Impact of Immunotherapy on Cancer Survivorship

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knowledge changing life

MEDICAL COLLEGE OF WISCONSIN

Objectives

- Discuss the mechanism of action, indications, and efficacy immune checkpoint inhibitors (ICIs)
- Characterize the side effects of ICIs.
- Understand the long-term impact of ICIs on survival and quality of life.

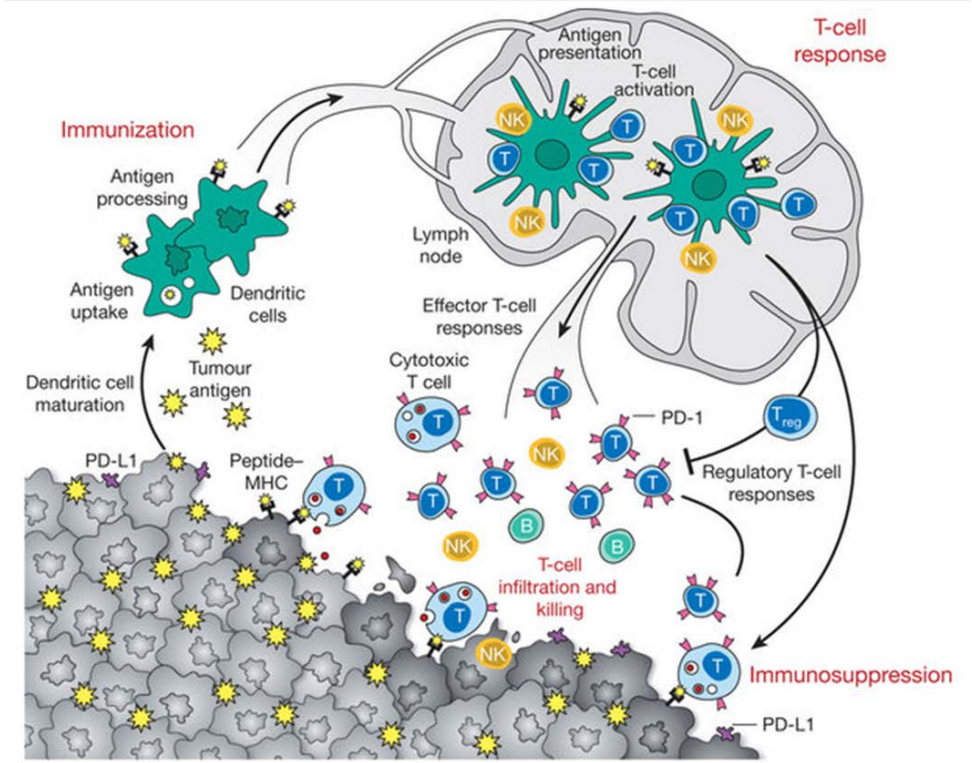
Ground Rules

- Immunotherapy is not chemotherapy

- There are many types of cancer immunotherapy. I will be focusing on immune checkpoint inhibitors (ICIs)

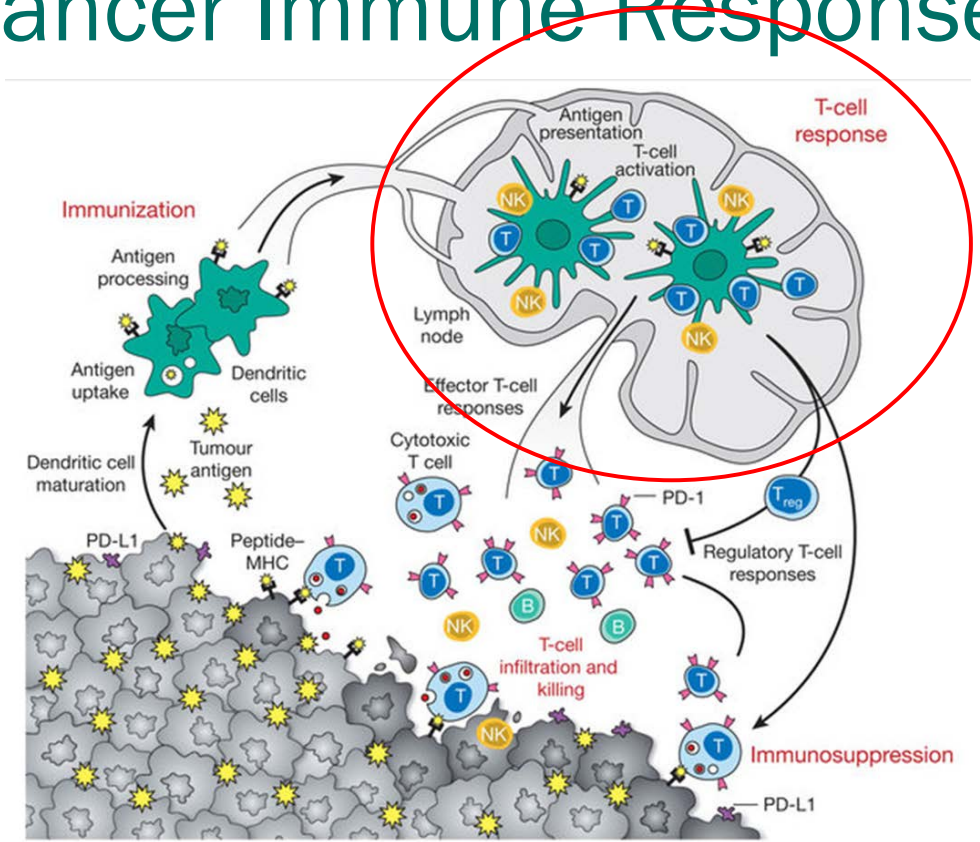
Immune Checkpoint Inhibitors (ICIs)

Anti-Cancer Immune Response



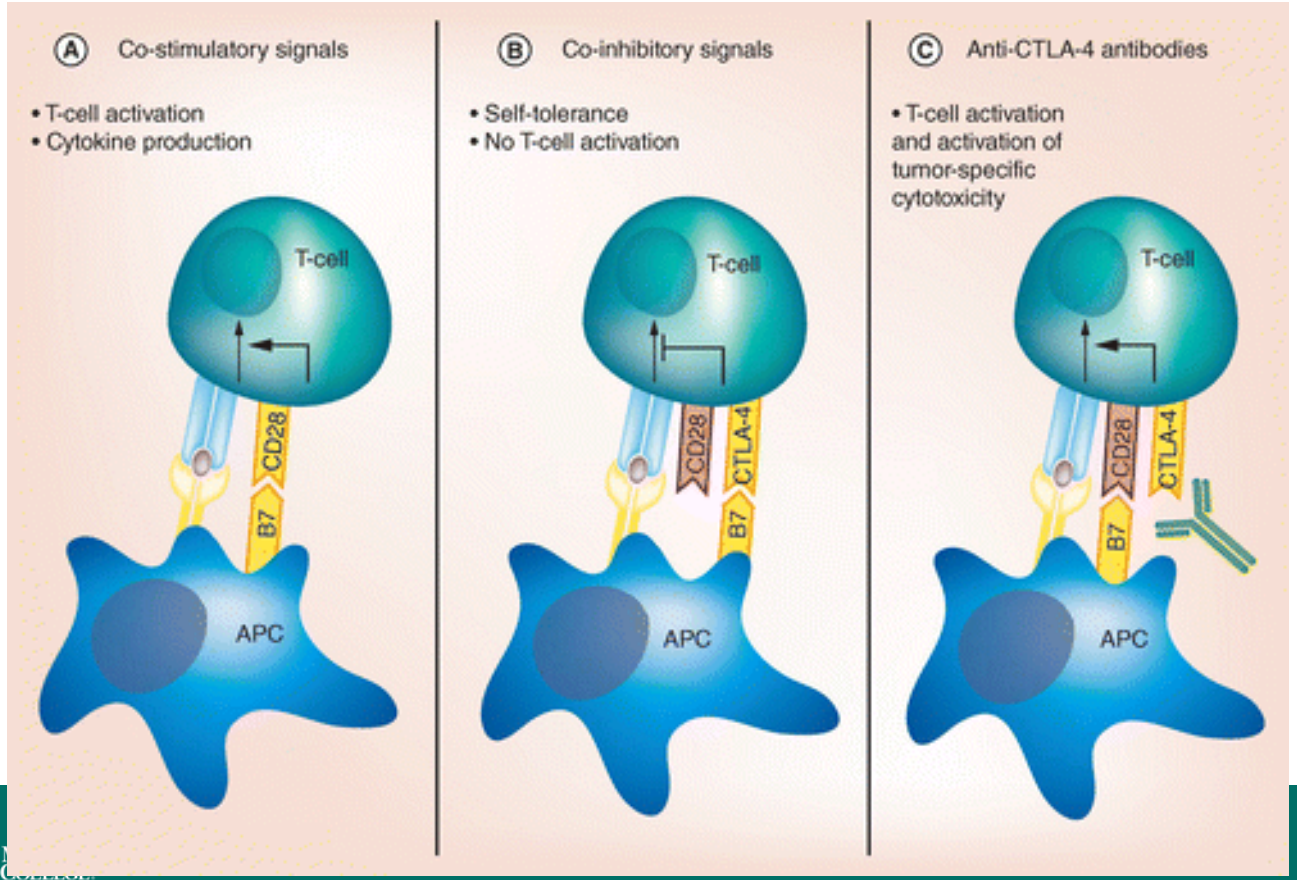
Mellman et al. *Nature* 2011;480(7378):480-9

Anti-Cancer Immune Response



Mellman et al. *Nature* 2011;480(7378):480-9

CTLA-4 Inhibitors



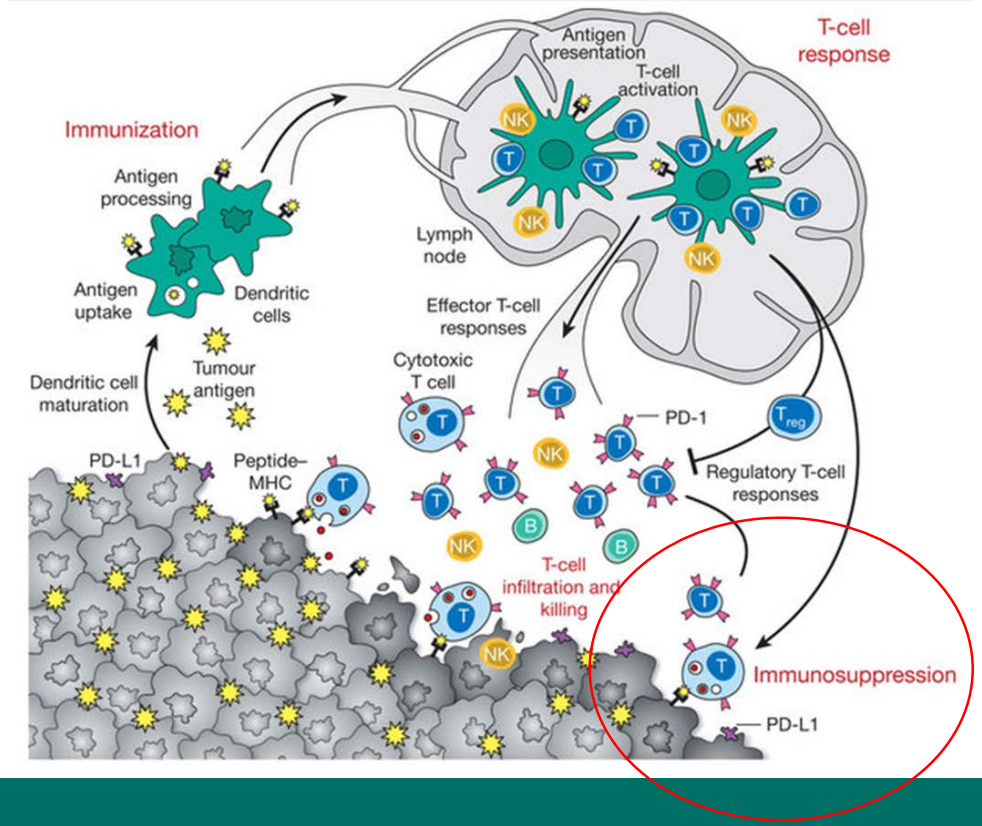
FDA-approved CTLA-4 Inhibitors

Ipilimumab (Yervoy®)

Tremelimumab (Imjudo®)

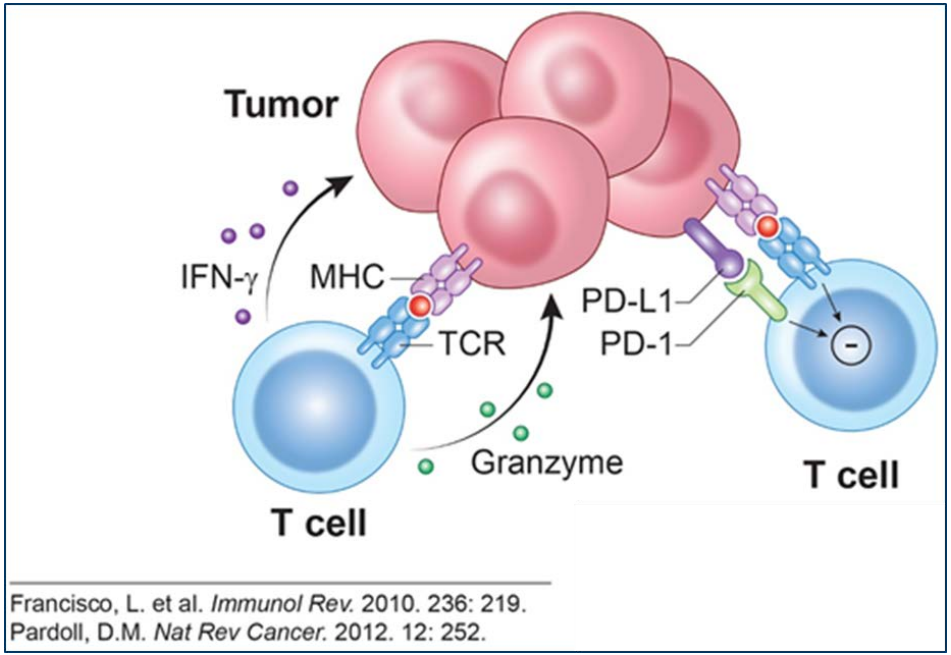
https://doi.org/10.2217/imt-2016-0123

Anti-Cancer Immune Response



Mellman et al. *Nature* 2011;480(7378):480-9

PD-1/PD-L1 Inhibitors



Francisco, L. et al. *Immunol Rev.* 2010. 236: 219.
Pardoll, D.M. *Nat Rev Cancer.* 2012. 12: 252.

FDA-approved PD-1/PD-L1 inhibitors

Nivolumab (Opdivo®)

Pembrolizumab (Keytruda®)

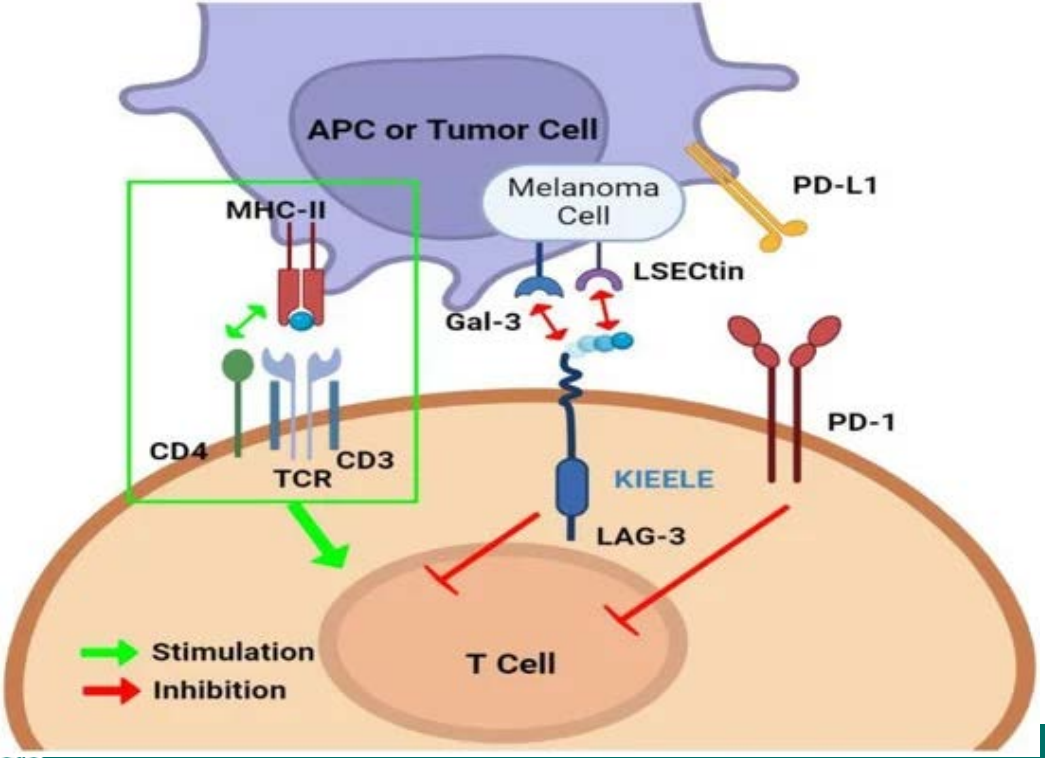
Atezolizumab (Tecentriq®)

Durvalumab (Imfinzi®)

Avelumab (Bavencio®)

Cemiplimab (Libtayo®)

LAG-3 Inhibitor

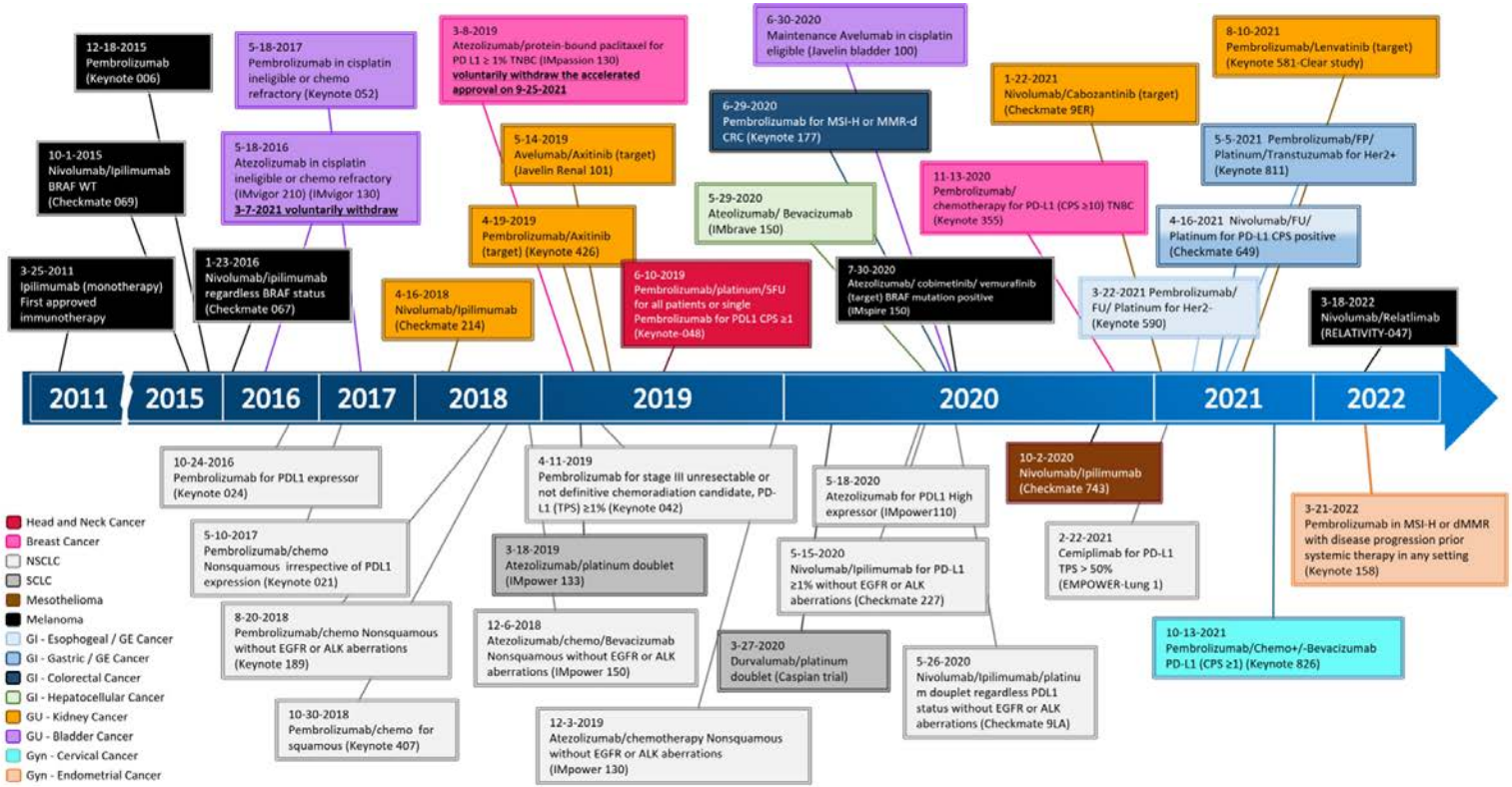


FDA-approved LAG-3 inhibitor

Renlantlimab + Nivolumab (Opdualag®)

Ibrahim et al, Biomedicines 2023.

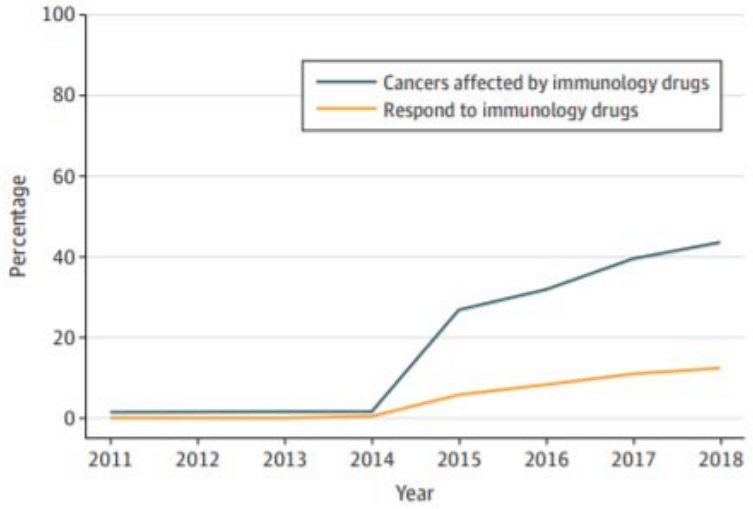
Immune Checkpoint Inhibitor Indications



Ma et al, Experimental Hematology & Oncology, 2023.

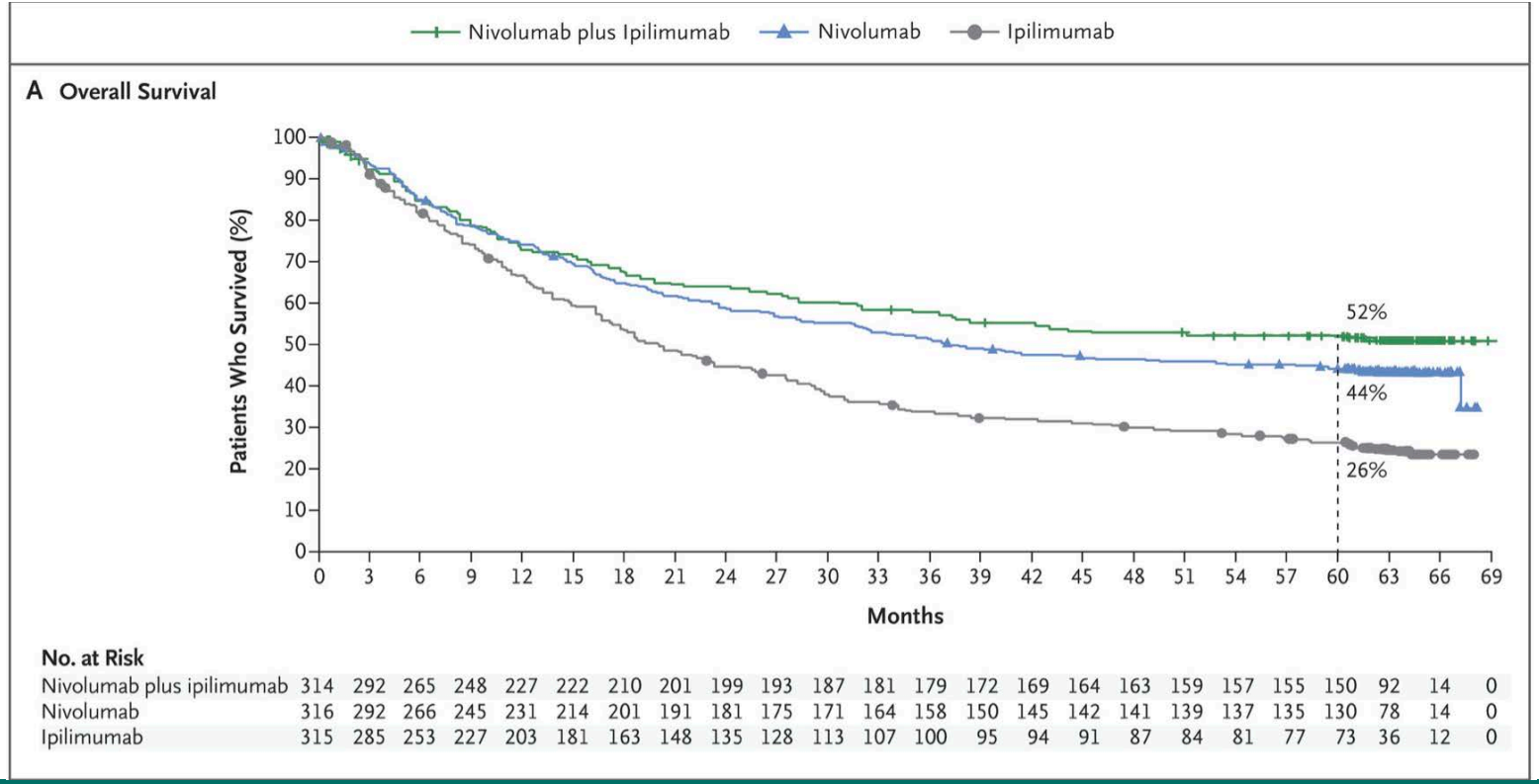
Immune Checkpoint Inhibitor Use is Rapidly Expanding

Figure 1. Percentage of US Patients With Cancer Who May Benefit From and Respond to Checkpoint Inhibitor Immunology Drugs (2011-2018)



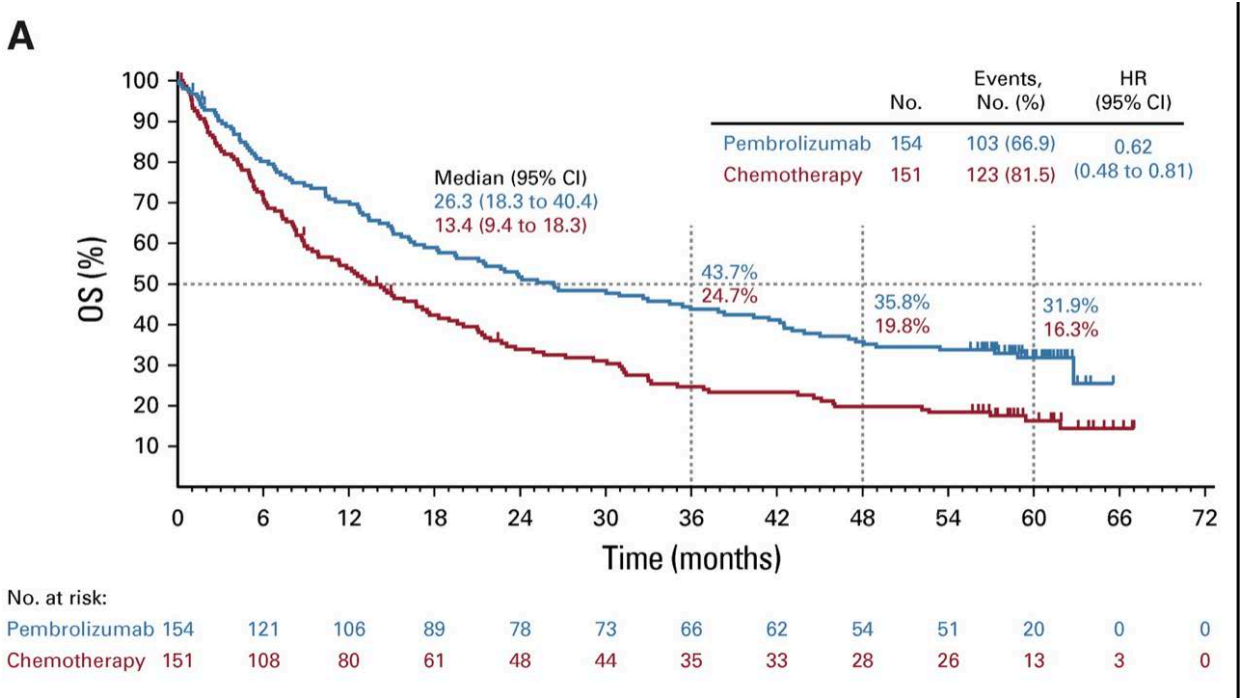
JAMA Network Open. 2019;2(5):e192535. doi:10.1001/jamanetworkopen.2019.2535

Ipilimumab + Nivolumab – Stage 4 Melanoma



Larkin et al, N Engl J Med, 2019.

Pembrolizumab – PD-L1 high, stage 4 NSCLC

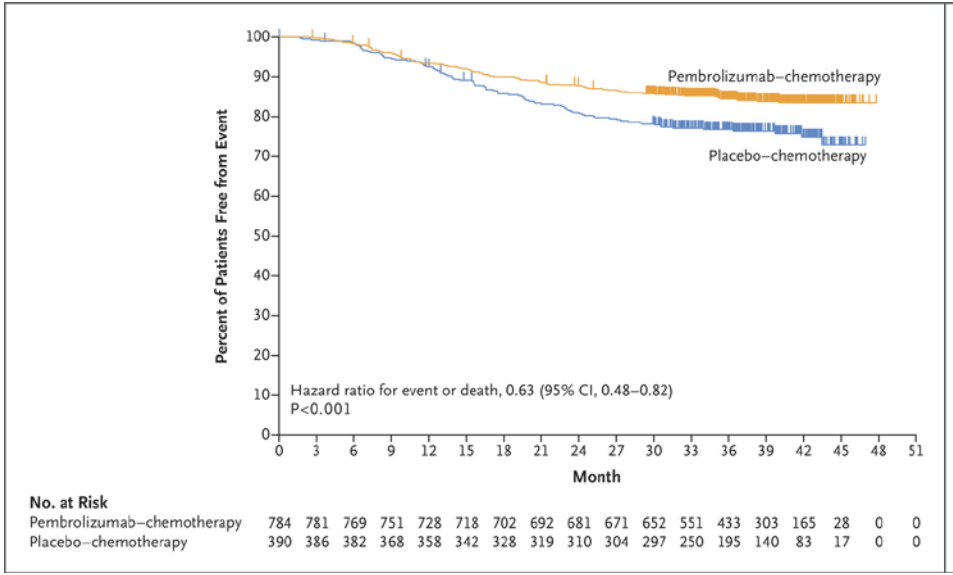


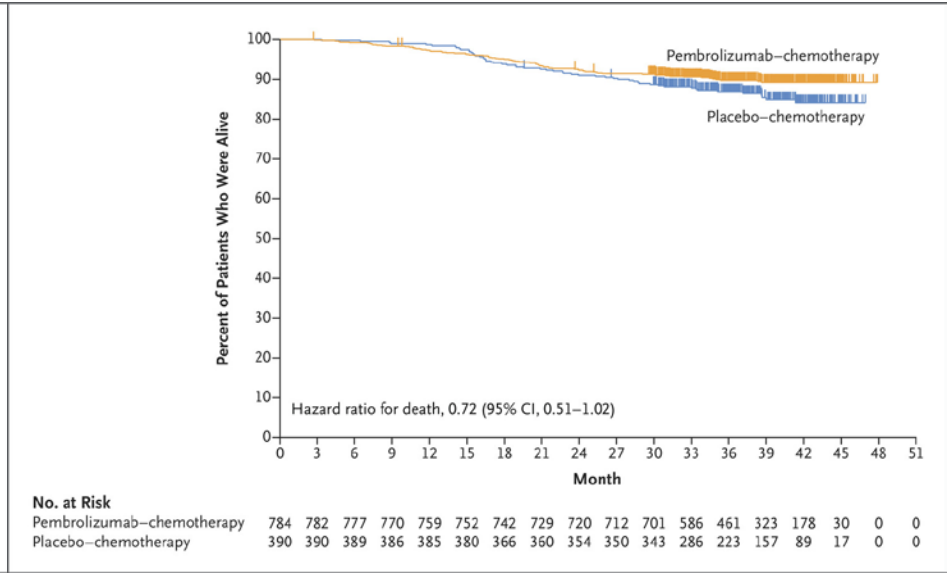
5-year survival 31%

Reck et al. *J Clin Oncol* 2021.

Neoadjuvant Chemotherapy + Pembrolizumab

Early-stage triple-negative breast cancer

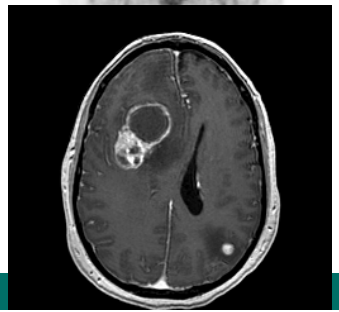


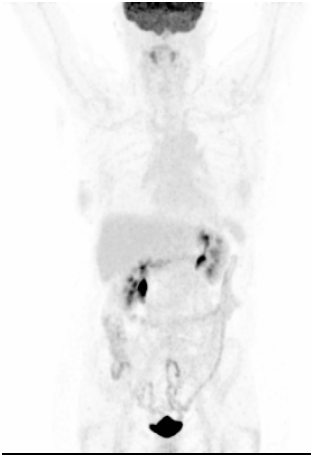


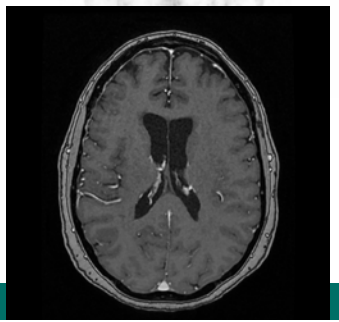
Schmid et al, N Engl J Med, 2022.

Immunotherapy – Good effect, good tolerance

» 58 yo with metastatic lung adenocarcinoma







January 2022
Started Pembrolizumab

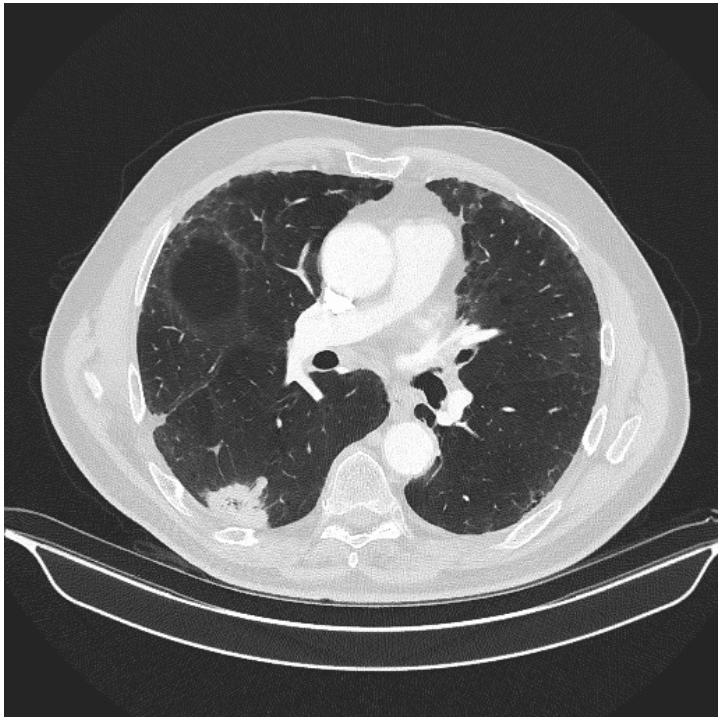
Now
Only side effect: minor rash

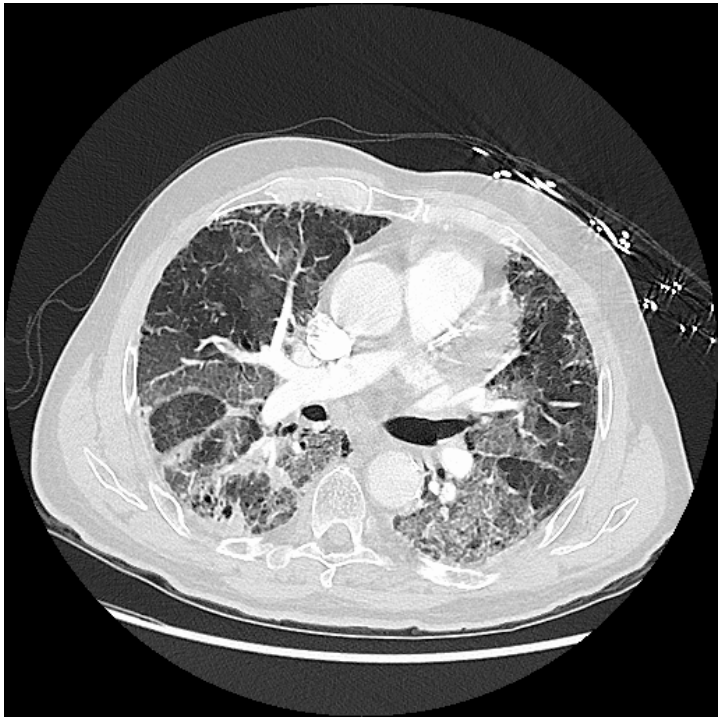
Immunotherapy – Good effect, poor tolerance

- 62 yo with malignant pleural mesothelioma involving R hemithorax, history of mild, seropositive rheumatoid arthritis (+RF, +CCP).
- Cancer progression through standard chemotherapy
- 5/25/21: Started Immunotherapy (Ipilimumab & Nivolumab)
  - Immediately after developed diffuse rash requiring oral prednisone
- 7/27/21: Resumed Ipilimumab and Nivolumab
- 11/2021: Developed dyspnea and cough. Ipi/nivo held.
  - CT chest w/diffuse GGOs.
  - Lung biopsy positive for interstitial fibrosis with areas of diffuse alveolar damage including acute fibrinous organizing pneumonia
  - High-dose prednisone improved dyspnea but recurred with taper. Infliximab added.
- RA subsequently flared → transitioned to adalimumab
- 9/2024: Remains off cancer immunotherapy without cancer progression, but still struggles with RA, remains on adalimumab, hydroxychloroquine.

Immunotherapy – Life threatening complications

» 71 yo with metastatic lung adenocarcinoma



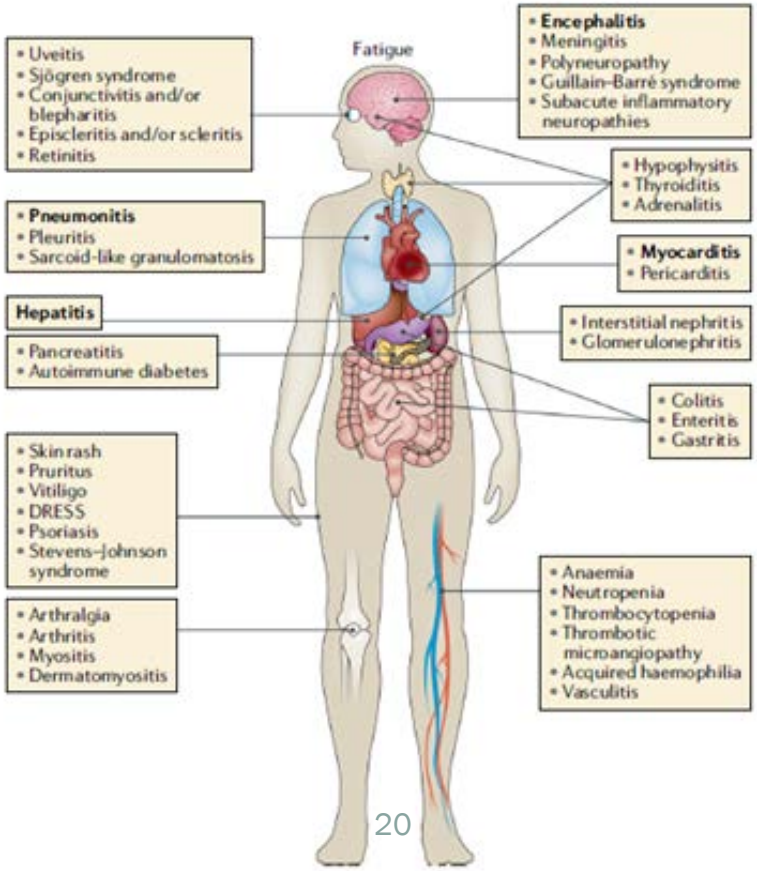


December 2023
Started chemotherapy + pembrolizumab

June 2024

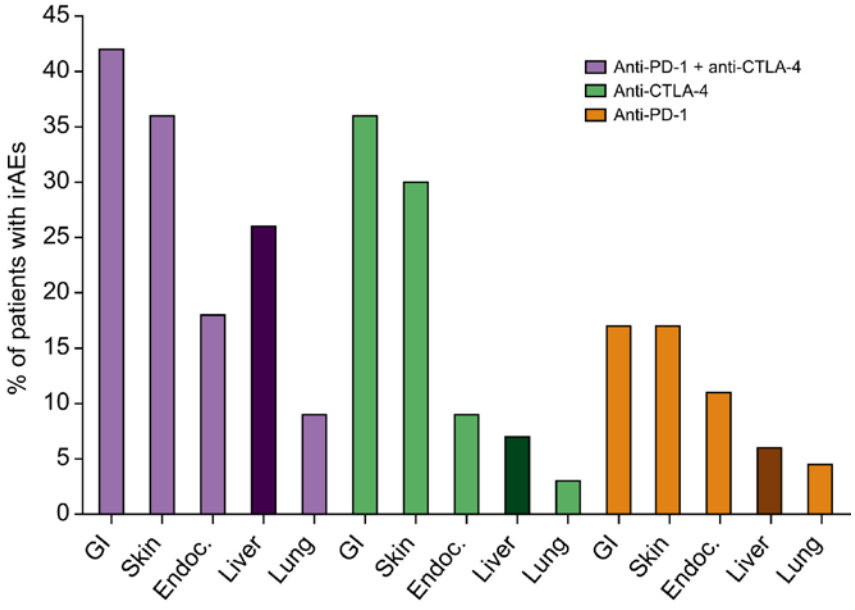
Immune-related adverse events (irAEs)

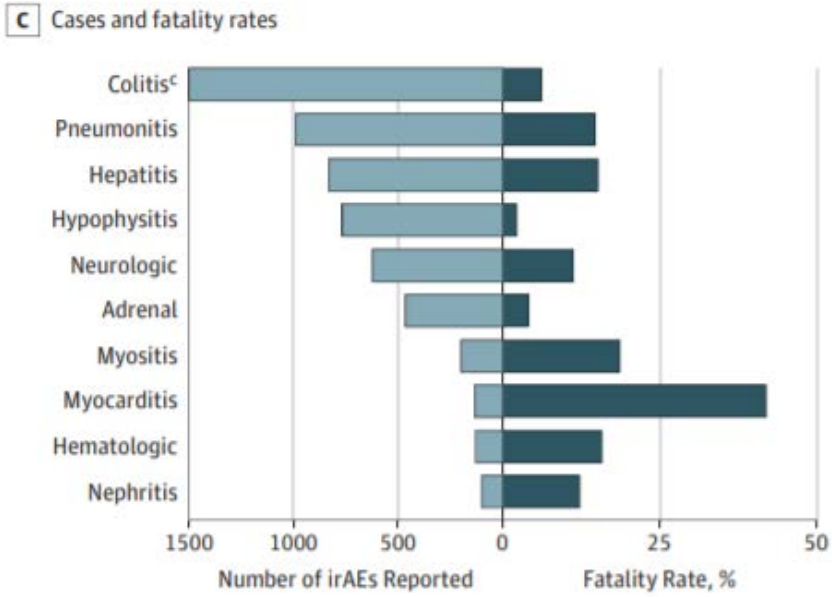
irAEs can affect any organ system



Martins et al., *Nat Rev Clin Oncol.* 2019;16:563-580

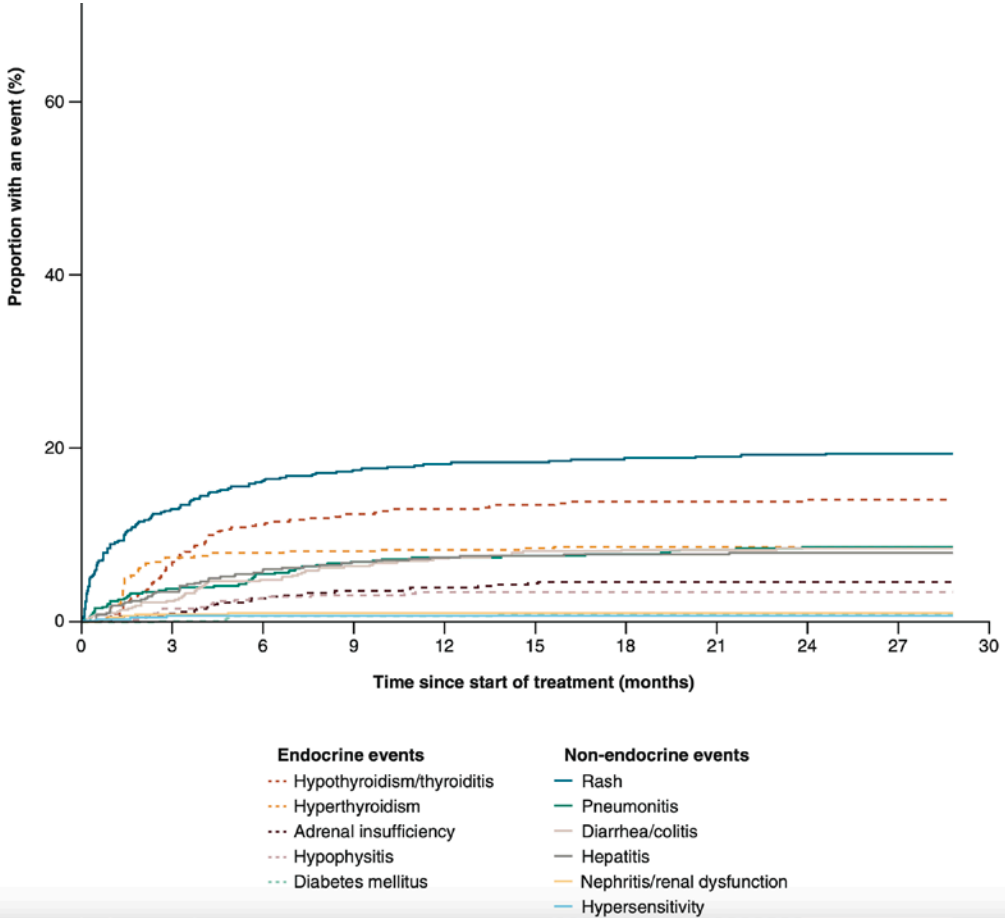
irAEs are common and vary in severity





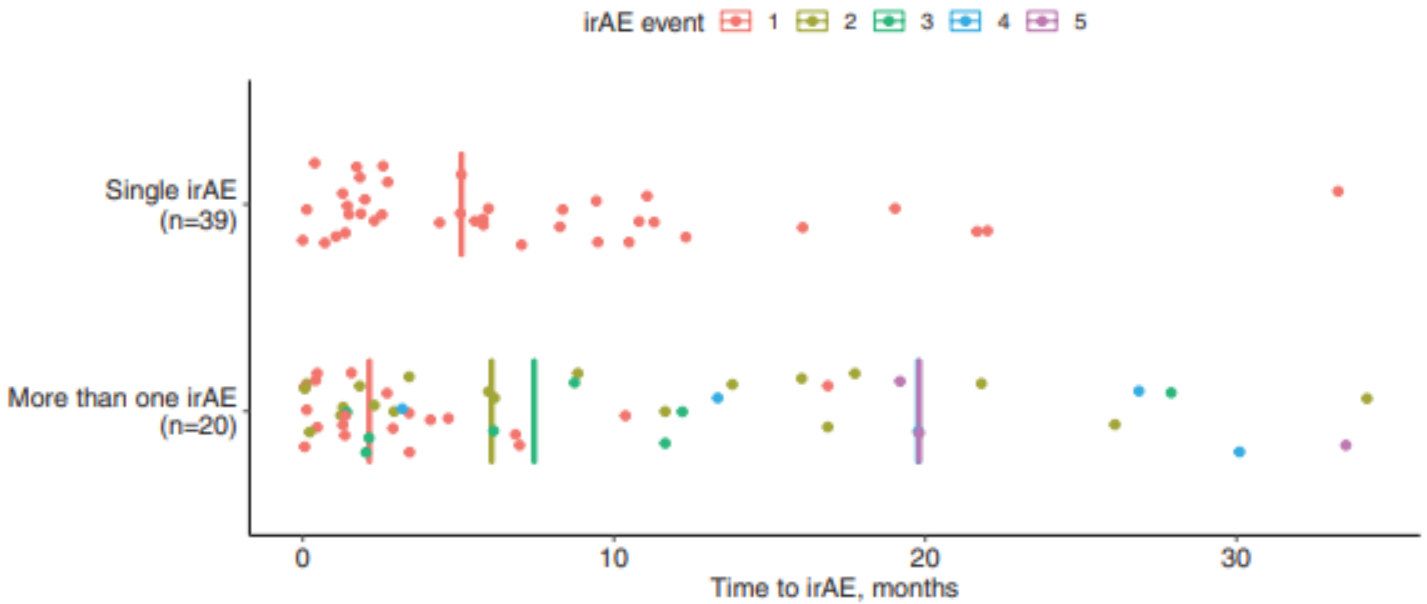
De Martin et al, *JHEP Reports, 2020.*
Wang et al., *JAMA Oncol*, 2018.

irAE onset



Paz-Ares et al, J Thorac Oncol, 2021.

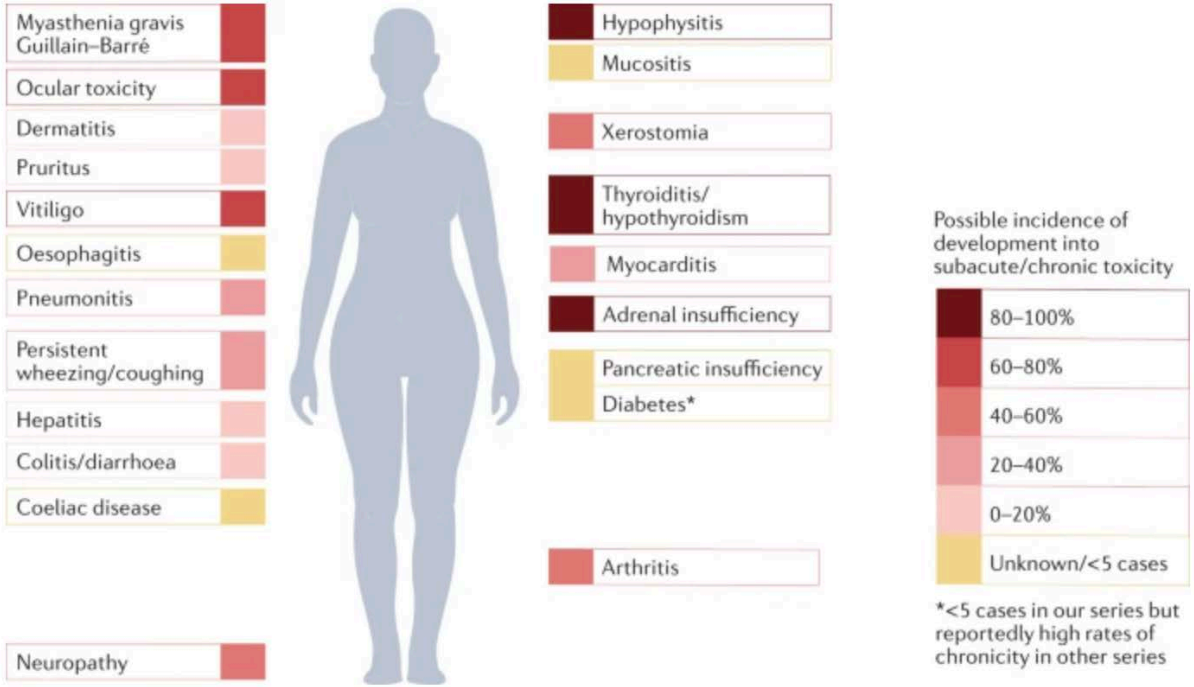
irAE timeline



Hsu et al, Oncologist, 2022.

Chronicity of irAEs

Fig. 3: Possible frequencies of chronic immune-checkpoint inhibitor-induced toxicities.



Risk factors for irAEs

- Retrospective studies
  - Increased irAE risk
    - Pre-existing autoimmune diseases
    - Pre-existing interstitial lung disease
    - Prior solid organ transplantation
    - Elevated BMI
    - Gender (women ↑ endocrinopathies and ↓ neuro/skin/vascular toxicities compared with men)
    - NSAIDs (↑ risk of enterocolitis, nephritis)
    - Antibiotic exposure

Khan et al., *JAMA Oncol*. 2016;2:1507-1508.
Shimoji et al., *JAMA Netw Open*. 2020;3:E2022906
Kumar et al., Oncologist. 2020;25:505-514.
Eun et al., *Sci Rep*. 2019;9:14039.
Toi et al., *JAMA Oncol*. 2019;5:376-383.
Duma et al., *Oncologist*. 2019;24:e1148-1155.
Jing et al., J Immunother Cancer. 2022;10:e00379.
Marthey et al., *J Crohns Colitis*. 2016;10:395-401

Chronic irAEs

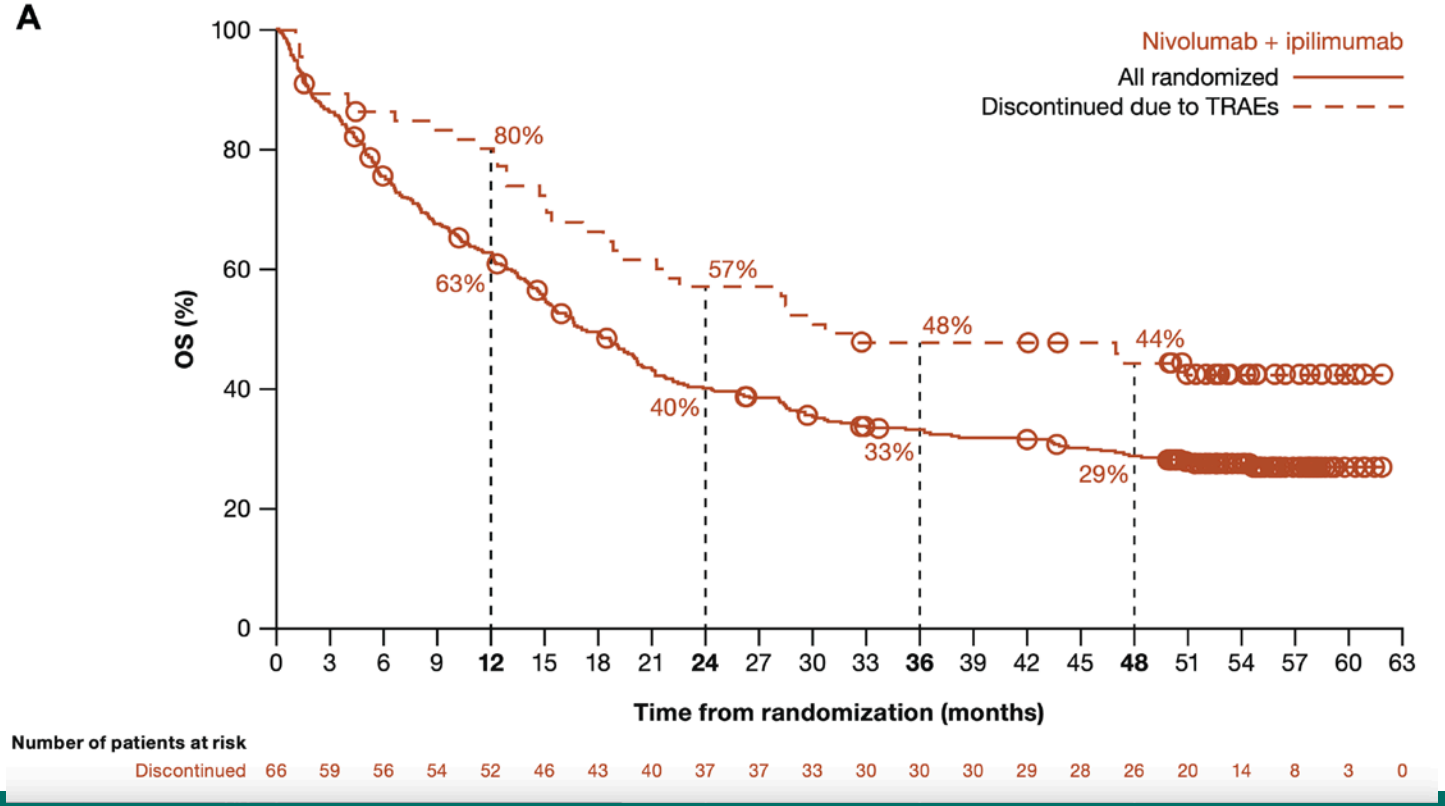
- **Multicenter retrospective cohort study**
- **43% of advanced melanoma pt tx with PD-1 inhibitor had chronic irAE (occurred>12 weeks after discontinuing ICI)**

Table 2. Incidence of Chronic Immune-Related Adverse Events (irAEs)

Chronic irAEs	Patients, No. (%)	
	With chronic irAEs	Ongoing chronic irAE at last follow-up
Total chronic irAEs	167 (100)	NA
Required steroids	55 (32.9)	NA
Symptomatic	82 (49.1)	NA
Resolved	24 (14.4)	NA
≥Grade 2	90 (53.9)	NA
Grade 3-5	6 (3.6)	NA
irAE Type[a]		
Adrenal insufficiency	12 (3.1)	12 (100)
Arthritis/arthralgias	22 (5.7)	22 (100)
Colitis/diarrhea	6 (1.6)	2 (33.3)
Dermatitis/pruritus	19 (6.6)	17 (89.5)
Xerostomia[b]	9 (2.3)	8 (88.9)
Hypophysitis	8 (2.1)	8 (100)
Neuropathy	3 (1.8)	1 (33.3)
Ocular toxic effect[c]	5 (1.3)	5 (100)
Other neurotoxicity[d]	8 (2.1)	5 (63.0)
Pneumonitis	6 (1.6)	4 (66.7)
Thyroiditis/hypothyroid	54 (14.0)	54 (100)

Patrinely et al, JAMA Oncol, 2021.

irAEs may predict for better ICI efficacy



Paz-Ares et al, J Thorac Oncol, 2021.

Management of irAEs

VOLUME 36 · NUMBER 17 · JUNE 10, 2018
JOURNAL OF CLINICAL ONCOLOGY
ASCO SPECIAL ARTICL
Check for updates

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 ıca D. Santomasso, Carole Seigel, Alexander Jedd D. Wolchok, and John A. Thompson in

Annals of Oncology 28 (Supplement 4): iii119–iii142, 2017
doi:10.1093/annonc/mdx225

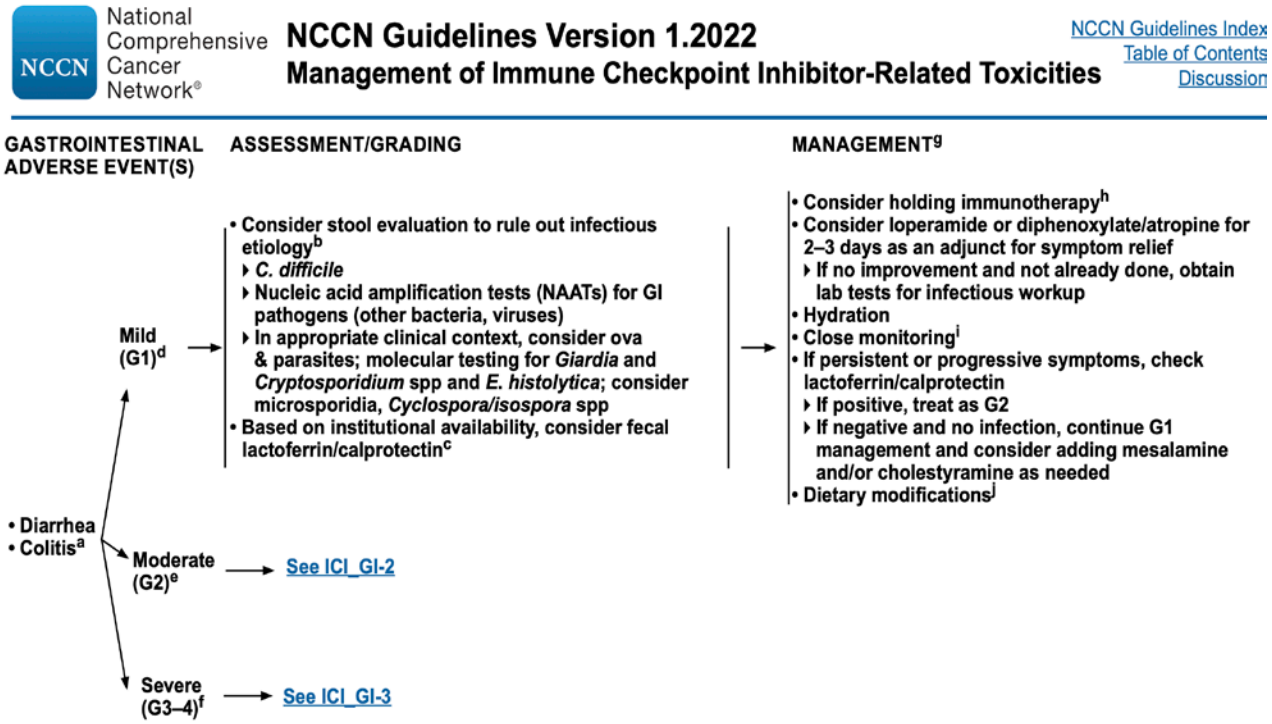
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

CLINICAL PRACTICE GUIDELINES

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

J. B. A. G. Haanen[1], F. Carbonnel[2], C. Robert[3], K. M. Kerr[4], S. Peters[5], J. Larkin[6] & K. Jordan[7], on behalf of the ESMO Guidelines Committee*

Colitis



G1: Increase of fewer than four stools per day over baseline; mild increase in ostomy output compared with baseline

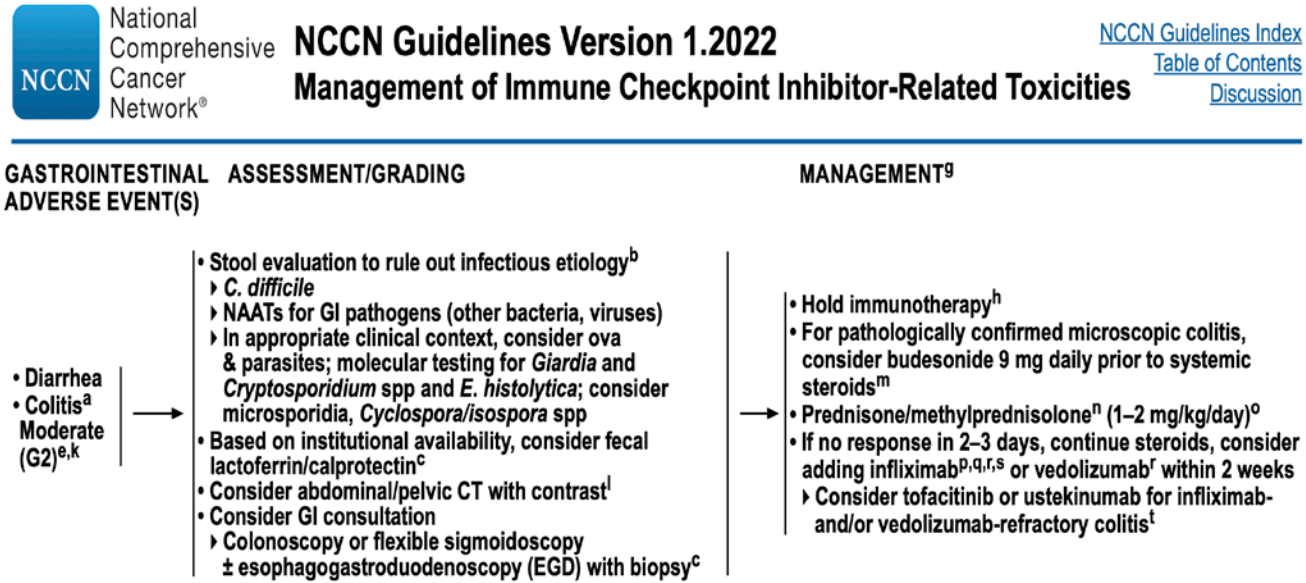
G2: Increase of four to six stools per day over baseline; moderate increase in ostomy output compared with baseline

G3: Increase of seven or more stools per day over baseline, incontinence, hospitalization indicated, severe increase in ostomy output compared with baseline, limiting self-care ADL

G4: Life-threatening consequences; urgent intervention indicated

https://www.nccn.org/guidelines/guidelines-detail?category=3&id=1486

Colitis



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G4: Life-threatening consequences; urgent intervention indicated

Case #1

- 72 yo M with h/o metastatic lung adenocarcinoma who presented with diarrhea after being on pembrolizumab for ~1.5 years
  - Up to 12 stools per day with bloating
  - CBC and CMP wnl
  - Infectious stool studies wnl
  - CT A/P without abnormalities
  - Colonoscopy: Diffuse, confluent erythema, loss of vascular pattern and linear ulcerations throughout the colon.

Case #1

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  - CBC and CMP wnl
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  - CT A/P without abnormalities
  - Colonoscopy: Diffuse, confluent erythema, loss of vascular pattern and linear ulcerations throughout the colon.
  - R and L colon biopsies showed moderate to severely active colitis, CMV negative

Case #1

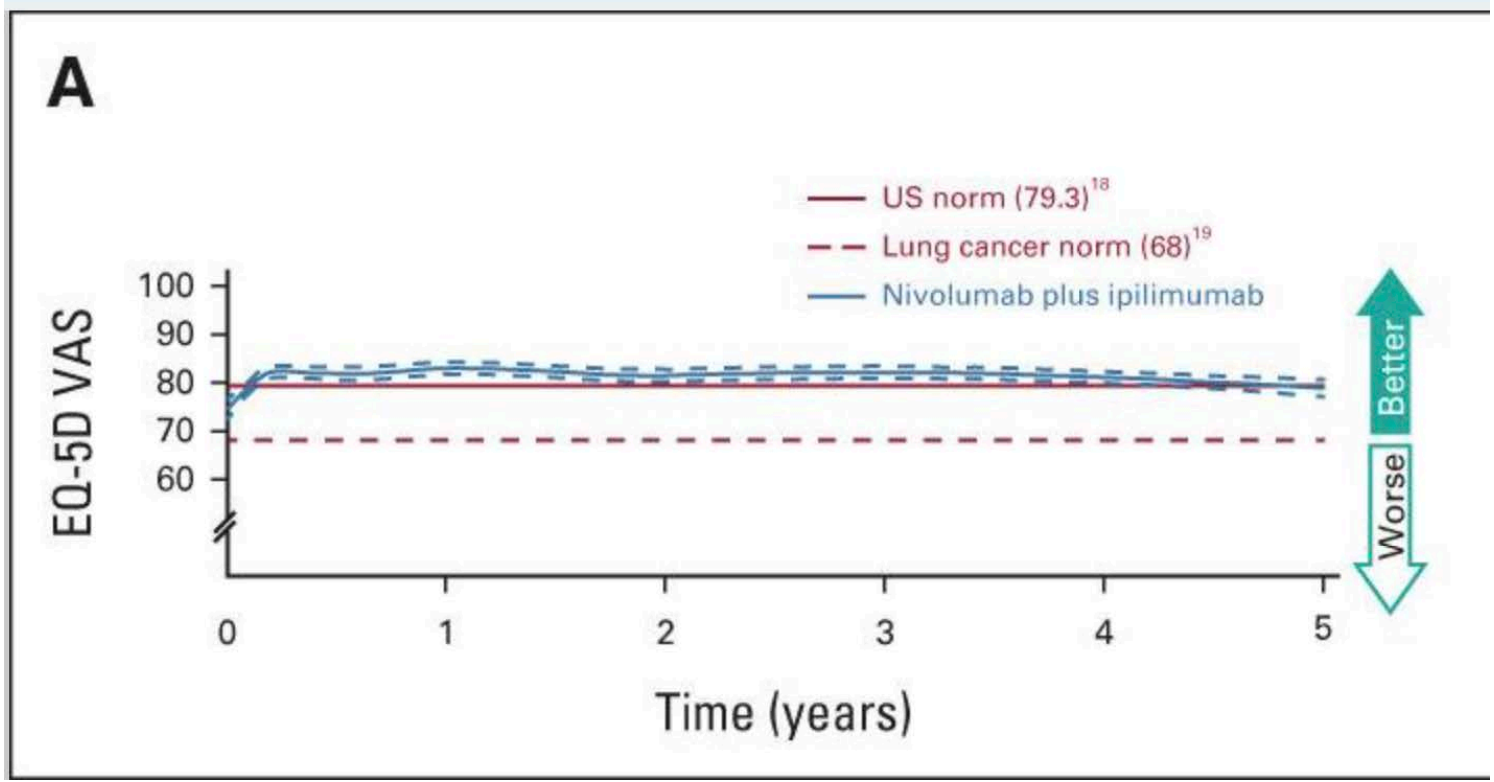
- Methylprednisolone 1 mg/kg/day started
- Diarrhea resolved quickly
- Prednisone slowly tapered over ~ 2 months
- Diarrhea recurred within a few days after taper completed
- Colonoscopy and biopsies continued to show colitis in distal colon and proximal rectum
- High-dose prednisone resumed, diarrhea improved but did not resolve
- Vedolizumab added
  - Diarrhea subsequently completely resolved
  - Colonoscopy 6 months later without colitis
  - Vedolizumab discontinued after ~10 months
  - No recurrence of diarrhea over the past 4 years

Quality of Life and Other Survivorship Concerns

Knowledge gaps in immunotherapy survivorship

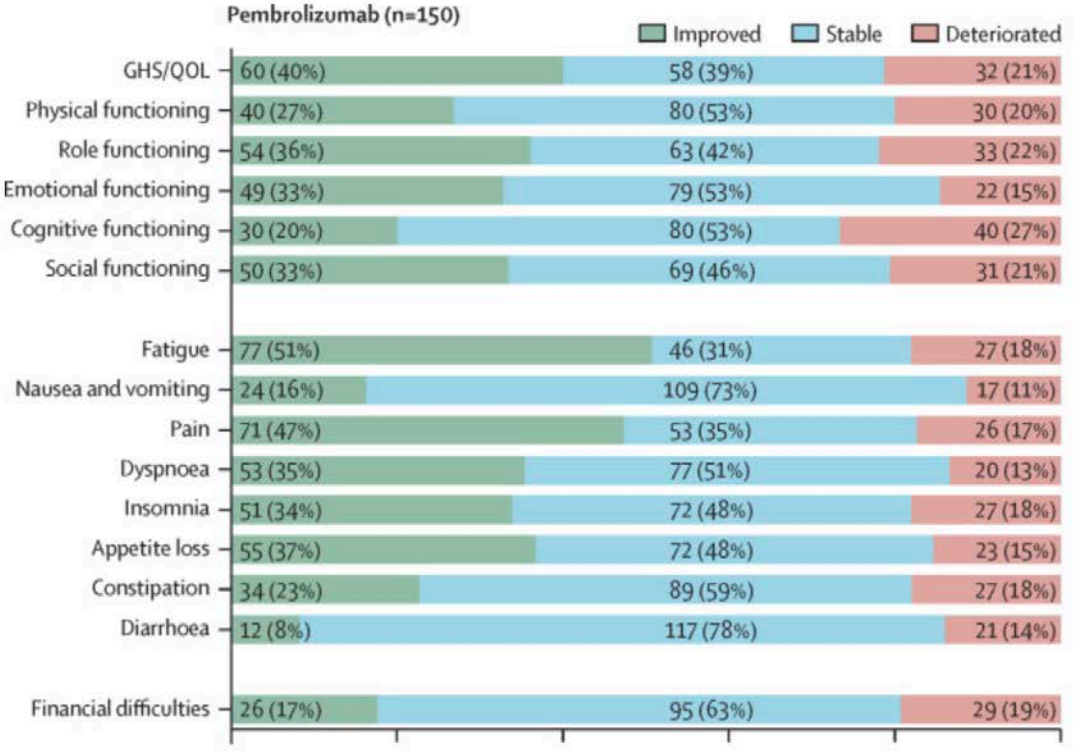
- Most clinical trials track acute toxicity and quality of life outcomes
- Trials focus on frequent adverse events, and infrequent (though clinically impactful) adverse events are under-appreciated
- Little attention paid to effect of ICIs on sexual, mental, and financial health
- Little if any evidence on management for long-term immunotherapy toxicity

Quality of Life – Metastatic NSCLC treated with immunotherapy



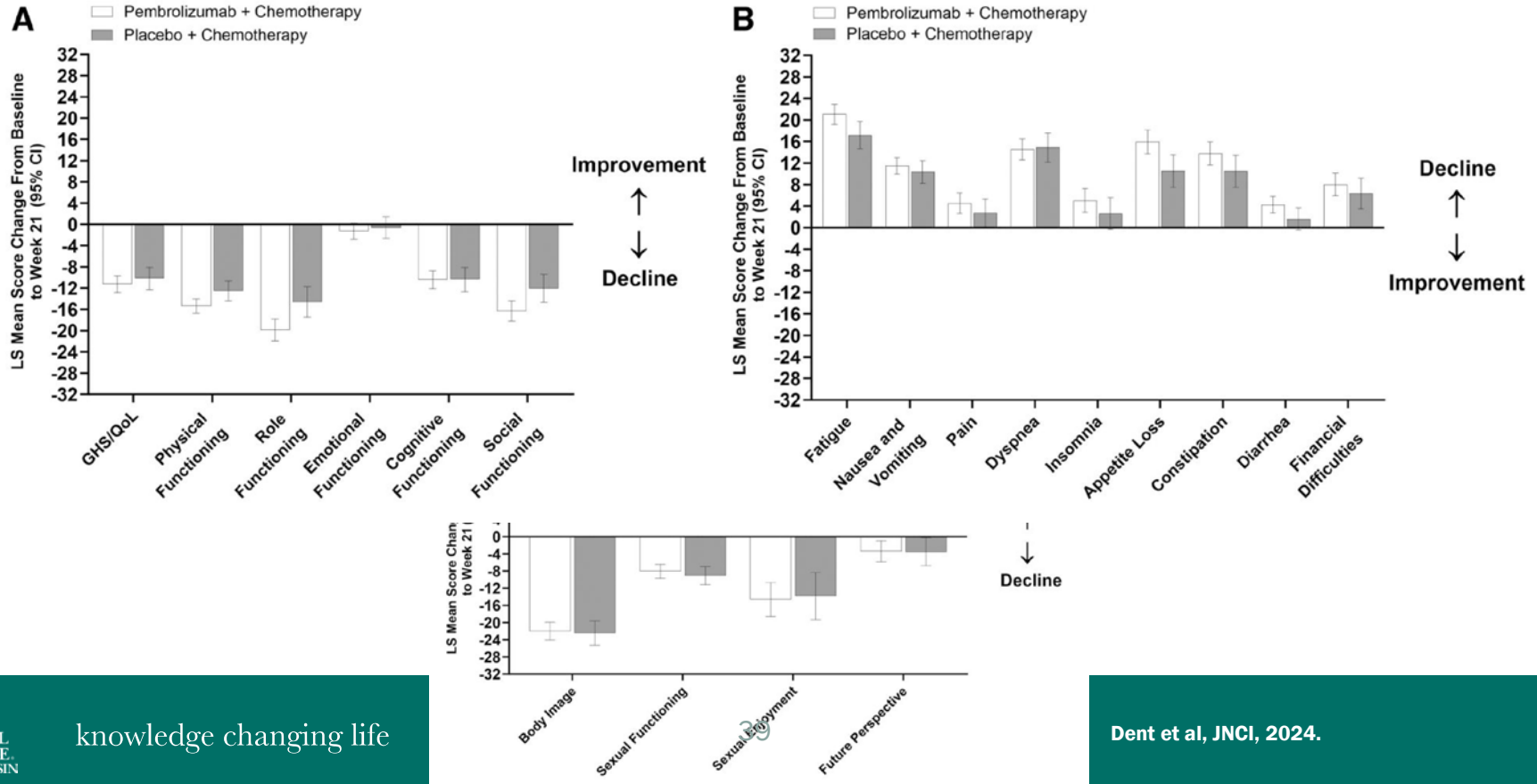
Brahmer et al, J Clin Oncol, 2023

Quality of Life Pembrolizumab and NSCLC



Brahmer et al, J Clin Oncol, 2023

Quality of Life in early-stage breast cancer patients receiving neoadjuvant chemoimmunotherapy



Dent et al, JNCI, 2024.

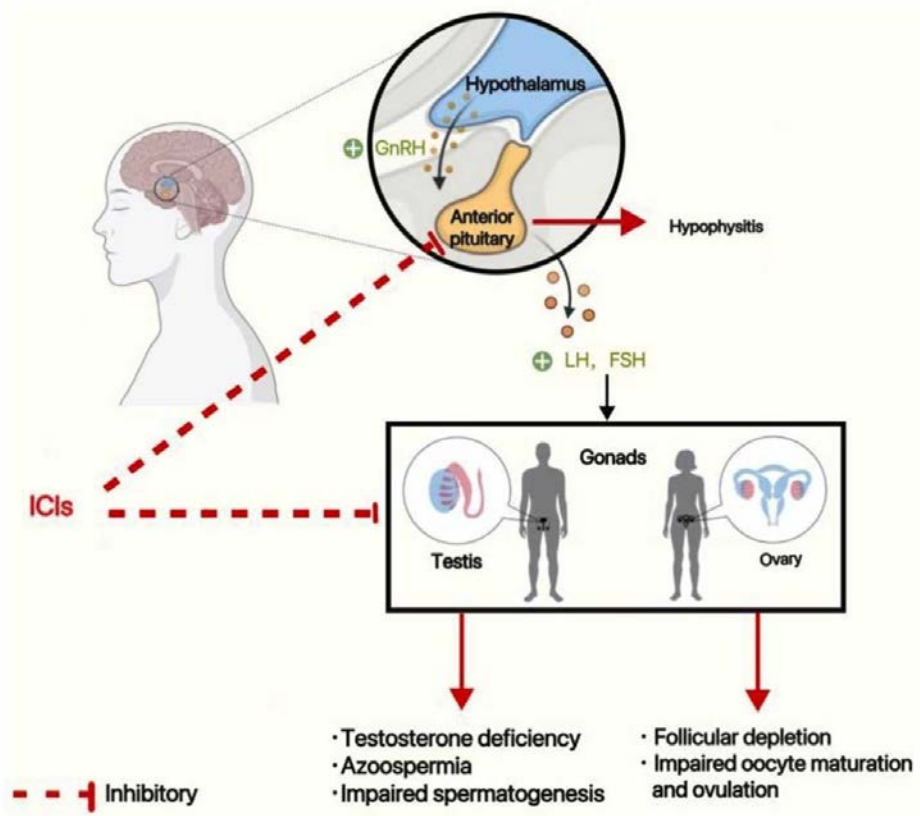
Survivorship Outcomes with ICIs

- Scoping review of real-life cohort ICI studies
- Any irAE: 50%
  - Grade 3 or higher: 10-15%
- Late/long-term irAEs (occurring 6-12 months after ICI initiation)
  - 24-30% of survivors
- Anxiety and Depression 30-82% during ICI tx
- Neurocognitive function (attention/memory/executive function) impairment 32-41%
- Financial Toxicity 23-52%

Can Guven et al, J Cancer Surviv, 2024.

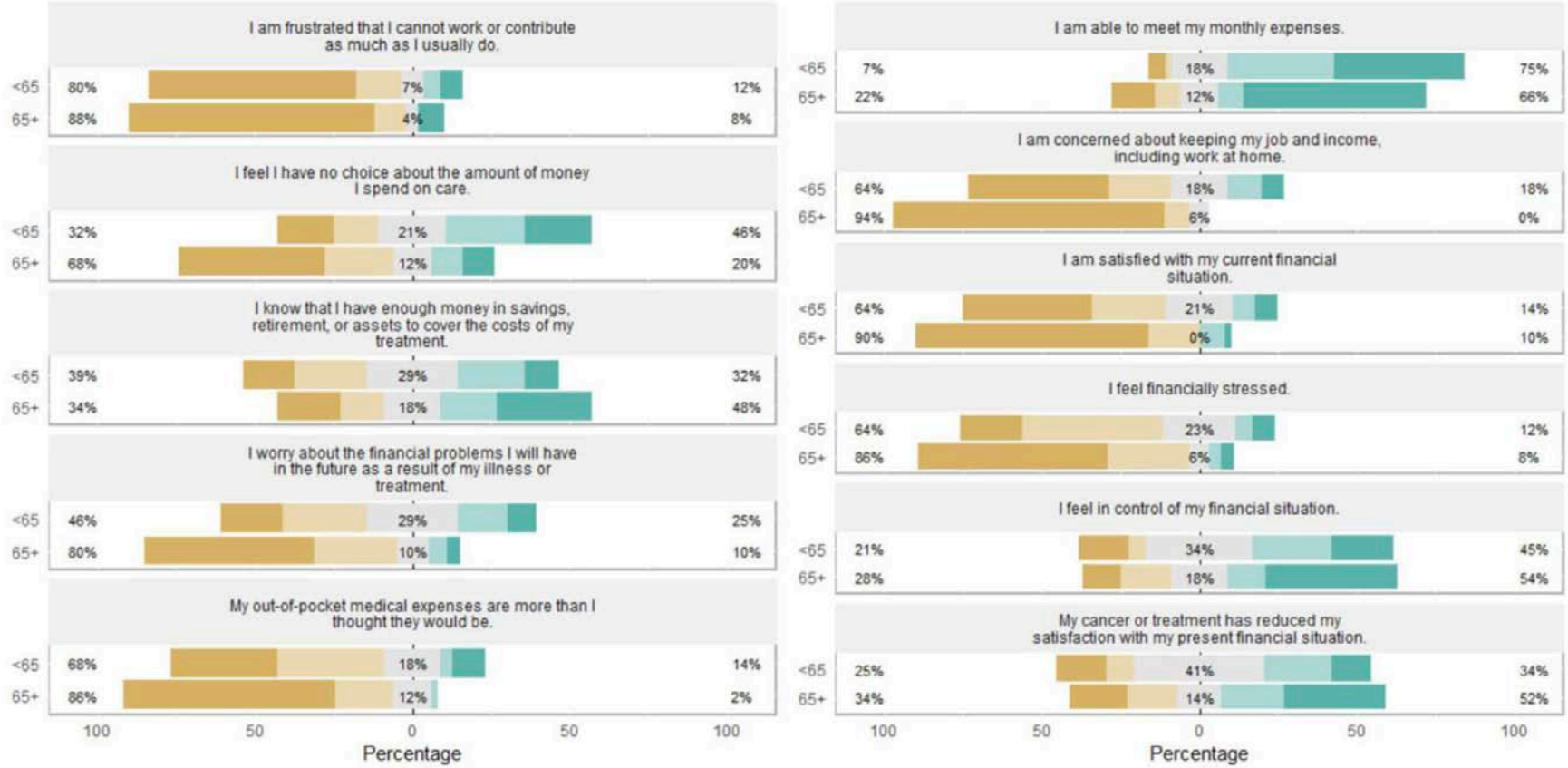
Immunotherapy and Reproductive/Sexual Health

Incidence and mechanism poorly studied



Tuerxun et al, Crit Rev Oncol Hematol, 2023.

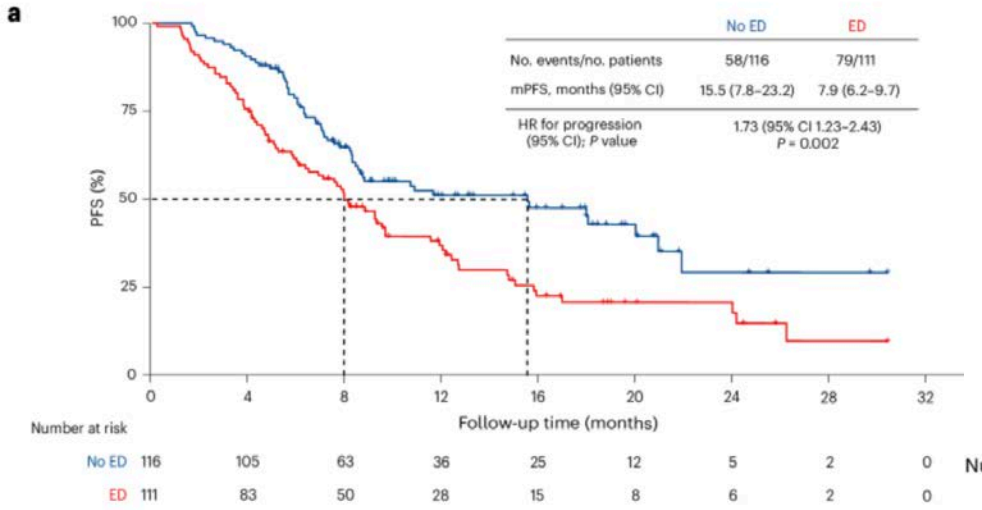
Immunotherapy and Financial Toxicity

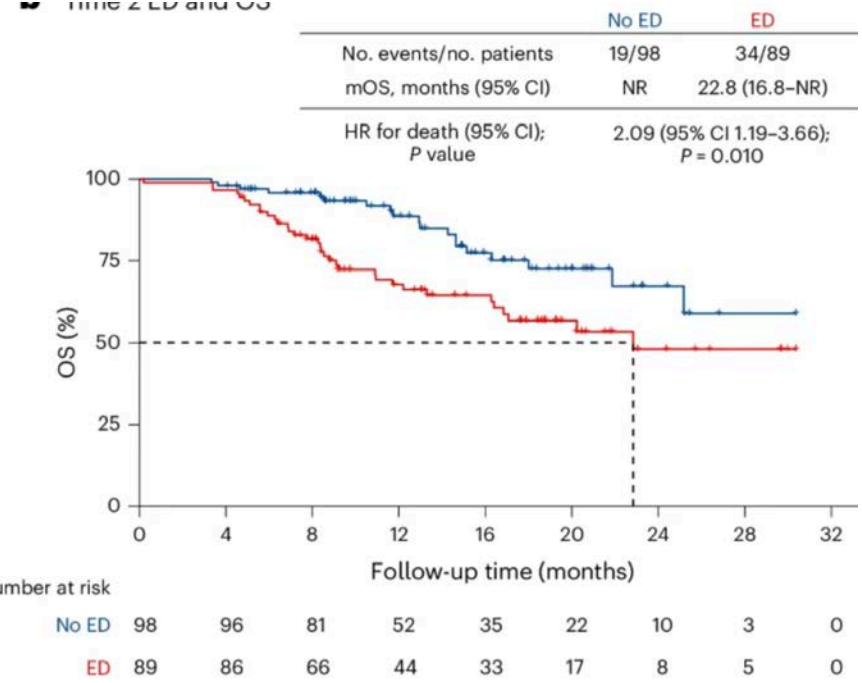


Thom et al, J Psychosoc Oncol, 2021

Emotional Distress (PHQ-9/GAD-7) and Immunotherapeutic Efficacy

Fig. 2: Kaplan–Meier curve and subgroup analysis of investigator-assessed PFS by baseline ED.





Zeng et al, Nat Med, 2024.

MCW Immunotherapy Toxicity Group

MCW Immunotox Group (immunotoxgroup@mcw.edu)

- Multidisciplinary Group of physicians, APPs, pharmacists who have interest and expertise in diagnosis and management of immunotherapy toxicities

- Goals:
  - Provide rapid input to providers regarding diagnosis and management options for patients who experience immunotherapy toxicities
  - Expedite care
  - Standardize management to align with guidelines/best practices
  - Improve awareness of immunotherapy toxicity across disciplines
  - Build research programs to improve the understanding and treatment of immunotherapy toxicities

Team Members

- **Oncology**
  - Jonathan Thompson
  - Ariel Nelson
  - Amy Harker-Murray
  - Juliana Alvarez Argote
  - Ravi Narra
  - Jennifer Ross
  - Jennifer Walters
- **GI/Hepatology**
  - Daniel Stein
  - Veronica Loy
  - Srivats Madhavan
- **Endocrinology**
  - Abubakr Mohamed
- **Infectious Disease**
  - Kartikey Acharya
- **Rheumatology**
  - Richard Hariman
- **Pulmonology**
  - Amit Taneja
  - Mark Barash
- **Nephrology**
  - Paul Hanna
- **Cardiology**
  - David Lewandoski
- **Neurology**
  - Ahmed Obeidat
- **Dermatology**
  - Barbara Wilson
  - Karolyn Wanat
  - Kara Young
- **Pathology**
  - John Evans
  - James Miller
  - Alexander Gallan
  - Saryn Doucette
- **Pharmacy**
  - Erin McGurty
  - Nichole Ruffcorn
  - Emma Carroll

Immunotherapy Toxicity Group: Case Example

Case

- 70 yo F with metastatic squamous cell lung cancer who developed grade 3 diarrhea after ~ 2 years on pembrolizumab
  - Question: Can we expedite the diagnostic evaluation of an otherwise stable patient with high-grade diarrhea to avoid hospitalization
  - Outcome:
    - Patient presents to clinic Friday, infectious stool studies negative, CT A/P unremarkable
    - Monday: colonoscopy (minimal endoscopic changes)
    - Wednesday (day before Thanksgiving): Path diagnosis of lymphocytic colitis
      - Started prednisone
      - Enrolled in A151804 (national biorepository to advance studies of immune-related adverse events)

Summary

- Cancer immunotherapy is increasingly utilized and familiarity with side effects is essential for all medical practitioners

- Impact of immunotherapy on mental, sexual, and financial health is poorly understood.

- Multidisciplinary collaboration/communication is key to ensuring best patient outcomes
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