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Immune Related Adverse Events in Breast Cancer Patients

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Disclosures

- No relevant financial relationships to disclose

Learning Objectives

- Brief Overview of Immune Checkpoint Inhibitors (ICIs)
- Brief Overview of Immune Related Adverse Events (irAEs)
- Case Discussion: Navigating Pembrolizumab side effects in the neoadjuvant setting
  - Infusion Reactions, Thyroid Dysfunction, Colitis
  - General Management
  - Rechallenge with ICIs

How is Immunotherapy different from Chemotherapy?

	Chemotherapy	Immunotherapy
Target	Tumor or the area around the tumor	Immune System
Limitations	Side Effects, often cumulative *(neuropathy, heart problems)*	Requires a working immune system function (*tumor size, multiple prior therapies may limit effectiveness*)
Tumor Evolution/ New Mutations	Resistance to therapy	New targets for the immune system which may result in better effects
Anti-Tumor Effects	Often immediate	Can be Delayed (*may get better over time, e.g., booster vaccinations*)
Memory Response*	No	Yes

Adapted from Gulley JL. 2013. ASCO Education Book

FDA Approved ICI for Solid Tumors

	Nivolumab	Pembrolizumab	Cemiplimab	Dostarlimab	Atezolizumab	Durvalumab	Avelumab	Ipilimumab
Brand Name	Opdivo	**Keytruda**	Libtayo	**Jemperli**	**Tecentriq**	Imfinzi	Bavencio	Yervoy
Pharma	BMS	**Merck**	Regeneron	**GSK**	**GenenT**	AZ	EMD	BMS
Target	PD-1 on T-cells				PD-L1 on tumor and APCs			CTLA-4 on T-cells
Half-life	25 days	**23 days**	19 days	**23 days**	**27 days**	17 days	6 days	15 days
Premeds	No	**No**	No	**No**	**No**	No	Yes (≥ 4 doses)	No
Infusion Rxn G3+	<1%	**0.2%**	0.2%	**0.2%**	**0.2%**	0.3%	0.9%	n.a.
Dose-Safety Response	No	**No**	No	**No**	**No**	No	No	**Yes**

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AZ = AstraZeneca; APC = antigen presenting cells (NK, DC, macrophages); BMS – Bristol-Myers Squibb; EMD = EMD Serono; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; GenenT = Genentech; GSK = GlaxoSmithKline; ***ICI; Immune checkpoint inhibitor****; PD-1 = Programmed cell death protein 1; PD-L1 = Programmed death ligand-1;*

Immune Related Adverse Events (IrAEs)

- Can involve almost any system in the body
  - Most common fatigue, dermatologic, endocrine, GI and rheumatologic.
- Most are low grade but can be long lasting
- ICI-related inflammatory toxicities are different from those with chemotherapy

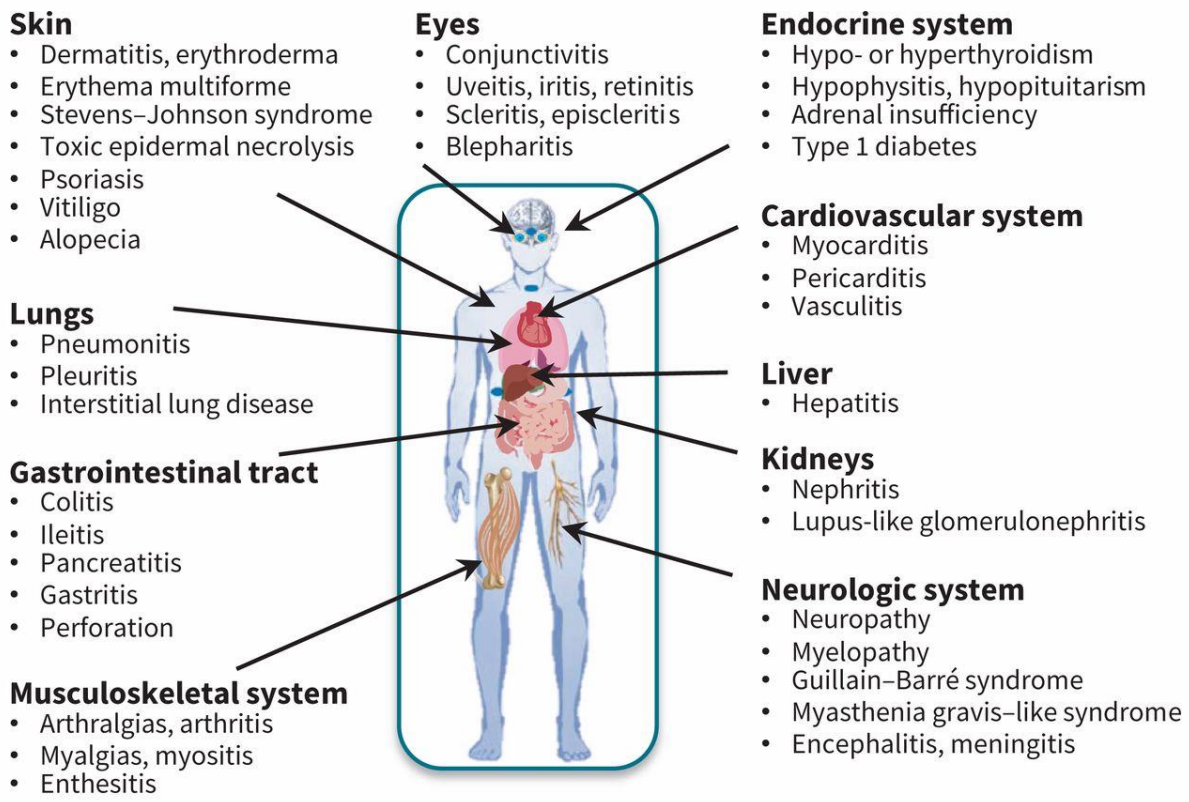

Figure: Khashayar Esfahani et al. CMAJ 2019;191:E40-E46

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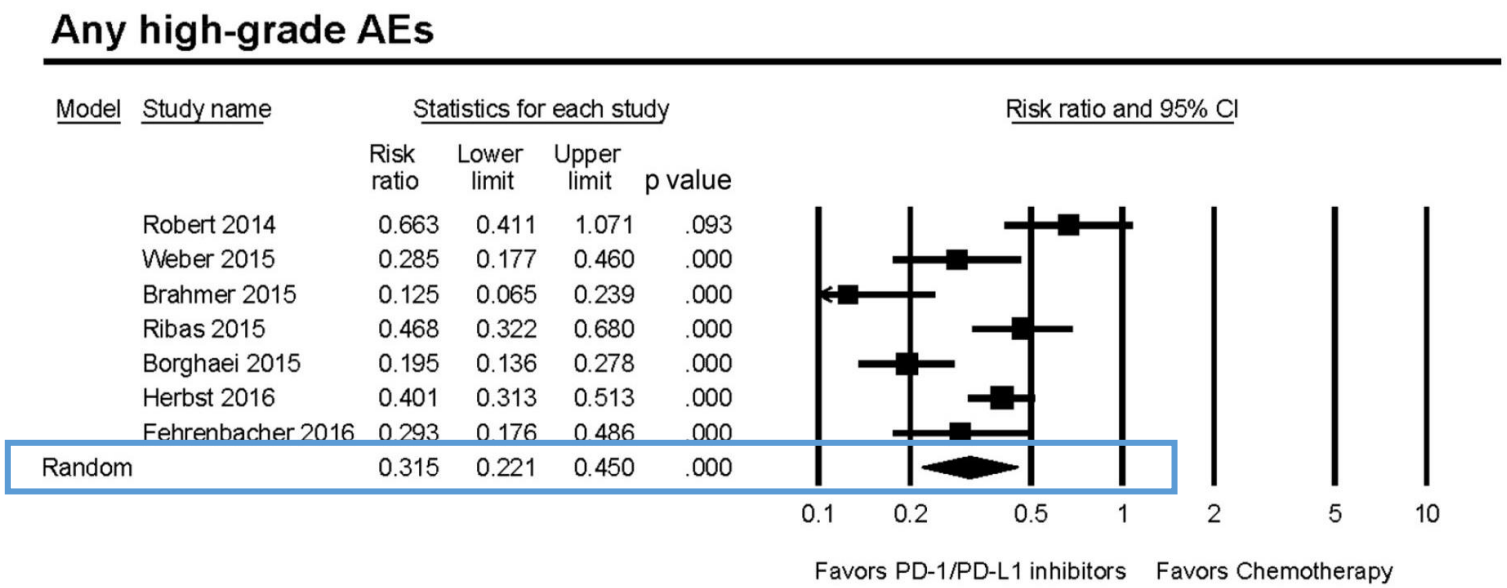
Varricchi et al. 2017. ESMO; Thapa et al. 2019. ASCO

ICIs have fewer high-grade AEs than Chemotherapy



- Lower total AEs* (67.6% vs 82.9%)
- Lower high-grade AEs* (11.4% vs 35.7%)
- Lower treatment discontinuation* (4.5% vs 11.1%)
- Lower treatment-related deaths (0.6% vs 1.4%)

* Statistically significant

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Nishijima et al. 2017. The Oncologist

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Position article and guidelines

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events

Julie R Brahmer,[1] Hamzah Abu-Sbeih,[2] Paolo Antonio Ascierto ,[3] Jill Brufsky,[4] Laura C Cappelli,[5] Frank B Cortazar,[6,7] David E Gerber,[8] Lamya Hamad,[9] Eric Hansen,[10] Douglas B Johnson,[11] Mario E Lacouture,[12] Gregory A Masters,[13] Jarushka Naidoo,[1,14] Michele Nanni,[10] Miguel-Angel Perales,[12] Igor Puzanov,[10] Bianca D Santomasso,[15] Satish P Shanbhag,[5,16] Rajeev Sharma,[10] Dimitra Skondra,[17] Jeffrey A Sosman,[18] Michelle Turner,[1] Marc S Ernstoff [19]

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017
doi:10.1093/annonc/mdx225

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*

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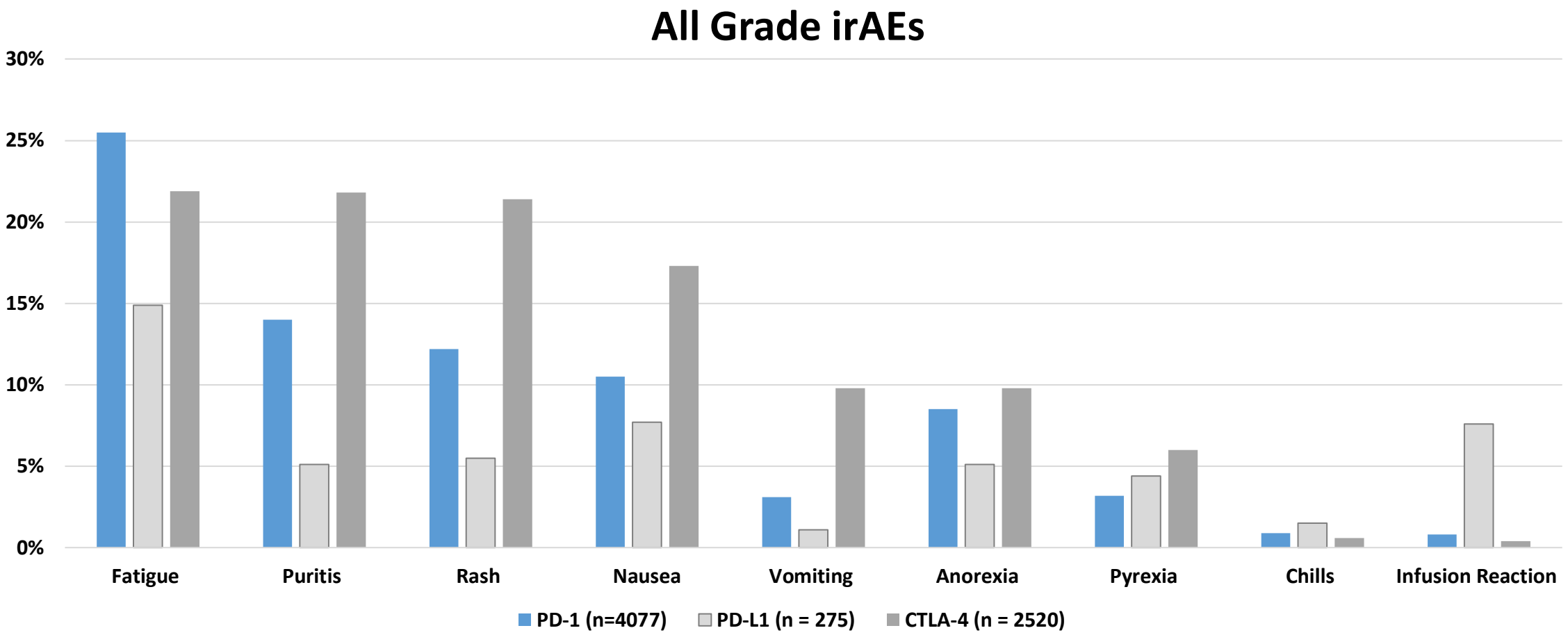
NCCN Version 4.2021

ASCO special articles

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update

Bryan J. Schneider, MD[1]; Jarushka Naidoo, MD[2,3]; Bianca D. Santomasso, MD, PhD[4]; Christina Lacchetti, MHSc[5]; Sherry Adkins, MS[6]; Milan Anadkat, MD[7]; Michael B. Atkins, MD[8]; Kelly J. Brassil, PhD[6]; Jeffrey M. Caterino, MD, MPH[9]; Ian Chau, MD[10]; Marianne J. Davies, DNP[11]; Marc S. Ernstoff, MD[12]; Leslie Fecher, MD[1]; Monalisa Ghosh, MD[13]; Ishmael Jaiyesimi, DO, MS[14]; Jennifer S. Mammen, MD, PhD[15]; Aung Naing, MD[6]; Loretta J. Nastoupil, MD[6]; Tanyanika Phillips, MD[16]; Laura D. Porter, MD[17]; Cristina A. Reichner, MD[18]; Carole Seigel, MBA[19]; Jung-Min Song, MSN, RN, CNS[20]; Alexander Spira, MD, PhD[21]; Maria Suarez-Almazor, MD[6]; Umang Swami, MD[22]; John A. Thompson, MD[23]; Praveen Vikas, MD[24]; Yinghong Wang, MD[6]; Jeffrey S. Weber, MD, PhD[25]; Pauline Funchain, MD[20]; and Kathryn Bollin, MD[26]

Side Effect Profiles Vary by ICI Class



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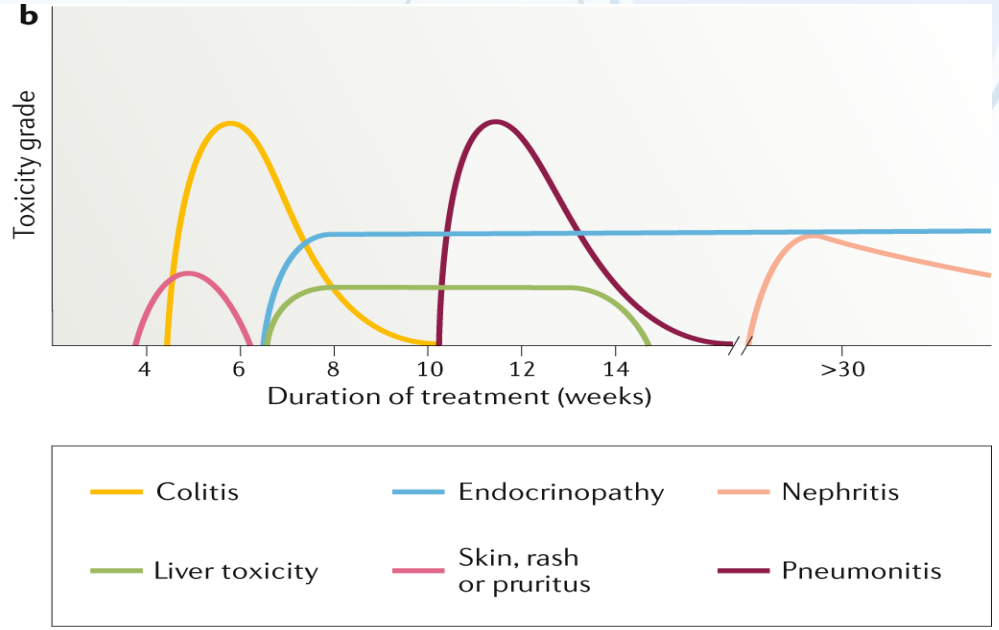
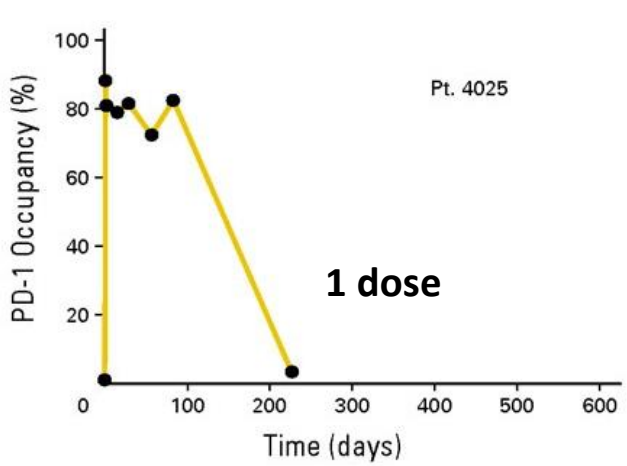
Khoja et al. 2017. Annals of Onc

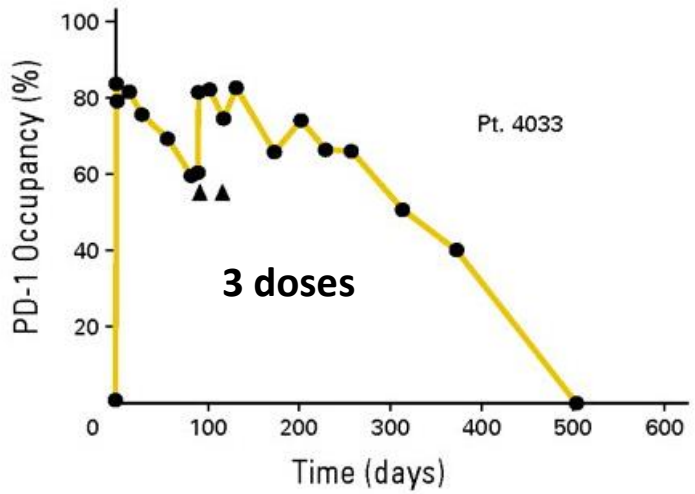
Kinetics of most common irAEs



- Most occur within 12 weeks after initiation of ICI
  - Median 40 days
- First onset of irAE documented within days to as long as 1 year AFTER discontinuation of treatment
- *Biologic effects persist long after drug clearance*

Nivolumab Target Occupancy





Martins et al. 2019. Nat Rev Clin Onc
Boutros et al. 2016. Nat Rev Clin Onc
Haanen et al. 2017. Ann Onc
Brahmer et al. 2010. JCO. ; Raschi et al. 2020. Target Oncol.

Case Discussion

Navigating Pembrolizumab Side Effects in the Neoadjuvant Setting

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CASE DISCUSSION

- 35 year old female notices RIGHT nipple retraction and a large breast mass. Imaging confirms a 4.0cm subareolar mass, with at least 2 concerning axillary nodes. Biopsy confirms triple negative breast cancer in the breast and node. Staging scans are negative for metastatic disease.

- She starts neoadjuvant chemotherapy with Pembrolizumab + Chemotherapy.
  - *Counseled about potential impact of ICIs/Chemotherapy on fertility*

- During cycle 1, she develops flushing and a “funny feeling” in her chest 5 minutes into the pembrolizumab infusion.

Infusion Reactions from ICIs

- **Infusion reactions include**: fever/sweating, chills/rigors, urticaria/pruritis, angioedema, flushing, headache, hyper/hypotension, shortness of breath, coughing/wheezing, hypoxia, dizziness/syncope

- **Infusion Reactions are rare (<10%) and generally low grade**
  - Anti-PD1 (Pembrolizumab) = All grade ~1-2% with 0.2% ≥G3
  - Anti-PD-L1 (Atezolizumab) = All grade ~1-2% (up to 25% with avelumab) with 0.2 to 0.4% ≥ G3
  - Anto-CLTA4 (Ipilimumab) = All grade ~2 to 6% with 0% ≥G3

- **Most reactions will occur during first or second infusion, are self-limited and resolve with slowing or stopping the infusion**
  - If resume ICI, consider half the rate*
  - If systemic treatment needed, consider premedications with Tylenol, Benadryl +/- H2 blocker during future infusions

Schneider et al. 2022. JCO.; Brahmer et al. 2022. JITC
Infusion Reaction Rates from FDA Package Inserts for each respective agent

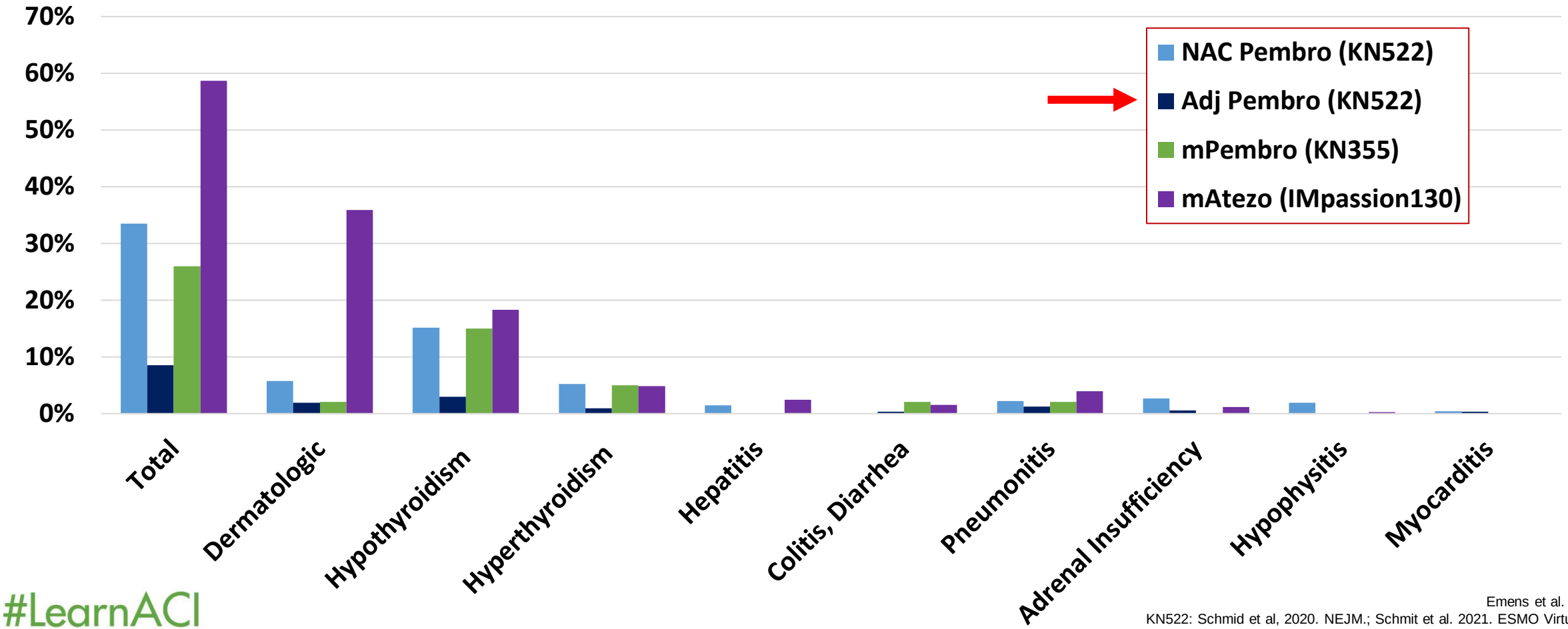
CASE DISCUSSION CON'T

- The infusion rate of pembrolizumab is halved and the patient tolerated subsequent pembrolizumab treatments without issue.

- During cycle 2 of Pembrolizumab/Paclitaxel/Carboplatin, her routine labs show TSH < 0.004 and Free T4 is high.

  - She denied tachycardia, diarrhea, sweating, anxiety, tremor, weight loss or emotional lability.

Most Common irAEs (all grade) in Breast Cancer



Emens et al. JITC 2021
KN522: Schmid et al, 2020. NEJM.; Schmit et al. 2021. ESMO Virtual Plenary
KN355: Cortes, J. Lancet. 2020; Rugo et al. ESMO Congress. 2021.
IM130: Schmid P et al. N Engl J Med 2018; Schmid P et al. Lancet Onc 2020

ICI-Induced Thyroid Dysfunction

- **Hypothyroidism (12%) and Hyperthyroidism (5%) are common irAEs in breast cancer patients (*almost all G1, G2*)**
  - Routine evaluation of TSH, Free T4 every 4 to 6 weeks during ICI therapy and every 6 to 12 months after ICI therapy
  - Median time to thyrotoxicosis is 5 weeks, to hypothyroidism is 10 weeks

- ICIs can lead to thyroiditis/thyrotoxicosis but rarely lead to Grave's Disease
  - Symptomatic treatment with beta blocker but generally methimazole is not indicated
  - **Hyperthyroidism often evolves into hypothyroidism**
    - Levothyroxine 1.6 µg/kg/day for young healthy patients; patients ≥ 65yo, 25-50 µg/day
    - Once repletion started, can resume ICI therapy with close monitoring of TSH

Schneider et al. 2022. JCO.; Brahmer et al. 2022. JITC

CASE DISCUSSION CON'T

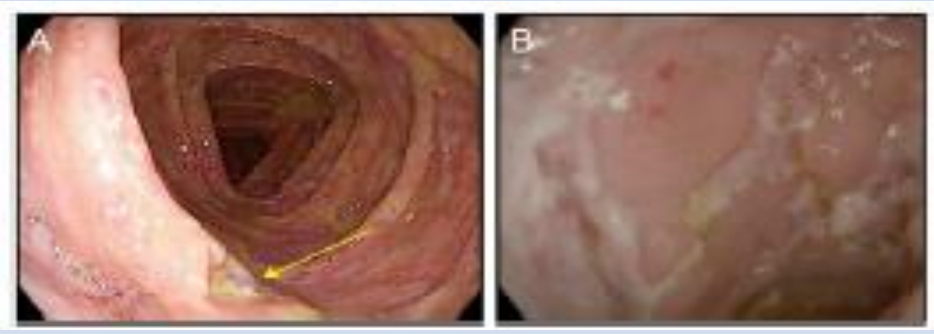
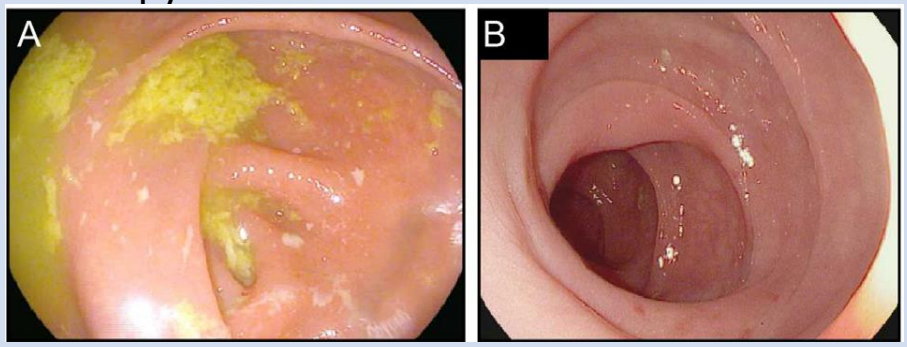
- TSH rechecked during cycle 4 of Pembrolizumab + chemotherapy and was now 100. Levothyroxine started. Progressive fatigue improved within weeks.

- **During C3 of AC, she developed diarrhea. At clinic visit prior to C4 she reported 12 liquid stools per day (G3) for the last 4 days.**
  - Rule out infectious causes: Clostridium difficile, CMV, GI stool panel (O&P), COVID
  - Labs and Imaging: fecal calprotectin, Abdominal CT
  - Supportive Care: IVF, electrolyte replacement, Imodium prn (avoid G3+)
  - Early consultation to GI for potential sigmoidoscopy
  - Early initiation of steroids
    - median time until resolution of ICI-induced colitis = 16 days
    - Severe irAEs unresponsive to steroids within 48 to 72 hours, consider addition of other immunomodulators

Boutros et al. 2016. Nat Rev Clin Onc;
Haanen et al. 2017. Ann Onc
NCCN 2019 Immunotherapy-Related Toxicities;
Dougan M. 2017. Frontiers in Immunol.
Abu-Sbeih et al. 2018. JITC

Boutros et al. 2016. Nat Rev Clin Onc;
Haanen et al. 2017. Ann Onc
NCCN 2022 Immunotherapy-Related Toxicities;
Dougan M. 2017. Frontiers in Immunol.

Gastrointestinal Toxicity for ICIs

	CTLA-4	PD-1/L1
Clinical Symptoms	Watery diarrhea (25-55%) due to enterocolitis (10-20%) with ≤ 25% with extra-intestinal manifestations such as arthralgias; severe colitis (8%)	Diarrhea (10-20%) followed by nausea/vomiting and abdominal pain. Severe colitis is rare (< 2.5%) ***In Breast cancer, all grade colitis 2.5% with 0.45% high grade***
Fatal Colitis	Colonic perforation 1-6%; ~1% death from ipilimumab-induced enterocolitis	Colonic perforation or death are very rare.
Flex Sigmoidoscopy	Patchy erythema (50%), loss of vascular pattern, erosions, ulcerations in distal colon and sigmoid 	Isolated colitis or enteritis, often appears normal on endoscopy 
Biopsy	Severe inflammation, lymphocytic infiltration, apoptotic bodies, cryptitis, crypt abscess	Lymphocytic colitis

General* Management of irAEs

	Grade 1	Grade 2	Grade 3	Grade 4
ICI Status	Continue, could consider holding	Strongly consider holding	Discontinue; Consider restarting once improves	Discontinue, except for endocrinopathies
Supportive Care	Topical creams, loperamide, consider imaging and labs	Repeat labs, Imaging, Topical creams, loperamide	Close monitoring with repeat labs, Imaging, Topical creams	
Biopsy	No	Consider skin biopsy	Consider biopsy	
Systemic Therapy	---	Oral or IV steroids	High Dose IV steroids, consider infliximab, mycophenolate, vedolizumab, IVIG	
Other	Consider specialist consultations	Specialist consultations; infectious workup	Specialist consultation; infectious workup	

Mild: *Prednisone 0.5-1mg/kg/day*
Moderate or Severe*: Methylprednisolone 1-2 mg/kg/day*
[75mg Prednisone = 60mg Methylprednisolone]

Schneider et al. 2022. JCO.; Brahmer et al. 2022. JITC.
Downey et al. 2007. Clin Cancer Res; Horvat et al. 2015. JCO.
Haanen et al. 2017. Ann Onc; Hinrichs et al. 2005. J Immunother
Schadendorf et al. 2017. JCO; Weber et al. 2017. ASCO Conf

Steroid Refractory ICI-Induced Colitis

- **Infliximab:** Anti-TNF-α antibody (anti-neutrophil): 5mg/kg
  - Early intervention may be beneficial for patients unresponsive to steroids (G3/G4)
  - Do not use in hepatitis
  - Duration unclear; typically 1 to 3 doses at 2 week intervals (week 0, 2 and 6)

- **Vedolizumab**; α4β7 integrin antagonist (anti-T-cell): 300mg
  - Blocks α4β7 integrin interaction with mucosal addressing cell adhesion molecule-1 and inhibits migration of T-cells across the endothelium
  - FDA approved for UC and Crohn's
  - Duration unclear, median doses 3 (week 0, 2 and 6)

- **Other**: fecal microbiota transplant, JAK inhibitor tofacitinib, IL-12 inhibitor ustekinumab

Schneider et al. 2022. JCO.; Brahmer et al. 2022. JITC
Boutros et al. 2016. Nat Rev Clin Onc. ; Haanen et al. 2017. Ann Onc.
Brahmer et al. 2018. JCO.; Abu-Sbeih et al. 2019. JITC.

Treating irAEs

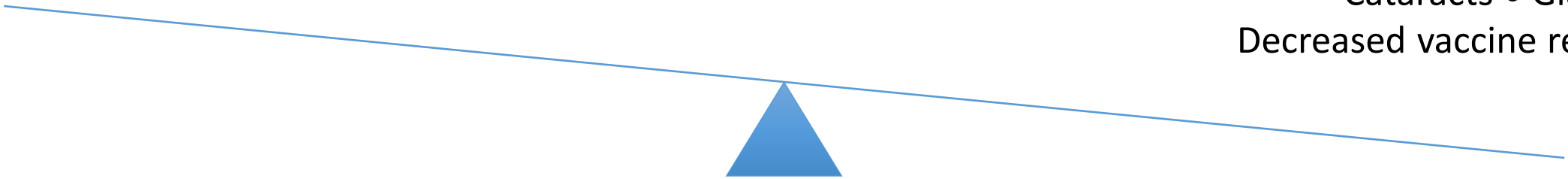
- Long-term (>4-6 weeks) treatment sometimes needed to prevent recurrence
  - Rapid steroid tapers are not advised (*once G1/resolved, taper over 4-6 weeks*) especially with pneumonitis and hepatitis
  - Consider prophylaxis for opportunistic infections
    - PJP → Start if ≥20 prednisone equivalent for more than 4 weeks
    - Fungal → Start fluconazole if ≥20mg prednisone equivalent for more than 6-8 weeks
  - Consider gastrointestinal prophylaxis with proton pump inhibitors or H2 blockers in patients with higher risk of gastritis (NSAIDs, anticoagulation)
  - Consider Vitamin D and Calcium supplementation to decrease risk of osteoporosis if patient is expected to receive an extended course of steroids

Downey et al. 2007. Clin Cancer Res; Horvat et al. 2015. JCO.
Haanen et al. 2017. Ann Onc; Hinrichs et al. 2005. J Immunother
Schadendorf et al. 2017. JCO; Weber et al. 2017. JCO

Long Term Effects of Steroids

↓ Cytokines (IL-1, IL-2, IL-6, IL-8, TNF)
↓ T cells (all types)
↓ Immature Natural Killer (NK) cells
↑ Mature NK cells
↓ Circulating DCs
↓ Endothelial dysfunction
↓ Vascular permeability

Hyperglycemia
Skin bruising/thinning
Sleep problems • Mood disturbances • Acne
Bone fractures
Infection • Myopathy • Osteonecrosis
Osteoporosis
HPA insufficiency
Cushing syndrome • Weight gain
Fluid retention • Insulin resistance Gastric ulcer • Hirsutism
Cataracts • Glaucoma
Decreased vaccine response



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Curtis et al. Arthritis & Rheum. 2006
Van der Goes, Jacobs, Bijlsma. Arthritis Res & Ther. 2014

NCCN 4.2021 Guidelines

*May resume once patients on ≤ Prednisone 10mg daily

	Rechallenge (≤ Grade (G) 1)	Do not Rechallenge
Skin	Rash, pruritis	**G3/4** Severe, life threatening bullous disease
Endocrine	After hormone repletion started	Symptomatic pituitary swelling
GI	G2/3 PD-1/L1 colitis*	CTLA4 colitis, **G4 colitis**
Liver	G2 transaminitis without elevated bilirubin*	**G3/4** hepatitis
Pancreatitis	Symptomatic, G2	**G3/4** pancreatitis
Lung	G1/2, off steroids	**G3/4** pneumonitis
Renal	G1/2 renal irAEs*	**G3/4** proteinuria
Eye	G1/2 ocular irAEs	**G3/4** uveitis, episcleritis
Neurologic	G1 myasthenia gravis, G1/2 peripheral neuropathy, mild aseptic meningitis	GBS, encephalitis, transverse myelitis, **G2+** myasthenia gravis,
Cardiovascular	G1 myocarditis	**G2-4** myocarditis
Musculoskeletal	Resume after stabilization, management	Severe inflammatory arthritis that impairs ADLs

CASE DISCUSSION CON'T

- **Infectious workup was positive for C.Diff Diarrhea** which resolved after oral vancomycin therapy.
  - She completed neoadjuvant Pembrolizumab + chemotherapy without additional irAEs
  - **Pre-surgery **random cortisol** was normal range**
  - At surgery she had residual cancer (RCB1)

- 18 months after she completed adjuvant pembrolizumab, she developed shortness of breath.
  - CT Chest showed multiple lung nodules and a pleural effusion concerning for metastatic disease.
  - Biopsy of a lung nodule confirmed metastatic TNBC which is PDL1+ (CPS 20)

- What's her first line therapy in the metastatic setting?

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  - ✓General Management of irAEs
  - ✓Rechallenge with ICIs

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