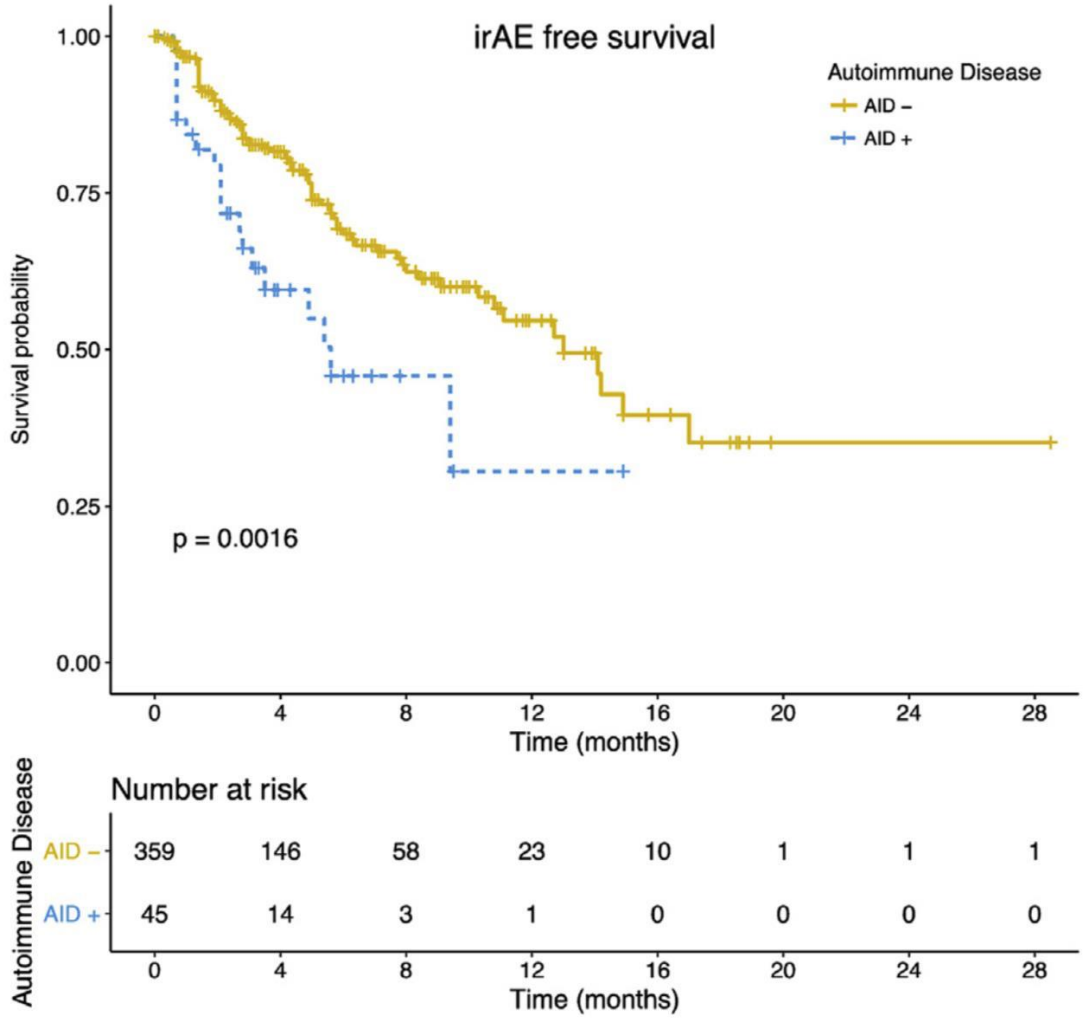
Immune related adverse events (irAE's)



Varrichi ey al. ESMO Open 2017

Patients with preexisting autoimmune disease





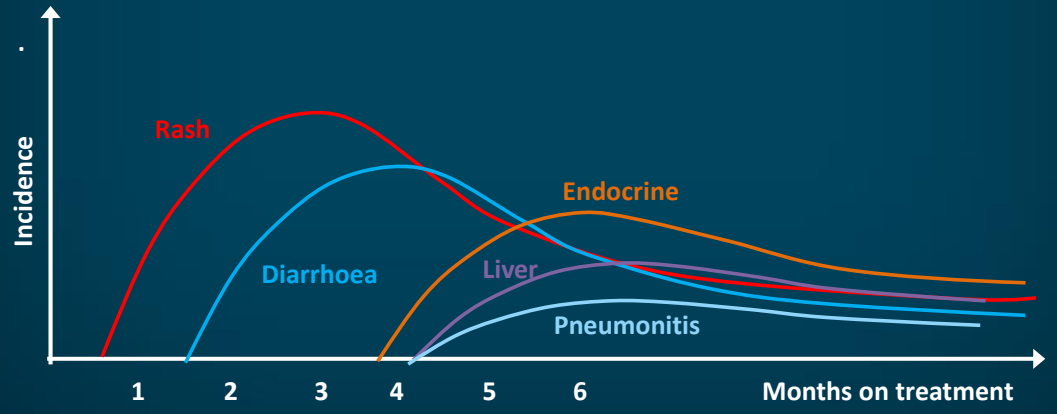
Danlos et al. Eur. J. Cancer 2018;91:21–29

Courtesy of S. Aspeslagh

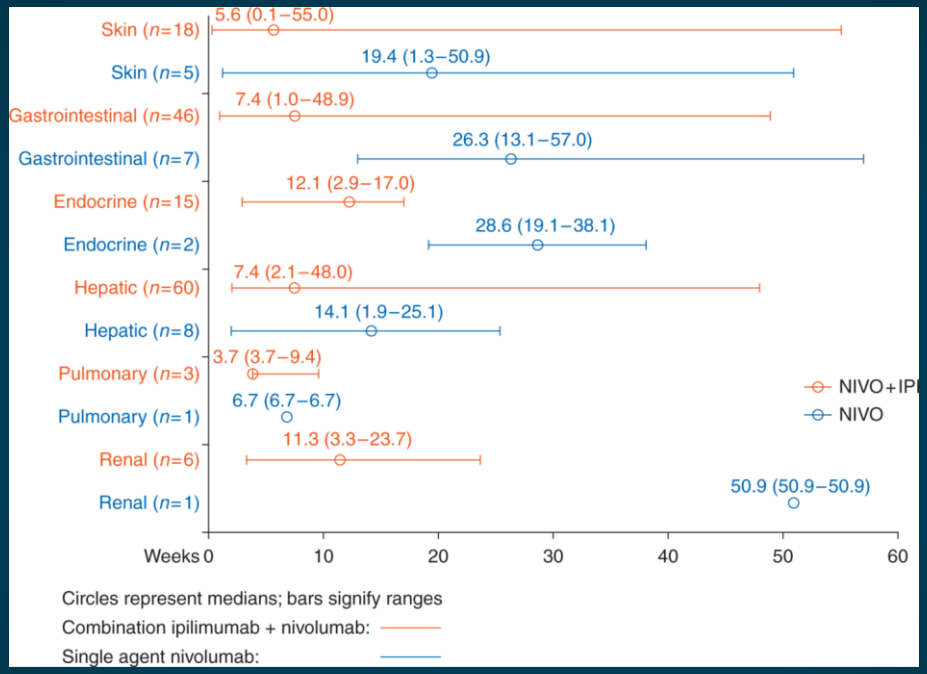
irAE's: Kinetics

Toxicities with Checkpoint Protein Inhibitors (continued)

- Most irAEs are reversible with steroids or other immune suppressants.
- Early recognition and treatment will reduce risk of complications
- Consultation with an available team of specialists is critical
- Little evidence that type of irAE varies across histologies except pneumonitis in lung CA, vitiligo in melanoma
- .



Onset of immune related toxicities with IPI + NIVO versus NIVO alone



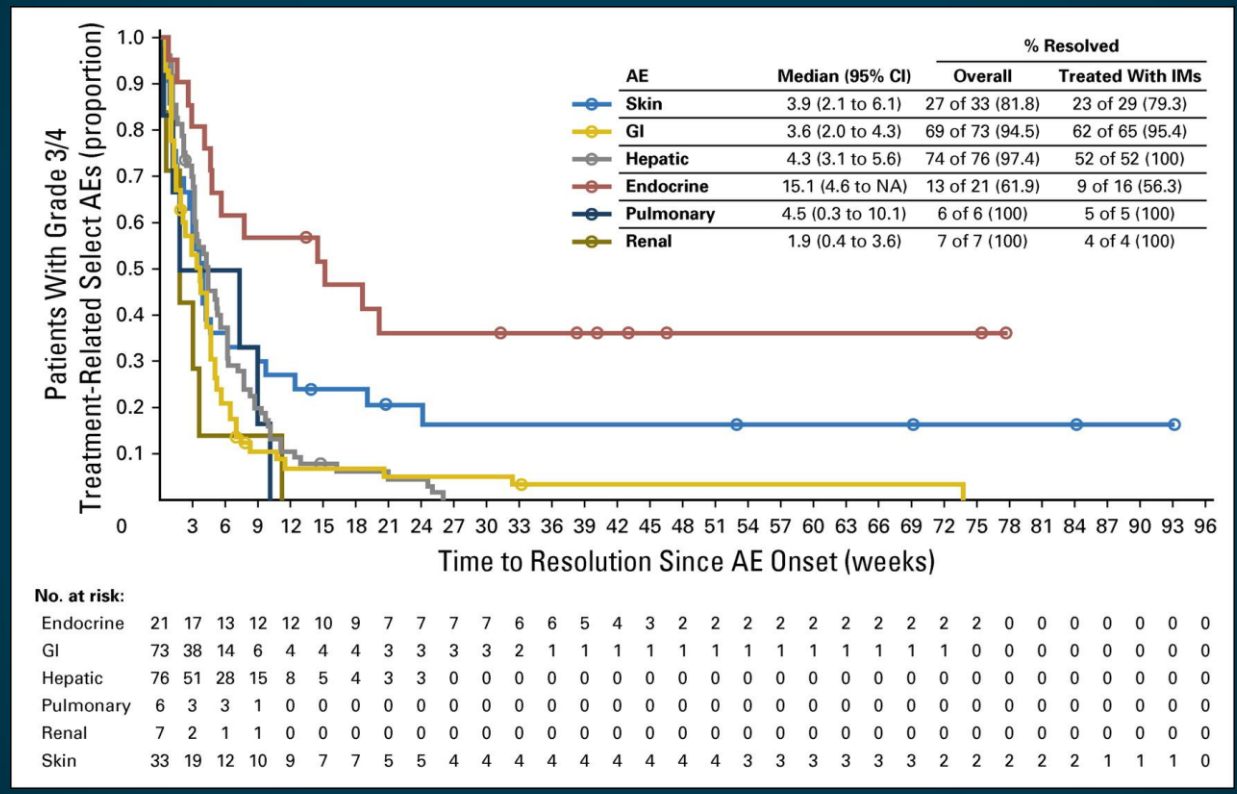
Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

Ann Oncol. 2017;28(suppl_4):iv119-iv142. doi:10.1093/annonc/mdx225

J. Weber, ESMO Immuno-Oncology 2017

irAE's: What is the evolution over time?

Most irAEs resolve except for endocrine and skin



AE	Median (95% CI)	% Resolved Overall	% Resolved Treated With IMs
Skin	3.9 (2.1 to 6.1)	27 of 33 (81.8)	23 of 29 (79.3)
GI	3.6 (2.0 to 4.3)	69 of 73 (94.5)	62 of 65 (95.4)
Hepatic	4.3 (3.1 to 5.6)	74 of 76 (97.4)	52 of 52 (100)
Endocrine	15.1 (4.6 to NA)	13 of 21 (61.9)	9 of 16 (56.3)
Pulmonary	4.5 (0.3 to 10.1)	6 of 6 (100)	5 of 5 (100)
Renal	1.9 (0.4 to 3.6)	7 of 7 (100)	4 of 4 (100)

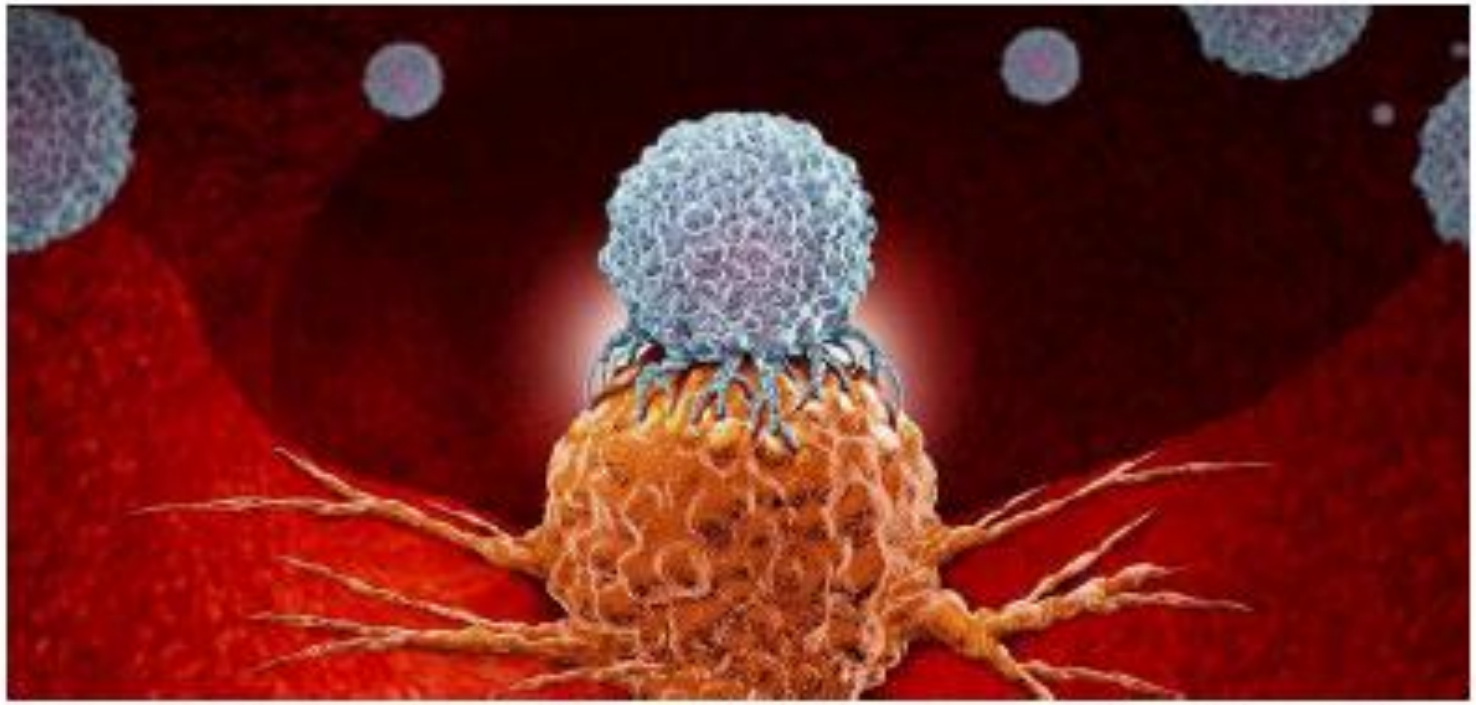
No. at risk:

Endocrine	21	17	13	12	12	10	9	7	7	7	7	6	6	5	4	3	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0
GI	73	38	14	6	4	4	4	3	3	3	3	2	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0
Hepatic	76	51	28	15	8	5	4	3	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pulmonary	6	3	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Renal	7	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Skin	33	19	12	10	9	7	7	5	5	4	4	4	4	4	4	4	4	4	3	3	3	3	3	3	2	2	2	2	2	1	1	1	0

Published in: Mario Sznol; Pier Francesco Ferrucci; David Hogg; Michael B. Atkins; Pascal Wolter; Massimo Guidoboni; Celeste Lebbé; John M. Kirkwood; Jacob Schachter; Gregory A. Daniels; Jessica Hassel; Jonathan Cebon; Winald Gerritsen; Victoria Atkinson; Luc Thomas; John McCaffrey; Derek Power; Dana Walker; Rafia Bhore; Joel Jiang; F. Stephen Hodi; Jedd D. Wolchok; *JCO* Ahead of Print DOI: 10.1200/JCO.2016.72.1167

J. Weber, ESMO Immuno-Oncology 2017

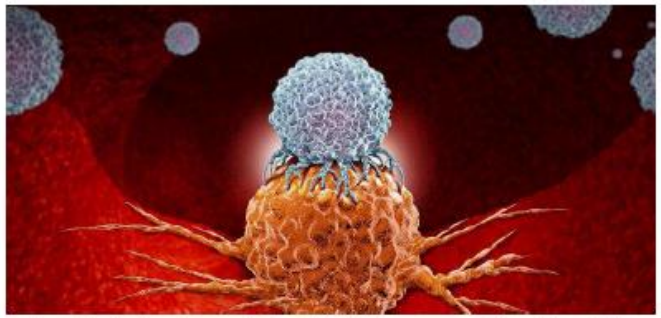
What is the risk of a fatal irAE?



Fatal Toxicity Associated With Immune Checkpoint Inhibitors

Posted on September 25, 2018 (https://www.primeoncology.org/primelines/fatalities-due-to-checkpoint-inhibitors/) Posted in Medical Journal Updates (https://www.primeoncology.org/primelines-categories/medical-journal-updates/)

What is the risk of a fatal irAE?



Fatal Toxicity Associated With Immune Checkpoint Inhibitors

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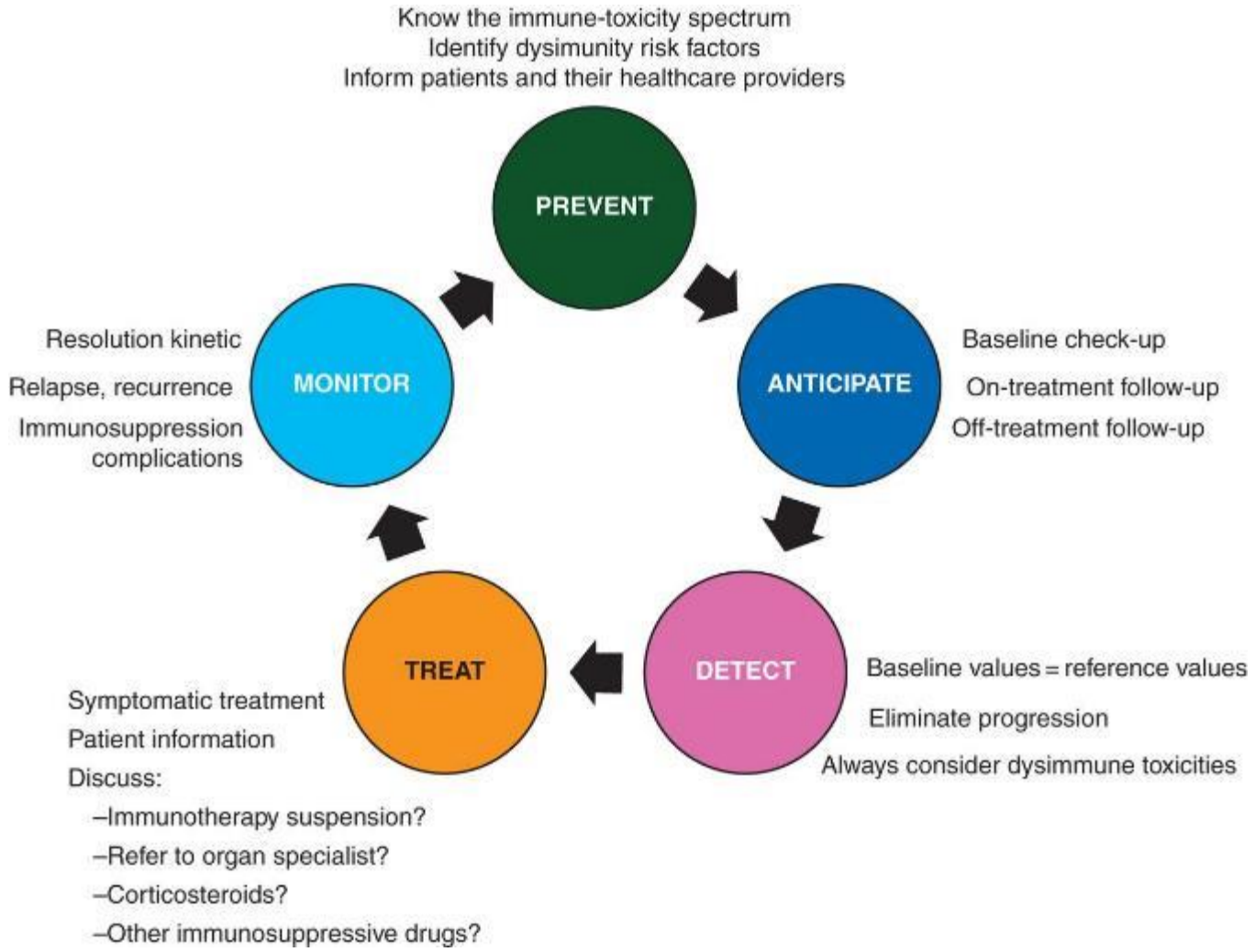
Risico op een fatale bijwerking	
anti-PD1	0,36 %
anti-PDL1	0,38 %
anti-CTLA4	1,08 %
Anti-CTLA4 + anti-PD1	1,23%

Type fatale bijwerking		
Anti-CTLA4	**Anti-PD1/anti-PDL1**	**Anti-PD1 + anti-CTLA4**
Colitis (70%)	Pneumonitis (35%)	Colitis (37%)
	Hepatitis (22%)	Myocarditis (25%)
	Neurotoxicity (22%)	Hepatitis (22%

JAMA Oncol. doi:10.1001/jamaoncol.2018.3923
Published online September 13, 2018.

The five pillars of immunotherapy toxicity management:



S. Champiat et al. Ann Oncol 2016;annonc.mdv623

Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0

Published: May 28, 2009 (v4.03: June 14, 2010)

U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute

How does the CTCAE grade adverse events[1]?

Grade 1	Asymptomatic or mild symptoms; other than clinical or diagnostic observation, intervention is not indicated
Grade 2	Moderate symptoms requiring minimal, local, or noninvasive intervention; limiting the patient's ability to perform age-appropriate instrumental activities of daily living (ADLs)[a]
Grade 3	Symptoms are severe or medically significant, but not immediately life-threatening; symptoms are disabling and require hospitalization or prolong the hospital stay. Self-care ADLs are limited[b]
Grade 4	Life-threatening symptoms that require immediate intervention
Grade 5	Death related to an adverse event

[a]Instrumental ADLs refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

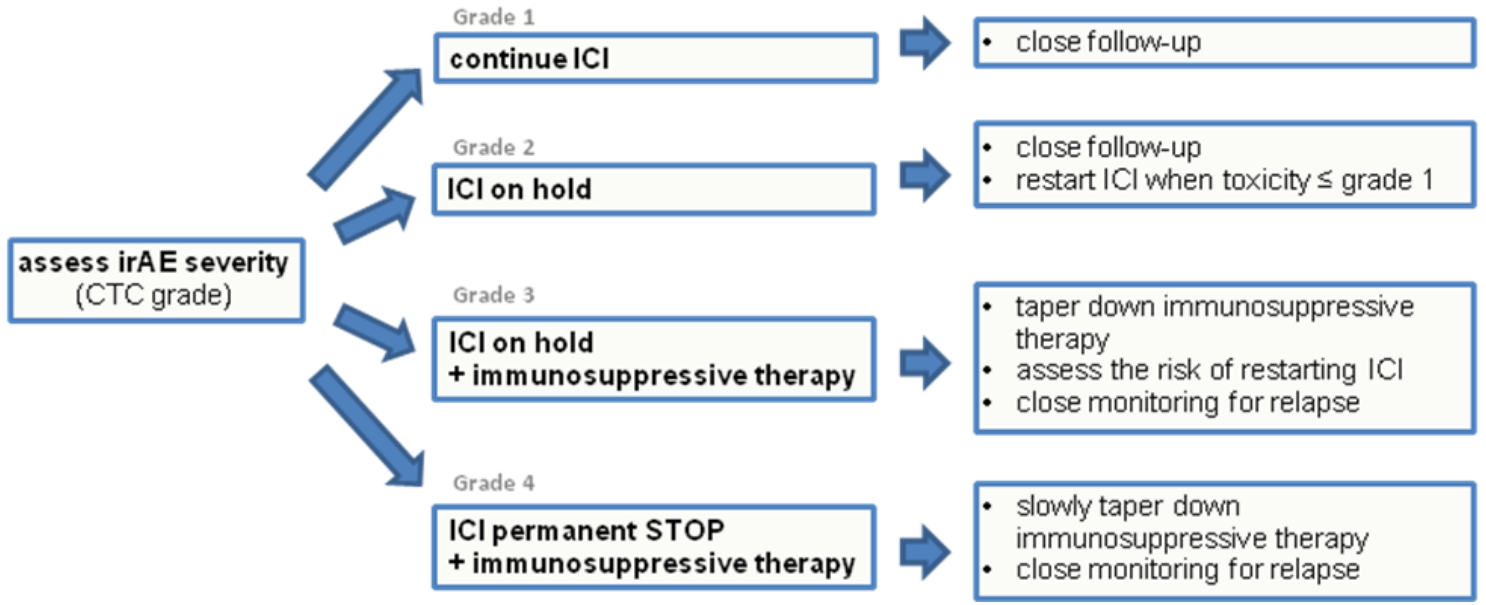
[b]Self-care ADLs refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

CTCAE = Common Terminology Criteria for Adverse Events

1. National Cancer Institute. *Common Terminology Criteria for Adverse Events* (*CTCAE*); v4.0. Bethesda, MD: National Cancer Institute 2009. NIH publication 09-5410. Updated version CTCAE v4.03 published 14 June 2010.

General principles of irAE management

Figure 2: Treatment principles of irAE management



Introduction BSMO ImmunoManager

https://www.bsmo.be/immunomanager

Case 1

Melanoom – adjuvant

40 jarige patiënte

- **Mei 2001: diagnose MELANOOM pT2aN1aM0 stadium IIIA (rechter onderbeen)**

- **Okt 2017: start adjuvante therapie volgens studieprotocol na resectie van een macrometastase thv de rechter knie**

Case 1

Melanoom – adjuvant

1

LABO 27/11/2017:

TSH	< 0,020 mU/L (0,27 – 4,2)
FT3	4,9 pg/ml (2,5-4,4)
FT4	2,0 pg/ml (0,9 – 1,7)
TPO AL	120 U/ml (0-34)
Verder geen bijzonderheden	

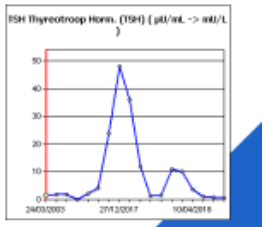
na 4 weken therapie

LABO 14/12/2017:

TSH	4,2 mU/L (0,27 – 4,2)
FT3	1,6 pg/ml (2,5-4,4)
FT4	0,4 pg/ml (0,9 – 1,7)
TPO AL	100 U/ml (0-34)
Verder geen bijzonderheden	

Evolutie TSH:

24/10/2017	1,7
31/10/2017	1,7
29/11/2017	< 0,020
13/12/2017	2,1
20/12/2017	24
27/12/2017	48
10/01/2018	36
24/01/2018	12



DIAGNOSE :

- **Thyreoiditis**, initieel thyreotoxische fase (positieve TPO AL) → **hypothyroidie**

2

- 19/03/2018: **22ste week van therapie**
- Anamnese:
  - **gevoel van vochtophoping, moe+++,** hoofdpijn sinds enkele dagen, waarvoor enkele keren paracetamol, geen visusstoornissen
- LABO?

TSH	11,0 mU/L (0,27 – 4,2)
FT3	3,4 pg/ml (2,5-4,4)
FT4	1,0 pg/ml (0,9 – 1,7)
Cortisol	< 0,1µg/dL (6,02 – 18,4)
DHEA	< 0,1µg/L (0,63 - 4,7)
ACTH	< 3 pg/ml (7,2 - 63,3)

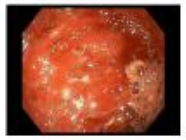
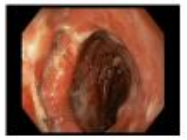
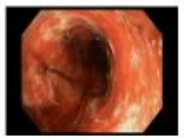
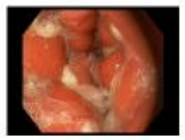
- DIAGNOSE : **Hypofysitis**

3

- **Spoed 16/04/2018** (26 weken na start studie):

Pangastritis

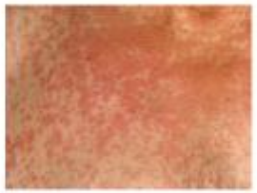
  - **Aanslepend braken, epigastrische pijn, enkele malen beperkte hematemesis** en algemene malaise
  - **Gastroscopie**: **refluxoesophagitis graad B** met zeer uitgesproken **ulceratieve pangastritis** en bulbitis. Pantomed 2x 40w gestart voor 4 weken.

- **APD:** *Biopten bulbitis:* forse ulceratieve bulbitis.
  Biopten forse gastritis: granulatieweefsel bedekt met fibrinopurulent materiaal, passend bij een ulceratie.

4

- **Rash ?**



→ **irAE vs medicamenteuze rash?**

- **12/06/2018 huidbiopsie:**
  Beeld van oppervlakkige perivasculaire dermatitis met interface veranderingen, in de 1e plaats passend bij een toxisch medicamenteuze eruptie.
- **BELEID:**
  - Medrol® opdrijven
  - Fenistil® IN

RASH
(medicamenteus DD irAE)

Case 1

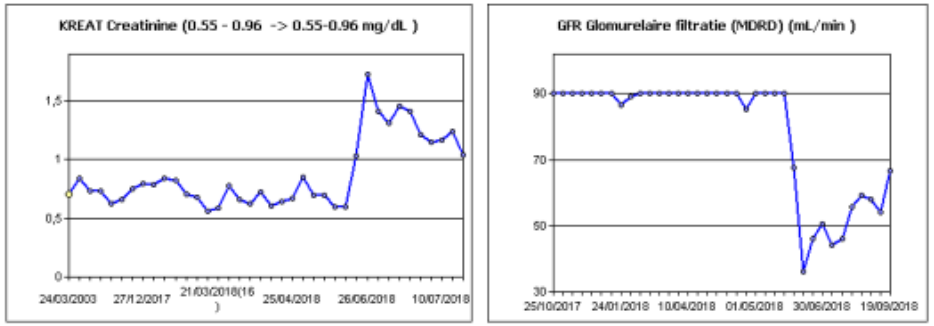
Melanoom – adjuvant

Case 1

5

Bijkomend probleem…

LABO 25/6/2018:

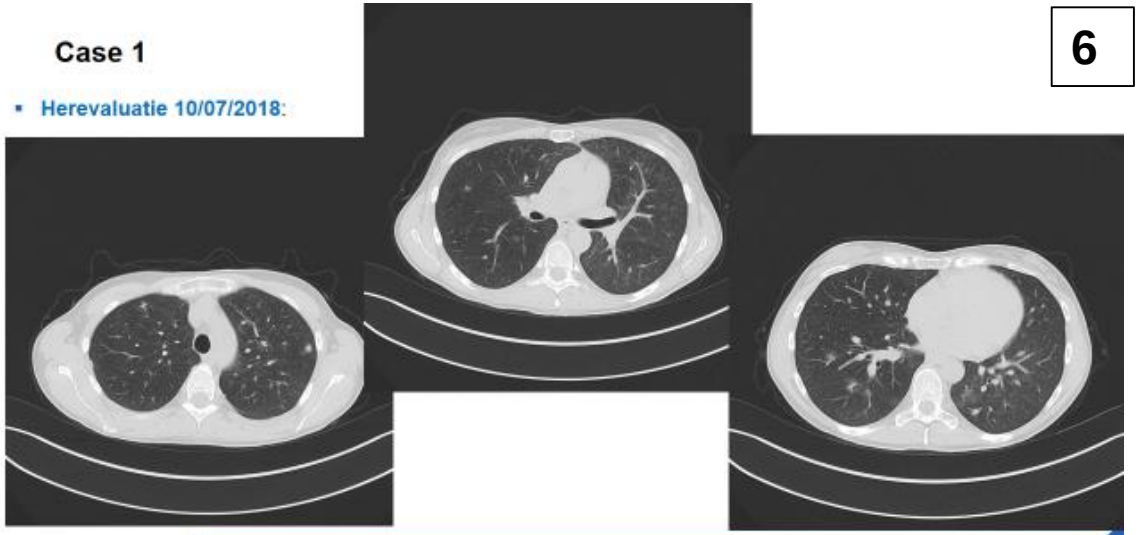


Acute nierinsufficiëntie

Case 1

6

- Herevaluatie 10/07/2018:



BELEID?

BAL:
zwak tot matige fungale lading van PJP, galactomanan negatief, zuur-vaste kleuring negatief, geen bacteriële groei, mycobacteriële kweek volgt

Pneumonitis DD opportunistische infectie

Case 2

'We expect more toxicity with a combination of drugs, but…'

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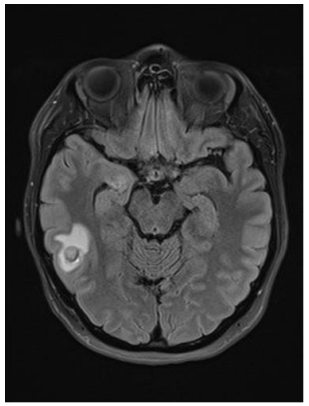
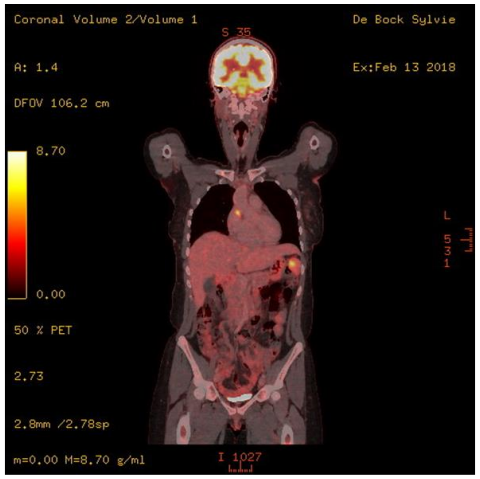
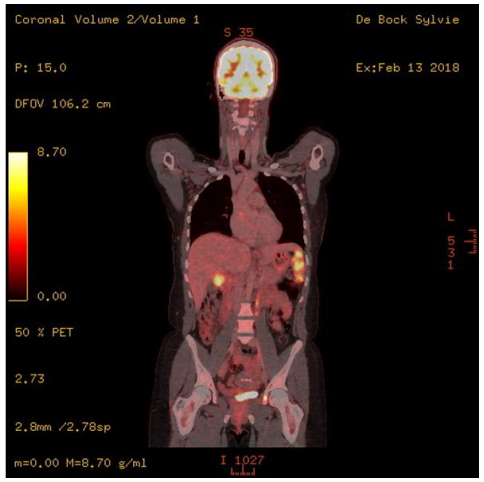
Case 2







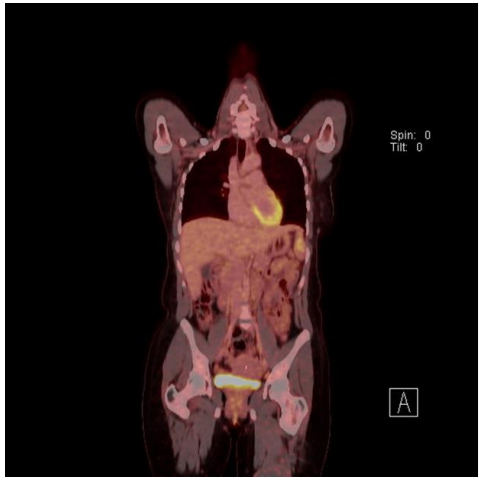
Melanoom – gemetastaseerd

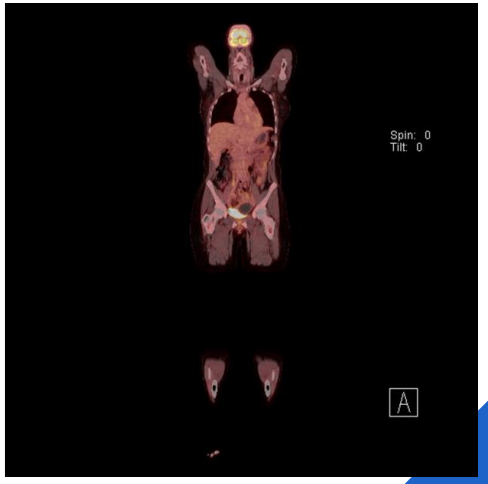
Which treatment to start ?

Decision made by the MOC:

Ant-CTLA4 + Anti-PD1

	NIVO + IPI (n = 313)		NIVO (n = 313)		IPI (n = 311)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Patients reporting event, % (n)						
Treatment-related AEs	96 (300)	59 (184)	86 (270)	21 (67)	86 (268)	28 (86)
Treatment-related AE leading to discontinuation	39 (123)	30 (95)	12 (37)	8 (24)	16 (49)	14 (43)
Treatment-related death, % (n)	0.6 (2)[a]		0.3 (1)[b]		0.3 (1)[b]	





Adapted from Wolchok JD, et al. *N Engl J Med* 2017;377:1345-1356.

Case 3

‘Progression of an irAE after treatment interuption’

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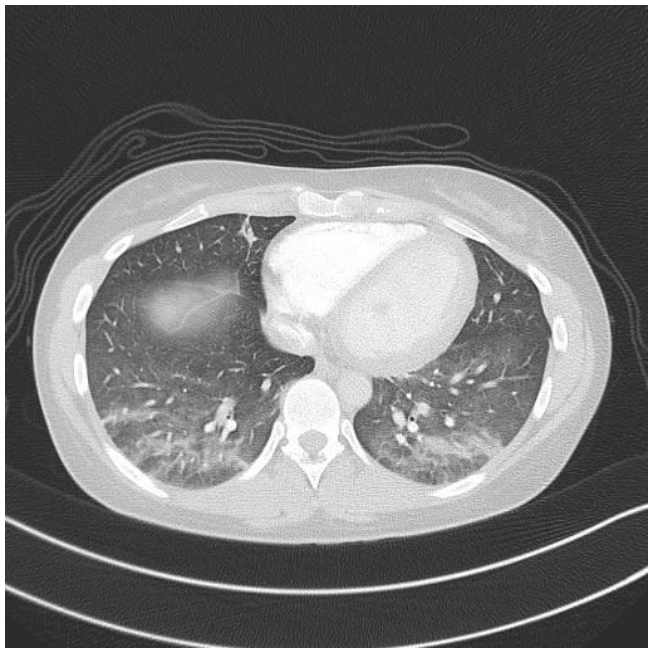
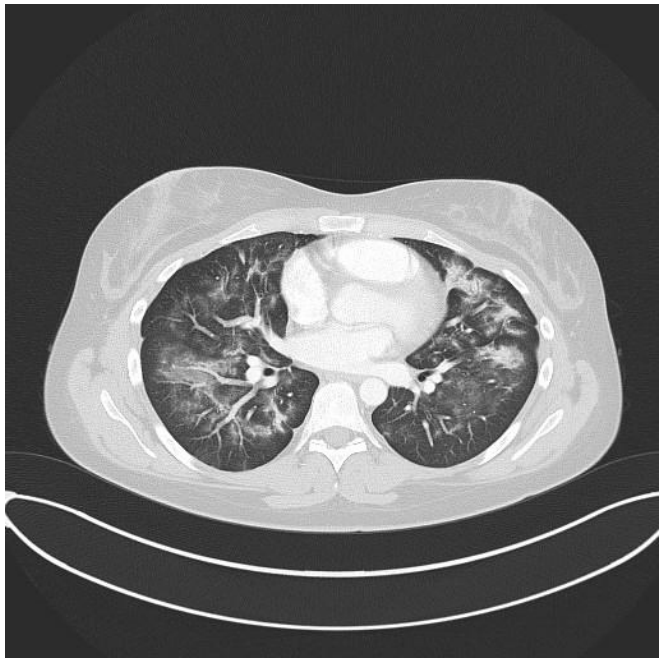
Case 3

Patiënte met een gemetastaseerd melanoom,
start NIVO+IPI 01/2017



Mei 2017. R/ therapiepauze



CT juli 2017

Pneumonitis

5. Gradatie/presentatie:

Graad 1: asymptomatisch, toevallige klinisch vondst (beeldvorming)

- Vervolledig diagnostische work-up (longfunctie, bronchoscopie). Hanteer hoge graad van alertheid. Bij verandering op beeldvorming met longfunctionele impact, zelfs in afwezigheid van significante symptomen, behandel als **graad 2**.

Graad 2: symptomatisch doch beperkte impact op dagelijkse activiteiten en zelfredzaamheid; therapeutische interventie vereist

- **Onderbreek immunotherapie**.
- Snelle diagnostische workup, mag eventueel ambulant.
- In afwachting op testresultaten microbiologie, start **orale systemische steroiden, methylprednisolone 32 mg/d + antibiotica (vb moxifloxacine 400 mg/d 10 d)**. Progressieve afbouw van steroiden met maximum 8 mg/week tot regressie naar graad 1.
- Indien resolutie naar graad < 1, poging tot herstarten immunotherapie (onvoldoende evidentie voor dosisverlaging).
- **Bij recidief pneumonitis**: immunotherapie definitief stoppen.

Auteur Karim Vermaelen

Is there a link between antitumoral response and irAEs?

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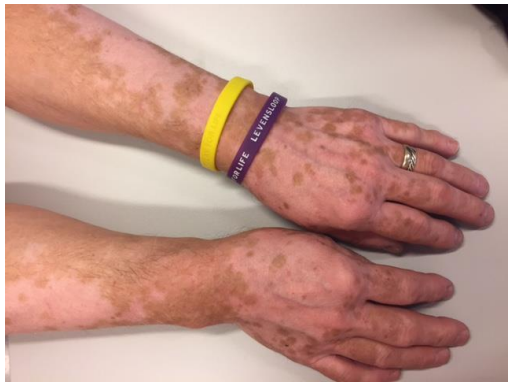
Is there a link between antitumoral response and irAEs?

- 34% of patients (n = 290 in total) treated with an anti-PD1 in MD Anderson developed an irAE (all degrees)
- Patients with ≥ grade 3 irAE's had a better ORR (25% vs 6%, p = 0.039) and a longer time to progression (median; 30w vs 10 weeks; p: 0.0040) compared to patients without irAE
- In anti-PD1 treatment, skin toxicity and vitiligo are associated with anti-tumor response and survival in melanoma patients

Sanlorenze A et al JAMA oncology; Freeman-Keller et al. Clin Cancer Res 2016; Weber J en al JCO 2016. Fujii, T Invest New Drugs 2017

irAE – *prognostic value?*

- **Is there a link between response to immunotherapy and development of an irAE?**

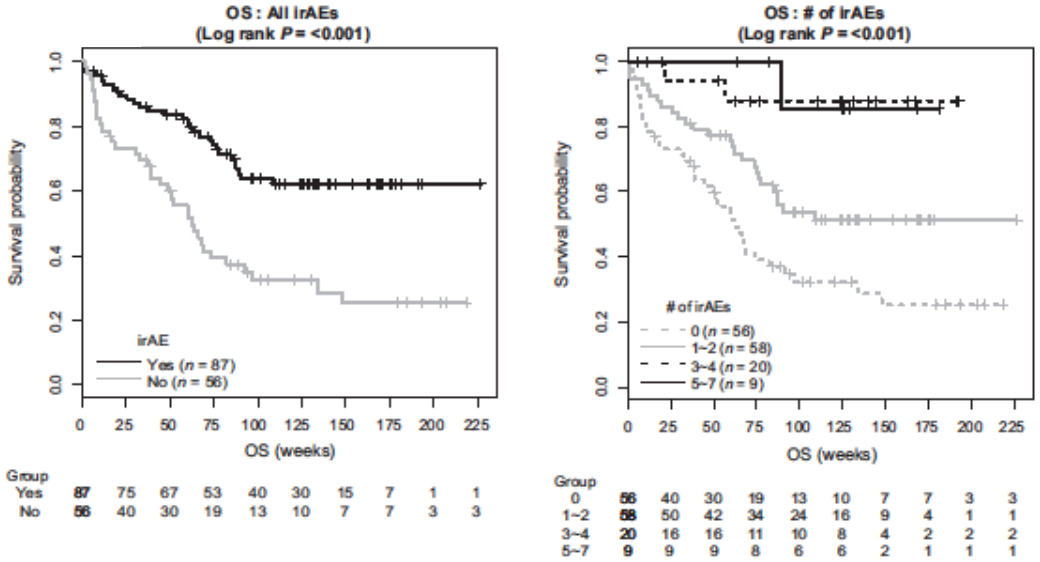


Cancer Therapy: Clinical

Nivolumab in Resected and Unresectable Metastatic Melanoma: Characteristics of Immune-Related Adverse Events and Association with Outcomes

Morganna Freeman-Keller[1], Youngchul Kim[2], Heather Cronin[3], Allison Richards[3], Geoffrey Gibney[4], and Jeffrey S. Weber[5]

- Some data support an association between clinical benefit and the induction of a **cutanous irAEs**



Freeman-Keller et al. Clin Cancer Res; 22(4) February 15, 2016

Pooled Ipi + Nivo Melanoma (067 + 069)
Best Overall Response

	NIVO+IPI	
	Discontinued due to AEs (n = 176)	Did not discontinue due to AEs (n = 233)
ORR, % (95% CI)	**68.2** (60.8, 75.0)	**50.2** (43.6, 56.8)
***P* value for comparison**	0.0200	
Best overall response, %		
Complete response	17.6	12.0
Partial response	50.6	38.2
Stable disease	15.9	10.7
Progressive disease	13.1	27.0
Unable to determine	2.8	12.0

SINGAPORE 2016 ESMO ASIA

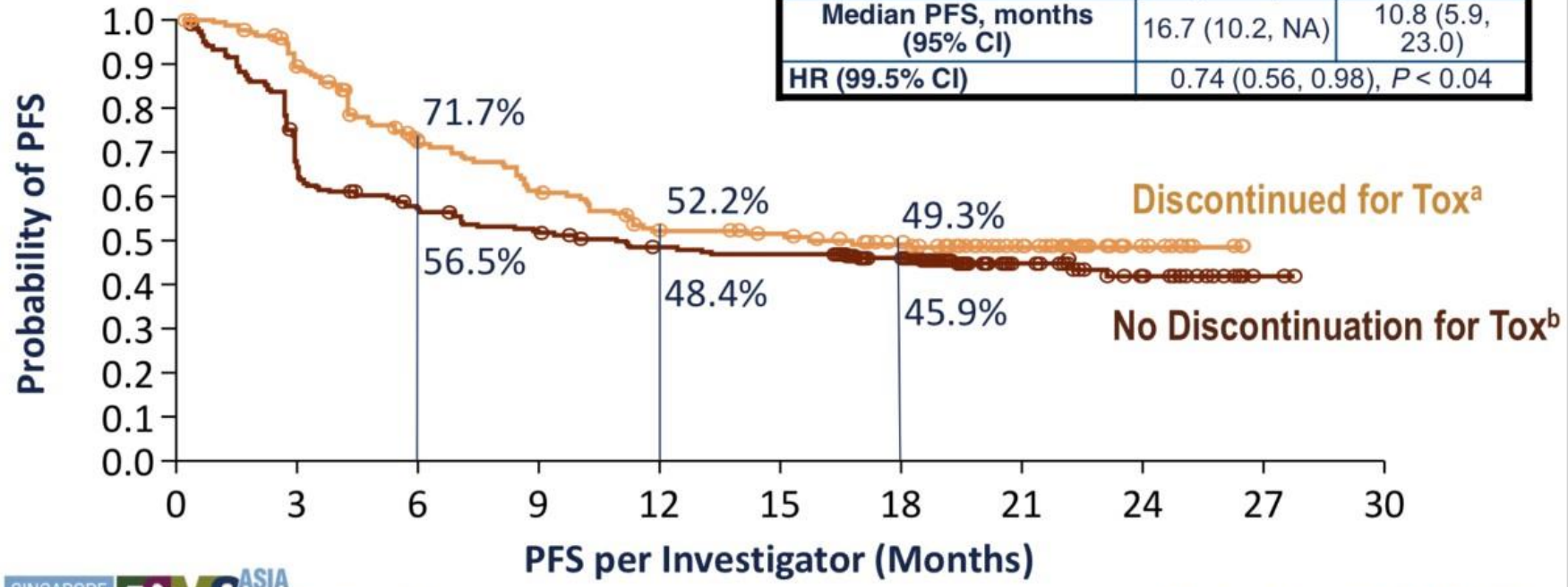
Courtesy of G Long

Schadendorf et al EADO 2016

Pooled Ipi + Nivo Melanoma (067 + 069)

Progression-Free Survival by Discontinuation due to Toxicity

	NIVO+IPI DC (n = 176)	NIVO+IPI no DC (n = 233)
Median PFS, months (95% CI)	16.7 (10.2, NA)	10.8 (5.9, 23.0)
HR (99.5% CI)	0.74 (0.56, 0.98), $P < 0.04$	



SINGAPORE 2016 ESMO ASIA

Courtesy of G Long

Schadendorf et al EADO 2016

‘Ik had al twee jaar dood moeten zijn’

Steeds meer succesverhalen met immuuntherapie bij huidkanker

‘Ook voor long- en nierkanker zitten er immunokuren aan te komen’

Does treatment of irAEs interfere with ICIs efficacy?

UZ GENT

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VOLUME 35 · NUMBER 7 · MARCH 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma

Jeffrey S. Weber, F. Stephen Hodi, Jedd D. Wolchok, Suzanne L. Topalian, Dirk Schadendorf, James Larkin, Mario Sznol, Georgina V. Long, Hewei Li, Ian M. Waxman, Joel Jiang, and Caroline Robert

Table 2. Impact of Treatment-Related Select AEs and IM Use on Response to Nivolumab Therapy

		Any-Grade Treatment-Related Select AEs*				Grade 3 to 4 Treatment-Related Select AEs		Patients Receiving Systemic IM	
	All Patients (N = 576)	Any (n = 255)	None (n = 321)	1-2 (n = 242)	≥ 3 (n = 13)	Yes (n = 18)	No (n = 558)	Yes (n = 114)	No (n = 462)
ORR, No. of patients (%)	181 (31.4)	124 (48.6)	57 (17.8)	113 (46.7)	11 (84.6)	5 (27.8)	176 (31.5)	34 (29.8)	147 (31.8)
95% CI	27.6 to 35.4	42.3 to 54.9	13.7 to 22.4	40.3 to 53.2	54.6 to 98.1	9.7 to 53.5	27.7 to 35.6	21.6 to 39.1	27.6 to 36.3
P		< .001		< .0001†	< .001†	1.00		.736	

Abbreviations: AE, adverse event; IM, immune-modulating agent; ORR, objective response rate.
*Data in these columns are for patients with the indicated numbers of any-grade treatment-related select AEs: any AE, no AEs, 1-2 AEs, and ≥ 3 AEs.
†Versus no treatment-related select AEs.

When a severe irAE happens, what are the consequences ?

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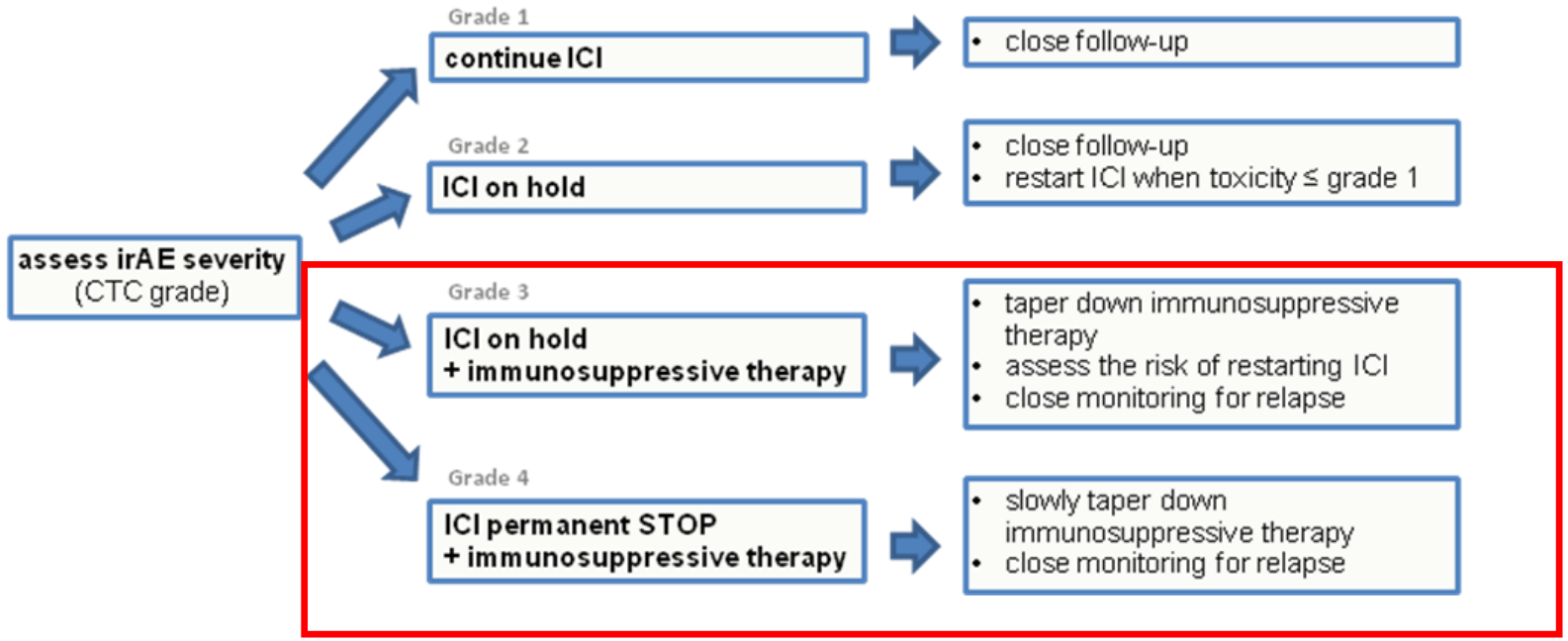
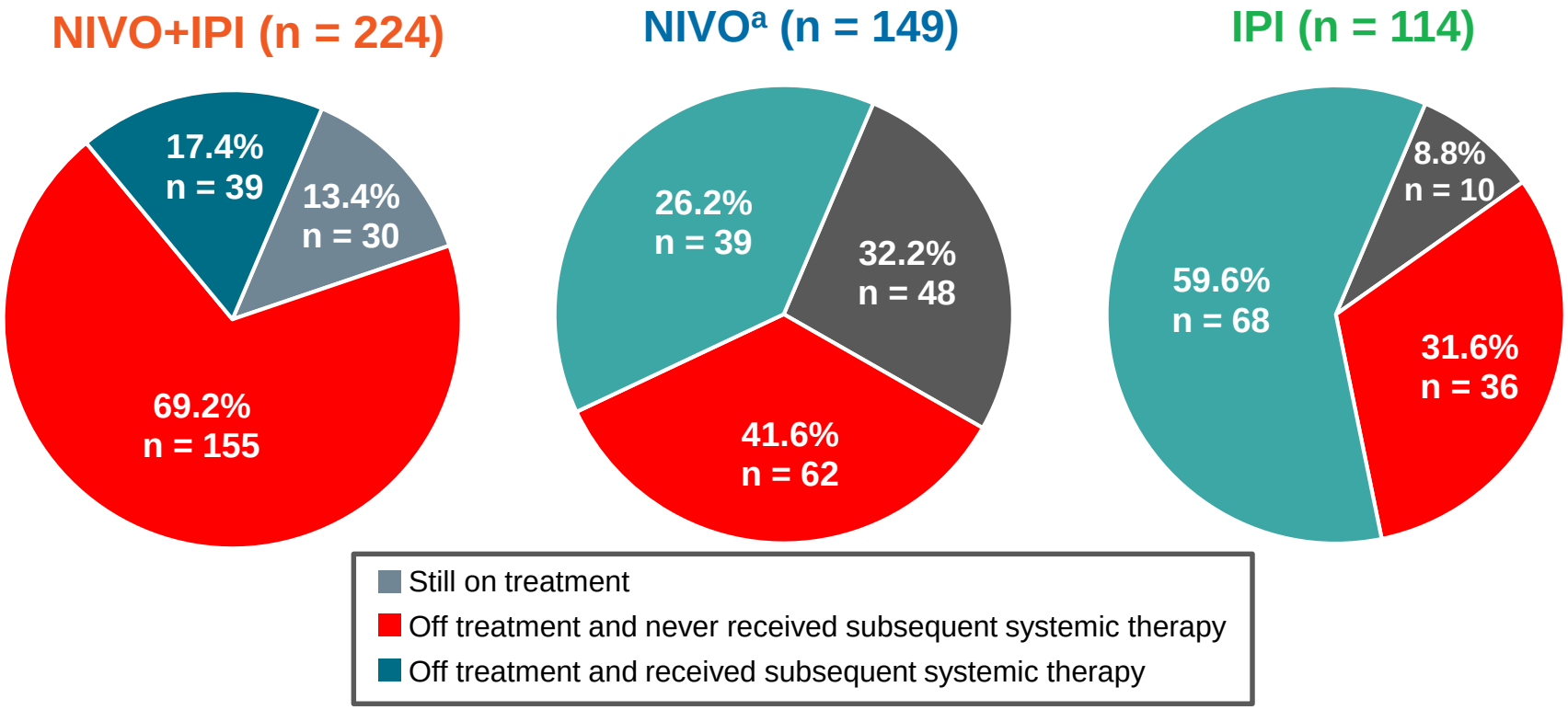
General principles of irAE managements

Figure 2: ***Treatment principles of irAE management***



Melanoom



- In the NIVO+IPI arm, median duration of response was not reached with 69% of patients alive and remaining treatment free

[a]NIVO arm was from CheckMate 067 study only

➢ **Response ongoing despite treatment interruption/cessation**

Risk of new toxicity

- Development of an irAE during treatment with anti-CTLA4 → higher risk of an irAE during treatment with anti-PD1 and *vice versa*

- Sequential:
  - Anti-PD1 → Ipilimumab: up to 35% risk of grade 3-4 toxicity
  - Patients who develop grade 3-4 toxicity during treatment with ipilimumab → anti-PD1: grade 3-4 toxicity > 20%

Menzies AM, et al Ann Oncol 2017 Bowyer, S et al Br J Cancer 2016

Kan immunotherapie de ziekteverzekering ondermijnen?

UZ GENT

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Prijs Nivolumab + Ipilimumab in euro (4 cycli)

PRIJS PER BEHANDELCYCLUS MET IPILIMUMAB NIVOLUMAB VAN 3m incl. beeldvorming en cons oncoloog bij start en herevaluatie		
	Ten laste V.I.	Ten laste pt
1ste cons oncoloog voor start therapie (basis)	48,93	12,00
Bespreking herevaluatie	48,93	12,00
Dagkliniek incl. medicatiekost	97769,92	0,00
PET/CT bij start therapie	631,61	30,70
PET/CT bij herevaluatie	592,39	18,60
MR hersenen start	156,48	12,01
MR hersenen herevaluatue	156,48	12,01
TOTAAL	99404,74	97,32

Prijs Nivolumab in euro (3m behandeling)

PRIJS PER BEHANDELCYCLUS MET NIVOLUMAB VAN 3m incl. beeldvorming en cons oncoloog bij start en herevaluatie		
	Ten laste V.I.	Ten laste pt
1ste cons oncoloog voor start therapie (basis)	48,93	12,00
Bespreking herevaluatie	48,93	12,00
Dagkliniek incl. medicatiekost	24598,14	3,08
PET/CT bij start therapie	631,61	30,70
PET/CT bij herevaluatie	592,39	18,60
MR hersenen start	156,48	12,01
MR hersenen herevaluatue	156,48	12,01
TOTAAL	26232,96	100,40

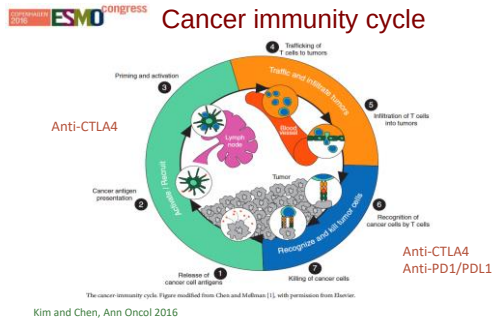
Prijs Nivolumab in euro (3m behandeling)

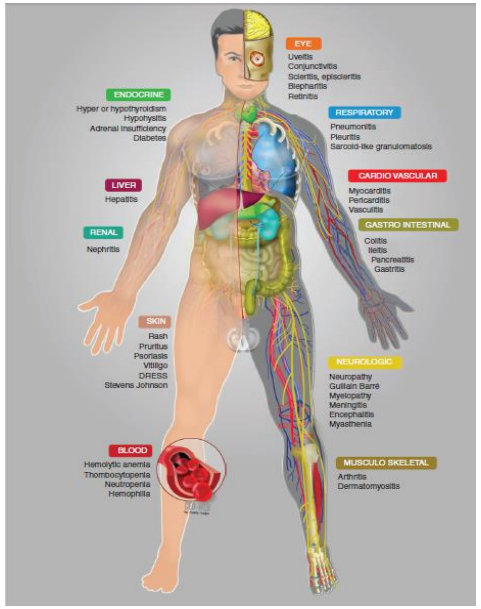
PRIJS PER BEHANDELCYCLUS MET NIVOLUMAB VAN 3m incl. beeldvorming en cons oncoloog bij start en herevaluatie		
	Ten laste V.I.	Ten laste pt
1ste cons oncoloog voor start therapie (basis)	48,93	12,00
Bespreking herevaluatie	48,93	12,00
Dagkliniek incl. medicatiekost	24598,14	3,08
PET/CT bij start therapie	631,61	30,70
PET/CT bij herevaluatie	592,39	18,60
MR hersenen start	156,48	12,01
MR hersenen herevaluatue	156,48	12,01
TOTAAL	26232,96	100,40

EXTRA KOST COMPLICATIES?

Take home messages checkpoint inhibitors // RISKS - toxicity :

- Every organ can be involved
- Severity can vary from grade 1 – 5
- Requires immediate action
- Hold further treatment (depending on severity)
- Involve organ specialist
- Start immunosuppression (depending on severity)
- Careful follow-up warranted
- Taper immunosuppression





Champiat *et al*. *Annals of Oncology*, 2016;27:559-74.

WHEN YOUR HARMONICA PLAYER WINS THE NOBEL PRIZE

THE CHECKPOINTS were born in 2007 on an escalator in Chicago. Here's the story...

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GUEST EDITORIAL
THANK YOU, JIM ALLISON

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CRAIG THOMPSON RESIGNS FROM TWO CORPORATE BOARDS AS MSK CRISIS SHIFTS TO BOARD ROLES

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ROY JENSEN: "IN GENERAL, I THINK CANCER CENTER DIRECTORS STILL ENJOY A CERTAIN AMOUNT OF RESPECT"

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TRIALS & TRIBULATIONS
HOW TUMOR-SPECIFIC MODULATION FREQUENCIES WERE DISCOVERED

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Thank you for your attention!