CATALYST: The Immuno-oncology Revolution Continues: A 3D View

Chapter 5: Response to Therapy and Management of Adverse Events from Targeted and Immuno-Therapies

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Disclosures

Dr. Luke has disclosed the following:

- Data and Safety Monitoring Board: TTC Oncology
- Scientific Advisory Board: 7 Hills, Actym, Alphamab Oncology, Array, BeneVir, Mavu, Tempest
- Consultancy: Aduro, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Castle, CheckMate, Compugen, EMD Serono, IDEAYA, Immunocore, Janssen, Jounce, Leap, Merck, Mersana, NewLink, Novartis, RefleXion, Spring Bank, Syndax, Tempest, Vividion, WntRx
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- Patents: (both provisional) Serial #15/612,657 (Cancer Immunotherapy), PCT/US18/36052 (Microbiome Biomarkers for Anti-PD-1/PD-L1 Responsiveness: Diagnostic, Prognostic and Therapeutic Uses Thereof)

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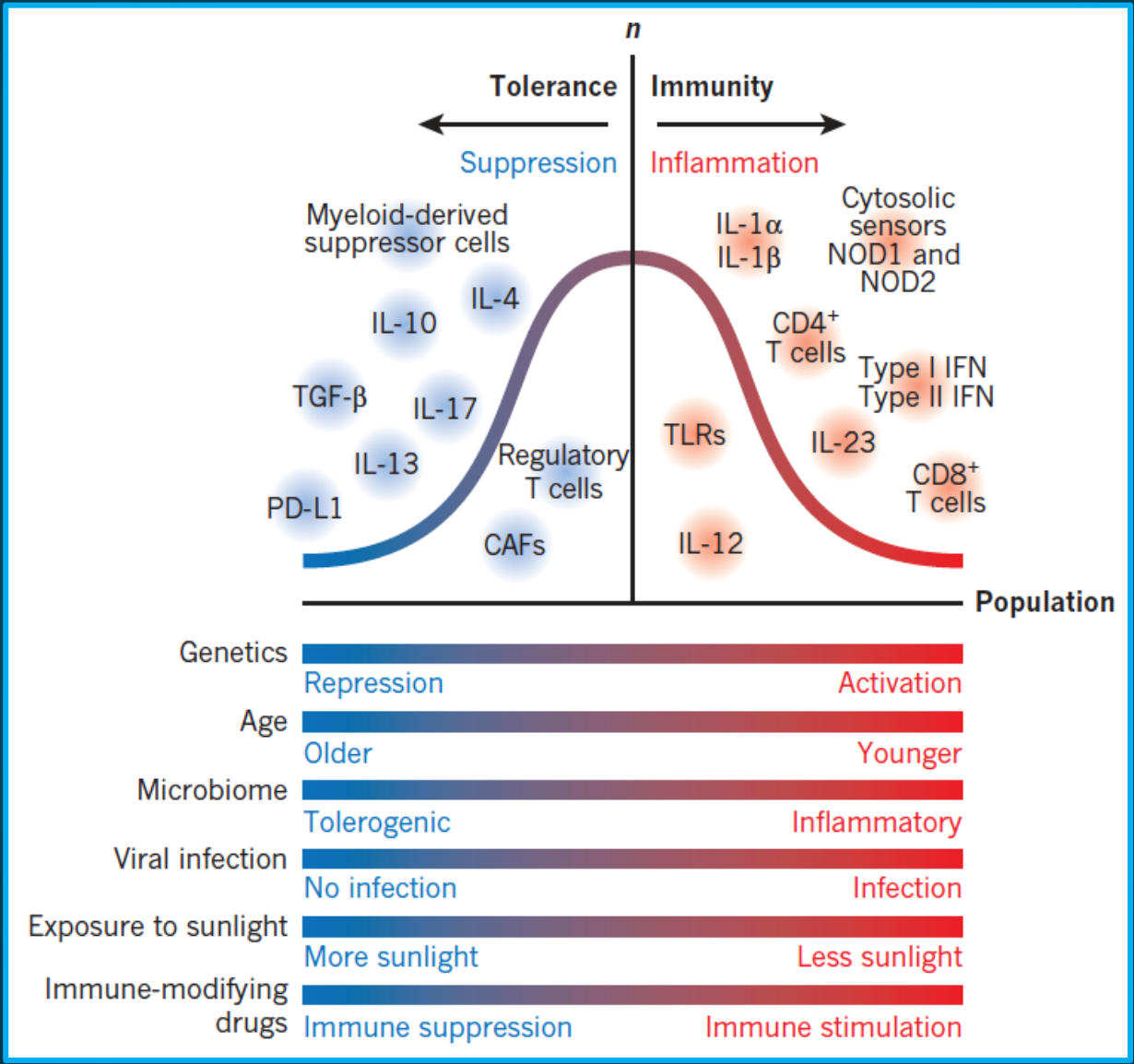
Learning Objectives

- Discuss the pathophysiology of adult malignancies with a focus on tumor immunosurveillance and immune evasion
- Review significant advances and unmet medical needs associated with currently available immuno-oncology therapies, including innate and adaptive resistance mechanisms (eg, T-cell exhaustion)
- Describe immune pathways that may be targeted to overcome immune-evasion mechanisms and emerging clinical data on novel immuno-oncology agents

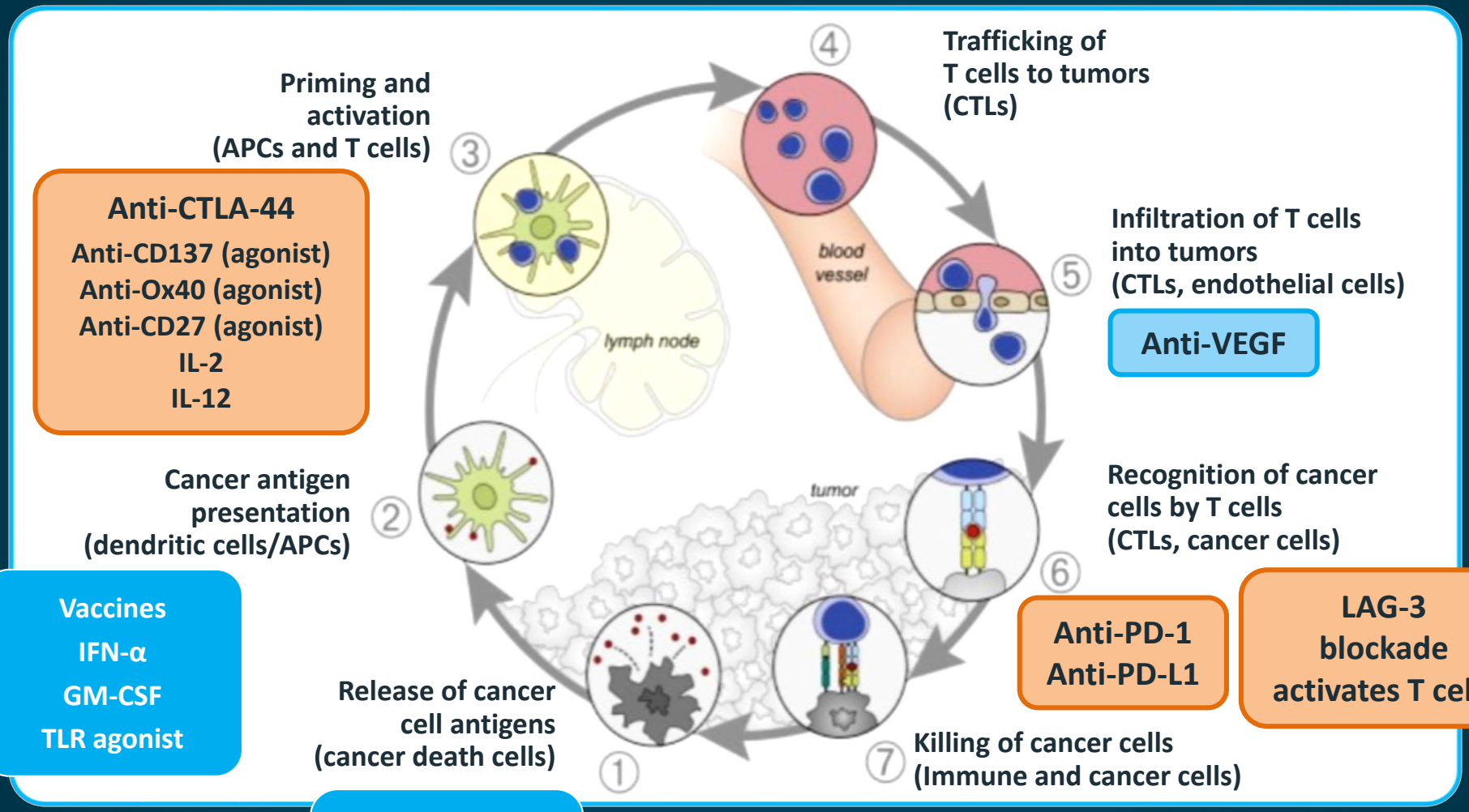
Multiple Factors Contribute to Generation of T-Cell Immunity or Tolerance



TGF = transforming growth factor; CAF = cancer-associated fibroblast; TLR = toll-like receptor.

Chen DS, Mellman I. *Nature.* 2017;541:321-330.

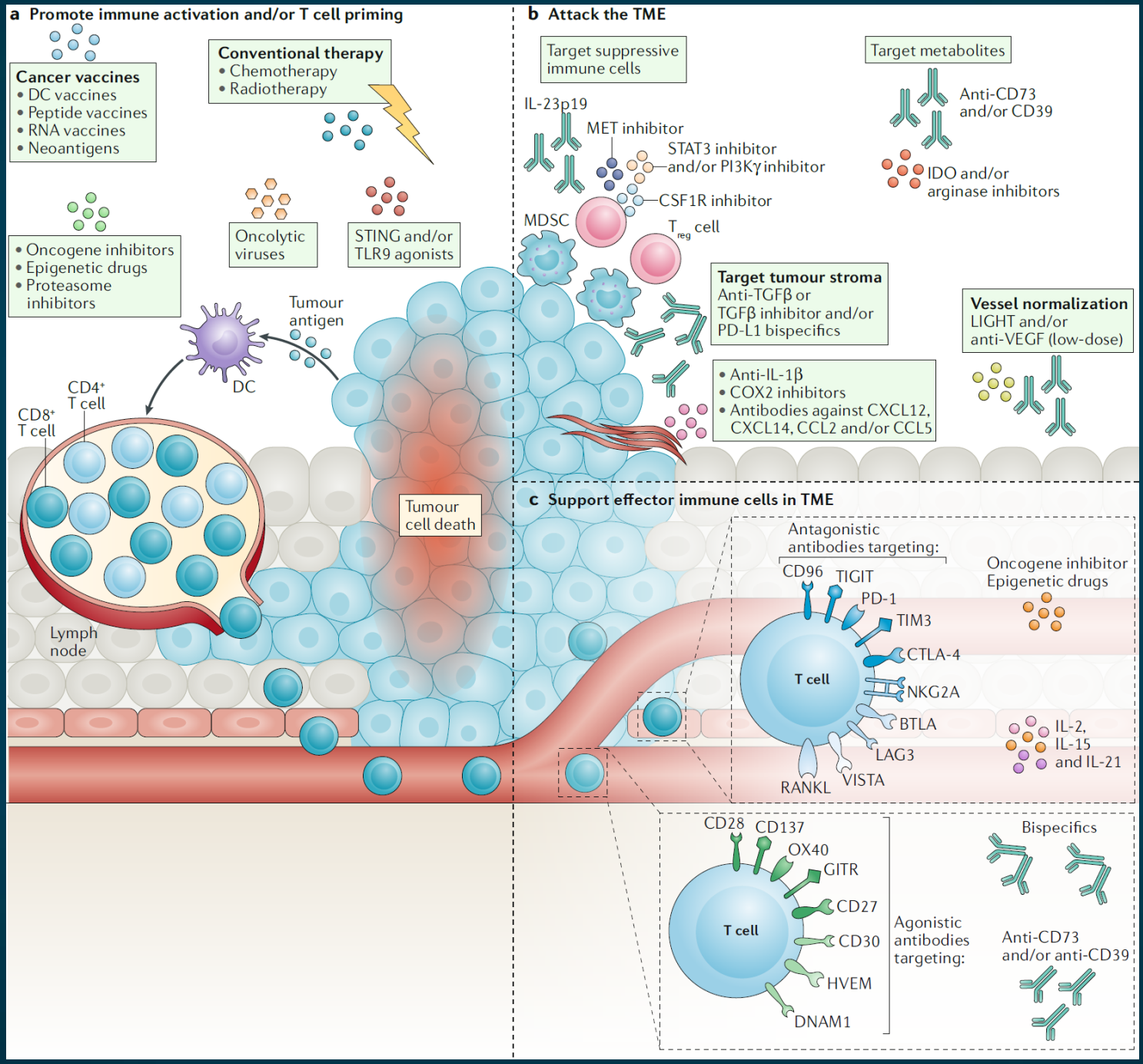
How to Modulate Responses to Checkpoint Inhibitors



GM-CSF = granulocyte macrophage colony-stimulating factor; TLR = Toll-like receptor; CARs = chimeric antigen receptors; CTL = cytotoxic T lymphocytes; LAG-3 = lymphocyte-activating gene 3 protein.

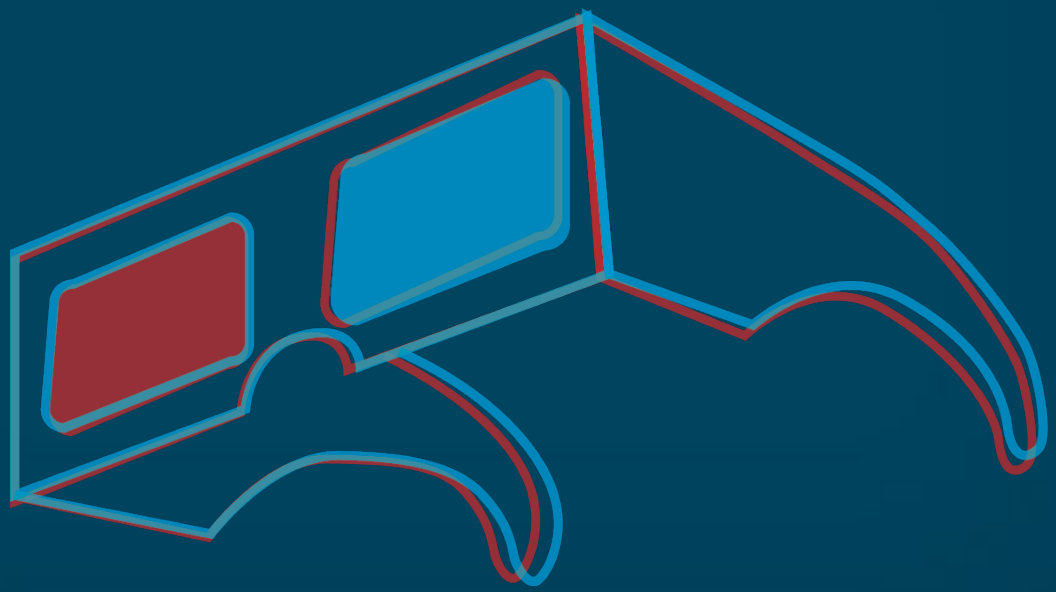
Adapted from Chen DS, Mellman I. *Immunity*. 2013;39:1-10.

Tumor Stratification and Microenvironment



O'Donnell JS et al. *Nature Reviews Clin Oncology*. 2018;16:151-67.

Please put on your 3D glasses

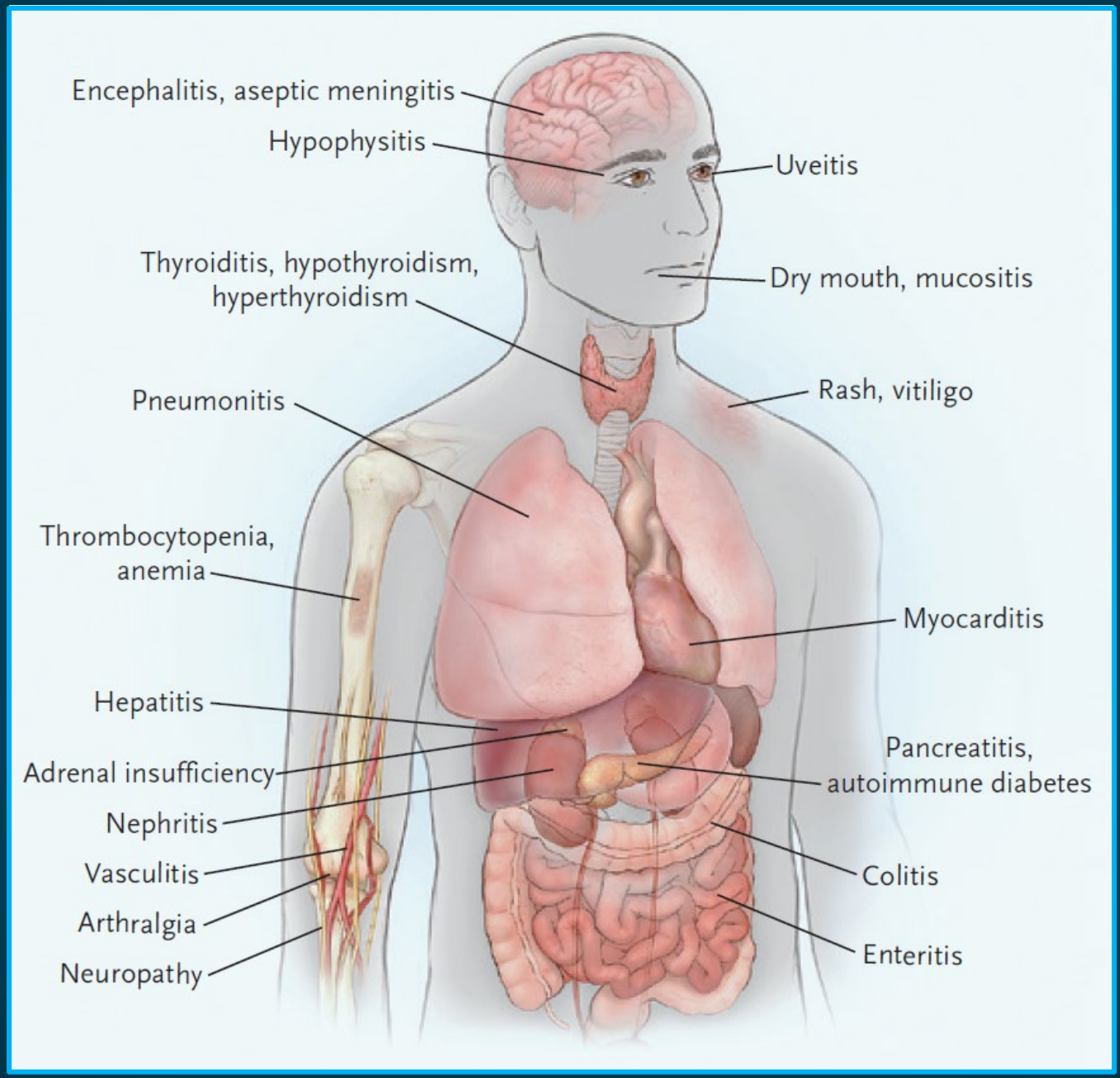


Immunotherapy Efficacy and Side Effects
3D video

That's the Good News; What's the Downside?

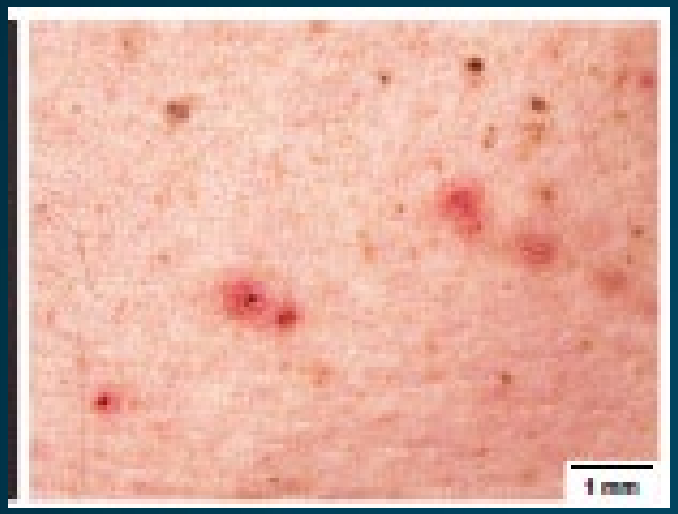
- Immune checkpoint inhibitor therapy results in the development of immune-related adverse events (irAEs)
- They are mechanism related, and almost always reversible with immune suppression, including steroids of TNF-blocking antibodies
- Immune-related adverse events may affect almost any organ

Virtually Any Organ Can Be Affected by irAEs

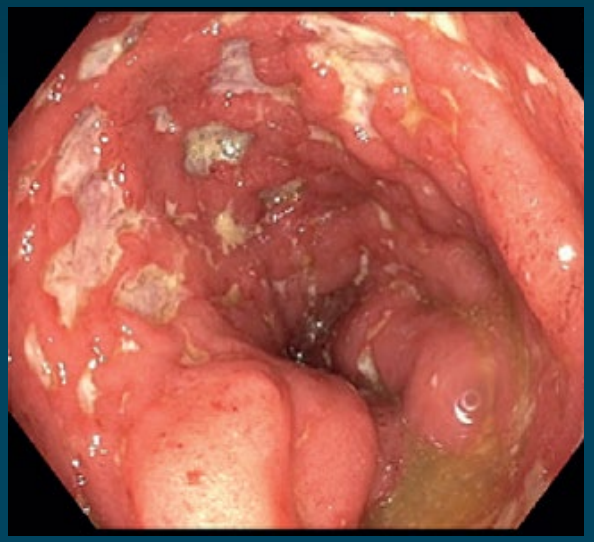


Postow MA, et al. *N Engl J Med*. 2018;378:158-168.

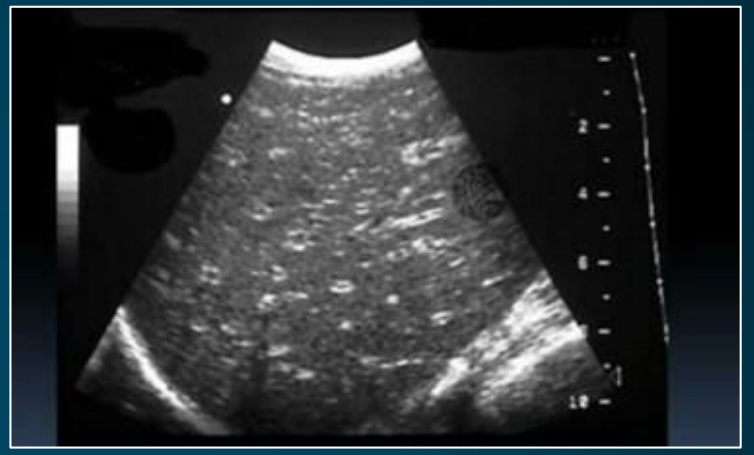
Spectrum of Immune-related Adverse Events



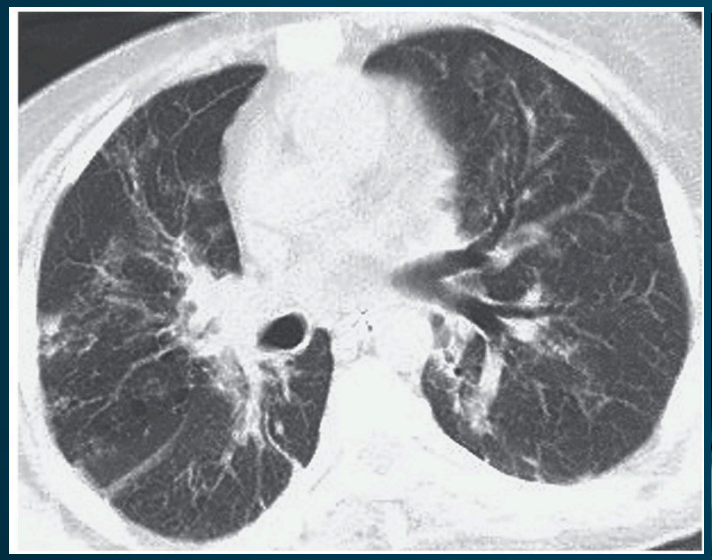
Rash[1]



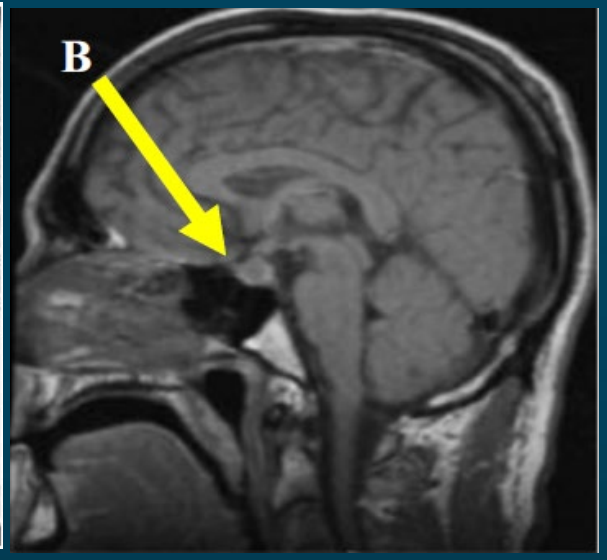
Colitis[2]



Hepatitis[3]



Pneumonitis[4]



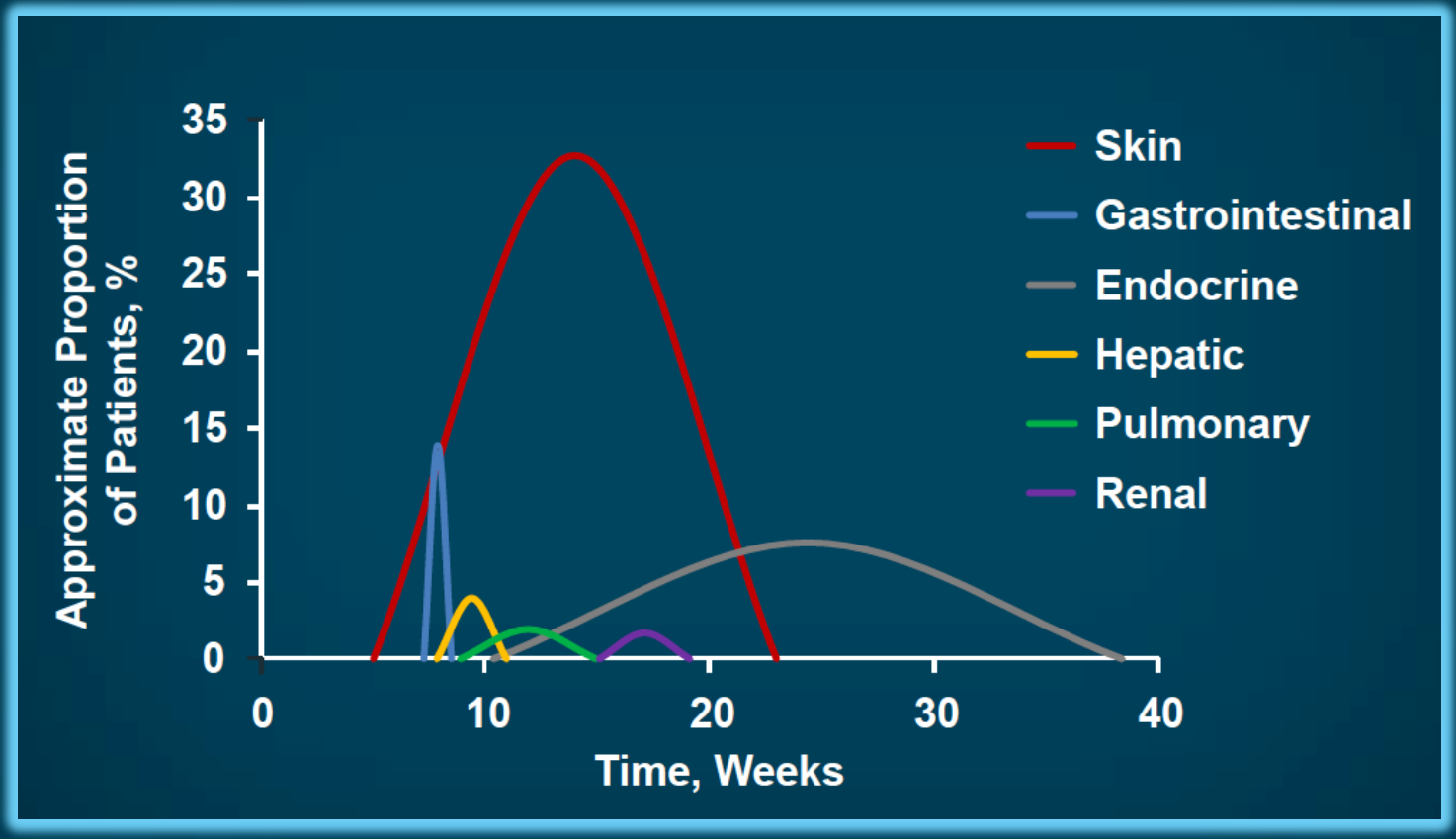
Hypophysitis[5]

Rare adverse events

- Pneumonitis
- Kidney toxicities[6]

1. Koelzer VH, et al. *J Immunother Cancer* 2016;4:47. 2. Geukes Foppen MH, *ESMO Open*. 2018;3(1):e000278. 3. Sanjeevaiah A, et al. *J Gastrointest Oncol.* 2018; 9: 220–224. 4. Nishino M, et al *N Engl J Med* 2015; 373:288-290. 5. Blansfield JA et al. *J Immunother.* 2005;28:593-598. 6. Puzanov I, et al. *J Immunother Cancer*. 2017;5:95.

Kinetics of irAEs (any grade) Associated with Nivolumab

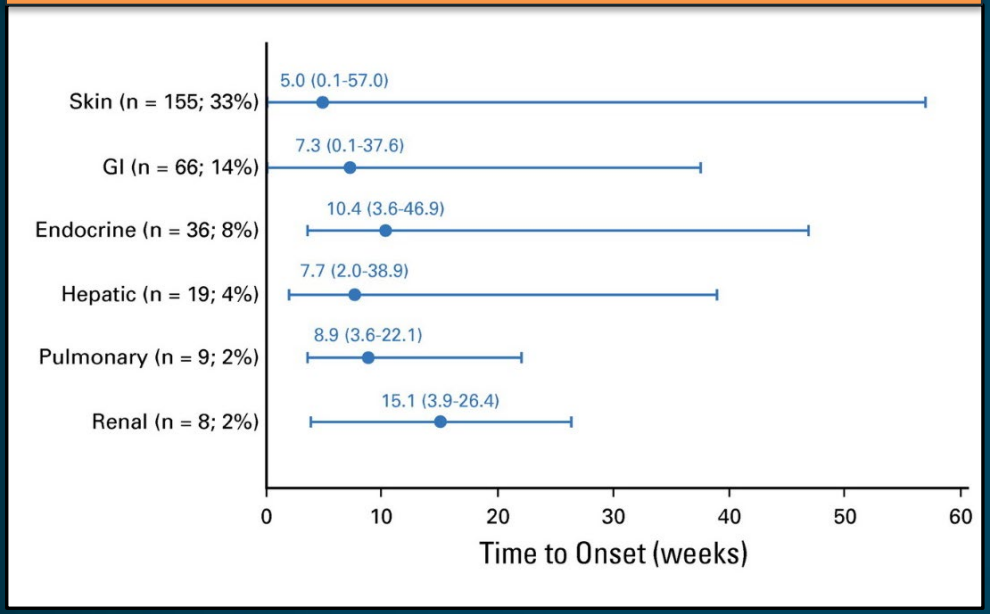


The beginning and end of each curve represents the median time to onset and median time to resolution, respectively. Each peak reflects incidence off the AE.

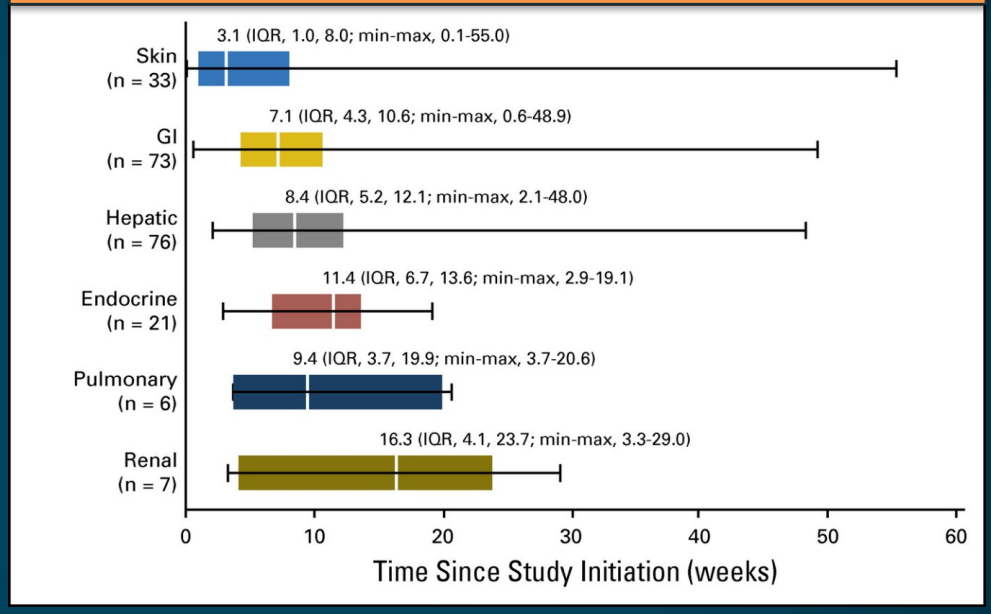
Weber J, et al. *JCO* 2017;35(5):785-92.

Time to Onset of Immune-Related Toxicities

Nivolumab (any grade)



Ipilimumab/Nivolumab (Grade 3/4)



Weber J, et al. *JCO* 2017;35(5):785-92. Sznol M, et al. *JCO*. 2017;35(34):3815-22.

Impact of irAEs and Immunosuppression on Nivolumab Response

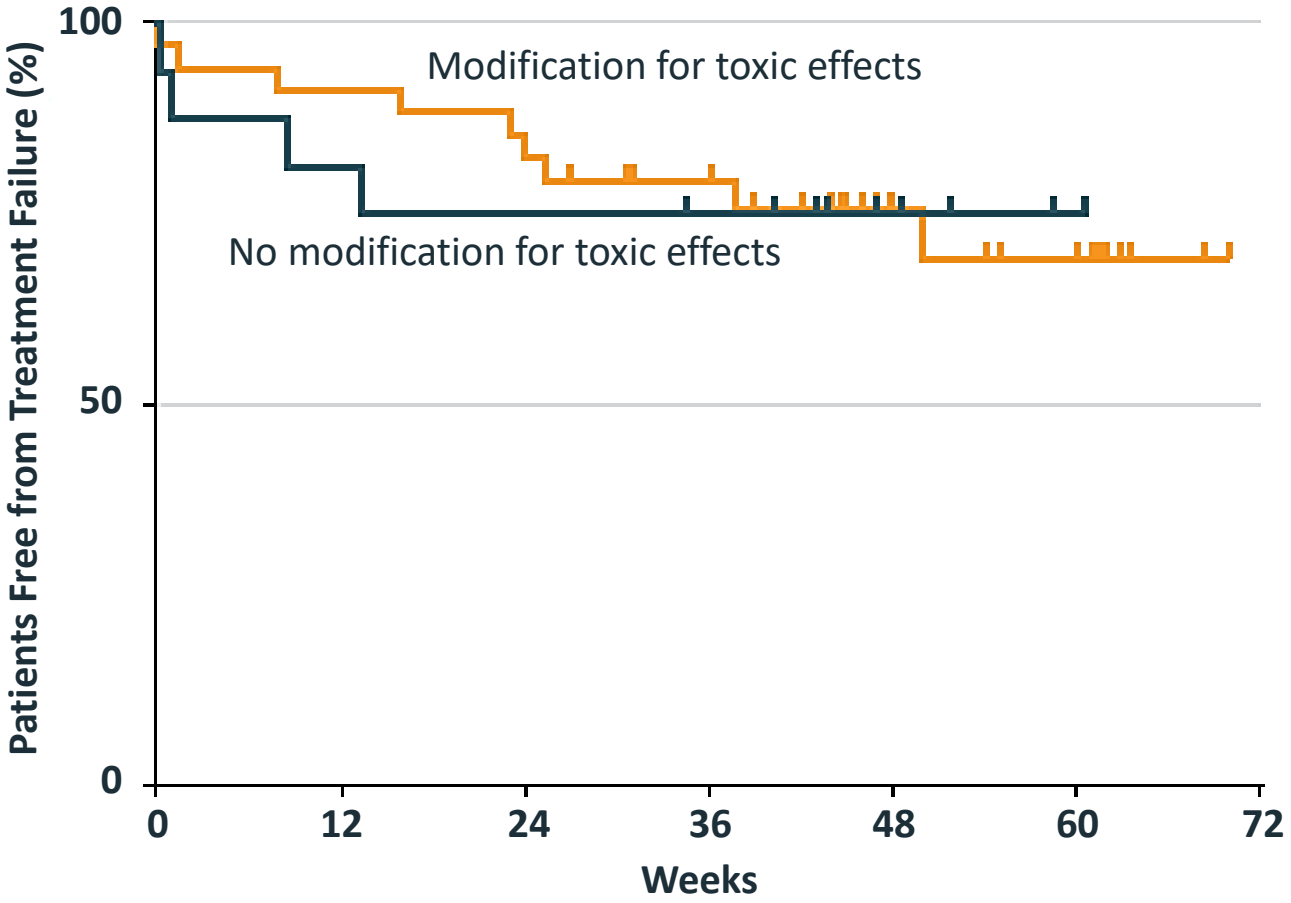
Impact of Treatment-Related Select AEs and IM Use on Response to Nivolumab Therapy

		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.

Weber J, et al. *JCO* 2017;35(5):785-92.

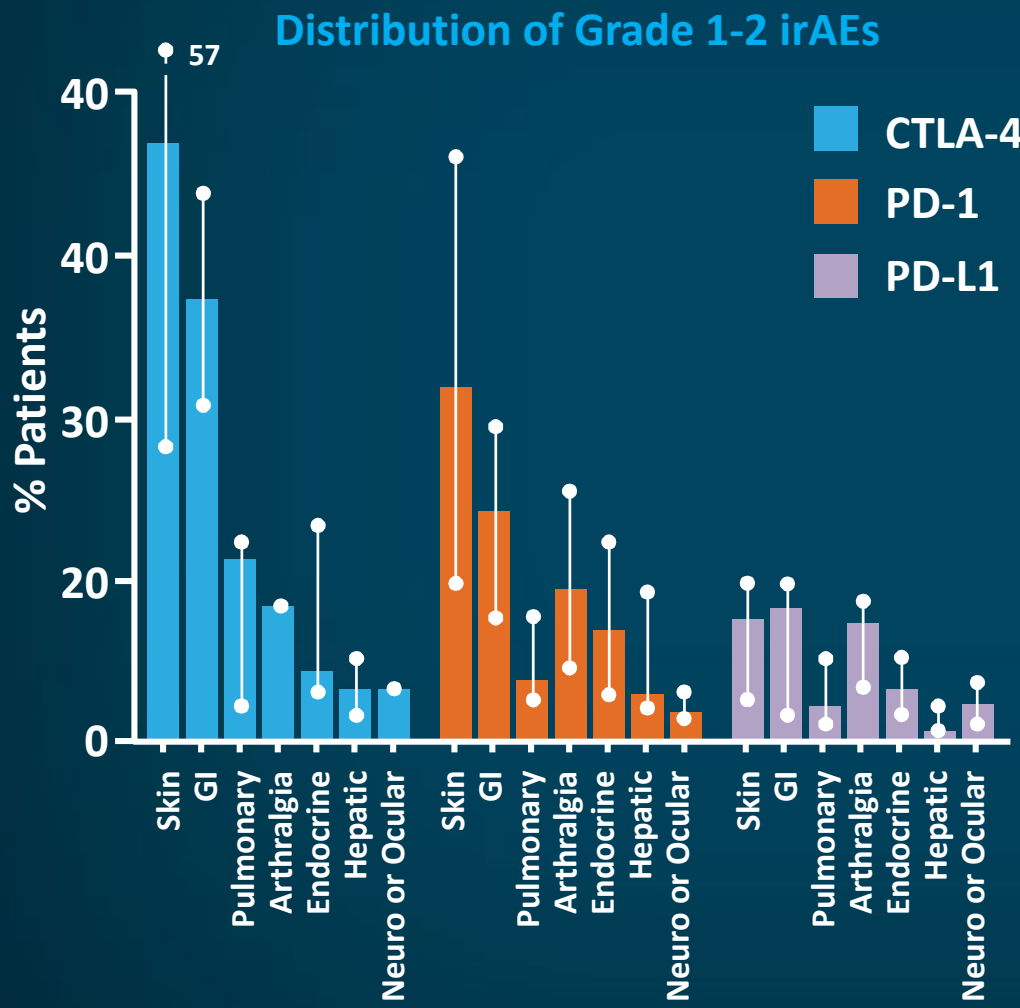
Impact of irAEs on Ipilimumab/Nivolumab Response

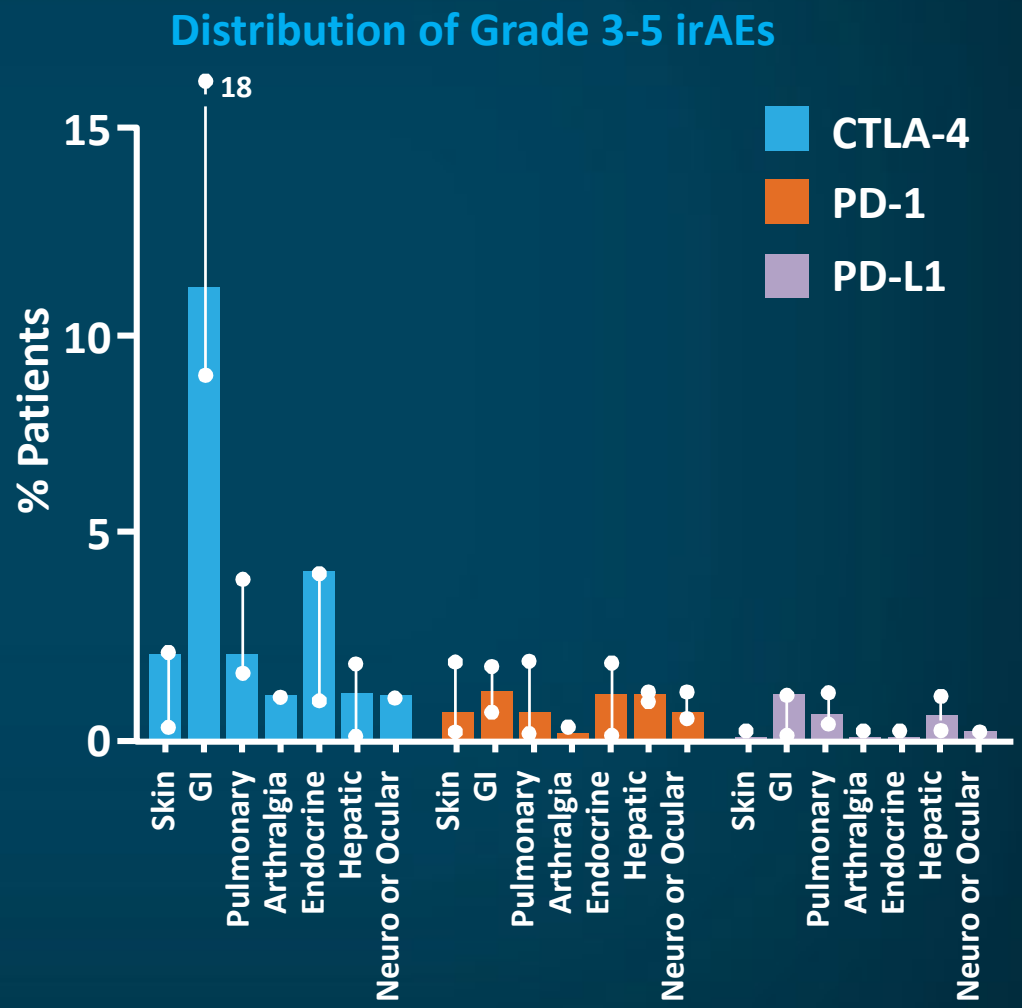


No. at risk							
Modification	34	31	27	21	12	7	0
No modification	16	13	12	11	4	1	0

Shoushtari et al. *JAMA Oncology*. 2018;4(1):98-101.

Distribution of Toxicities by Grade





Puzanov I et al. *J Immunother Cancer*. 2017; 5: 95. Michot JM et al. *Eur J Cancer*. 2016;54:139–148.

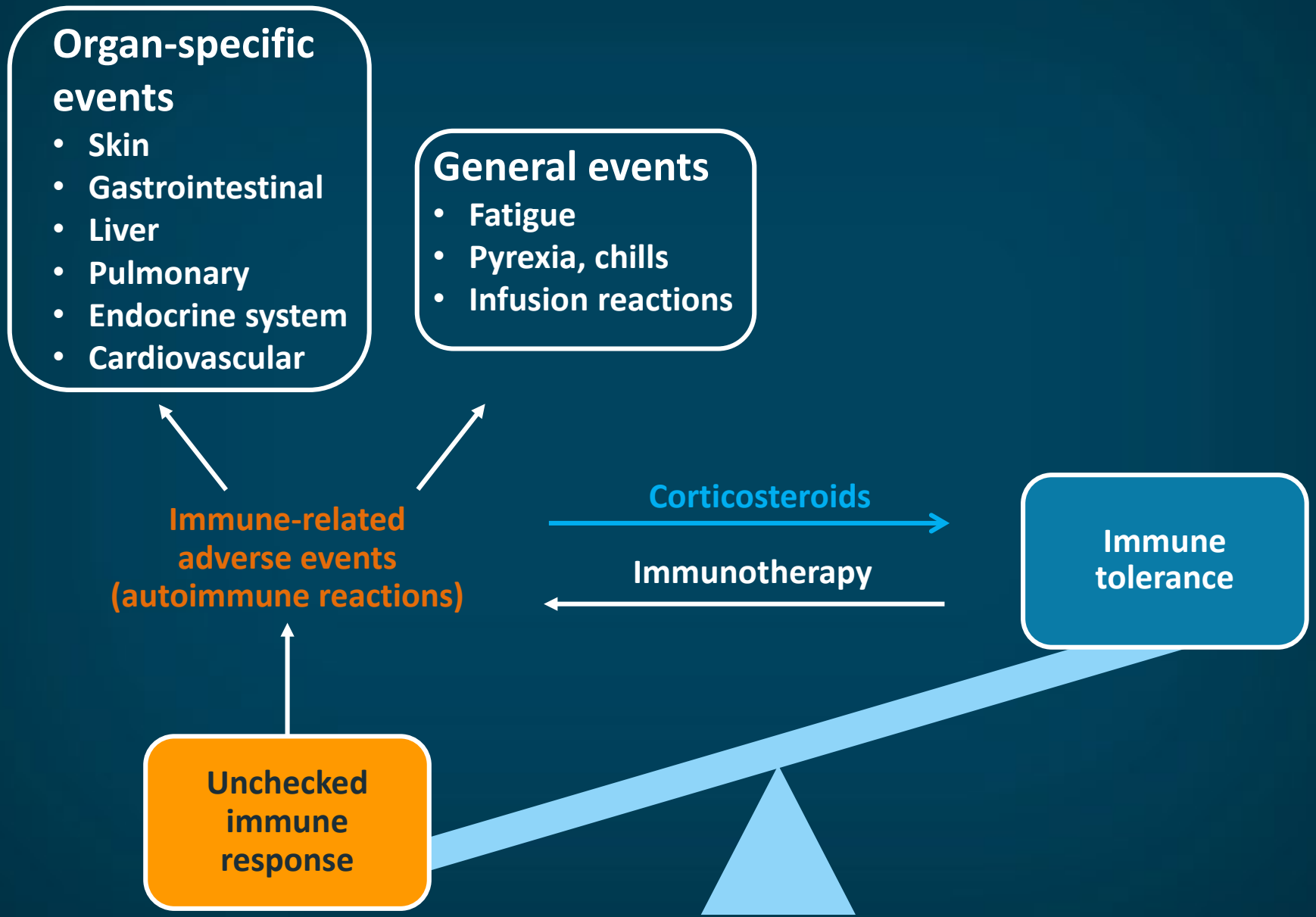
General Management of irAEs

Toxicity Grade	Management of irAE	Treatment with Checkpoint Inhibitor	Management of Persistent/Recurrent irAE
1	Symptomatic treatment; no systemic immunosuppression	Continue	n/a
2	Initiate systemic steroids for select irAEs and recurrent toxicities	Consider holding	Systemic steroids; may continue checkpoint inhibitor
3	Systemic steroids with prolonged taper over > 4 weeks	Hold or discontinue	Additional immunosuppression; discontinue checkpoint inhibitor
4	Systemic steroids with prolonged taper over > 4 weeks	Discontinue (except for endocrine irAE)	Add additional immunosuppression

Immunosuppressive regimens:

- Prednisone 1-2 mg/kg/day or equivalent
- Infliximab 5 mg/kg q2 weeks as needed
- Mycophenolate 500 - 1000 mg BID
- Anti-thymocyte globulin 1.5 mg/kg IV qd x 7-14 days
- Tacrolimus 0.1-0.15 mg/kg/day IV (trough 5-20 ng/mL)

Toxicities With Immune Checkpoint Inhibitors



Summary

- Multiple biomarkers are emerging to stratify the likelihood of treatment response (especially the T cell-inflamed phenotype and tumor mutational burden).
- Toxicities from immunotherapy are very different from chemotherapy, however they have been well-described.
- Inflammatory toxicities from immunotherapy can effect any organ system, however easy to follow treatment algorithms exist for toxicity management.