GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

ESMO ADVANCED COURSE ON LUNG CANCER IN IMMUNOTHERAPY

Management of IO toxicity

John Haanen MD PhD

Zürich, 3-4 July 2019

Netherlands Cancer Institute, Amsterdam

DISCLOSURE OF INTEREST

I have provided consultation, attended advisory boards, and/or provided lectures for: **Amgen, AZ/Medimmune, Bayer, BMS, GSK, Ipsen, Merck Serono, MSD, Novartis, Pfizer, Roche/Genentech, Sanofi, Seattle Genetics** for which NKI received honoraria

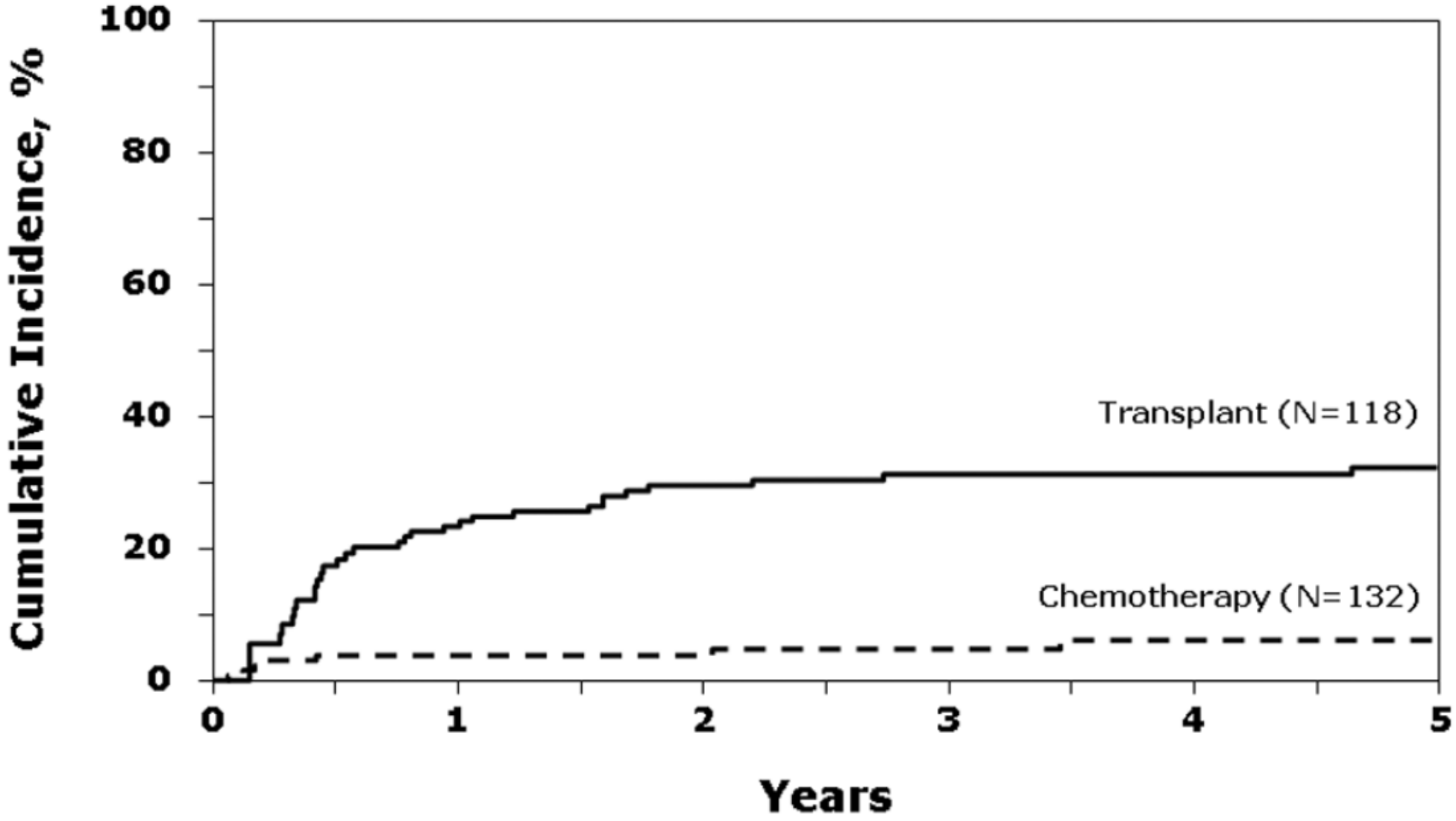
I am on the **SAB** of **AIMM, Celsius Therapeutics, Immunocore and Neon Therapeutics.** Financial compensation goes to NKI

Through my work NKI received grant support from **Bayer**, **BMS, MSD, Novartis, Neon Therapeutics, Pfizer**

Finding the balance between efficacy and toxicity

Marie Boyle: ‘Cherish’

How much toxicity from IO treatment do we accept?



Tawbi et al., NEJM 2018; Eggermont et al. NEJM 2016; Schlenk et al., Biol Blood Marrow Transpl 2008

Correlation between irAE and efficacy in NSCLC treated with anti-PD-(L)1

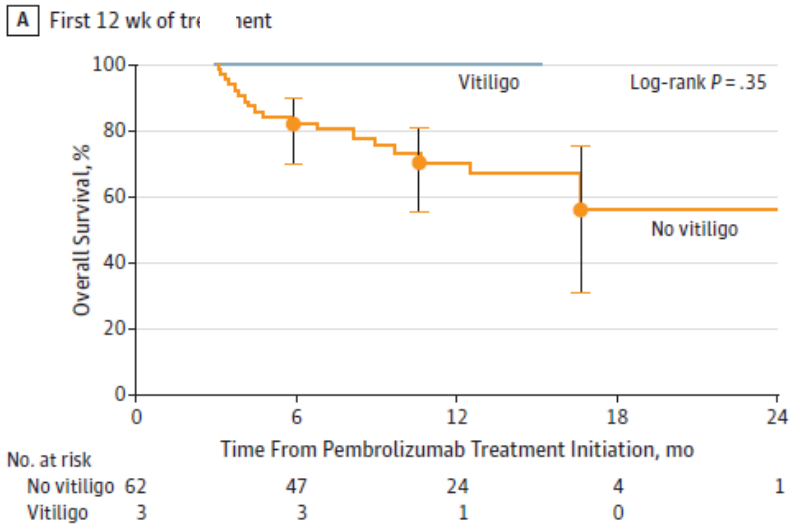
Study	ICI	n	Grade ≥ 3 irAEs, %	RR, %		PFS, mo		OS, mo		Cycles, n	
				irAEs	No irAEs	irAE's	No irAEs	irAEs	No irAEs	irAEs	No irAEs
Ricciuti et al.[12]	Nivolumab	195	7.6	43.5	10.0	5.7	2.0	17.8	4.0	13	2.5
Moor et al.[13]	Nivolumab	196	13.2	NR	NR	5.9	2.5	23.8	6.4	NR	NR
Toi et al.[14]	Nivolumab	70	NR	57	12	12	3.6	NR	NR	12	7[a]
Haratani et al.[15]	Nivolumab	134	9	52	28	9.2	4.8	Not R	11.1	NR	NR
Teraoka et al.[16,b]	Nivolumab	43	0	37	17	6.4	1.5	NR	NR	NR	NR
Sato et al.[17]	Nivolumab	38	NR	64	7.4	Not R	1.6	NR	NR	NR	NR
Lisberg et al.[c]	Pembrolizumab	97	3.1	39.5	8.9	8.2	2	16.4	4.8	NR[d]	NR
Von Pawel et al.[19,b]	Atezolizumab	823	6.0	22.3	9.9	5.4	2.3	20.7	10.6	NR	NR
Kfoury et al.[20]	Anti-PD-1/PD-L1	618[e]	Grade ≥2 28.3%[e]	NR	NR	14.2	13.4	23.7	16.2	NR	NR
Toi et al.[21]	Anti-PD-1	137	NR[f]	52	13	10.3	3.4	Not R	11.4	NR	NR
Shafqat et al.[22]	Anti-PD-1/PD-L1	157[g]	11.4	NR	NR	24.4	4.2	NR	NR	NR	NR

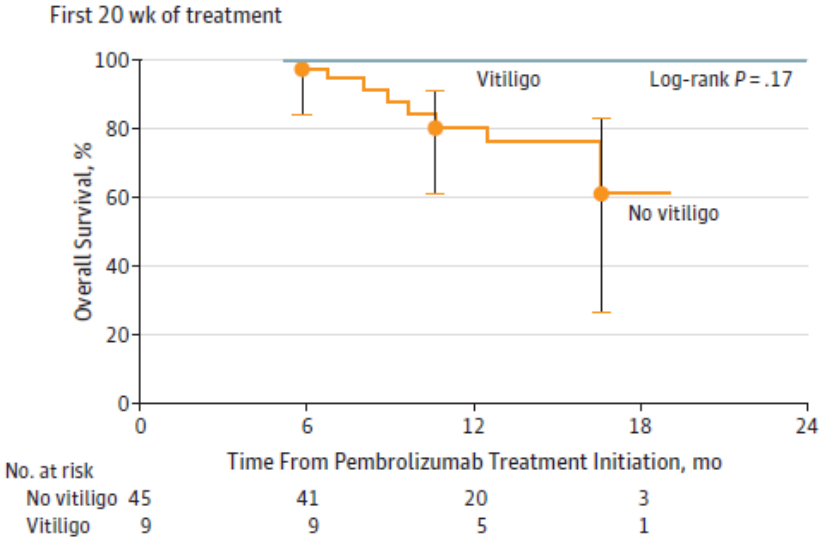
Remon et al., J Thor Oncol 2019; Cortellini et al., Clin Lung Cancer 2019

Vitiligo and clinical response to pembrolizumab

Patient	CR	PR	SD	PD	p*
Vitiligo (N=17)	3 (18)	9 (53)	3 (18)	2 (12)	0.002
Non vitiligo (N=50)	4 (8)	10 (20)	1 (2)	35 (70)	
Total (N=67)	7 (10)	19 (28)	4 (6)	36 (54)	

***Complete/partial response versus stable/ progressive disease/progression progression in patients disease/progression in patients with and without vitiligo, exact fisher test**

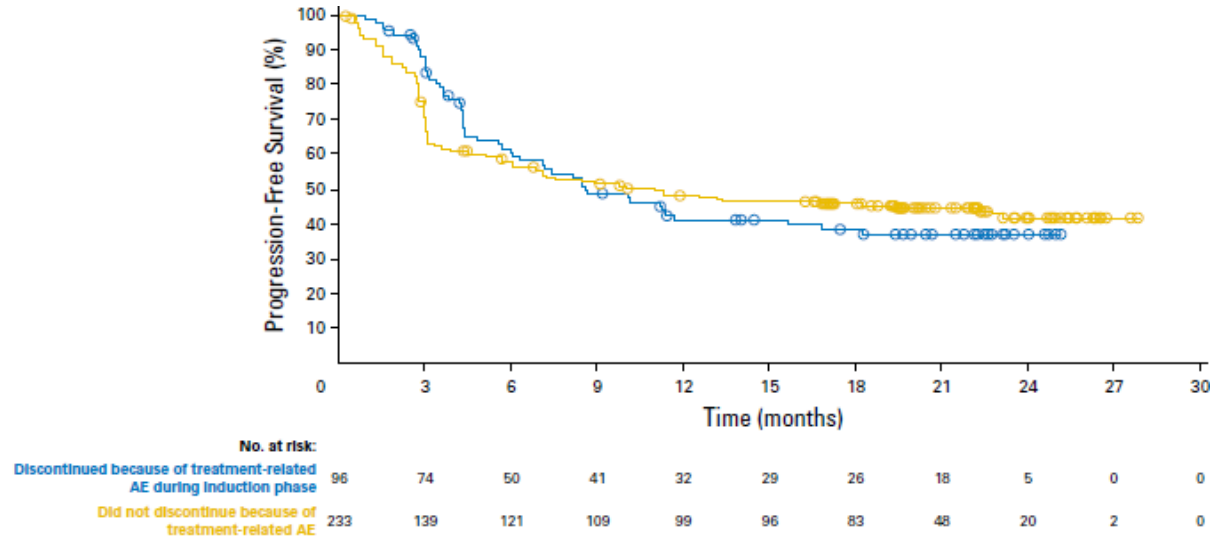


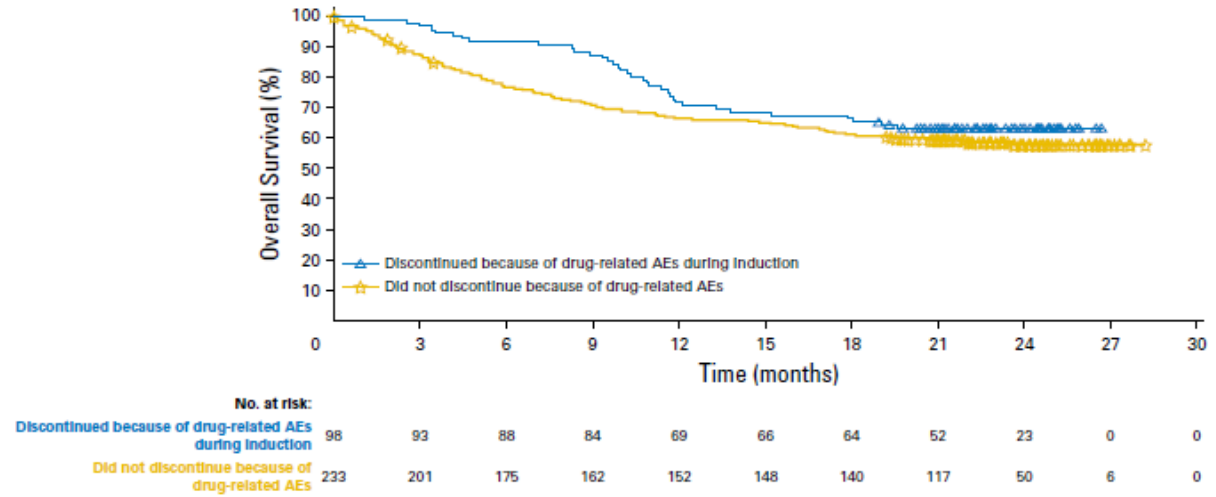


Hua et al JAMA Dermatol 2016

Correlation between irAE and efficacy in melanoma treated with anti-PD-1

Pooled analysis of PFS and OS of CheckMate-069 and-067: ipi/nivo





Weber et al., J Clin Oncol 2017; Schadendorf et al J Clin Oncol 2017

What do we know about IO toxicities?

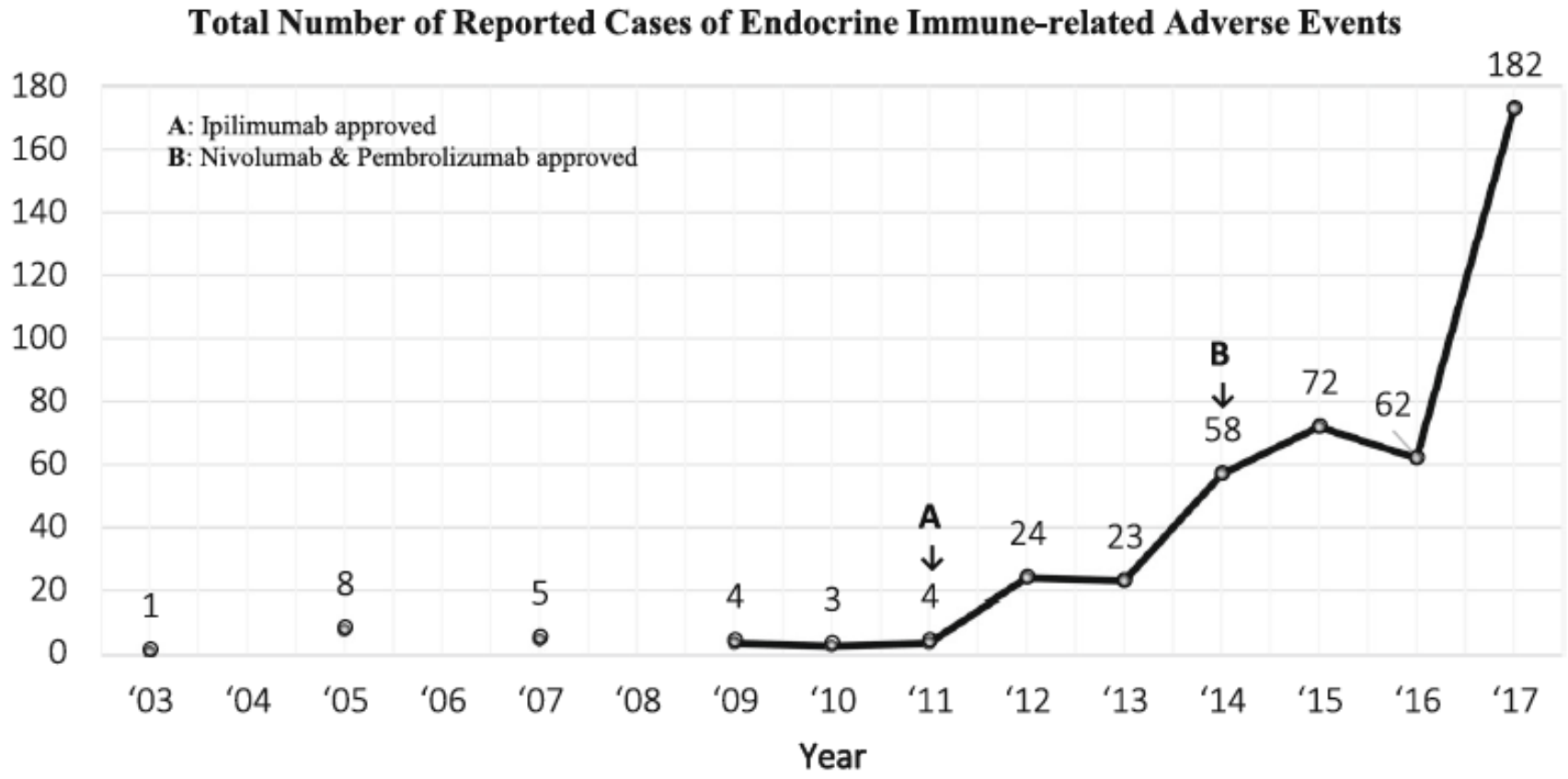
- What has been reported in peer-reviewed journals
  - Phase 1, phase 2, phase 3 and phase 4 trials
  - Expanded access programs
  - Compassionate use or Named Patient Programs
  - Case reports
  - Reports on real-world data
- Eminence-based (personal experience)
- How well are IO toxicities reported in clinical trial?
- What should we look at?
  - Treatment related AE?
  - Immune related AE?
  - All grade toxicity rate?
  - Grade 3-4 toxicity rate?
  - Grade 5 toxicity rate?
  - Treatment discontinuation rate?
  - Treatment delay?
  - Duration of AE (to grade 1 or lower)?

Checkpoint blockade drug classes and FDA/EMA-approved indications

		Disease sites approved										
Drug class	Name	Melanoma	NSCLC	RCC	HL	Urothelial	HNSCC	Merkel	MSI-H CRC	Gastric	HCC	MSI-H
CTLA4 blockade	Ipilimumab	x		x								
	Tremelimumab											
PD1 blockade	Nivolumab	x	x	x	x	x	x		x		x	
	Pembrolizumab	x	x		x	x	x		x	x		x
PDL1 blockade	Atezolizumab		x			x						
	Durvalumab		x			x						
	Avelumab					x		x				

Girotra et al., JNCI Spectrum 2018

Increase in frequency of reported of ir-endocrinopathies by ICI over the past 15 years



Tan et al., Clin Diab Endocrinol 2019

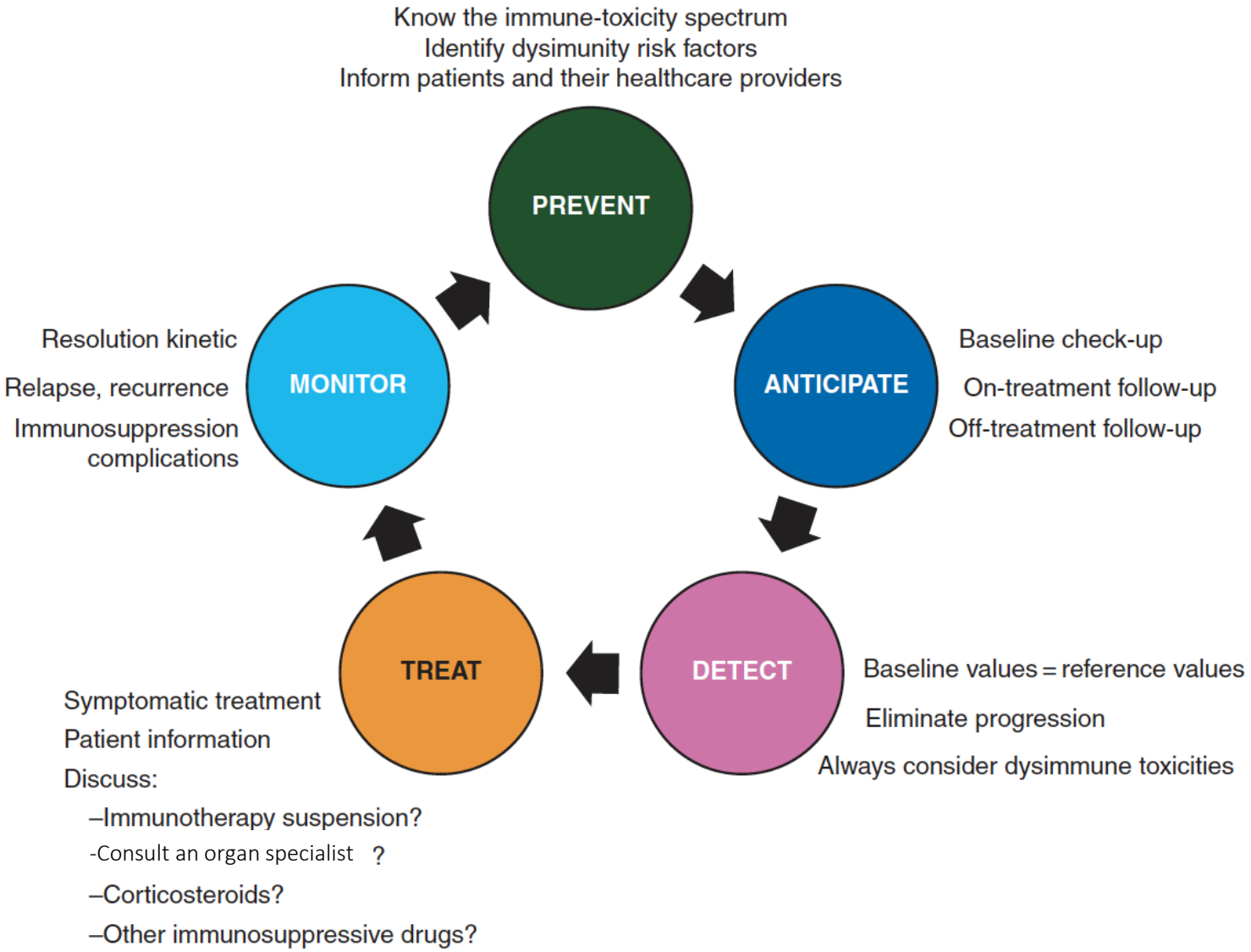
How do we treat IO toxicities?

- Pharma developed algorithms
- 2017: ESMO Guidelines
- 2017: SITC Guidelines
- 2018: ASCO Guidelines
- 2018: NCCN Guidelines

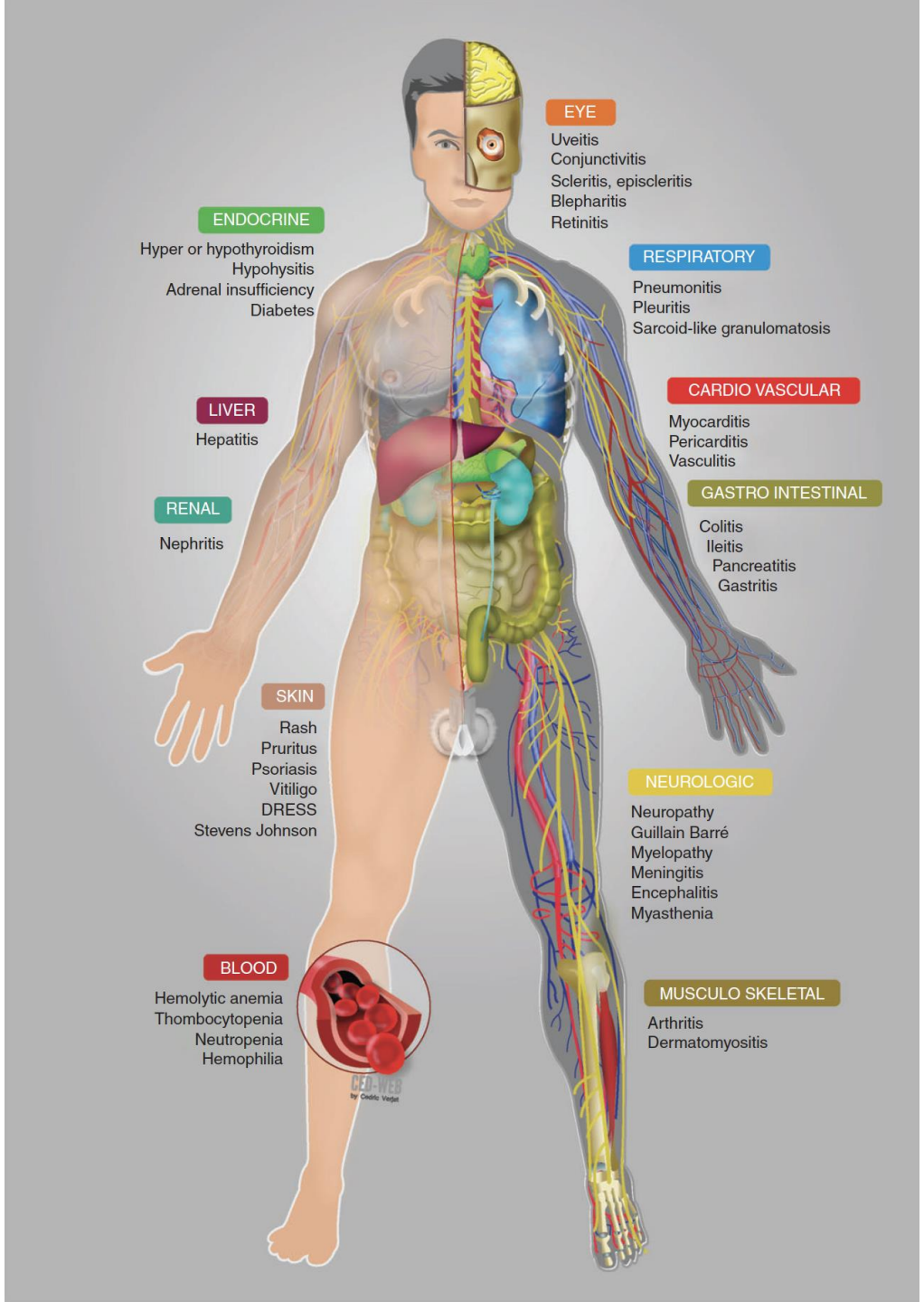
None of the Guidelines are based on outcomes of randomized controlled trials!

- Based on recommendations coming from treatment of auto-immune diseases, organ transplantations
- Empirically obtained data from key opinion leaders in the field
- Based on assumed mechanism of action of IO drugs

How should a patient starting with IO treatment be approached?



Champiat et al., Ann Oncol 2016



Champiat et al., Ann Oncol 2016

Case

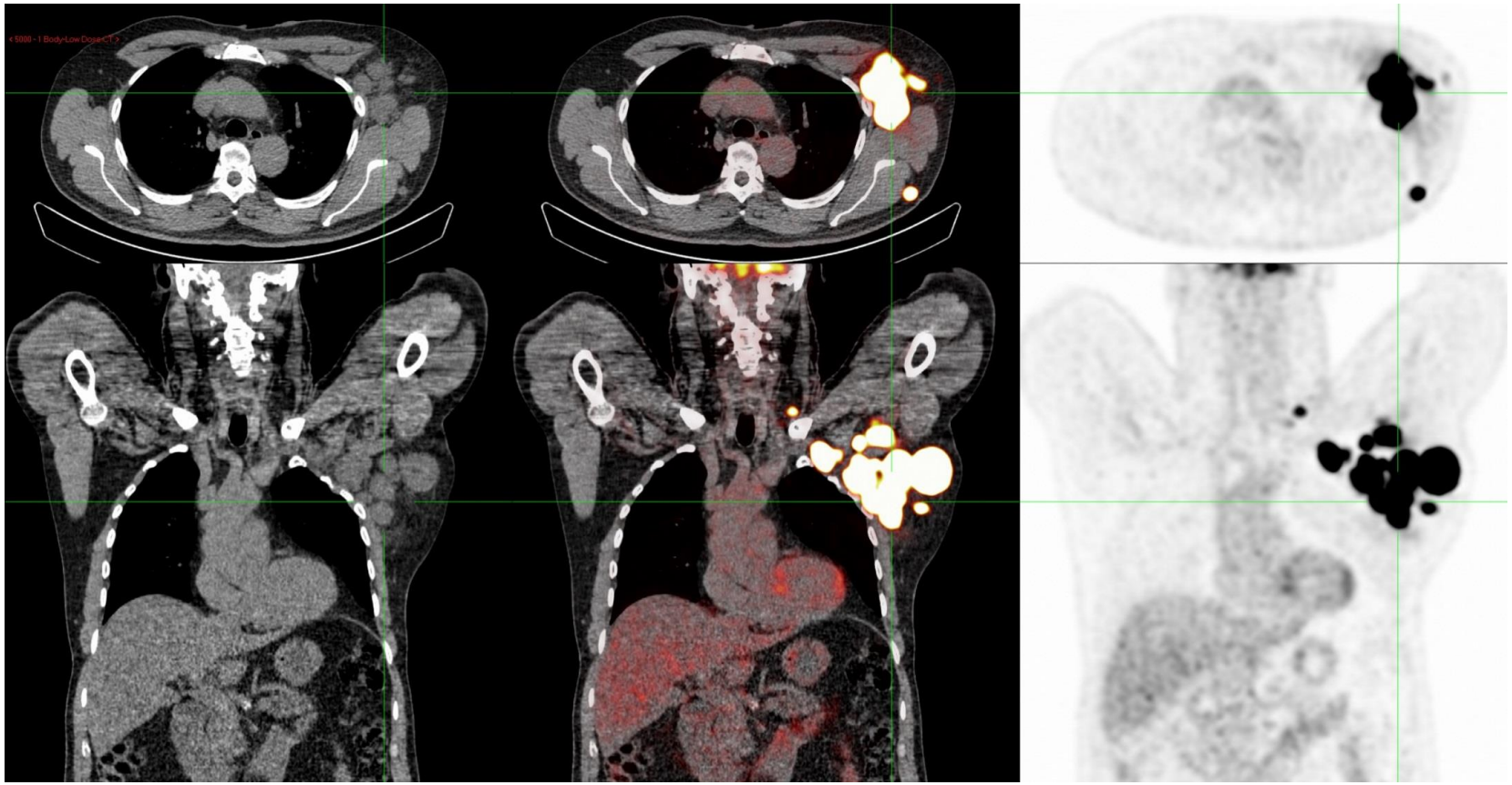
56-year old male patient. No comorbidities (no autoimmune disease)

2007: Superficial spreading melanoma on the back (left side). Breslow: 1.9 mm, no ulceration, pT2a

Nov 2018: bulky irresectable axillary metastases
NRAS Q61 mutation
No brain metastases
Lab: normal LDH
Referred to NKI

Haanen, unpublished

PET-CT-scan December 2018



Haanen, unpublished

Case

56-year old male patient. No comorbidities (no autoimmune disease)

2007: Superficial spreading melanoma on the back (left side). Breslow: 1.9 mm, no ulceration, pT2a

Nov 2018: bulky irresectable axillary metastases
NRAS Q61 mutation
No brain metastases
Lab: LDH normal, S100b: 1.73 μg/L (ULN: 0.10 μg/L)
Referred to NKI

Discussed in Multidisciplinary Team: advise: start ipilimumab + nivolumab

Dec 2018: start ipi 3 mg/kg + nivo 1 mg/kg

Haanen, unpublished

Case

Jan 2019: 2nd course ipi/nivo: no side effects of treatment
Lab: S100b: 2.49 μg/L; LDH 316 U/L (ULN 250 U/L)

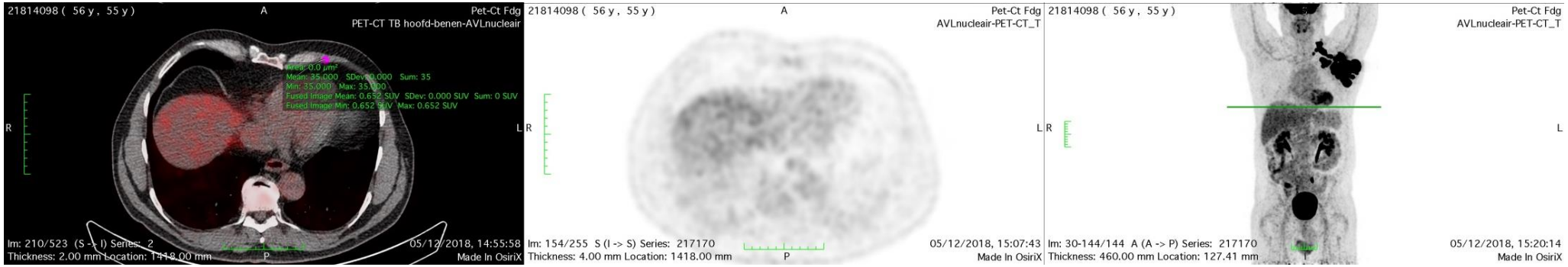
1 week later: Nausea, loss of appetite, especially coffee, headaches under control with paracetamol.
Started to cough once in while, dry, not productive. On physical exam: no abnormalities
Works 40 hrs/week, but more tired in the evenings

2 weeks later: slow deterioration, weight loss of 10 kg as of start of treatment
Worked now 50%. More tired. Dyspnea on exertion, no cough, no diarrhea, no abdominal pain, no rash.
Lab: further increase in S100b and LDH, rest including hormonal axes normal
3rd ipi + nivo was given, but because of likelihood of disease progression, PET was performed

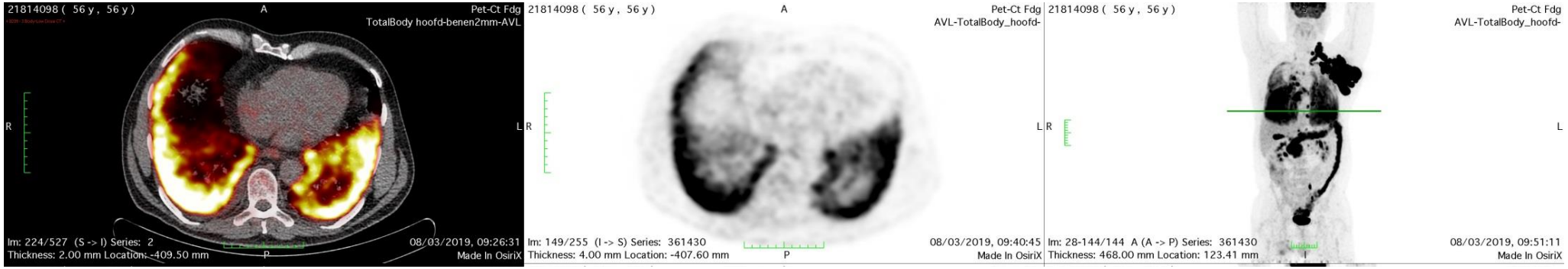
Haanen, unpublished

PET/CT evaluation after 2 courses of ipilimumab/nivolumab

Dec 2018



Mar 2019



Haanen, unpublished

Case

PET: more or less stable disease of left axillary metastases
Inflamed lower lung lobes
Symmetric mediastinal lymphadenopathy
Pleural effusion
Inflamed upper and lower GI tract, pancreas

Now also complaints of diarrhea, more nausea and increased shortness of breath.
Oxygen saturation: 91%
Lab: S100b stable: 4.56 μg/L and LDH 346 U/L, no other abnormalities

Multiple grade 1-2 (clinically) immune related adverse events:

- Upper GI tract
- Colitis
- Pancreatitis
- Pneumonitis
- Sarcoid-like disease

Haanen, unpublished

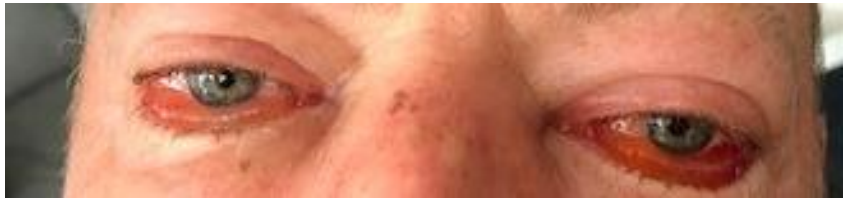
Case

Started with prednisone 1 mg/kg (100 mg)

1 week later: Diarrhea gone (normal stools); regained appetite, dyspnea more or less the same (Oxygen saturation: 95%)

Steroids were tapered after 2 weeks of high dose

During tapering he started complaining of dry and irritated eyes

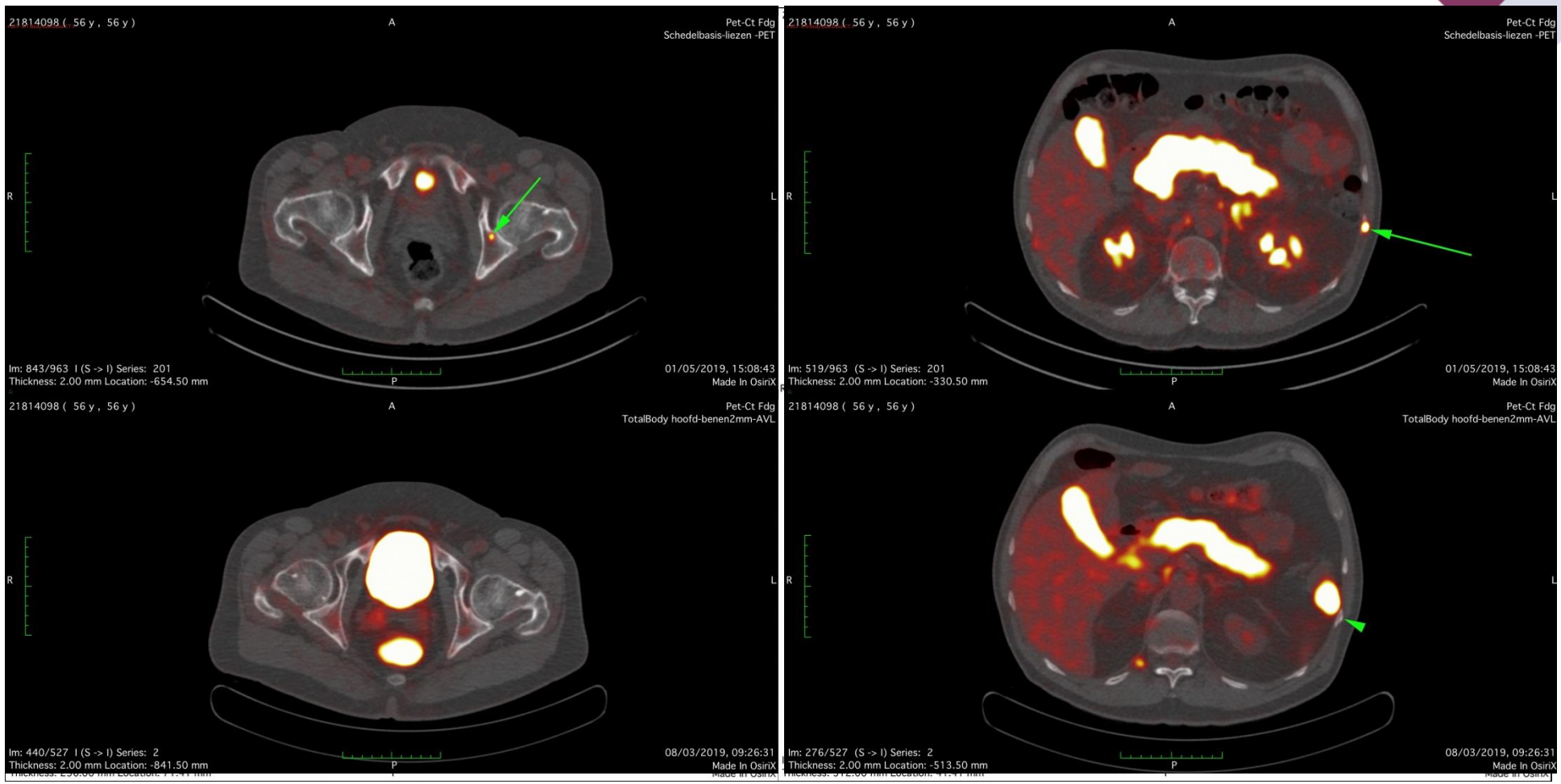


Haanen, unpublished, with patient consent

Papavasileiou et al., Ocular Immunol Inflamm, 2016

May 2019

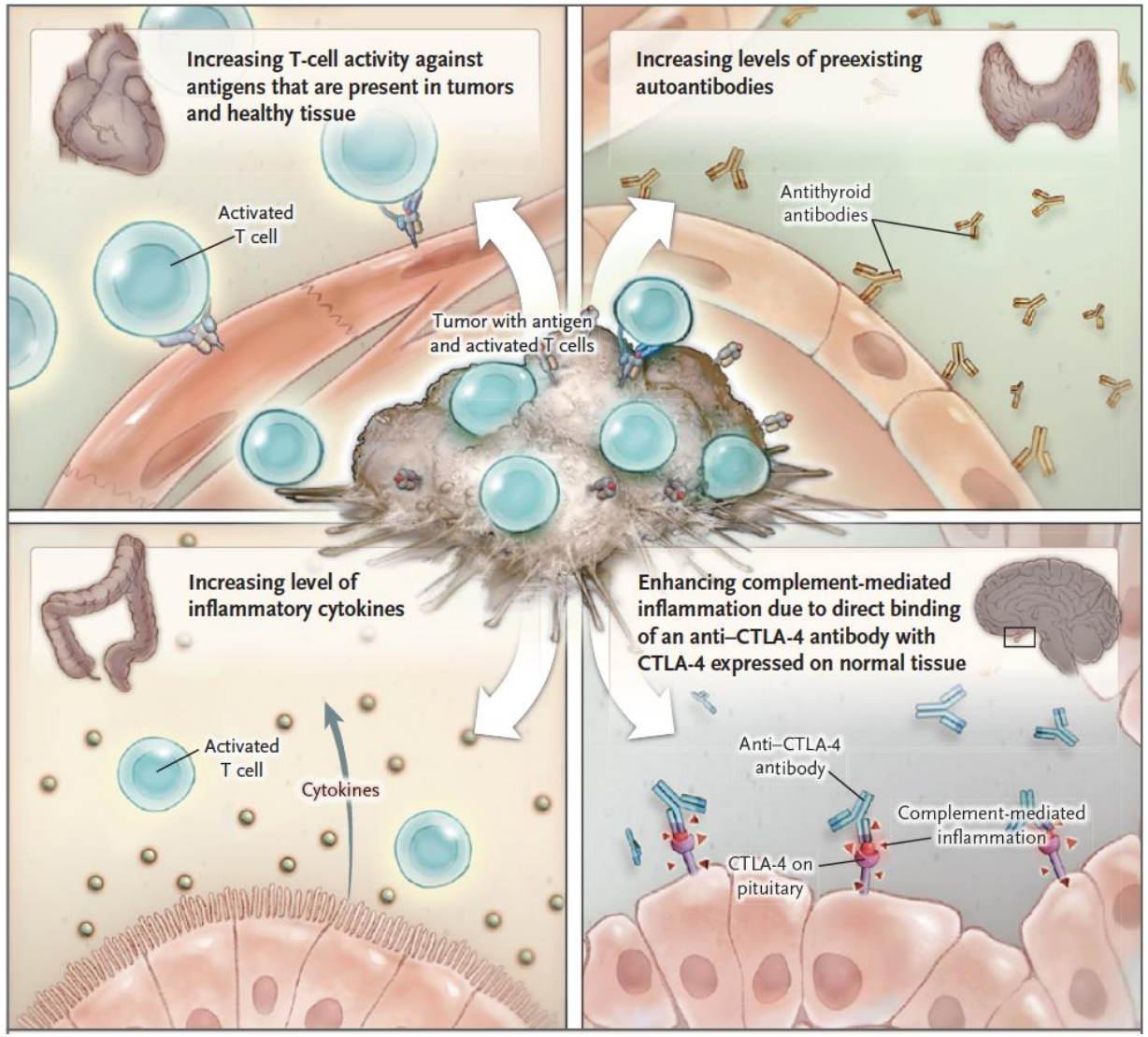
Mar 2019



S100b:	8.91 mg/L	4.14 mg/L
sLDH:	689 U/L	347 U/L

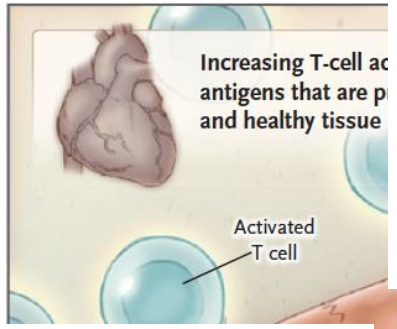
Haanen, unpublished

Potential mechanism by which immune related adverse events develop



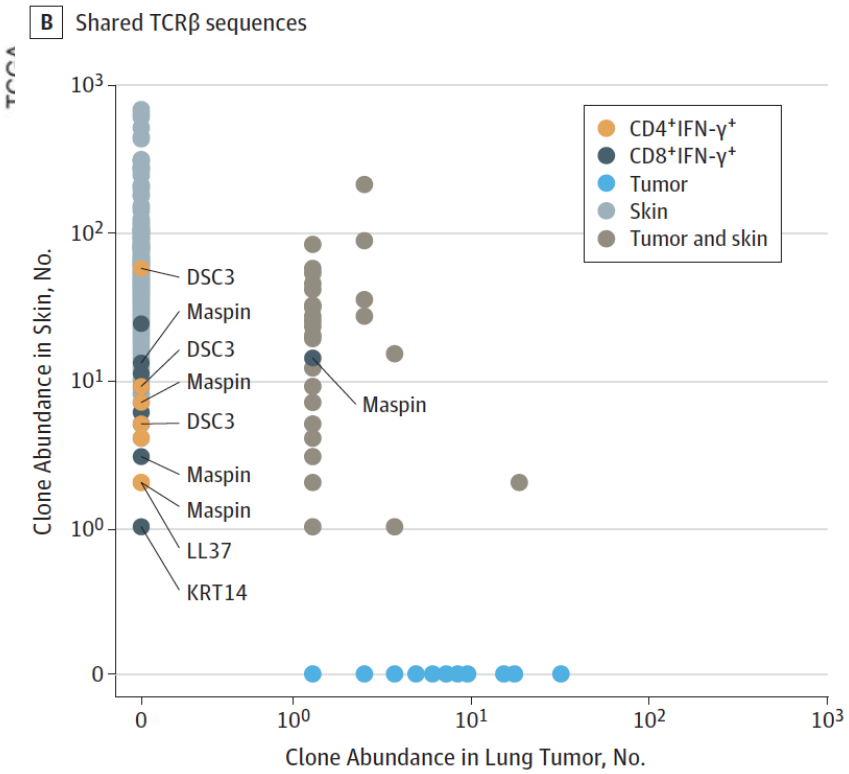
Postow et al., NEJM 2018

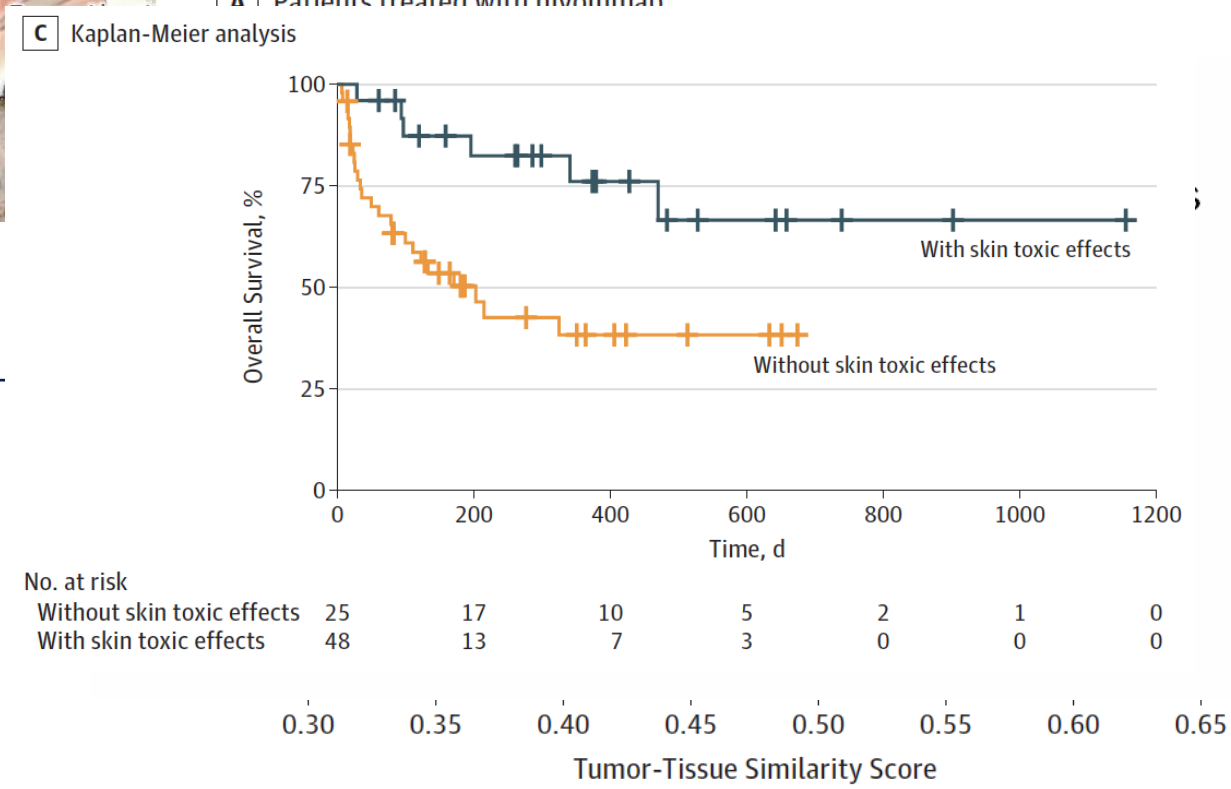
Increasing T cell activity against antigens that are present in tumors and healthy tissue



JAMA Oncology | Brief Report

Association of Checkpoint Inhibitor–Induced Toxic Effects With Shared Cancer and Tissue Antigens in Non–Small Cell Lung Cancer





Postow et al., NEJM 2018; Berner et al., JAMA Oncol 2019;

Preexisting autoantibodies

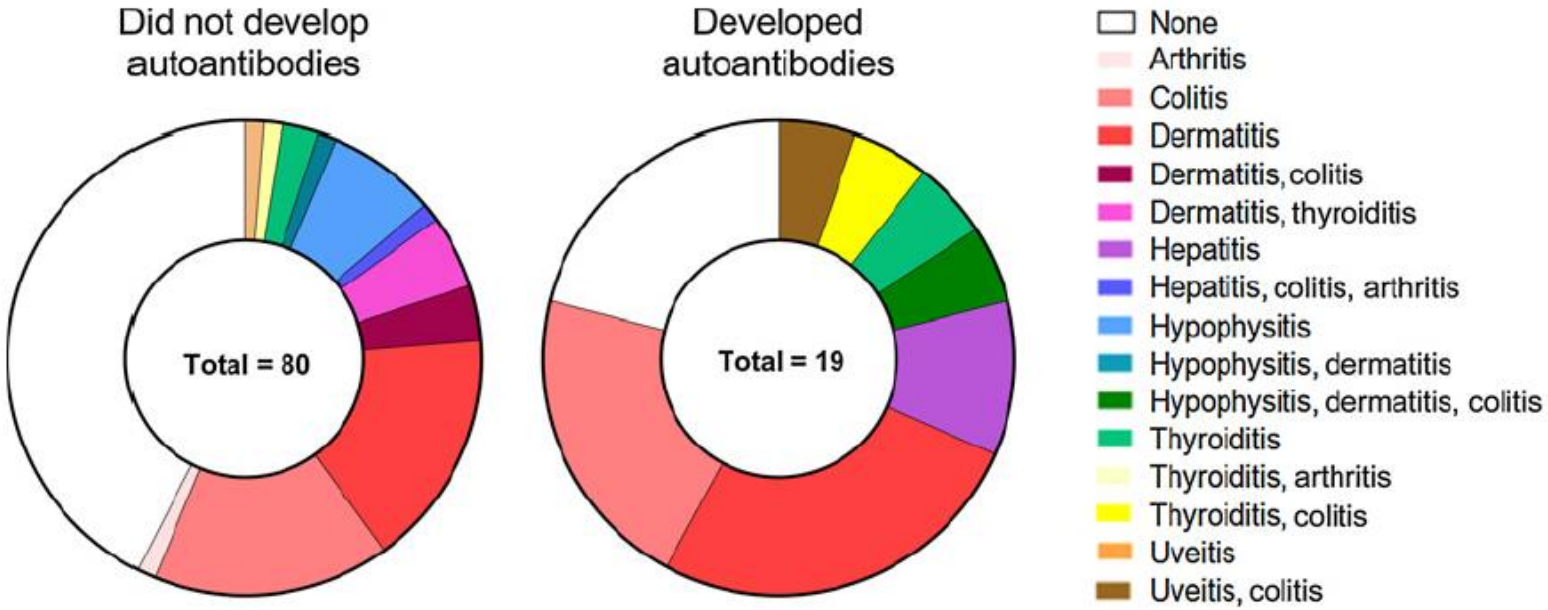
Cancer Immunology Miniature

Cancer Immunology Research

Autoantibody Development under Treatment with Immune-Checkpoint Inhibitors

Emma C. de Moel[1], Elisa A. Rozeman[2], Ellen H. Kapiteijn[3], Els M.E. Verdegaal[3], Annette Grummels[4], Jaap A. Bakker[4], Tom W.J. Huizinga[1], John B. Haanen[2,3], René E.M. Toes[1], and Diane van der Woude[1]

Pre-ipilimumab auto-antibody (AA) negative pts



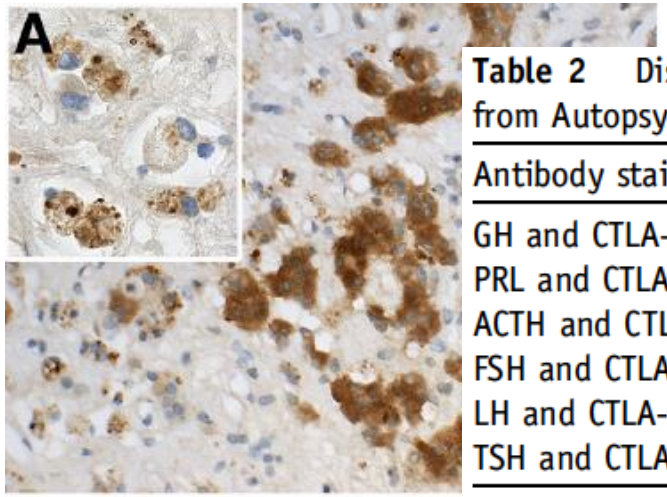
- 127 pts treated with ipilimumab
- 19% developed AA
- Mostly anti-TPO and anti-TG
- 15/19 (79%) pts that developed AA had irAE
- 46/80 (57%) pts with no AA developed irAE
- No correlation with specific AA and organ-specific irAE

Postow et al., NEJM 2018; de Moel et al., Cancer Immunol Res 2019

Direct binding of anti-CTLA-4 to CTLA-4 expressed on normal tissue

Hypophysitis Secondary to Cytotoxic T-Lymphocyte—Associated Protein 4 Blockade

Insights into Pathogenesis from an Autopsy Series



Enhancing complement-mediated

Table 2 Distribution of Hormone-Secreting and CTLA-4—Expressing Pituitary Cells by Double Indirect Immunofluorescence in the Gland from Autopsy Case 6

Antibody stainings	Total endocrine cells	Hormone-positive cells*	CTLA-4—positive cells*	Double-positive cells
GH and CTLA-4	116	64 (55)	1 (0.9)	0
PRL and CTLA-4	110	22 (20)	2 (1.8)	0
ACTH and CTLA-4	92	13 (14)	1 (1.1)	0
FSH and CTLA-4	114	12 (10)	3 (2.6)	2
LH and CTLA-4	106	6 (6)	2 (1.9)	2
TSH and CTLA-4	128	5 (4)	1 (0.8)	1

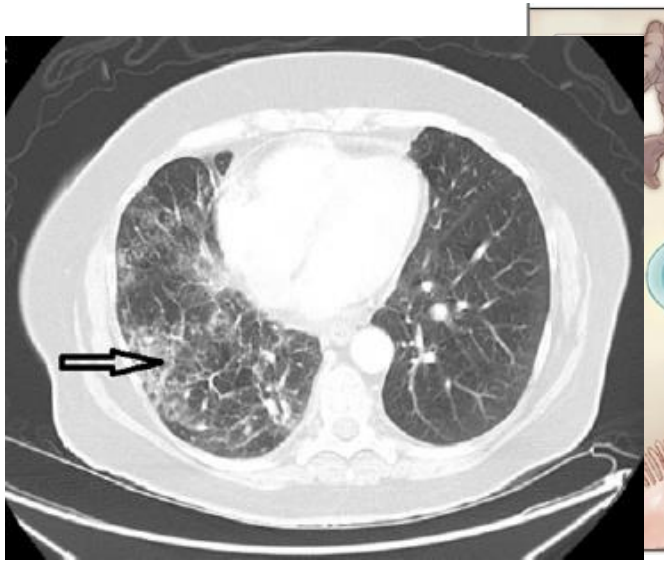
Postow et al., NEJM 2018; Caturegli et al., Am J Pathol 2016

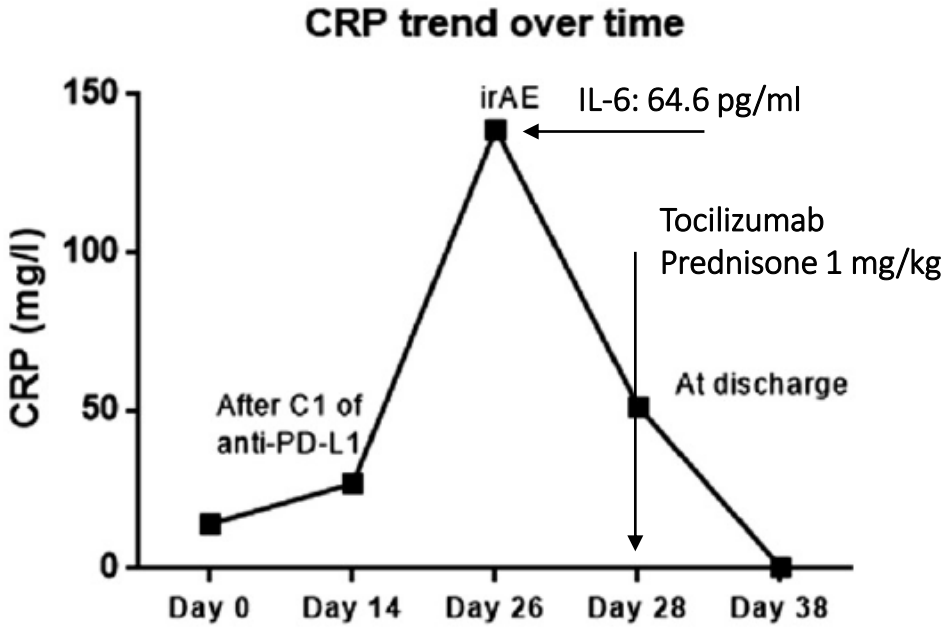
Increasing levels of inflammatory cytokines

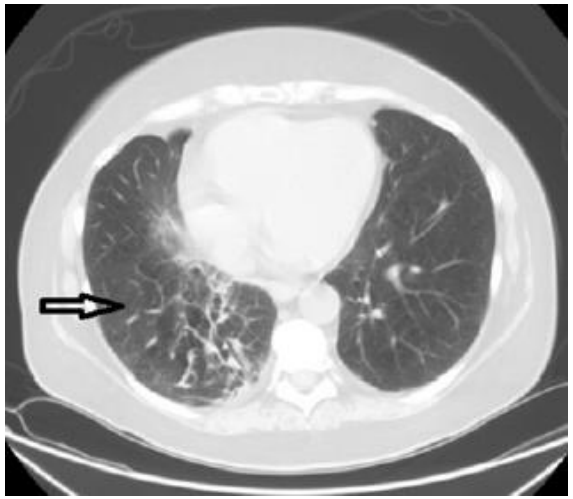
LETTER TO THE EDITOR

Interleukin-6 as one of the potential mediators of immune-related adverse events in non-small cell lung cancer patients treated with immune checkpoint blockade: evidence from a case report

Abdul Rafeh Naqash[a], Li V. Yang[a], Edward J. Sanderlin[a], Druid C. Atwell[a] and Paul R. Walker[b]



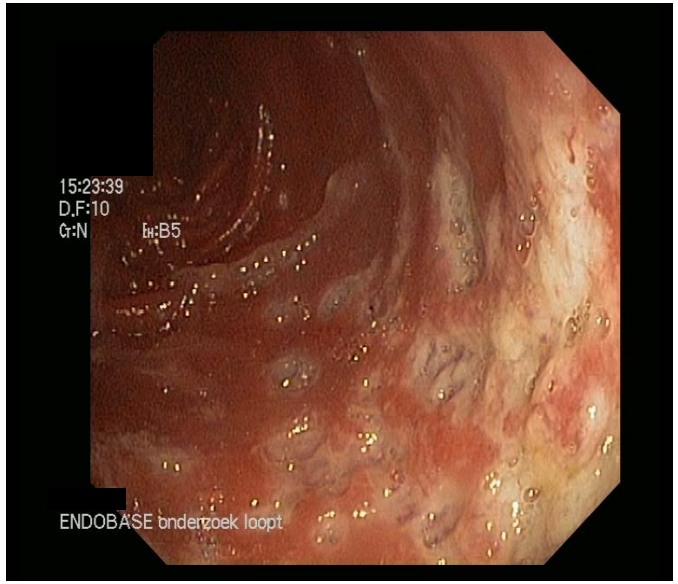




Postow et al., NEJM 2018; Naquash et al., Acta Oncologica 2018

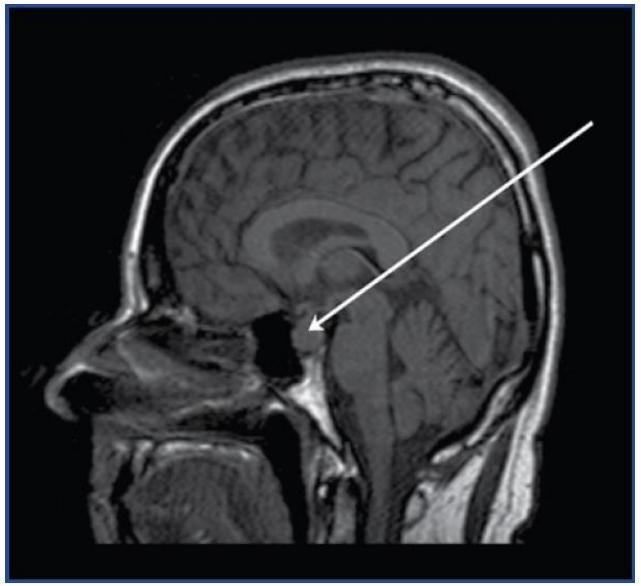
Immune related Adverse Events associated with anti-CTLA4

colitis

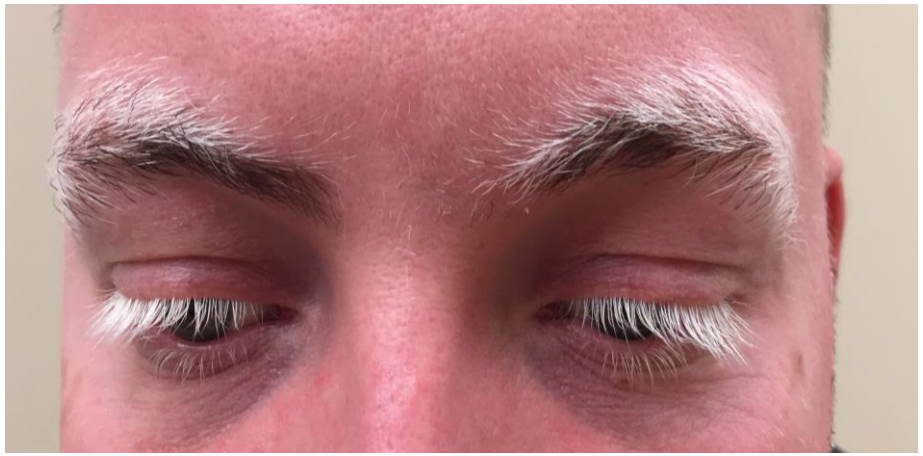


Thyroiditis
Hepatitis
Pneumonitis
Nephritis
Meningitis
etc.

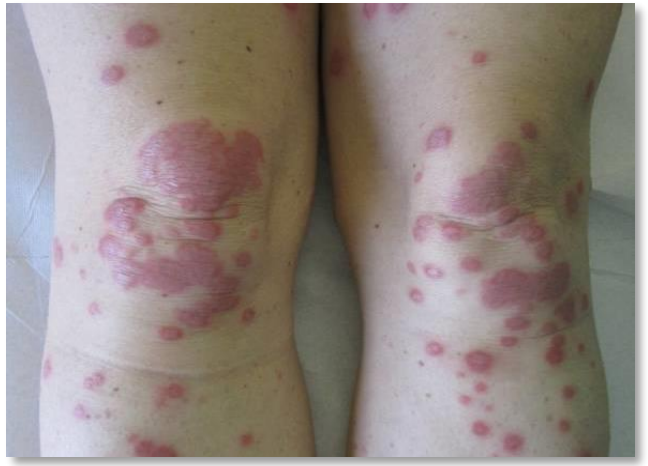
hypophysitis



vitiligo



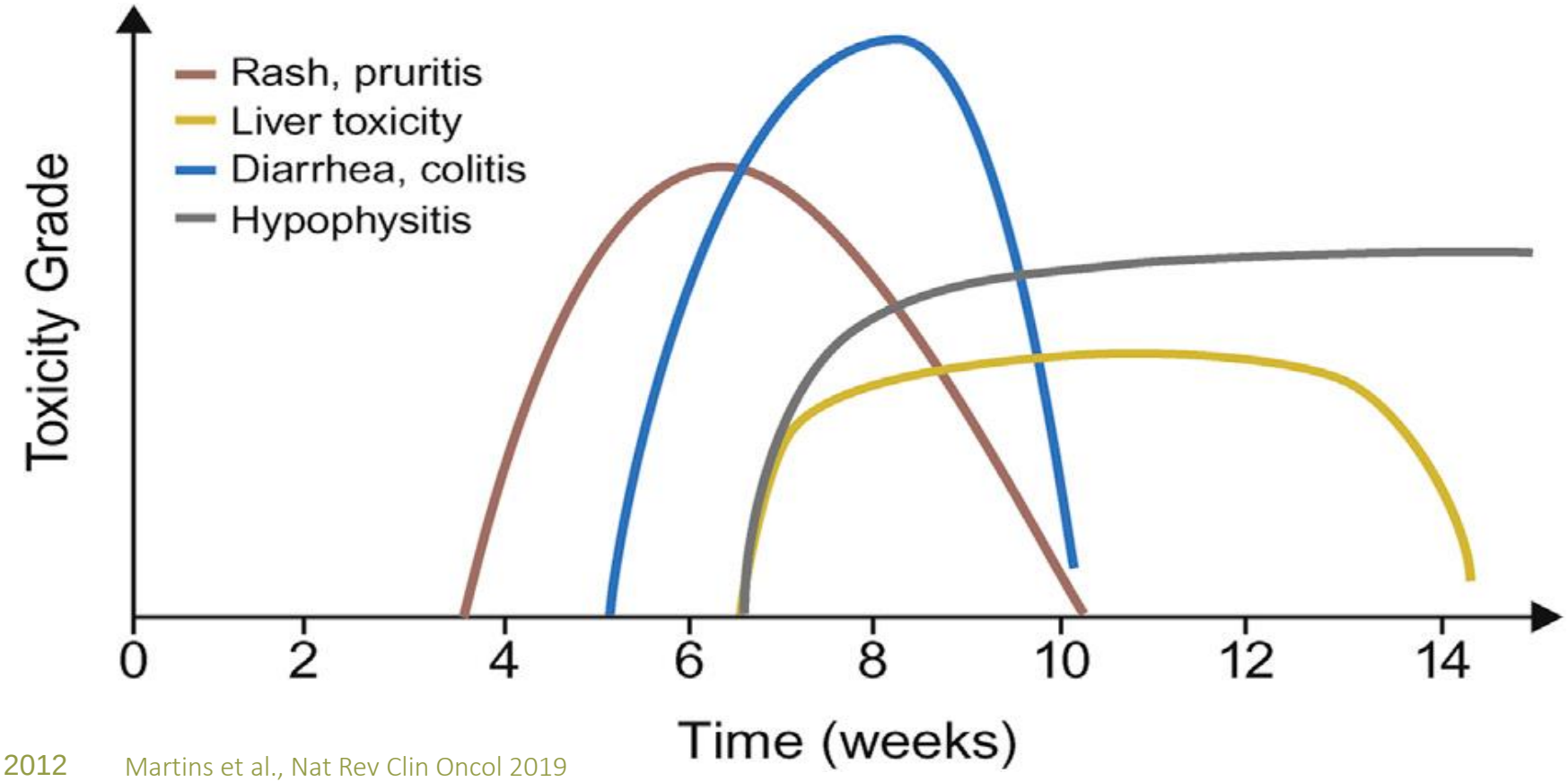
dermatitis



Haanen, unpublished, with patient consent

irAE Kinetics of ipilimumab

Study details		Any-grade adverse events (grade ≥3 adverse events)							
Study	**Dose (*n*)**	**Diarrhoea**	**Colitis**	**Pulmonary**	**Rash**	**Neurological**	**Endocrinopathy**	**Hepatic**	**Renal**
Ipilimumab									
EORTC 18071 (REF.[17])	10 mg/kg, 3-weekly (471)	41.2% (9.8%)	15.5% (8.2%)	–	34.2% (1.1%)	4.5% (1.9%)	37.8% (7.8%)	24.4% (10.9%)	–
Hodi et al.[166]	3 mg/kg, 3-weekly (131)	27.5% (4.6%)	7.6% (5.3%)	–	19.1% (0.8%)	–	7.6% (3.8%)	3.8% (0%)	–

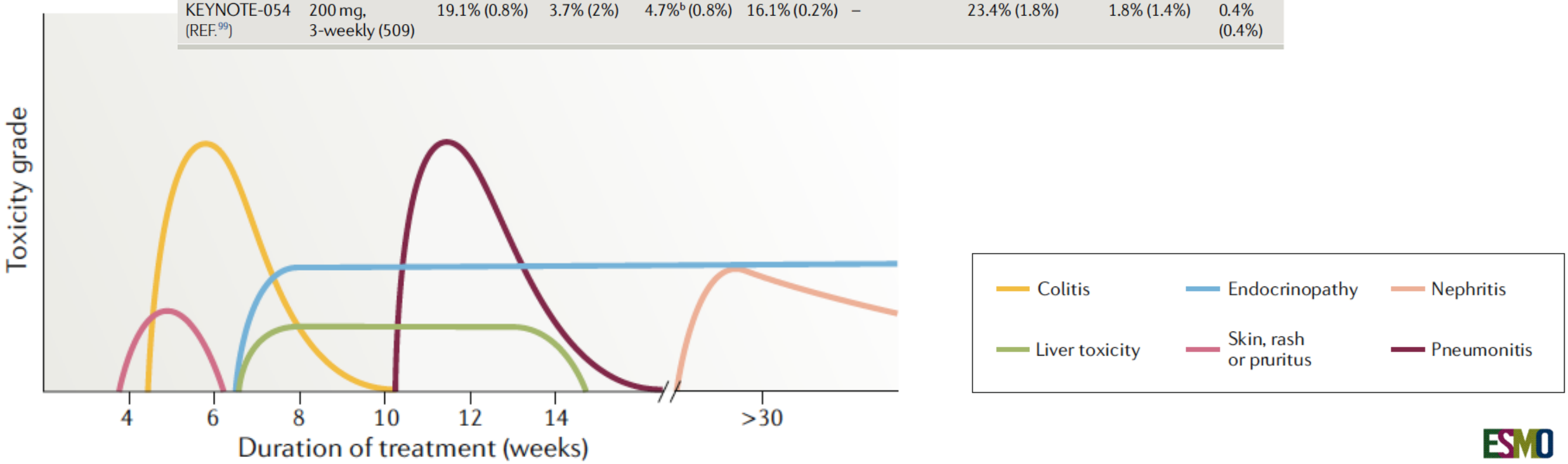


Weber et al J Clin Oncol 2012

Martins et al., Nat Rev Clin Oncol 2019

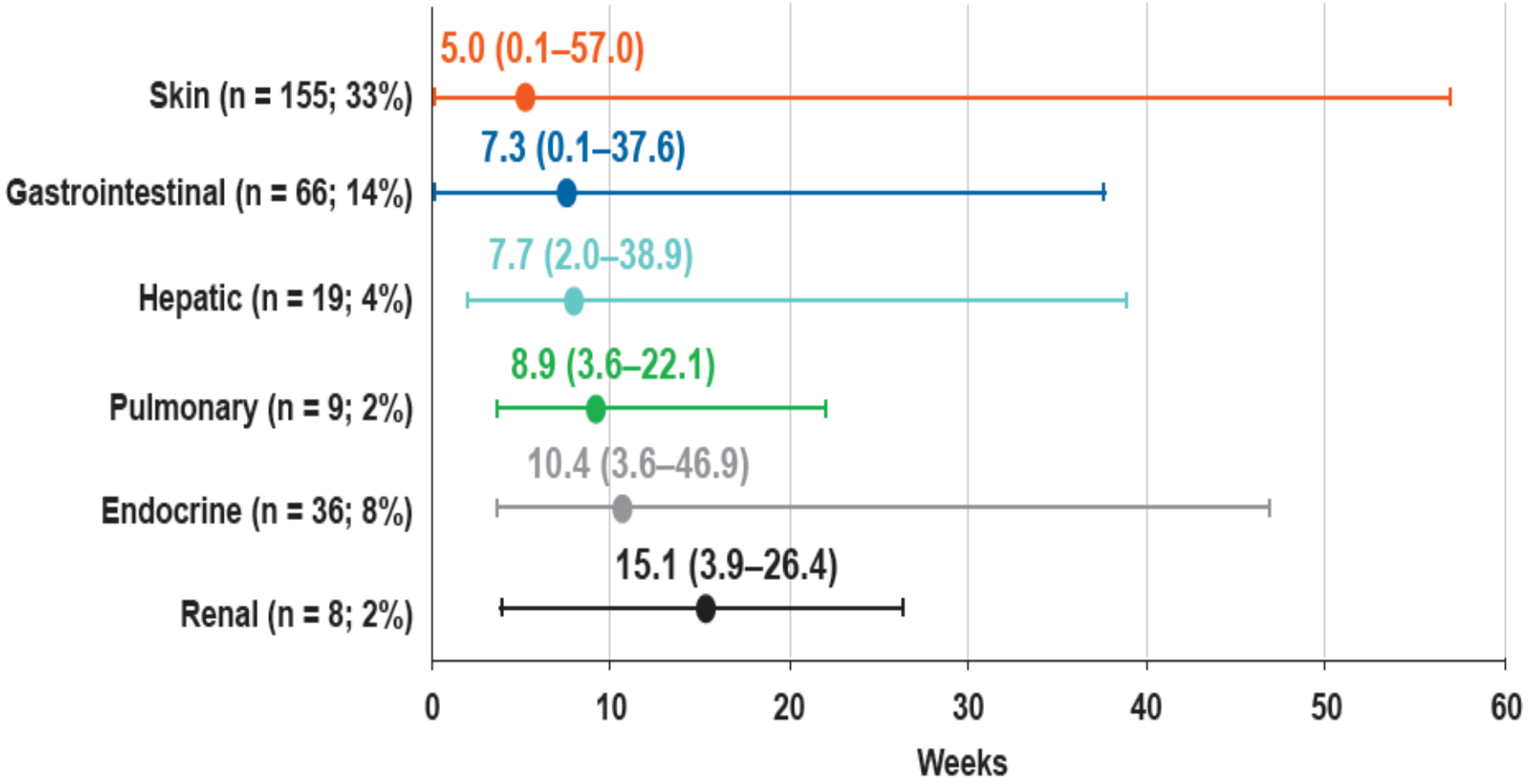
irAE kinetics of anti-PD-(L)1

Study details		Any-grade adverse events (grade ≥3 adverse events)							
Study	**Dose (*n*)**	**Diarrhoea**	**Colitis**	**Pulmonary**	**Rash**	**Neurological**	**Endocrinopathy**	**Hepatic**	**Renal**
Nivolumab									
CheckMate 066 (REF.[21])	3 mg/kg, 2-weekly (206)	16% (1%)	1% (0.5%)	1.5% (0%)	15% (0.5%)	–	7.3% (1%)	3.4% (1.5%)	1.9% (0.5%)
CheckMate 057 (REF.[167])	3 mg/kg, 2-weekly (287)	8% (1%)	1% (0.3%)	4.9% (1.4%)	9% (3.5%)	0.3% (0.3%)[a]	10.5% (0%)	10.8% (1.4%)	2% (0%)
Pembrolizumab									
KEYNOTE-010 (REF.[146])	2 mg/kg, 3-weekly (339)	7% (1%)	1% (1%)	5% (2%)	9% (0.3%)	–	15% (1%)	0.3% (0.3%)	–
KEYNOTE-010 (REF.[146])	10 mg/kg, 3-weekly (343)	6% (0%)	1% (0.3%)	4% (2%)	13% (0.3%)	–	16.5% (2%)	1% (0%)	–
KEYNOTE-054 (REF.[99])	200 mg, 3-weekly (509)	19.1% (0.8%)	3.7% (2%)	4.7%[b] (0.8%)	16.1% (0.2%)	–	23.4% (1.8%)	1.8% (1.4%)	0.4% (0.4%)



Martins et al., Nat Rev Clin Oncol 2019

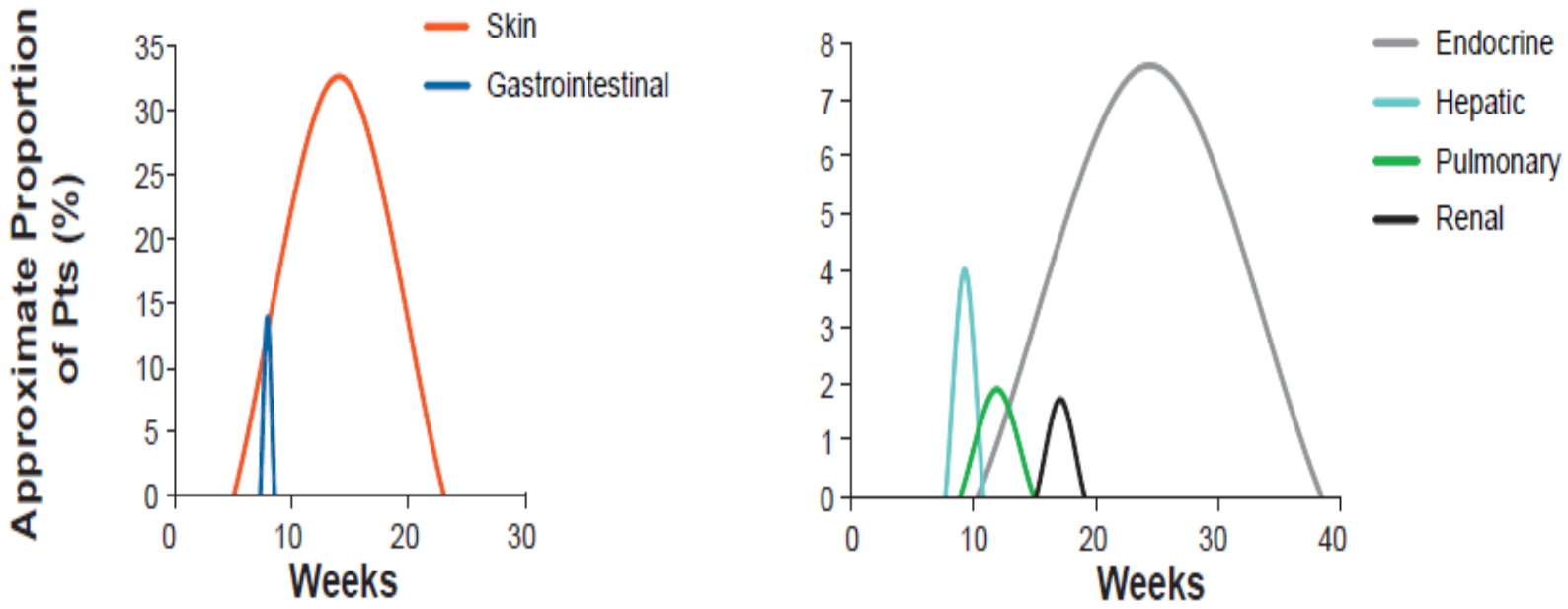
Anti-PD1 Nivolumab Pooled Safety Analysis
Time to Onset of Select Treatment-related AEs (Any Grade; N = 474)



Weber J et al J Clin Oncol 2017

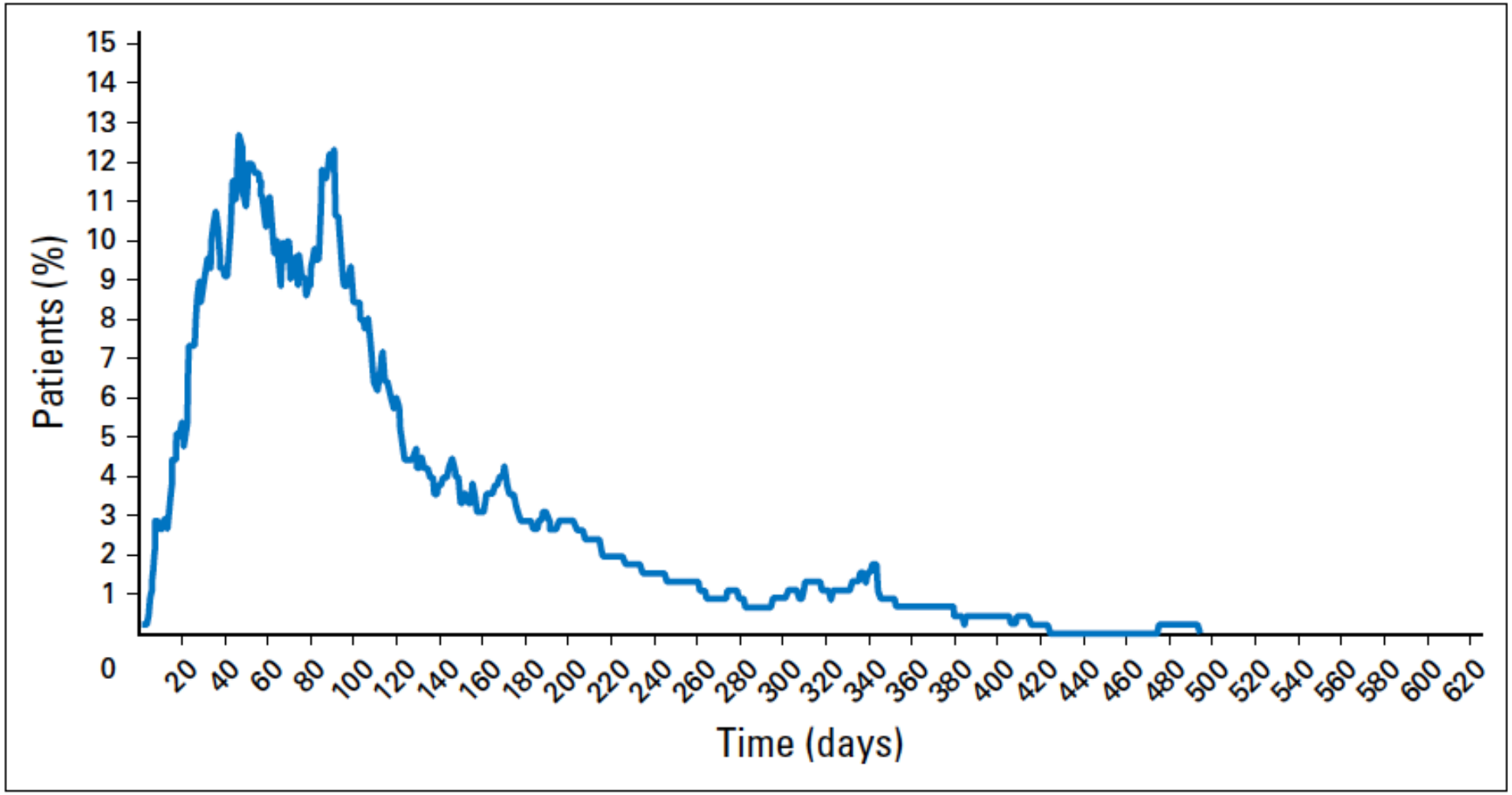
Anti-PD1 Nivolumab Pooled Safety Analysis
Kinetics of Onset and Resolution of Immune-related AEs

Incidence



Weber J et al J Clin Oncol 2017

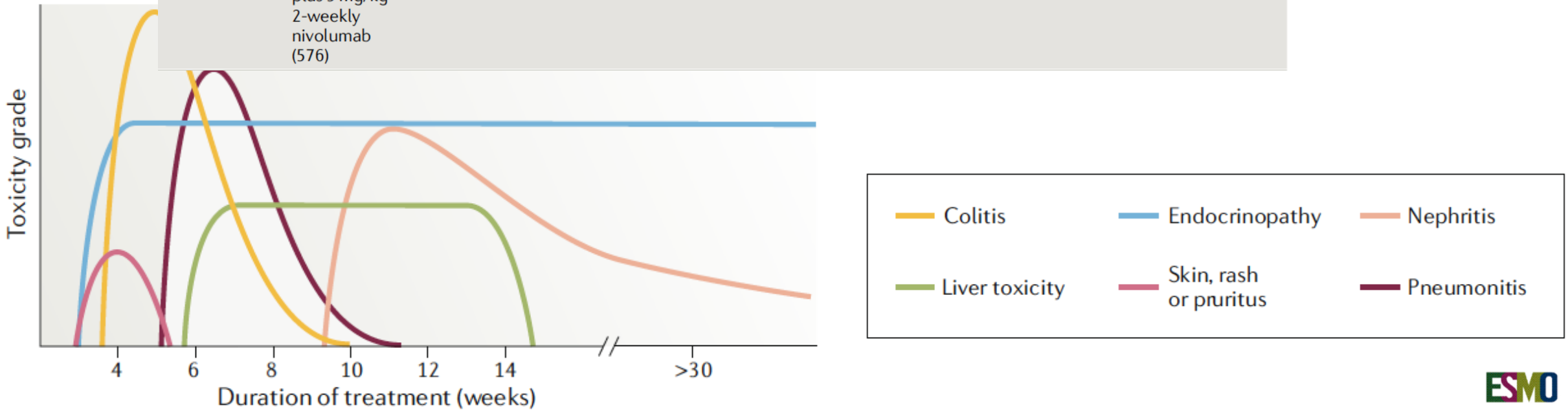
Grade 3-4 irAE over time in CheckMate-067: ipi/nivo and nivolumab vs ipilimumab



Sznol et al. J Clin Oncol 2018

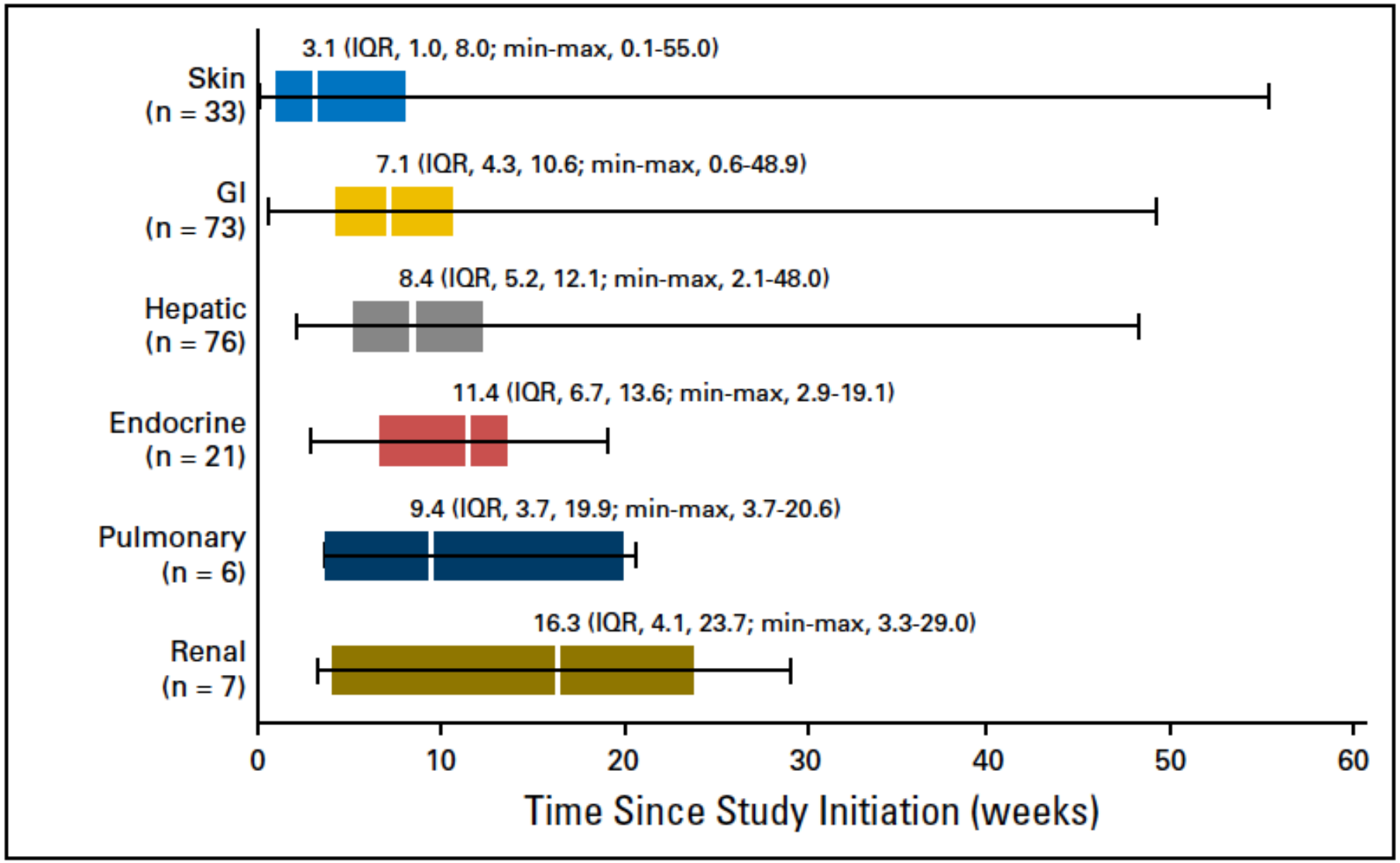
irAE kinetics of anti-CTLA-4 + anti-PD-(L)1

Study details		Any-grade adverse events (grade ≥3 adverse events)							
Study	**Dose (*n*)**	**Diarrhoea**	**Colitis**	**Pulmonary**	**Rash**	**Neurological**	**Endocrinopathy**	**Hepatic**	**Renal**
Ipilimumab plus nivolumab									
CheckMate 067 (REF.[168])	3 mg/kg ipilimumab plus 1 mg/kg nivolumab, 3-weekly (313)	45% (9%)	13% (8%)	7% (1%)	30% (3%)	–	34% (6%)	33% (20%)	7% (2%)
CheckMate 214 (REF.[9])	1 mg/kg ipilimumab plus 3 mg/kg nivolumab, 3-weekly (547)	27% (4%)	–	–	22% (1%)	–	16% (0.4%)[c]	–	–
CheckMate 227 (REF.[13])	1 mg/kg 6-weekly ipilimumab plus 3 mg/kg 2-weekly nivolumab (576)	16.3% (1.6%)	1% (0.5%)	3% (2%)	16.7% (1.6%)	–	12.3% (1%)[c]	3.5% (3%)	–



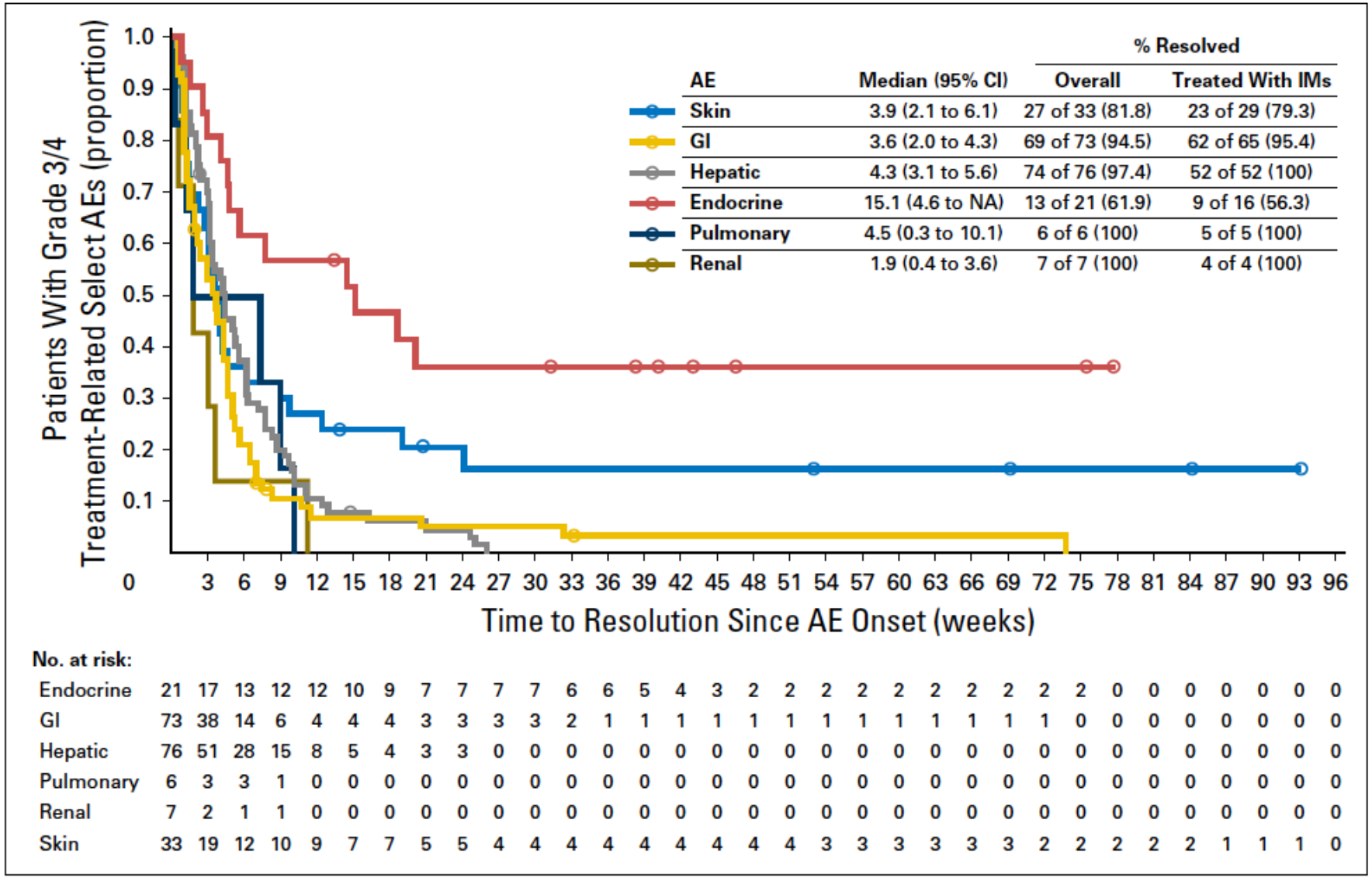
Martins et al., Nat Rev Clin Oncol 2019

Checkmate 067: Safety
Onset Grade 3–4 Treatment-Related Select AEs



Sznol et al. J Clin Oncol 2018

Time to resolution of AEs



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

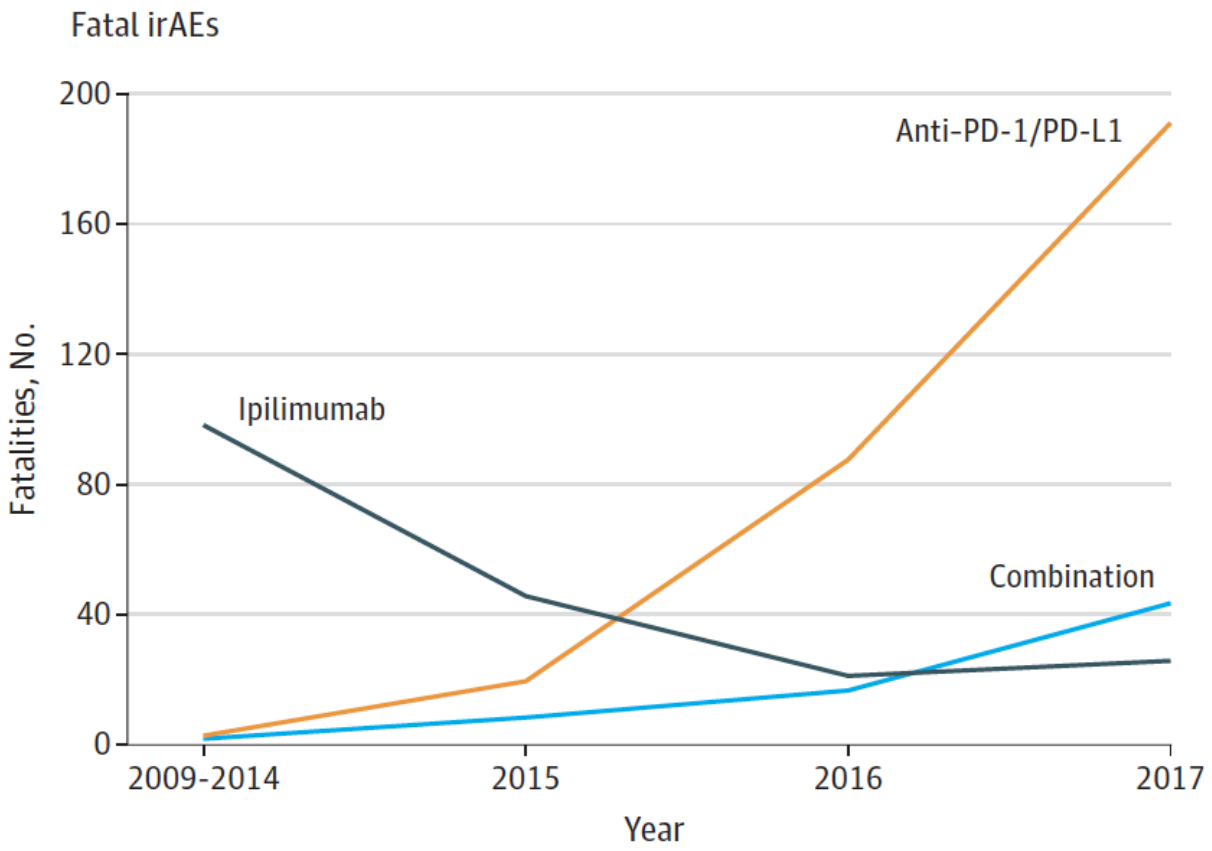
Sznol et al. J Clin Oncol 2018

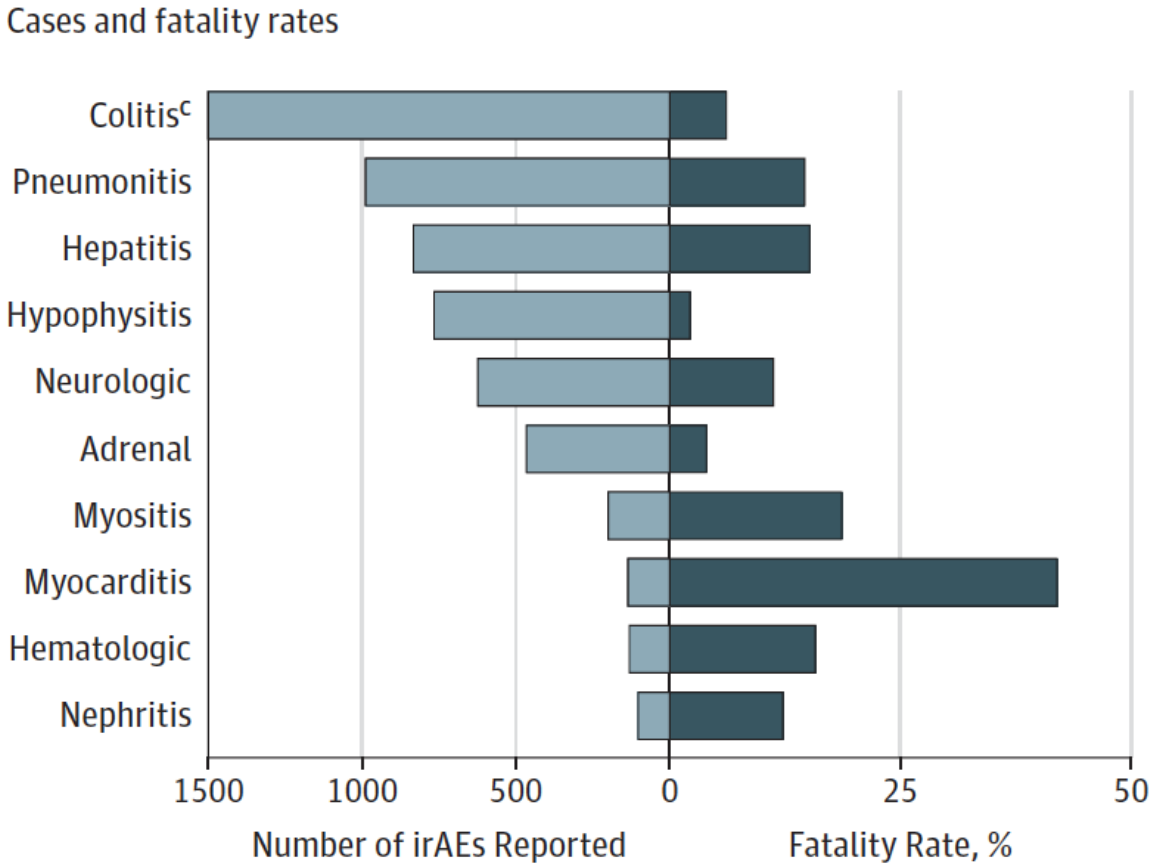
Spectrum of fatal immune related adverse events in Vigilyze (large database)

Variable	No. (%) Ipilimumab (n = 193)	Anti-PD-1/PD-L1 (n = 333)	Combination (n = 87)	*P* Value
Types of cancer[a]				<.001
Melanoma	136 (96)	50 (18)	49 (66)	
Lung cancer	0	152 (54)	17 (23)	
Other	5 (4)	78 (28)	8 (11)	
Type of fatal irAE				
Colitis	135 (70)	58 (17)	32 (37)	<.001
Pneumonitis	15 (8)	115 (35)	12 (14)	<.001
Hepatitis	31 (16)	74 (22)	19 (22)	.23
Hypophysitis	10 (5)	3 (1)	2 (2)	.01
Cardiac	3 (2)	27 (8)	22 (25)	<.001
Myositis	1 (0.5)	22 (7)	11 (13)	<.001
Nephritis	1 (0.5)	7 (2)	3 (4)	.19
Adrenal	8 (4)	6 (2)	3 (4)	.26
Neurologic	11 (6)	50 (15)	7 (8)	.003
Hematologic	3 (2)	14 (4)	2 (2)	.22
Other (skin, thyroid, diabetes, other gastrointestinal)	13 (7)	24 (8)	7 (8)	.93
Other clinical features				
Median time to irAE, days	40	40	14	.01
>1 concurrent irAE, %	27 (14)	51 (15)	24 (28)	.01
Reporting year				
2014 or before	98 (51)	3 (1)	2 (2)	<.001
2015	45 (23)	20 (6)	9 (10)	<.001
2016	21 (11)	88 (28)	17 (20)	.001
2017	26 (13)	192 (58)	44 (51)	<.001
2018 (up to January 15)	3 (2)	30 (9)	15 (17)	<.001

Wang et al., JAMA Oncol 2018

Incidence of fatal irAE and fatality rates





Fatal irAE occur following ICI at a rate of 0.3 to 1.3%

Wang et al., JAMA Oncol 2018

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017
doi:10.1093/annonc/mdx225

CLINICAL PRACTICE GUIDELINES

POSITION ARTICLE AND GUIDELINES Open Access

CrossMark

Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy:

New NCCN Guidelines: Recognition and Management of Immunotherapy-Related Toxicity

ESMO

Presented by John A. Thompson, MD

Management of Immunotherapy-Related Toxicities, Version 1.2019

MANAGEMENT OF IMMUNE CHECKPOINT INHIBITOR TOXICITIES: A REVIEW AND CLINICAL GUIDELINE FOR EMERGENCY PHYSICIANS

EXPERT CONSENSUS DOCUMENT

Management guidelines for paediatric patients receiving chimeric antigen receptor T cell therapy

Kris M. Mahadeo[1,20], Sajad J. Khazal[1], Hisham Abdel-Azim[2], Julie C. Fitzgerald[3,20], Agne Taraseviciute[4], Catherine M. Bollard[5], Priti Tewari[6], Christine Duncan[7,20], Chani Traube[8,20], David McCall[1], Marie E. Steiner[9,20], Ira M. Cheifetz[10,20],*

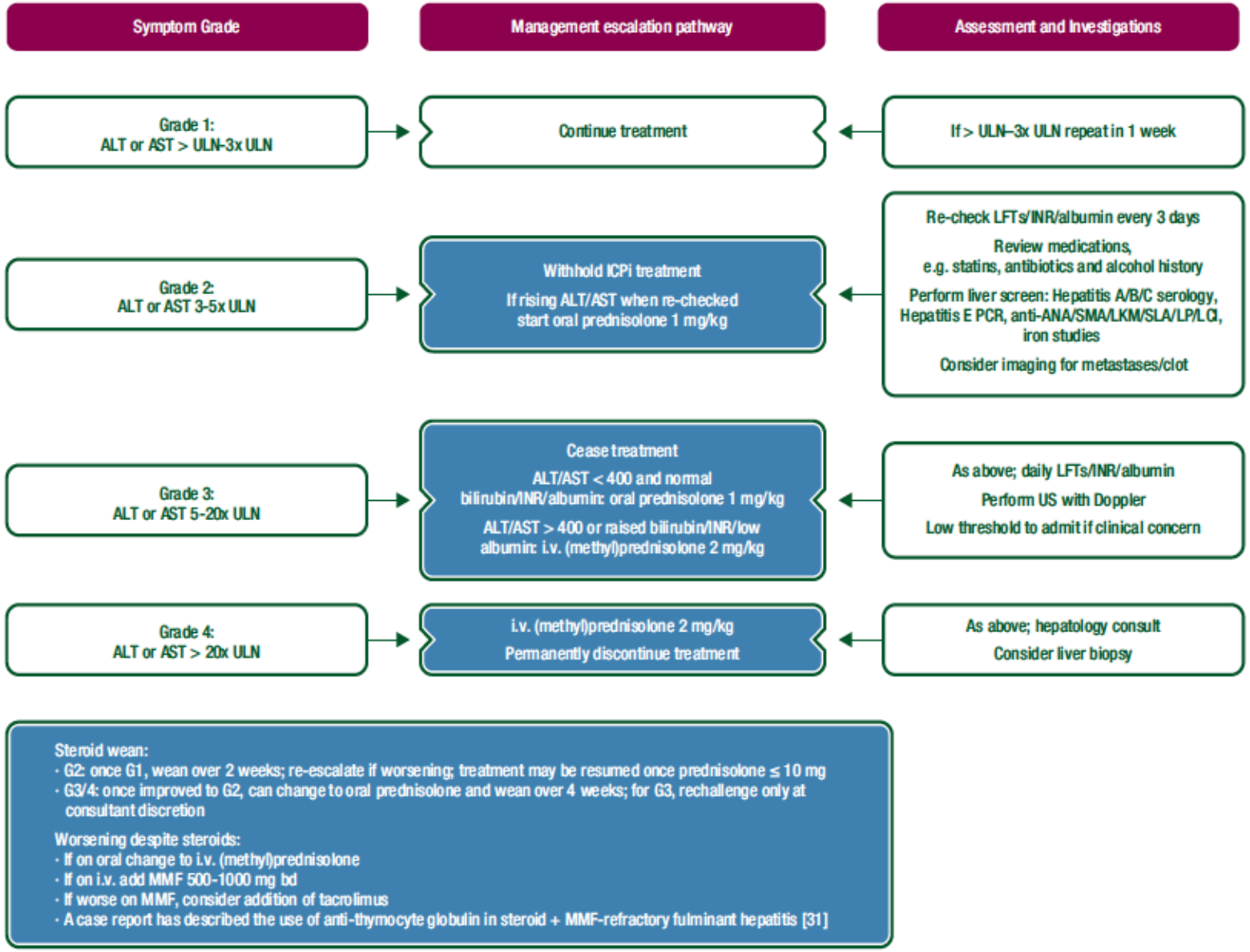
ESMO

Management of Immune-related Adverse Events

- Patient Education
- Clear Notification Pathway for Patients
- Infrastructure and Sub-specialty Consultants

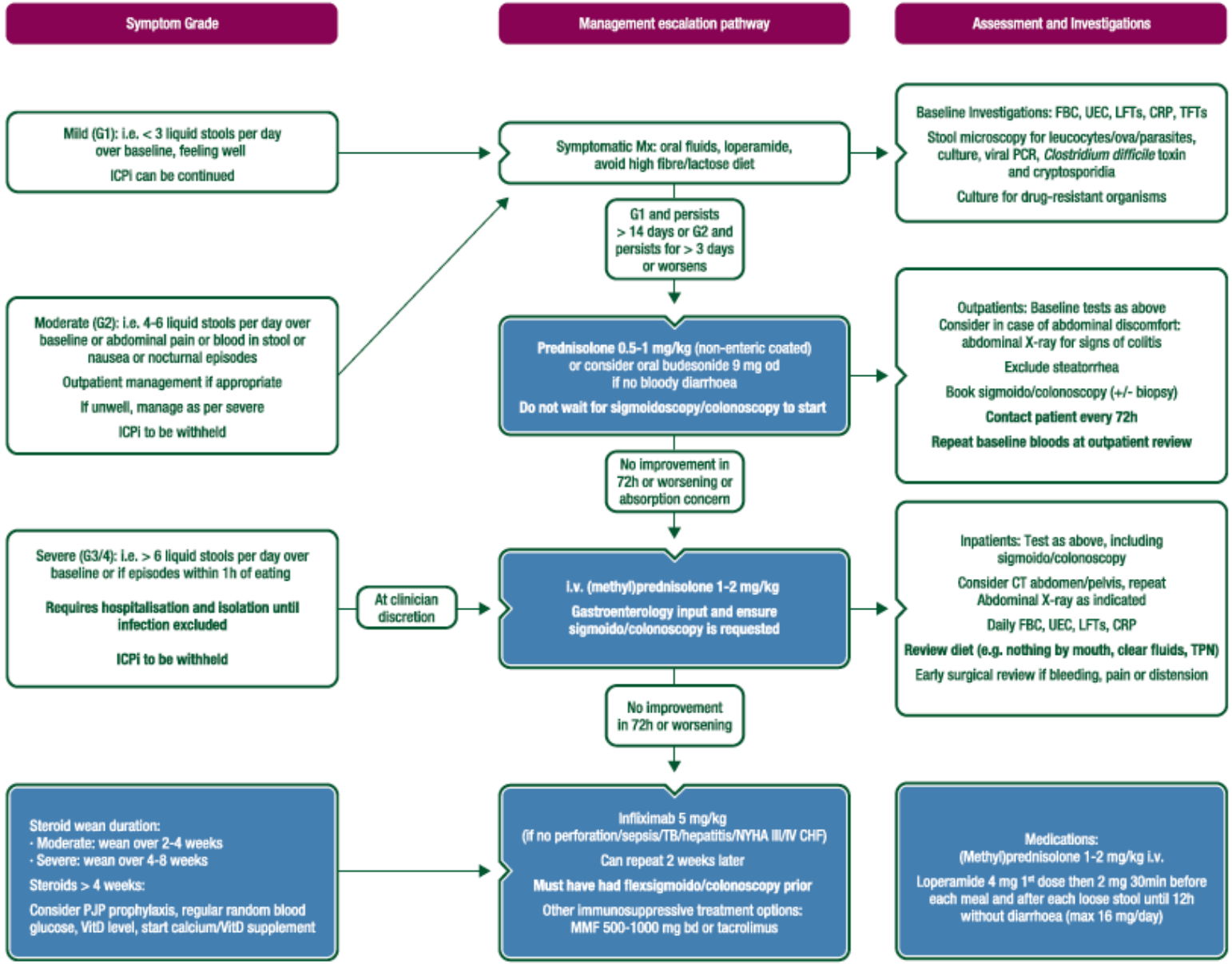
1. Identify Toxicity Early
2. Treat Early and Aggressively → Algorithms
   - **Start with corticosteroids**
3. Oncologist-led Management

Algorithm for hepatitis



Haanen et al., Ann Oncol 2017

Algorithm diarrhea and colitis



Haanen et al., Ann Oncol 2017

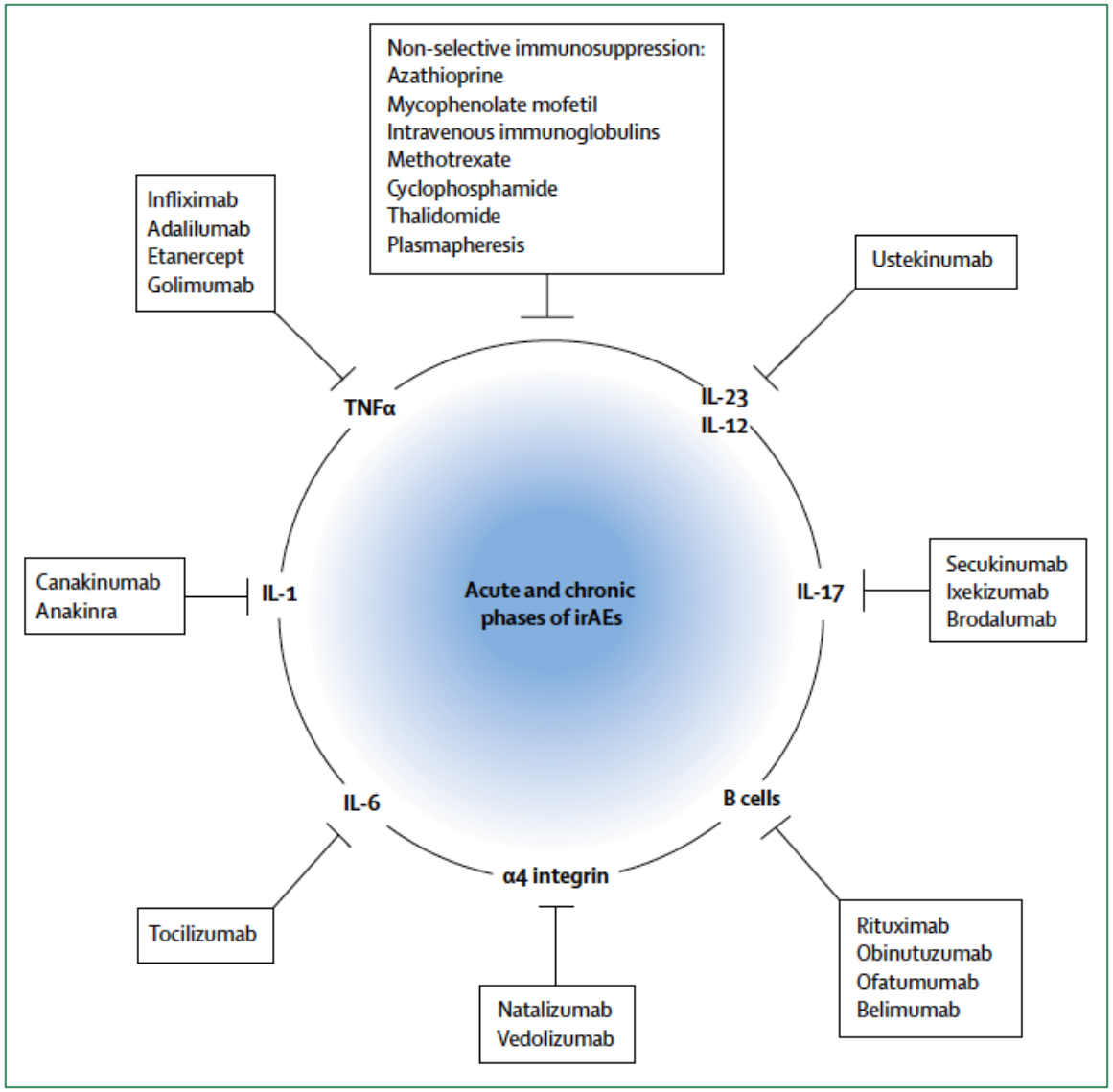
General Principles

- Low Grade
  - Monitor closely (grade 1 and 2)
  - Delay therapy (grade 2)

Moderate Grade ?

- High Grade → Immunosuppression
  - **Cease checkpoint inhibitor, consult sub-specialty and consider hospitalisation**
  - Systemic corticosteroids
  - Infliximab (anti-TNFa)
  - Mycophenolate mofetil
  - Tacrolimus
  - Other → plasmapheresis, anti-thymocyte globulin, IVIG

New therapeutics to manage refractory immune related adverse events



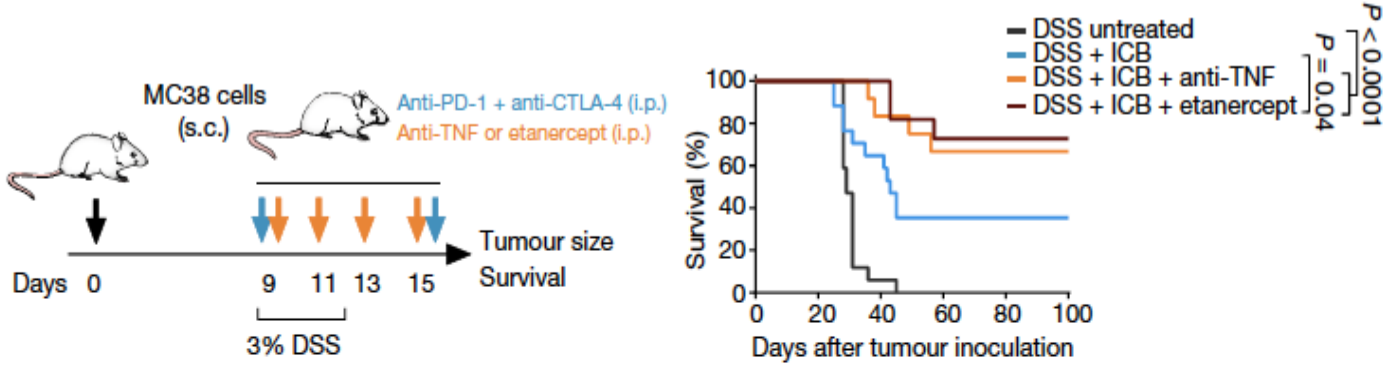
Martins et al., Lancet Oncol 2019

LETTER

https://doi.org/10.1038/s41586-019-1162-y

Prophylactic TNF blockade uncouples efficacy and toxicity in dual CTLA-4 and PD-1 immunotherapy

Elisabeth Perez-Ruiz[1,2,3,4,5], Luna Minute[1,2], Itziar Otano[1,2], Maite Alvarez[1,2], Maria Carmen Ochoa[1,2,6], Virginia Belsue[1,2], Carlos de Andrea[2,7], Maria Esperanza Rodriguez-Ruiz[1,3], Jose Luis Perez-Gracia[2,3,6], Ivan Marquez-Rodas[6,8], Casilda Llacer[9], Martina Alvarez[5,10,11], Vanesa de Luque[5,10], Carmen Molina[1,2], Alvaro Teijeira[1,2,6], Pedro Berraondo[1,2,6,13]* & Ignacio Melero[1,2,3,6,12,13]*



Perez-Ruiz et al., Nature 2019

Important Practical Questions

- Do immune-modulators used to treat toxicity affect efficacy?
- Does toxicity with Anti-CTLA4 predict toxicity with Anti-PD1 and vice versa?
- Can people with auto-immune disease be given checkpoint inhibitors?
- Can patients with organ transplants be treated with checkpoint inhibitors?

Safety Summary from Checkmate-067

	NIVO+IPI (n = 313)		NIVO (n = 313)		IPI (n = 311)	
Patients reporting event	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related AE, %	95.8	59.1	86.3	22.4	86.2	27.7
Treatment-related AE leading to discontinuation, %	40.3	30.4	12.5	8.0	15.1	13.5
Treatment-related death, n (%)	2 (0.6)		1 (0.3)		1 (0.3)	

- 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
  - Previously reported treatment-related deaths were cardiomyopathy and liver necrosis for NIVO+IPI (n = 1 each and both occurred >100 days after last treatment), neutropenia for NIVO (n = 1), and colonic perforation for IPI (n = 1)
- Patients who discontinued NIVO+IPI during induction due to a treatment-related AE had similar 4-year PFS (35%) and OS (54%) to patients in the overall population (37% and 53%, respectively)

Pooled Nivolumab Safety Study in Melanoma (N= 576)[1]

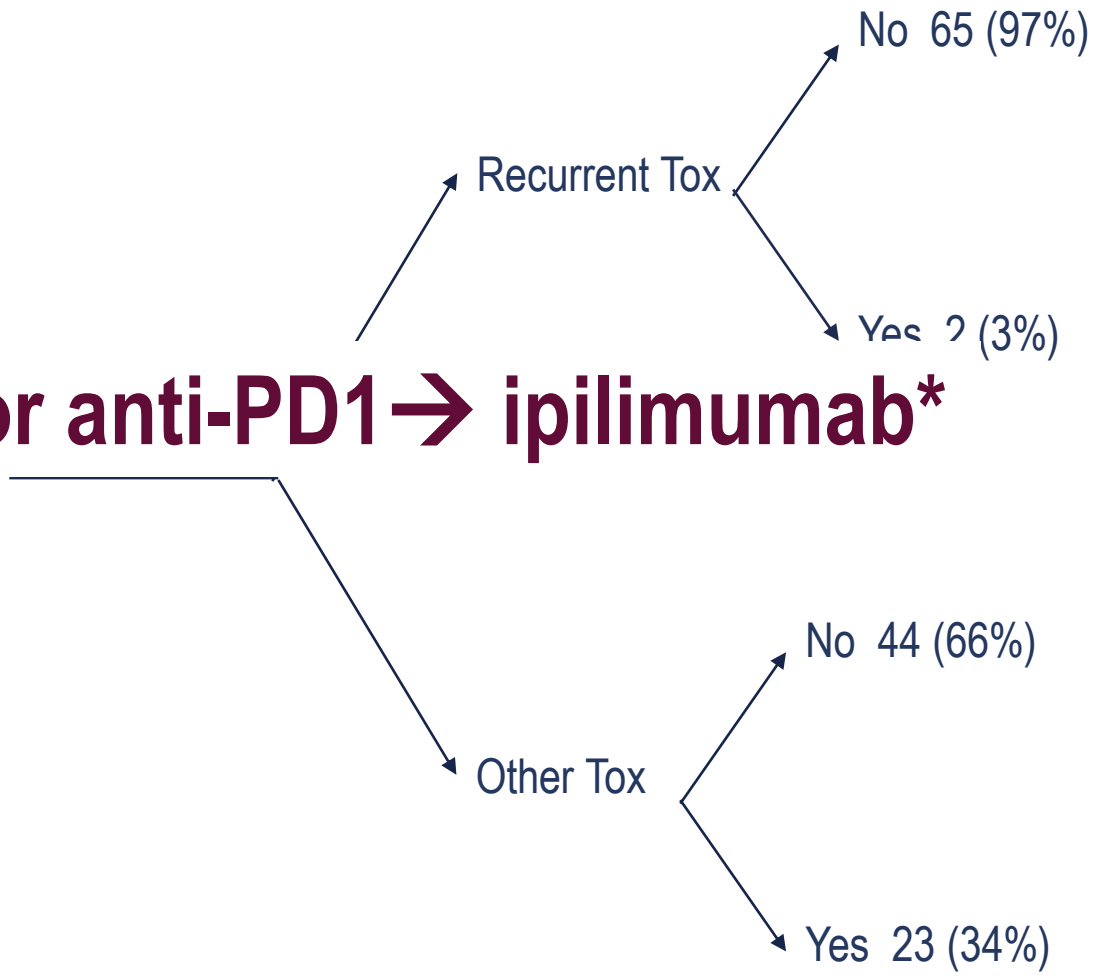
Needs investigation

	All Patients N=576	Any Select AE N=409	Grade 3/4 Select AE N=18*
ORR	31.4%	48.6%	27.8%
Med. Duration Response			

*57 patients of 576 (10%) experienced any Grade 3/4 Adverse event

67 Patients with immune toxicity due to ipilimumab

colitis	47 (70%)
endocrine	13 (19%)
dermatol	
rheumat	
hepatitis	3 (4%)
neurologic	2 (3%)
ocular	2 (3%)
hematologic	1 (1%)

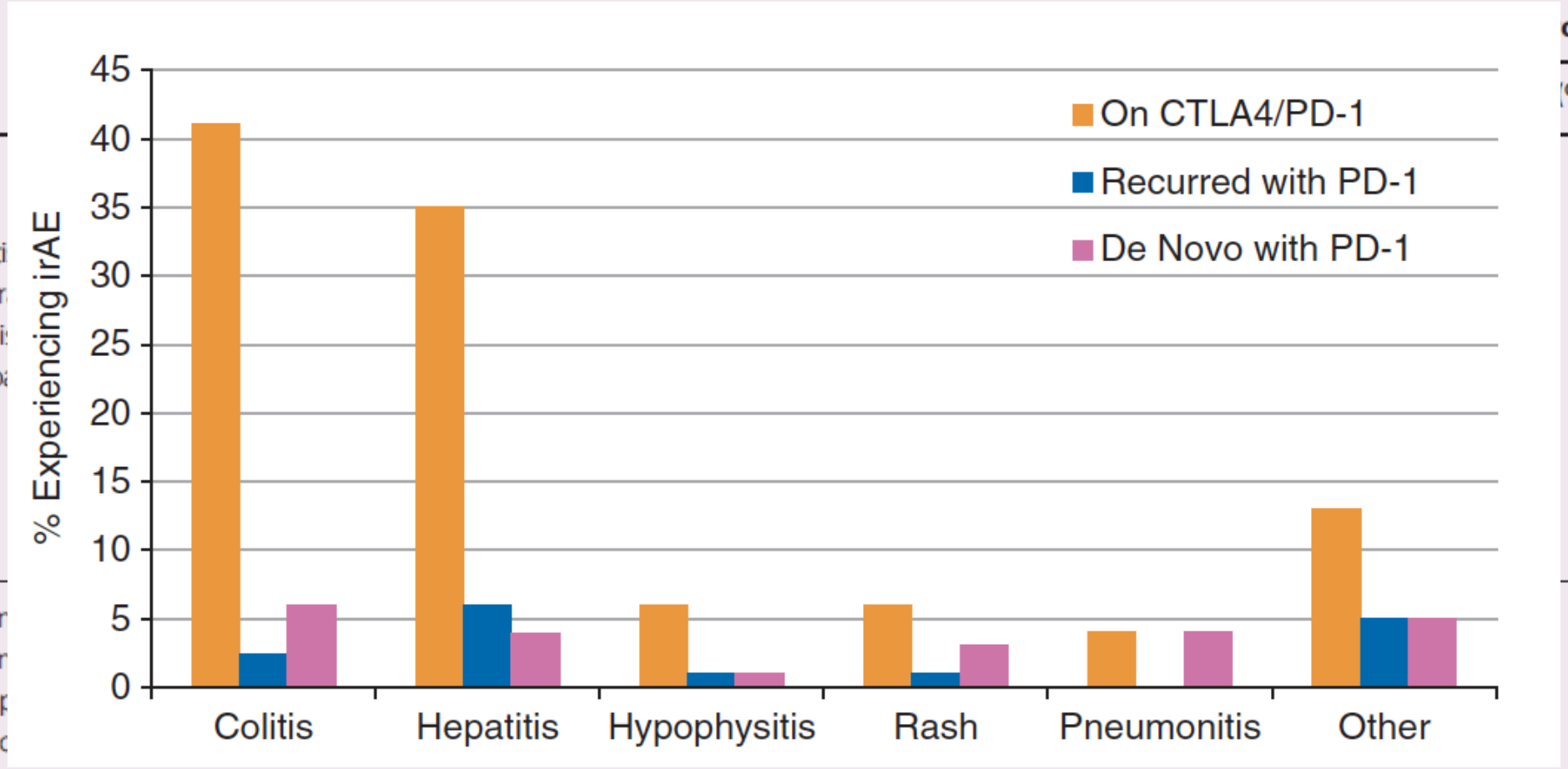


And same for anti-PD1→ ipilimumab*

Menzies A et al., Ann Oncol 2016; * Bowyer et al BJC 2016

Courtesy of G Long

Clinically significant toxicities with combination IT and anti-PD-1 resumption



Pollack et al., Ann Oncol 2018

Management of toxicities from immune checkpoint blockade

Take home messages

Risk assessment (AID, organ transpant etc)
Every organ can be involved
Severity can vary from grade 1 – 5
Requires immediate action
Hold further treatment (depending on severity)
Consult organ specialist if necessary
Start immunosuppression (depending on severity)
Careful follow-up warranted
Taper immunosuppression

As a (medical) oncologist: be in the lead!

Thank you for your attention

Questions?

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK