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
CANCER CENTER

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 cancers,
  - Research focus: irAEs, biomarkers

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Financial Disclosures

No relevant financial relationships to disclose

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Learning Objectives

- Review the various **modalities of immunotherapy** in cancer and their mechanisms of action
- Review 6 recent clinical **trials for ICIs** 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

- 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 therapies
  - CAR-T (chimeric antigen receptor T cell therapy)
  - TIL (tumor infiltrating lymphocytes)
  - Allogeneic stem cell transplant

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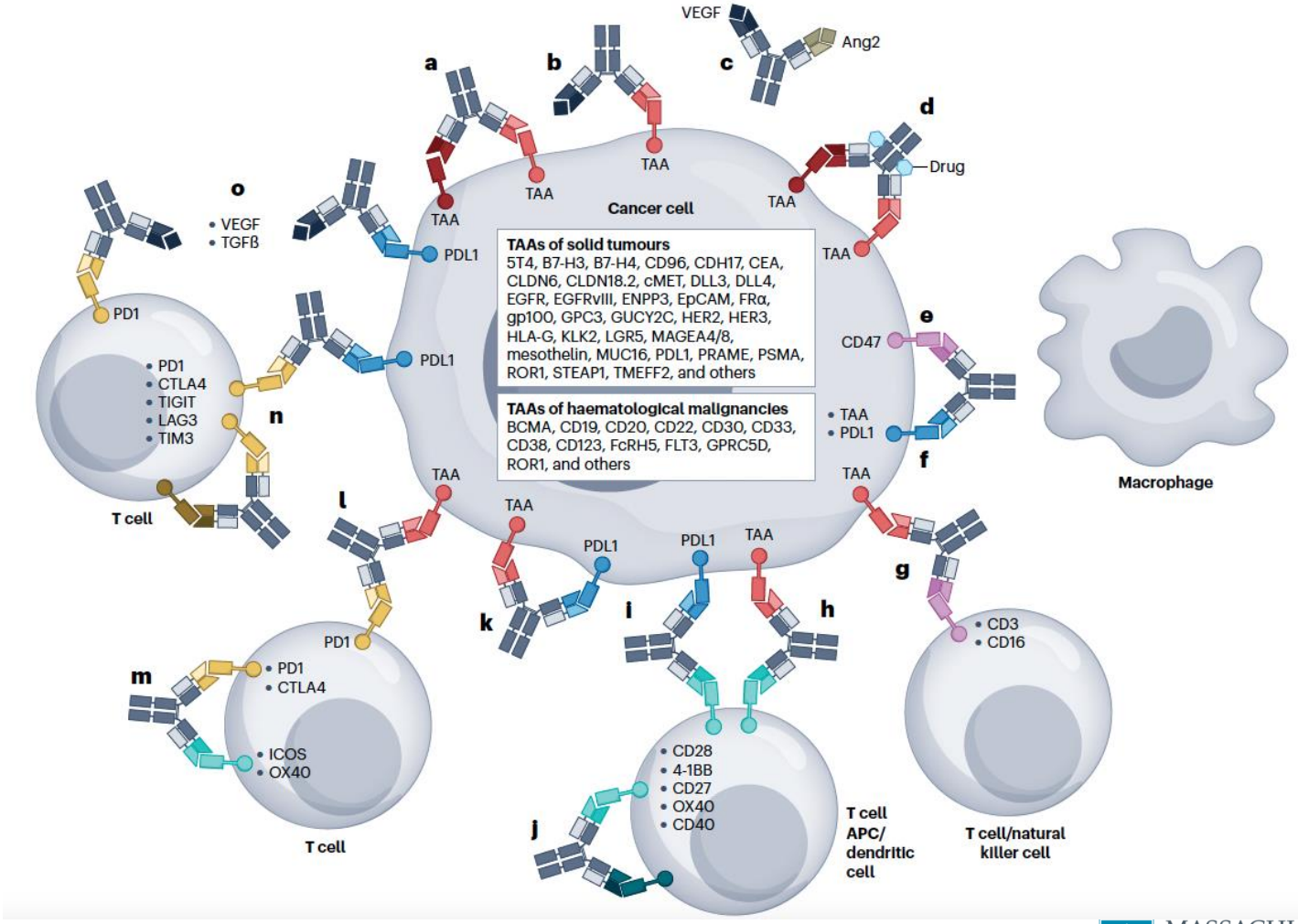
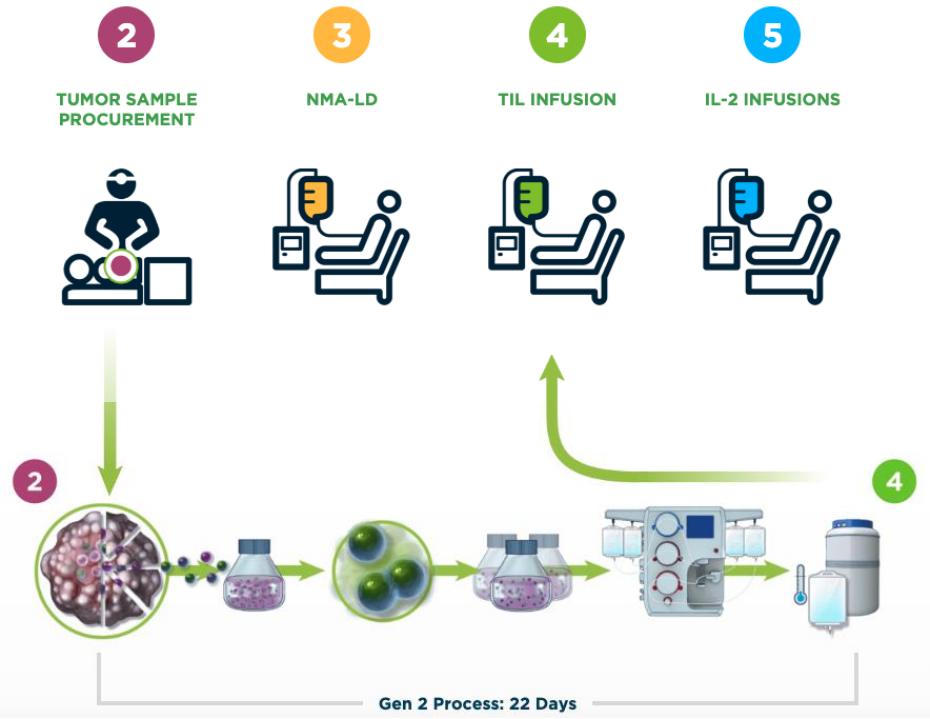
Bispecific antibody - mechanism of action



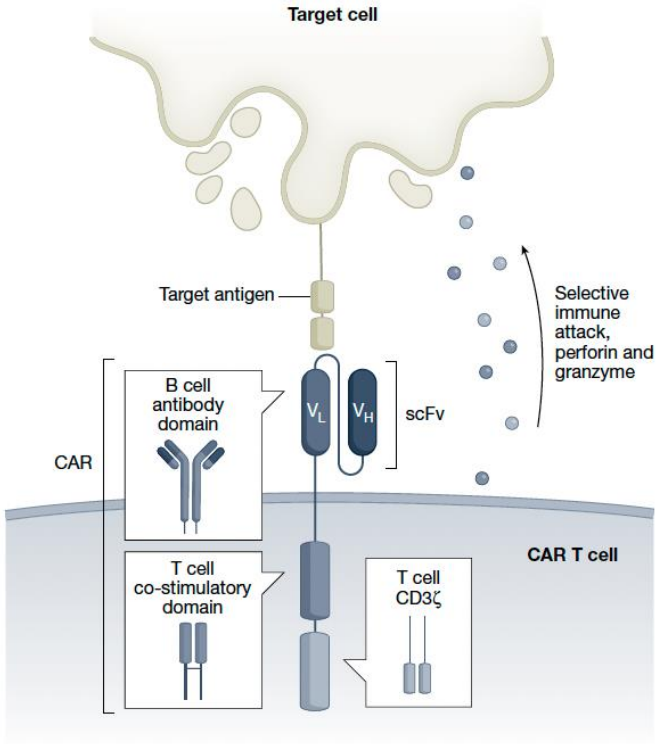
Klein et al. 2024, Nat Rev

Adoptive T cell therapies – production and mechanism

TIL



CAR-T



Iovance website; Baker et al. 2023, Nature

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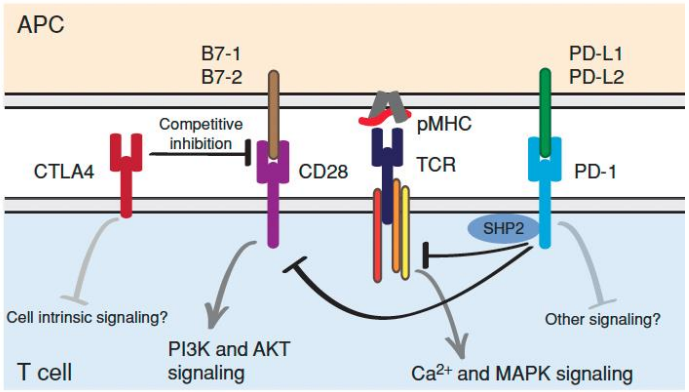
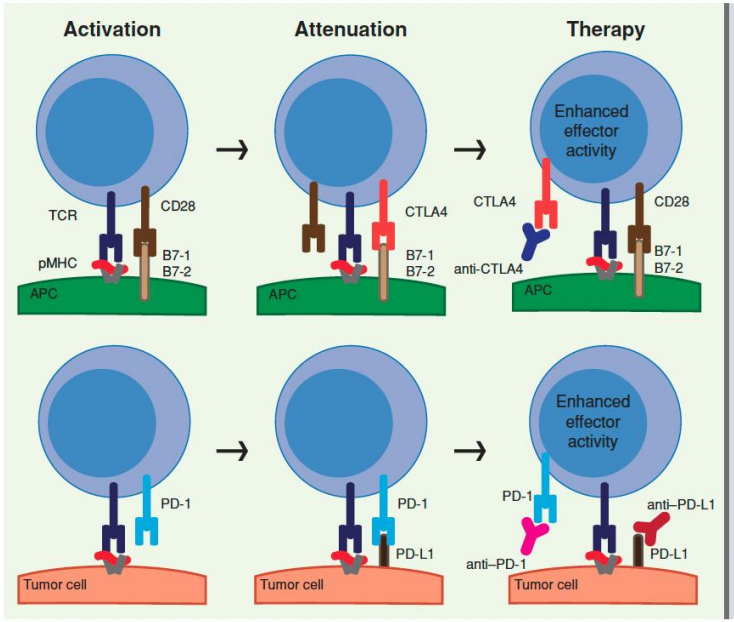
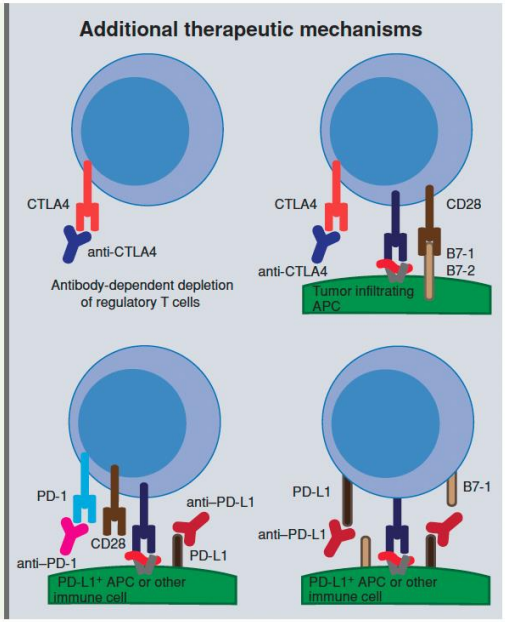
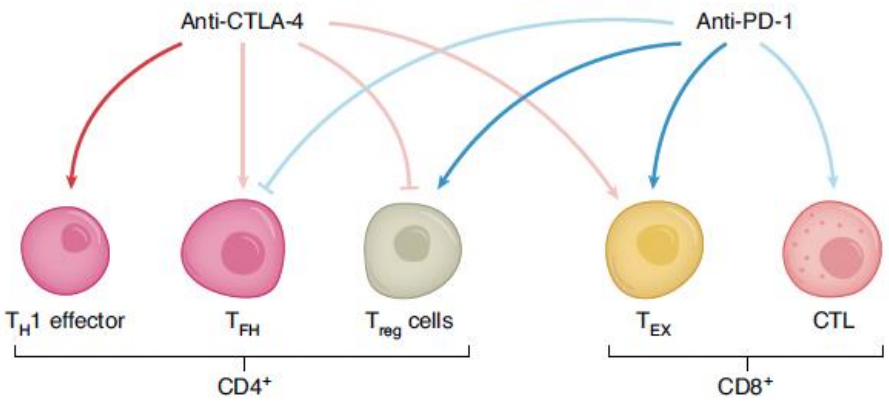
Classical and evolving understand of ICI mechanisms









Wei et al. 2018, Cancer Discov; Huang and Zappasodi 2022, Nature Immunology

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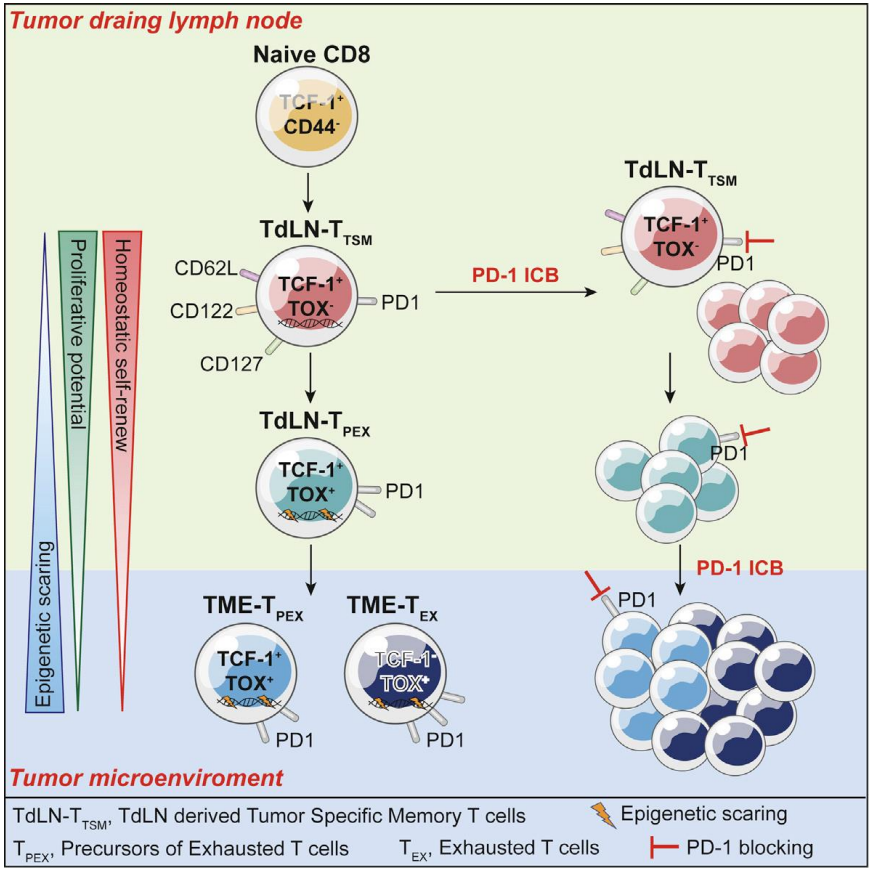
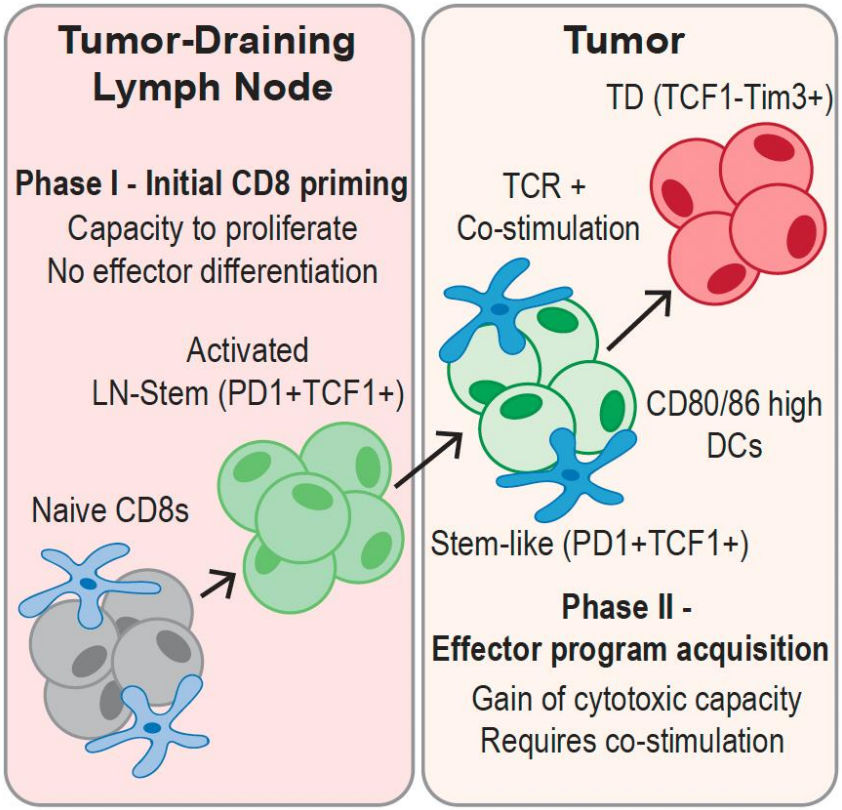
Recent insights into CD8 T cell anti-tumor immunity and its relation to ICI efficacy





Huang et al. 2022, Cell; Prokhnevska et al. 2023, Immunity

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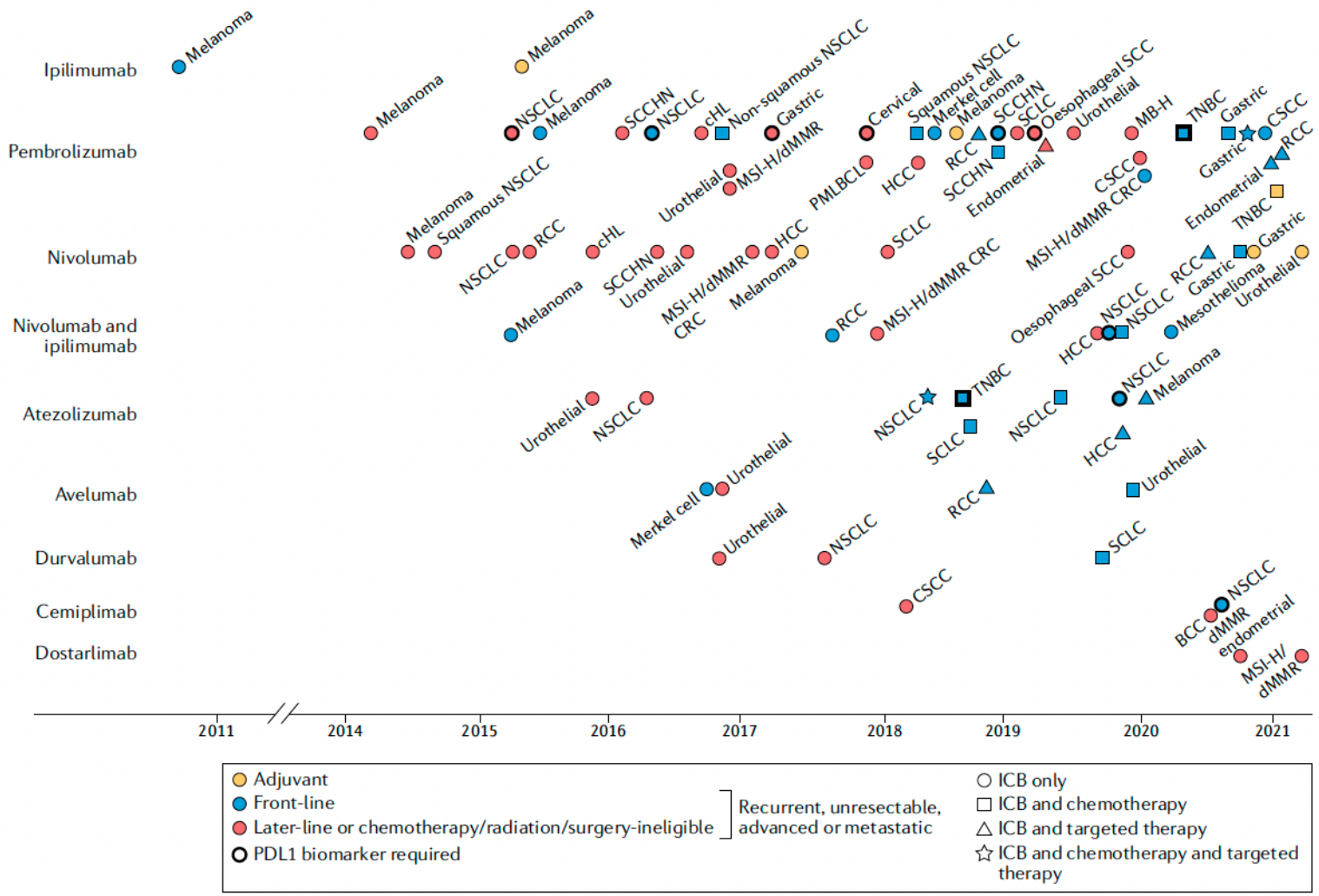
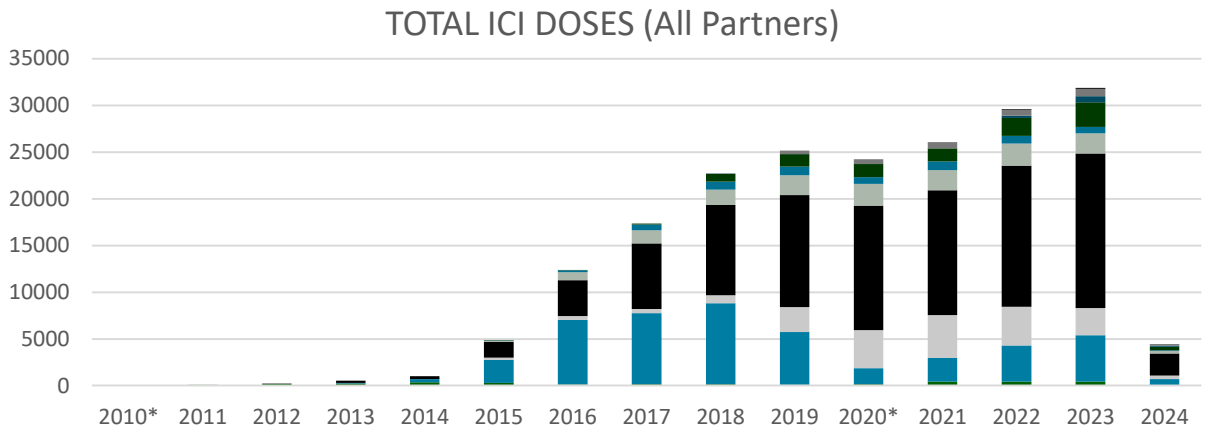
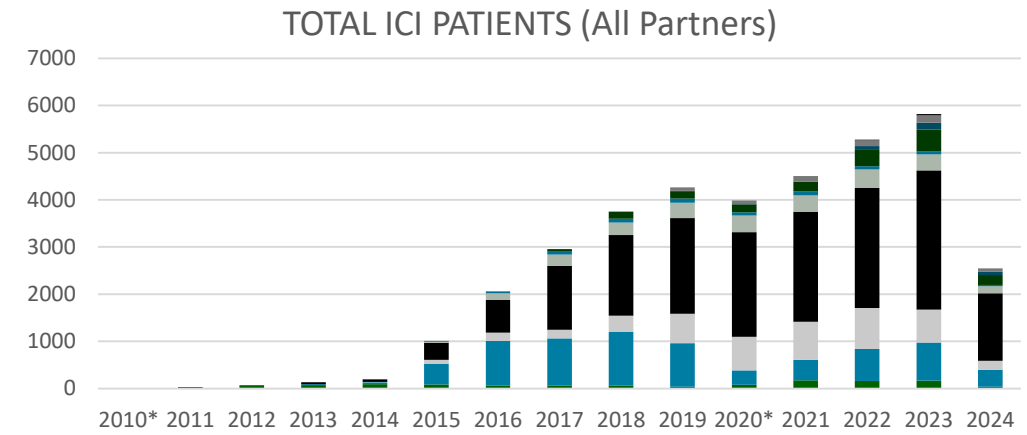
FDA approvals



Korman et al. 2022, Nat Rev Drug Discovery

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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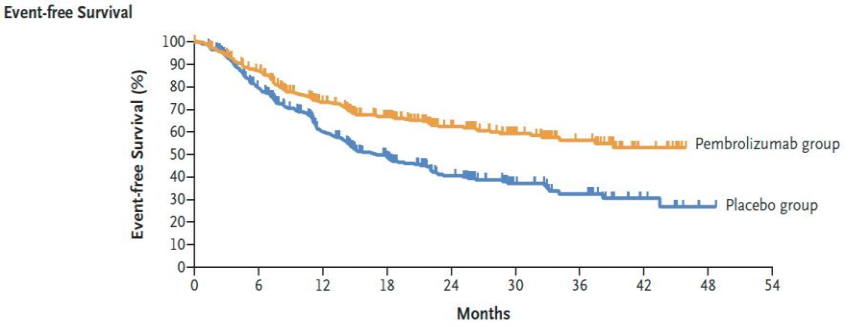
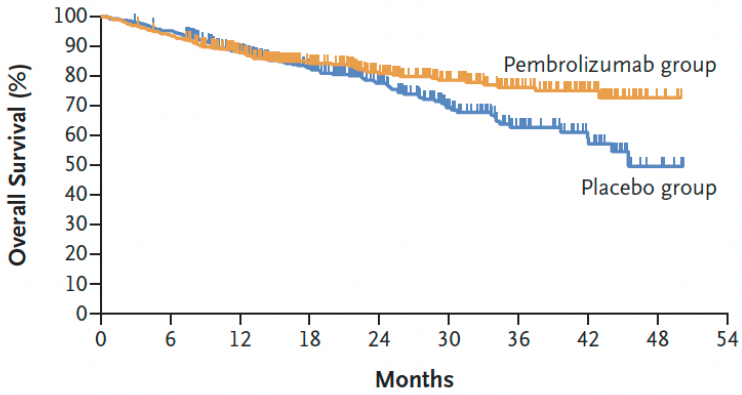
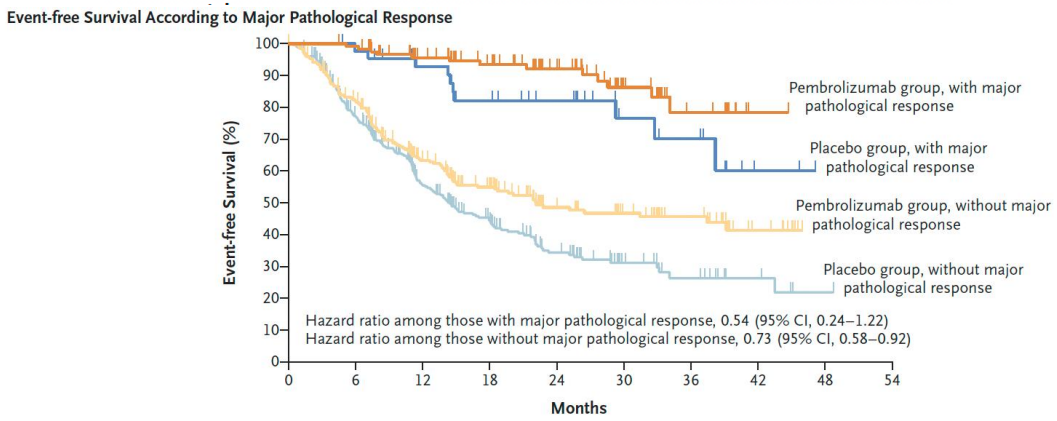
KEYNOTE-671: Neoadjuvant/adjuvant pembrolizumab + cisplatin doublet for II-IIIB NSCLC

- Randomized, placebo-controlled, phase 3, stage II-IIIB NSCLC, any PD-L1
- Pembro + chemo x4 doses → surgery → adjuvant pembro alone
- N=397
- 2 yr EFS: 62.4% vs 40.6%
- Major path response: 30.2% vs 11.0%



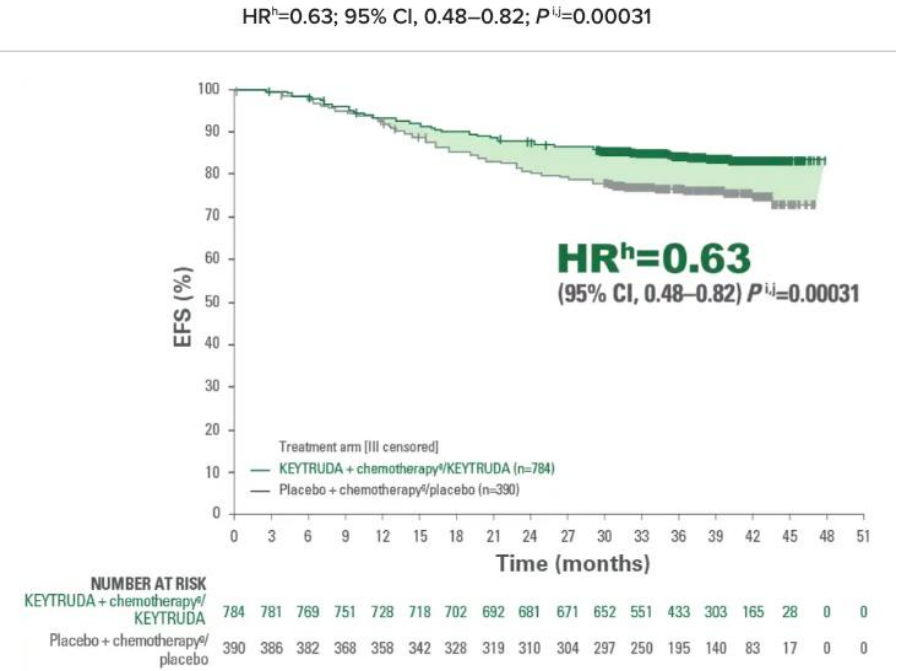




Wakelee et al. 2023, NEJM

KEYNOTE-522: Neoadjuvant/adjuvant pembrolizumab + chemo for early stage triple-negative breast carcinoma

- Randomized, placebo-controlled, phase 3, stage II-III TNBC, any PD-L1
- Pembro + chemo → Pembro + chemo → surgery → pembro +/- RT
- N=1174
- Path CR: 63.0% vs 55.6%
- 5 yr EFS: 81.3% vs 72.3%
- Only anti-PD-1 approved in breast cancer



Schimid et al. 2020, NEJM; Schimid et al. 2023, Ann Onc, Abstract

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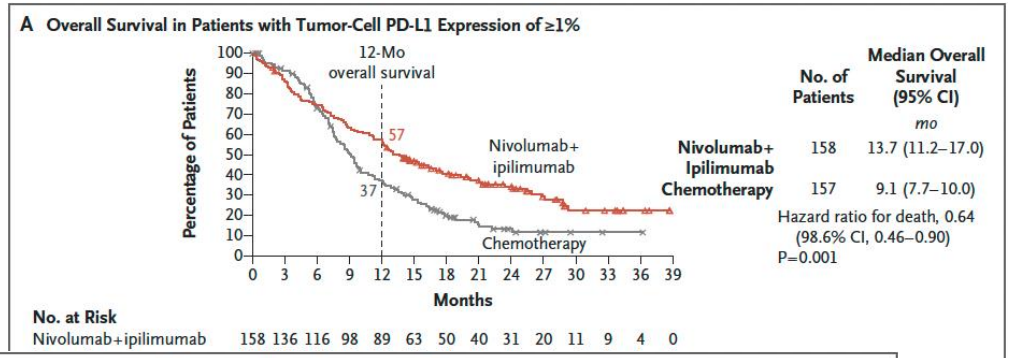
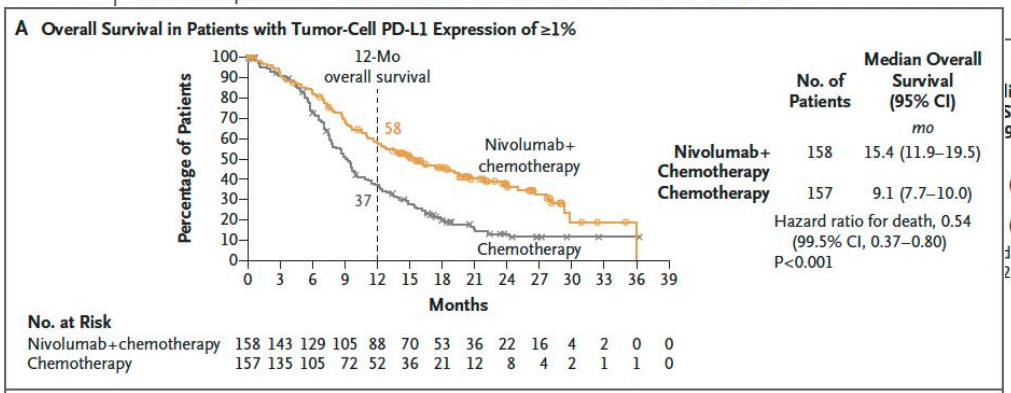
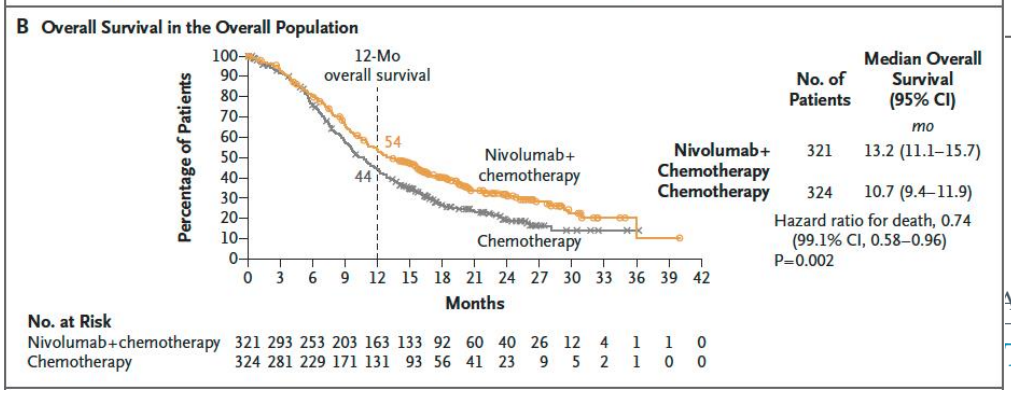
CheckMate-648: Nivolumab + chemotherapy or ipilimumab as first line in unresectable/recurrent/metastatic PD-L1+ esophageal SCC

- Randomized, open label, phase 3, incurable esophageal SCC without prior systemic therapy for advanced disease, any PD-L1
- Nivo/Ipi vs Nivo/Chemo vs Chemo
- N=970



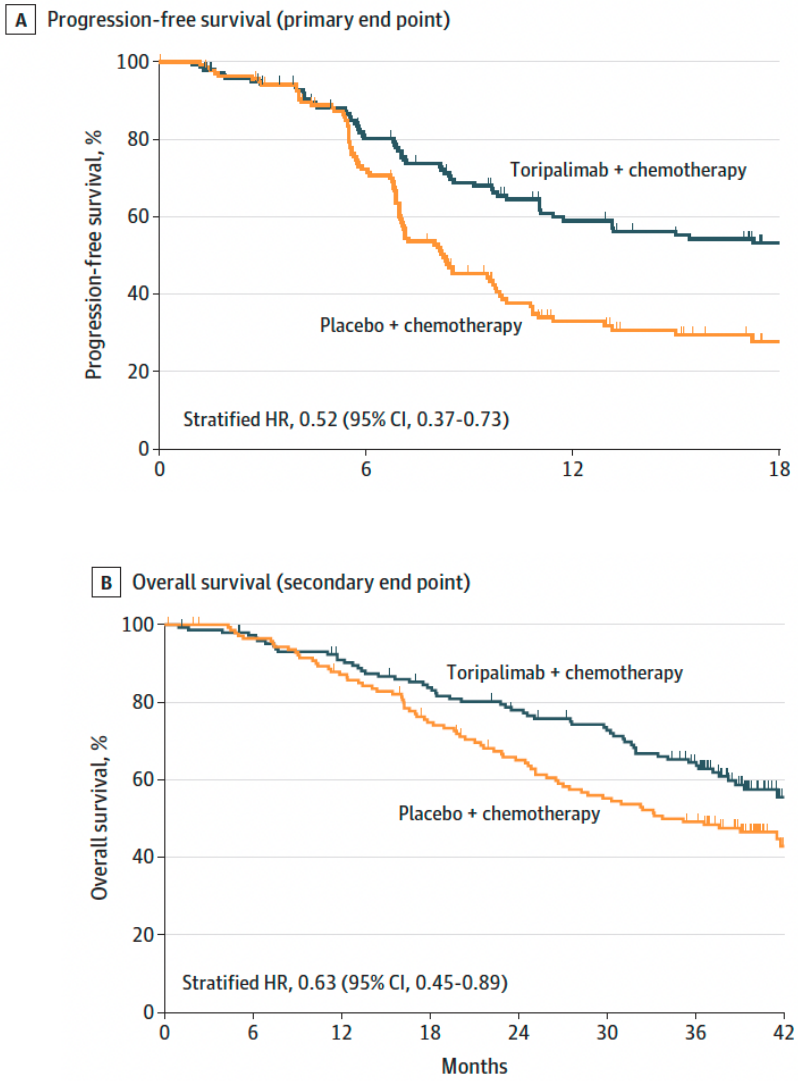




Doki et al. 2022, NEJM

JUPITER-02: Toripalimab (anti-PD-1) for R/M nasopharynx carcinoma

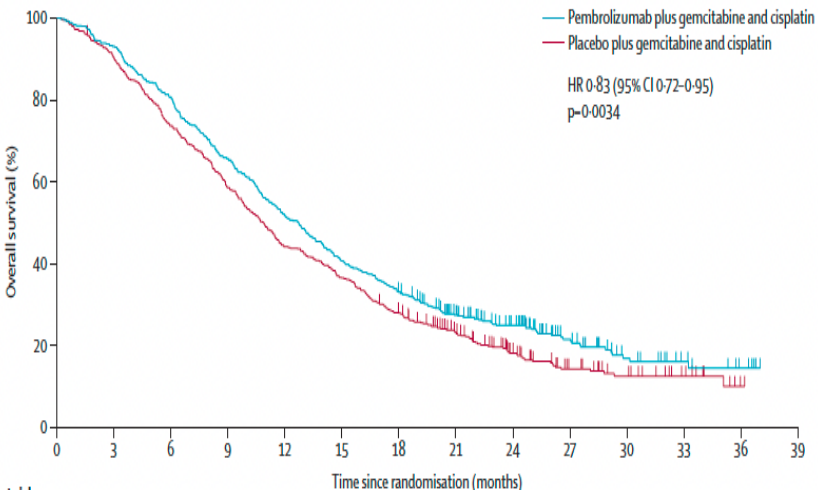
- Randomized, double-blind, phase 3, R/M NPC without prior systemic therapy in this setting, and PD-L1
- Tori + chemo x6 → Tori maintenance x2 yrs
- N=289
- mPFS: 21.4 vs 8.2 months
- mOS: NR vs 33.7 months
- First anti-PD-1 approved in this disease

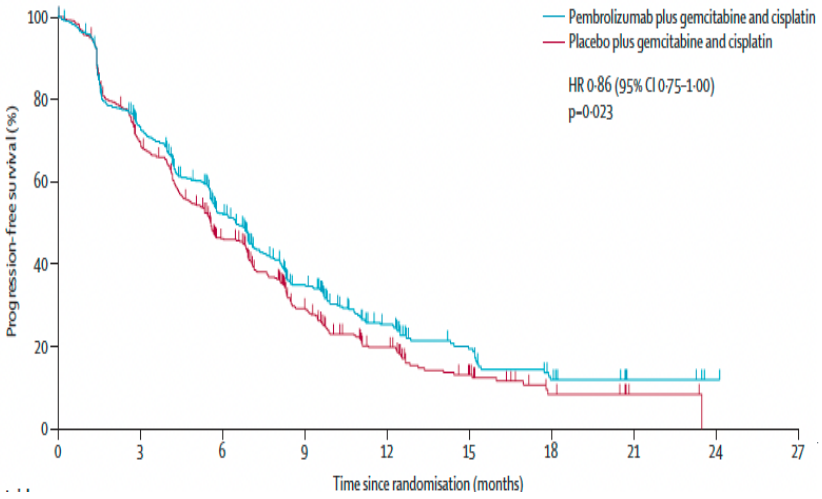


Mai et al. 2023, JAMA

KEYNOTE-966: Pembrolizumab + gemcitabine/cisplatin for biliary tract cancer

- Randomized, double-blind, phase 3, previously untreated unresectable or metastatic biliary tract cancer
- Pembro + gem/cis (no max duration)
- N=1069
- mOS: 12.7 vs 10.9 months
- Second anti-PD-1 approved in this setting

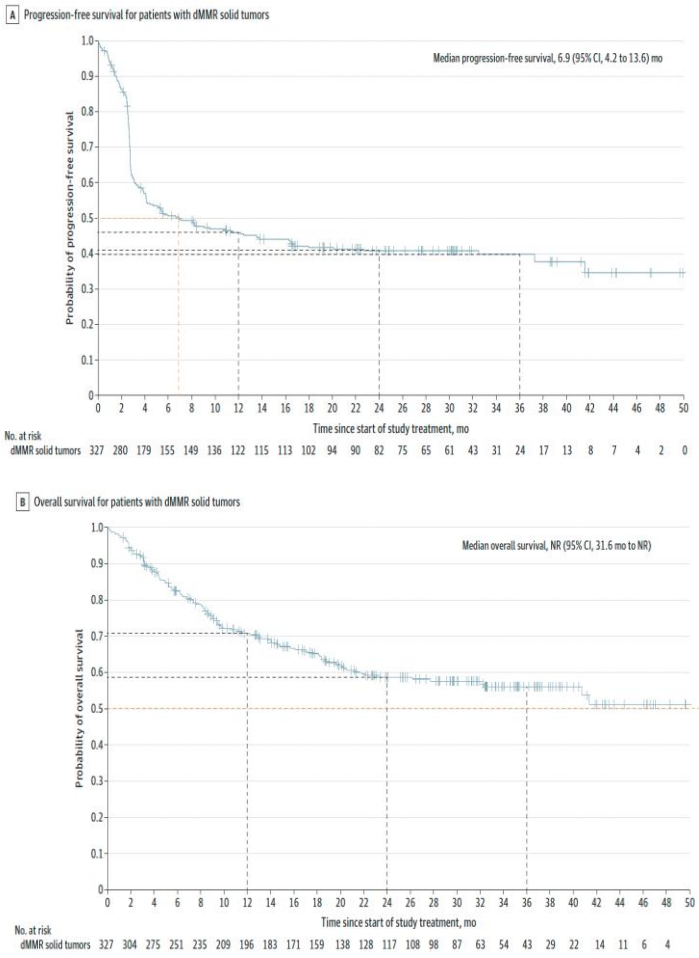




Kelley et al. 2023, Lancet

GARNET Trial: Dostarlimab as second line in advanced/recurrent mismatch repair (MMR)-deficient and microsatellite instability-high (MSI-H) or POLE-altered tumors

- Open label, phase 1, single group, any tumor histology provided it was MMRd (i.e., tumors with high mutational burden and therefore high tumor neoantigen burden)
- 2nd line or later
- N=327
- ORR 44.0%
- mDOR: NR
- mPFS: 6.9 months
- mOS: NR



Andre et al. 2023, JAMA Netw Open

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

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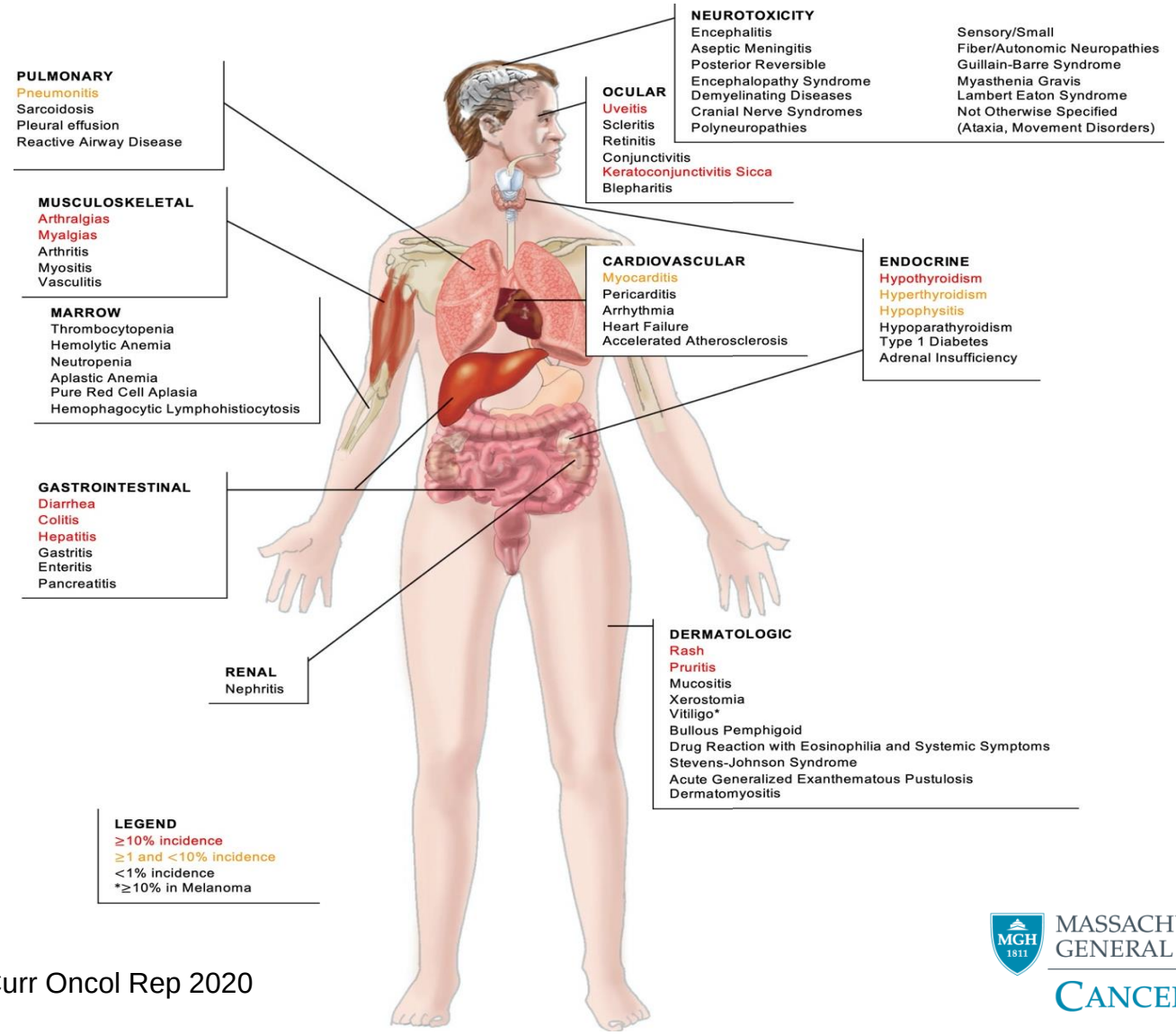
Immune-related AEs can affect any organ



Darnell and Reynolds Curr Oncol Rep 2020

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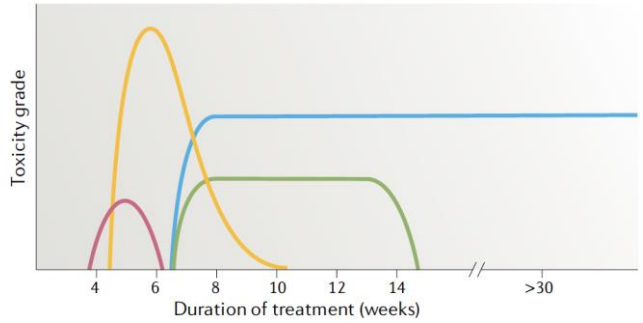
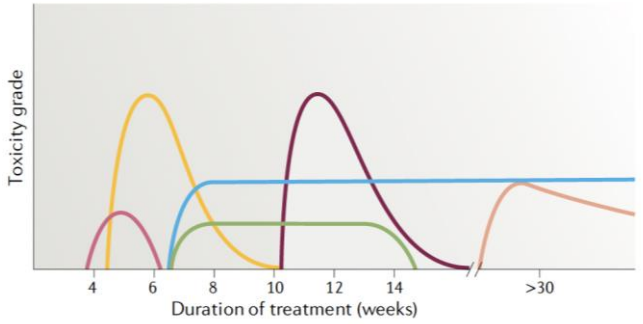
Kinetics of irAEs, 23 Clinical Trials, 8,436 Pts

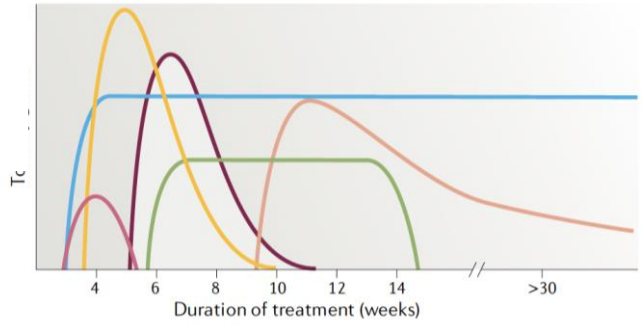
CTLA-4



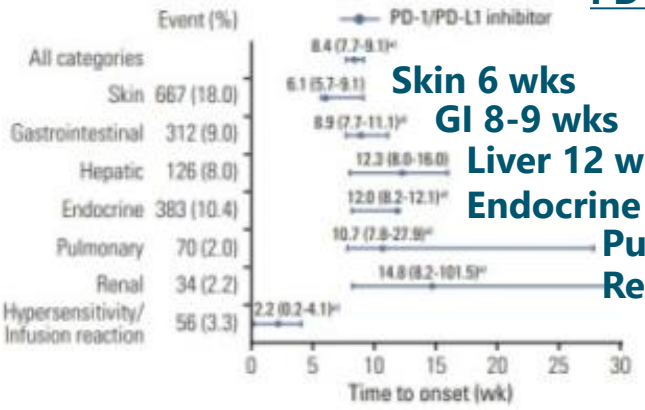
PD-(L)1



PD-(L)1 + CTLA-4

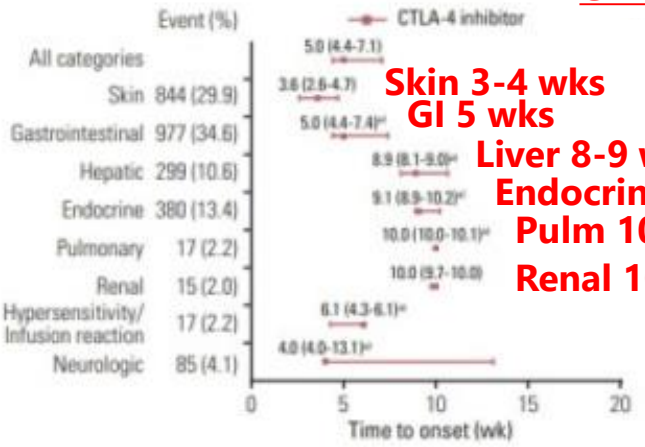


PD-(L)1 irAEs



Skin 6 wks
GI 8-9 wks
Liver 12 wks
Endocrine 12 wks
Pulm 10 wks
Renal 15 wks

CTLA-4 irAEs



Skin 3-4 wks
GI 5 wks
Liver 8-9 wks
Endocrine 9 wks
Pulm 10 wks
Renal 10 wks

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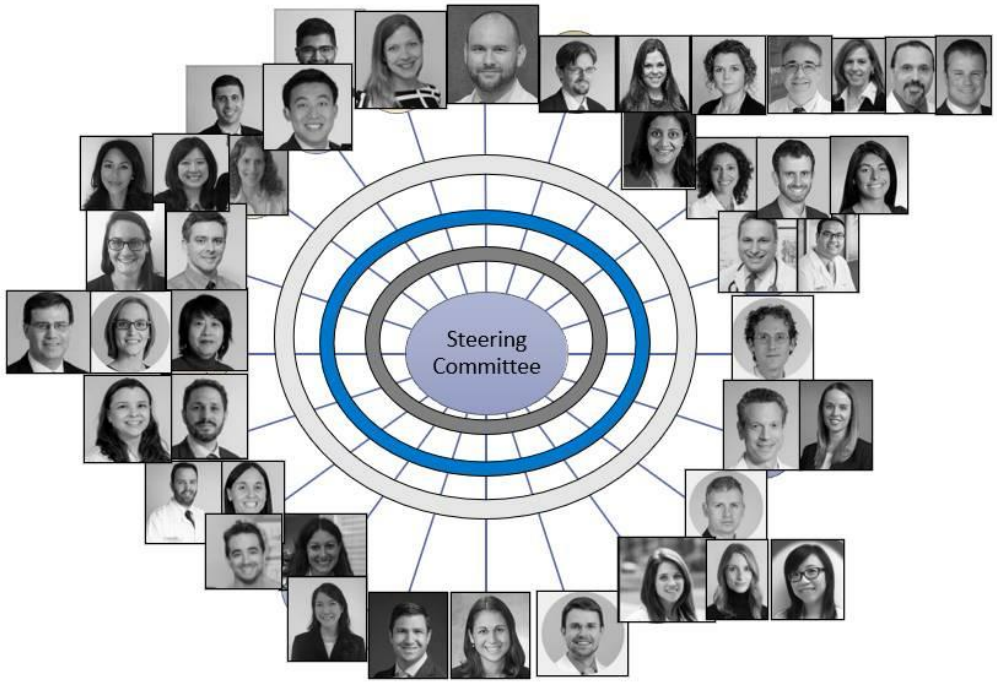
Tang, Cancer Res Treat, 2021; Martins, Nat Rev 2019

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

Case presentation #1

- 55 y/o M w/ metastatic HPV+ oropharyngeal SCC, PMH of former smokeless tobacco user and hypothyroidism, s/p 5 months ipi/nivo, **presents with syncope**.
  - Started nivolumab/ipilimumab 1/2018
  - 6/2018 reported feeling dizzy prior to an unwitnessed syncopal event
  - Denies any chest pain or palpitations preceding syncope.
  - Wife found patient confused with respiratory distress.
  - Denies any abnormal movements, urinary or stool incontinence.

Hospital Course

- Presented with unwitnessed syncope found to be bradycardic 40s and hypotension 80s/40s
- Junctional rhythm
- Started on epinephrine
- Atropine 0.5 mg x 2
- Telemetry notable for 6 second pause
- NT-proBNP = 551 ; hsTnT = 17
- Admitted to CCU for 22 days
- Emergent temporary pacing wire was placed

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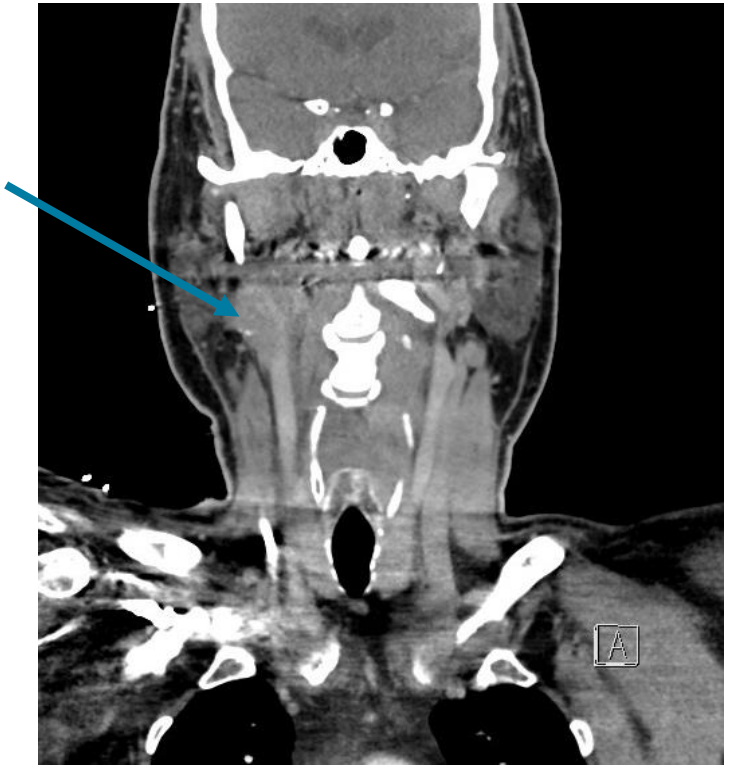
Diagnostic Studies

- CT PE negative for PE
- CT Neck → brady 2/2 mass effect on carotid body?



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Diagnostic workup

- **TTE**

Left Ventricle	Size & wall thickness normal. There are no segmental left ventricular wall motion abnormalities noted. EF is 62%
Right Ventricle	RV cavity is mildly dilated. The right ventricular systolic function is normal.
Left Atrium	LA is dilated.
Right Atrium	RA is dilated. The IVC is dilated (>2.1 cm). The IVC demonstrates reduced collapse with inspiration which is consistent with elevated RA pressure.
Aortic Valve	The aortic valve is tricuspid. No stenosis or AR

- **Endomyocardial Biopsy**

FINAL PATHOLOGIC DIAGNOSIS:
ENDOMYOCARDIUM (LEFT VENTRICLE) BIOPSY:
FOCAL LYMPHOCYTIC MYOCARDITIS.

Note: There is focal infiltration by lymphocytes and macrophages with associated myocyte injury. There is also endocardial fibrous thickening, mild interstitial fibrosis, and mild myocyte hypertrophy. Trichrome and PAS/D stains and immunohistochemical stains for CD3, CD4, CD8/PDL1, CD68, CD163, C4D, myeloperoxidase, and tryptase were also examined. The pathologic features are consistent with an immune checkpoint inhibitor associated myocarditis.

Myocarditis treatment

- Underwent pacemaker placement
- 1g IV methylprednisolone x 3d once biopsy returned as myocarditis
  - D/c on 60 mg prednisone QD
- Underwent PPM placement
- Repeat CMR 2 months after starting immunosuppression showed LVEF 56%, no e/o enhancement to suggest myocarditis

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Case presentation #2

Stage IV melanoma

- Metastatic mucosal melanoma arising from recurrence of a nasal polyp resected 5 years prior,
- Day 0: first cycle of ipilimumab/nivolumab
- Day 21: second cycle of ipilimumab/nivolumab
- Day 26: episode of vision loss
  - Prescribed 14-day prednisone taper (Day 26 – 39), 80 mg/day -> 10 mg/day
- Day 50: presents with diarrhea

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Workup

Micro

Stool C. diff Ag/PCR: negative

Stool culture:
- NORMAL ENTERIC FLORA PRESENT
- NEGATIVE FOR ENTERIC PATHOGENS
- Moderate STAPHYLOCOCCUS AUREUS

Blood cultures x 2 negative

Stool O&P negative

HBV serologies immune (surface Ab positive, surface Ag/core Ab neg

Blood CMV PCR negative

Tuberculosis IGRA positive (result returns after discharge)

Immunologic studies

*ESR, CRP not performed

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CT Abdomen/Pelvis (Hospital Day 1):

Narrative

GI TRACT: There is mild diffuse colonic wall thickening and mild injection of the pericolonic fat. There are air-fluid levels throughout the colon, corresponding to the known diarrhea. Normal appendix. No evidence of bowel obstruction.

Impression

1. Mild diffuse colitis, likely related to infection or drug therapy. Inflammatory and ischemic etiologies are considered less likely.

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Hospital Course and Treatment

- Admitted with Grade 3 diarrhea
- HD 1: Started on prednisone 45 BID, cipro, flagyl
  - Minimal improvement in diarrhea
- HD 3: Steroids increased to IV methylprednisolone 125 daily on day 3
  - No change in diarrhea
- HD 4: sigmoidoscopy/biopsies performed → confirm ICI-colitis
- HD 6: Given infliximab (Remicade)
  - Rapid improvement in diarrhea within 24 hours
- HD 8: discharged
  - Transitioned to PO steroids

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Sigmoidoscopy (Hospital Day 4)

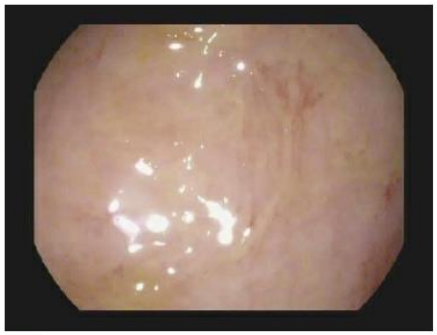
Findings:

Diffuse moderate inflammation characterized by congestion (edema), erosions, erythema, mucous, and shallow ulcerations was found in the rectum, in the proximal sigmoid colon and in the mid sigmoid colon. There was a short area of sparing at 20cm. Biopsies were taken with a cold forceps for histology.

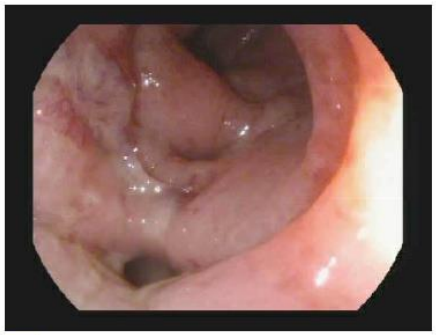
Multiple small and large-mouthed diverticula were found in the sigmoid colon.

Impression:

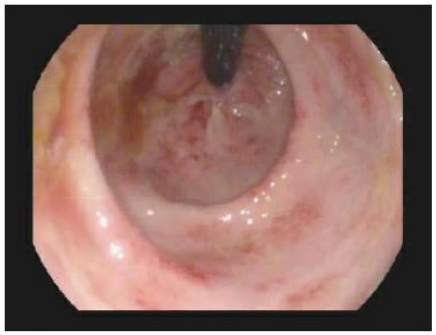
- Diffuse moderate inflammation was found in the rectum, in the proximal sigmoid colon and in the mid sigmoid colon secondary to colitis.



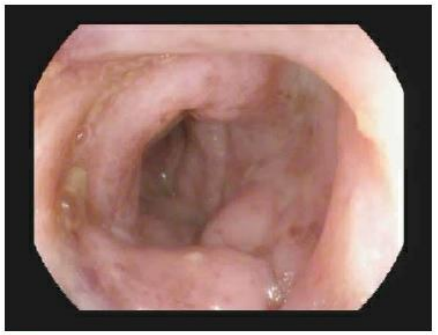
2 Sigmoid Colon : *Inflammation



3 Descending Colon : *Inflammation



4 Rectum : *Inflammation



5 Sigmoid Colon : *Inflammation

FINAL PATHOLOGIC DIAGNOSIS:

A. COLON BIOPSY, SIGMOID:

Severely active colitis with ulceration (see note).

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Oncologic /ICPI outcomes

- Scans at time of the initial colitis admission showed significant response to ICPI therapy
  - Residual bony metastases noted, no growth
- At 3.5 years following 2 doses ipilimumab/nivolumab patient has ongoing partial response
- No further therapy given; ongoing surveillance

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Summary

- Multiple immunotherapy modalities exist
- Mechanisms of immune-mediated anti-tumor efficacy remain areas of active research
- ICI are fundamentally important for nearly all solid tumors and some hematologic malignancy
- irAEs are potentially fatal but often treatable (contact the treating oncologist if you are concerned)

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Questions?

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