ImmunoScience Academy

Partnering for Education & Optimizing Treatment in ImmunoScience

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Workshop B1

Managing patients with underlying autoimmune diseases

Convention room 2, Floor 1

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Mercury number : ONCBE1908737-04
Date of preparation: December 2019

Learning objectives

- Pathophysiology underlying the development of irAEs under immune checkpoint inhibition
- Risk assessment of developing severe irAEs in patients with pre-existing auto-immune disease
- Potential clinical or biological biomarkers that could predict the risk of developing irAEs

irAEs, immune-related adverse events.

Contents

- Interactive case report
- Mechanisms of the development of irAEs under immune checkpoint inhibition
- Epidemiology and outcomes of patients with underlying autoimmune diseases treated with immune checkpoint inhibitors
- What is the tolerability profile associated with starting ICI in patients with cancer and pre-existing auto-immune disease?
- Management of irAEs in patients treated with immune checkpoint inhibitors
- Towards predictive biomarkers for toxicity under immune checkpoint inhibition
- Key take home messages
- Interactive case report revisited

Interactive case report

Patient case: 67 year old

- Patient history:
  - Elevated blood pressure
  - ACPA-rheumatoid arthritis for > 15 years; in clinical remission
- Current medication:
  - Bisoprolol (2.5 mg/day)
  - Methotrexate (10 mg/week)
  - Infliximab (200 mg/12 weeks)

ACPA, Anti-citrullinated protein antibodies.

Patient case: 67 year old

2014 — Cystoprostatectomy and Bricker ureterosigmoidostomy due to high grade urothelial carcinoma

2015 — Adjuvant chemotherapy; cisplatin – gemcitabine

2017 — Locoregional relapse, infiltration of colic mucosa + lymph nodes + hepatic metastases; R/carboplatin – gemcitabine

2019 — Progression of hepatic metastases → start pembrolizumab 3 weeks*

Patient case: 67 year old (*continued*)

March 2019 — Skin rash – lichen planus R/local corticosteroids

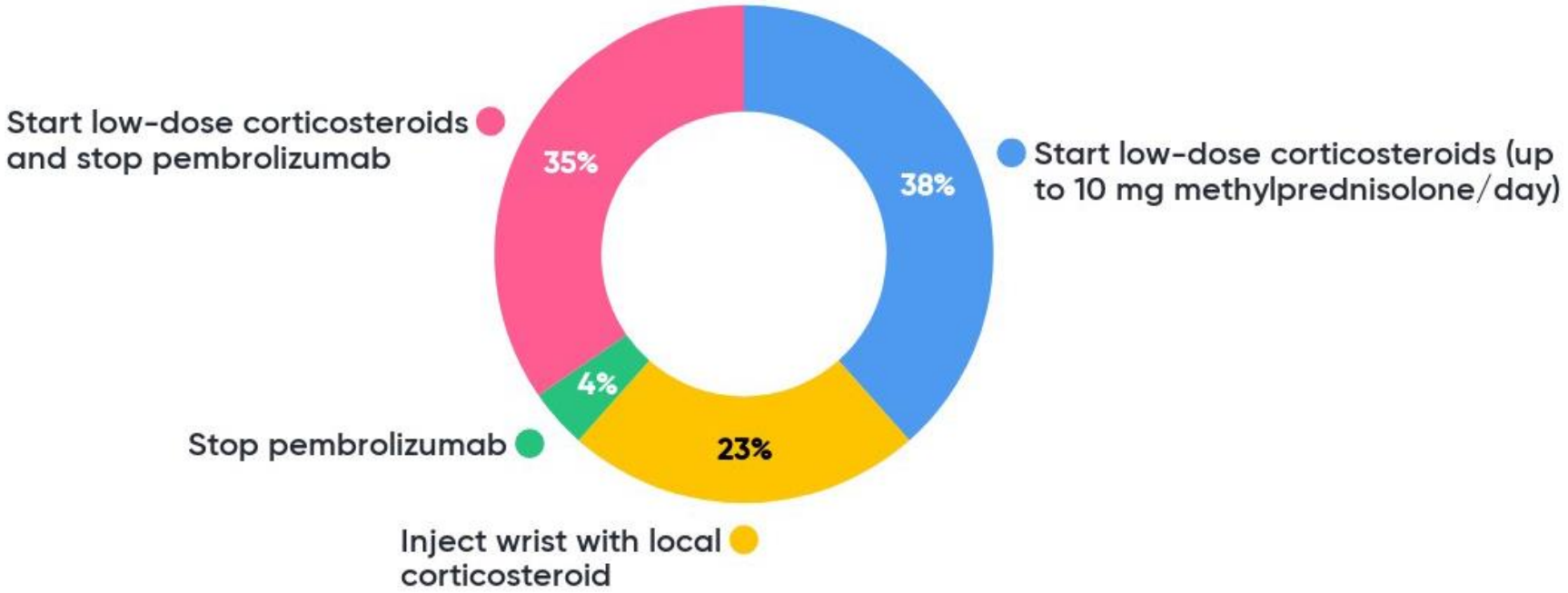
May 2019 — Arthritis of the right wrist

How would you manage this patient now?

How would you manage this patient now?

1. Start low-dose corticosteroids (up to 10 mg methylprednisolone/day)
2. Inject wrist with local corticosteroid
3. Stop pembrolizumab
4. Start low-dose corticosteroids and stop pembrolizumab
5. Resume infliximab therapy

How would you manage this patient now?



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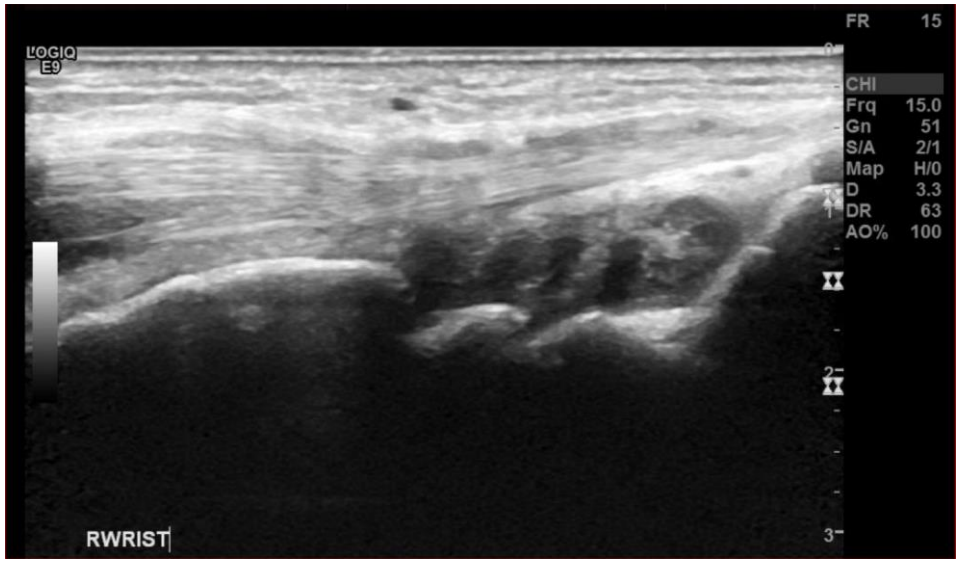
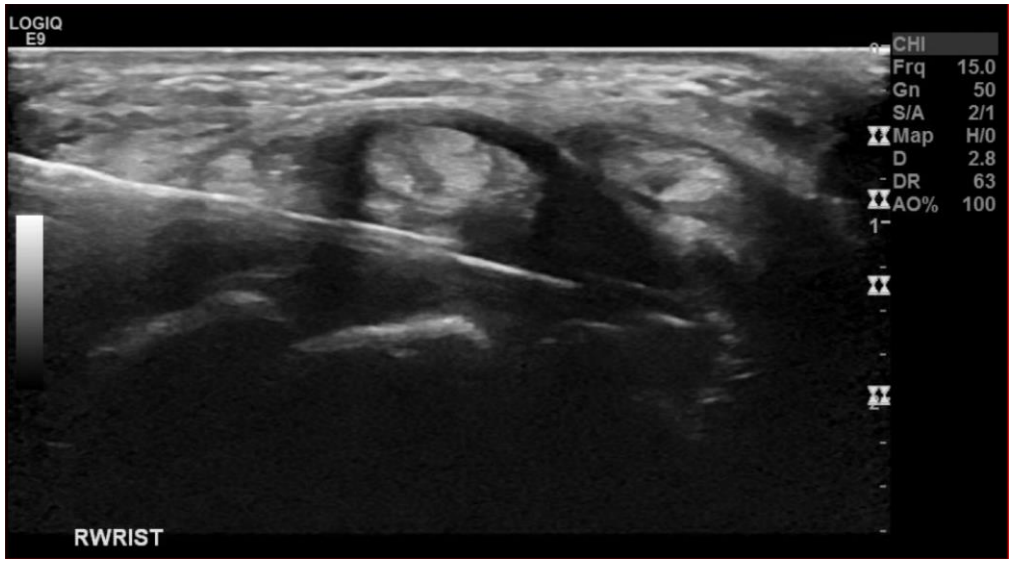
Patient case: 67 year old (*continued*)

- Synovial biopsy by L. Méric de Bellefon (PISCO study)
- Local injection with corticosteroids
- Pembrolizumab continued*





Patient case: 67 year old (*continued*)

March 2019 — Skin rash – lichen planus R/local corticosteroids

May 2019 — Arthritis of the right wrist

August 2019 — Severe arthritis both wrists, MCPs, IPPs, knees, ankles

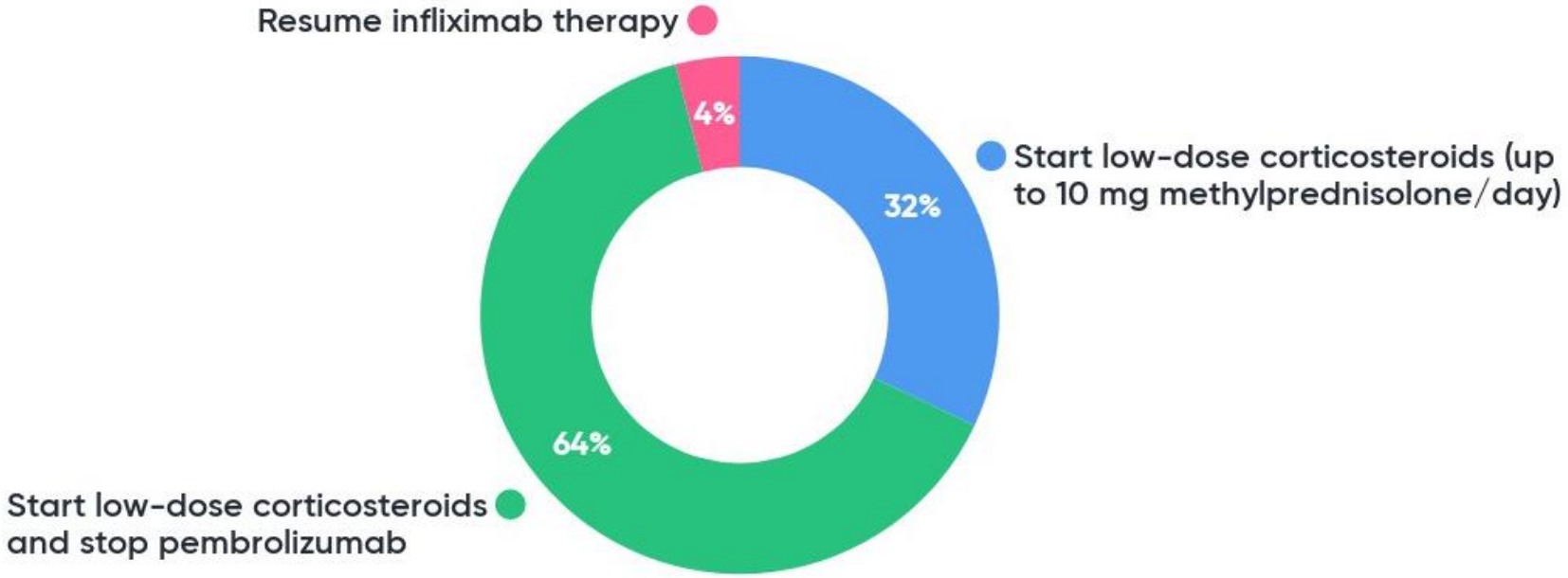
How would you manage this patient now?

IPP, Ile-Pro-Pro; MCP, monocyte chemoattractant proteins.

How would you manage this patient now?

1. Start low-dose corticosteroids (up to 10 mg methylprednisolone/day)
2. Stop pembrolizumab, but do not use corticosteroids
3. Start low-dose corticosteroids and stop pembrolizumab
4. Resume infliximab therapy

How would you manage this patient now?



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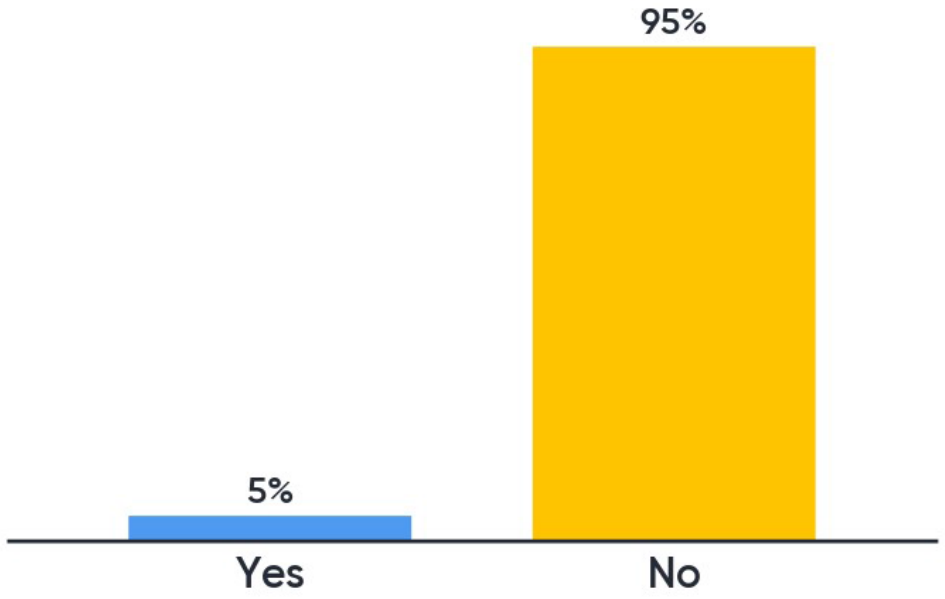
What is your opinion?

The use of corticosteroids (up to 10 mg methylprednisolone/day) will negatively impact the anti-tumoural effect of pembrolizumab

1. Yes
2. No

What is your opinion?

The use of corticosteroids (up to 10 mg methylprednisolone/day) will negatively impact the anti-tumoural effect of pembrolizumab



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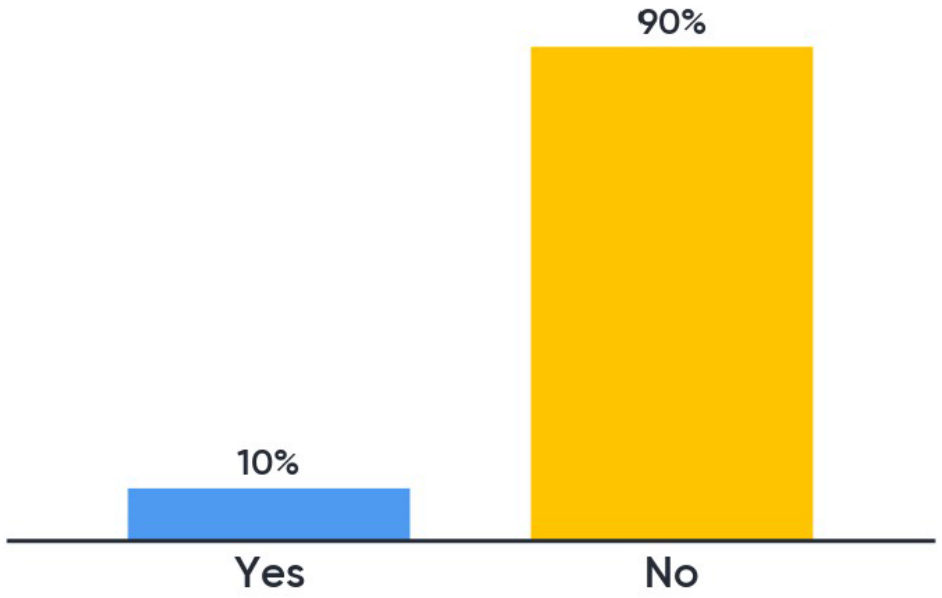
What is your opinion?

(Short-term) therapy using TNF-blocking agents is formally contraindicated in this situation, should low-dose corticosteroids be inefficient

1. Yes
2. No

What is your opinion?

(Short-term) therapy using TNF-blocking agents is formally contraindicated in this situation, should low-dose corticosteroids be inefficient



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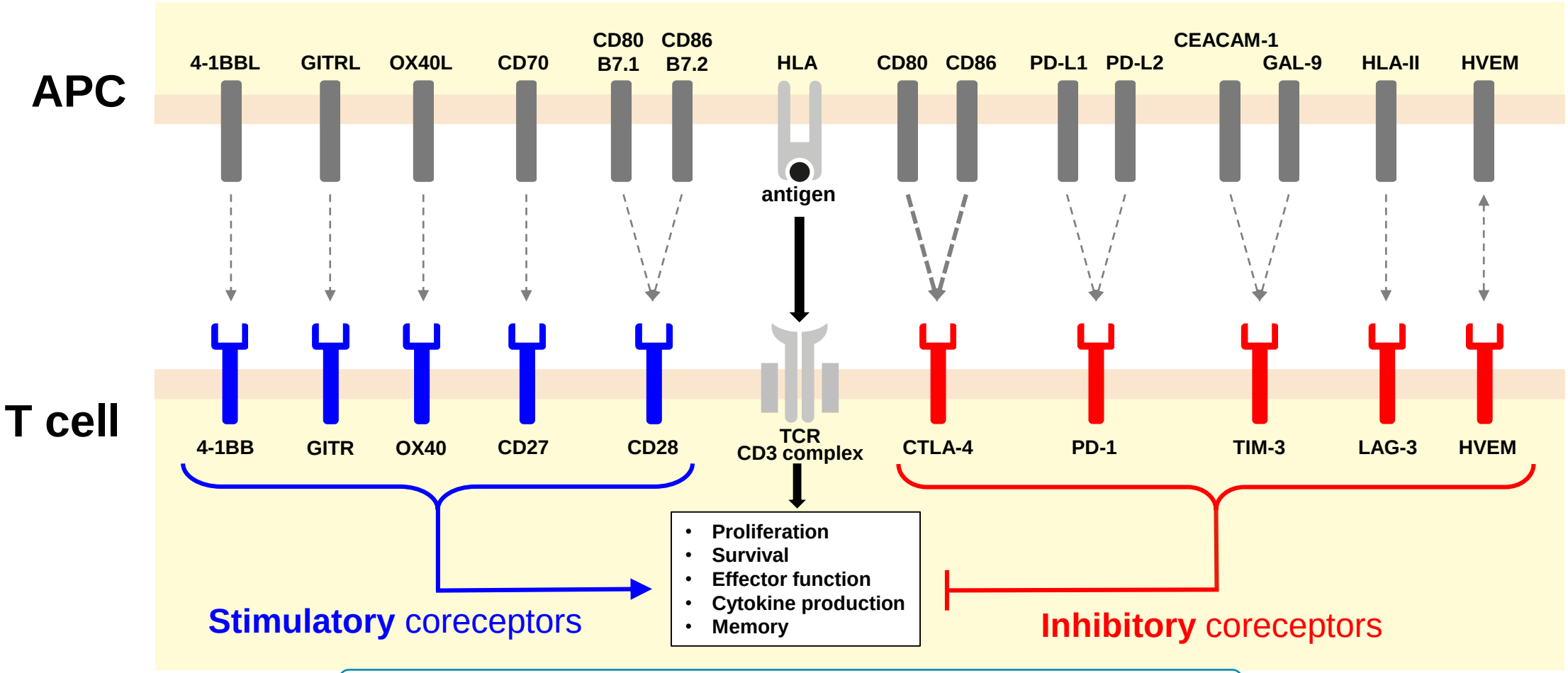
Mechanisms of the development of irAEs under immune checkpoint inhibition

T-cell regulation: stimulatory and inhibitory co-receptors



Function: fine-tuning of T-cell activation in time and space

APC, antigen-presenting cell; HLA, human leukocyte antigen; TCR, T-cell receptor.
Adapted from Kershaw et al. Nat Rev Cancer 2013;13:525–41. doi:10.1038/nrc3565 2. Dustin. Cancer Immunol Res 2014;11:1023–33. 3. Le Mercier et al. Front Immunol 2015; 6:1-15.

Anti-CTLA4 and anti-PD1/PDL1 antibodies and their targets

Immunotherapy type	Name of molecule	Target
CTLA-4 inhibitor	Ipilimumab[1]	CTLA-4
PD-1 inhibitor	Pembrolizumab[2] Nivolumab[3]	PD-1
PD-L1 inhibitor	Atezolizumab[4] Durvalumab[5] Avelumab[6]	PD-L1

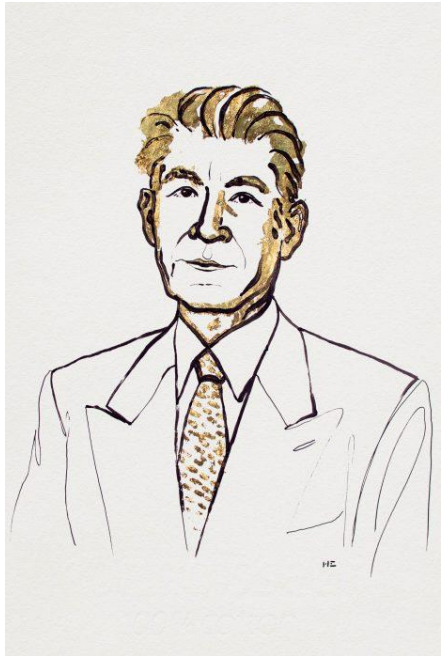
1. Yervoy. European Summary of Product Characteristics. 2019; 2. Keytruda®. European Summary of Product Characteristics. 2019; 3. Opdivo. European Summary of Product Characteristics. 2019;
4. Tecentriq. European Summary of Product Characteristics. 2019; 5. Imfinzi, European Summary of Product Characteristics; 6. Bavencio. European Summary of Product Characteristics. 2019.

Checkpoint inhibitors: a major paradigm shift in medicine

CTLA-4

Jim Allison

PD-1



Tasuku Honjo

2018 Nobel Prizes for Medicine and Physiology for the discovery of two key molecules restraining T-cell responses

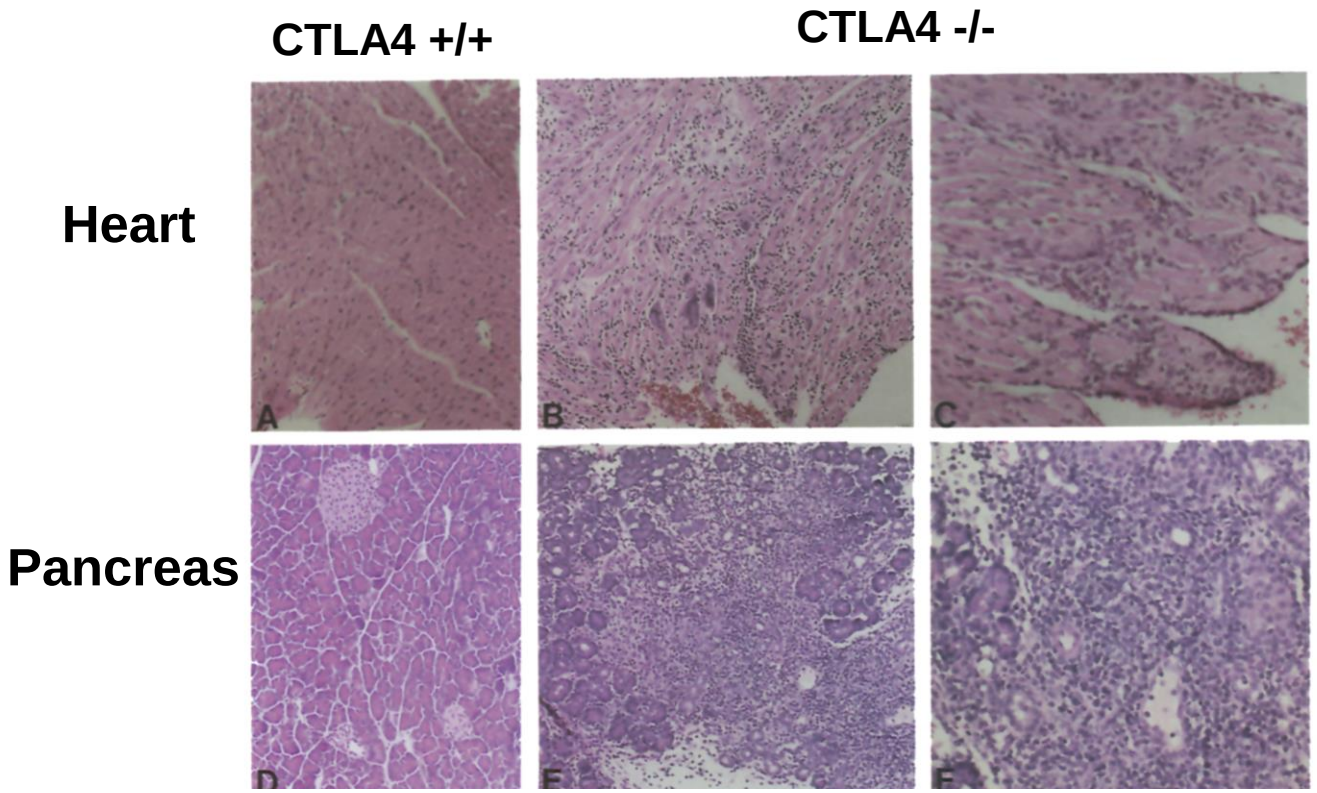
Press release: The Nobel Prize in Physiology or Medicine 2018. Available at: https://www.nobelprize.org/prizes/medicine/2018/press-release/ [Accessed December 2019].

Autoimmune toxicity under checkpoint blockade is no surprise

Immunity, Vol. 3, 541–547, November, 1995, Copyright © 1995 by Cell Press

Loss of CTLA-4 Leads to Massive Lymphoproliferation and Fatal Multiorgan Tissue Destruction, Revealing a Critical Negative Regulatory Role of CTLA-4

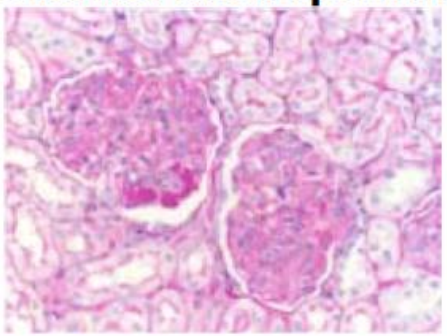
Elizabeth A. Tivol,* Frank Borriello,*
A. Nicola Schweitzer*, William P. Lynch,*
Jeffrey A. Bluestone,† and Arlene H. Sharpe*



Autoimmune toxicity under checkpoint blockade is no surprise

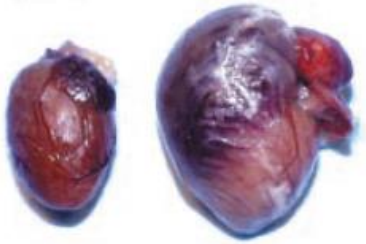
PD1 gene-deficiency results in an auto-immune phenotype

Glomerulonephritis

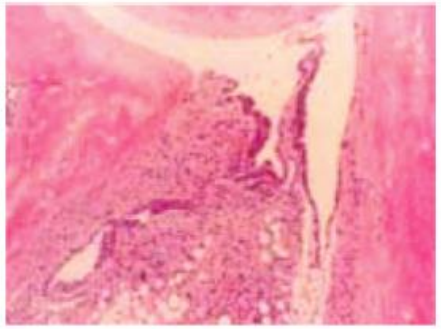


Cardiomyopathy

$PD\text{-}1^{+/+}$ $PD\text{-}1^{-/-}$

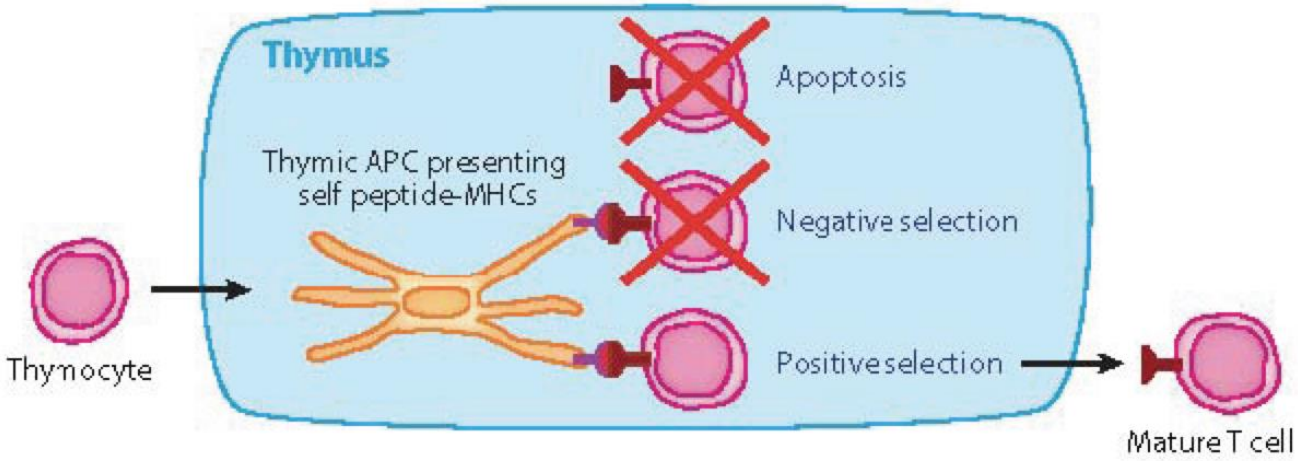


Arthritis



Nishimura H, et al. *Immunity* 1999;11:141–51.

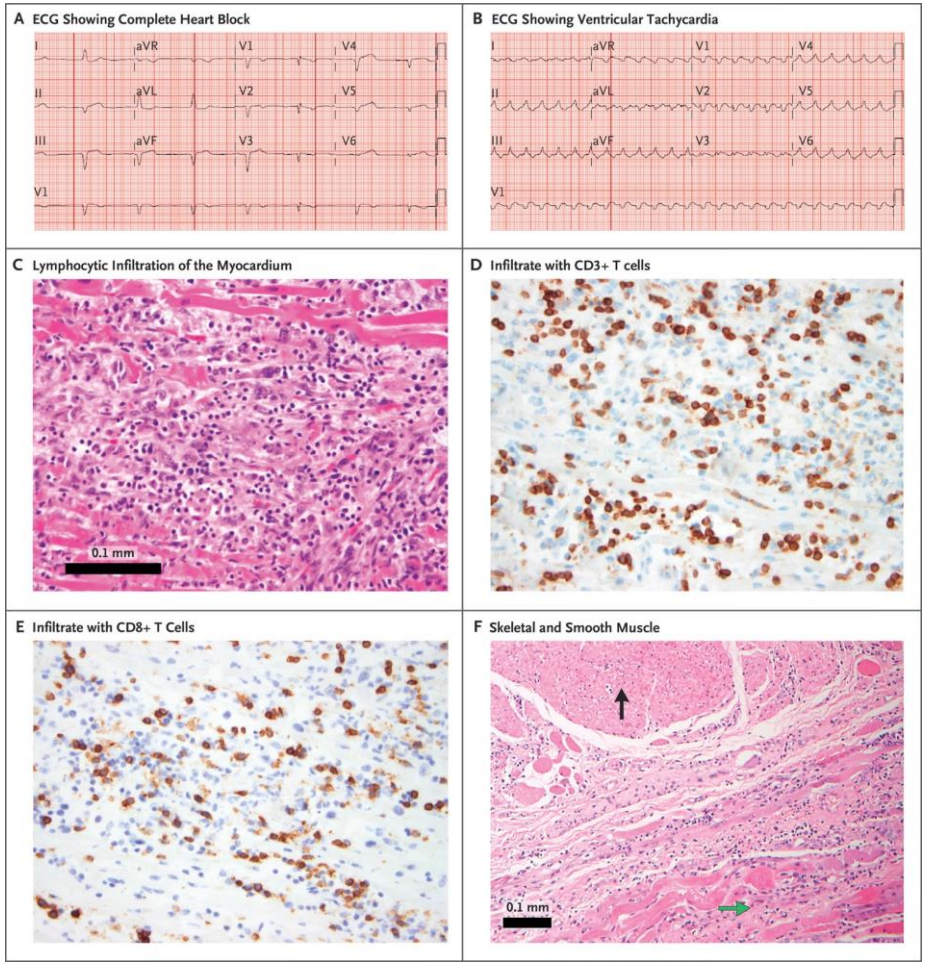
Thymic selection of T cells: a key mechanism in understanding irAEs of checkpoint inhibitors

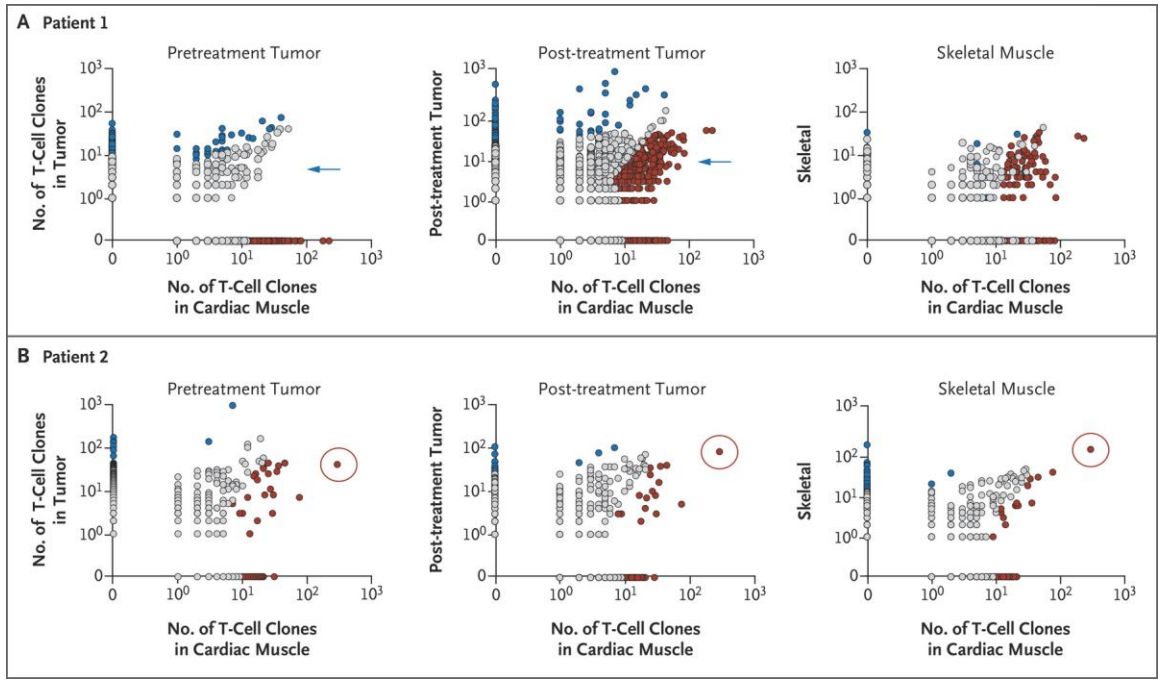


Peripheral T cells:
Low affinity for self-antigens
Importance of peripheral tolerance

Messerschmidt J, et al. *Oncologist* 2016;21:233–43.

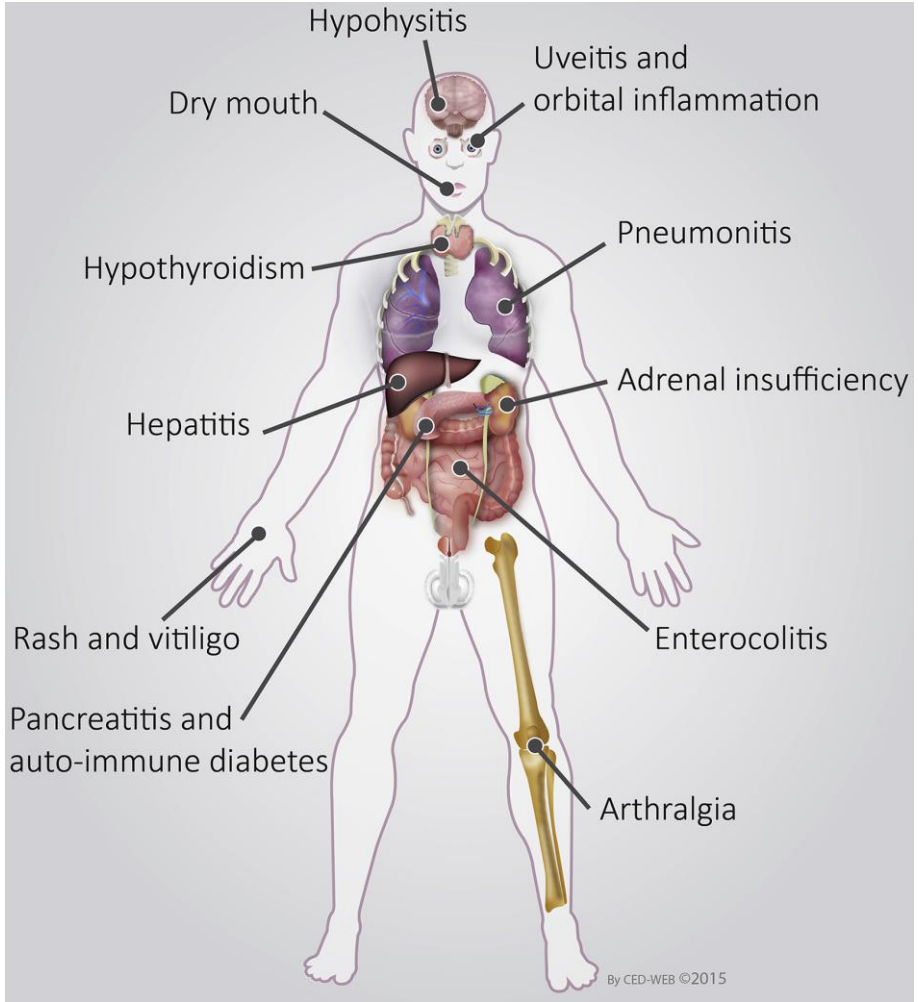
Fulminant myocarditis in a patient treated with combination ipilimumab and nivolumab





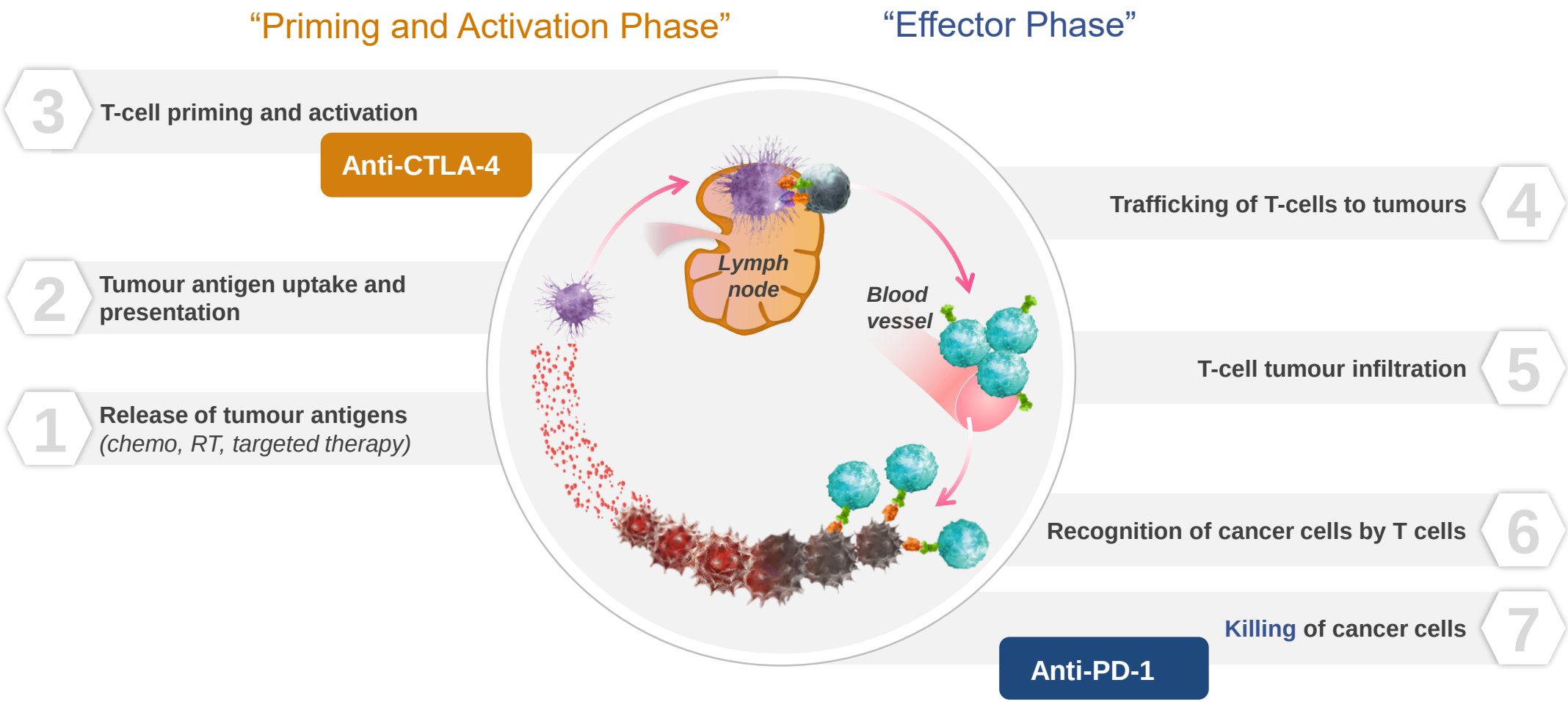
Johnson D, et al. *N Engl J Med* 2016;375:1749–55.

Checkpoint inhibitors: unusual toxicity pattern for an oncology drug



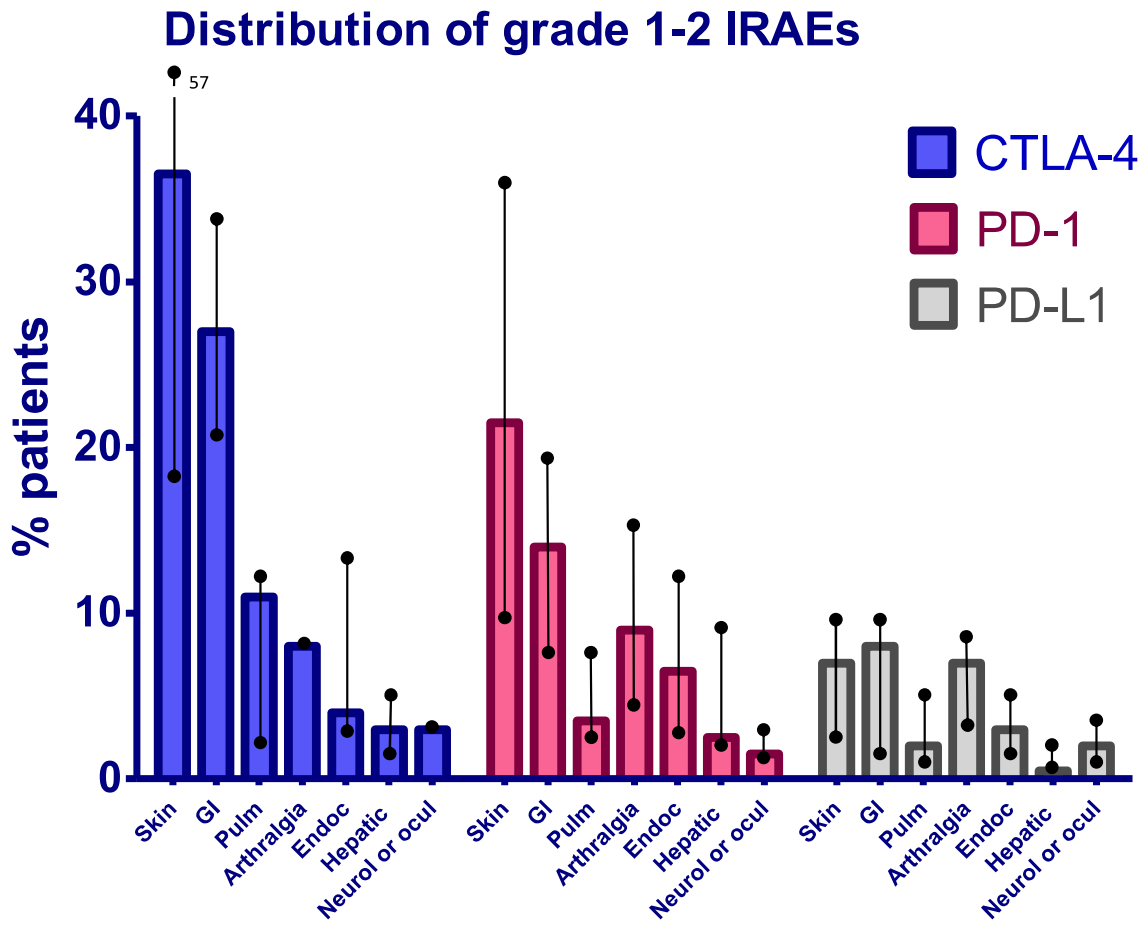
Adapted from Champiat S, et al. *Ann Oncol* 2016;27:559–74.

Immunotherapies can act on various steps of the cancer immunity cycle



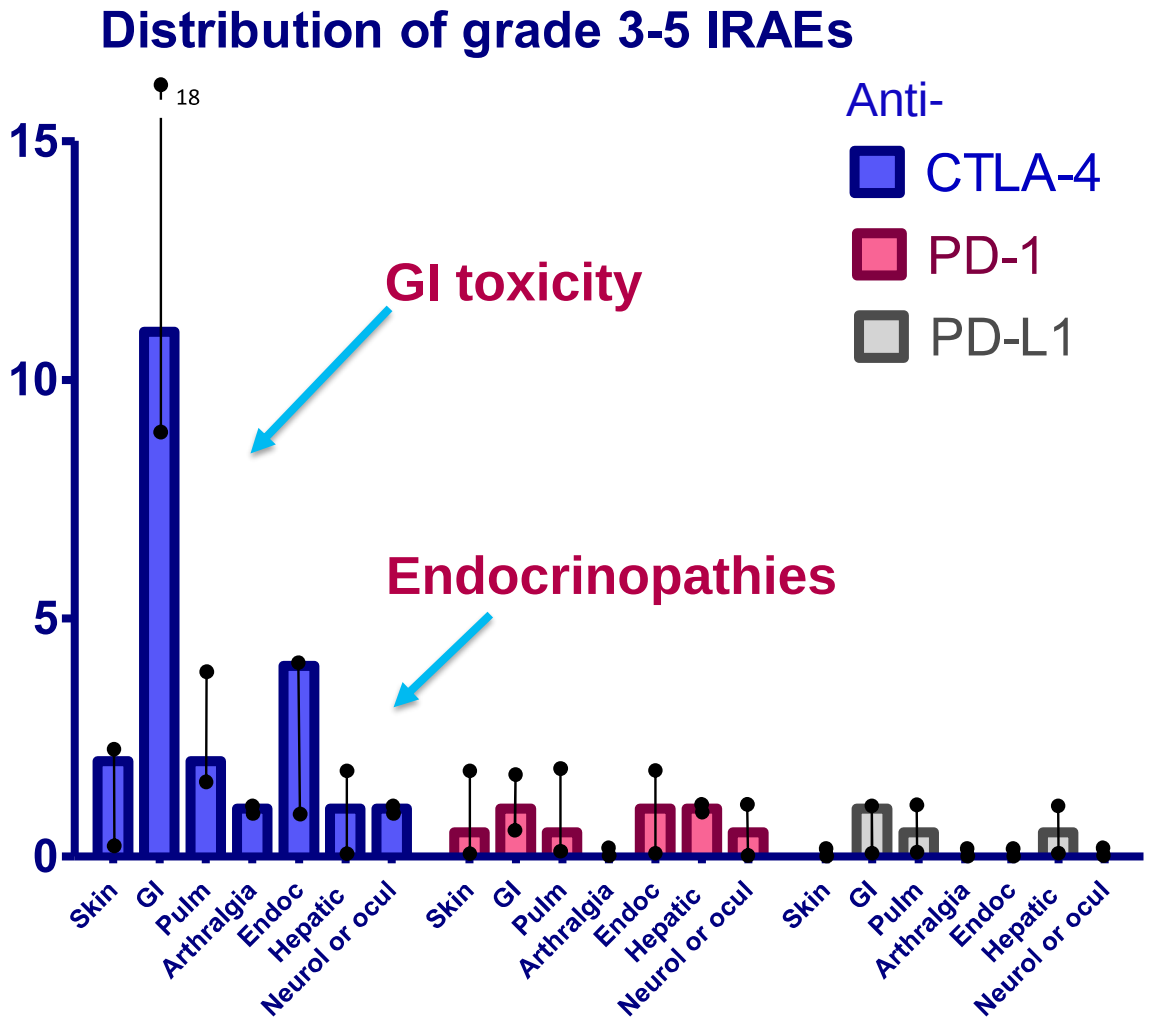
APC=antigen-presenting cells, anti-VEGF=antivascular endothelial growth factor; CTLA-4=cytotoxic T-lymphocyte antigen 4; CT=chemotherapy; IDO=indoleamine 2,3-dioxygenase; I-O=immuno-oncology; RT=radiotherapy; PD-1=programmed death receptor-1; PD-L1=programmed death ligand 1; VEGF=vascular endothelial growth factor.
Modified from: Alsina M et al. *Target Oncol.* 2016;11(4):469-477.

Immune-related toxicity under ICI: anything, anywhere, anytime



Michot J, et al. *Eur J Cancer* 2016;54:139–48.

Immune-related toxicity under ICI: anything, anywhere, anytime

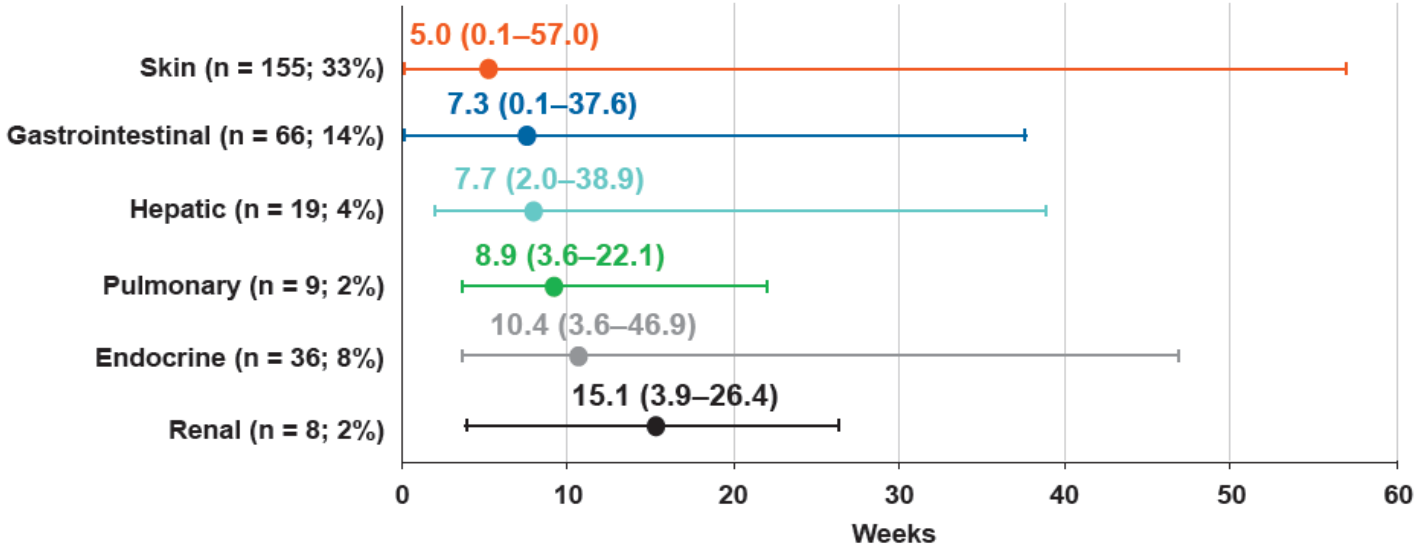


Michot J, et al. *Eur J Cancer* 2016;54:139–48.

Toxicity of PD1/PDL checkpoint blockade: time to onset and resolution

- Study design: retrospective safety review of 4 ongoing phase I–III trials, in which patients with melanoma received nivolumab 3 mg/kg Q2W until disease progression or unacceptable toxicity
- Objectives: to describe the safety profile of nivolumab across melanoma studies, including 4 studies in which guidelines for the management of AEs were utilised

Time to onset of select treatment-related AEs for nivolumab (any grade; N=474)



- Median time to onset for treatment-related select AEs ranged from 5.0 weeks for skin AEs to 15.1 weeks for renal AEs

Weber J, et al. *J Clin Oncol* 2015;33:9018.

Cancer patients with pre-existing autoimmune disease key questions for the healthcare provider:

- What is the prevalence of pre-existing AD in patients treated with immune checkpoint inhibitors?
- Is it safe to start ICI in patients with pre-existing AD?
  - What is the pattern of toxicities observed?
  - Are toxicities as manageable as in other patients?
- Can we learn from the field of auto-immune diseases to find predictive biomarkers for the development of irAE under ICI?

AD, autoimmune disease; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event.

Epidemiology of patients with underlying autoimmune diseases treated with immune checkpoint inhibitors

Prevalence of pre-existing AD in ICI-treated cancer patients

- Study design: Surveillance Epidemiology and End Results (SEER)-Medicare data 1991–2010 reviewed to identify patients with lung cancer and ICD-9 codes for 7 systemic and 36 organ-specific autoimmune conditions
- Objective: to determine the prevalence of autoimmune conditions among patients with lung cancer

Prevalence of auto-immune diseases in NSCLC population (SEERS)

Autoimmune disease	Prevalence, %
Rheumatoid arthritis	5.9
Psoriasis	2.8
Polymyalgia rheumatica	1.8
Addison’s disease	1.0
SLE	0.9
Ulcerative colitis	0.8
Giant cell arthritis	0.8
Sicca syndrome	0.6
Regional enteritis	0.5
Ménière's disease	0.5
Total (any autoimmune disease)	15.6

Khan, S, et al. *J Clin Oncol* 2016;34:9039. DOI: 10.1200/JCO.2016.34.15_suppl.9039

Prevalence of pre-existing AD in ICI-treated cancer patients

- Patients with pre-existent AD when starting immunotherapies varies by type of tumour, but in general there is a high proportion of rheumatologic and dermatologic ADs:

Treatment	N	Tumour	Pre-existing ADs, %	Reference
PD-1/PD-L1 inhibitors: 44% PD-1/PD-L1 + CTLA-4 inhibitors: 16% PD-1/PD-L1 + VEGF inhibitors: 40%	271 25 with AD	RCC	D: 36; Rh: 24; E: 24; R: 8; O: 8	Martinez et al.[1]
IPI	41 15 with AD	mMEL	E: 37; Rh: 27; D: 22; GI: 7; N: 5; O: 7	Kahler et al.[2]
IPI: 92% NIVO: 8%	119 52 with AD	mMEL	Rh: 52; D; 15; GI; 12; N: 10; E: 8; Rp: 4; H: 4	Menzies et al.[3]
NIVO: 80%; PEMBRO: 18%; ATEZO: 2%	56 with AD	NSCLC	Rh: 45; D; 29; E: 16; GI: 11; N: 5; O: 5	Leonardi et al.[4]

AD, autoimmune disease; D, dermatologic; E, endocrine; GI, gastrointestinal; H, hematologic; N, neurologic; O, others; R, renal; Rh, rheumatologic; Rp, respiratory.

1. Martinez Chanza N, et al. Seventeenth International Kidney Cancer Symposium. Nov 2–3, 2018; 2. Kähler KC, et al. *Cancer Immunol Immunother* 2018;67:825–34; 3. Menzies AM, et al. *Ann Oncol* 2017;28:368–76; 4. Leonardi GC, et al. *J Clin Oncol* 2018;36:1905–15.

What is the tolerability profile associated with starting ICI in patients with cancer and pre-existing auto-immune disease?

Tolerability profile of ICI in patients with cancer and pre-existing AD

- Autoimmune disease is not necessarily a contraindication to anti–PD-1/L1 therapy; patients with autoimmune disease respond to I-O therapy at a rate similar to the general population, but should be monitored closely for toxicities[1]

Treatment	N	Tumour	Pre-existing ADs (%)	Comments	Conclusions	Refs
PD-1/PD-L1 inhibitors: 44% PD-1/PD-L1 + CTLA-4 inhibitors: 16% PD-1/PD-L1 + VEGF inhibitors: 40%	271 25 with AD	RCC	D: 36; Rh: 24; E: 24; R: 8; O: 8	AD flares: 32% new irAEs: 48%	• IRAEs were manageable with drug interruptions and systemic CS in most patients	Martinez et al.[2]
IPI	41 15 with AD	mMEL	E: 37; Rh: 27; D: 22; GI: 7; N: 5; O: 7	AD flares: 29% new irAEs: 29%	• Flares of pre-existing autoimmune disease were manageable; RRs and occurrence of new irAEs were comparable to previous trials	Kahler et al.[3]
IPI: 92% NIVO: 8%	119 52 with AD	mMEL	Rh: 52; D; 15; GI; 12; N: 10; E: 8; Rp: 4; H: 4	AD flares: 38% new irAEs: 34%	• In pts with preexisting disease, or major irAEs with IPI, anti-PD-1 induced frequent adverse events, but these were often mild and easily managed	Menzies et al.[4]
NIVO: 80%; PEMBRO: 18%; ATEZO: 2%	56 with AD	NSCLC	Rh: 45; D; 29; E: 16; GI: 11; N: 5; O: 5		• Incidence of irAEs was similar to rates in trials where pts with pre-existing autoimmune disease were excluded. AEs were manageable	Leonardi et al.[5]

AD, autoimmune disease; CTLA-4, cytotoxic T-lymphocyte antigen-4; D, dermatologic; E, endocrine; GI, gastrointestinal; H, hematologic; irAE, immune-related adverse event; mMEL, metastatic melanoma; N, neurologic; NSCLC, non-small cell lung cancer; O, others; PD-1, programmed death (PD)-1; PD-L1, programmed death ligand 1; R, renal; RCC, renal cell carcinoma; Rh, rheumatologic; Rp, respiratory; VEGF, vascular endothelial growth factor.

1. Cancer Network. http://www.cancernetwork.com/oncology-journal/immune-checkpoint-inhibitor-therapy-patients-autoimmune-disease/page/0/1. Accessed October 9, 2018; 2. Martinez Chanza N, et al. Seventeenth International Kidney Cancer Symposium. Nov 2–3, 2018; 3. Kähler KC, et al. *Cancer Immunol Immunother* 2018;67:825–34; 4. Menzies AM, et al. *Ann Oncol* 2017;28:368–76; 5. Leonardi GC, et al. *J Clin Oncol* 2018;36:1905–15.

Safety of ICI in cancer patients with pre-existing AD

- Study design: retrospective review of patients with advanced melanoma and pre-existing ADs and/or major irAEs with ipilimumab (requiring systemic immunosuppression) that were treated with anti-PD-1 between 1 July 2012 and 30 September 2015
- Objective: to explore the safety and efficacy of anti-PD-1 in such patients

Toxicity of anti-PD-1 antibodies in patients with autoimmune disease

	Number (%) (*N* = 52)	Details
Flare AD on PD1		
No	32 (62%)	
Yes	20 (38%)	
Time to flare, median (range), d	38 (8–161)	
Grade of flare		
G1-2	17 (33%)	
G3	3 (6%)	
G4	0 (0%)	
Flare by AD subtype		
Rheumatologic	14 of 27 (52%)	7/13 RA, 3/3 PMR, 1/2 scleroderma, 2/2 Sjogren's, 1/2 psoriatic arthritis
Dermatologic	3 of 8 (38%)	3/6 psoriasis
Gastrointestinal	0 of 6 (0%)	
Neurologic	0 of 5 (0%)	
Endocrine	1 of 4 (25%)	1/4 Graves
Respiratory	0 of 2 (0%)	
Hematologic	2 of 2 (100%)	2/2 ITP

- **38% flare of auto-immune disease**
- **8% permanent discontinuation due to flare**

Menzies A, et al. *Ann Oncol* 2017;28:368–76.

Safety of ICI in cancer patients with pre-existing AD

- Systematic literature review to summarise the evidence on AEs associated with ICI in patients with cancer and pre-existing AD
- 123 patients in 49 publications were identified; 92 (75%) had exacerbation of pre-existing autoimmune disease, irAEs, or both

- There was no difference in irAE in patients with active vs inactive AD
- Most flares and irAEs were managed with corticosteroids
- Less than half of flares required discontinuation of the checkpoint blocker
- *De novo* auto-immune flares unrelated to primary auto-immune disease

AD, autoimmune disease; AE, adverse event; ICI, immune checkpoint inhibitor; irAE, immune-related adverse events.
Abdel-Wahab N, et al. *Ann Intern Med* 2018;168:121–30.

Safety of ICI in cancer patients with pre-existing AD

Understanding flares of AD or prior immune-related AEs during treatment with checkpoint inhibition

Study [Reference]	Drug Target	Number of Patients	Patient Population	ORR	Flares	irAEs	Treatment for Flares
Kyi et al [12]	CTLA-4	2	AI	50%	1/2 flare of prior AI	Arthritis	Celecoxib
Johnson et al [14]	CTLA-4	30	AI	20%	27%	Hypophysitis, colitis	Corticosteroids (10), infliximab (2); 1 death
Lee et al [15]	CTLA-4	8	AI	57%	62.5%	50% colitis, 50% flare of prior arthritis	5/8 flares required discontinuation of drug
Menzies et al [18]	PD-1	119	52 with preexisiting AI	33%	38%	Arthritis, dermatologic	Corticosteroids (14%), permanent discontinuation of anti–PD-1 (8%)
			67 with prior CTLA-4–related AEs	40%	3% flares of prior CTLA-4–related AEs, 34% distinct irAEs	Colitis, hepatitis, pneumonitis	Corticosteroids (21%), steroid-sparing agents (4%), discontinuation of anti–PD-1 (12%)
Bender et al [19]	PD-1	10	Prior CTLA-4–related AEs	NA	10% distinct irAEs	Pancreatitis	Corticosteroids, mycophenolate mofetil
Pollack et al [20]	PD-1	80	Prior CTLA-4 + PD-1 combination irAEs	70%	18% recurrent irAEs, 21% distinct irAEs	Colitis less likely than other irAEs	NA
Gutzmer et al [21]	PD-1	41	19 with AI	32%	42% flares of prior AI, 16% distinct irAEs	Pneumonitis, hypophysitis	Corticosteroids
			22 with prior CTLA-4–related AEs	45%	4.5% flares of prior ipi-related AEs, 23% distinct irAEs	Pancreatitis, arthralgias	Corticosteroids
Danlos et al [22]	PD-1/PD-L1	45	AI	35%	55% flares of prior AI, 22% distinct irAEs	Thyroiditis, colitis	Corticosteroids (13%), discontinuation (8%)

AE, adverse event; AI, autoimmune disease; irAE, immune-related adverse events; ORR, objective response rate.

Immune Checkpoint Inhibitor Therapy in Patients With Autoimmune Disease. Available at: https://www.cancernetwork.com/oncology-journal/immune-checkpoint-inhibitor-therapy-patients-autoimmune-disease/page/0/1 [accessed December 2019].

Safety of ICI in cancer patients with pre-existing AD

- Study design: real-world retrospective, multicentre observational study of patients with advanced cancer treated with anti-PD-1 agents
- Objectives: to perform comparative safety and efficacy analyses according to the history of pre-existing AIDs

- Increased risk of developing irAEs in patients with pre-existing AIDs who were treated with anti-PD-1
- Toxicities were mild and incidence of grade 3/4 irAEs was not significantly higher compared with those of controls

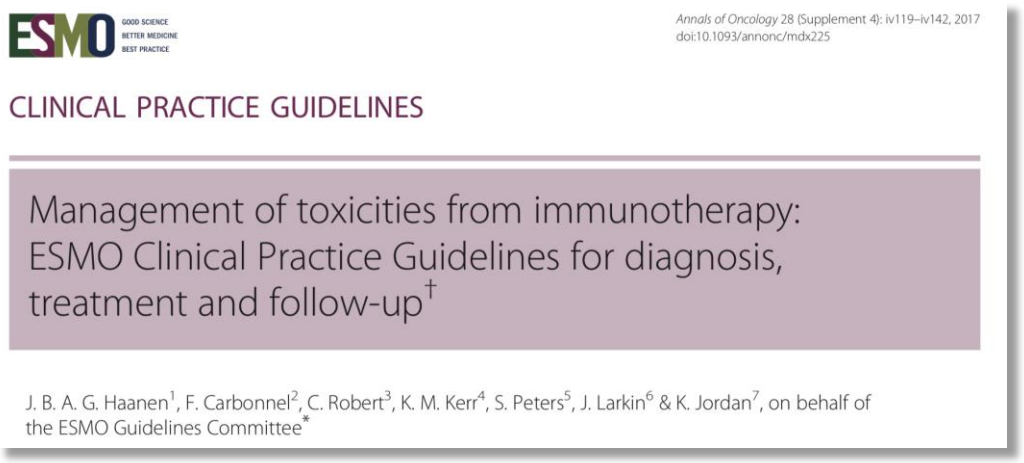
Univariate analysis of irAEs of any grade

Variable (comparator)	Events ratio	Incidence (95% CI)	*p* value
Overall	322/751	42.9 (38.3–47.8)	
Pre-existing AIDs			
Yes	56/85	65.9 (49.7–85.5)	<.0001
No	266/666	39.9 (35.2–45.0)	
Inactive AID (No AIDs)	45/70	64.3 (46.8–86.0)	.0001
Active AID (No AIDs)	11/15	73.3 (44.9–92.2)[a]	.0402
Primary tumor			
(NSCLC)	201/492	40.9 (35.4–46.9)	—
Melanoma	75/159	47.2 (37.1–59.1)	.1617
Kidney	46/94	48.9 (35.8–65.2)	.1470
Others	0/6	—	.9977
Sex			
Female	135/252	53.6 (44.9–63.4)	<.0001
Male	187/499	37.5 (32.3–43.2)	
Age			
Elderly	139/351	39.6 (33.3–46.7)	.0896
Nonelderly	183/400	45.8 (39.4–52.9)	
ECOG-PS			
0–1	296/655	45.2 (40.2–50.6)	.0008
≥2	26/96	27.1 (17.7–39.7)	
Treatment line			
First	74/174	42.5 (33.3–53.4)	.9159
Further lines	248/577	43.1 (37.8–48.7)	
Burden of disease			
≤2 sites	168/365	46.0 (39.3–53.5)	.0899
>2 sites	154/386	39.9 (33.8–46.7)	

AID, autoimmune disease; ECOG, Eastern Cooperative Oncology Group; irAE, immune-related adverse events; NSCLC, non-small cell lung cancer.
Cortellini A, et al. *Oncologist* 2019;24:e327–37.

Management of irAEs in patients treated with ICI

Management of irAEs in patients treated with ICI



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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

CLINICAL PRACTICE GUIDELINES

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

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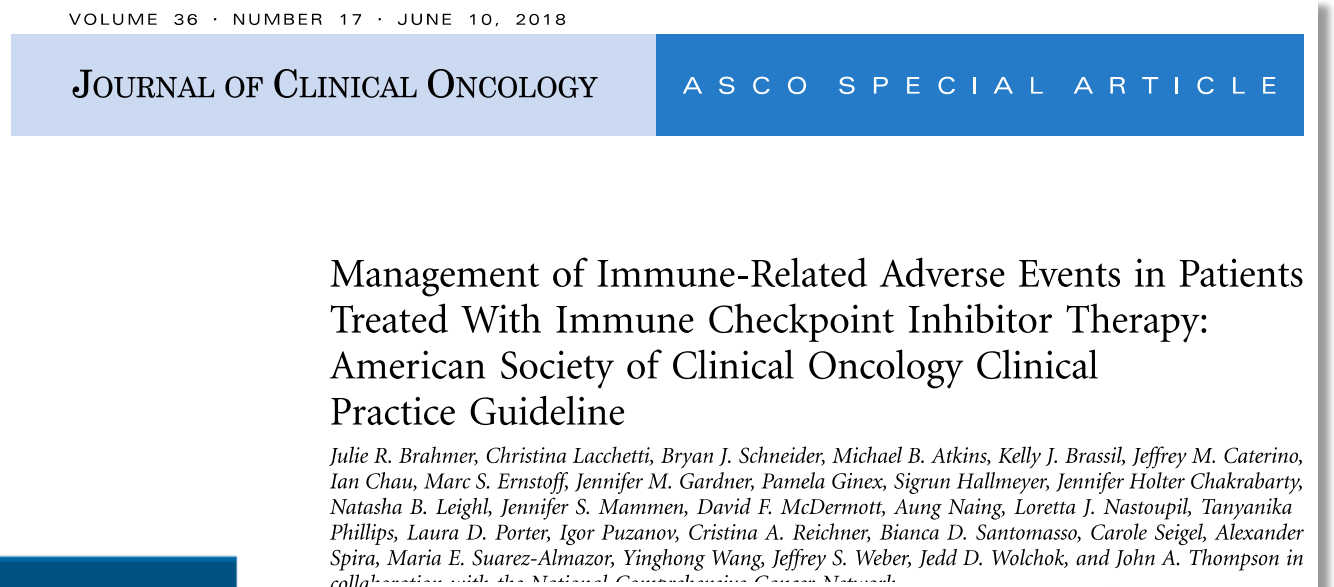

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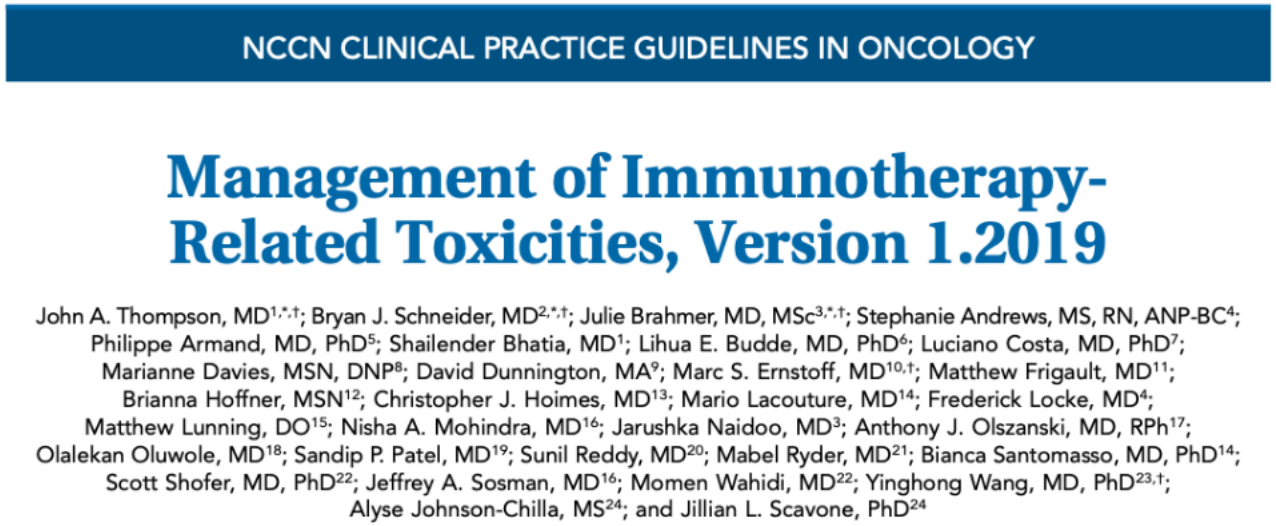
ASCO SPECIAL ARTICLE

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Julie R. Brahmer, Christina Lacchetti, Bryan J. Schneider, Michael B. Atkins, Kelly J. Brassil, Jeffrey M. Caterino, Ian Chau, Marc S. Ernstoff, Jennifer M. Gardner, Pamela Ginex, Sigrun Hallmeyer, Jennifer Holter Chakrabarty, Natasha B. Leighl, Jennifer S. Mammen, David F. McDermott, Aung Naing, Loretta J. Nastoupil, Tanyanika Phillips, Laura D. Porter, Igor Puzanov, Cristina A. Reichner, Bianca D. Santomasso, Carole Seigel, Alexander Spira, Maria E. Suarez-Almazor, Yinghong Wang, Jeffrey S. Weber, Jedd D. Wolchok, and John A. Thompson in collaboration with the National Comprehensive Cancer Network



NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY

Management of Immunotherapy-Related Toxicities, Version 1.2019

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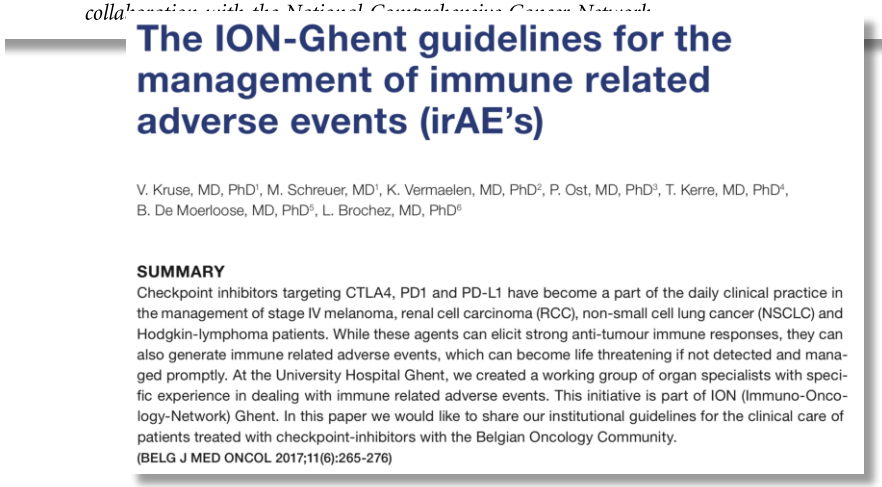


The ION-Ghent guidelines for the management of immune related adverse events (irAE's)

V. Kruse, MD, PhD[1], M. Schreuer, MD[1], K. Vermaelen, MD, PhD[2], P. Ost, MD, PhD[3], T. Kerre, MD, PhD[4], B. De Moerloose, MD, PhD[5], L. Brochez, MD, PhD[6]

SUMMARY

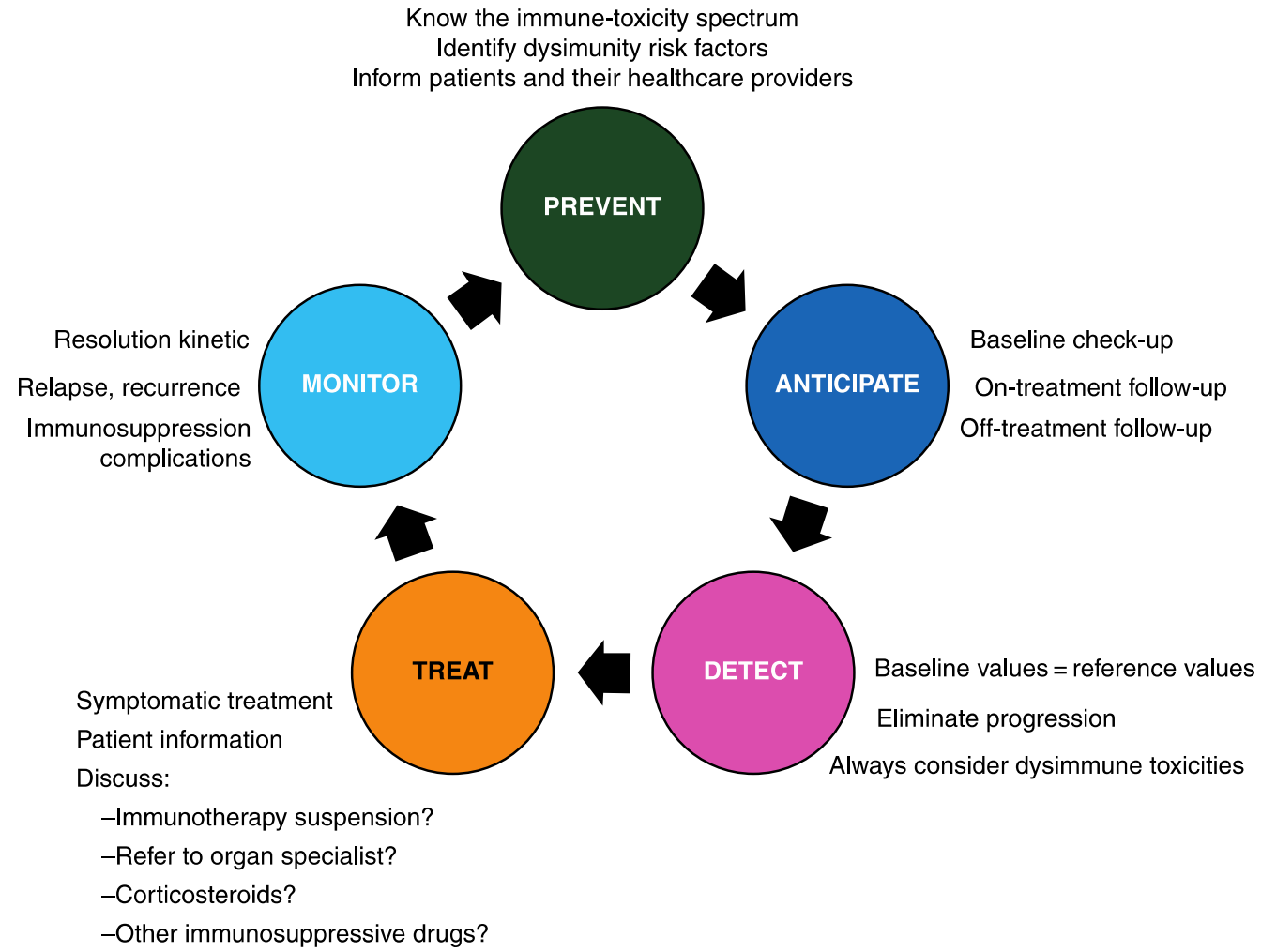
Checkpoint inhibitors targeting CTLA4, PD1 and PD-L1 have become a part of the daily clinical practice in the management of stage IV melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC) and Hodgkin-lymphoma patients. While these agents can elicit strong anti-tumour immune responses, they can also generate immune related adverse events, which can become life threatening if not detected and managed promptly. At the University Hospital Ghent, we created a working group of organ specialists with specific experience in dealing with immune related adverse events. This initiative is part of ION (Immuno-Oncology-Network) Ghent. In this paper we would like to share our institutional guidelines for the clinical care of patients treated with checkpoint-inhibitors with the Belgian Oncology Community.

(BELG J MED ONCOL 2017;11(6):265-276)

ICI, immune checkpoint inhibitors.

Haaanen J, et al. *Ann Oncol* 2017;28:iv119–42; Brahmer J, et al. *J Clin Oncol* 2018;36:1714–68; NCCN Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities. Version 2.2019 — April 8, 2019; Kruse V, et al. *BJMO* 2017;11:265–75.

Management of irAEs in patients treated with ICI



Champiat S, et al. *Ann Oncol* 2016;27:559–74.

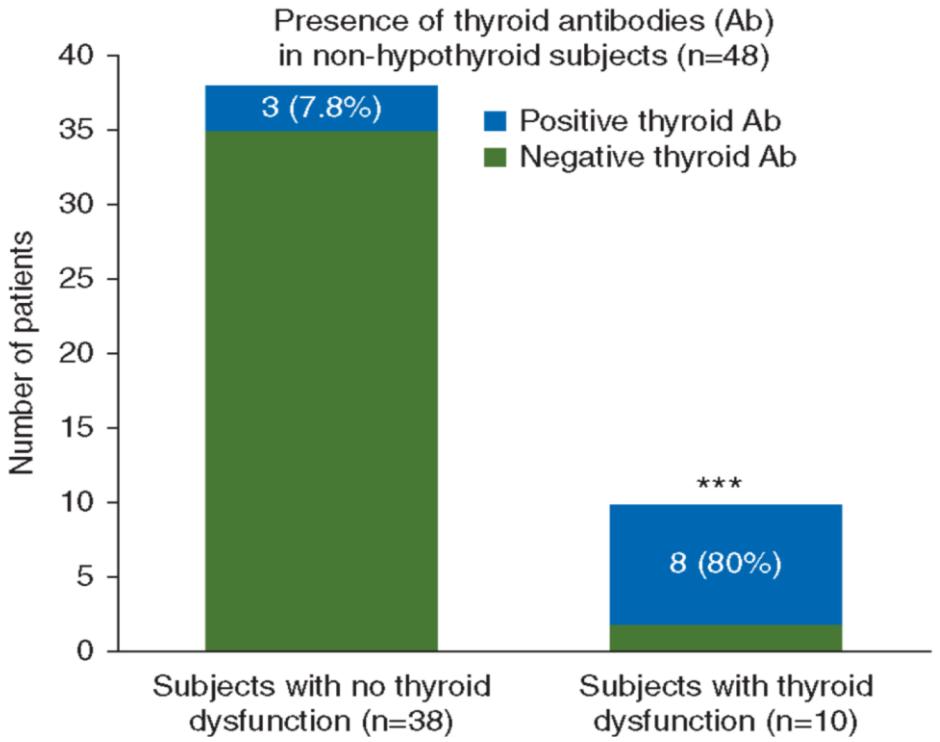
Towards predictive biomarkers for toxicity under immune checkpoint inhibition

Can we learn from the field of auto-immune diseases?

Auto-antibodies that are induced under ICI

- Insulin-dependent DM: only 40% auto-antibody+ (vs 90% in type 1 DM)[1]
- Symmetrical small joint arthritis: 0% RF, anti-CCP or ANA[2]

- Thyroiditis does show an association with auto-antibody development[3]



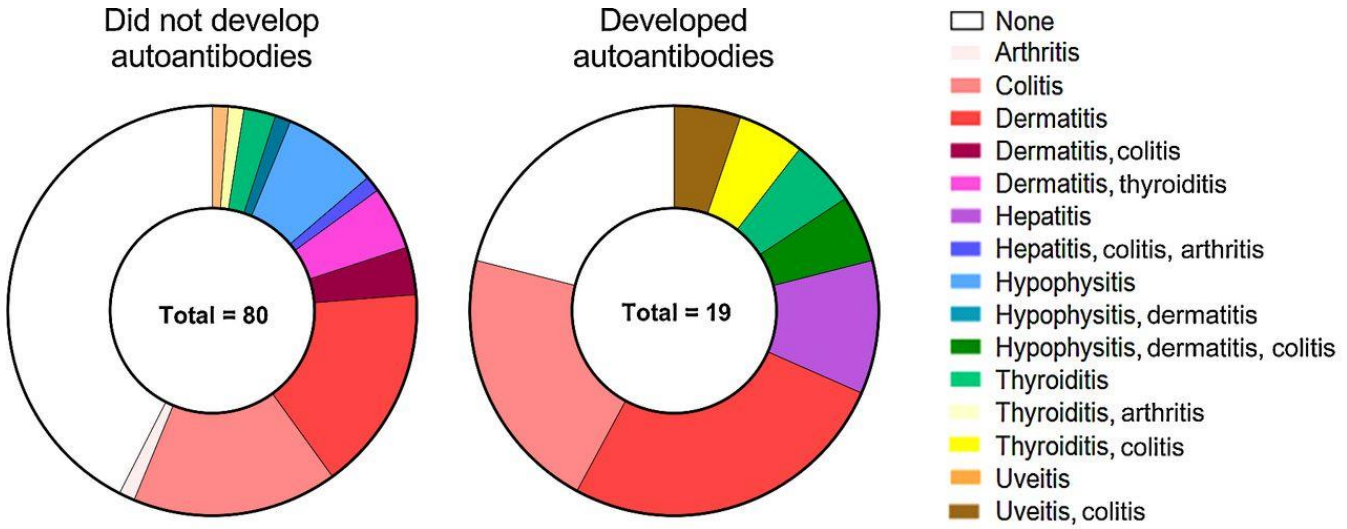
ANA, antinuclear antibodies; CCP, cyclic citrullinated peptide; DM, diabetes mellitus; RF, rheumatoid factor.

1. Stamatouli A, et al. *Diabetes* 2018;67:1471–80; 2. Cappelli L, et al. *Ann Rheum Dis* 2017;76:43–50; 3. Osorio J, et al. *Ann Oncol* 2017;28:583–9.

Auto-antibodies that are induced under ICI

- Study to determined if AD-associated autoantibodies were formed with ICI treatment and investigated their association with irAEs and clinical outcome
- Inclusion: 133 patients with late-stage melanoma who were treated with ipilimumab, and for whom pre- and post-treatment serum or plasma samples were available
- Results: autoantibodies developed in 19.2% of patients who were autoantibody-negative pre-treatment

Frequency of irAEs in pre-ipilimumab autoantibody-negative patients who did not develop autoantibodies (left) versus those who developed autoantibodies (right) after ipilimumab treatment



A non-significant association was observed between development of any autoantibodies and any irAEs [OR, 2.92; 95% CI 0.85–10.01]; autoantibodies develop under ipilimumab treatment and could be a potential marker of ICI toxicity and efficacy

AD, autoimmune disease; CI, confidence interval; ICI, immune checkpoint inhibitors; irAEs, immune-related adverse events; OR, odds ratio.
de Moel E, et al. *Cancer Immunol Res* 2019;7:6–11.

Quid pre-existing auto-antibodies under ICI?

Existence of pre-existing antibodies represents an independent factor associated with developing irAEs

- Study design: retrospective medical records analysis
- Objective: to assess the safety and efficacy of anti–PD-1 treatment in patients with subclinical disease with advanced NSCLC and with or without pre-existing autoimmune markers; and to assess potential clinical biomarkers that may be meaningfully and conveniently associated with clinical benefit or with irAEs following anti–PD-1 treatment

	No. (%) of Patients											
	Any Preexisting Antibody			Preexisting RF			Preexisting ANA			Preexisting Antithyroid		
Response	With (n = 80)[a]	Without (n = 57)	*P* Value[b]	With (n = 38)[c]	Without (n = 99)	*P* Value[b]	With (n = 48)[d]	Without (n = 89)	*P* Value[b]	With (n = 25)[e]	Without (n = 112)	*P* Value[b]
Objective response rate[f]	33 (41)	10 (18)	.006	17 (45)	26 (26)	.06	18 (38)	25 (28)	.35	12 (48)	31 (28)	.08
Disease control rate[g]	65 (81)	31 (54)	.001	31 (82)	65 (66)	.11	37 (77)	59 (66)	.26	22 (88)	74 (66)	.05
Development of irAE	48 (60)	18 (32)	.002	26 (68)	40 (40)	.006	29 (60)	37 (42)	.05	15 (60)	51 (46)	.28
Development of irAE >grade 3	6 (8)	3 (5)	.86	3 (8)	6 (6)	>.99	4 (8)	5 (6)	.80	1 (4)	8 (7)	.90
Skin reaction	32 (40)	10 (18)	.009	18 (47)	24 (24)	.02	18 (38)	24 (27)	.28	10 (40)	32 (29)	.38
Pneumonitis	8 (10)	6 (11)	>.99	4 (11)	10 (10)	>.99	4 (8)	10 (11)	.81	3 (12)	11 (10)	>.99
Hypothyroidism	6 (8)	0	.07	2 (5)	4 (4)	>.99	3 (6)	3 (3)	.51	5 (20)	1 (1)	<.001
Hyperthyroidism	1 (1)	0	>.99	0	1 (1)	>.99	1 (2)	0	.66	1 (4)	0	.48
Hepatitis	3 (4)	3 (5)	>.99	2 (5)	4 (4)	>.99	1 (2)	5 (6)	.60	0	6 (5)	.52
Myositis or peripheral neuropathy	4 (5)	1 (2)	.62	0	5 (5)	.38	3 (6)	2 (2)	.45	2 (8)	3 (3)	.58
Treatment discontinued due to irAE	9 (11)	6 (11)	>.99	3 (8)	12 (12)	.69	8 (17)	7 (8)	.20	4 (16)	11 (10)	.59

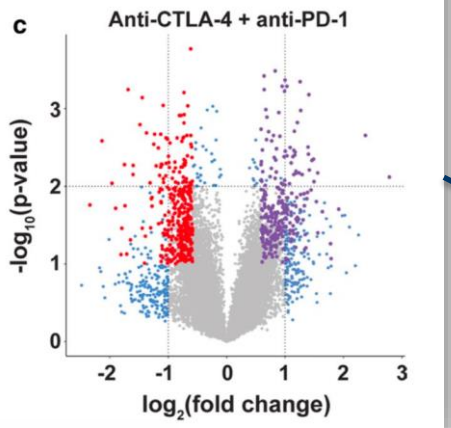
- Multivariate analysis indicated that the presence of the examined pre-existing antibodies was independently associated with irAEs (odds ratio, 3.25; 95%CI, 1.59–6.65; P = 0.001)

Presence of the examined pre-existing rheumatoid factor, antinuclear antibody, anti-thyroglobulin, and anti-thyroid peroxidase was associated with the development of irAEs in patients with NSCLC treated with nivolumab or pembrolizumab

Toi Y, et al. *JAMA Oncol* 2019;5:376–83.

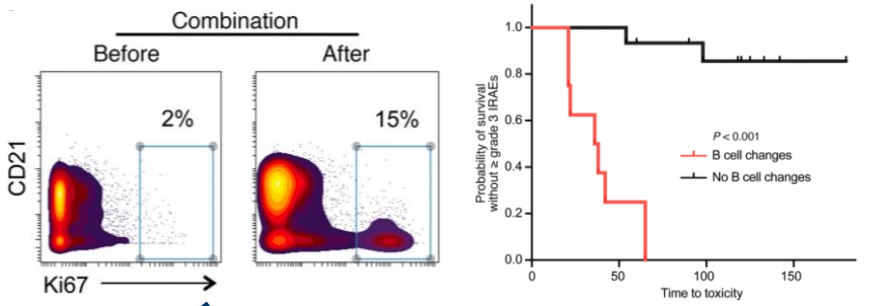
The search for toxicity biomarkers is still on…

baseline serum AB?

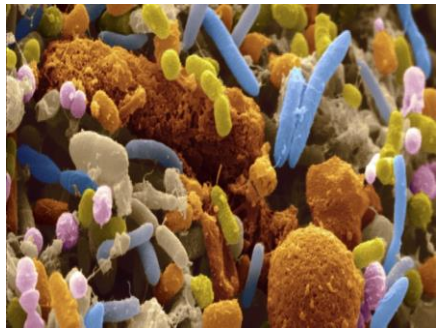


host polymorphisms?
(e.g. HLA-DR4?)

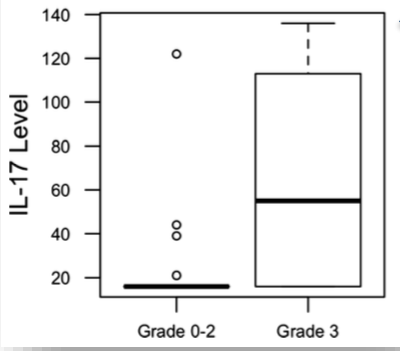
early B-cell changes?



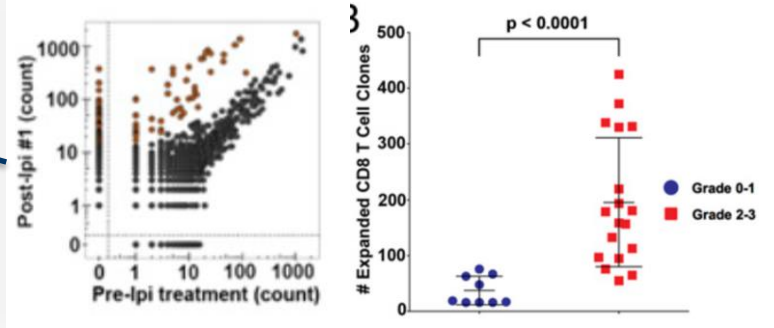
microbiome?



baseline IL-17?



early CD8 T-cell clonal expansion?



Gowen M, et al. *J Transl Med* 2018;16:82; Stamatouli A, et al. *Diabetes* 2018;67:1471–80; Das R, et al. *J Clin Invest* 2018;128:715–20; Subudhi S, et al. *Proc Natl Acad Sci U S A* 2016;113:11919–24; Tarhini A, et al. *J Immunother Cancer* 2015;3:39.

Key take-home messages

- The development of ICI have resulted in a major paradigm shift in medicine[1]
- HCPs, however, need to be aware that patients treated with ICI may experience irAEs[2–6]
  - irAEs mainly involve the gut, skin, endocrine glands, liver, and lung but can potentially affect any tissue[7]
- Patients treated with ICI may have pre-existent AD, which will vary by tumour; in general rheumatologic and dermatologic ADs are common amongst these patients[8–11]
- It's all about balancing:
  - Risk: "will I exacerbate a potentially debilitating auto-immune pathology?" → caution with neurological or life-threatening AD!
  - Benefits: "this patient will die of metastatic cancer if I don't start treatment" → incorporate predictors of response in your assessment!
- Remember: the very large majority of flares under ICI treatment can be controlled in patients with pre-existing AD[8–14]
- Several studies have reported that the existence of pre-existing antibodies represents an independent factor associated with developing irAEs; the search for biomarkers associated with irAEs continues[15–21]

AD, autoimmune disease; HCP, healthcare professional; ICI, immune checkpoint inhibitors; irAE, immune-related adverse event.
References in the speaker notes.

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