University of Colorado **Anschutz Medical Campus**

Immunotherapy Toxicities and Lung Biomarkers

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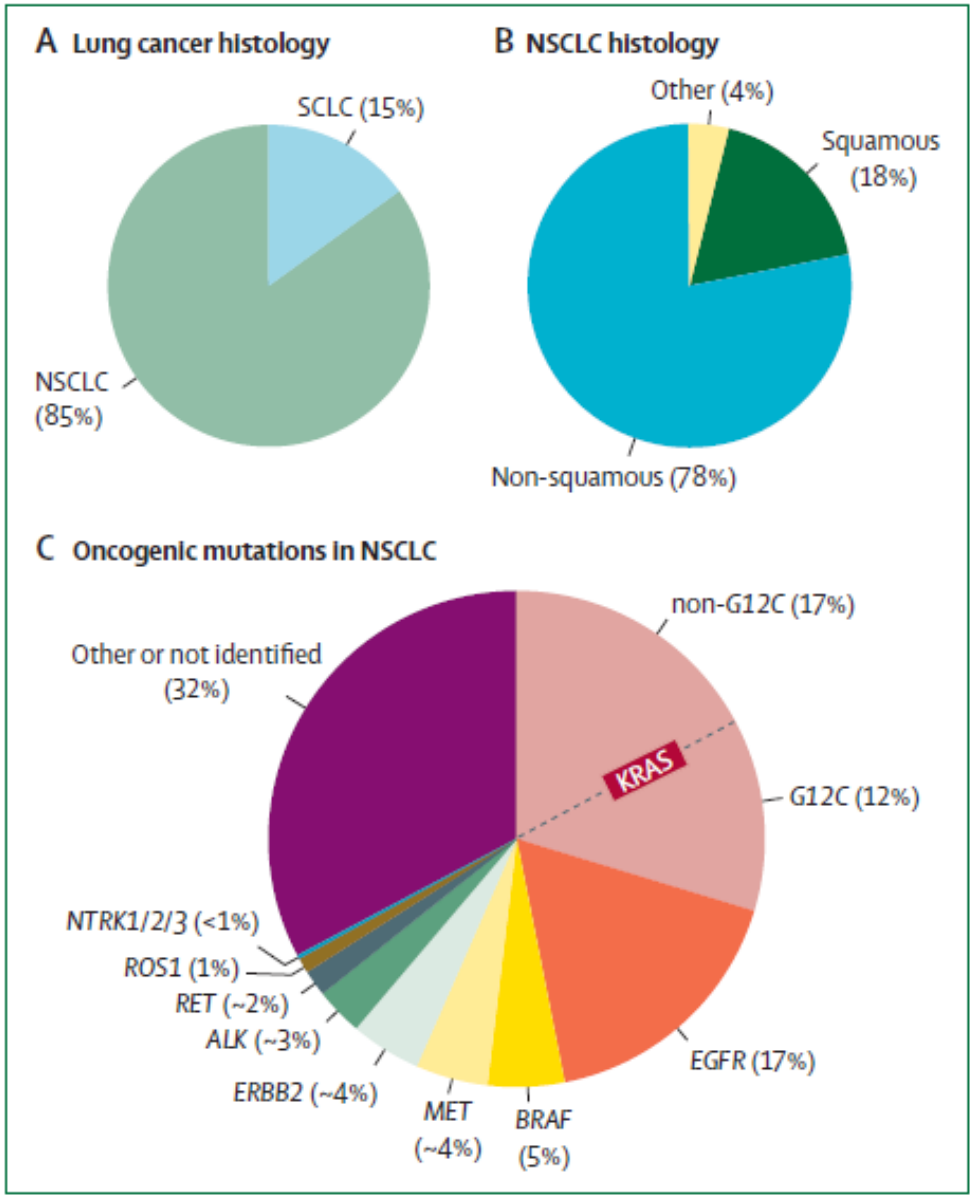
Immunotherapy for Lung Cancer



- ~240,000 patients diagnosed / year
- ~160,000 patients / year eligible to receive IO as part of SOC
  - 27,000 ES-SCLC
  - Stage IV NSCLC
    - 20,000 SQ NSCLC
    - 50,000 NSQ NSCLC (AGA excluded)
  - Stage II or III
    - PACIFIC/IMpower010/PEARLS/CM816/KN-617
    - 61,000 patients

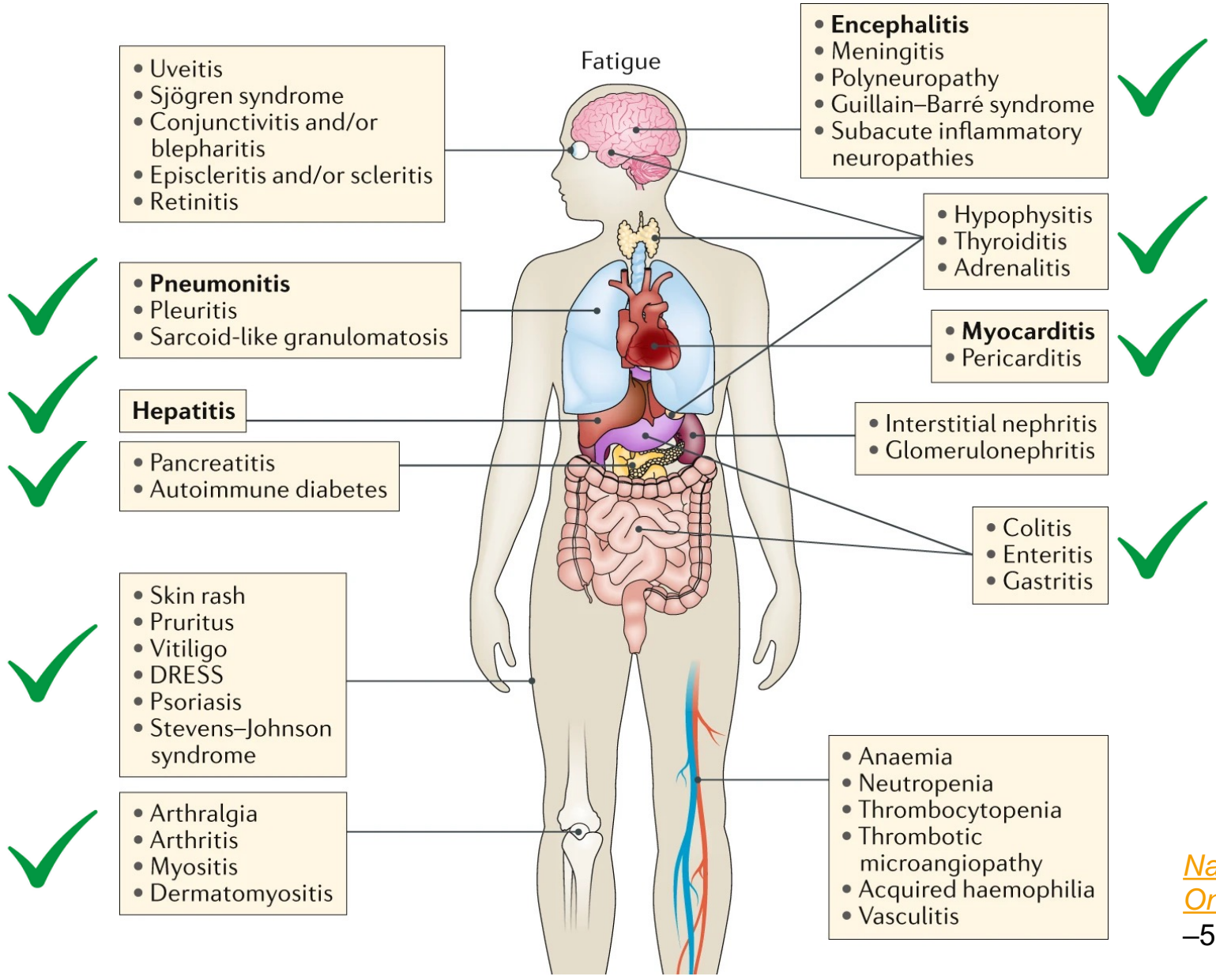
Siegel RL *et al.* CA Cancer J Clin.2023;73:17–48
Thai AA *et al.* Lancet 2021; 398: 535–54

Challenges of Immunotherapy for Cancer

- PD-L1 IHC is the only biomarker
  - Therapeutic decisions for IO based therapy
  - Some predictive role
- Unable to predict who will benefit
- Unclear optimal duration of therapy
- Primary and acquired resistance mechanisms are unknown

- Toxicities can be lifelong
- Identifying IrAEs requires integration of multiple non-specific, non-sensitive data points: clinical, laboratory, radiographic
- IrAEs can happen ANY time
- Unclear why some people develop and IrAE

IrAE Impacts Every Organ



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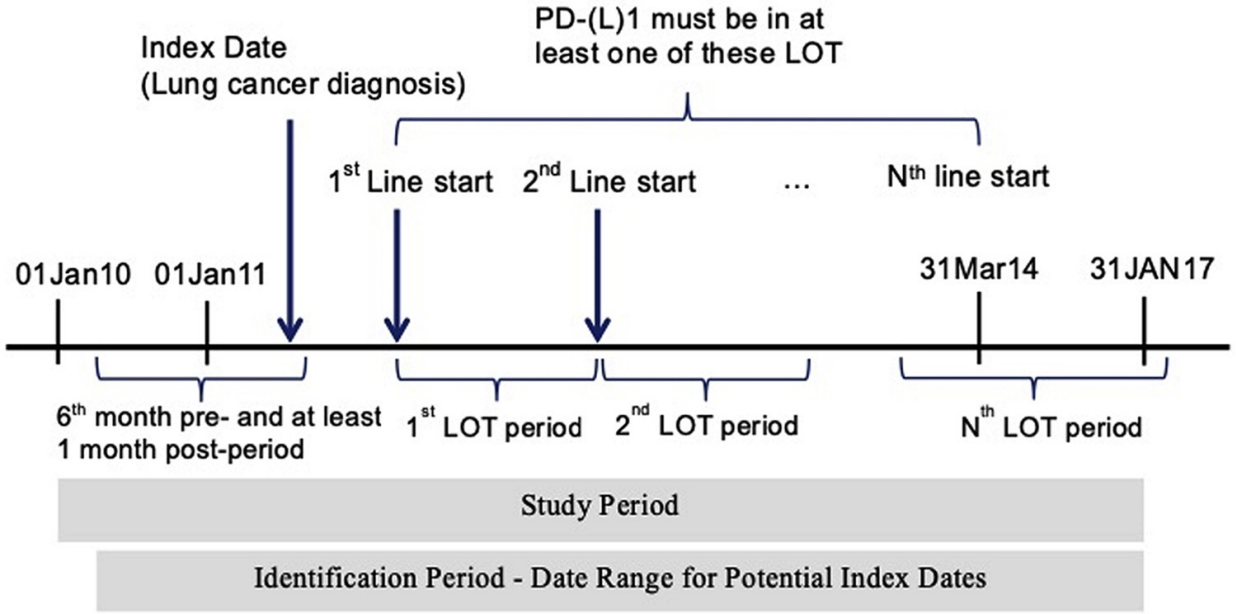
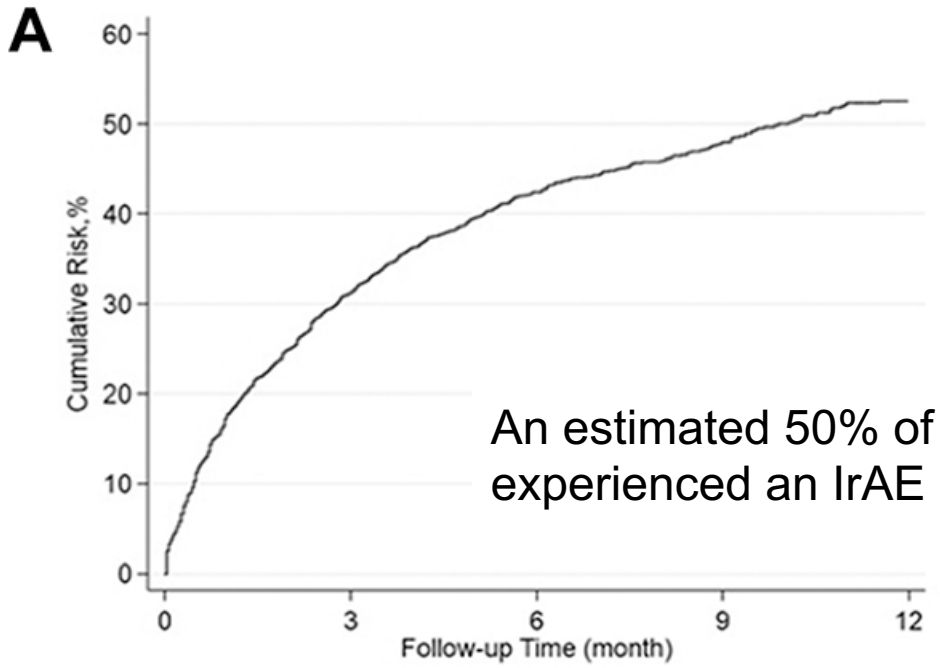
Nature Reviews Clinical Oncology **volume 16**, pages563–580(2019)

Frequency of IrAE in NSCLC



Retrospective review of insurance claims



An estimated 50% of patients experienced an IrAE in 12 mo

	Month 0	Month 3	Month 6	Month 9	Month 12
Number at Risk	3164	1835	804	391	211
Cumulative Risk % (CI)	0%	31.2 (29.6, 32.9)	42.4 (40.5, 44,4)	47.9 (45.7, 50.2)	52.5 (49.9, 55.2)

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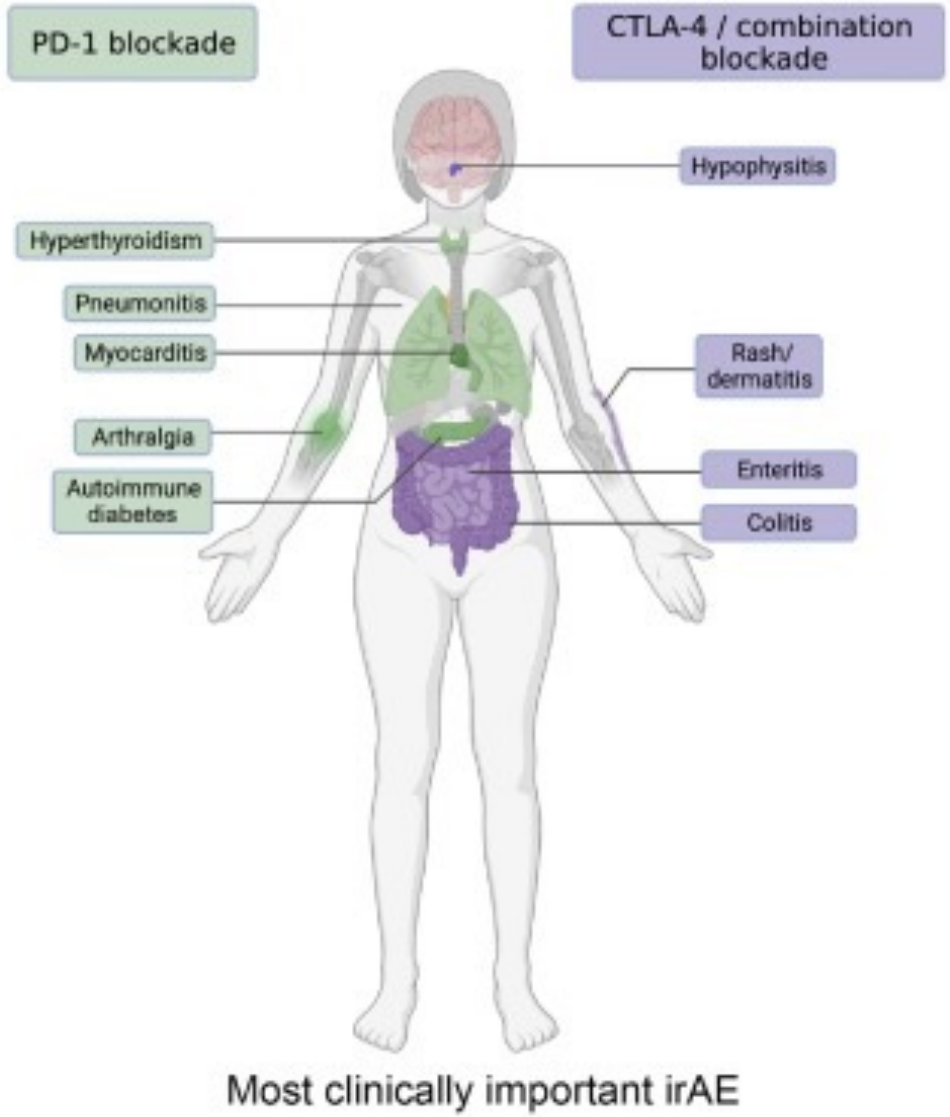
Cathcart-Rake EJ *et al. Clin Lung Cancer. 2020 Sep; 21(5): 421–427.e2.*

Class of ICI and IrAE in NSCLC

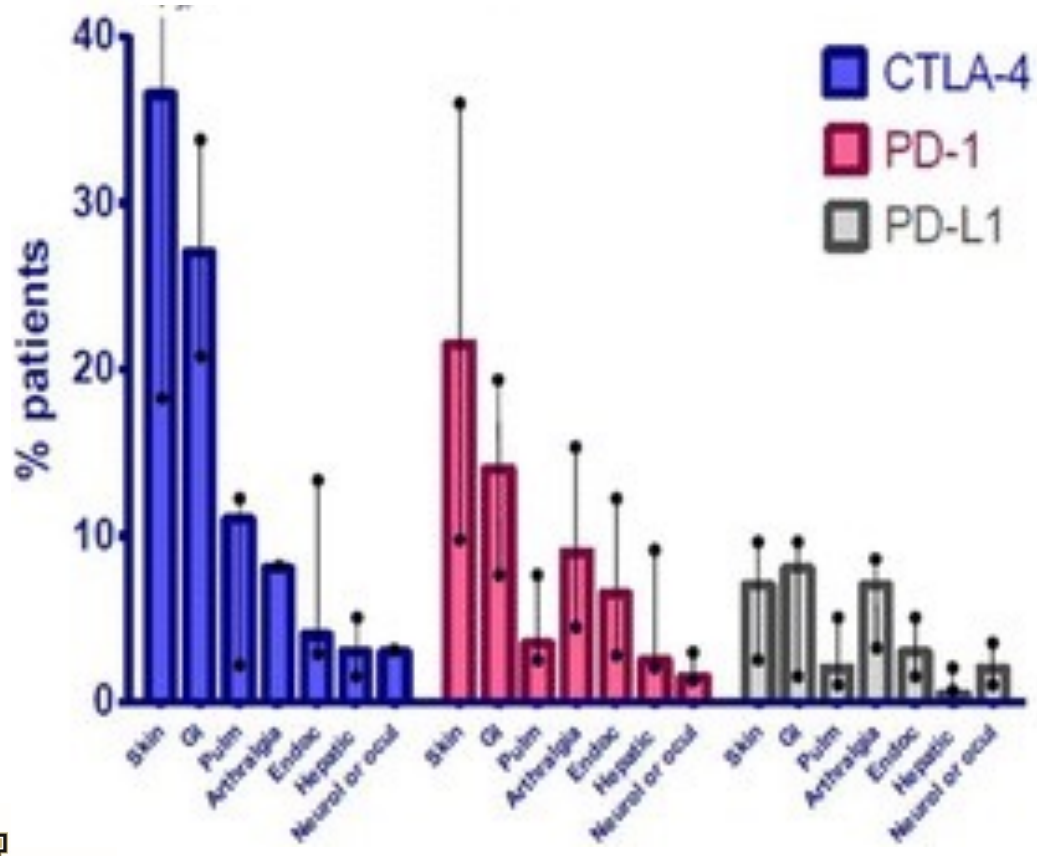


- CTLA-4
  - reduces the activation of naïve T cells by APCs
  - may interfere with ongoing stimulation of T cells in inflamed tissues
  - Major MoA of Tregs
- PD-1/PD-L1
  - Regulation of activated T cells

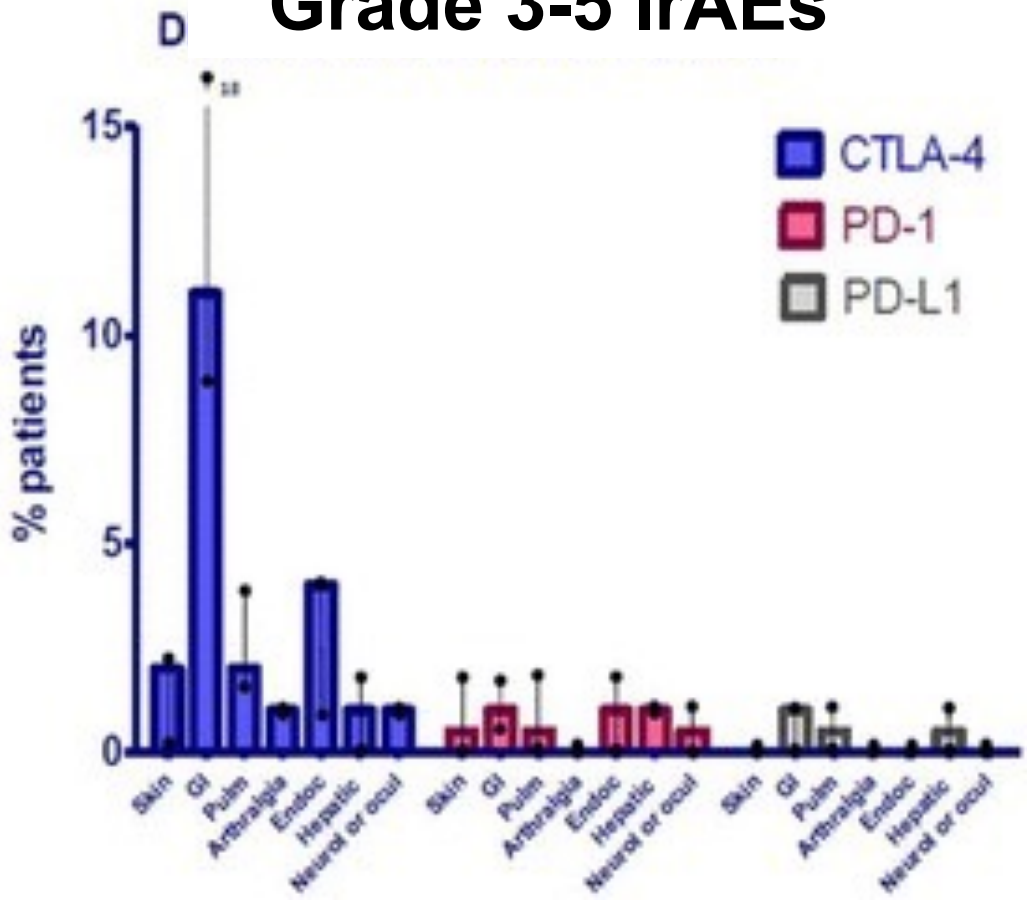
Wang SJ *et al.* Trends in Cancer Volume 9, Issue 7, July 2023, Pages 543-553

Severity of IrAE in NSCLC

Grade 1-2 IrAEs



Grade 3-5 IrAEs



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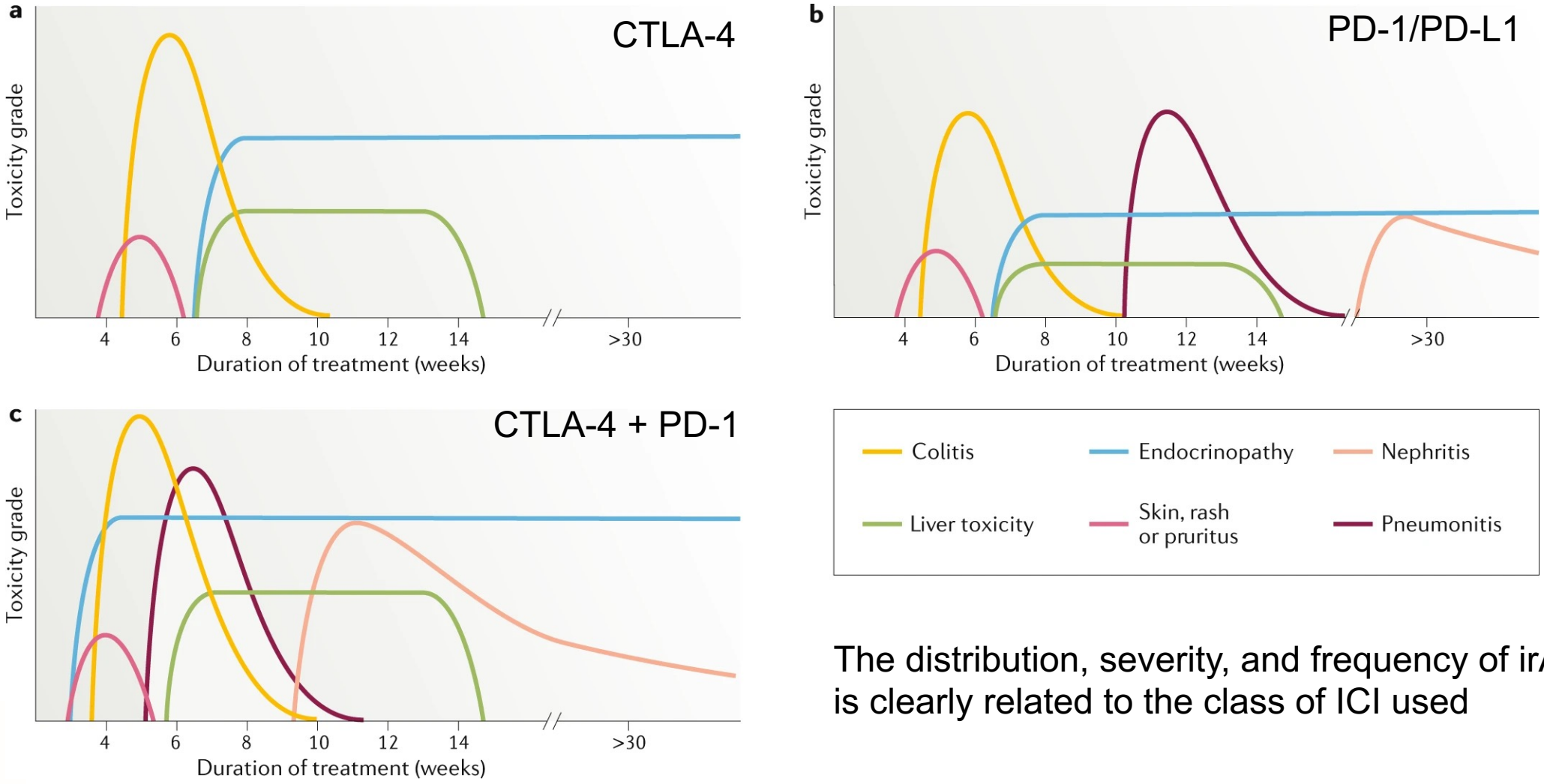
I. Puzanov *et al.* J Immunother Cancer. 2017; 5: 95

IrAE Timing: Patterns of Development



The distribution, severity, and frequency of irAEs is clearly related to the class of ICI used

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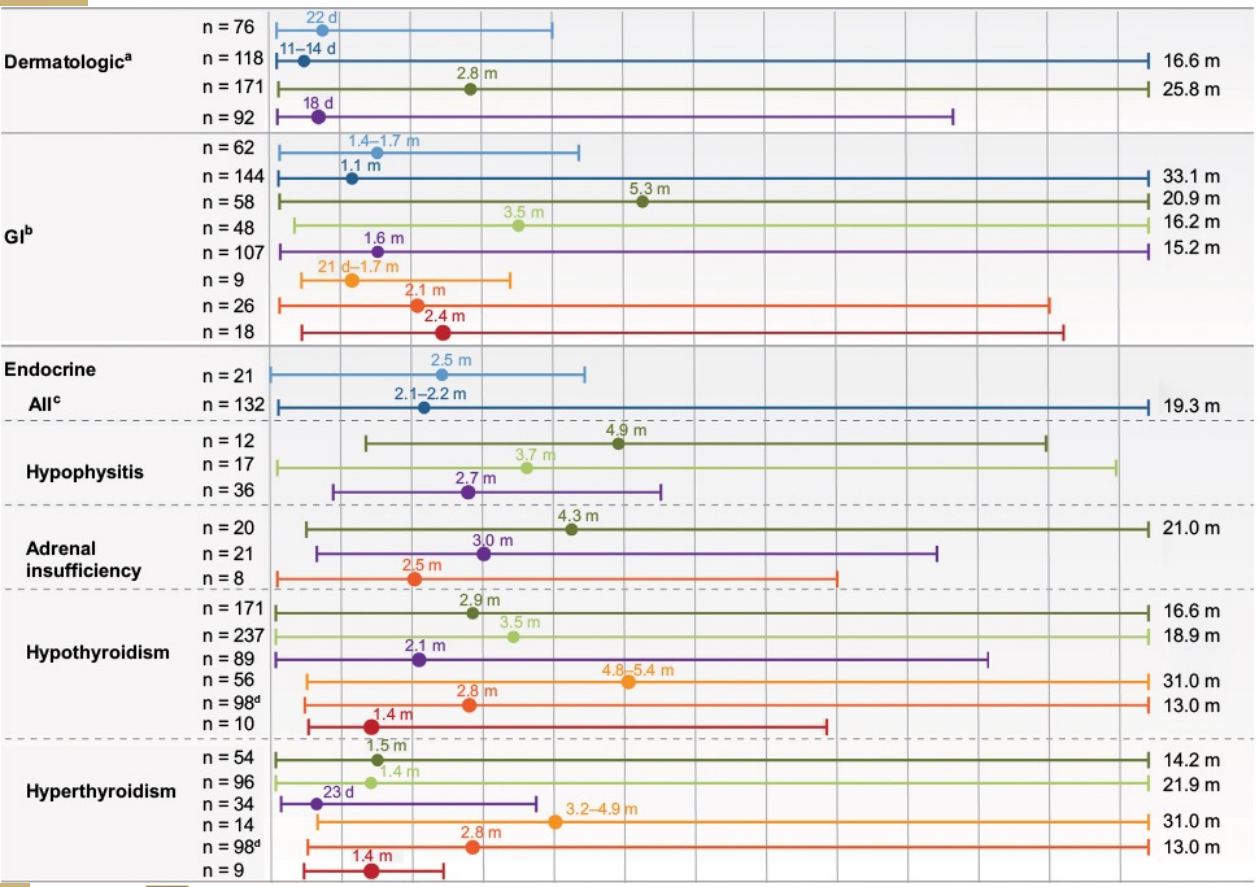
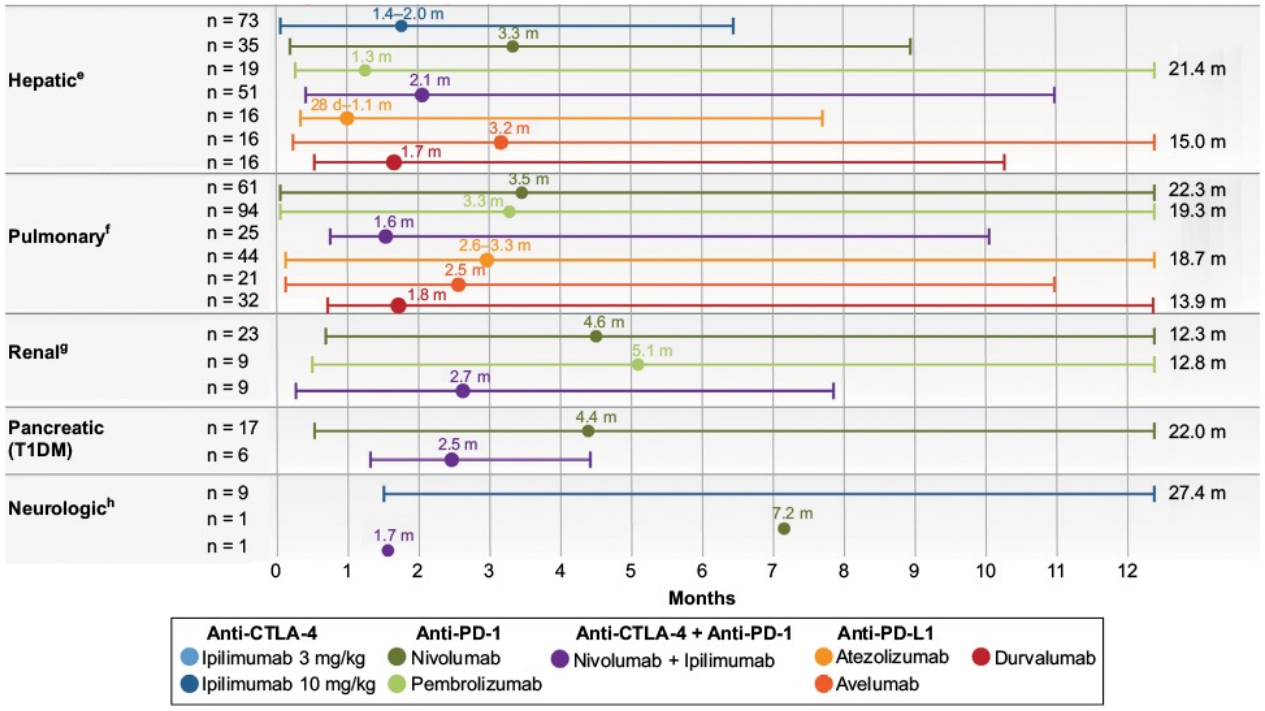
Nature Reviews Clinical Oncology **volume 16**, pages563–580(2019)

IrAE Timing: Patterns of Development





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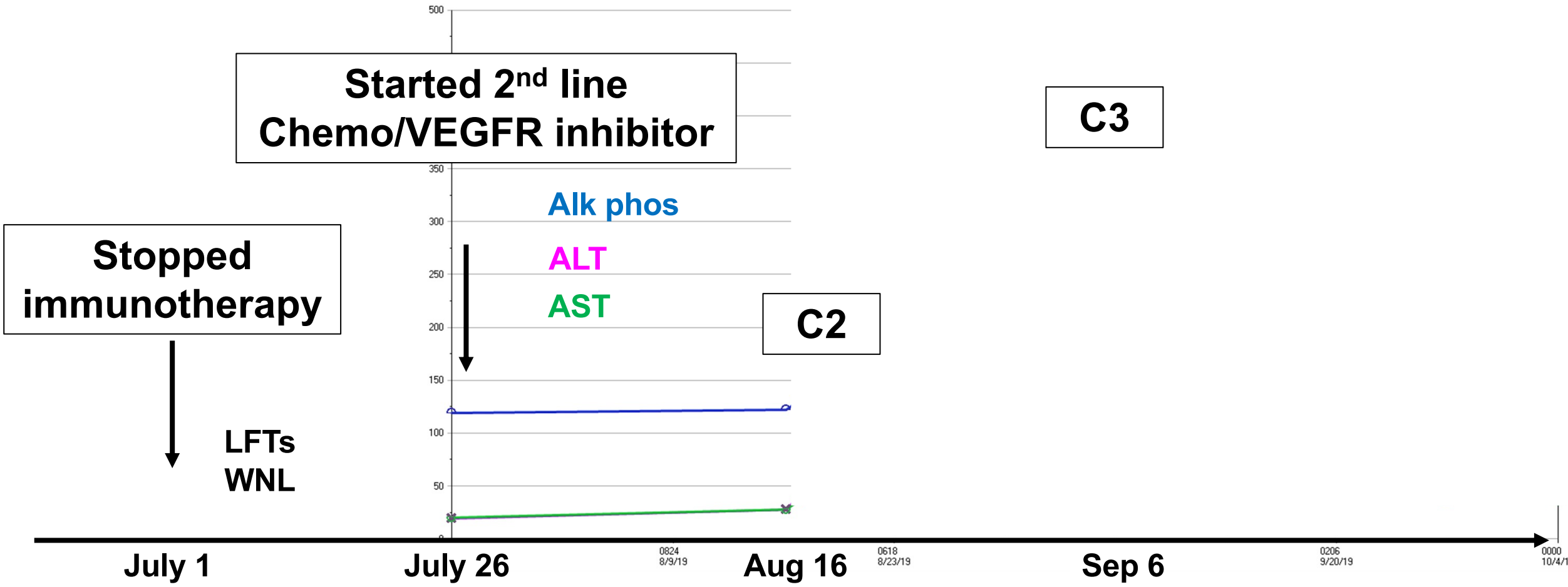
Adapted from: Davis M and Duffield EA. ImmunoTargets and Therapy 2017:6 51–71

IrAE Timing: Never quite out of the woods



Conventional Cancer Therapy

Stearman Model 75

Drug/metabolite directly responsible for efficacy and toxicity

Predictable window of toxicity

MoA predicts AEs

Immunotherapy

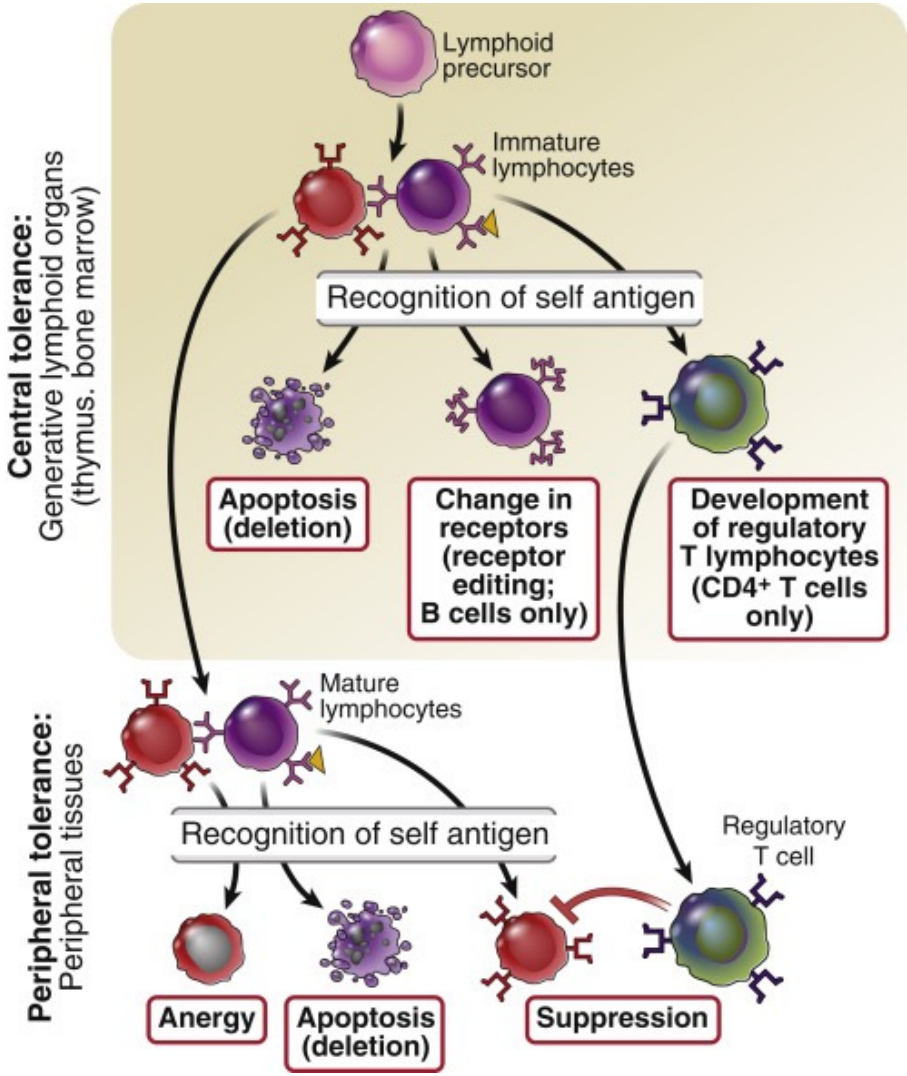
The ‘drug’ is the patient’s immune system

Downstream modulation of a patient’s immune system mediates both response and toxicity… and not necessarily through the same mechanism

The Immune System Prevents Autoimmunity… most of the time

Central tolerance in the thymus and bone marrow eliminates T cell and B cell clones that react against self antigens

Peripheral tolerance is enforced via Tregs, iDCs, and immune check points (i.e. CTLA-4, PD-1)



https://www.onlinebiologynotes.com/immunological-tolerance-central-and-peripheral/

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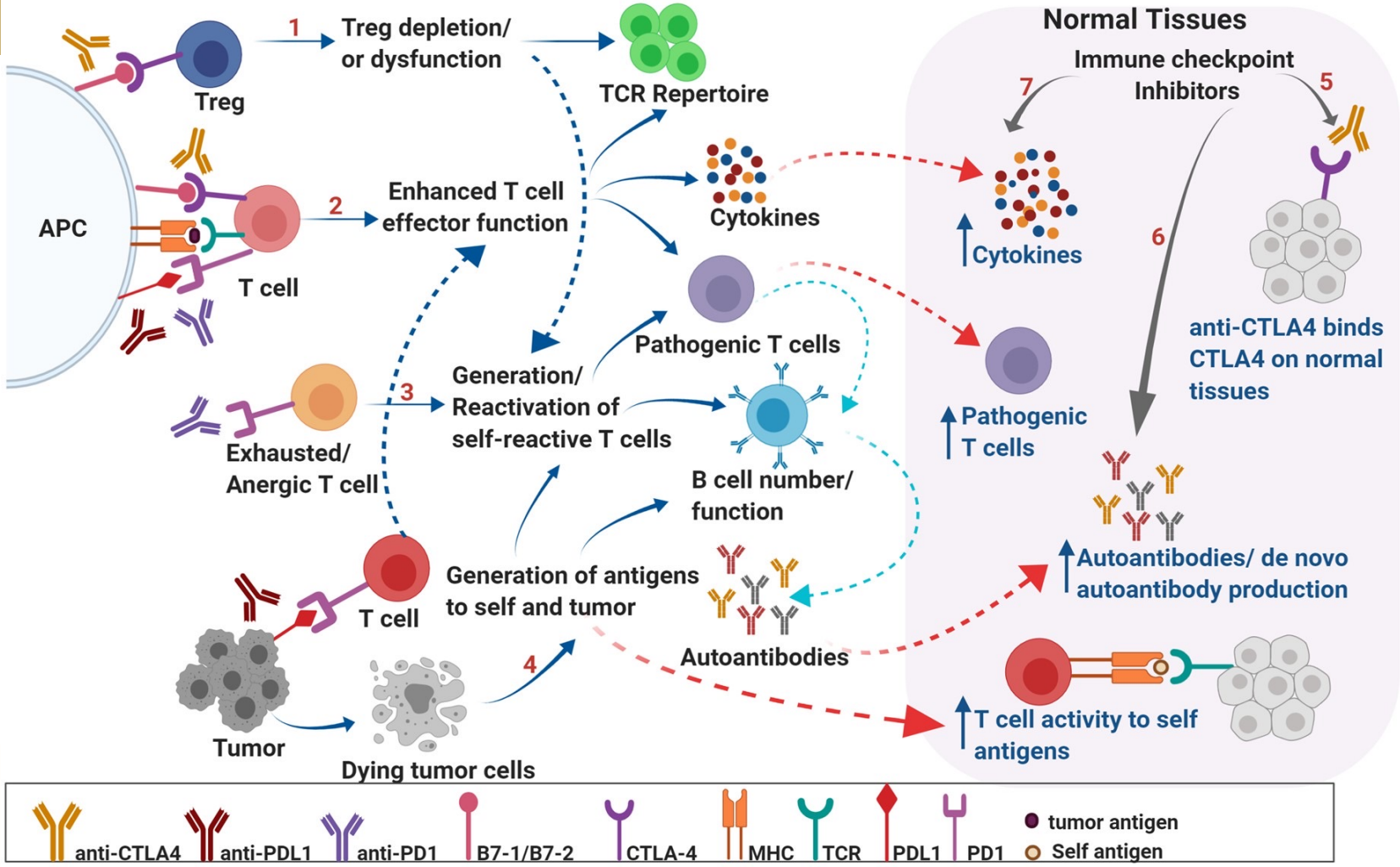
Potential Mechanisms of IrAEs



- Loss of Treg function
- Increased activity of effector T cells
- Re-activation of peripherally tolerant T cells
- Release of self antigen from tumors
  - Autoantibodies

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Clin Chem, Volume 66, Issue 6, June 2020, Pages 779–793

IrAE Risk Factors: Pre-existing AD

- Ipilimumab in melanoma
- 30 patients with pre-existing autoimmune conditions
- 50% experienced IrAE or flare of underlying autoimmune disease

Table 2. Autoimmune Exacerbations and Grade 3 to 5 Immune-Related Adverse Events

Patient No.	Baseline Condition	Autoimmune Exacerbation	Treatment	Immune-Related Adverse Event	Treatment	Outcome Notes
2	Sarcoidosis	...	...	Glaucoma	Ocular steroids	
3	RA	Joint pain	As for hypophysitis	Hypophysitis	Prednisone 1 mg/kg tapered over 6 wk; now receiving 7.5 mg	Durable CR
4	RA	...	...	Thyroiditis	Prednisone 1 mg/kg tapered over 2 wk	
5	Psoriasis	Worsening plaques	As for colitis	Colitis	Methylprednisolone 2 mg/kg tapered over 6 wk	After 1 dose
6	Psoriasis, Graves disease	...	...	Hypophysitis	Prednisone 30 mg ×1 wk, transition to hydrocortisone over 5 d	PR
8	RA, polymyalgia rheumatica	Joint pain, myalgias	Prednisone 30 mg/d tapered over 1 mo	...	...	After 3 d
9	RA	Joint pain	Prednisone 15 mg/d down to 10 mg	...	...	After 7 mo
11	Transverse myelitis	...	...	Colitis	Prednisone 1 mg/kg tapered over 8 wk	
12	Crohn disease	...	...	Colitis	Methylprednisolone 1 mg/kg tapered over 8 wk	After 1 dose
14	Ulcerative colitis	Diarrhea, disease flare	Infliximab, dexamethasone 2 mg daily[a]	...	...	PR
15	Inflammatory arthritis[b]	Joint pain	As for colitis	Colitis	Prednisone 1 mg/kg tapered over 4 wk, infliximab	...
20	Psoriasis	...	...	Hypophysitis	Prednisone 50 mg ×1 dose, then 5 mg daily	...
23	Sarcoidosis	Hypercalcemia, renal insufficiency	Prednisone 25 mg/d, tapered to 20 mg after 4 wk	...	...	Ongoing SD
24	RA	Joint pain	Prednisone 10 mg/d, now receiving 8 mg/d	...	...	Ongoing PR
28	Psoriasis	...	...	Presumed colitis grade 5	Methylprednisolone 1 mg/kg	Patient died

Abbreviations: CR, complete response; ellipses, none; PR, partial response; RA, rheumatoid arthritis; SD, stable disease.

[a] Receiving dexamethasone for brain metastases; infliximab was added with onset of diarrhea.

[b] Patient developed a chronic, inflammatory-appearing arthritis during nivolumab therapy that improved with use of low-dose steroids and hydroxychloroquine.

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Johnson DB *et al.* JAMA Oncol. 2016;2(2):234-240. doi:10.1001/jamaoncol.2015.4368

IrAE Risk Factors: Pre-existing AD

- Anti-PD-1 in melanoma
- 52 patients with pre-existing autoimmune conditions
  - 38% experienced flare of underlying AD
- 67 patients with prior Gr 3 or Gr 4 ipilimumab toxicity
  - 2 experienced Ipi IrAE

Table 2. Toxicity of anti-PD-1 antibodies in patients with autoimmune disorders

	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%)	

Table 4. Toxicity of anti-PD-1 antibodies in patients with major ipilimumab toxicity

	Number (%) (*N* = 67)	Details
Ipi irAE recurrence on PD1		
No	65 (97%)	
Yes	2 (3%)	Arthritis, colitis
Other irAEs with PD1		
No	44 (66%)	
Yes	23 (34%)	

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Menzies AM *et al.* Annals of Oncology Volume 28, Issue 2, February 2017, Pages 368-376

IrAE Risk Factors: Solid Organ Transplant

- Pooled analysis of 64 patients with solid organ transplants
- Overall rejection rate with IO ~41%
  - Rate with PD-1 > CTLA-4
- 71% who experienced rejection developed organ failure

Table 1. Characteristics of patients with organ transplant who received treatment with an ICI

Characteristics	Total, *n* = 64 (100%)	No rejection, *n* = 38 (59%)	Rejection, *n* = 26 (41%)
Solid organs			
Kidneys	39	21 (54)	18 (46)
Liver	19	13 (68)	6 (32)
Heart	5	4 (80)	1 (20)
Cornea	1	0 (0)	1 (100)
Type of immunotherapy			
CTLA-4 inhibitor	13	10 (77)	3 (23)
PD-1/PD-L1 inhibitors	43	23 (53)	20 (47)
Sequential ICIs	8	5 (62.5)	3 (37.5)
Number of doses, median (range)			
CTLA-4 inhibitors	4 (1–4)	4 (4–4)	1 (1–2)
PD-1 inhibitors	3 (1–25)	4 (1–25)	2 (1–11)
Prior history of significant rejection			
Yes	8	3 (37.5)	5 (62.5)
No	33	19 (57)	14 (43)
Response to therapy			
Yes	25	16 (62.5)	9 (37.5)
CTLA-4 inhibitors	7	6 (86)	1 (14)
PD-1/PD-L1 inhibitors	15	9 (60)	6 (40)
Both	3	1 (33)	2 (66)
No	31	20 (64.5)	11 (35.5)
CTLA-4 inhibitors	6	4 (67)	2 (33)
PD-1/PD-L1 inhibitors	20	12 (60)	8 (40)
Both	5	4 (80)	1 (20)

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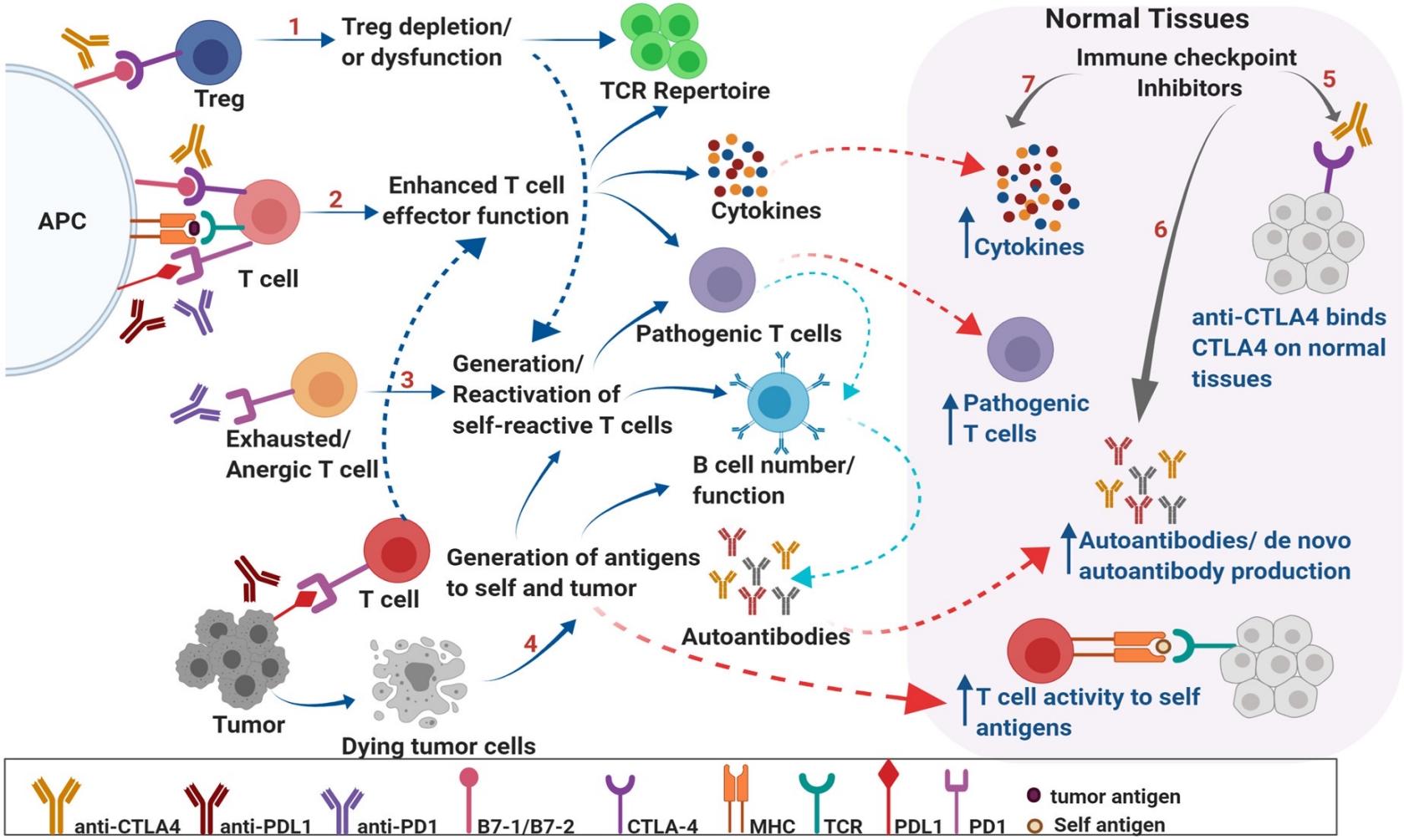
Kumar V *et al.* The Oncologist2020;25:505–514

Where are the Biomarkers for IrAE?

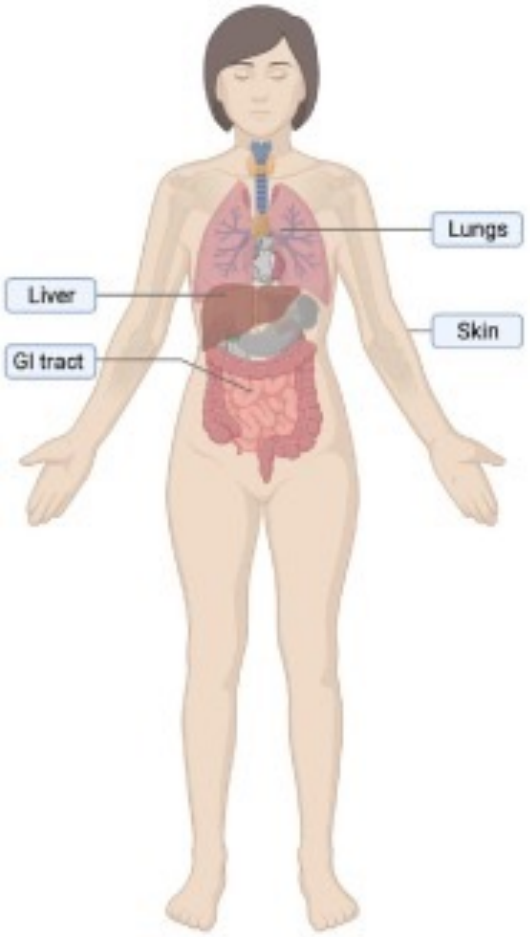


- Inadequate model systems
- Inter-rater reliability showed poor agreement for the incidence, severity, and timing of IrAEs
- Multiple mechanisms may result in the same IrAE

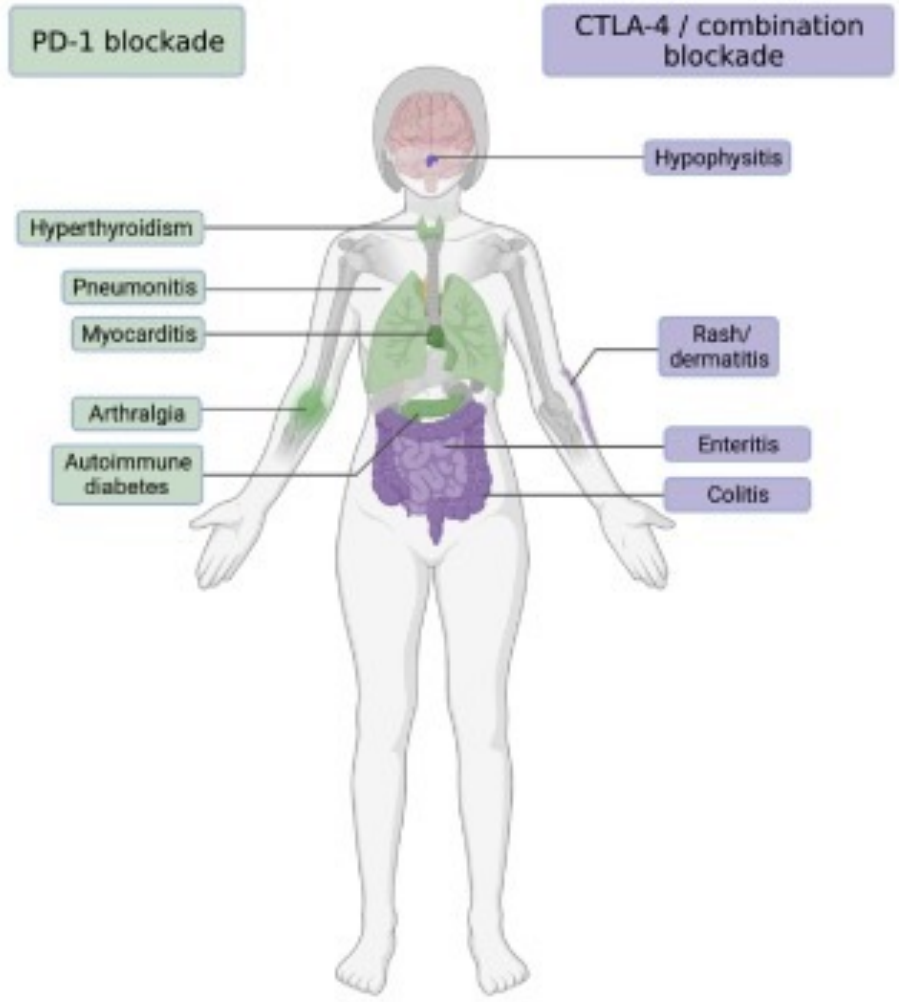
Clin Chem, Volume 66, Issue 6, June 2020, Pages 779–793

Major Barrier Organs as the Most Frequent Site of IrAE

- Large quantity of microbial and environmental antigens
- Immune cells at these sites are regulated by peripheral tolerance via CTLA-4 and/or PD-1/ PD-L1



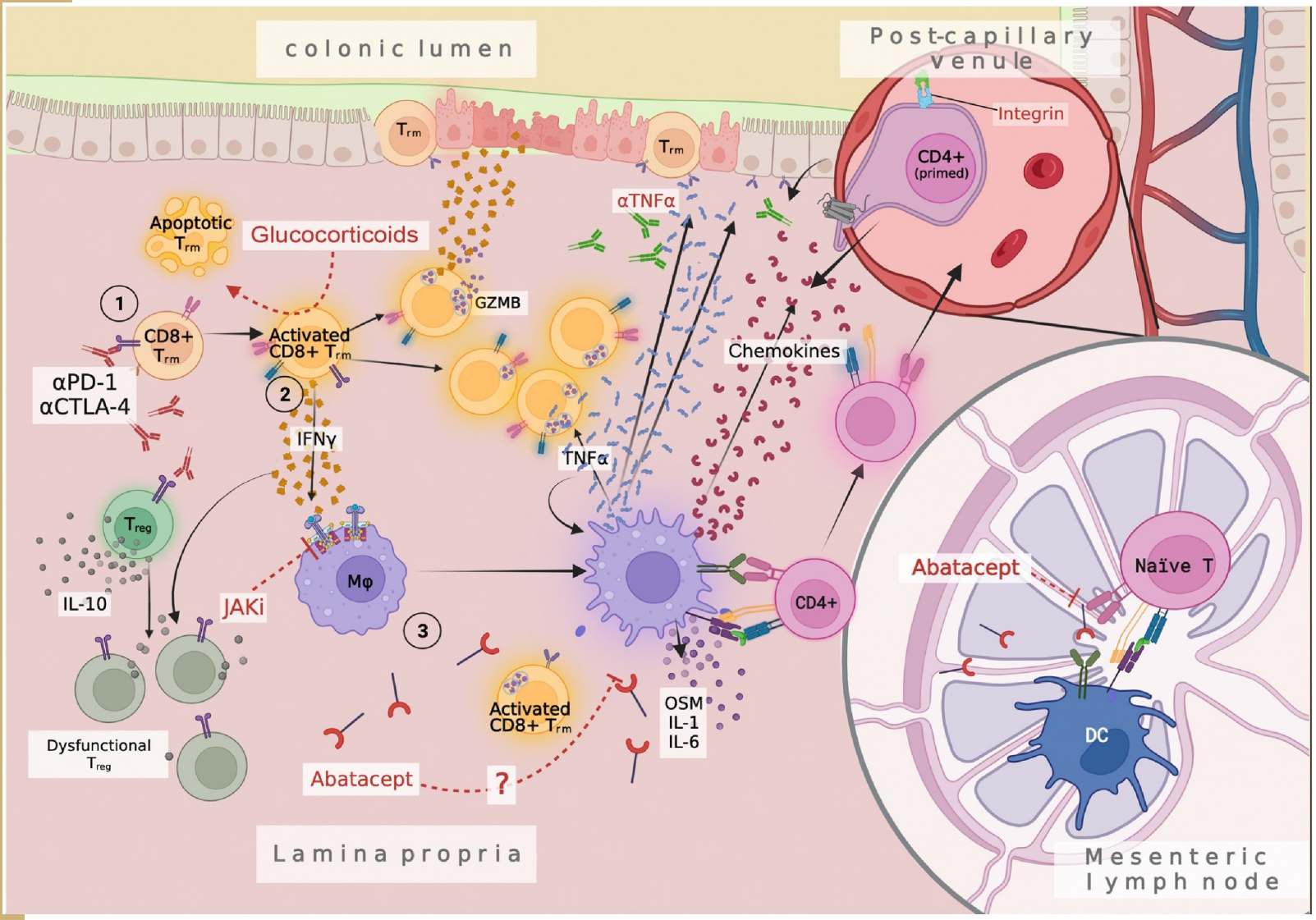
Major barrier organs



Most clinically important irAE

Wang SJ *et al.* Trends in Cancer Volume 9, Issue 7, July 2023, Pages 543-553

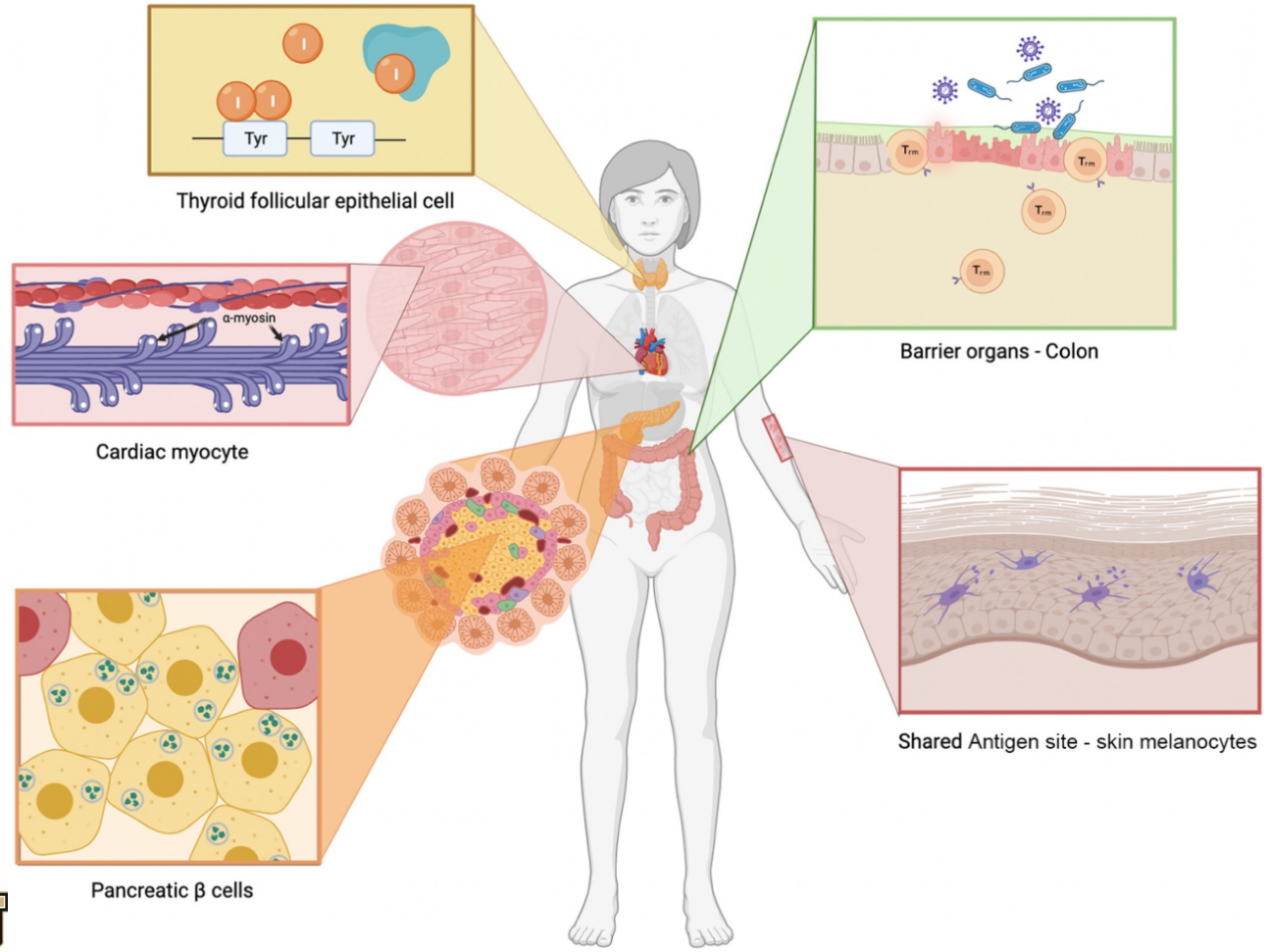
Drivers of ICI Colitis



- Biopsies of ICI colitis
- Expanded $CD8^+$ T cell population not present in controls that produce granzyme B and IFNg
- Population were TRMS
- Primarily recognize microbial antigens
- Overactivation disrupted normal tissue homestasis
- Why some not all?

Wang SJ *et al.* Trends in Cancer Volume 9, Issue 7, July 2023, Pages 543-553

What Drives Non-Barrier IrAEs?



- Tissues produce specialized proteins
- Expression of tissue specific proteins
- Shared antigens between tissues and tumor targets

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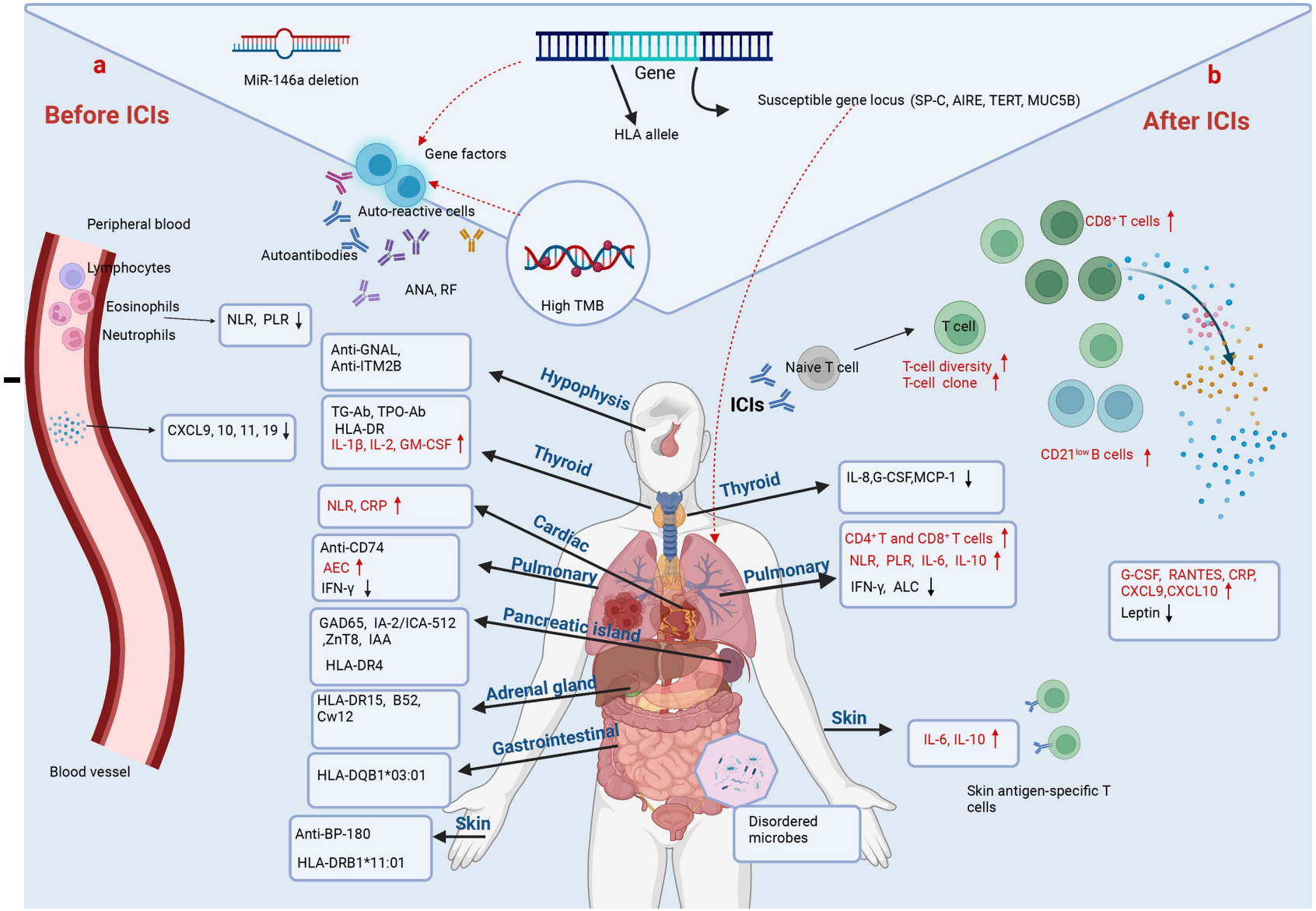
Wang SJ *et al.* Trends in Cancer Volume 9, Issue 7, July 2023, Pages 543-553

Predictive Biomarkers for IrAE

- Hypophysitis: pre-existing anti-GNAL and anti-ITM2B
- Thyroid: pre-existing TG-Ab and TPO-Ab
- HLA alleles associated with IrAE diabetes, colitis, adrenal and skin adverse events.



Hu *et al.* Front. Immunol., 06 March 2023

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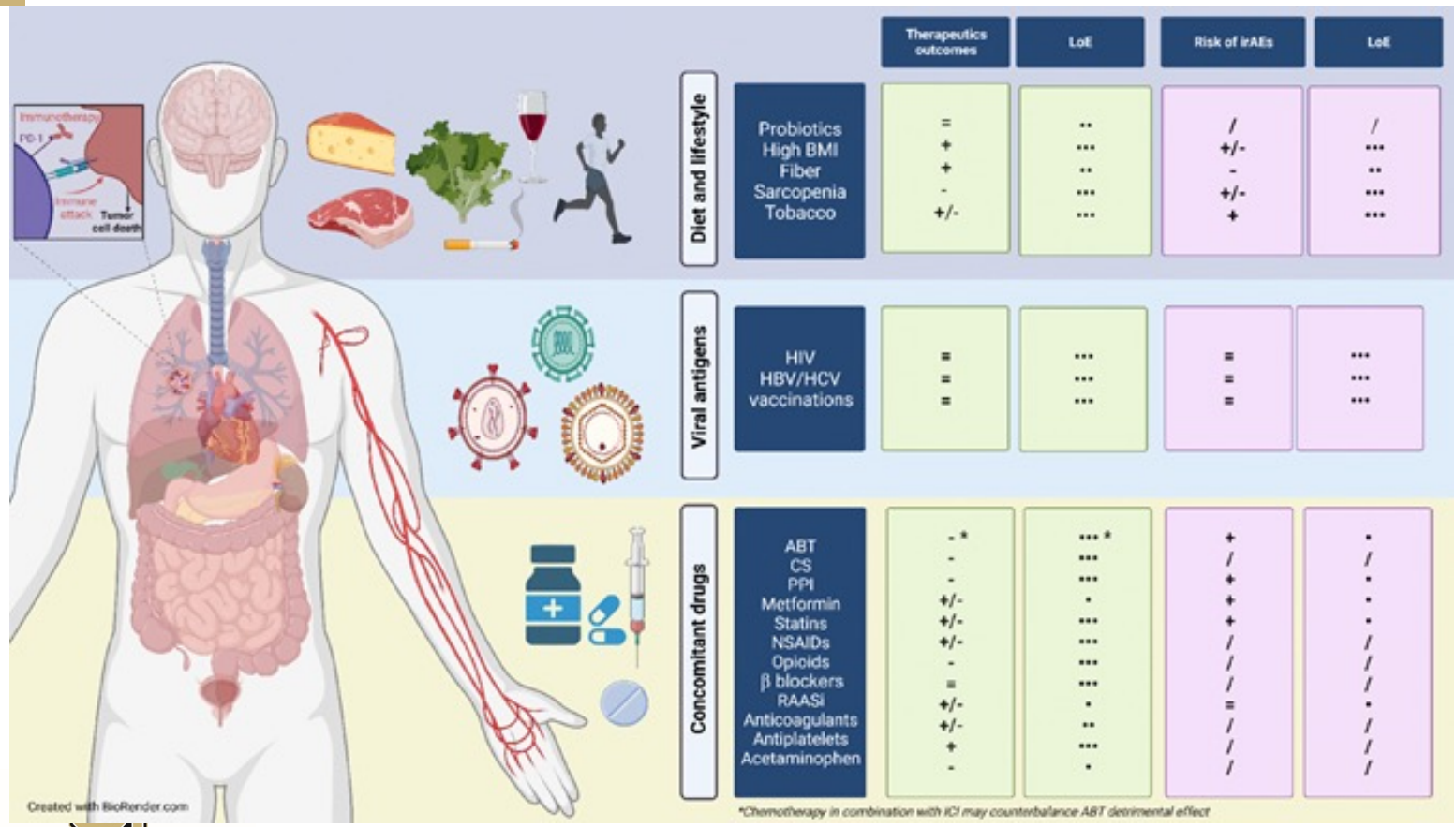
Host-Extrinsic Factors and IrAEs



- Associations noted between IrAE development
- Lifestyle
  - Tobacco
- Viral antigens
- Concomitant drugs
  - Antibiotics
  - PPIs
  - Statins

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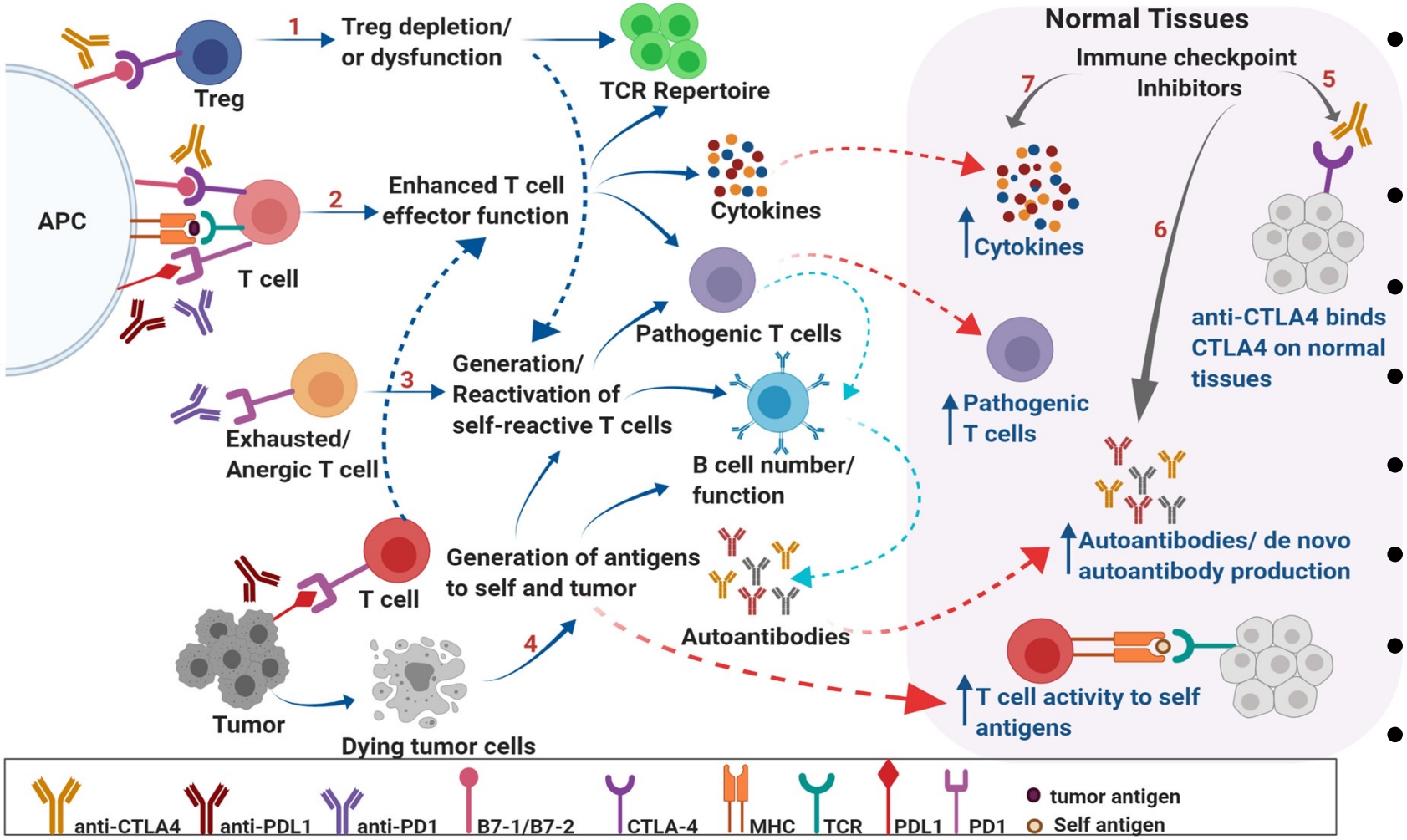
Cancer Res. 2023;83(14):2283-2296. doi:10.1158/0008-5472.CAN-23-0161

Barriers for IrAE Biomarkers



- Integration of complex data sets:
- T cell repertoires
- Autoantibodies
- Cytokines/chemokines
- HLA haplotypes
- Somatic mutations
- Microbiome
- Circulating immune cells

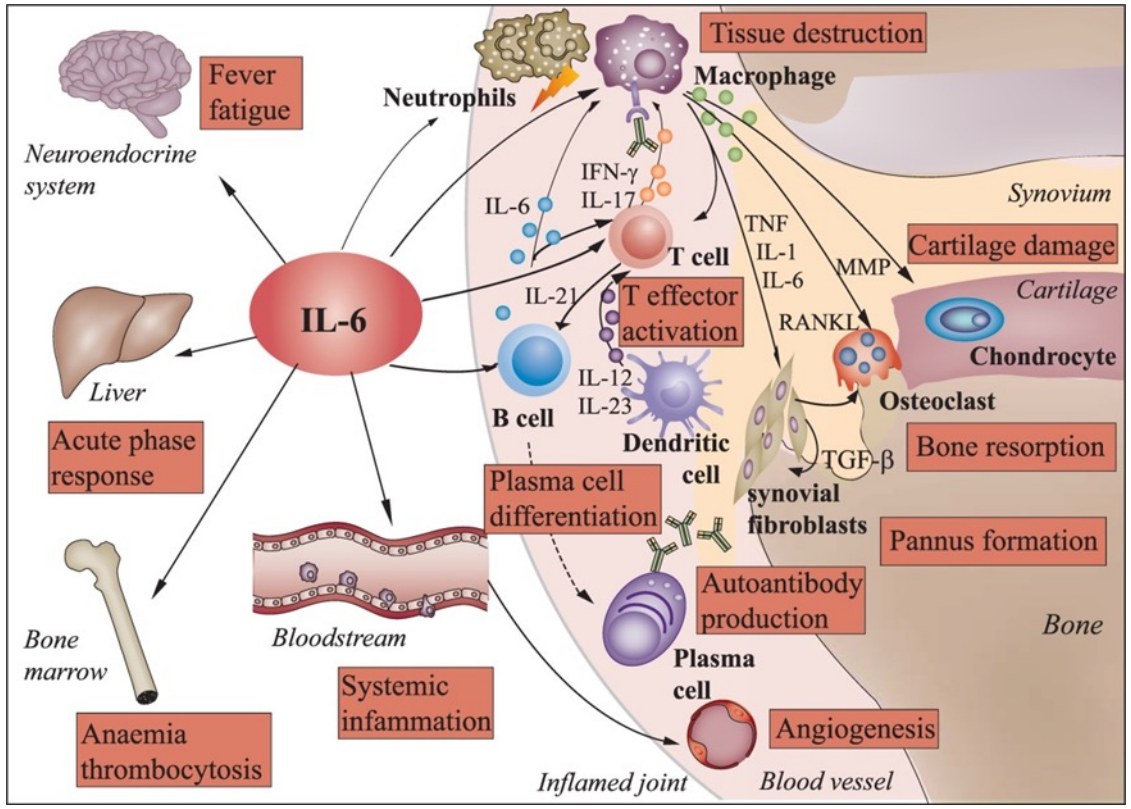
Clin Chem, Volume 66, Issue 6, June 2020, Pages 779–793

Putting It All Together in the Clinic

- PD-1/PD-L1 immunotherapy is the backbone of multiple curative and life-prolonging systemic therapy options for lung cancer
- Did not offer IO in 2 clinical scenarios:
  - 64M with recurrent sqNSCLC and lung transplant
  - 67F with never smoking ES-SCLC and hx ILD flares with RA
- Coordination with the physician who directs care for a patient's AD is necessary prior to starting IO

Putting It All Together in the Clinic

- 68F with IV NSCLC, PD-L1 60%
- RA currently on low dose prednisone with mild joint symptoms
- Hx of flares requiring steroid bursts, MTX, TNFa inhibitors
- Received pembrolizumab plus tocilizumab and had good control of NSCLC and her joint symptoms



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Clin Experimental Immun, Volume: 189, Issue: 1, Pages: 12-20, First published: 01 April 2017, DOI: (10.1111/cei.12966)

Conclusions

- Immunotherapy is SoC for 2/3 of all patients with lung cancer
- IrAE are common, unpredictable in timing and severity, and there are limited ways to identify at risk populations
- Challenges with IrAE reflect the complexity of immunotherapy activity on the patient's immune system
- Coordination with a patient's treating physician for AD is key


Question and
Discussion
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