Brigham and Women's Hospital
Founding Member, Mass General Brigham

Immunotherapy for the Internist

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CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

MASSACHUSETTS GENERAL HOSPITAL
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HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Ross Merkin, MD

- Stony Brook University School of Medicine
- Medicine Residency @ Montefiore Medical Center
- Hematology/Oncology Fellowship @Yale Cancer Center
- Instructor of Medicine @ HMS
- Medical Oncologist, Center for Head and Neck Cancers @ MGH Cancer Center
  - Clinical focus: HNSCC, salivary gland cancer, non-melanoma skin cancer
  - Research focus: irAEs, biomarkers

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Financial Disclosures

No relevant financial relationships to disclose

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Learning Objectives

- Review the mechanisms of action of immune checkpoint blockade in cancer
- Review recent clinical trials of ICI that redefine standard of care
- Review the proper evaluation and management of suspected or confirmed ICI-related AEs (irAE)

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Immunotherapy – a broad term for therapies that leverage the immune system to achieve anti-tumor efficacy

	Examples
• Antibody therapies	
– Immune checkpoint inhibitors	PD-(L)1, CTLA-4, LAG-3
– Bispecific antibodies	
• BiTE (x + CD3)	CD19, BCMA, gp100-HLA-A*02
• Non-BiTE	EGFR + MET

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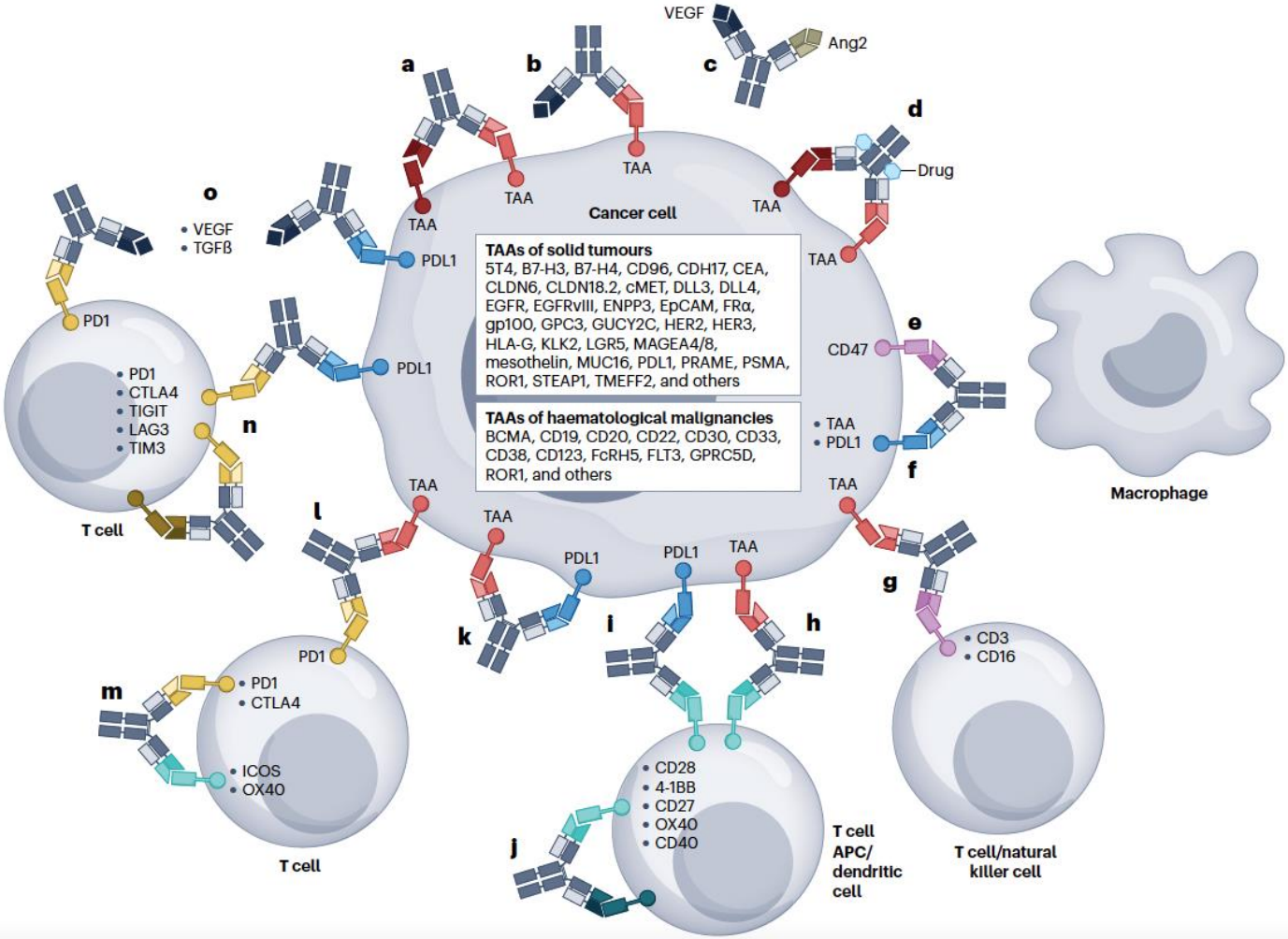
Bispecific antibody - mechanism of action



Klein et al. 2024, Nat Rev

Immunotherapy – a broad term for therapies that leverage the immune system to achieve anti-tumor efficacy

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• Antibody-drug conjugates	
– α-Her2 + deruxtecan	Her2+ tumors (breast, salivary)
– Gemtuzumab + ozogamicin	CD33+ AML

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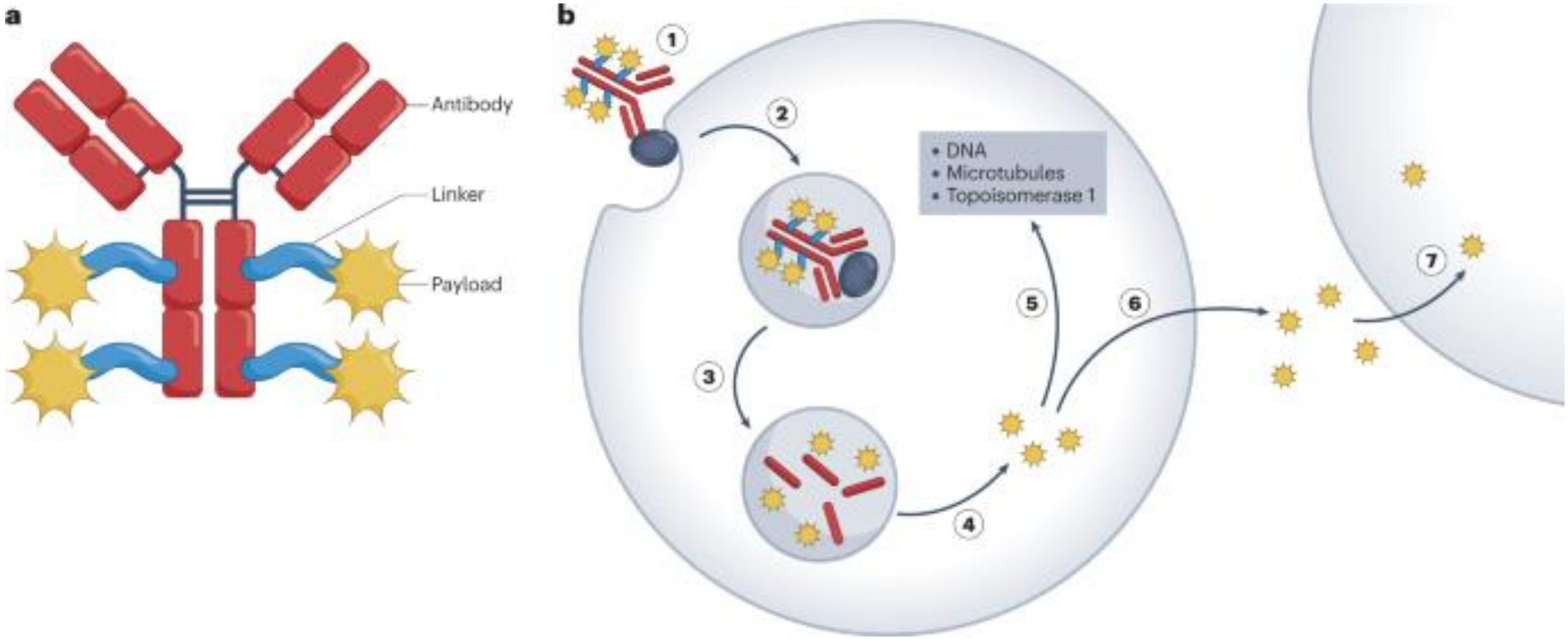
Antibody-drug conjugate mechanism of action



Dumontet et al. 2023, Nat Rev Drug Discov

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Immunotherapy – a broad term for therapies that leverage the immune system to achieve anti-tumor efficacy

- **Antibody therapies** — **Examples**
  - Immune checkpoint inhibitors — PD-(L)1, CTLA-4, LAG-3
  - Bispecific antibodies
    - BiTE (x + CD3) — CD19, BCMA, gp100-HLA-A*02
    - Non-BiTE — EGFR + MET
- **Antibody-drug conjugates**
  - α-Her2 + deruxtecan — Her2+ tumors (breast, salivary)
  - Gemtuzumab + ozogamicin — CD33+ AML
- **Cell and oncolytic therapies**
  - Allogeneic/Autologous stem cell transplant
  - CAR-T (chimeric antigen receptor T cell therapy)
  - TIL (tumor infiltrating lymphocytes)
  - Oncolytic virus therapy

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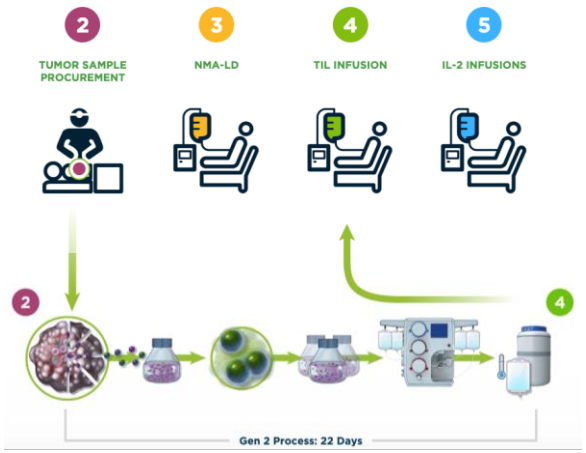
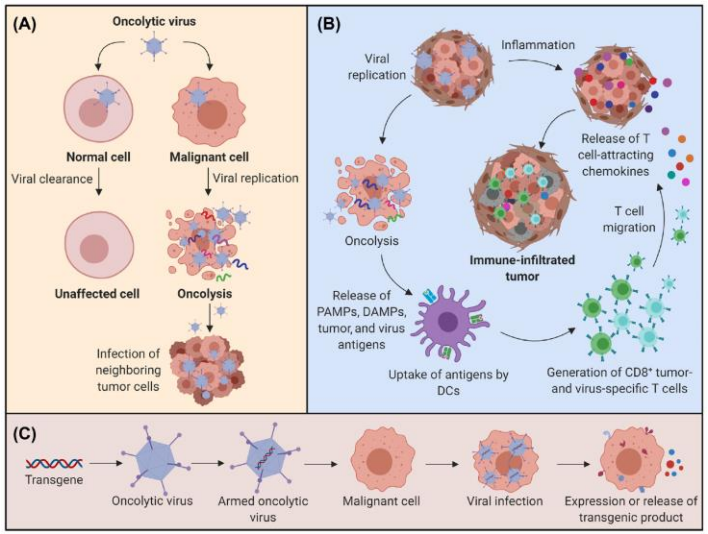
Adoptive T cell therapies – production and mechanism

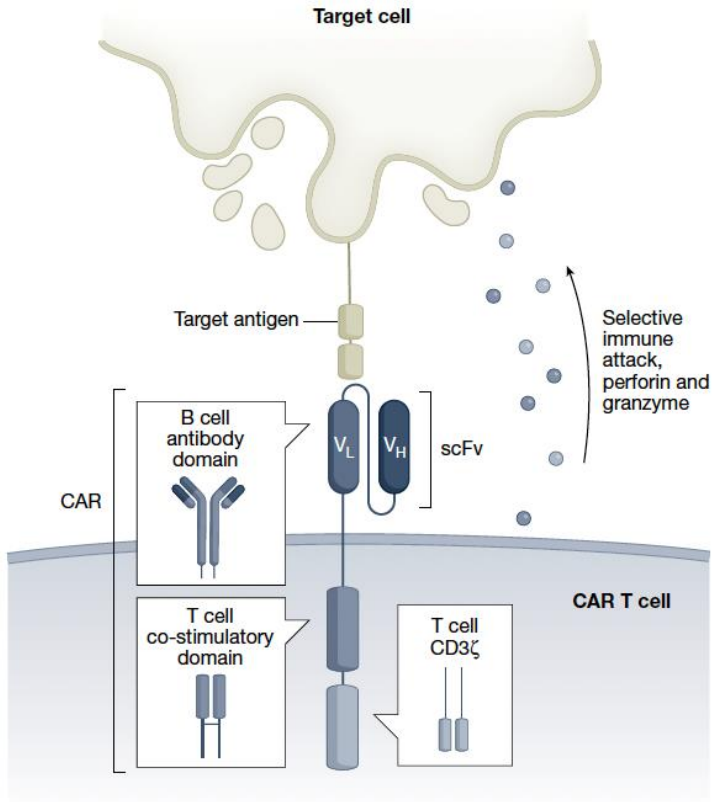
TIL



Oncolytic Virus



CAR-T



Iovance website; Baker et al. 2023, Nature; Groeneveldt 2020, Cell Reviews

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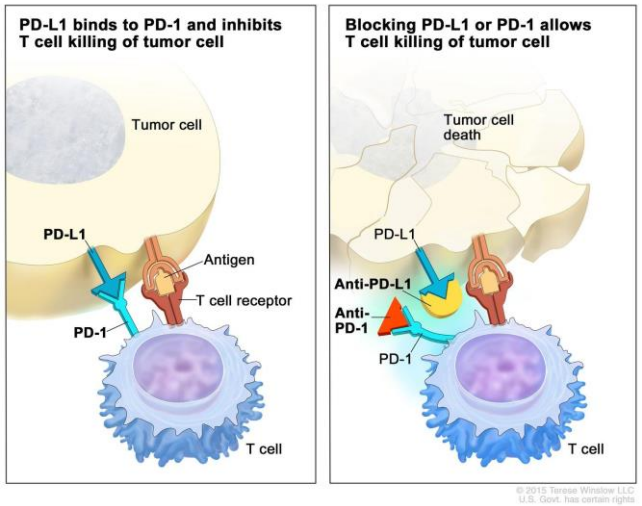
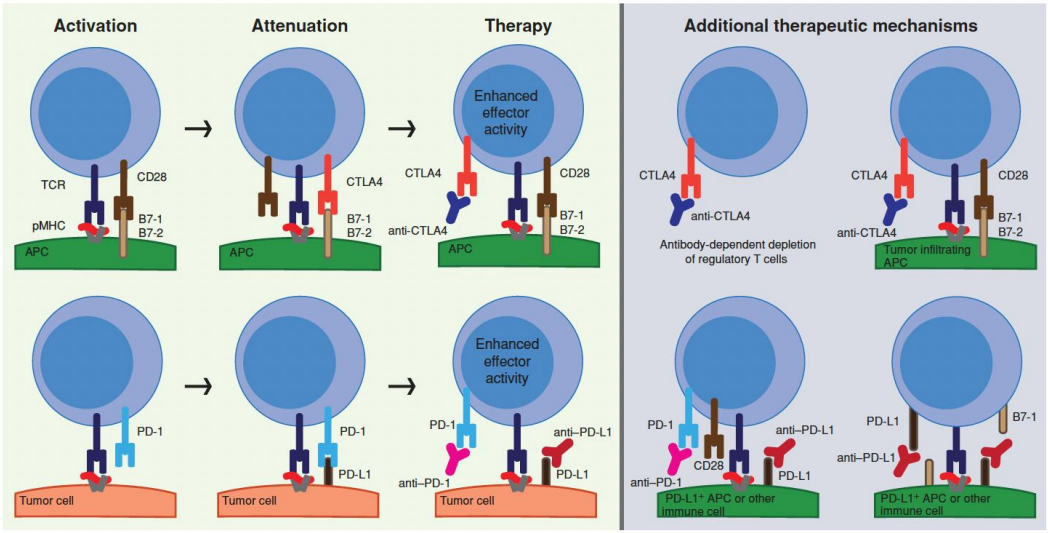
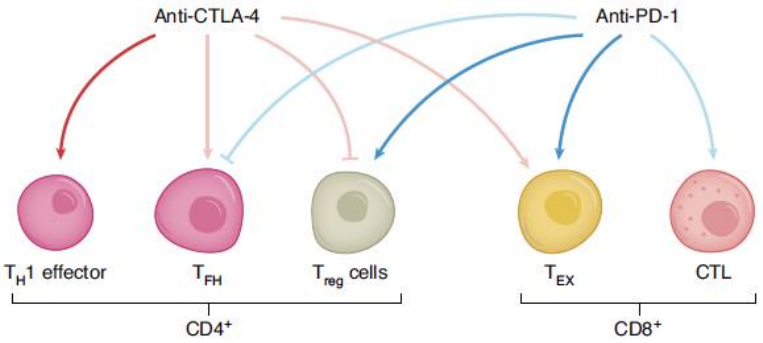
Classical and evolving understand of ICI mechanisms



Classical model of ICI



T cell priming (role of tdLN)
T cell effector program
ADCC
Actions on APCs



Preferential effects of specific immune checkpoint blockade subtypes on different T cell subtypes

Wei et al. 2018, Cancer Discov; Huang and Zappasodi 2022, Nature Immunology;
https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/checkpoint-inhibitors

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Learning Objectives

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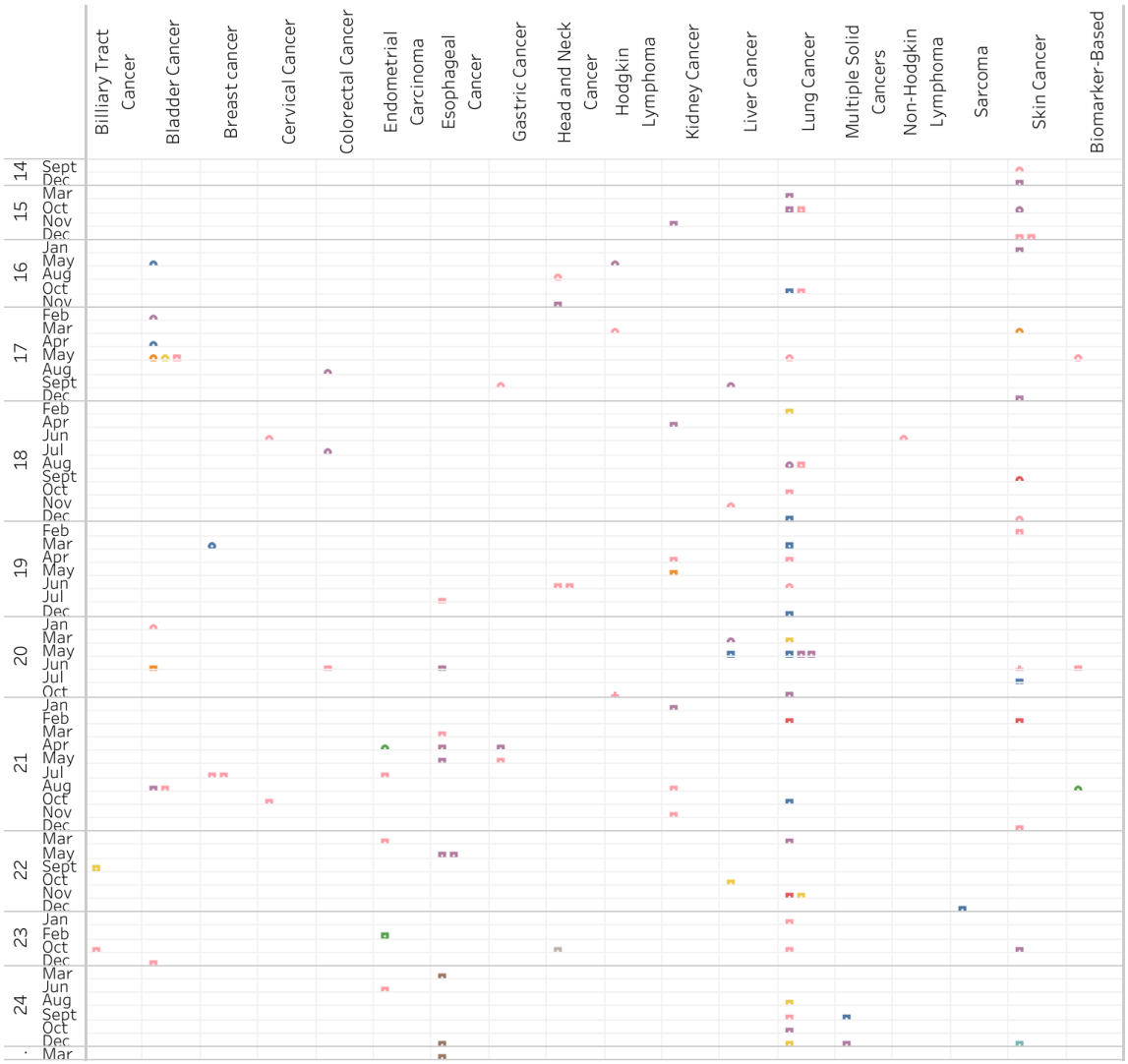
PD-(L)1 FDA approvals



https://www.cancerresearch.org/regulatory-approval-timeline-of-active-immunotherapies, Accessed 4/15/25

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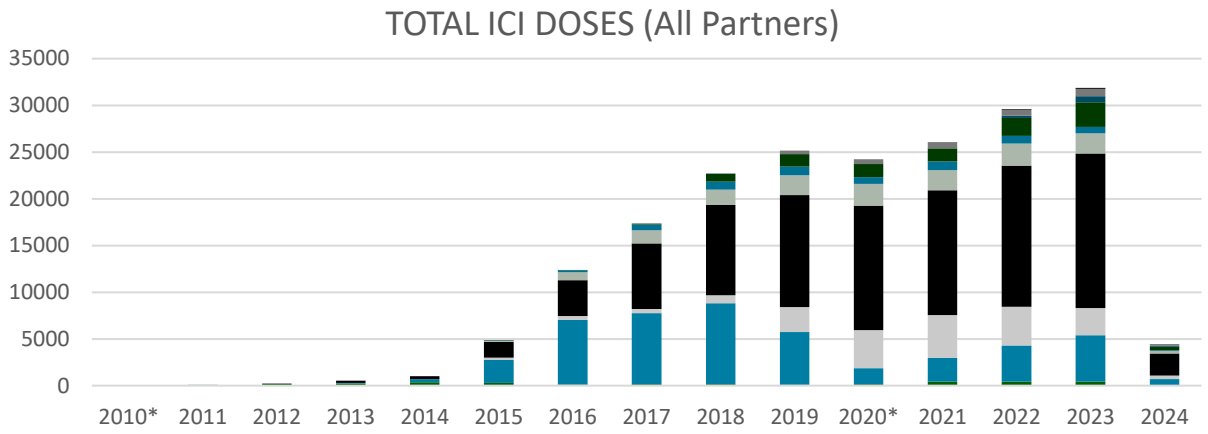
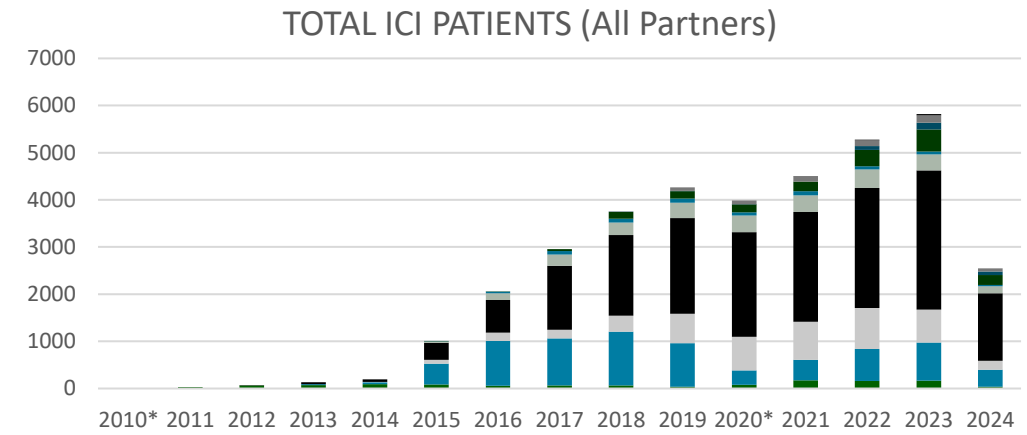
ICI Treatment in MGB System through February 2024





ipilimumab
ipilimumab AND nivolumab
atezolizumab
durvalumab
cemiplimab
nivolumab
pembrolizumab
avelumab
nivolumab AND relatlimab
dostarlimab

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Last year we reviewed:

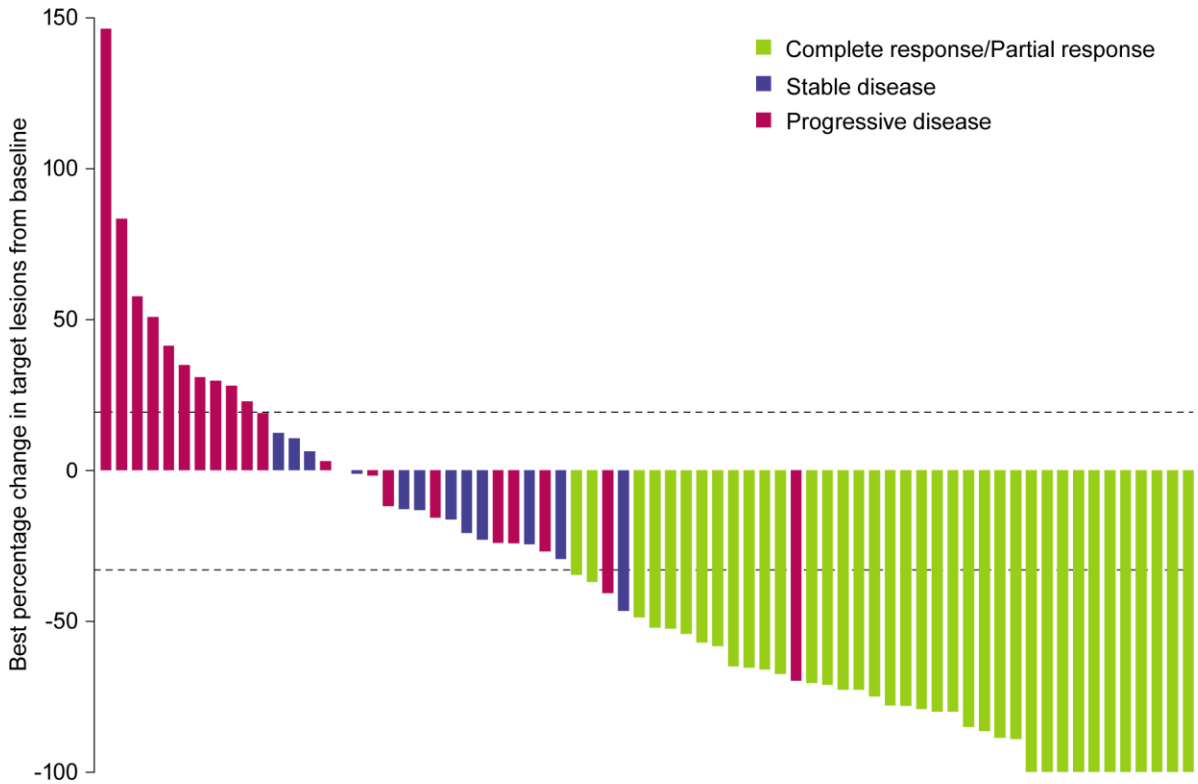
- KEYNOTE-671: Neoadjuvant/adjuvant pembrolizumab + cisplatin doublet for II-IIIB NSCLC (2023)
- KEYNOTE-522: Neoadjuvant/adjuvant pembrolizumab + chemo for early stage triple-negative breast carcinoma (2020)
- CheckMate-648: Nivolumab + chemotherapy or ipilimumab as first line in unresectable/recurrent/metastatic PD-L1+ esophageal SCC (2022)
- JUPITER-02: Toripalimab (anti-PD-1) for R/M nasopharynx carcinoma (2023)
- KEYNOTE-966: Pembrolizumab + gemcitabine/cisplatin for biliary tract cancer (2023)
- GARNET Trial: Dostarlimab as second line in advanced/recurrent mismatch repair (MMR)-deficient and microsatellite instability-high (MSI-H) or POLE-altered tumors (2023)

Cosibelimab in metastatic cutaneous SCC

Table 2 Tumor response by ICR according to RECIST V.1.1

Parameter, n (%)*	mCSCC (N=78)
Best overall response	
Complete response	6 (7.7)
Partial response	31 (39.7)
Stable disease	12 (15.4)
Progressive disease	21 (26.9)
Not evaluable	8 (10.3)
ORR in ITT population, % (95% CI)	47.4 (36.0 to 59.1)
ORR in modified ITT population, % (95% CI)	48.7 (37.0 to 60.4)†
Response ongoing	27 (73.0)
Median DOR, months (min, max)	NR (1.4+ to 34.1+)
Kaplan-Meier-estimated 6-month DOR probability, % (95% CI)	88.9 (73.1 to 95.7)
Kaplan-Meier-estimated 12-month DOR probability, % (95% CI)	73.0 (54.2 to 85.0)
Kaplan-Meier-estimated 24-month DOR probability, % (95% CI)	73.0 (54.2 to 85.0)
Median duration of follow-up, months (95% CI)	15.4 (12.0 to 21.0)

*Unless otherwise denoted.
†Participants who died of COVID-19 before a post-baseline response assessment were excluded from ORR calculations in the modified ITT population.
DOR, duration of response; ICR, independent central review; ITT, intent-to-treat; mCSCC, metastatic cutaneous squamous cell carcinoma; NR, not reached; ORR, objective response rate; RECIST V.1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.



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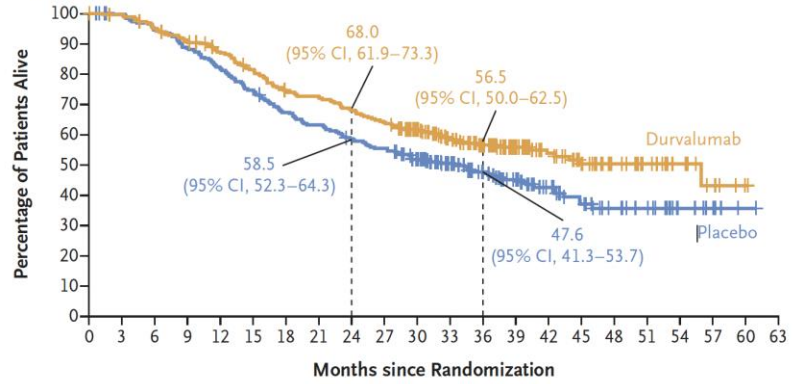
ADRIATIC Trial: adjuvant durvalumab in limited-stage small cell lung cancer after completing chemoradiation

A Overall Survival

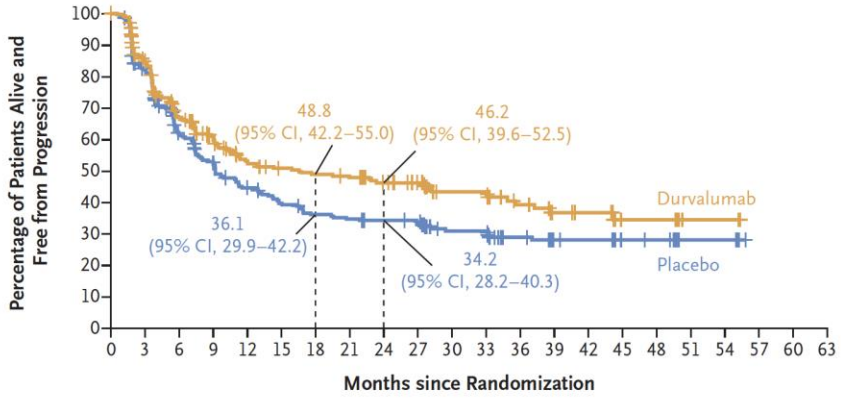


No. at Risk																					
Durvalumab	264	261	248	236	223	207	189	183	172	162	141	110	90	68	51	39	27	19	11	5	1	0
Placebo	266	260	247	231	214	195	175	164	151	143	123	97	80	62	44	31	23	19	8	5	1	0

	No. of Deaths/ Total No. (%)	Median Overall Survival (95% CI)
		mo
Durvalumab	115/264 (43.6)	55.9 (37.3–NR)
Placebo	146/266 (54.9)	33.4 (25.5–39.9)

Stratified hazard ratio for death, 0.73 (98.321% CI, 0.54–0.98)
P=0.01

A Progression-free Survival



No. at Risk																					
Durvalumab	264	212	161	135	113	105	101	98	84	78	51	51	33	21	19	10	10	4	4	0	0	0
Placebo	266	208	146	122	100	88	79	76	71	69	47	47	34	23	22	15	14	5	5	0	0	0

	No. of Events/ Total No. (%)	Median Progression-free Survival (95% CI)
		mo
Durvalumab	139/264 (52.7)	16.6 (10.2–28.2)
Placebo	169/266 (63.5)	9.2 (7.4–12.9)

Stratified hazard ratio for disease progression or death, 0.76
(99.816% CI, 0.53–1.08)
(97.195% CI, 0.59–0.98)
P=0.02

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Anticipated results: C-POST and KEYNOTE-630 trials

- Adjuvant cemiplimab (C-POST) and pembrolizumab (KEYNOTE) after surgery and post-operative radiation for advanced cutaneous squamous cell carcinoma
  - C-POST reportedly improved disease-free survival (68% reduction in recurrence or death)
  - KEYNOTE-630 reportedly did not improve recurrence-free survival
  - Awaiting published data, only press releases available at this time

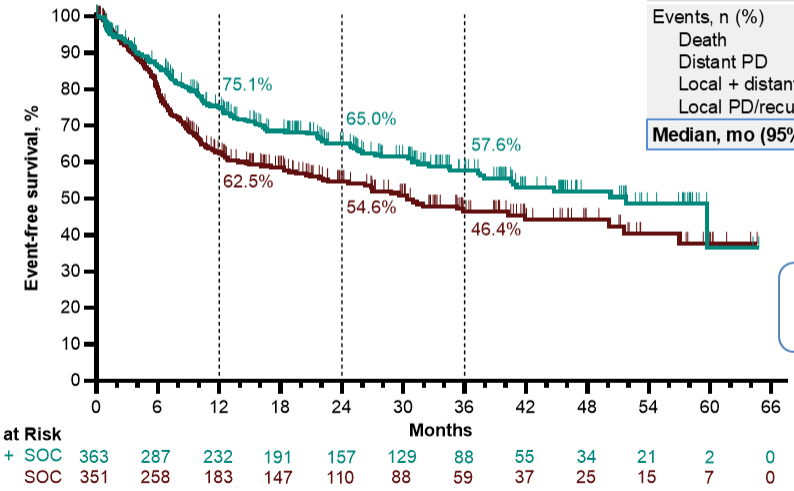
KEYNOTE-689: neoadjuvant/adjuvant pembrolizumab for locally-advanced resectable head and neck squamous cell carcinoma

- Data not yet published but press release suggests the study met its primary endpoint, presented at AACR
- Would change the landscape of curable head and neck cancer undergoing surgery

Uppaluri KN689 AACR 2025

Primary Endpoint: EFS

All Participants



	Pembro + SOC (N = 363)	SOC (N = 351)
Events, n (%)	136 (37.5)	159 (45.3)
Death	67 (18.5)	64 (18.2)
Distant PD	26 (7.2)	51 (14.5)
Local + distant PD	4 (1.1)	7 (2.0)
Local PD/recurrence	39 (10.7)	37 (10.5)
Median, mo (95% CI)	**51.8 (37.5–NR)**	**30.4 (21.8–50.1)**

HR 0.73, 95% CI 0.58–0.92, P=.0041*

Data cutoff date: 25 July 2024

NR, not reached.
*Significance boundary was met at IA1.

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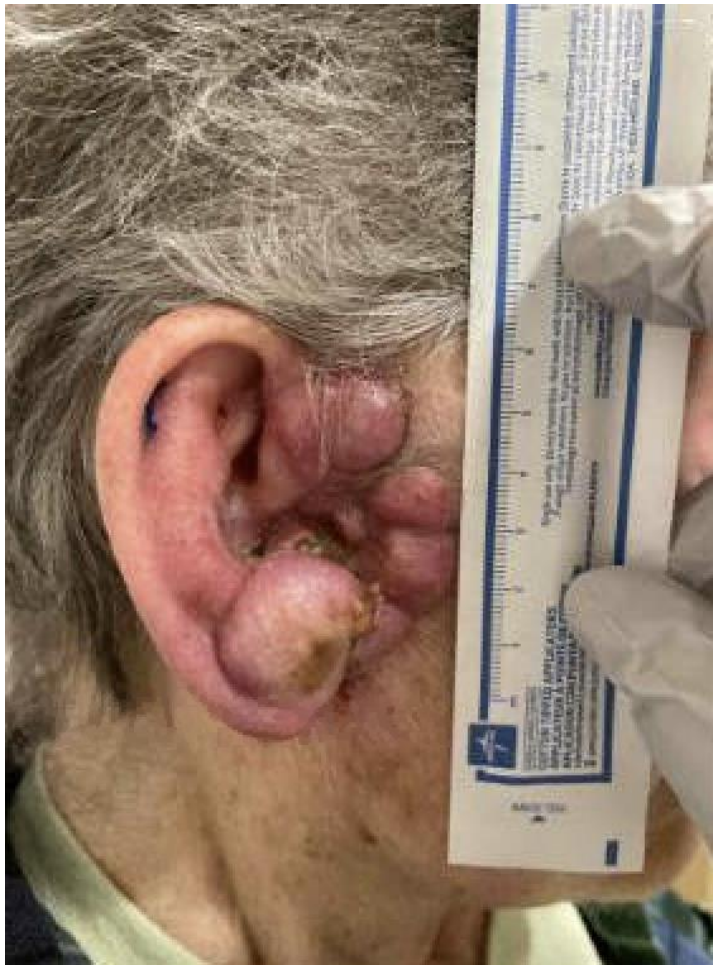
A patient-level experience – recurrent cutaneous squamous cell carcinoma after surgical resection



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Autoimmune toxicities of immunotherapy typically arise from immune checkpoint blockade and cellular therapies

- Immune checkpoint blockade
  - Can cause any type of toxicity in any organ
  - Primary focus of this discussion
- CAR-T and BiTE is associated with two main toxicities, both of which can be classified as autoimmune toxicities but are distinct from the toxicities of immune checkpoint blockade
  - Cytokine release syndrome (CRS)
  - Immune effector cell-associated neurotoxicity syndrome (ICANS)
  - Both typically can be easily recognized and are often treated with immunosuppression (dexamethasone ([good CNS activity], anti-IL-1 [ICANS], anti-IL-6 [CRS])
- TIL therapy toxicities are primarily due to (a) the conditioning regimen and/or (b) IL-2 infusion to promote TIL expansion in vivo (not autoimmune)
- Allogeneic bone marrow transplant toxicities are primarily related to (a) infection in the immunocompromised patient and/or (b) GvHD

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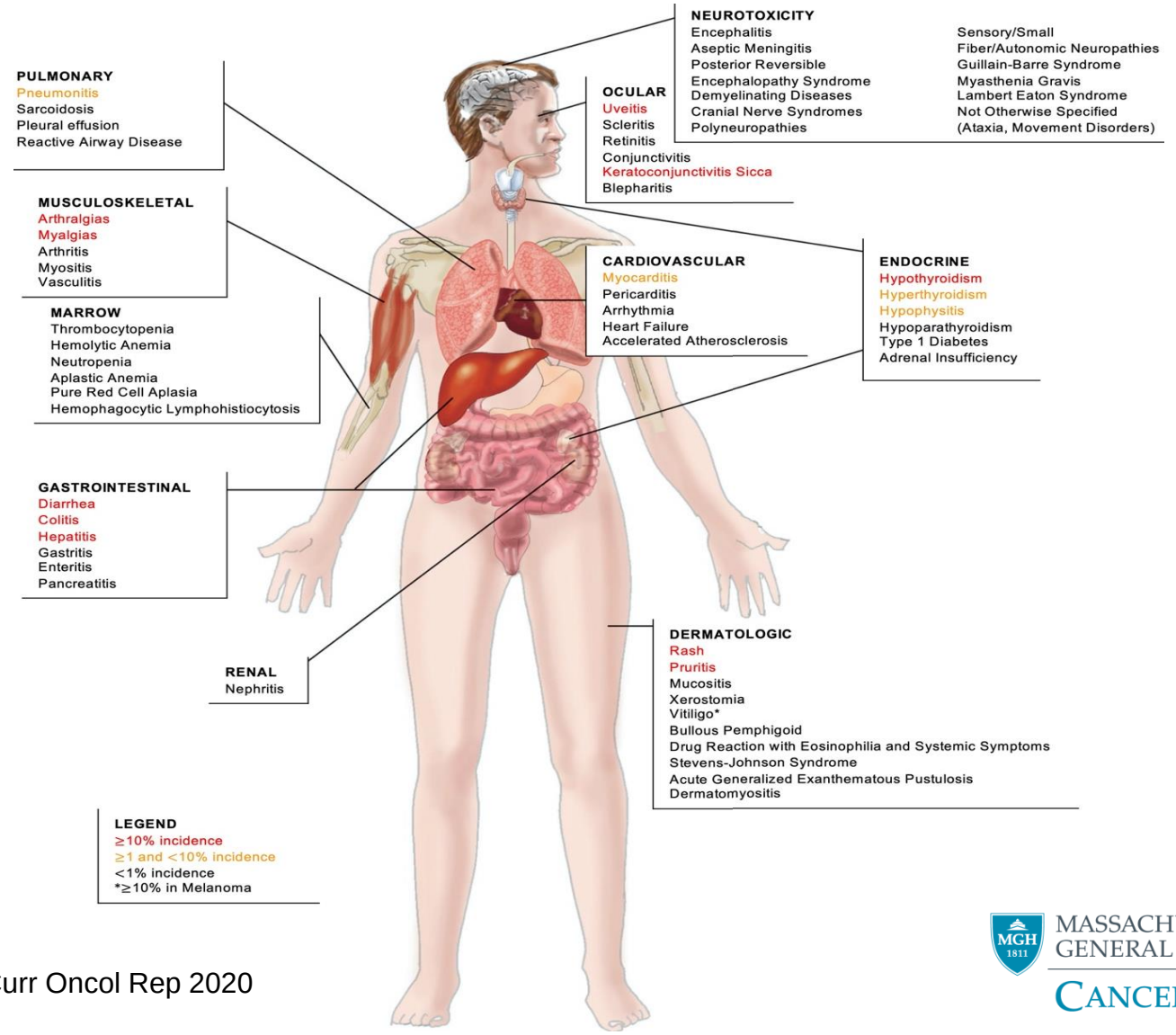
Immune-related AEs can affect any organ



Darnell and Reynolds Curr Oncol Rep 2020

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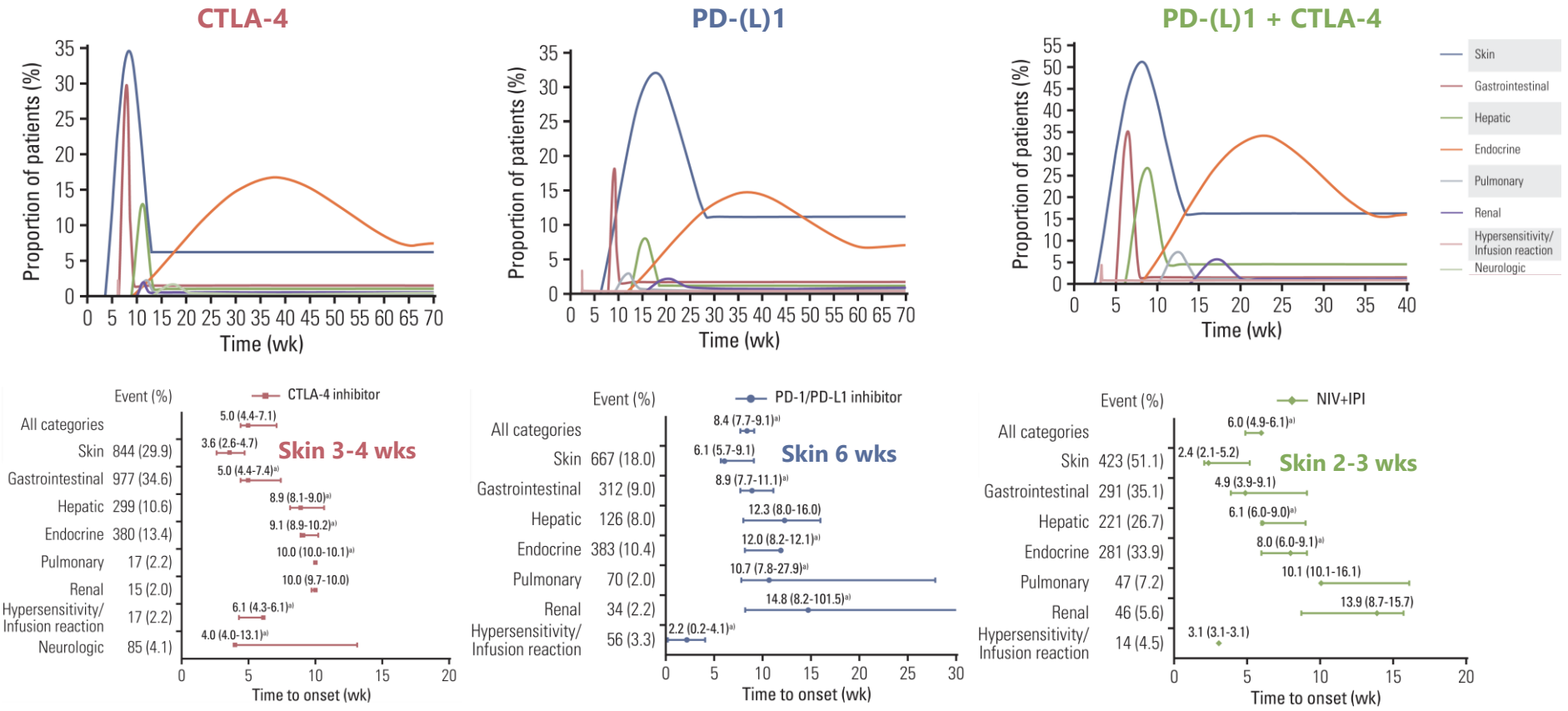
Kinetics of irAEs, 23 Clinical Trials, 8,436 patients



Tang, Cancer Res Treat, 2021; Martins, Nat Rev 2019

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Management of irAEs

- Glucocorticoids are the backbone of immunosuppressive therapy for irAEs but may impair ICI anti-tumor efficacy
- Steroid-sparing immunosuppressive therapy is used primarily in steroid-refractory cases
- Future of irAE treatment will hopefully focus on upfront use of steroid-sparing immunosuppressive therapies that decouple the irAE mechanism from ICI anti-tumor activity mechanism
- Prednisone tapers are prescribed empirically and according to toxicity grade
  - G1: observe, may continue ICI treatment
  - G2: hold ICI, may start a 0.5 mg/kg prednisone taper
  - G3/4: hold ICI, start 1-2 mg/kg prednisone taper, depending on disease severity may also incorporate steroid sparing agents early in treatment

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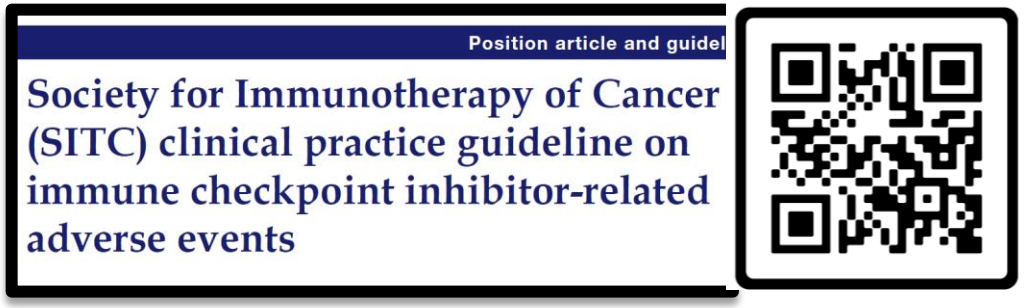
Society management guidelines (ESMO, ASCO, NCCN, SITC)

Haanen, *Annals of Onc*, October 2022

Schneider BJ, et al. *J Clin Oncol.* 2021

NCCN, V1.2025, December 2024



Brahmer JR, et al. *J Immunother Cancer.* June 2021

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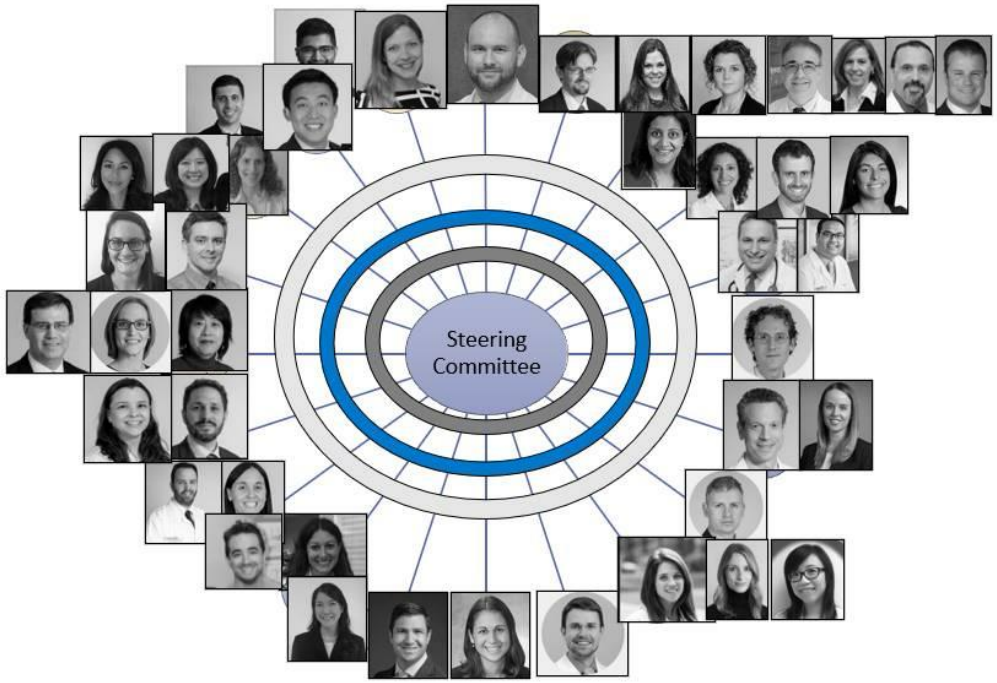
MGH Immunotherapy Toxicity Service (SIC)

Dedicated Severe Immunotherapy Complications Effort
Est: 2017

> 60 members *across 6 departments and 10 divisions of Medicine*

> 20 members *actively bridging between clinical and laboratory work*



Gathering experts & champions across division of medicine

Last year's cases

- ICI-related myocarditis
  - Presented with syncope
  - Endomyocardial biopsy positive for T cell infiltrate consistent with myocarditis
  - Successfully treated with steroids
  - Required PPM
- ICI-related colitis
  - Steroid-refractory
  - Subsequently treated with 1 dose of infliximab with essentially complete resolution of symptoms
  - Patient had long-term disease control

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Case Presentation #1

- 79 y/o male with PMH of CKD-3a presents with a lower lip cutaneous SCC
- He is started on cemiplimab as neoadjuvant therapy
- He presents for pre-operative evaluation after 2 cycles and is found to have new Cr elevation from 1.5 to 8.9
- He is admitted for workup and treatment

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What additional workup should be ordered?

- TSH/fT4
- AM cortisol
- Troponin
- LFTs
- CBC
- All of the above

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What additional workup should be ordered?

- TSH/fT4
- AM cortisol
- Troponin
- LFTs
- CBC
- **All of the above**

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Case presentation #1

- “Rubber stamp” workup to rule out commonly co-occuring irAEs showed troponin elevation
- Cardiac MR was performed and showed severe myocarditis
- He was started on pulse steroids, then high-dose steroid taper, and enrolled into the ATRIUM trial, a randomized trial evaluating if abatacept can treat ICI-related myocarditis
- Re-admitted 1.5 months after discharge with ADHF/HFpEF trigger by steroid taper
- His surgery is still pending, he has experienced a significant surgical delay

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Case presentation #2

- 65 y/o woman with newly diagnosed NSCLC and high PD-L1 (60%)
- She presents to the hospital after 4 doses of pembrolizumab monotherapy with 2 weeks of GI symptoms,
  - Nausea/vomiting (about 6 x/d)
  - Mild diarrhea (about 2 x/d, small volume)

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What should be included in the differential diagnosis?

- Colitis
- Gastritis
- Enteritis
- Infection
- Adrenal insufficiency
- Acute coronary syndrome
- All of the above
- None of the above

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What should be included in the differential diagnosis?

- Colitis
- Gastritis
- Enteritis
- Infection
- Adrenal insufficiency
- Acute coronary syndrome
- **All of the above**
- None of the above

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Workup reveals:

- Troponin normal
- TFTs normal
- 6:00 AM cortisol 0.9
- Cort stim, 30 minutes post-Cosyntropin revealed cortisol increased to 4.9
- Is this consistent with adrenal insufficiency? Yes!
- Colonoscopy was unremarkable
- Stomach endoscopically was inflamed but no biopsies were taken. Duodenum was endoscopically normal but findings of mild duodenitis were seen microscopically, more consistent with PUD

- Started on prednisone 5 mg daily and symptoms nearly fully resolved over the 2 subsequent days
- Stool calprotectin came back after discharge and was low

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Case presentation #2

- Patient was readmitted 2 weeks later with similar but less severe symptoms
- Symptoms resolved fully with ”sick-day” dosing of steroids
- Patient was found to have empty sella, no adrenal insufficiency previously but second hit (pembrolizumab) superimposed on empty sella likely precipitated secondary adrenal insufficiency from hypophysitis

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Recognizing irAEs in the primary care setting

- Multiple immunotherapy modalities exist
- ICI are fundamentally important for nearly all solid tumors and some hematologic malignancies
- irAEs are potentially fatal but often treatable
- irAEs can present with any symptoms and any organ can be affected
- Have a high index of suspicion for ICI toxicity
- Treatment guidelines have some variation but are fairly well-aligned on the initial management of most toxicities and subsequent line management of many irAEs
- If you have any concern reach out to your friendly neighborhood medical oncologist

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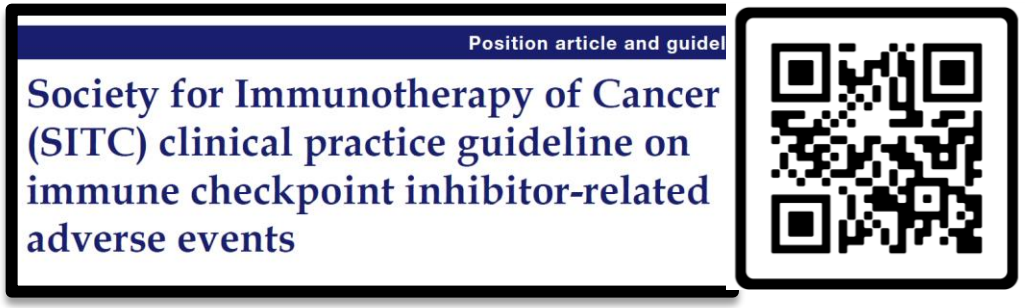
Reference slide with society management guidelines (ESMO, ASCO, NCCN, SITC)

Haanen, *Annals of Onc*, October 2022

Schneider BJ, et al. *J Clin Oncol.* 2021

NCCN, V1.2025, December 2024



Brahmer JR, et al. *J Immunother Cancer.* June 2021

Please reach out with questions:
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