



Acute Management of Immunotherapy Toxicities

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DISCLOSURES

Advisory Board: Merck and Co., Inc.

Off-label discussion

Most medication uses discussed today will be on-label

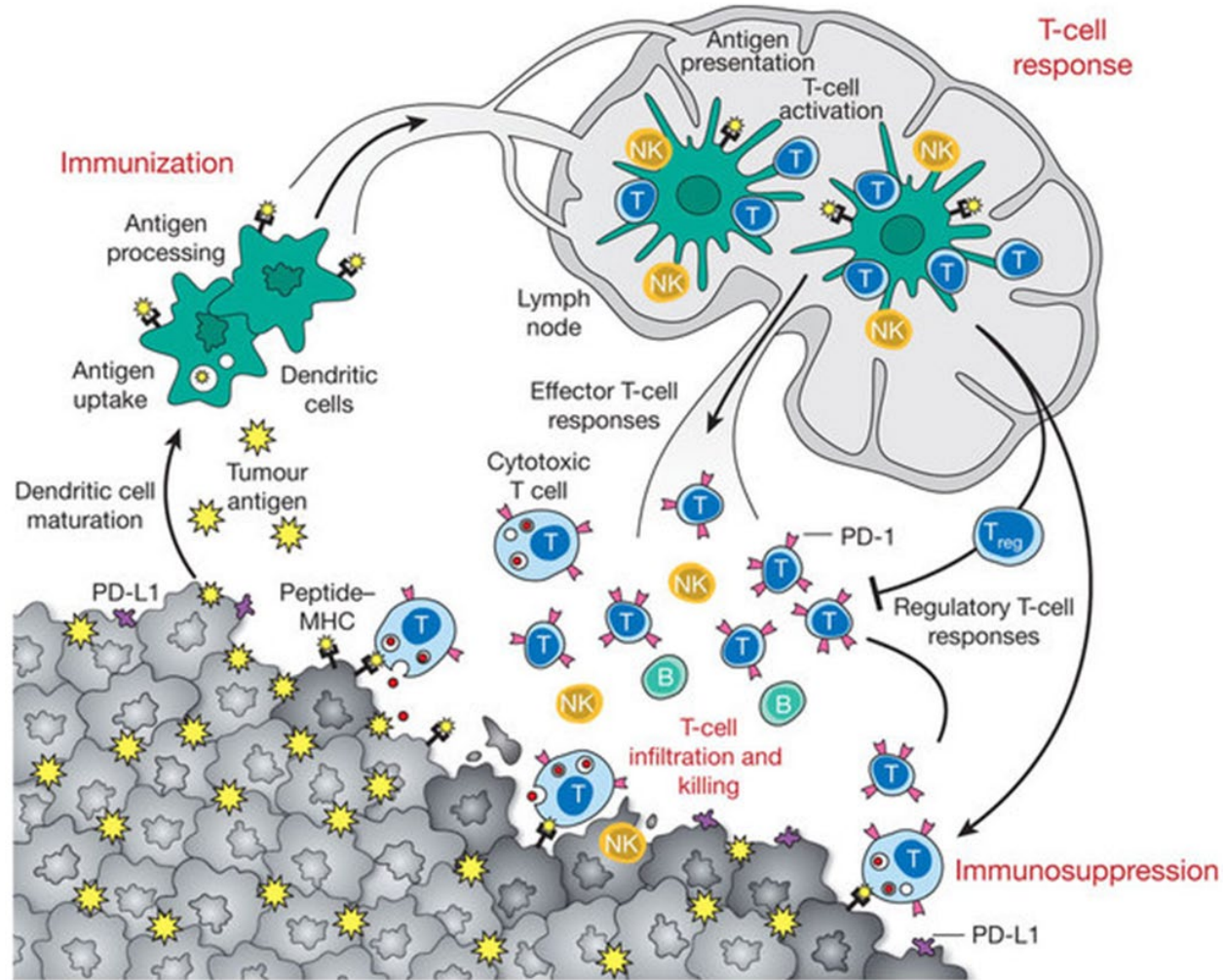
There are no treatments with FDA indications for immune-related adverse events (irAEs) and any medications discussed to treat irAEs will be off-label.

Objectives

- Recognize common immune-related adverse events associated with immune checkpoint inhibitors (ICIs)
- Learn how to initiate evidence-based stepwise pharmacologic management strategies for acute immune-related adverse events (irAEs)
- Differentiate acute ICI toxicities from other causes of similar symptoms.

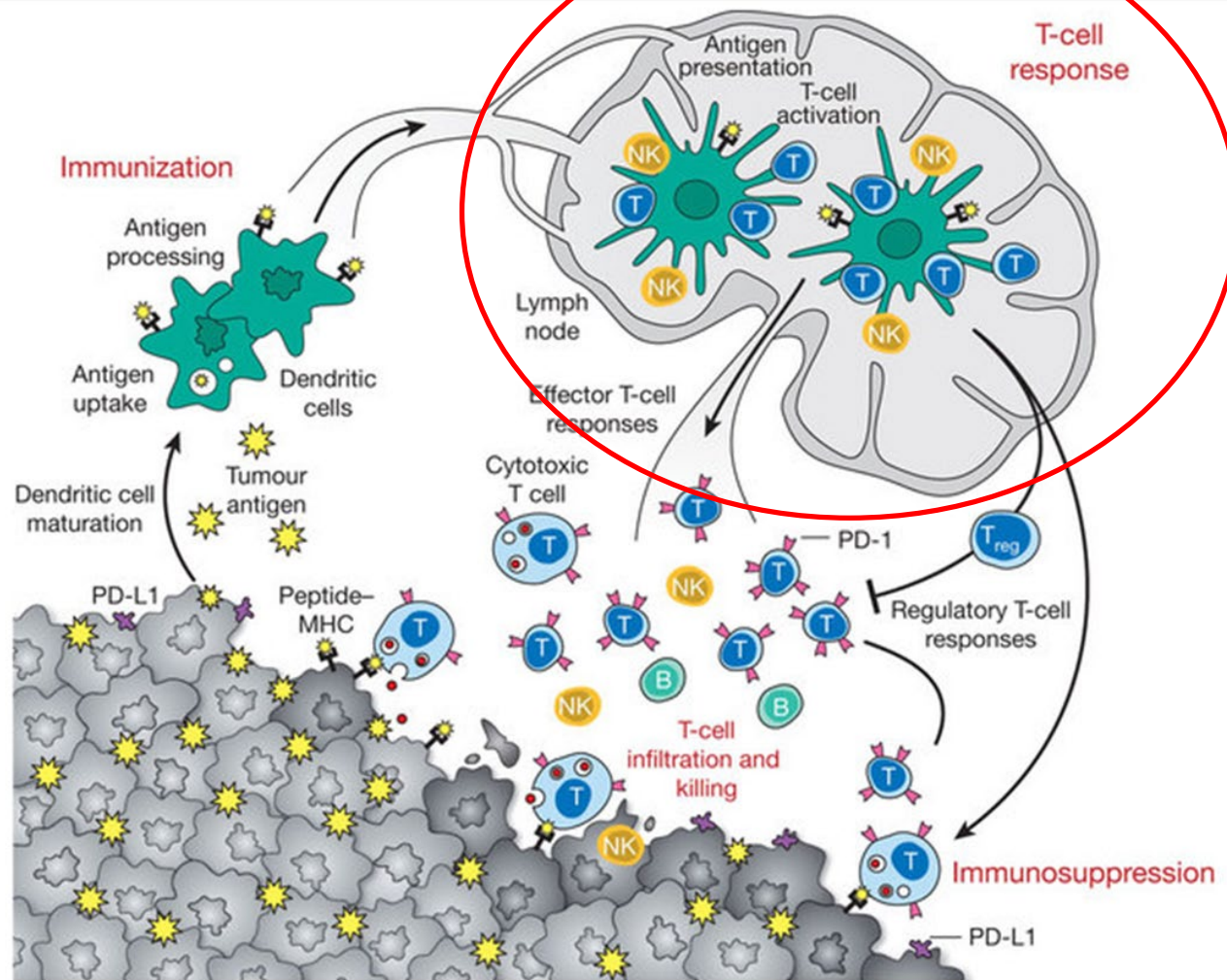
Immune Checkpoint Inhibitors (ICIs)

Anti-Cancer Immune Response



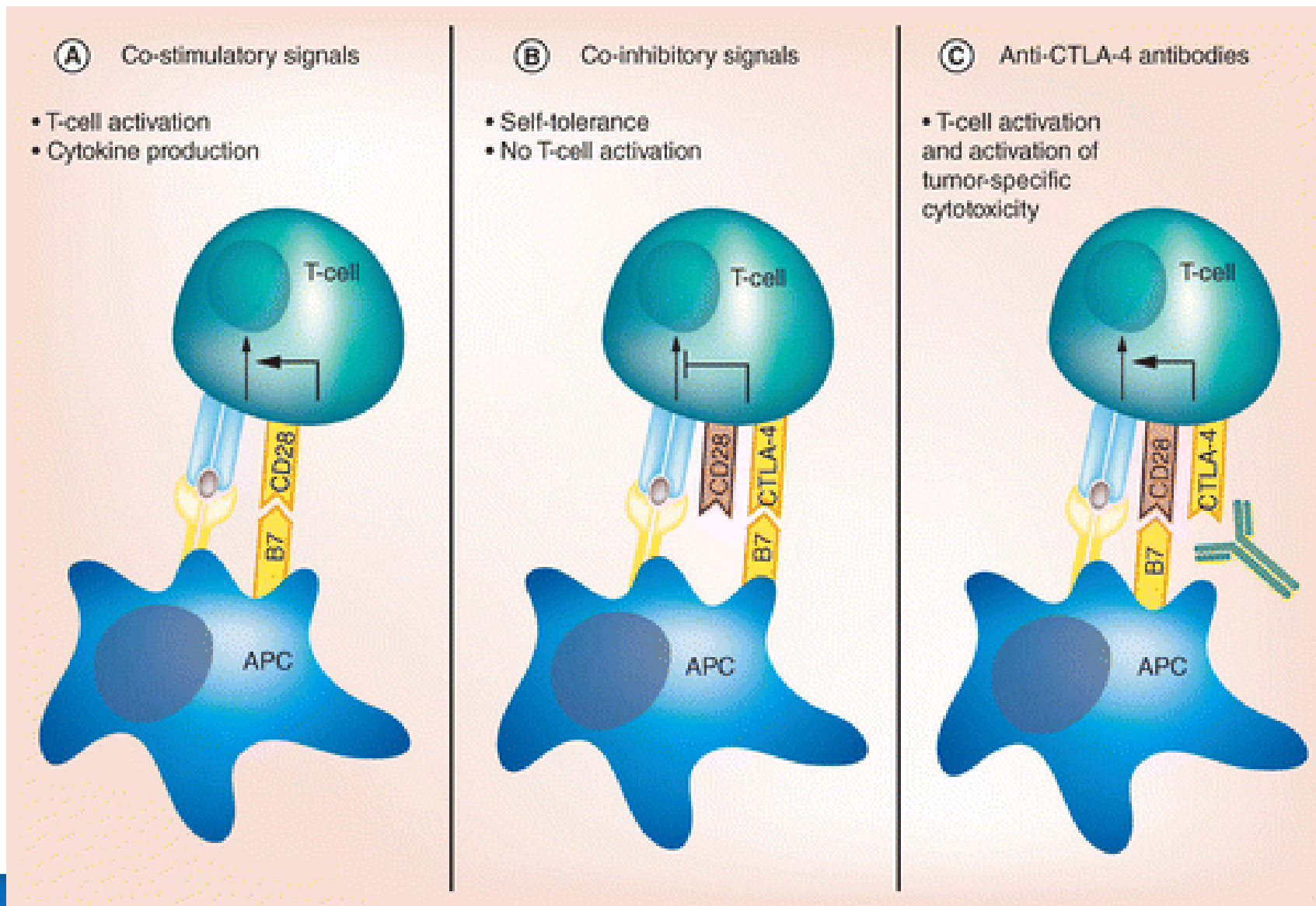
Mellman et al. *Nature* 2011;480(7378):480-9

Anti-Cancer Immune Response



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

CTLA-4 Inhibitors



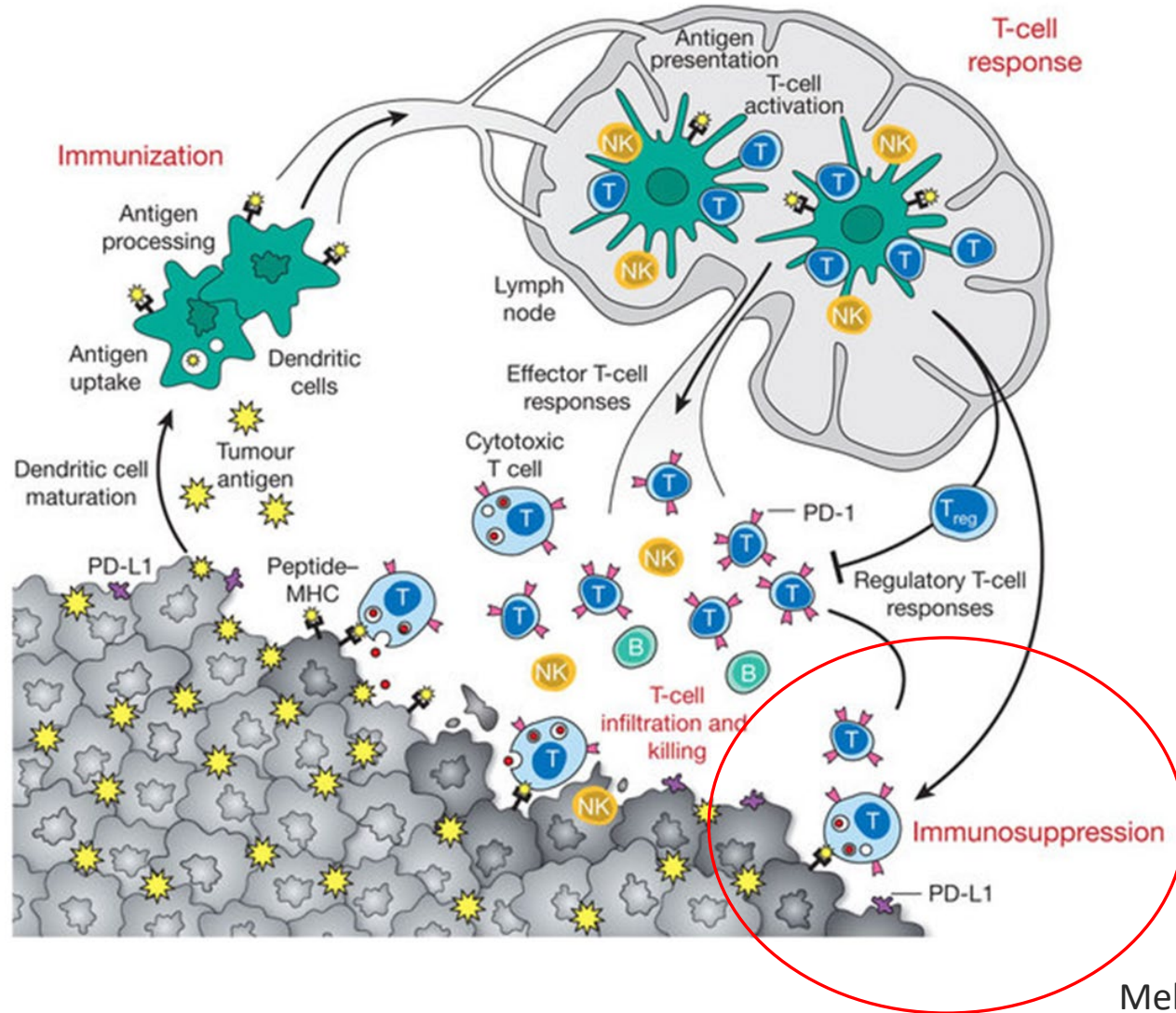
FDA-approved CTLA-4 Inhibitors

Ipilimumab (Yervoy®)

Tremelimumab (Imjudo®)

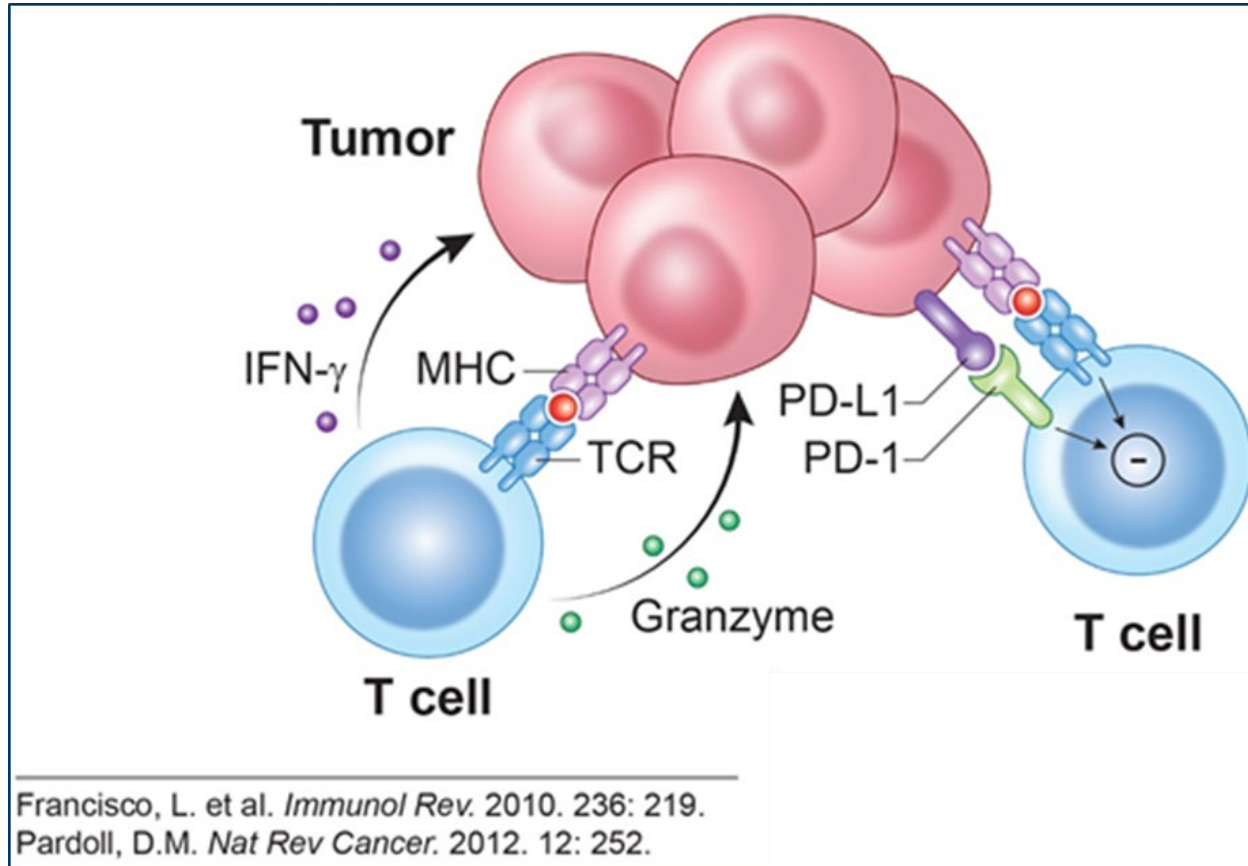
<https://doi.org/10.2217/imt-2016-0123>

Anti-Cancer Immune Response



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

PD-1/PD-L1 Inhibitors



FDA-approved PD-1/PD-L1 inhibitors

Nivolumab (Opdivo®)

Pembrolizumab (Keytruda®)

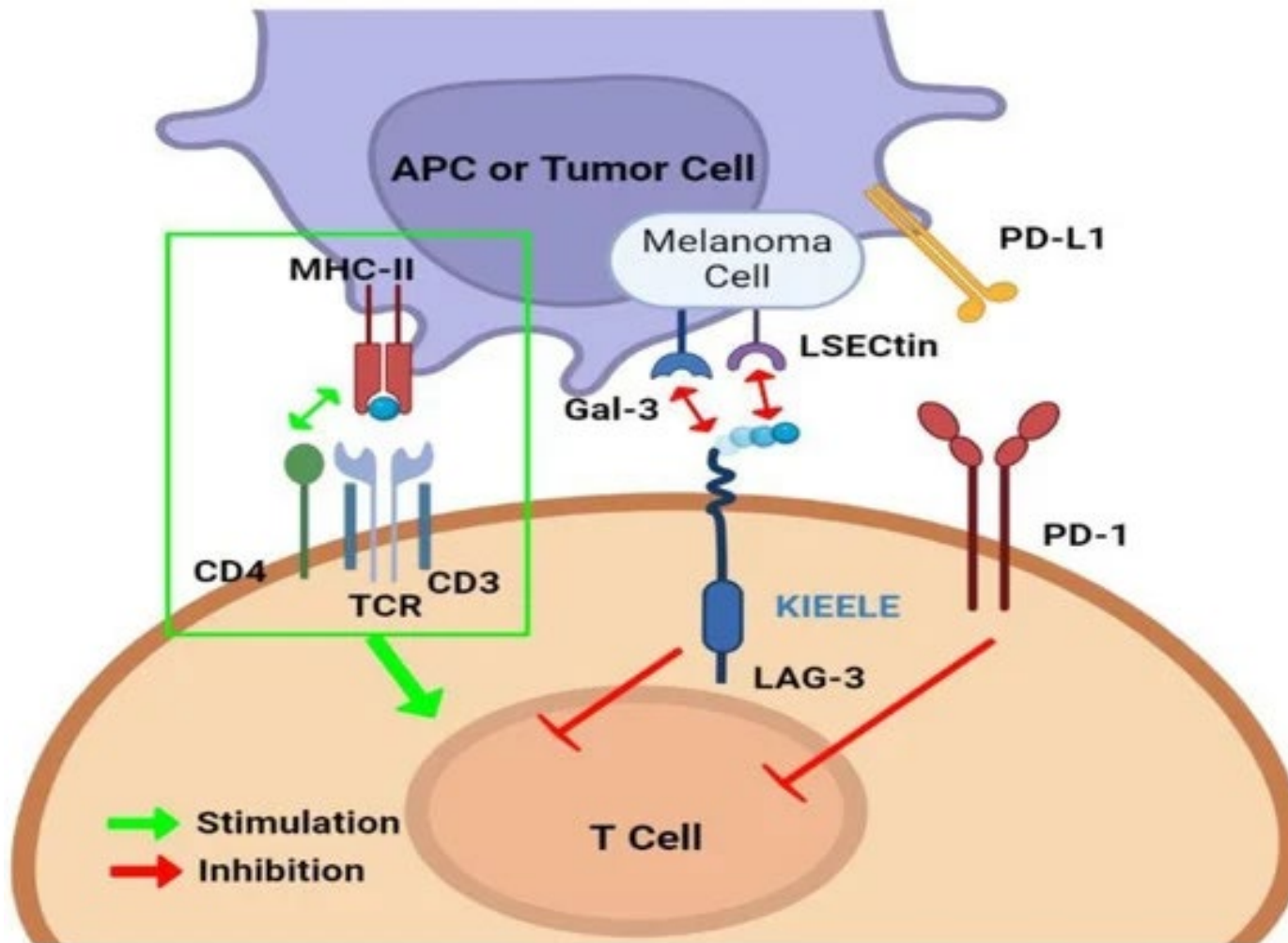
Atezolizumab (Tecentriq®)

Durvalumab (Imfinzi®)

Avelumab (Bavencio®)

Cemiplimab (Libtayo®)

LAG-3 Inhibitor



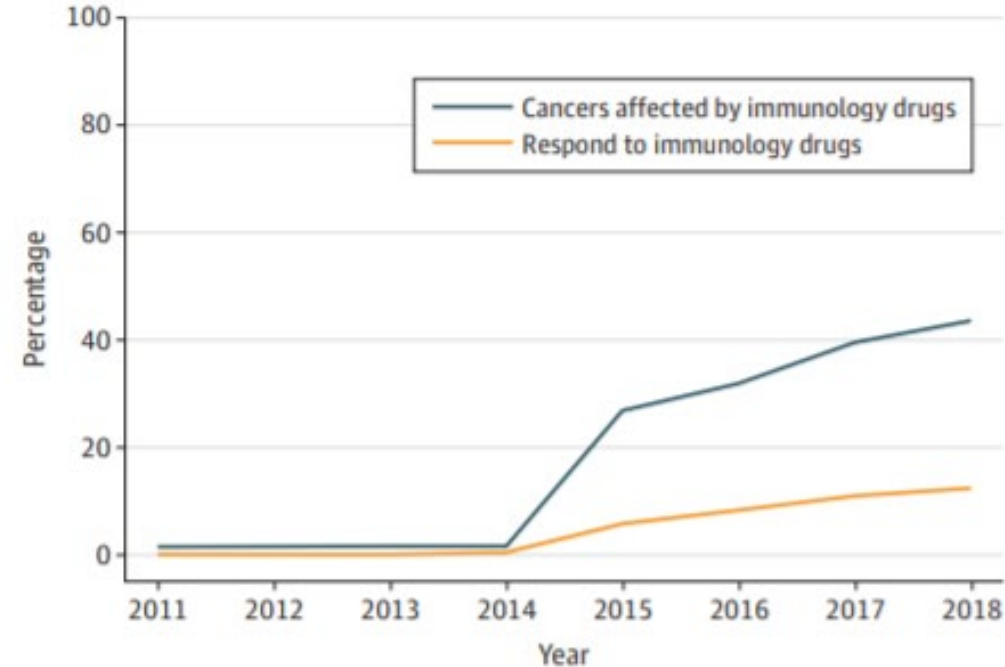
FDA-approved LAG-3 inhibitor

Renlantalimab + Nivolumab (Opdualag®)

Ibrahim et al, Biomedicines 2023

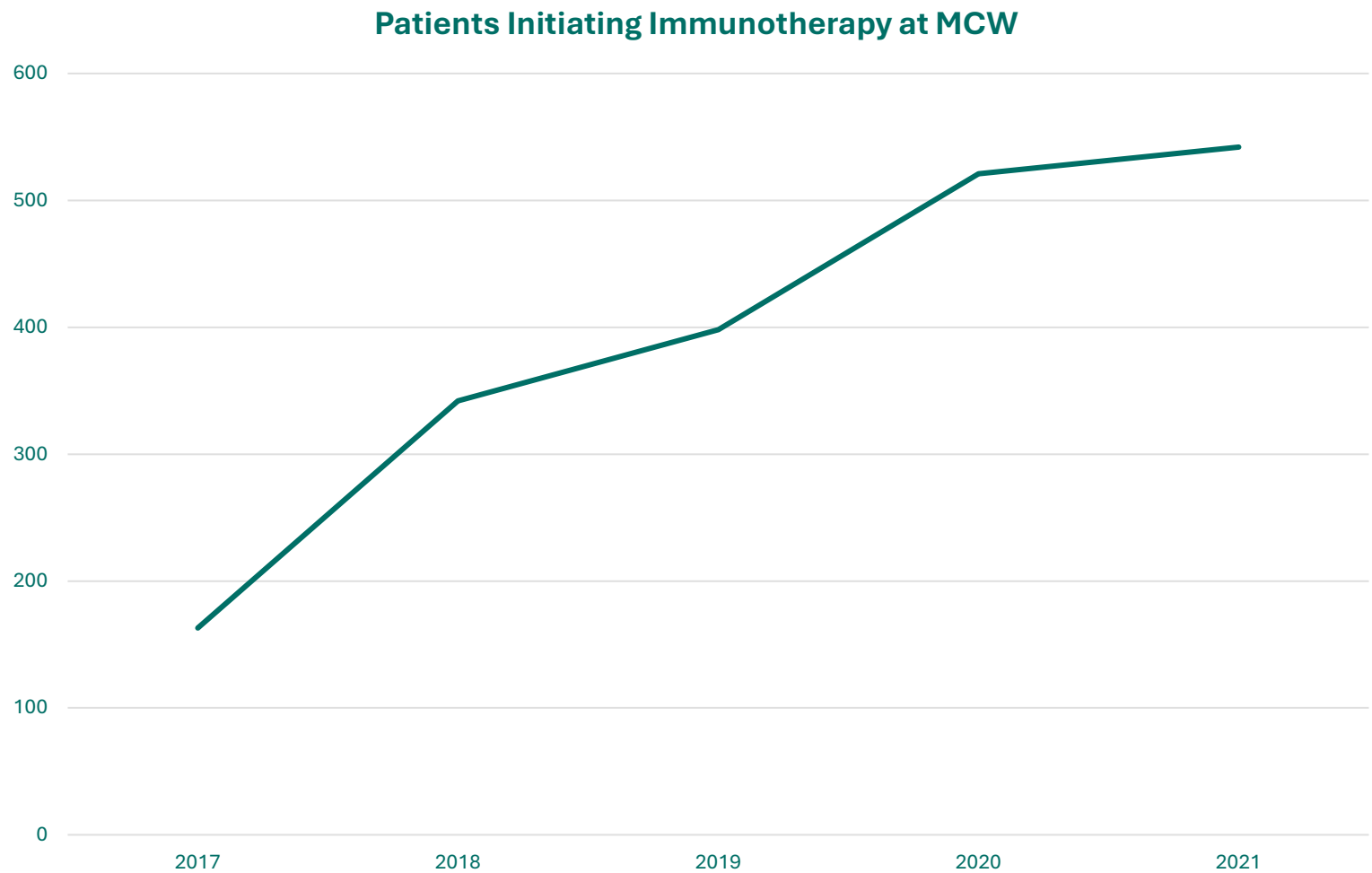
Immune Checkpoint Inhibitor Use is Rapidly Expanding

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

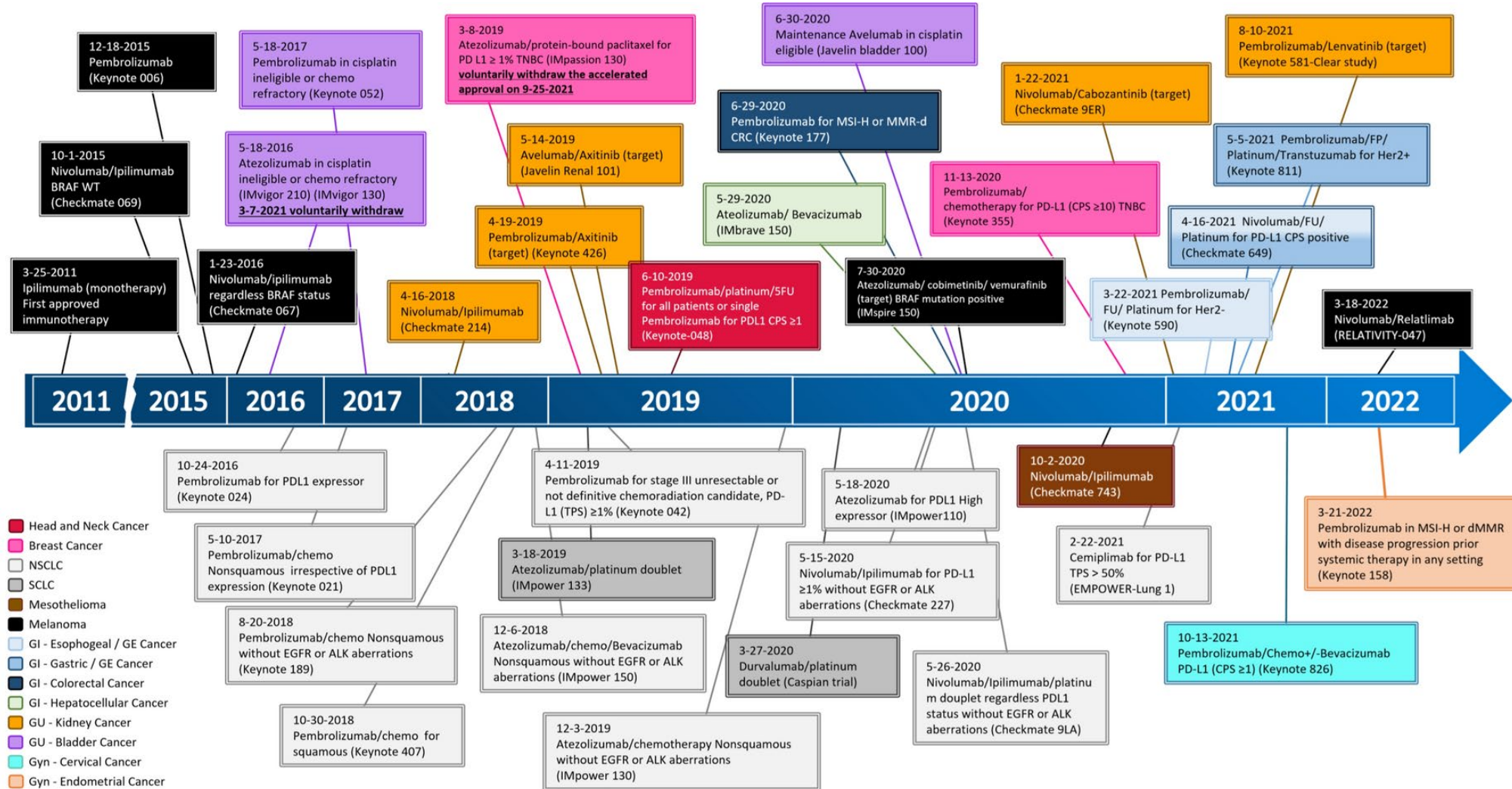


 JAMA Network Open. 2019;2(5):e192535. doi:10.1001/jamanetworkopen.2019.2535

Immune Checkpoint Inhibitor Use is Rapidly Expanding

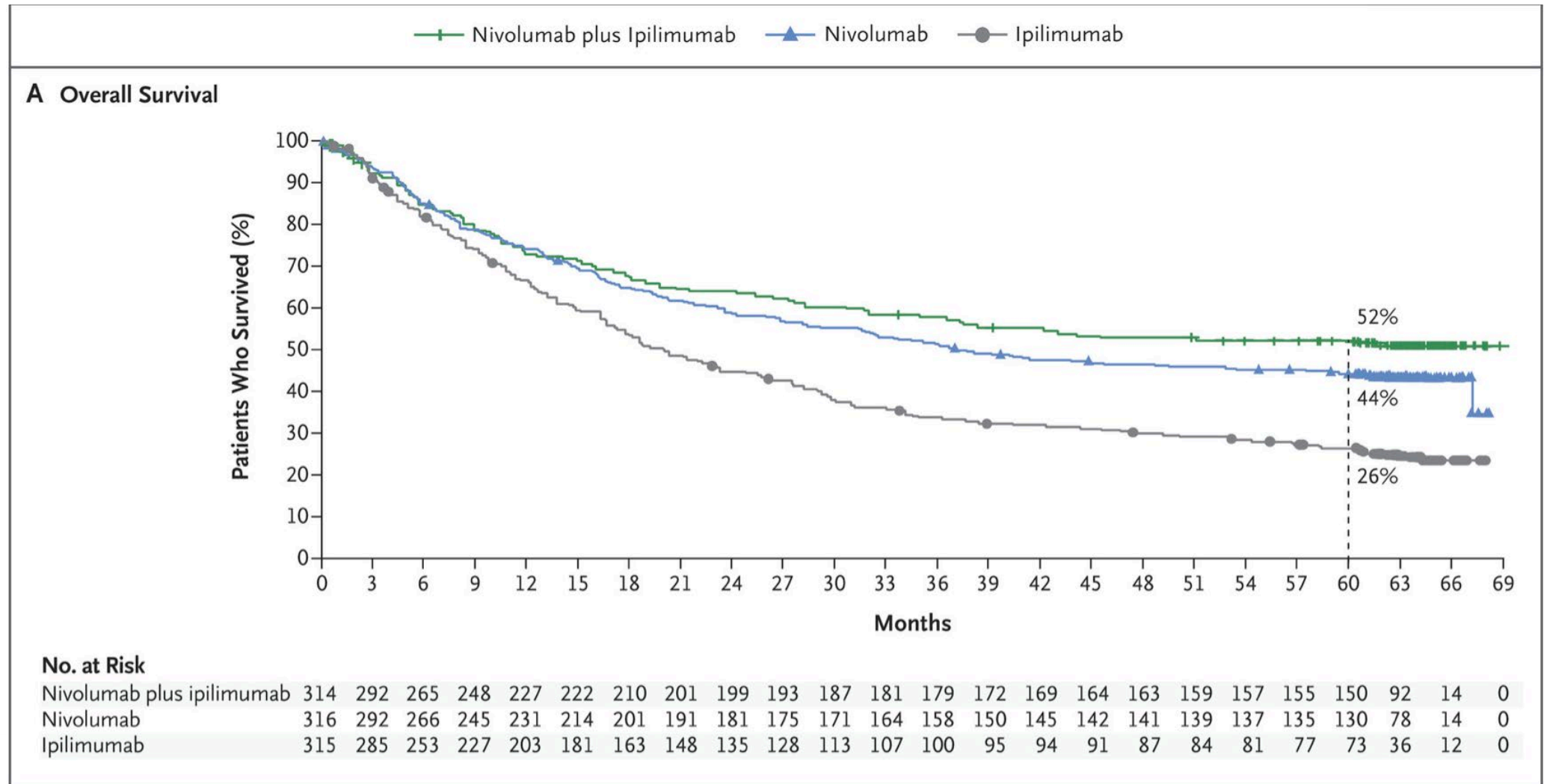


Immune Checkpoint Inhibitor Indications



Ma et al, Experimental Hematology & Oncology, 2023

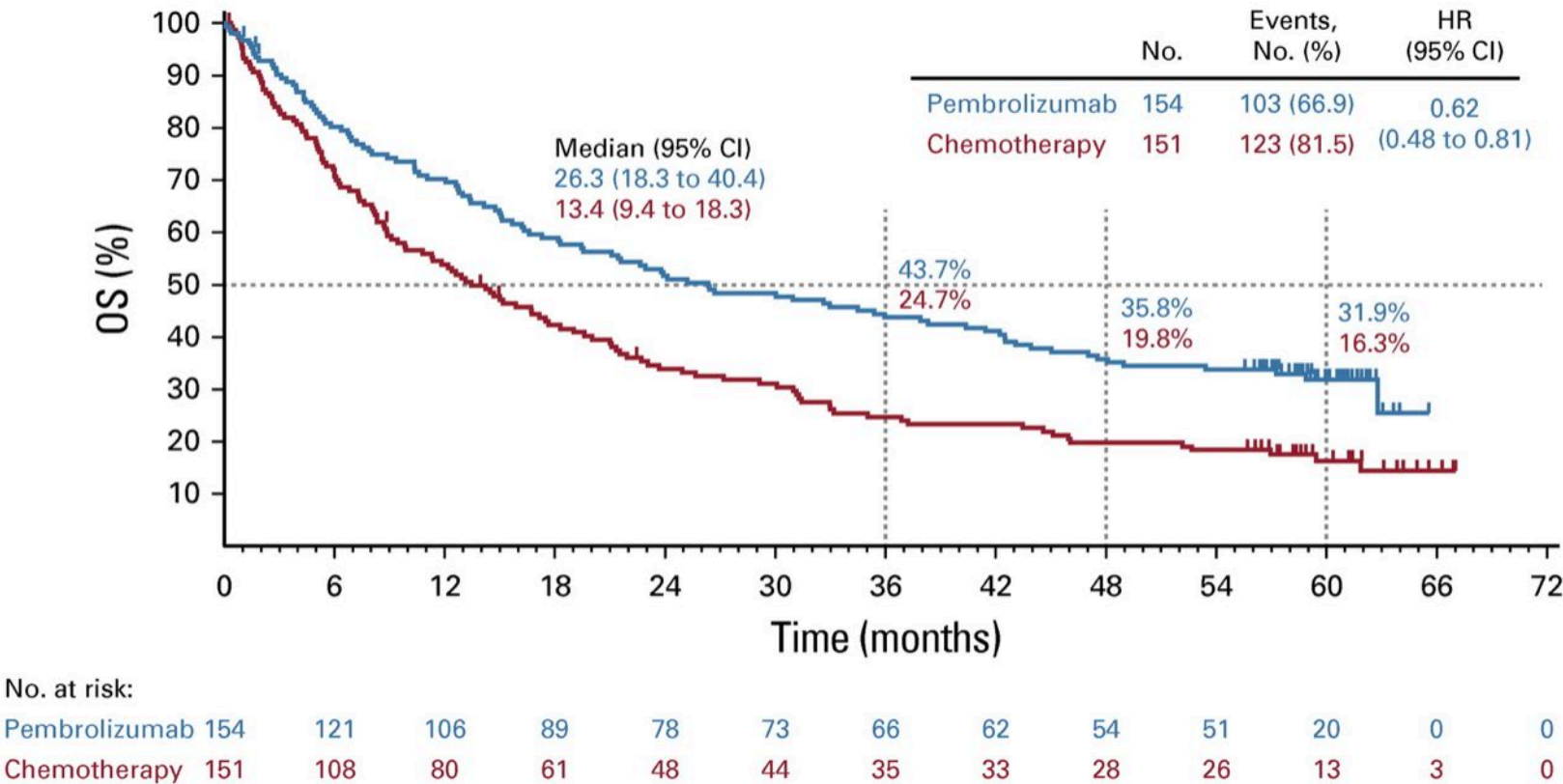
Ipilimumab + Nivolumab - Melanoma



Larkin et al, N Engl J Med, 2019.

Significant survival improvements with Immunotherapy
First-line treatment of metastatic non-small cell lung cancer (NSCLC)

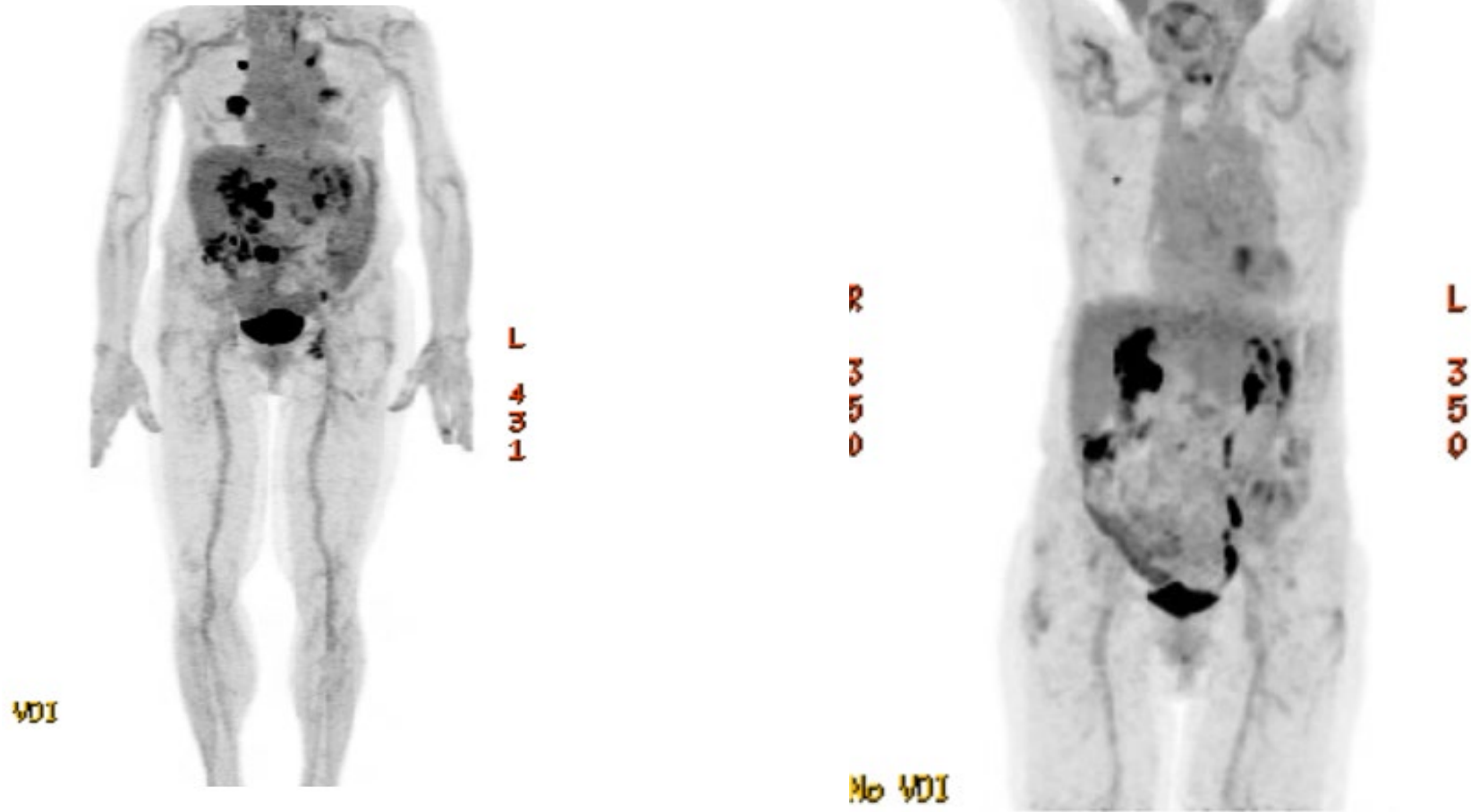
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**5-year
survival
31%**

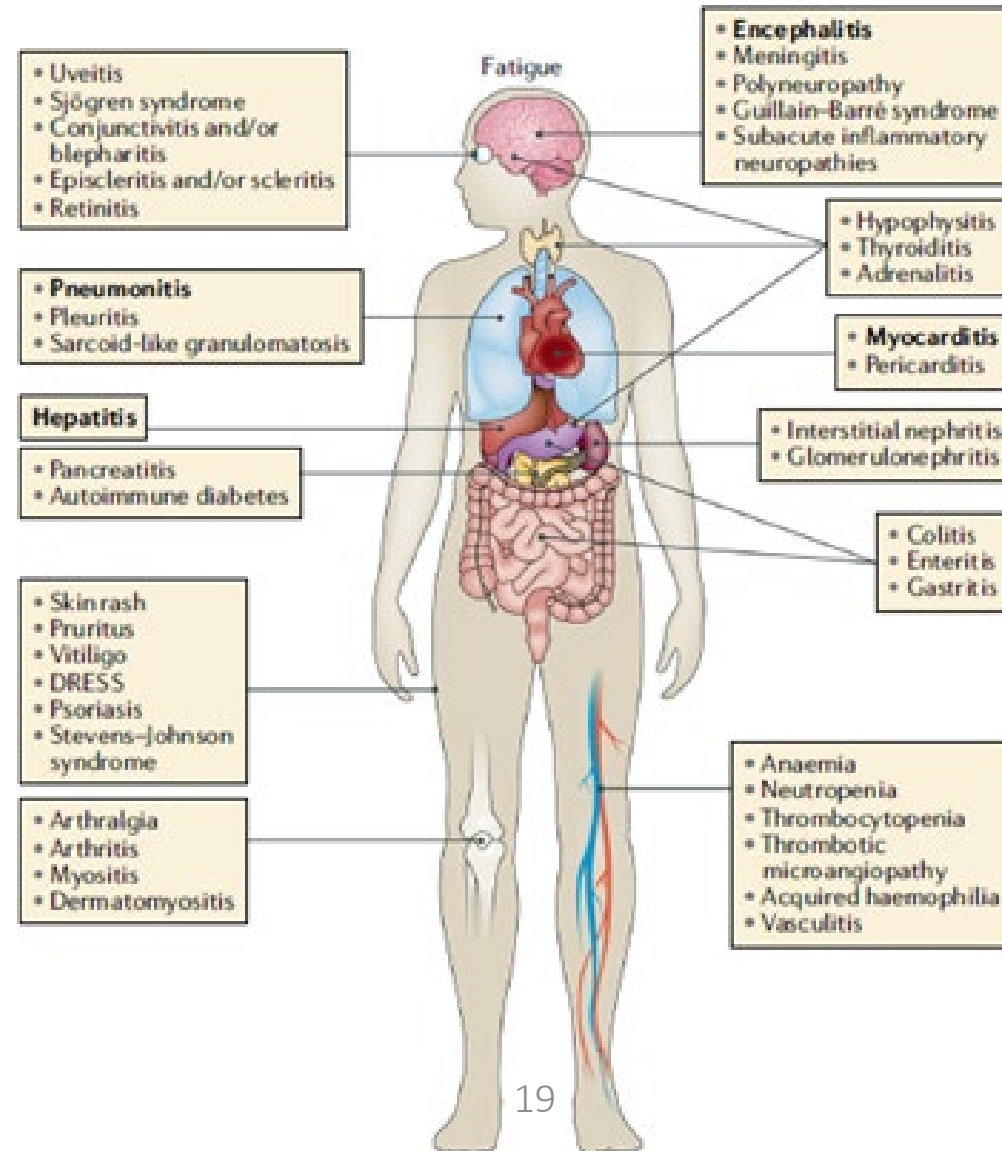
Reck et al. *J Clin Oncol* 2021.

Single dose of pembrolizumab induces long-term response



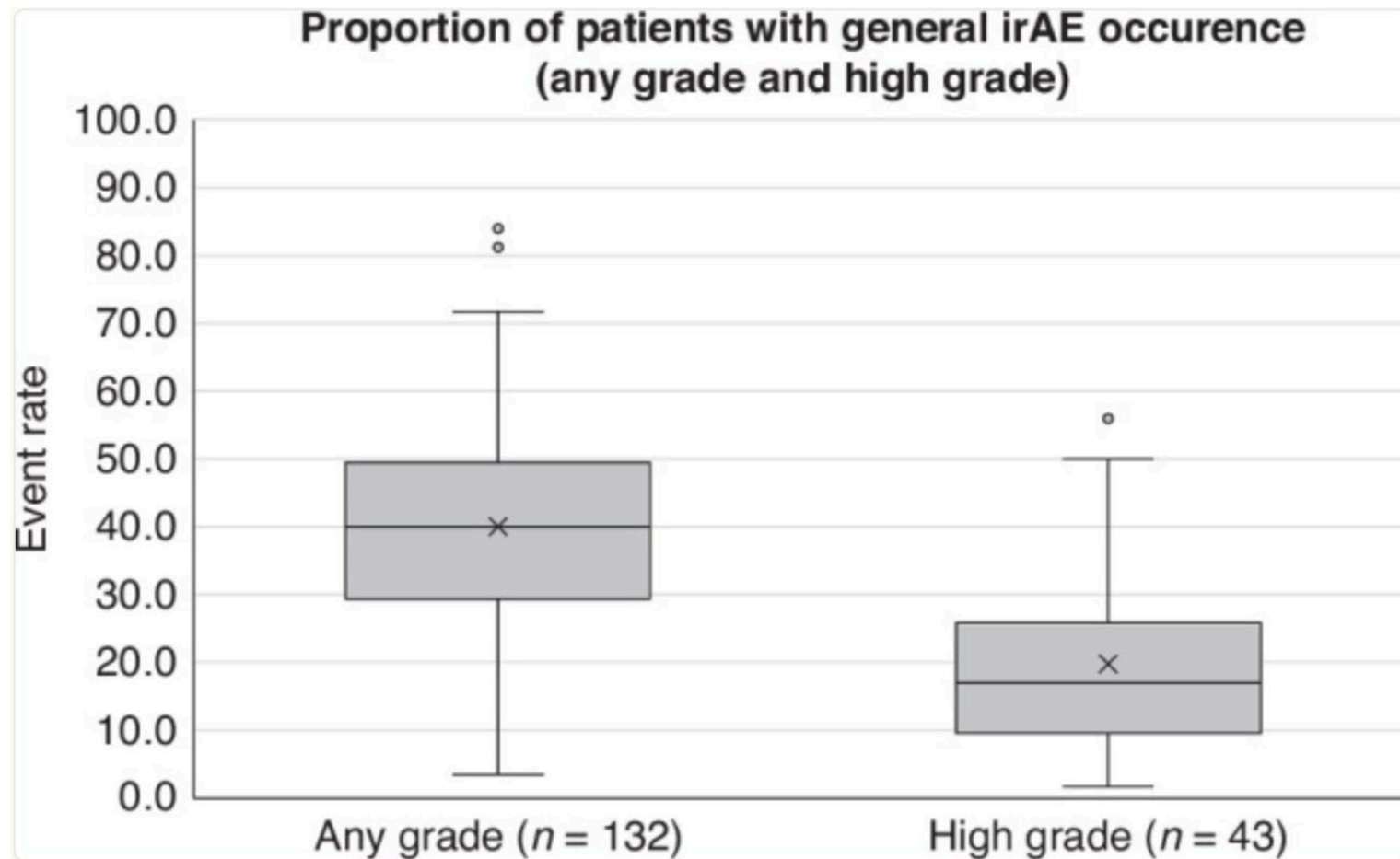
Immune related Adverse Events (irAEs)

irAEs can affect any organ system



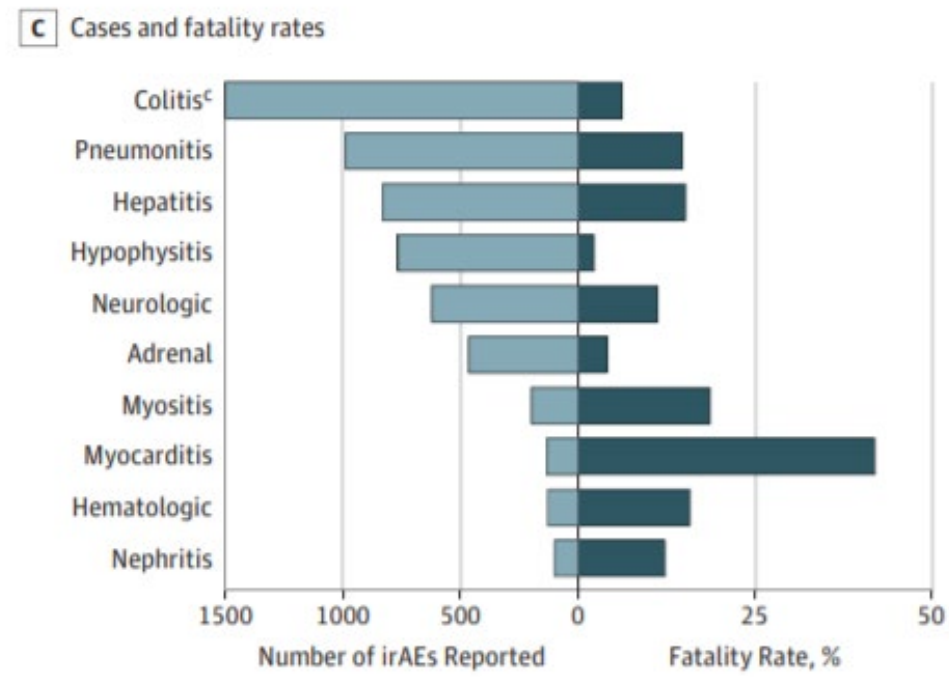
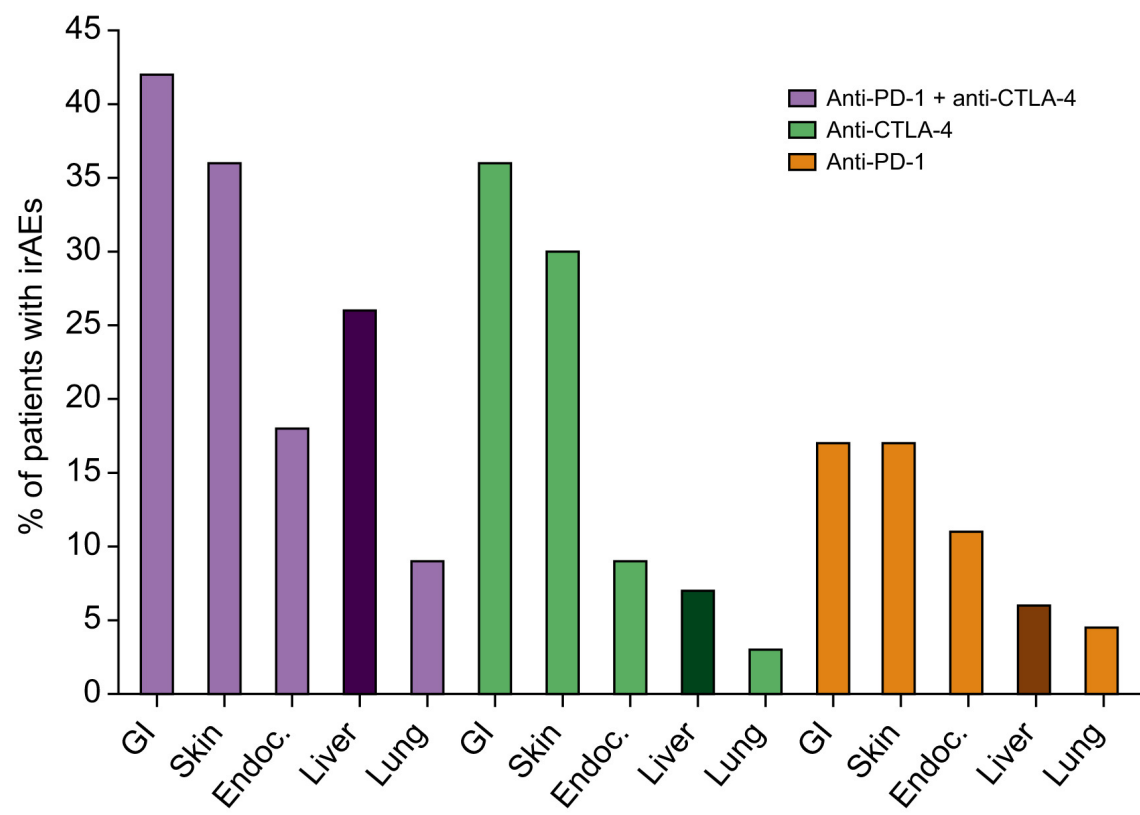
Martins et al., *Nat Rev Clin Oncol.* 2019;16:563-580

irAEs are common and vary in severity



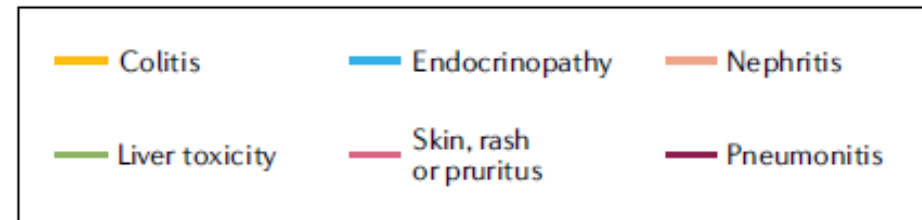
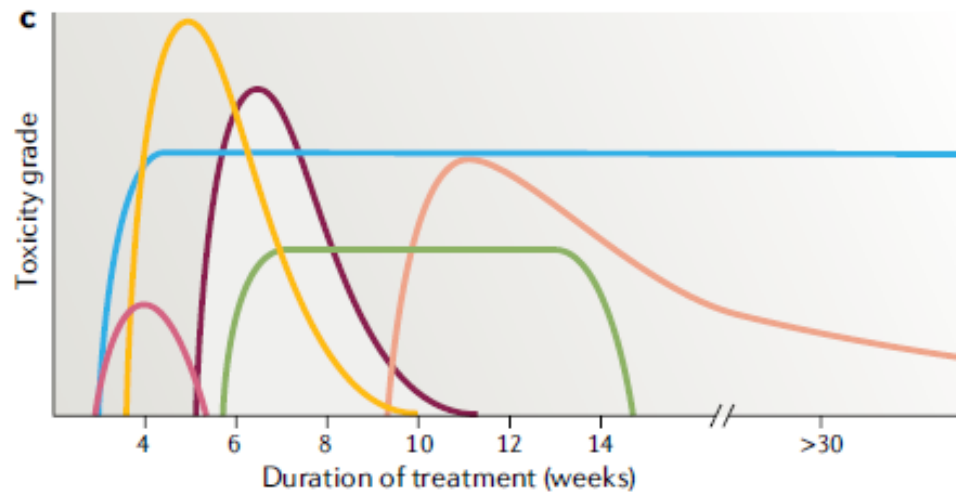
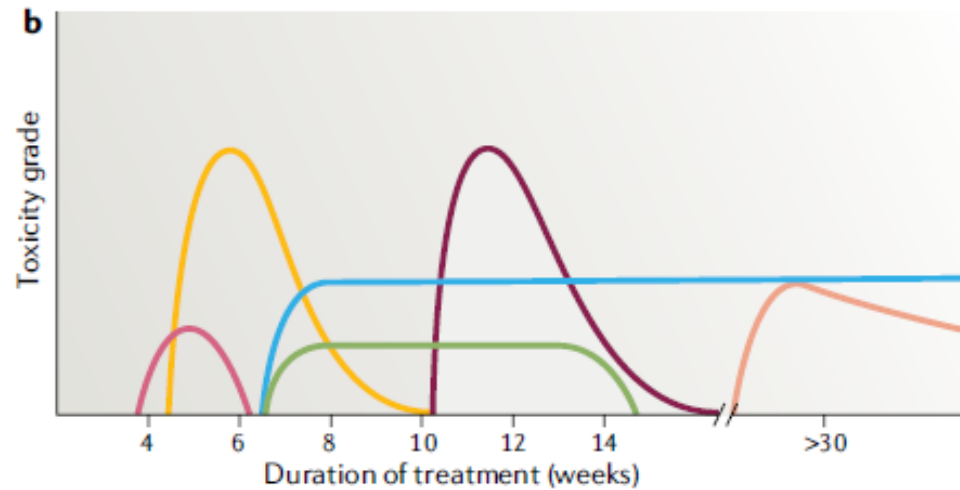
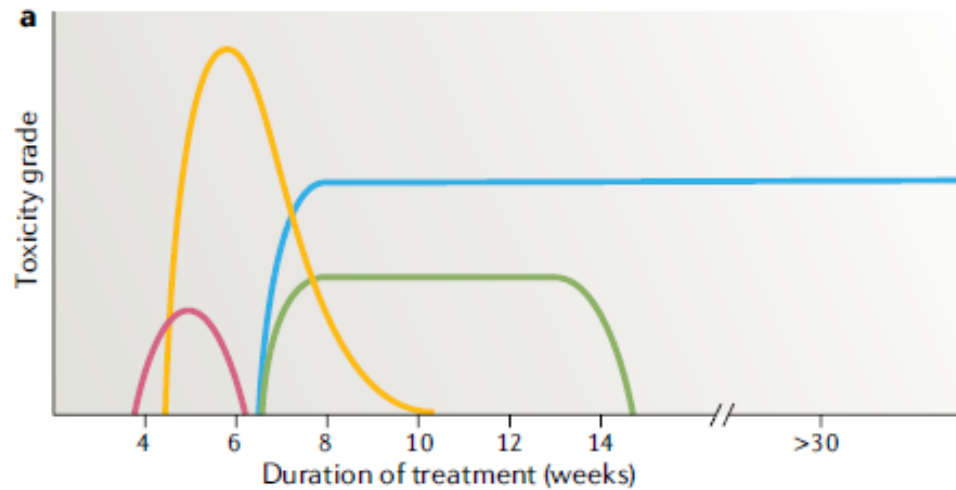
Jayathilaka et al., Br J Cancer, 2024.

irAEs are common and vary in severity



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

irAE Kinetics



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

irAE Impact on ICI discontinuation

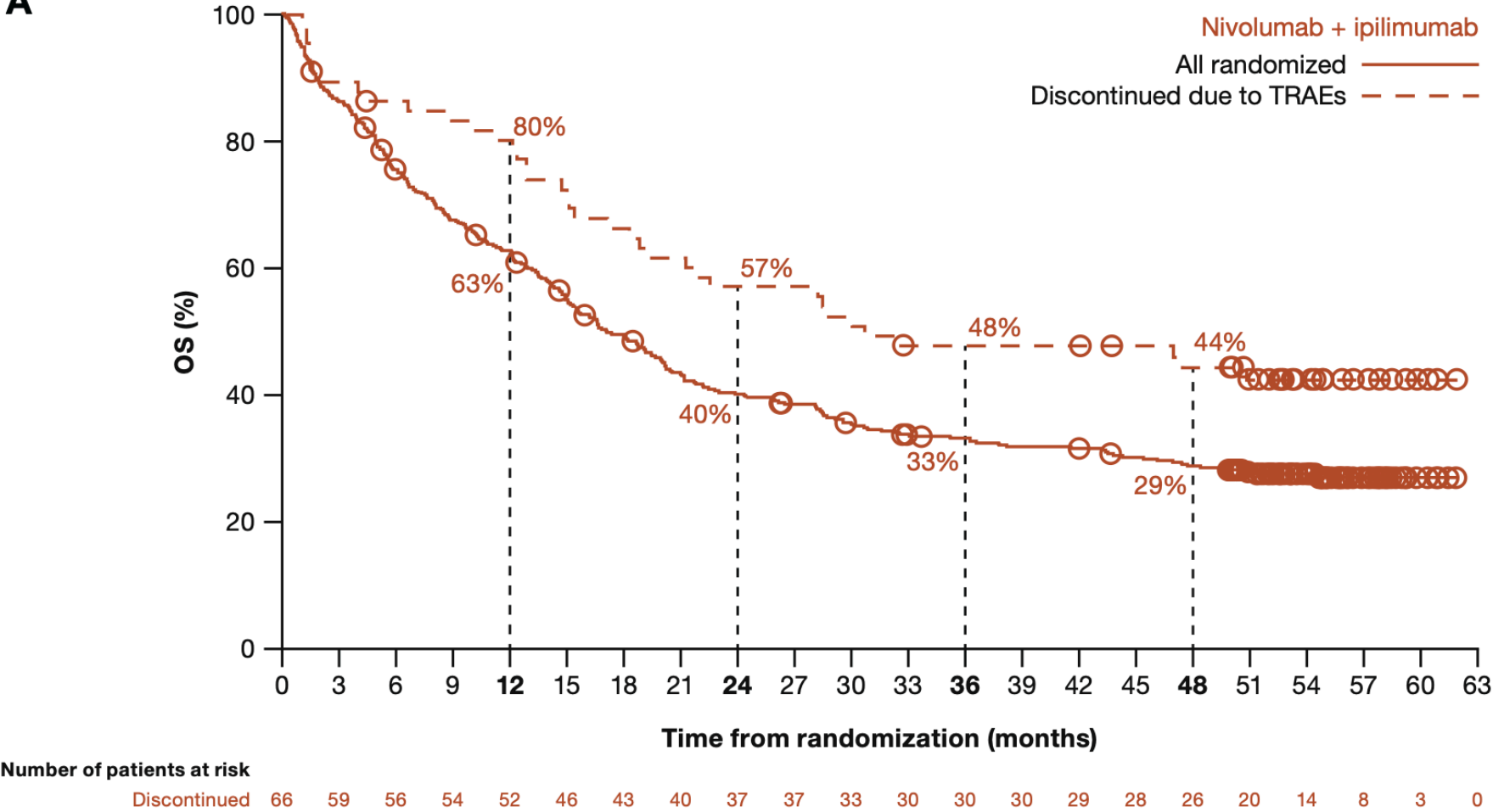
Table 1 The rate of permanent discontinuation of different ICIs because of treatment-related adverse events

Indication	Drug	Discontinuation rate, %
Metastatic melanoma	Ipilimumab	14.8 ⁶⁰ , 9.4 ⁶¹
	Nivolumab	7.7 ⁶⁰
	Ipilimumab+nivolumab	36.4 ⁶⁰
	Pembrolizumab	6.9 ⁶¹ (every 3 weeks), 4 ⁶¹ (every 2 weeks)
Metastatic renal cell cancer	Ipilimumab+nivolumab	22 ⁶²
	Nivolumab	8 ⁶³
NSCLC	Pembrolizumab	9 ⁶⁴

ICI, immune checkpoint inhibition.

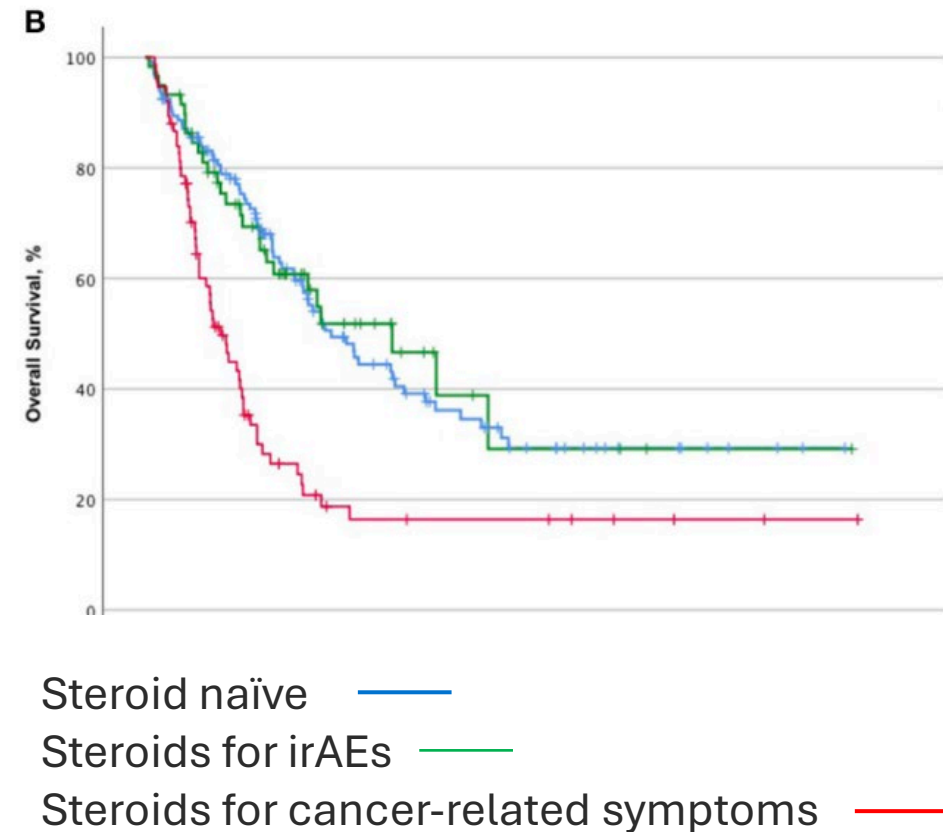
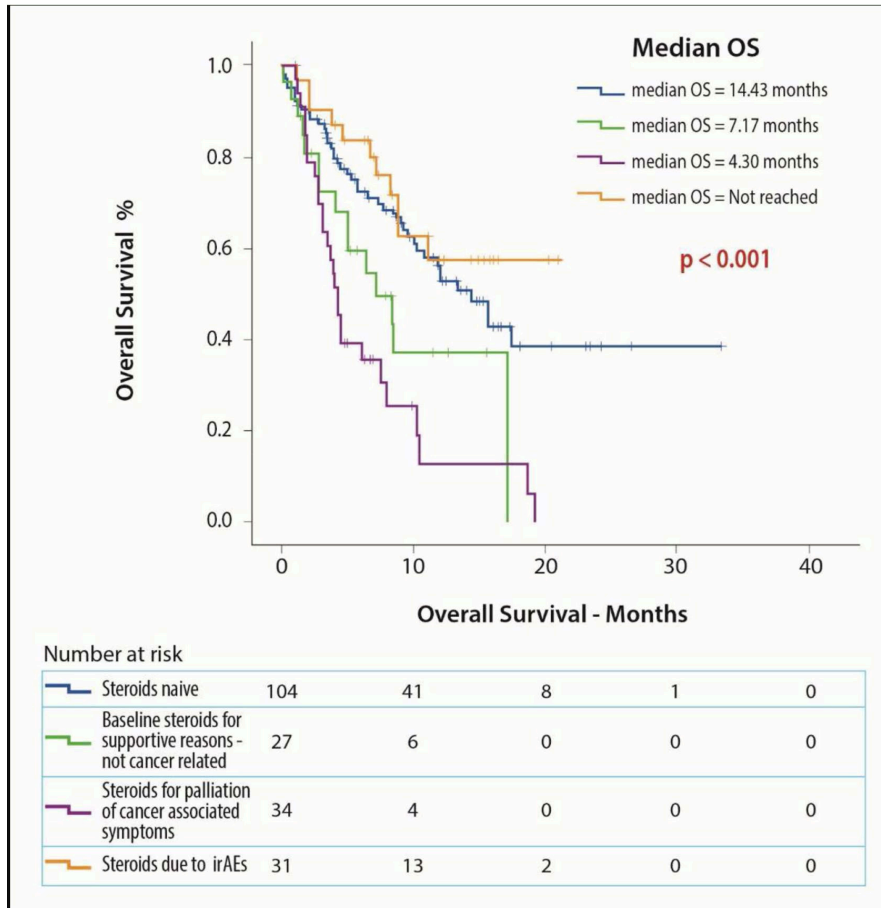
irAEs and ICI efficacy – Checkmate 227

A



Paz-Ares et al., J Thorac Oncol. 2022 17:289-308.

Does steroid tx for irAEs impact ICI efficacy?



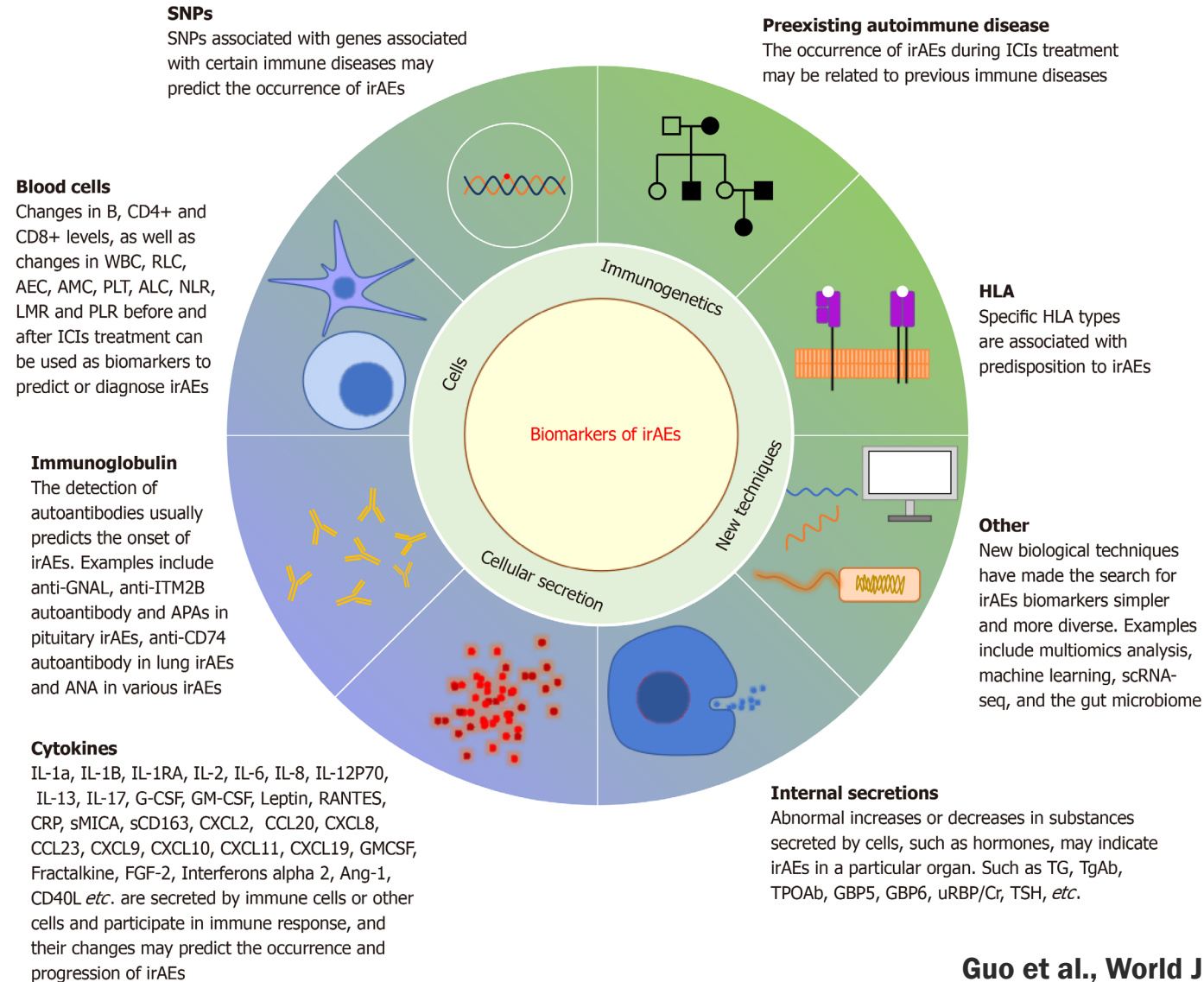
Skribek et al., Eur J Cancer, 2021.
Riudavets et al., Front Oncol, 2020.

Can you re-treat with ICI after irAEs?

Study	Tumor type	ICI type	Number of patients with initial irAE	Number of patients retreated	Grade of initial irAE	New or recurrent irAEs (%): total/new/recurrent	Grade of new or recurrent irAE
Santini et al ³	NSCLC	Anti-PD-1/PD-L1 +/- anti-CTLA-4 ^b	68	38 (56%)	1-2: 66% 3-4: 34%	52/26/26	1-2: 60% 3-4: 40% ^a
Simonaggio et al ⁶	Melanoma (33%) Lung (16%) Lymphoma (9%) CRC (9%) Other (33%) ^d	Anti-PD-1/PD-L1	93	40 (43%)	2: 46% 3-4: 54%	55 ^c /12.5/42.5	2: 38% 3-4: 62%
Pollack et al ⁴	Melanoma	Anti-PD-1/PD-L1 +/- anti-CTLA-4 ^e	80	80 (100%)	2: 31% 3-4: 69%	50/32/18	Significant: 39% ^f
Abou Alaiwi et al ⁵	RCC	Anti-PD-1/PD-L1 +/- other ^g	80	36 (45%)	1-2: 41% 3-4: 59%	50/33.3/16.7	1-2: 61% 3-4: 39%
Allouchery et al ⁷	Melanoma (43.9%) Lung (41.1%) RCC (6.1%) Other (8.8%) ^h	Anti-PD-1/PD-L1 +/- anti-CTLA-4 ^e	180	180 (100%)	2: 52% 3-4: 48%	39/27/12	≥ 2: 65% ⁱ 3-4: 35%

<https://dailynews.ascopubs.org/doi/managing-immune-related-adverse-events-patients-metastatic-non-small-cell-lung-cancer#>

Risk Factors/Biomarkers for irAEs



Guo et al., World J Clin Oncol, 2024.

Management of irAEs



National Comprehensive
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36 • NUMBER 17 • JUNE 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE



NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Management of Immune Checkpoint Inhibitor-Related Toxicities

Version 1.2026 — October 23, 2025

[NCCN Guidelines for Patients®](#)

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available.
Trials should be designed to maximize inclusiveness and broad representative enrollment.

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

Annals of Oncology 28 (Supplement 4): i1119–i1142, 2017
doi:10.1093/annonc/mdx225

ES

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

Colitis



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NCCN Guidelines Version 1.2026

Management of Immune Checkpoint Inhibitor-Related Toxicities

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

GASTROINTESTINAL ADVERSE EVENT(S)

ASSESSMENT/GRADING

MANAGEMENT^P

• Diarrhea
• Colitis^l

Mild
(G1)^k

- Consider stool evaluation to rule out infectious etiologyⁿ
 - ▶ *C. difficile*
 - ▶ Nucleic acid amplification tests (NAATs) for GI pathogens (other bacteria, viruses)
 - ▶ In appropriate clinical context, consider ova & parasites; molecular testing for *Giardia*, *Cryptosporidium* spp, *E. histolytica*, microsporidia, and *Cyclospora/isospora* spp
- Fecal calprotectin ± lactoferrin^o

Moderate
(G2)^l

[ICI_GI-3](#)

Severe
(G3-4)^m

[ICI_GI-4](#)

- Hydration
- Close monitoring^q
- Dietary modifications^r
- Consider holding immunotherapy^e
- Consider loperamide or diphenoxylate/atropine for 2–3 days as an adjunct for symptom relief
 - ▶ If no improvement and not already done, obtain lab tests for infectious workup
 - ▶ Caution is warranted to avoid masking symptoms; discontinue antidiarrheals if diarrhea persists, to assess response to immunosuppressive therapy
- If persistent or progressive symptoms, check lactoferrin/calprotectin
 - ▶ If positive, treat as G2
 - ▶ If negative and no infection, continue G1 management and consider adding mesalamine and/or cholestyramine

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

Colitis



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Management of Immune Checkpoint Inhibitor-Related Toxicities

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

GASTROINTESTINAL ADVERSE EVENT(S)

ASSESSMENT/GRADING

MANAGEMENT^P

- Diarrhea
- Colitis^j
- Moderate (G2)^l

- Stool evaluation to rule out infectious etiologyⁿ
 - *C. difficile*
 - NAATs for GI pathogens (other bacteria, viruses)
 - In appropriate clinical context, consider ova & parasites; molecular testing for *Giardia*, *Cryptosporidium* spp, *E. histolytica*, microsporidia, and *Cyclospora/isospora* spp
- Fecal calprotectin ± lactoferrin^o
- Consider abdominal/pelvic CT with contrast^s
- Consider GI consultation
 - Colonoscopy or flexible sigmoidoscopy ± EGD with biopsy^o

- Hold immunotherapy^e
- For pathologically confirmed microscopic colitis, consider budesonide 9 mg daily prior to systemic steroids^t
- Prednisone/IV methylprednisolone^{u,v} (1–2 mg/kg/day)^w
- If no response to oral steroids after 3 days, consider IV steroids:
 - If colonoscopy or flexible sigmoidoscopy shows significant ulceration, non-ulcerative inflammation, or microscopic colitis on histology,^x consider adding infliximab^{g,h,i,y} or vedolizumab^{h,y,z}
 - ◇ Consider tofacitinib or ustekinumab for infliximab- and/or vedolizumab-refractory colitis^{aa}
- For persistent diarrhea that does not resolve after the management described above, consider other etiologies (eg, pancreatic exocrine insufficiency, celiac disease)
- For immunosuppressant-refractory colitis, fecal transplantation may be considered based on institutional availability and expertise

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

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Colitis



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Management of Immune Checkpoint Inhibitor-Related Toxicities

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

GRADING	ASSESSMENT/GRADING	MANAGEMENT ^P
• Diarrhea • Colitis - Severe (G3–4)^m	• Stool evaluation to rule out infectious etiologyⁿ ▸ <i>C. difficile</i> ▸ NAATs for GI pathogens (other bacteria, viruses) ▸ In appropriate clinical context, consider ova & parasites; molecular testing for <i>Giardia</i>, <i>Cryptosporidium</i> spp, <i>E. histolytica</i>, microsporidia, and <i>Cyclospora/isospora</i> spp • Fecal calprotectin ± lactoferrin^o • Consider abdominal/pelvic CT with contrast^s • Recommend GI consultation ▸ Colonoscopy or flexible sigmoidoscopy ± EGD with biopsy^o	• G3: If using combination IO therapy, discontinue current therapy^e • G4: Discontinue immunotherapy agent responsible for toxicity^e • Consider inpatient care for provision of supportive care • IV methylprednisolone^v (1–2 mg/kg/day)^w • If no response in 1–2 days or unable to transition to oral steroids, additional immunosuppression required ▸ If colonoscopy or flexible sigmoidoscopy shows significant ulceration, non-ulcerative inflammation, or microscopic colitis on histology,^x continue steroids and strongly consider adding infliximab^{g,h,i,y} or vedolizumab^{h,y,z,aa} ◇ Consider tofacitinib or ustekinumab for infliximab- and/or vedolizumab-refractory colitis^{aa} • For persistent diarrhea that does not resolve after the management described above, consider other etiologies (eg, pancreatic exocrine insufficiency, celiac disease) • For immunosuppressant-refractory colitis, fecal transplantation may be considered based on institutional availability and expertise

^e [Principles of Immunotherapy Rechallenge \(IMMUNO-C\)](#).

^g Start infliximab at 5 mg/kg.

^h 160 mg IV q8w for 4 doses, then 80 mg IV q8w for 4 doses, then 80 mg IV q12w thereafter.

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

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

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.
- 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 2 years

Colitis – Identifying “High Risk” Patients

Colonoscopy

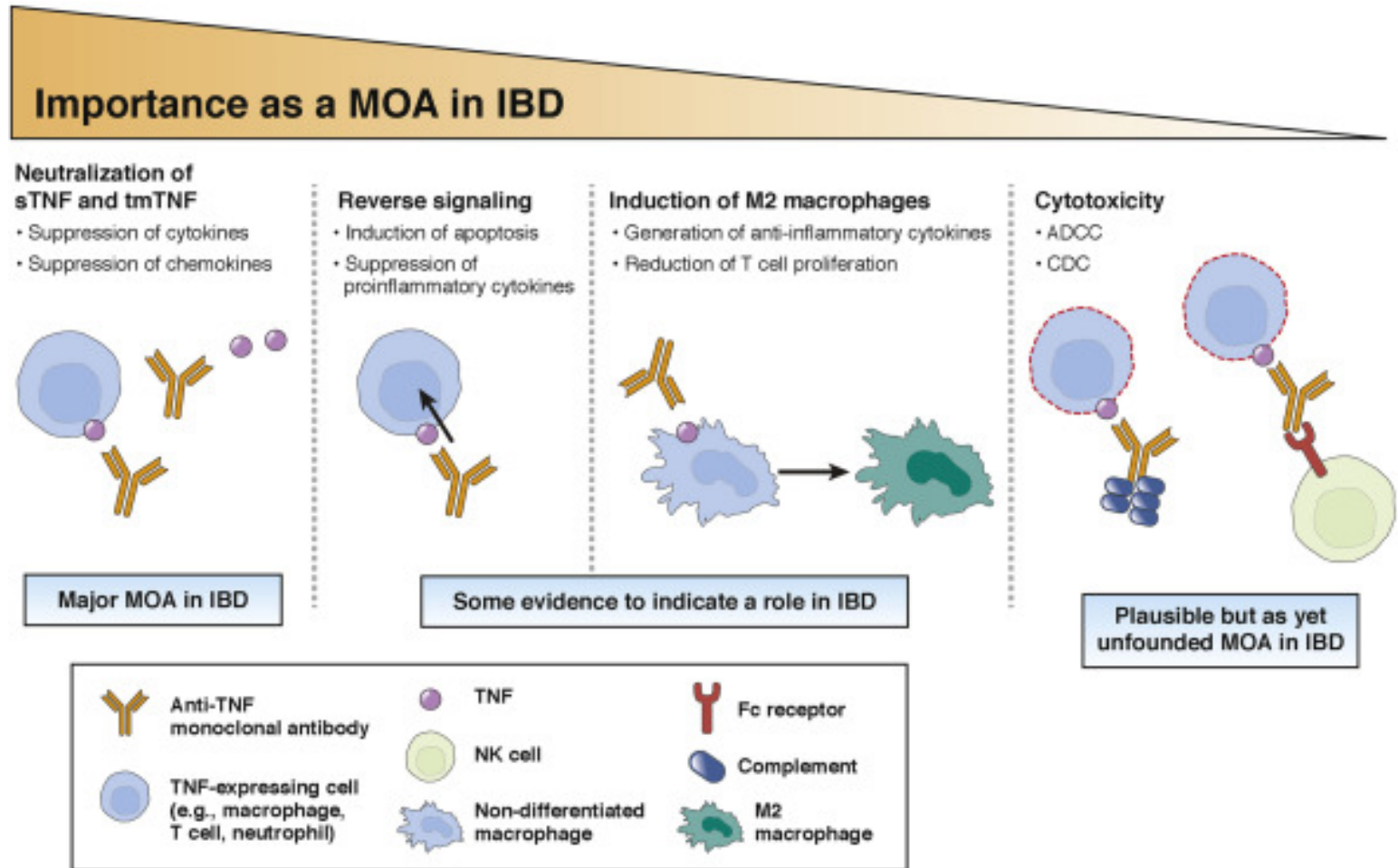
- Series of 182 patients with immunotherapy colitis
 - 27% with mucosal ulceration, 36% with non-ulcerative inflammation, 37% with normal colonoscopy
 - Ulceration more common in patients with high fecal calprotectin
 - Fecal Lactoferrin 90% sensitive at predicting histologic inflammation and 70% sensitive at predicting endoscopic inflammation
 - Early colonoscopy (<7 days after onset of diarrhea) associated with shorter duration of diarrhea
 - Later colonoscopy (>30 days after symptom onset) associated with longer duration of steroids, recurrent symptoms and higher use of adjunctive therapies (infliximab/vedolizumab)
 - High risk endoscopic features (ulcers deeper than 2 mm or larger than 1 cm, extensive colonic involvement) associated with higher need for infliximab/vedolizumab (OR 3.89)
- Series of 92 patients with immunotherapy colitis
 - Grade of diarrhea did not correlate well with endoscopic severity of colitis
 - 56% of patients required infliximab

**Abu-Sbeih et al., *J Immunother Cancer*. 2018;6:95.
Guekes Foppen et al., *ESMO Open*. 2018, e000278.**

Colitis - Infliximab

Steroid refractory immunotherapy colitis case series (n=5)

- 4 of 5 patients had complete clinical remission of symptoms after 1 dose of infliximab
- 1 of 5 patients required 2nd dose of infliximab to induce remission



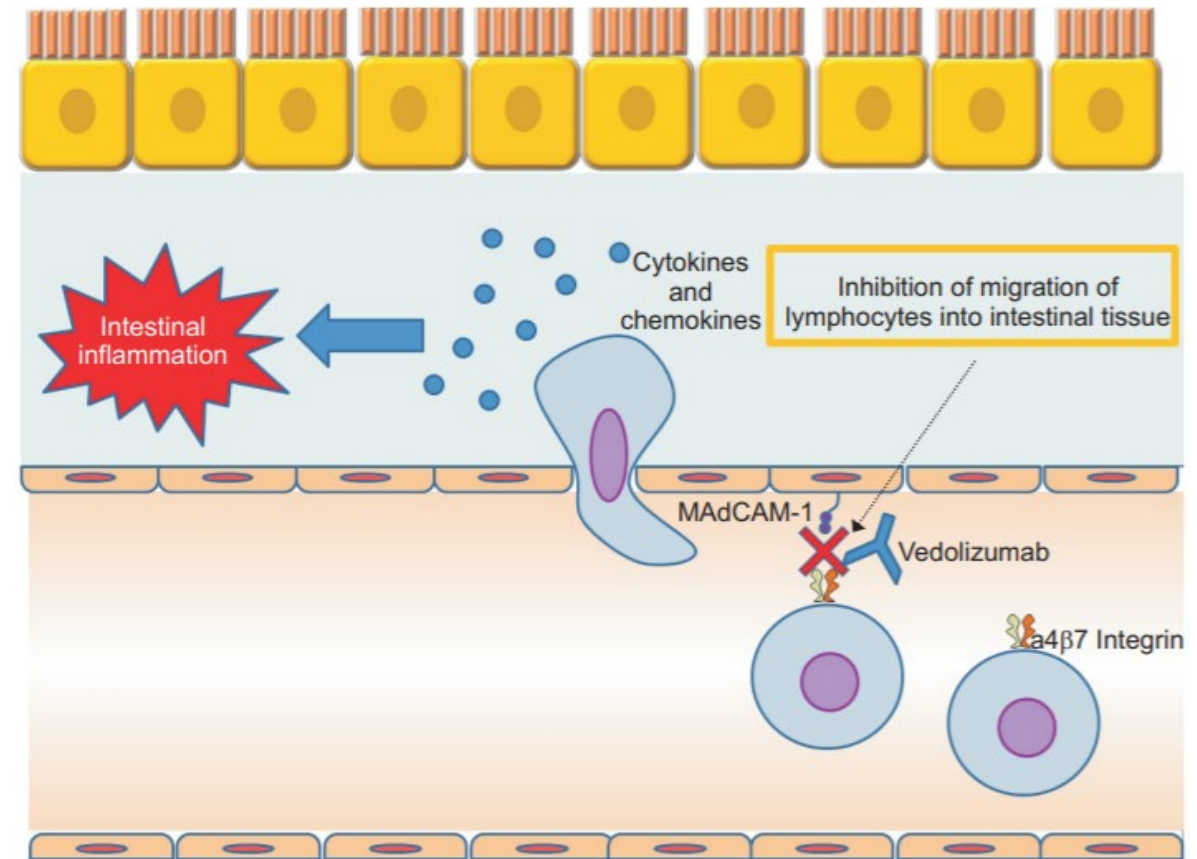
Johnston et al., *Dig Dis Sci.* 2009;54:2538-40.

Ben-Horin et al., *Clin Gastroenterol Hepatol.* 2016;14:1685-1696

Colitis - Vedolizumab

Retrospective case series of steroid refractory colitis (n=28)

- 9 had also received infliximab
- Vedolizumab induced sustained clinical remission in
 - 95% patients who had not received infliximab
 - 67% patients who had received infliximab
- Patients who had lower baseline fecal calprotectin and fewer mucosal ulcerations had better outcomes with vedolizumab



Infliximab vs Vedolizumab

Retrospective multi-center study

- 156 patients with immunotherapy-mediated colitis
 - Vedolizumab n= 62
 - Infliximab n-94
- Patients treated with infliximab more commonly
 - Had melanoma
 - Exposure to anti-CTLA-4
 - Prolonged steroid use prior to adjunctive therapy
 - Hospitalizations
 - Shorter course of immunotherapy prior to colitis
 - Did not have diagnostic colonoscopy

Zou et al., J Immunother Cancer. 2021;e003277.

Infliximab vs Vedolizumab - Continued

Rate of clinical remission equal ~ 88%

Vedolizumab with delayed time to clinical response

- 18 vs 13 days, $p = 0.01$

Vedolizumab had lower rate of colitis recurrence

- 14% vs 29%, $p = 0.008$

Infliximab group with higher risk of cancer progression and death

Zou et al., J Immunother Cancer. 2021;e003277

Infliximab vs Vedolizumab – Meta-analysis

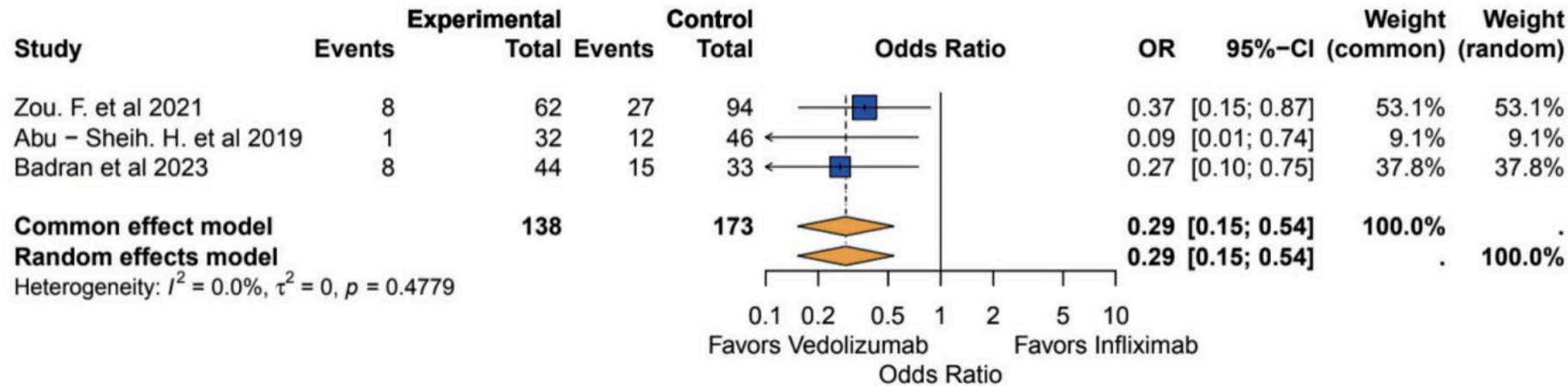


Figure 3. Recurrence of colitis: vedolizumab vs. infliximab. OR: odds ratio; CI: confidence interval.

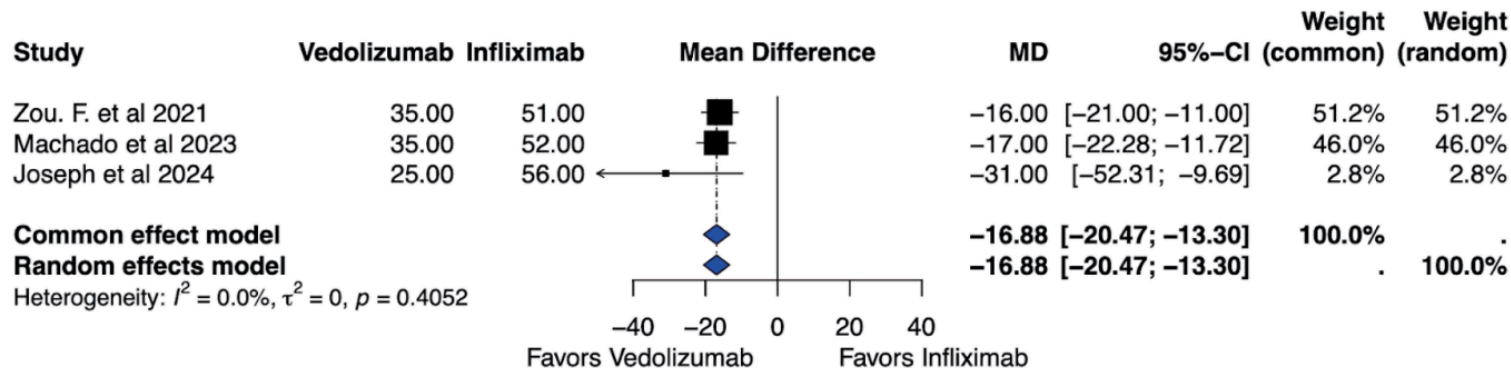


Figure 4. Median dose of steroid exposure: vedolizumab vs. infliximab. MD: mean difference; CI: confidence interval.

- Lower risk of colitis recurrence with vedolizumab
- Less steroid exposure with vedolizumab

Shambhavi et al., World J Oncol, 2025.

Microscopic colitis and Budesonide

ICI microscopic colitis

- Colitis with clinical and histopathologic evidence of colitis but without endoscopic inflammation

Compared with non-microscopic colitis, pts with microscopic colitis

- Received budesonide
- Continued ICI

Table 2 Colitis outcomes

	Overall	Microscopic colitis	Non-microscopic colitis	p-value
Interventions				
Budesonide	15/38 (39.5%)	12/13 (92.3%)	3/25 (12.0%)	< 0.001*
Any systemic glucocorticoids	25/38 (65.8%)	3/13 (23.1%)	22/25 (88.0%)	< 0.001*
Systemic glucocorticoids < 1 mg/kg/d	14/38 (36.8%)	2/13 (15.4%)	12/25 (48.0%)	0.077
Systemic glucocorticoids ≥ 1 mg/kg/d	12/38 (31.2%)	1/13 (7.7%)	11/25 (44.0%)	0.030*
Time from symptom onset to initiation of glucocorticoids (days)				
Mean +/- SD	32.4 +/- 37.1	33.2 +/- 26.0	32.0 +/- 42.7	0.928
Median	21.0	28.0	18.0	
Proportion continuing CPI course	14/38 (36.8%)	10/13 (76.9%)	4/25 (16.0%)	< 0.001*
Proportion eventually discontinuing immunotherapy	29/38 (76.3%)	8/13 (61.5%)	21/25 (84.0%)	0.226
Due to toxicity alone	22/38 (57.9%)	6/13 (46.2%)	16/25 (64.0%)	1.000
Due to any progressive disease	7/38 (18.4%)	2/13 (15.4%)	5/25 (25.0%)	
Average number of additional infusions [#]	3.0 +/- 5.7	5.8 +/- 6.8	1.6 +/- 4.5	0.030*
Additional irAEs after colitis	8/38 (21.1%)	3/13 (23.1%)	5/25 (20.0%)	1.000
Response to first line treatment	22/38 (67.9%)	9/13 (69.2%)	14/25 (56.0%)	0.429
Proportion of patients requiring second-line immunosuppression	23/38 (60.5%)	5/13 (38.5%)	18/25 (72.0%)	Not calculated
Proportion requiring TNFα inhibitor	16/38 (42.1%)	4/13 (30.8%)	11/25 (44.0%)	0.429

Hughes et al., *J Immunother Cancer*. 2019;7:292.

ICI Colitis Summary

Consider early colonoscopy to stratify severity

- Microscopic colitis (without evidence of inflammation on colonoscopy) may be associated with better outcomes with oral budesonide
- Mucosal ulceration may portend more severe, potentially steroid-refractory colitis and earlier use of adjunctive immunosuppression (infliximab/vedolizumab) may be necessary

Pneumonitis

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Management of Immune Checkpoint Inhibitor-Related Toxicities

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

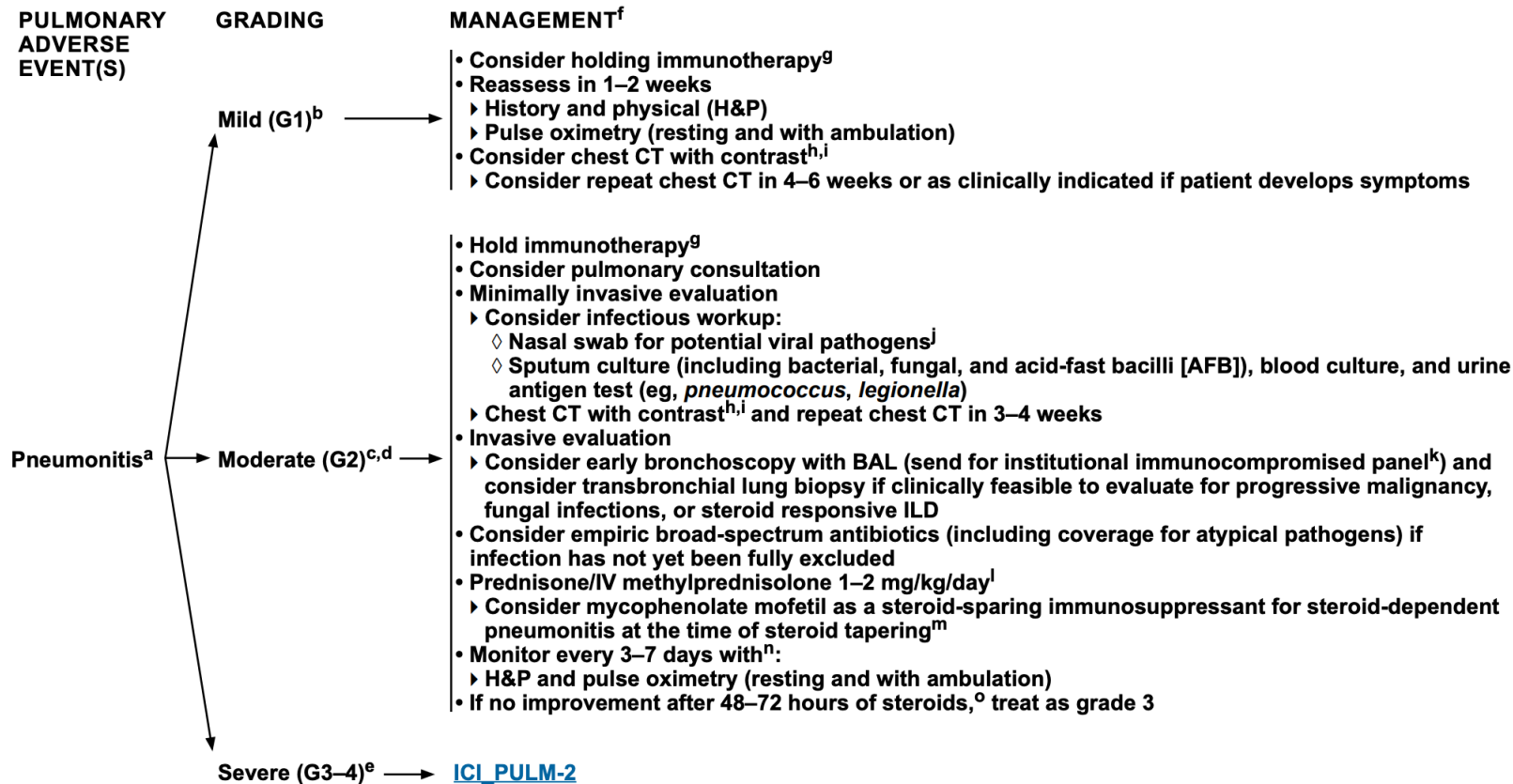


Table 2: National Cancer Institute CTCAE Pneumonitis Grading System

Grade	Symptom
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Symptomatic; medical intervention indicated; limiting instrumental ADL
3	Severe symptoms; limiting self-care ADL; oxygen indicated
4	Life-threatening respiratory compromise; urgent intervention indicated (ie, tracheostomy or intubation)
5	Death

Source.—Reference 26.

Note.—ADL = activities of daily living.

Pneumonitis



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Management of Immune Checkpoint Inhibitor-Related Toxicities

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

ASSESSMENT/ GRADING

MANAGEMENT^f

Severe (G3–4)^e
pneumonitis^a →

- Hold immunotherapy^g
- Inpatient care
- Pulmonary and ID consultation
- Minimally invasive evaluation
 - Infectious workup:
 - Consider that the patient may be immunocompromised
 - ◊ Nasal swab for potential viral pathogens^j
 - ◊ Sputum culture (including bacterial, fungal, and AFB), blood culture, and urine antigen test (eg, *pneumococcus*, *legionella*)
 - ◊ Consider cardiac evaluation to exclude cardiac causes for clinical presentation
- Invasive evaluation
 - Bronchoscopy with BAL (send for institutional immunocompromised panel^k) if feasible to rule out infection, malignant lung infiltration, or steroid responsive ILD and consider transbronchial lung biopsy if feasible and clinically indicated
- Consider empiric broad-spectrum antibiotics (including coverage for atypical pathogens) if infection has not yet been fully excluded
- IV methylprednisolone 1–2 mg/kg/day. Assess response within 48 hours and plan taper over ≥6 weeks^f
- Consider adding any of the following if no improvement after 48 hours:
 - Preferred:
 - ◊ IVIG^p
 - ◊ Tocilizumab^q
 - Other recommended:
 - ◊ Mycophenolate mofetil 1–1.5 g BID then taper in consultation with pulmonary service^m
 - Consider mycophenolate mofetil as a steroid-sparing immunosuppressant for steroid-dependent pneumonitis at the time of steroid tapering^m
 - ◊ Infliximab^r 5 mg/kg, a second dose may be repeated 14 days later at the discretion of the treating provider

Table 2: National Cancer Institute CTCAE Pneumonitis Grading System

Grade	Symptom
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Source.—Reference 26.

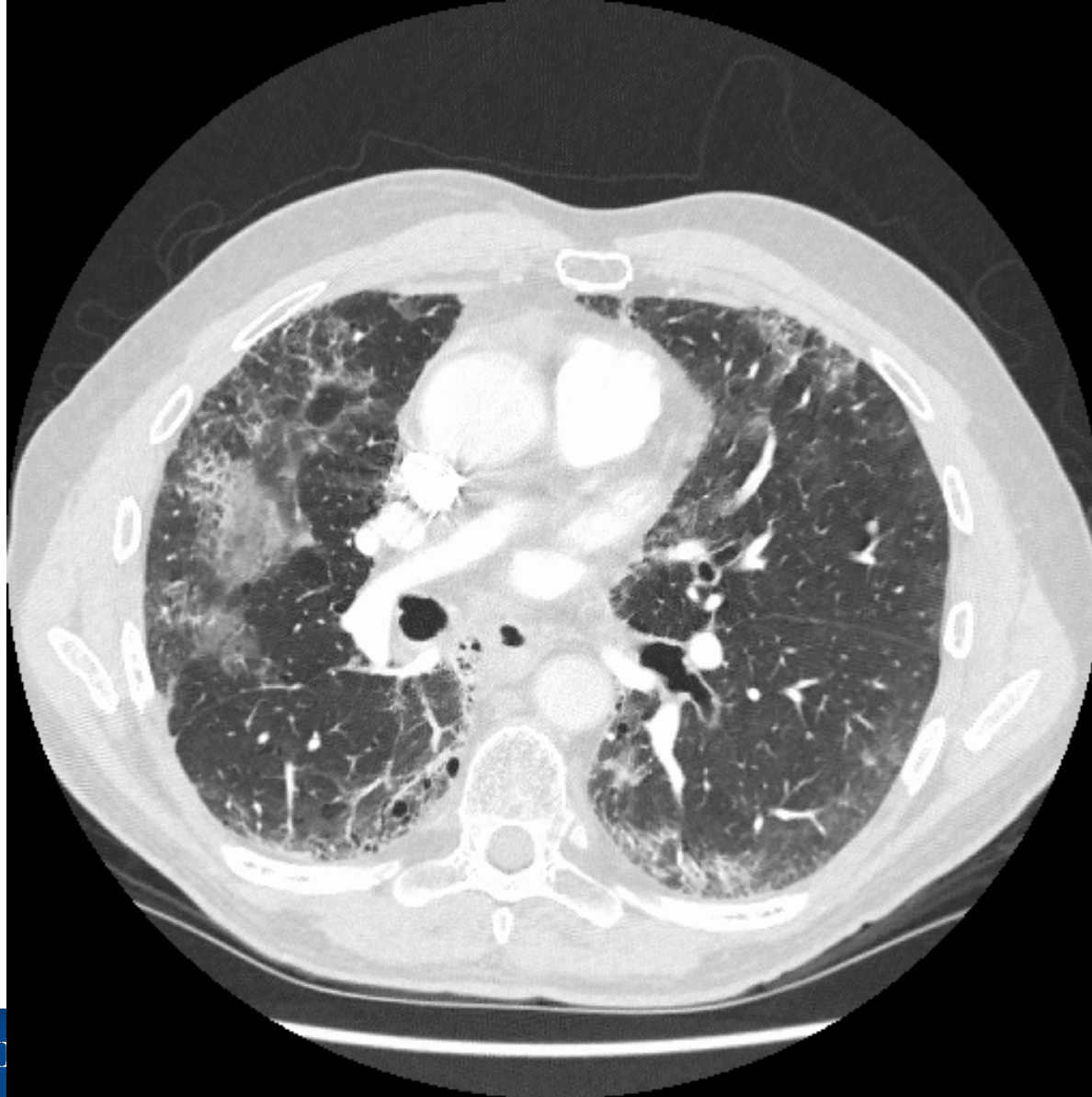
Note.—ADL = activities of daily living.

Pneumonitis Radiographic Patterns

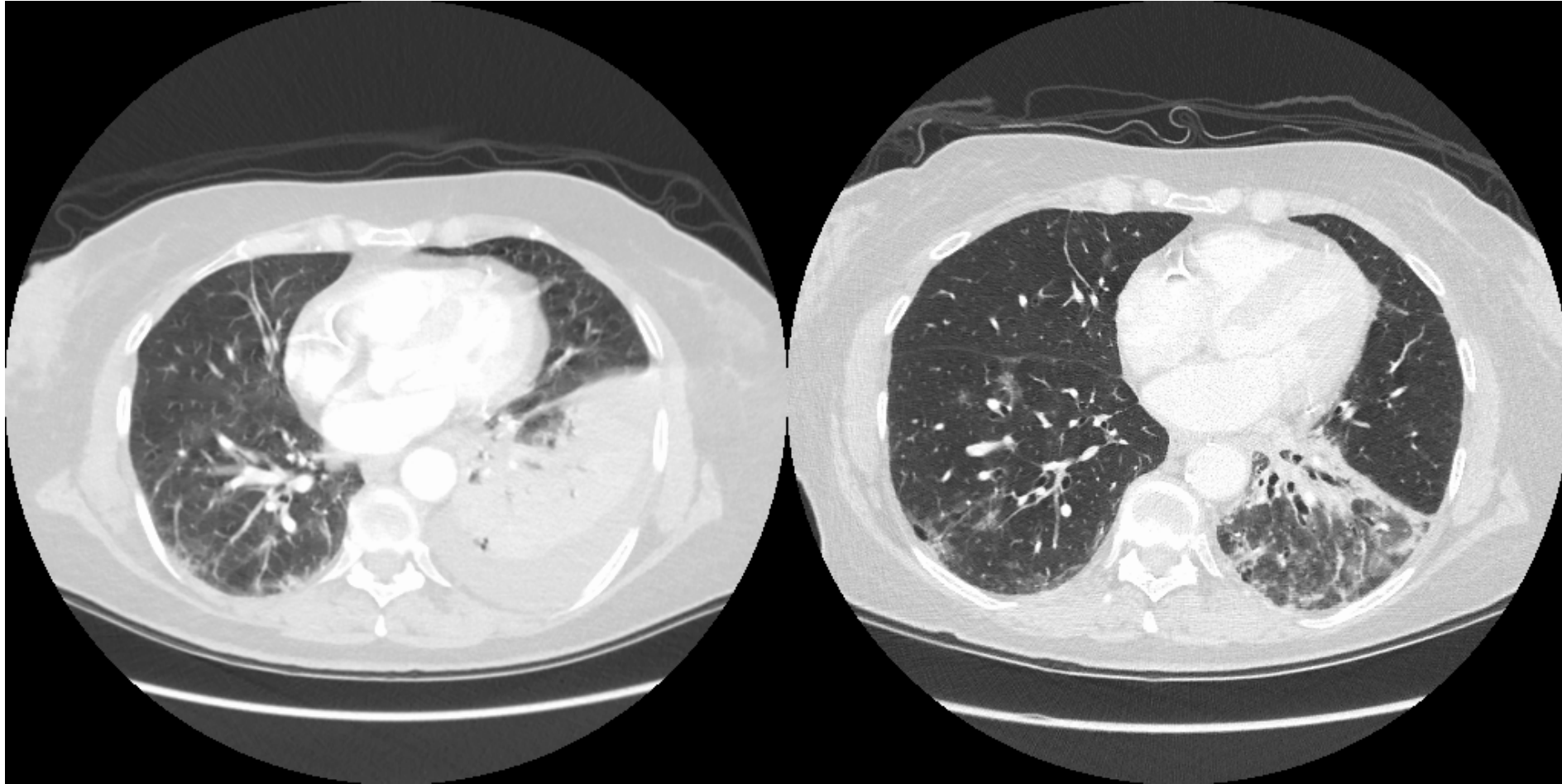
	Nonspecific interstitial pneumonia (NSIP) Type • Patchy areas of ground glass opacity (GGO) +/- consolidation; • Progression to irregular reticular opacities architectural distortion, and traction bronchiectasis • Bilateral, symmetric; lower-lung involvement
	Organizing Pneumonia Type • Multifocal patchy alveolar opacities • Peribronchovascular +/- peripheral • May demonstrate reversed halo sign
	Hypersensitivity Pneumonia • Small centrilobular nodules; bilateral GGO • Large or lobular areas of decreased attenuation/ vascularity
	Diffuse Alveolar Damage • Extensive GGO & airspace consolidation (exudative phase) • Traction bronchiectasis and decreased lung volumes in organizing and fibrotic phases
	Simple Pulmonary Eosinophilia • Nonsegmental consolidation GGO • Unilateral or bilateral, transient and migratory

O'Leary et al., J Thorac Oncol, 2024.

Scattered Ground Glass Opacities



Pneumonitis – Lobar infiltrate



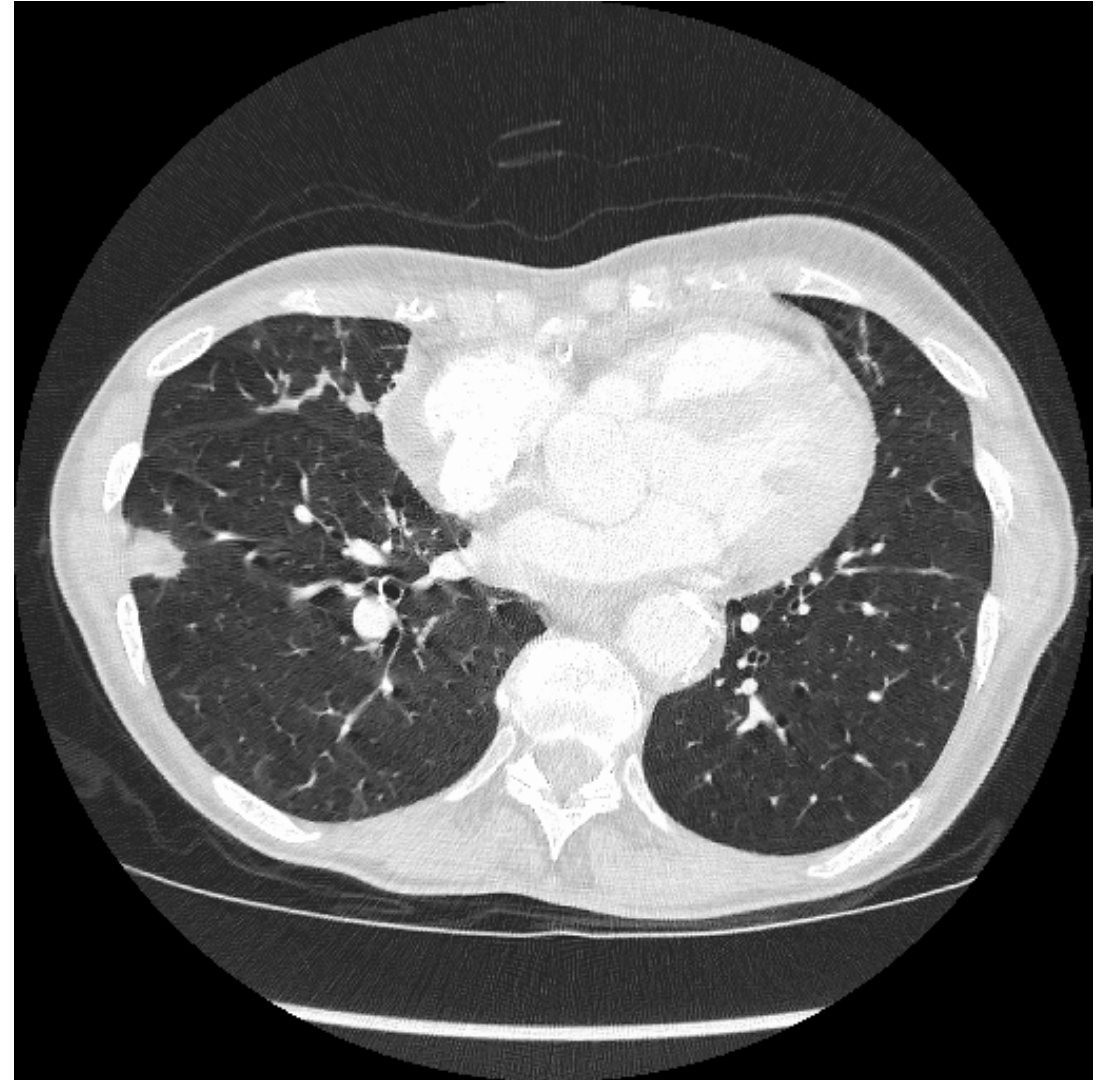
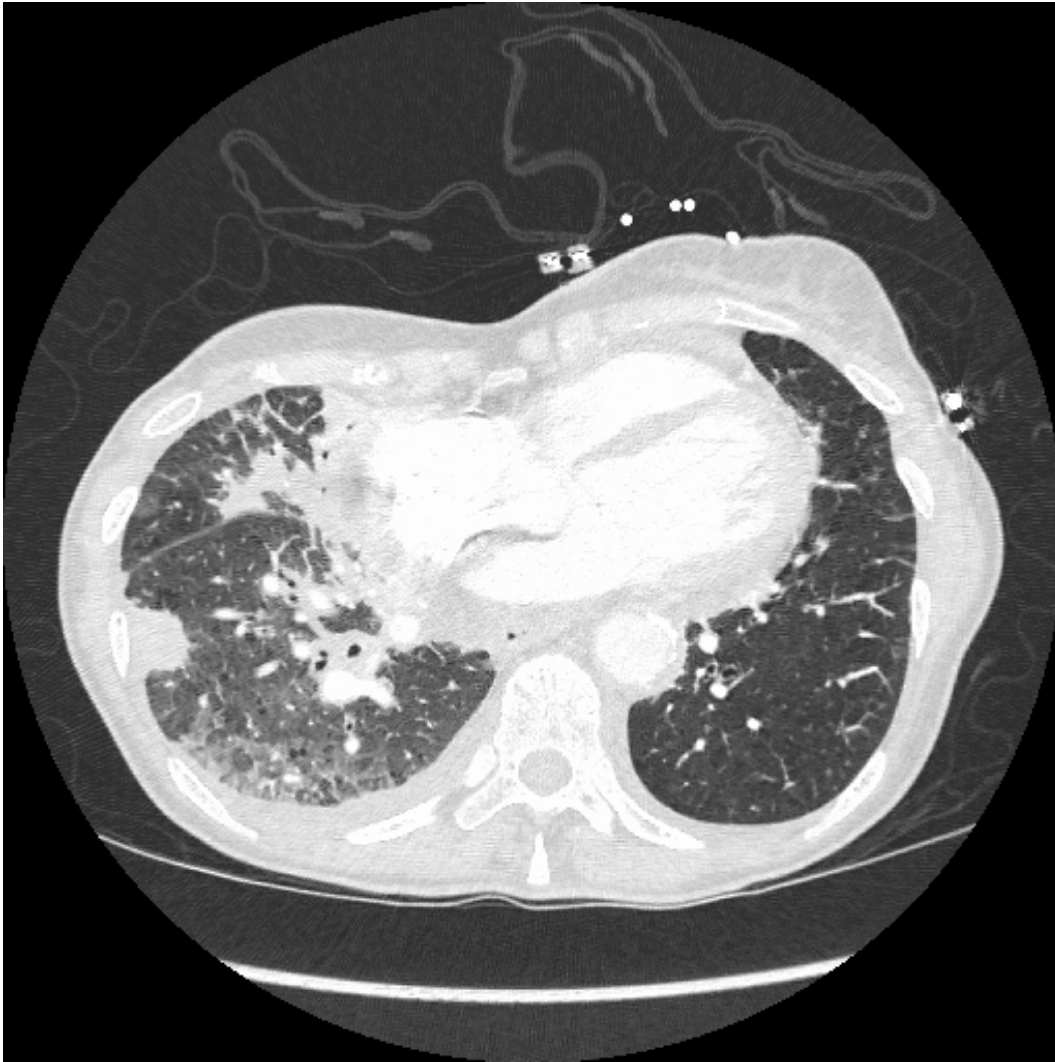
At Diagnosis

After Steroids

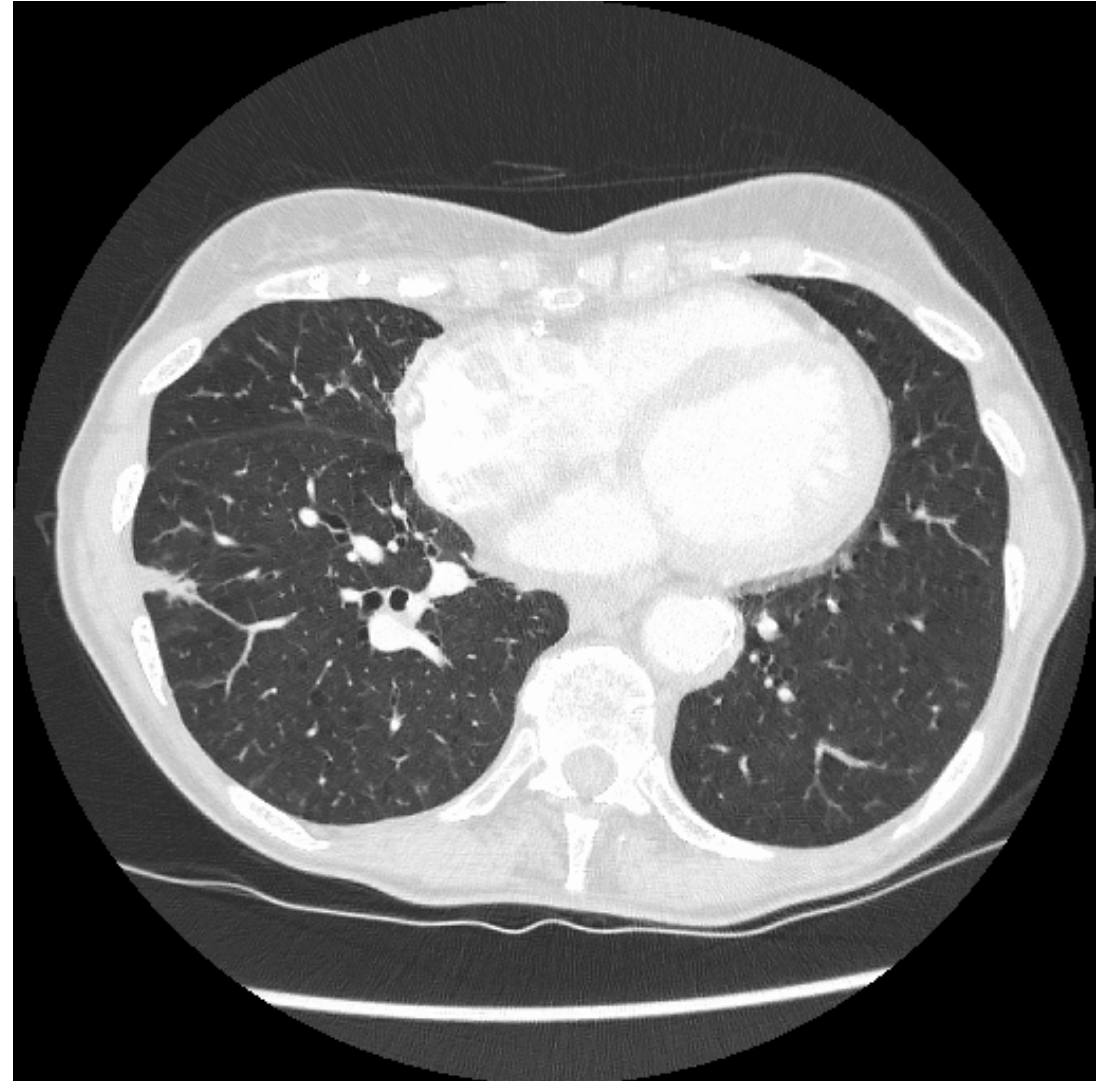
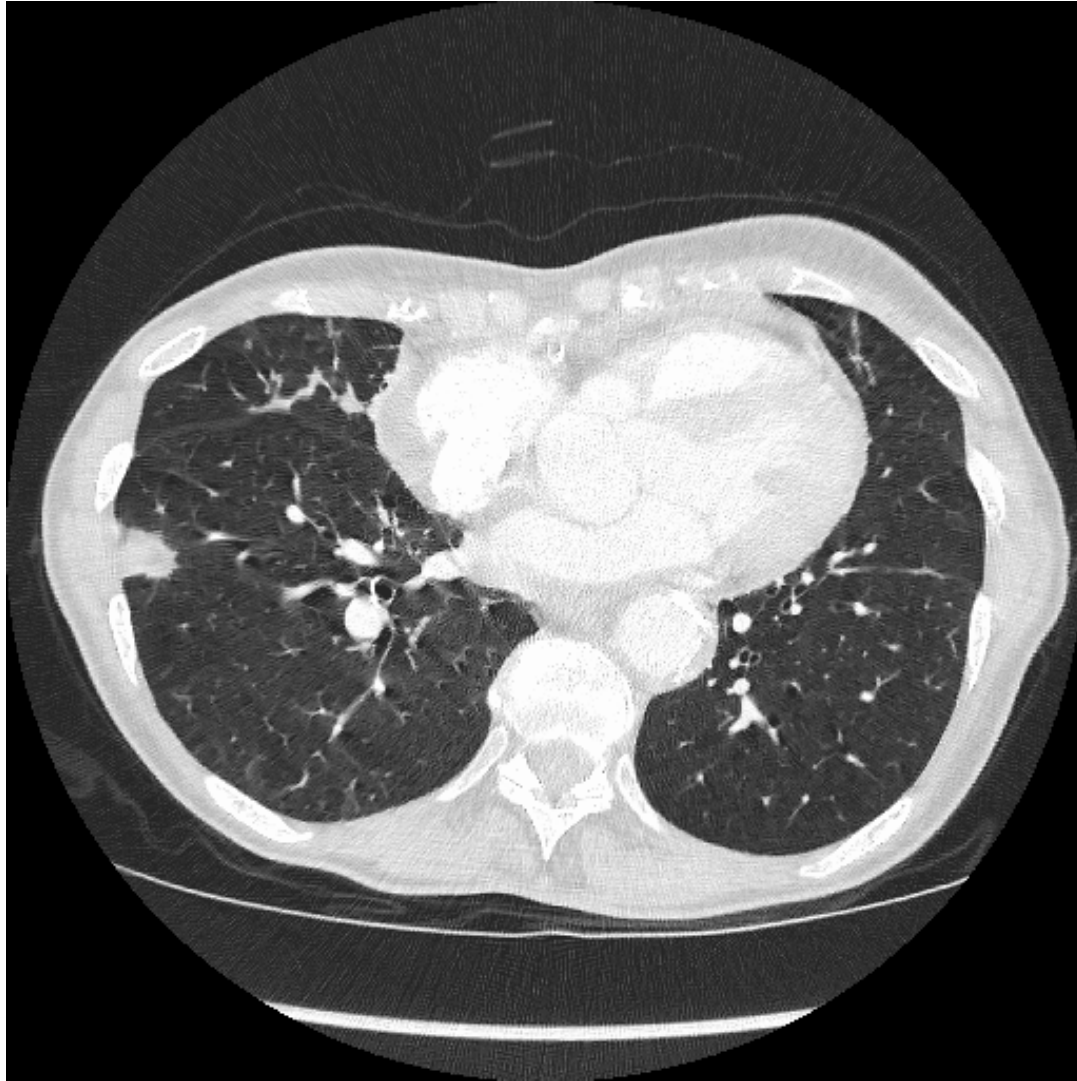
Mixed Nodular and Interstitial Infiltrates



Mixed Nodular and Interstitial Infiltrates (improving on prednisone)



Mixed Nodular and Interstitial Infiltrates (improving on prednisone)



Pneumonitis Management

Table 3. Pneumonitis Management and Outcomes

Highest CTCAE Grade	Highest Treatment Required for Pneumonitis Management, No. (%)				Total
	Treatment Hold	Oral Corticosteroids	Intravenous Corticosteroids	Additional Immunosuppression*	
1	15 (83)	2 (12)	0 (0)	0 (0)	17
2	0 (0)	10 (71)	4 (29)	0 (0)	14
3	0 (0)	2 (20)	4 (40)	4 (40)	10
4	0 (0)	0 (0)	1 (100)	0 (0)	1
5	0 (0)	0 (0)	0 (0)	1 (100)	1
Total	15	14	9	5	43

Highest CTCAE Grade	Clinical Outcomes of Pneumonitis Management, No. (%)				Total
	Completely Resolved	Improved	Worsened	Unknown	
1	17 (100)	0 (0)	0 (0)	0 (0)	17
2	10 (71)	3 (21)	0 (0)	1 (8)	14
3	4 (40)	2 (20)	4 (40)	0 (0)	10
4	1 (100)	0 (0)	0 (0)	0 (0)	1
5	0 (0)	0 (0)	1 (100)	0 (0)	1
Total	32	5	5	1	43

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events (version 4).

*Additional immunosuppression: Three patients received infliximab alone (all grade 3), and two patients received both infliximab and cyclophosphamide (one grade 3 and one grade 5).

Naidoo et al., *J Clin Oncol*. 2017;35:709-717.

Steroid Refractory Pneumonitis – Tocilizumab

Table 1. Patient characteristics.

Patient characteristics	Tocilizumab N (%) Total = 34	No tocilizumab N (%) Total = 53
Age (years)	63 (36–81)	64 (45–88)
Gender		
Male	17 (50.0)	29 (54.7)
Female	17 (50.0)	24 (45.3)
ECOG performance status at the time of nivolumab initiation		
0	3 (8.8)	17 (32.1)
1	16 (47.1)	17 (32.1)
2	9 (26.5)	12 (22.6)
3	6 (17.6)	7 (13.2)
Malignancy		
NSCLC—adenocarcinoma	13 (38.2)	19 (35.8)
NSCLC—squamous	11 (32.4)	19 (35.8)
Small cell lung cancer	6 (17.7)	3 (5.7)
Other	4 (11.8)	12 (22.6)
Number of prior unique therapies	1 (0–3)	1 (0–3)
Nivolumab doses	4 (1–11)	6 (1–12)
Baseline CRP (mg/L)	23.0 (0.1–238.5)	20.8 (0.2–192.9)
Index grade 3/4 irAE		
Pneumonitis	12 (35.3)	–
Serum sickness/SIRS	12 (35.3)	–
Cerebritis	5 (14.7)	–
Hypophysitis	1 (2.9)	–
Colitis	1 (2.9)	–
Pancreatitis	1 (2.9)	–
Hepatitis	1 (2.9)	–
Coagulopathy	1 (2.9)	–
Number of tocilizumab doses		
1	17 (50.0)	–
2	13 (38.2)	–
3	3 (8.8)	–
4	1 (2.9)	–

NSCLC Non Small Cell Lung Cancer; CRP C- reactive protein; irAE immune related adverse event; SIRS Systemic Immune Response Syndrome.

Table 3. Discharge disposition of patients receiving tocilizumab in the inpatient setting.

Disposition of patient at discharge	Inpatient tocilizumab N (%) Total = 27
Home	20 (74.1)
Hospice	4 (14.8)
SNF	2 (7.4)
Readmit	1 (3.7)

Stroud et al., *J Oncol Pharm Pract.* 2019;25:551-557.

Steroid Refractory Pneumonitis - Infliximab

Case	Age, Years	Sex	Cancer	Immunotherapy	Corticosteroid, mg/kg [*]	Time, Days [^]	Ventilatory Support, FIO2%	irAEs	Bronchoscopy, Lymphocytes, %	Outcome
1	66	M	Melanoma	Ipilimumab	1.2	2	Nasal cannula, 24%	–	No	Improved
2	66	M	Pancreatic	Ipilimumab	1.3	5	High-flow, 45%	Hepatic [®]	No	Improved
3	52	F	AML	Ipilimumab, nivolumab	3.3	9	High-flow, 60%	–	Yes [‡]	Improved
4	69	F	AML	Ipilimumab, nivolumab	1.1	7	MV, 90%	Dermatologic, gastrointestinal	Yes [‡]	Improved
5	79	M	AML	Nivolumab	2.4	34	High-flow, 50%	Renal	Yes, 13	Death ⁺
6	72	M	AML	Ipilimumab, nivolumab	1.1	Chronic	High-flow, 30%	Hematologic	Yes, 26	Death ⁺
7	72	F	MDS	Ipilimumab, nivolumab	2.0	2	BiPAP, 70%	Dermatologic	Yes, 18	Death
8	68	F	Lung	Nivolumab	0.8	9	High-flow, 75%	–	No	Death
9	61	M	Urothelial	Nivolumab	1.2	7	High-flow, 75%	–	Yes [‡]	Death

AML: acute myeloid leukemia; MDS: myelodysplastic syndrome; MV: mechanical ventilation; BiPAP: bi-level positive airway pressure

^{*}Maximal dosage (all patients were initiated on intravenous methylprednisone, and those that improved were transitioned to oral prednisone)

[^]Time from steroid administration to infliximab dosing

⁺Initially had improvement

[®]irAE occurred prior to pneumonitis

[‡]No bronchoalveolar lavage cell count and differential performed

Lai et al., *Journal of Immunology and Precision Oncology*. 2020;3:172-174.

Steroid-Refractory Pneumonitis Infliximab and IVIG

12/65 pneumonitis patients = 18.5% patients steroid refractory

Table 2 Clinical features and management of steroid-refractory ICI-pneumonitis by immunosuppressive treatment			
Therapy type	Intravenous immunoglobulin	Infliximab	Combination
Total patients, n (%)	7	2	3
Clinical outcome			
Improved	2 (29)	0 (0)	0 (0)
Worsened	2 (29)	0 (0)	0 (0)
Death from steroid-refractory pneumonitis	3 (43)	2 (100)	3 (100)

Pneumonitis Take Aways

Imaging findings for pneumonitis can be heterogenous

Bronchoscopic evaluation and biopsy can be helpful to r/o infection or progression of malignancy

While most patients respond to steroids, steroid refractory/resistant patients have poor outcomes, tocilizumab appears to drive the best outcomes in the limited literature

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

Why do we need an Immunotherapy Toxicity Group?

Case from 2019:

- 80 yo M receiving durvalumab (PD-L1 inhibitor) for stage 3 NSCLC presents with epigastric abdominal pain, nausea and diarrhea for 1-2 weeks (4+ loose stools per day).
 - Same day: hemodynamically stable, stool infectious studies negative, CT A/P wnl
 - Urgent GI referral placed in Epic
 - 6 days later: Patient seen by GI. EGD and colonoscopy ordered.
 - 13 days later: EGD/colonoscopy performed
 - EGD shows duodenal erythema and edema
 - Colonoscopy without evidence of colitis, random colon biopsies normal.
 - 15 days later: duodenal biopsies show duodenitis

Team Members

Oncology

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- Ravi Narra
- Jennifer Ross
- Jennifer Walters

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- Srivats Madhavan
- Phaedra Tachtatzis

Endocrinology

- Abubakr Mohamed

Infectious Disease

- Kartikey Acharya

Rheumatology

- Richard Hariman

Pulmonology

- Amit Taneja
- Mark Barash

Nephrology

- Paul Hanna

Cardiology

- David Lewandowski

Neurology

- Ahmed Obeidat

Dermatology

- Karolyn Wanat
- Kara Young

Pathology

- James Miller
- Alexander Gallan
- Saryn Doucette

Pharmacy

- Erin McGurty
- Nichole Ruffcorn

MCW 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

Immunotherapy side effects are heterogenous and diagnosis can be difficult

Multidisciplinary collaboration/communication is key to ensuring best patient outcomes

- Reach out to treating oncologist if concerns
- immunotoxgroup@mcw.edu

Questions?

immunotoxgroup@mcw.edu