Management of Adverse Events of Check Point Inhibitors and Antibody Drug Conjugates in Solid Tumors

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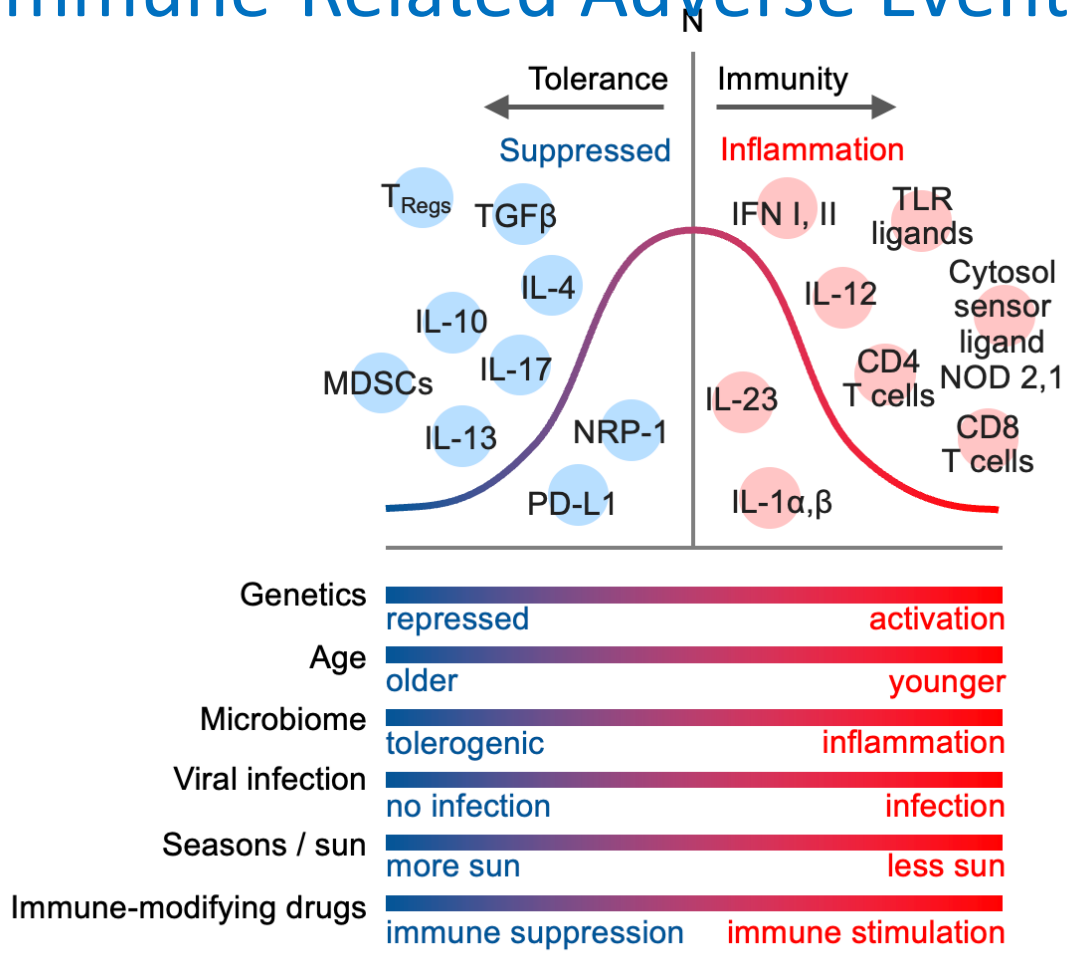
Immune-Related Adverse Events with Checkpoint Inhibitors

Objectives

Immune-Related Adverse Events With Checkpoint Inhibitors

- Review the spectrum of immune mediated adverse events (irAEs) induced by immune checkpoint inhibitors (ICIs)
- Review the kinetics of irAEs with ICIs
- Discuss the effect of baseline corticosteroid use on outcome with ICIs
- Review national guidelines for the management of irAEs

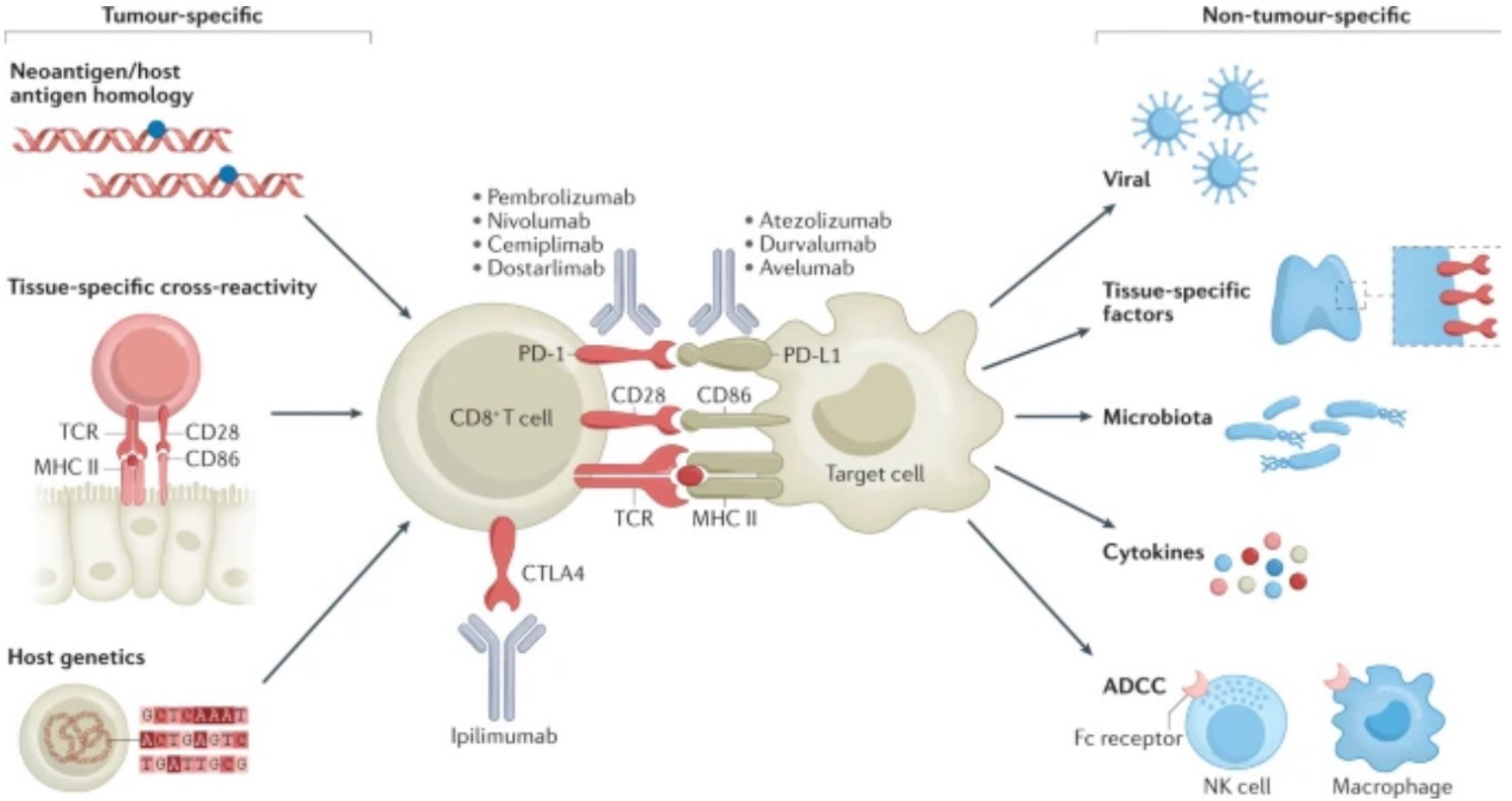
The Cancer–Immune Set Point: Multivariate Factors Influence Tolerance and Immunity Immune-Related Adverse Events With Checkpoint Inhibitors



- Cancer immunity is influenced by a complex set of tumor, host and environmental factors[1]
- The cancer-immune set point is considered the threshold that must be surpassed for a person with cancer to respond to immunotherapy and varies between individuals

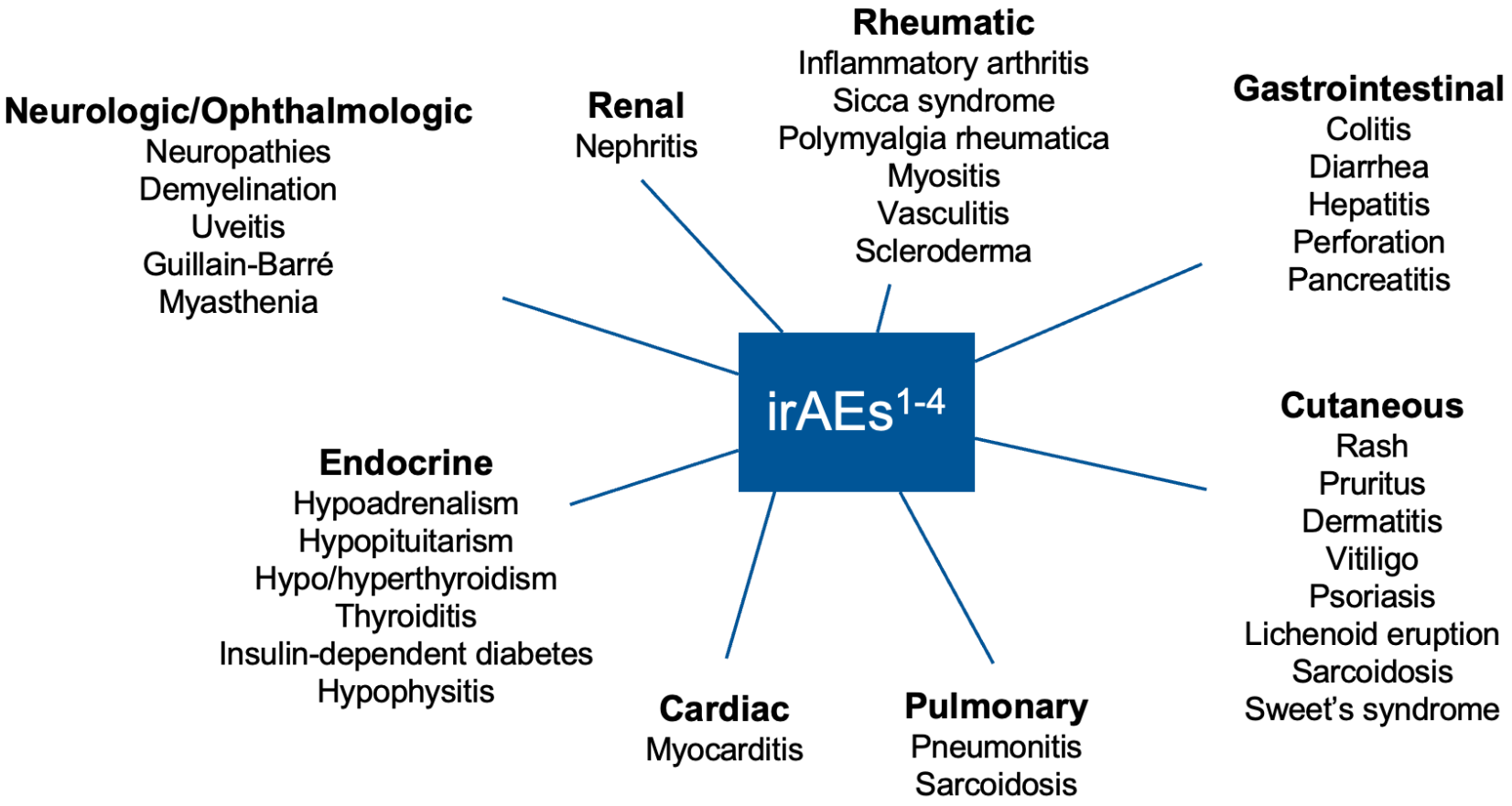
1. Chen DS and Mellman I. *Nature*. 2017;541:321-330

Mechanism of immune-related adverse events



Johnson, D.B., Nebhan, C.A., Moslehi, J.J. *et al.* Immune-checkpoint inhibitors: long-term implications of toxicity. *Nat Rev Clin Oncol* **19**, 254–267 (2022). https://doi.org/10.1038/s41571-022-00600-w

Spectrum of Immune-Related Toxicities

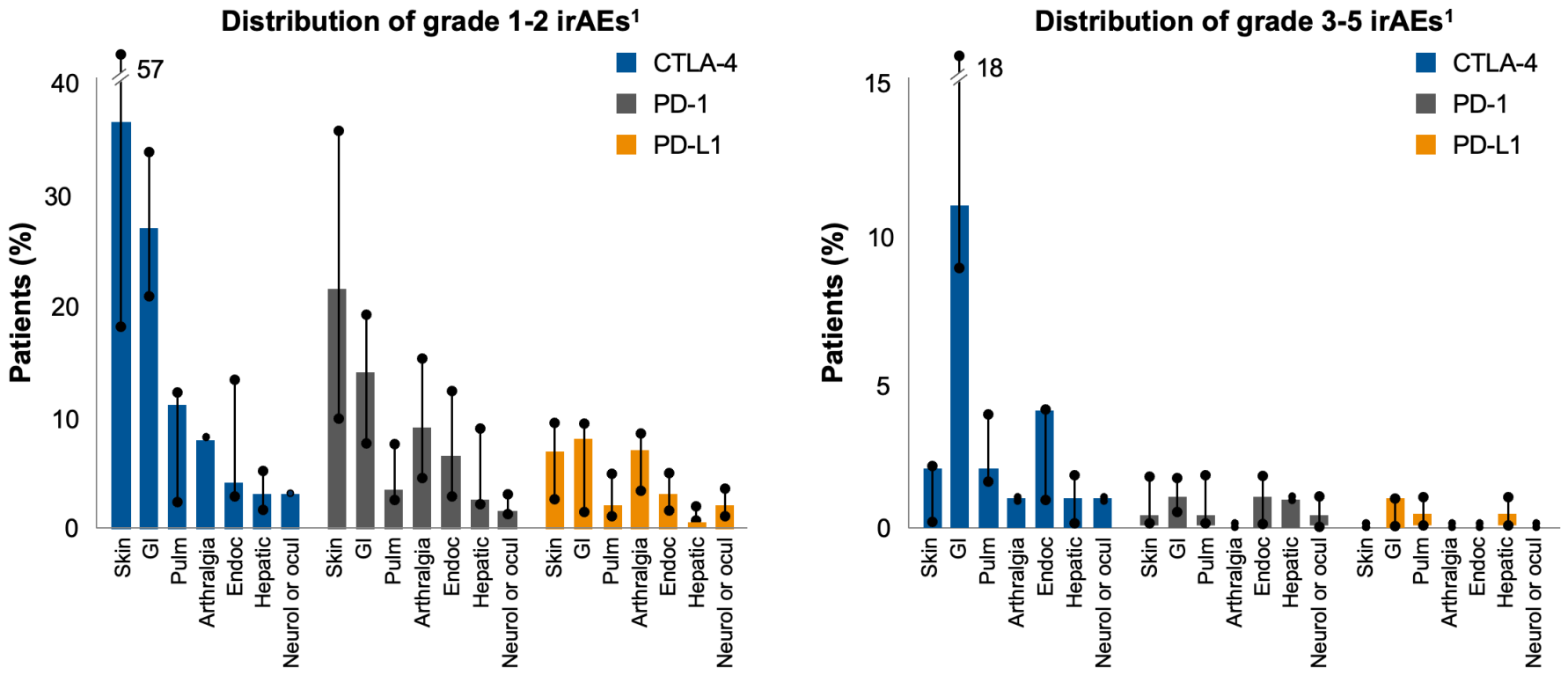


Not all toxicities are listed. 1. Abdel-Wahab N, et al. *Add Exp Med Biol*. 2017;995:155-174. 2. Calabrese LH, et al. *Nat Rev Rheumatol*. 2018;14:569-579. 3. Lemiale V, et al. *Ann Intensive Care*.2019;9:25. 4. Naidoo J, et al. *Ann Oncol*. 2015;26:2375-2391.

Frequencies of ICI - Induced irAEs

Frequencies of ICI - Induced irAEs

Immune-Related Adverse Events With Checkpoint Inhibitors



1. Michot JM, et al. *Eur J Cancer*. 2016;54:139-148.

Incidence of ICI -Induced Adverse Events – PD-1/PD-L1 Antagonists

All-grade AEs[1]

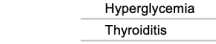
AE	Incidence (95% CI)
Fatigue	18.26 (16.49-20.11)
Pruritus	10.61 (9.46-11.83)
Diarrhea	9.47 (8.43-10.58)
Rash	9.31 (8.29-10.41)
Nausea	8.39 (7.46-9.39)
Decreased appetite	7.18 (6.36-8.06)
Hypothyroidism	6.07 (5.35-6.85)
Arthralgia	5.83 (5.15-6.59)
Asthenia	5.58 (4.92-6.31)
Pyrexia	4.77 (4.18-5.42)
Cough	4.17 (3.64-4.77)
Dyspnea	3.88 (3.38-4.45)
Anemia	3.84 (3.35-4.38)
Infusion-related reaction	3.63 (3.15-4.17)
Constipation	3.60 (3.12-4.13)

Overall mean incidence of all-grade AEs (1.66%)

Grade 3 or higher AEs[1]

AE	Incidence (95% CI)
Fatigue	0.89 (0.69-1.14)
Anemia	0.78 (0.59-1.02)
AST increased	0.75 (0.56-0.99)
Lipase increased	0.71 (0.51-0.98)
ALT increased	0.70 (0.52-0.93)
Pneumonitis	0.67 (0.50-0.89)
Diarrhea	0.59 (0.45-0.77)
Colitis	0.47 (0.34-0.65)
GGT increase	0.47 (0.30-0.69)
Hepatitis	0.43 (0.30-0.62)
Dyspnea	0.42 (0.30-0.59)
Lymphopenia	0.40 (0.26-0.60)
Hyponatremia	0.39 (0.25-0.59)
Asthenia	0.34 (0.25-0.48)
Amylase increased	0.30 (0.17-0.47)

Overall mean incidence of grade 3 or higher AEs (0.11%)



- Systemic review and meta-analysis including 125 clinical trials and 20,128 patients
- Overall AE rates:
  - All-grade: 66.0%
  - ≥ Grade 3: 14.0%
- Overall incidence of treatment-related death was 0.45%

All-grade irAEs[1]

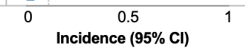
AE	Incidence (95% CI)
Endocrine dysfunction	
Hypothyroidism	6.07 (5.35-6.85)
Hyperthyroidism	2.82 (2.40-3.29)
Hyperglycemia	1.20 (0.91-1.55)
Thyroiditis	0.75 (0.52-1.04)
Adrenal insufficiency	0.69 (0.50-0.93)
Hypophysitis	0.60 (0.42-0.82)
Type 1 diabetes	0.43 (0.27-0.65)
Hypopituitarism	0.26 (0.12-0.50)
Autoimmune thyroiditis	0.20 (0.07-0.45)
Other disorder	
Diarrhea	9.47 (8.43-10.58)
AST increased	3.39 (2.94-3.89)
Vitiligo	3.26 (2.80-3.79)
ALT increased	3.14 (2.71-3.62)
Pneumonitis	2.79 (2.39-3.23)
Colitis	1.24 (0.99-1.54)
Bilirubin increase	1.05 (0.75-1.41)
Hepatitis	0.85 (0.64-1.10)
Uveitis	0.29 (0.15-0.51)

Overall mean incidence of all-grade AEs (1.66%)

Grade 3 or higher irAEs[1]

AE	Incidence (95% CI)
Endocrine dysfunction	
Hyperglycemia	0.24 (0.13-0.38)
Adrenal insufficiency	0.18 (0.10-0.30)
Type 1 diabetes	0.18 (0.10-0.30)
Hypophysitis	0.16 (0.09-0.27)
Hyperthyroidism	0.08 (0.04-0.13)
Hypopituitarism	0.07 (0.02-0.16)
Thyroiditis	0.04 (0.01-0.10)
Hyperthyroidism	0.04 (0.02-0.10)
Autoimmune thyroiditis	0.02 (0.00-0.09)
Other disorder	
AST increased	0.75 (0.56-0.99)
ALT increased	0.70 (0.52-0.93)
Pneumonitis	0.67 (0.50-0.89)
Diarrhea	0.59 (0.45-0.77)
Colitis	0.47 (0.34-0.65)
Hepatitis	0.43 (0.30-0.62)
Bilirubin increase	0.15 (0.07-0.28)
Uveitis	0.02 (0.00-0.07)
Vitiligo	0.02 (0.00-0.06)

Overall mean incidence of grade 3 or higher AEs (0.11%)



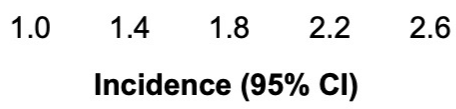
GGT, gamma-glutamyl transferase. 1. Wang Y, et al. *JAMA Oncol*. 2019. doi: 10.1001/jamaoncol.2019.0393

Wang Y, et al. *JAMA Oncol*. 2019. doi: 10.1001/jamaoncol.2019.0393.

AEs by Cancer Type

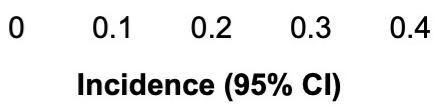
All-grade AEs[1]

Type	Mean Incidence (95% CI)	Overall mean incidence of all-grade AEs (1.66%)
Lung	1.55 (1.23-1.81)	
Gastrointestinal	1.61 (1.27-1.94)	
Other	1.64 (1.40-1.94)	
Genitourinary	1.67 (1.43-2.01)	
Mixed	1.68 (1.43-2.05)	
Hematologic malignant neoplasm	1.69 (1.39-2.35)	
Melanoma	1.72 (1.45-2.27)	
Overall	1.66 (1.47-1.86)	



Grade 3 or higher AEs[1]

AE	Mean Incidence (95% CI)	Overall mean incidence of grade 3 or higher AEs (0.11%)
Melanoma	0.09 (0.05-0.13)	
Lung	0.09 (0.06-0.13)	
Mixed	0.10 (0.07-0.15)	
Genitourinary	0.11 (0.08-0.15)	
Other	0.12 (0.09-0.17)	
Gastrointestinal	0.12 (0.08-0.19)	
Hematologic malignant neoplasm	0.13 (0.08-0.25)	
Overall	0.11 (0.08-0.14)	

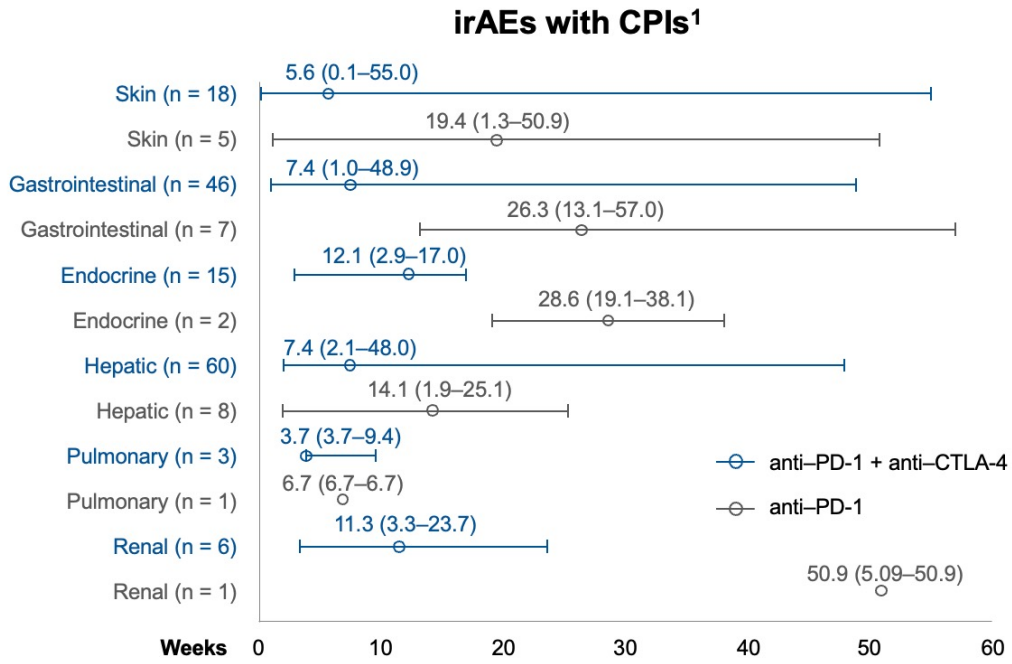


- The overall mean incidence of adverse events were similar across cancer types[1]

1. Wang Y, et al. *JAMA Oncol*. 2019. doi: 10.1001/jamaoncol.2019.0393

Kinetics of ICI - Induced irAEs

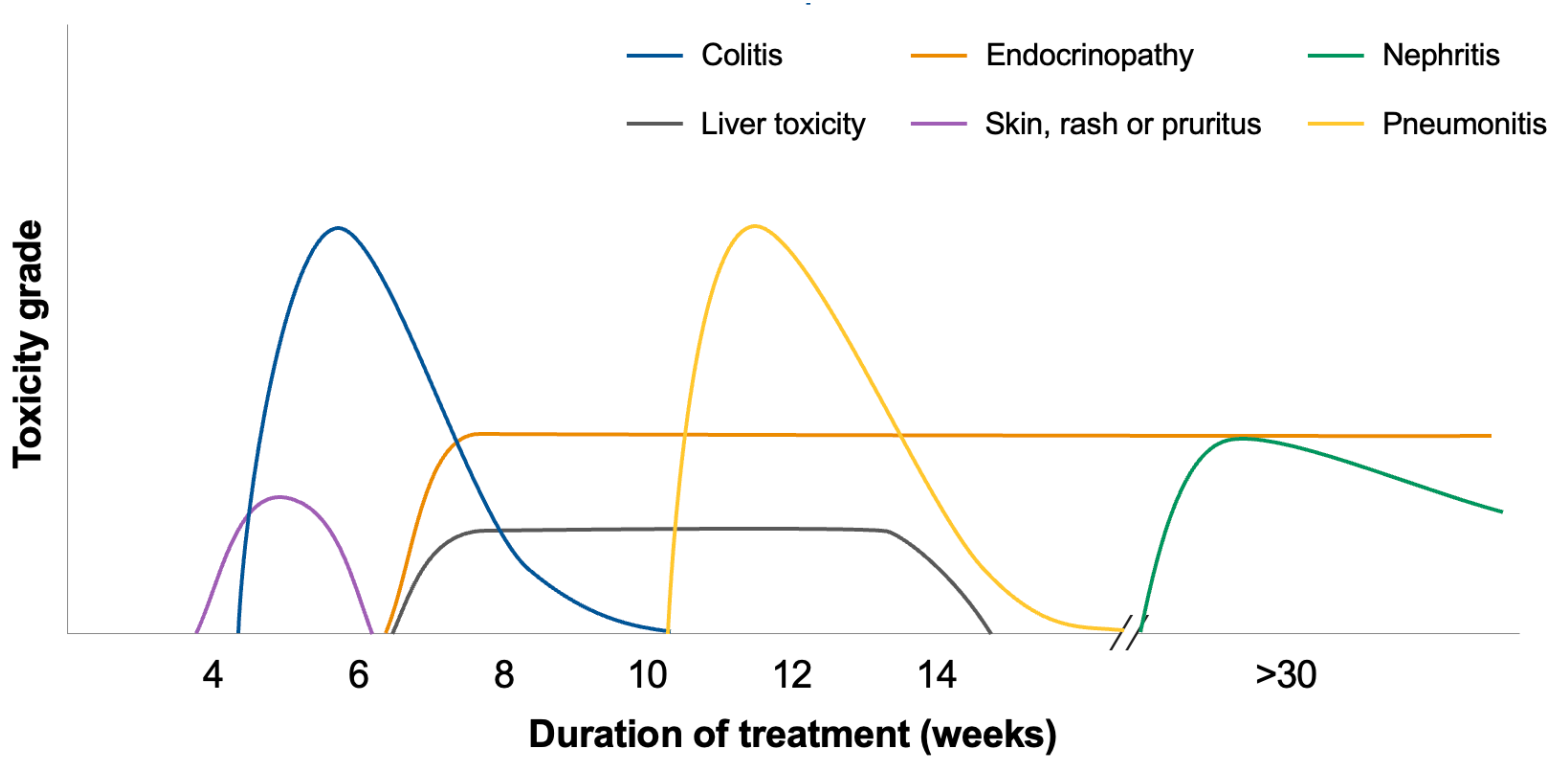
- Can occur months after treatment initiation, even after treatment discontinuation[2]
- More defined time window for some AEs than others[3]
- Onset generally earlier in patients who receive combination therapy[4]



1. Haanen JBAG, et al. *Ann Oncol*. 2017;28:iv119-iv142. 2. Michot JM, et al. *Eur J Cancer*. 2016;54:139-148. 3. Remon J, et al. *J Thorac Dis*. 2018;10:S1516-S1533 4: Naidoo J, et al. *J Clin Oncol*. 2017;35:709-717

Kinetics of ICI - Induced irAEs – PD-1/PD-L1 Antagonists

- Kinetics of ICI - Induced irAEs – PD-1/PD-L1 Antagonists



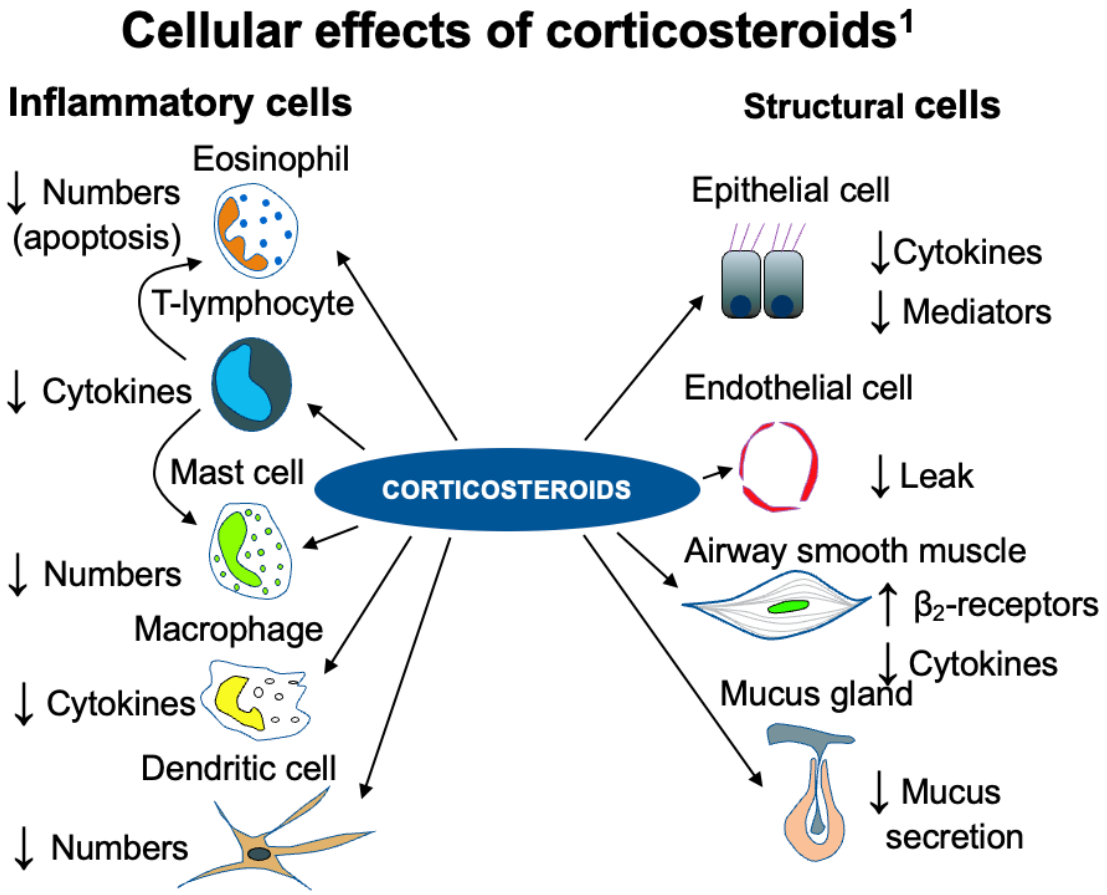
Martins et al. Nat Rev Clin Oncol 2019;16:563-580

Clinical Course of Pneumonitis With Anti–PD-1/PD-L1 Therapy[1]

- 915 patients received anti–PD-1 or anti–PD-L1 as monotherapy or in combination with anti–CTLA-4[1]
  - Overall incidence of pneumonitis was 5%, with a greater incidence in patients who received combination therapy than in those who received monotherapy (10% vs 3%; $P < 0.001$)
  - Median 2.8 months (9 days to 19 months)[2]
  - Radiologic and pathologic features of pneumonitis were diverse
  - 100% of patients (5/5) who received an aTNF ± csDMARDs for worsening pneumonitis ultimately died
    - Pneumonitis (1), infections associated with immunosuppression (3), progressive cancer (1)

1. Naidoo J, et al. *J Clin Oncol*. 2017;35:709-717.
2. Owen CN et al. Delayed immune-related adverse events with anti-PD-1-based immunotherapy in melanoma. Ann Oncol. 2021 Jul;32(7):917-925. doi: 10.1016/j.annonc.2021.03.204. Epub 2021 Mar 30. PMID: 33798657.

Association Between Use of Corticosteroids and Outcomes



Corticosteroids have wide-ranging anti-inflammatory and other effects

Studies have shown similar clinical outcomes in patients who require immunosuppression to treat irAEs and in those who do not require treatment[2,3]

It is likely that corticosteroids inhibit at least some elements of effective antitumor responses[4]

In a literature review of 15 studies with 14,123 patients, corticosteroids decreased PFS and OS[2]

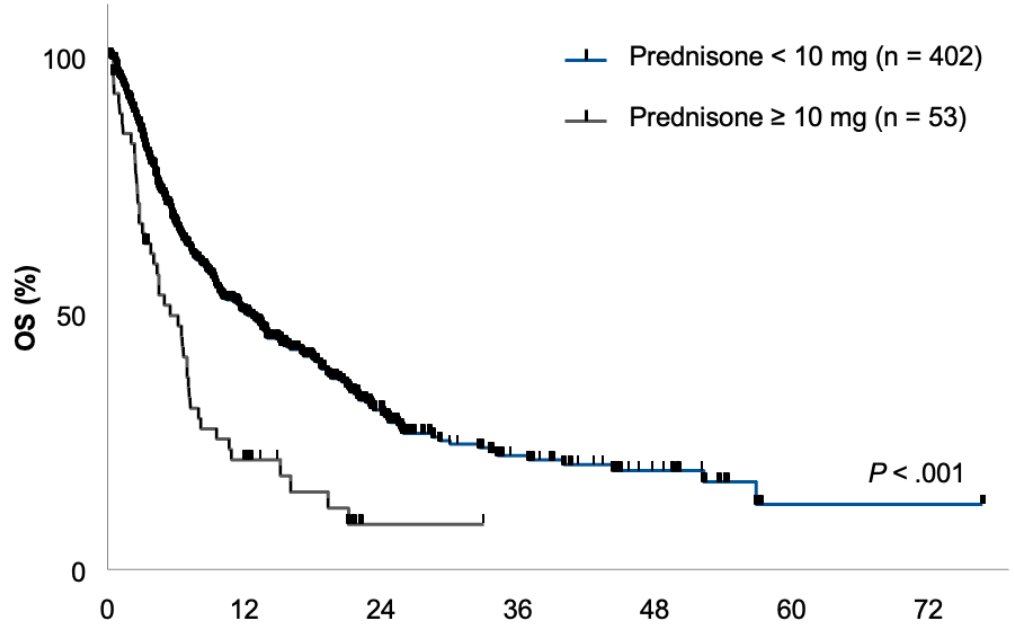
The specific cellular and molecular immune mechanisms underlying toxicity are unlikely to precisely match those that cause tumor rejection e.g. IFN-γ vs TNF-α[7]

Rheumatic irAEs often require high-dose corticosteroids and may require synthetic or biologic DMARD therapy[8,9]

1. Barnes PJ. *Pharmaceuticals*. 2010;3:514-540. 2. Weber JS, et al. *J Clin Oncol*. 2017;35:785-792. 3. Horvat TZ, et al. *J Clin Oncol*. 2015;33:3193-3198. 4. Faje AT, et al. *Cancer*. 2018;124:3706-3714. 5. Arbour KC, et al. *J Clin Oncol*. 2018;36:2872-2878. 6. Ricciuti B et al. *J Clin Oncol*. 2019. doi: 10.1200/JCO.19.00189. [Epub ahead of print] 7. Dougan M. *Front Immunol*. 2017;8:1547. 8. Calabrese LH, et al. *Nat Rev Rheumatol*. 2018;14:569-579. 9. Mitchell EL, et al. *Eur J Cancer*. 2018;105:88-102.
2. Jiarui Li, Kaili Yang, Lin Zhao, Chunmei Bai, and Zhao Sun Journal of Clinical Oncology 2020 38:15_suppl, e15234-e15234

Effect of Baseline Corticosteroid Use on Outcome with ICIs

- Retrospective review (N = 640)
- Baseline steroid dose > or = 10 mg prednisone equivalents (N = 90; 14%)
- Indication for corticosteroid use
  - Dyspnea – 33%
  - Fatigue – 22%
  - CNS mets – 19%
- Multivariate analysis (smoking history, PS, hx of CNS mets) - prednisone > or < 10 mg
  - PFS – 1.31 (95% CI 1.03 - 1.67)
  - OS – 1.66 (95% CI 1.28 – 2.16)
- Dose-related effect observed

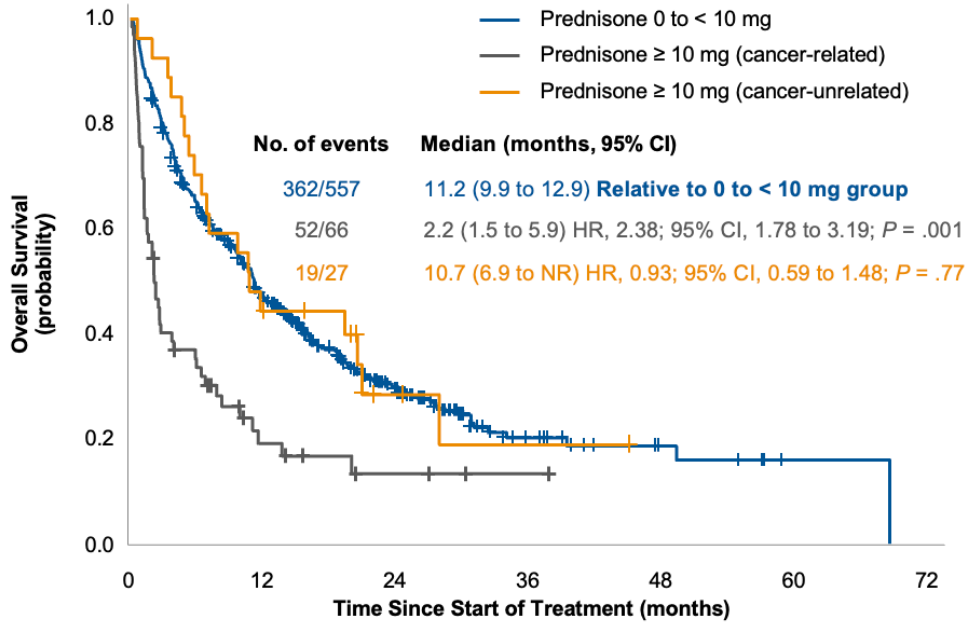


No. at risk:							
< 10 mg:	402	180	67	28	13	2	2
≥ 10 mg:	53	11	1	0	0	0	0

Response rates, progression-free survival (PFS), and overall survival (OS) of patients treated with programmed death-ligand 1 blockade on the basis of reported corticosteroid usage at Memorial Sloan Kettering Cancer Center (MSKCC) and Gustave Roussy Cancer Center (GRCC). Four hundred fifty-one of 455 patients were evaluable for response in the MSKCC cohort and 185 of 185 patients were evaluable for response in the GRCC cohort. CR, complete response; POD, progression of disease; PR, partial response; SD, stable disease. Arbour et al. J Clin Oncol 2018;36:2872-2878.

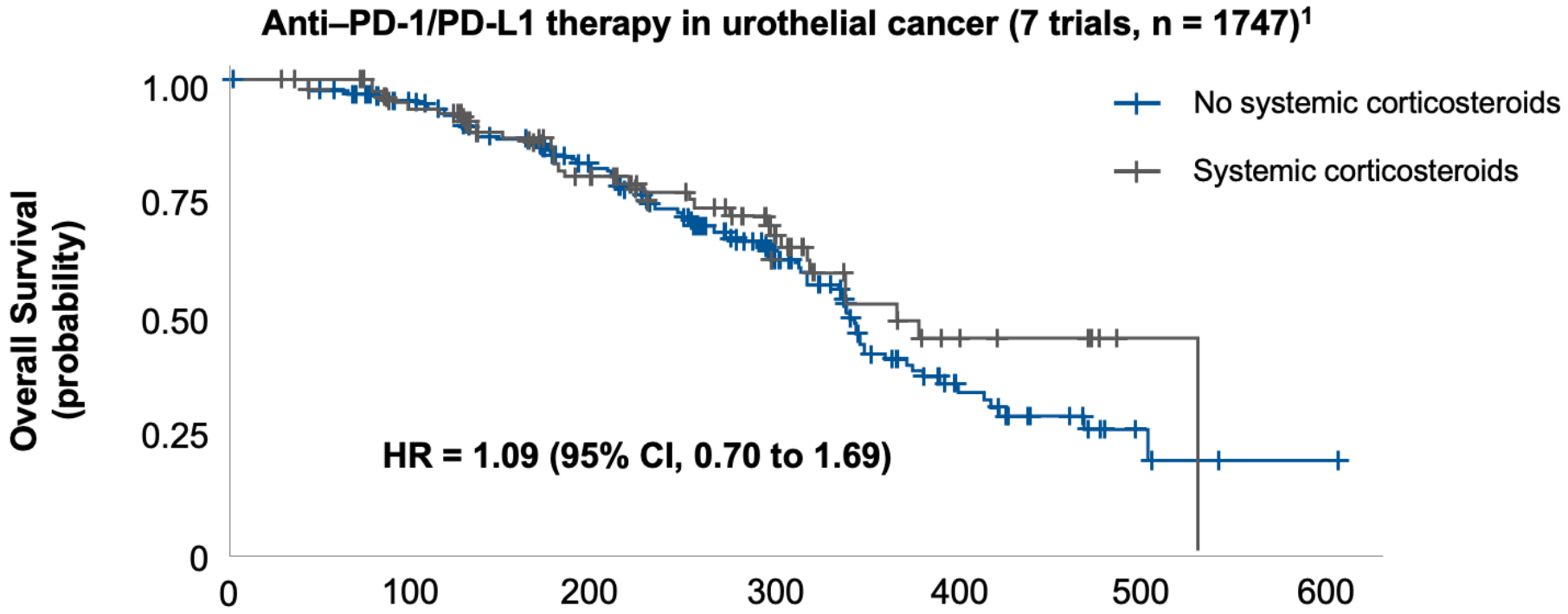
Effect of Baseline Corticosteroid Use on Outcome with ICIs

- Retrospective review (N = 650)
- Baseline steroid dose > or = 10 mg prednisone equivalents
- Malignancy-related steroid use (10.2%, N = 66)
  - CNS mets – 57.6%
  - Cancer related dyspnea – 18.2%
  - Pain from bone mets – 16.7%
  - Anorexia – 7.6%
- Malignancy unrelated steroid use (4.2%, N = 27)
  - Pneumonitis from prior chemo/CRT – 25.9%
  - COPD – 22.2%
  - Autoimmune disease – 18.5%
  - Iodinated contrast prophylaxis – 14.8%
- **No difference** in outcomes when isolating pts on corticosteroids for malignancy related indications



Outcomes to immunotherapy in the group of patients treated with $ 10 mg of prednisone for cancer-related palliative indications or cancer-unrelated indications compared with the group of patients receiving less than 10 mg of prednisone according to overall response rate, progression-free survival (PFS), and overall survival (OS). HR, hazard ratio; NR, not reached. Ricciuti et al. J Clin Oncol 2019;37:2872-2878

Association Between Use of Corticosteroids and Outcomes



No. at risk (No. censored)							
No systemic corticosteroids	267 (0)	232 (23)	160 (64)	72 (121)	20 (146)	4 (158)	1 (160)
Systemic corticosteroids	84 (0)	76 (3)	55 (13)	28 (33)	8 (46)	1 (53)	0 (53)

1. Maher VE, et al. *J Clin Oncol.* 2019. doi: 10.1200/JCO.19.00318.

Treatment Considerations

- Interprofessional collaboration regarding intensity and duration of concomitant therapies and compatibility with continued CPI therapy[1]
- Restarting CPIs after an irAE
  - Depends on severity of irAE and patient's tumor response status[2]
  - Retrospective studies have shown that irAEs associated with one class of agent (eg, anti–CTLA-4) may not recur with subsequent treatment (eg, anti–PD-1)[3]

1. Naidoo J, et al. *J Natl Compr Canc Netw*. 2019;17:712-720 2. Brahmer JR, et al. *J Clin Oncol*. 2018;36:1714-1768. 3. Menzies AM, et al. *Ann Oncol*. 2017;28:368-376.

ASCO Guidelines

- Patient and families should receive up-to-date information about immunotherapies, mechanism of action and possible irAEs prior to therapy.
- High level of suspicion when symptoms occur
- ICPi therapy should be continued with close monitoring for grade 1 toxicities except if neurologic, cardiac or hematologic.
- May consider holding ICPis for grade 2 toxicities and resume when symptoms/labs regress to grade 1. Steroids – initial dose 0.5-1 mg/kg/d of prednisone/equivalent
- Hold ICPis for grade 3 toxicities and initiate high dose steroids 1-2 mg/kg/d. If symptoms do not improve – infliximab
- When symptoms regress to < grade 1 – rechallenge with PD-1/PD-L1 monotherapy if previously combined with CTLA-4
- Grade 4 toxicities – permanent discontinuation of ICPis. Unless endocrinopathies if controlled with hormone replacement.

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update
Bryan J. Schneider et al. Journal of Clinical Oncology 2021 39:36, 4073-4126

Treatment of Patients With Pre-Existing Rheumatic Diseases

- Patients with pre-existing rheumatic diseases were not included in clinical trials of CPIs
- Up to 44% of patients with immune-mediated inflammatory diseases treated with CPIs will experience disease flares[1-4]
- 27% to 29% may develop de novo irAEs after receiving CPIs[1-3]
  - Small prospective study showed patients with pre-existing autoimmunity were more likely to have earlier onset of irAEs than those without pre-existing autoimmunity[4]
- Patients with rheumatic disease should be considered for preemptive referral to a rheumatologist prior to immunotherapy and early referral in the event of rheumatic irAEs[5]
- Rheumatic irAEs often require high-dose corticosteroids and may require synthetic or biologic DMARD therapy[5-6]
  - Risks and benefits of prolonged DMARD therapy (conventional and biologic)

1. Johnson DB, et al. *JAMA Oncol*. 2016;2:234-240. 2. Johnson DB, et al. *Cancer*. 2017;123:1904-1911. 3. Menzies AM, et al. *Ann Oncol*. 2017;28:368-376. 4. Danlos FX, et al. *Eur J Cancer.* 2018;91:21–29. 5. Calabrese LH, et al. *Nat Rev Rheumatol*. 2018;14:569-579.
6. Mitchell EL, et al. *Eur J Cancer*. 2018;105:88-102

Summary

- Incidences of irAEs are independent of cancer types, but anti–PD-1 and anti–PD-L1 therapies may be associated with different incidences of AEs[1]
- The relationship between development of irAEs and treatment outcome is evolving[2-4]
- Corticosteroids do not seem to impair outcomes when used to treat irAEs[5-6]
- Detailed consensus guidelines have been developed for the diagnosis and management of irAEs[7-10]; algorithms for personalized treatment of refractory irAEs have also been published[11]
- For patients with pre-existing rheumatic disease, pre-emptive referral to a rheumatologist prior to immunotherapy and early referral in the event of rheumatic irAEs should be considered[12]
- CPIs are generally well tolerated in patients with HIV, and Phase I and II clinical studies of patients with HIV treated with CPIs are ongoing[13]

1. Wang Y, et al. *JAMA Oncol*. 2019. doi: 10.1001/jamaoncol.2019.0393. [Epub ahead of print]. 2. Hodi FS, et al. Poster. ASCO. 2016 (abstract 9518). 3. Freeman-Keller M, et al. *Clin Cancer Res*. 2016;22:886-894. 4. Maher VE, et al. *J Clin Oncol.* 2019. doi: 10.1200/JCO.19.00318. [Epub ahead of print]. 5. Weber JS, et al. *J Clin Oncol*. 2017;35:785-792. 6. Horvat TZ, et al. *J Clin Oncol*. 2015;33:3193-3198 7. Brahmer JR, et al. *J Clin Oncol*. 2018;36:1714-1768. 8. Thompson JA, et al. *J Natl Compr Canc Netw*. 2019;17:255-289. 9. Haanen JBAG, et al. *Ann Oncol*. 2017;28:v119-iv142. 10. Puzanov I, et al. *J Immunother*. 2017;5:95. 11. Martins F, et al. *Lancet Oncol*. 2019;20:e54-64. 12. Calabrese LH, et al. *Nat Rev Rheumatol*. 2018;14:569-579. 13. Cook MR and Kim C. *JAMA Oncol*. 2019. doi: 10.1001/jamaoncol.2018.6737

Managing antibody drug conjugate toxicity

Objectives

Managing antibody drug conjugate toxicity

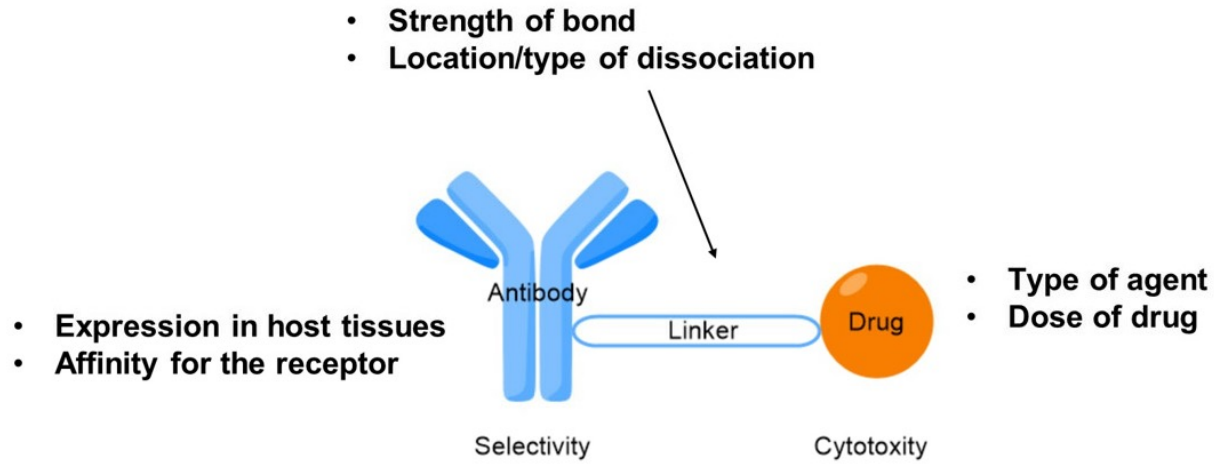
- Review the spectrum of adverse events induced by antibody drug conjugates (ADCs)
- Review the kinetics of adverse events with ADCs
- Review national guidelines for the management of ADCs

Overview – Antibody Drug Conjugates (ADCs)

- Therapeutic agents composed of monoclonal antibody (mAb) carrying a cytotoxic drug (payload) through a linker.

- Allows for selective delivery to tumor cells expressing the mAb target antigen, limiting the potential toxicities.

- Common targets include human epidermal growth factor receptor 2, human epidermal growth factor receptor 3, trophoblast cell surface antigen 2, c-MET, carcinomembryonic antigen-related cell adhesion molecule 5 and B7-H3.



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Overview of ADCs

T0	Target	payload	MOA
Trastuzumab emtansine	HER-2	maytansine	MTD
Sasatuzimab vedotin	TROP2	SN-38	TOPO1
Trastuzumab Deruxtecan	HER-2	deruxtecan	TOPO1
Enfortumab vedotin	Nectin-4	MMAE	MTD
Disitimab vedotin	HER-2	MMAE	MTD

Key questions:

1. Does target expression relate to the toxicity?
2. Do agents with similar payloads have similar toxicity?
3. What role dose the linker molecule play in toxicity?

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Alteration of toxicity by changing payload/target

- Does expression of target relate to the spectrum of toxicity?
  - Yes

- Do agents with similar payloads have similar toxicity?
  - Only partially

Adverse Event	RC48	Enfortumab Vedotin	Trastuzumab Deruxtecan
target	HER-2	Nectin-4	HER-2
Payload	MMAE	MMAE	TOPO-1
Neuropathy	+	+	-
↑ AST	+	-/+	-
↓ neutrophils	+	-/+	+
Rash	-/+	+	-
↑ glucose	+	+	-
Diarrhea	-	-	+
Pneumonitis	-	-	+

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Enfortumab Vedotin

Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma

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Article Figures/Media Metrics

29 References 426 Citing Articles Letters

March 25, 2021
N Engl J Med 2021; 384:1125-1135
DOI: 10.1056/NEJMoa2035807

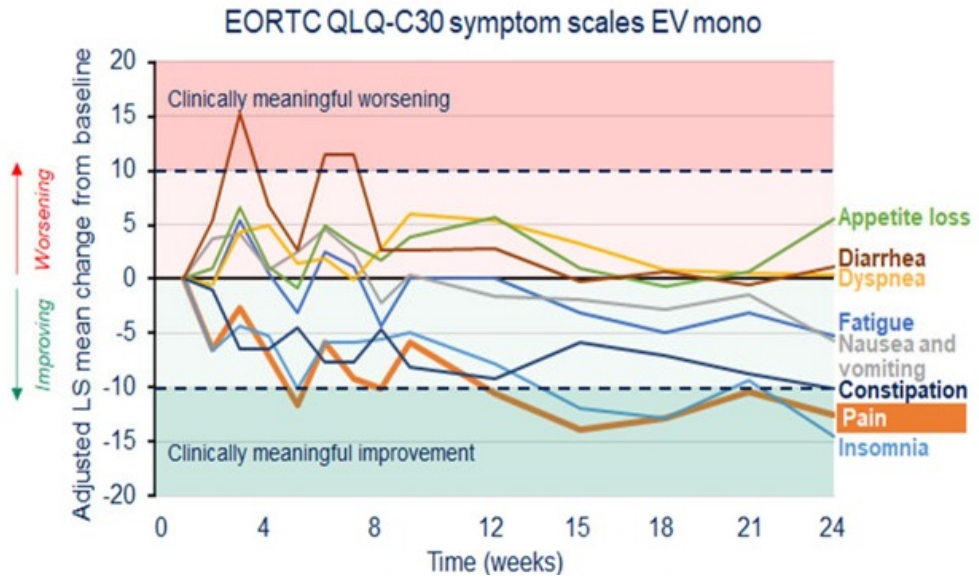
- Global, open-label, phase 3 trial for treatment of patients with locally advanced or metastatic urothelial carcinoma whom previously received platinum containing chemotherapy and had disease progression during/after treatment with PD-L1 or PD-1 inhibitor
- Received EV 1.25 mg/kg on D1, 8 and 15 of 28 day cycle or chemotherapy q3 weeks
- End point – overall survival
- Results:
  - OS 12.88 mo EV vs. 8.97 mo chemotherapy
  - PFS 5.55 mo EV vs. 3.71 mo chemotherapy

Powles et al. NEJM. 2021

Adverse event profile and QOL of Enfortumab Vedotin

Adverse Event	Enfortumab Vedotin N=296	
	All Grade	Grade ≥3
Any adverse event	**94%**	**51%**
Alopecia	45%	0
Peripheral sensory neuropathy	34%	3%
Pruritus	32%	1%
Fatigue	31%	6%
Decreased appetite	31%	3%
Diarrhea	24%	3%
Dysgeusia	24%	0
Nausea	23%	1%
Rash maculopapular	16%	7%
Anemia	12%	3%
Neutrophil count decreased	10%	6%
Neutropenia	7%	5%
White blood cell decreased	5%	1%
Febrile neutropenia	1%	1%

Treatment-Related Adverse Event of special interest	Enfortumab Vedotin N=296	
	All Grade	Grade ≥3
Skin Reactions[a]	**47%**	**15%**
Rash	44%	15%
Severe cutaneous adverse reactions[b]	20%	5%
Peripheral neuropathy	**46%**	**5%**
Sensory events	44%	4%
Motor events	7%	2%
Hyperglycemia	**6%**	**4%**

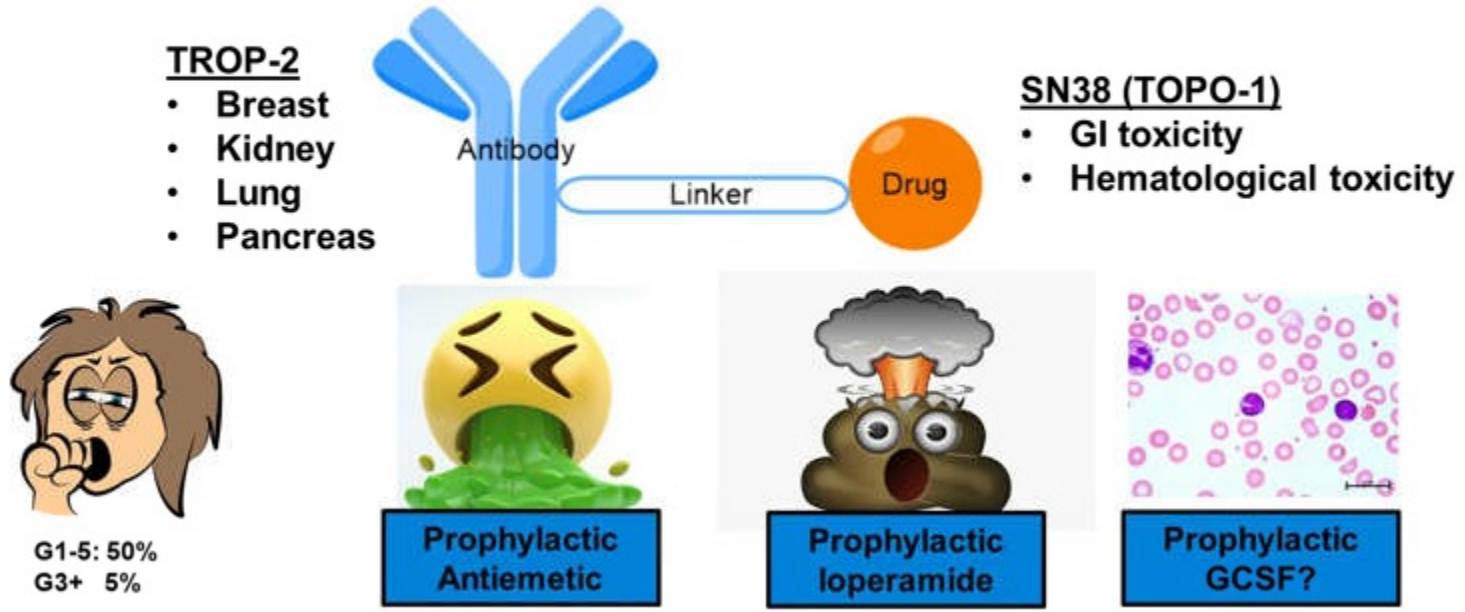


Rosenberg et al. NEJM. 2022
Powles et al. 2021. NEJM

Management of Toxicities

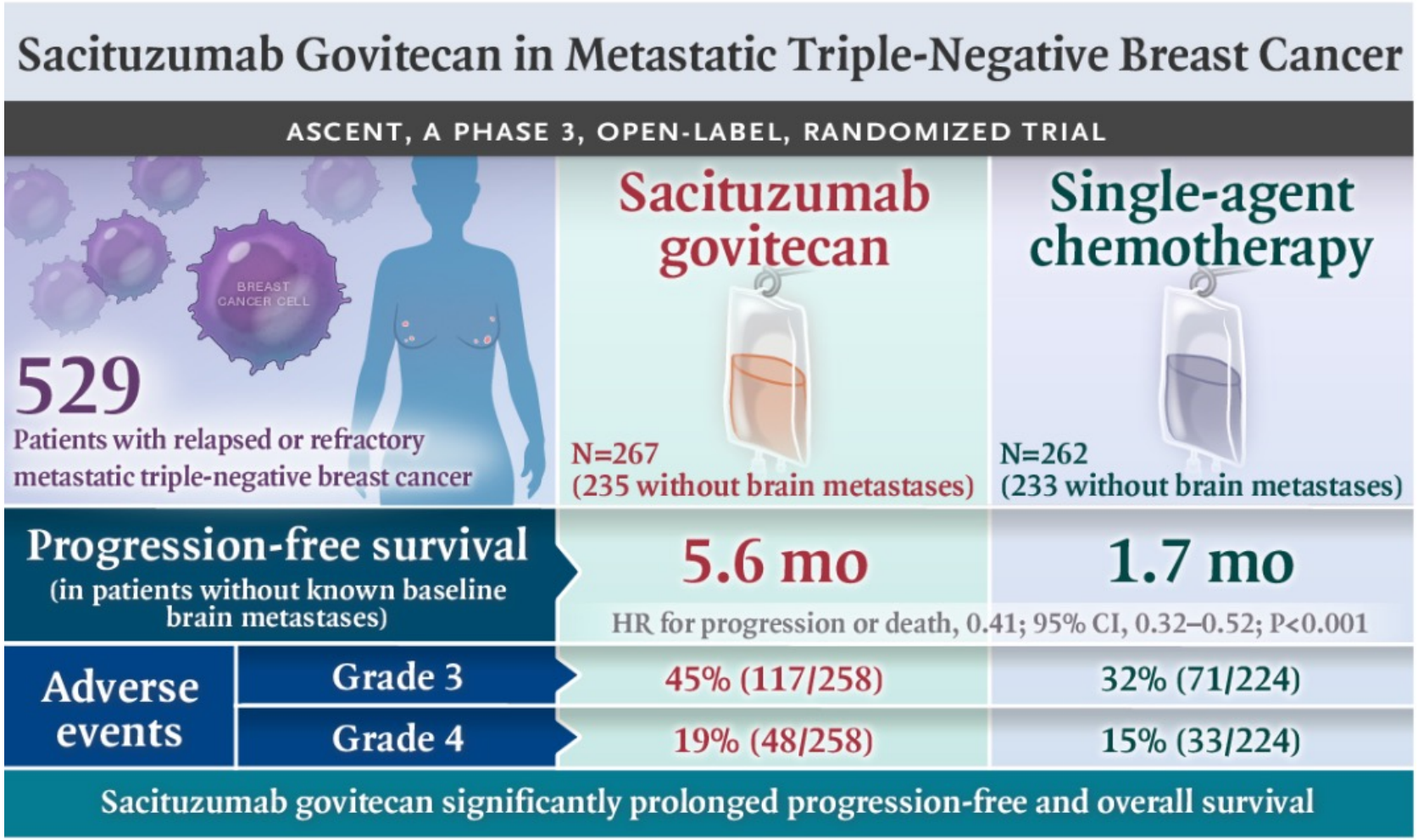
- Dermatologic – Skin Rash
  - Maculopapular rash, pruritus, skin necrosis, xeroderma, bullous dermatitis, palmar-plantar erythrodysesthesia, Steven-Johnson syndrome and toxic epidermal necrolysis
  - Tx: therapy interruption, dose reduction and/or discontinuation
- Hyperglycemia
  - Therapy interruption glucose >250 mg/dL
- Ocular side effects
  - Ophthalmology
- Peripheral neuropathy
  - Therapy interruption, dosage reduction or permanent discontinuation
- Pneumonitis
  - Permanent discontinuation

Sacituzumab govotecan



Powles ASCO 2023

ASCENT Trial



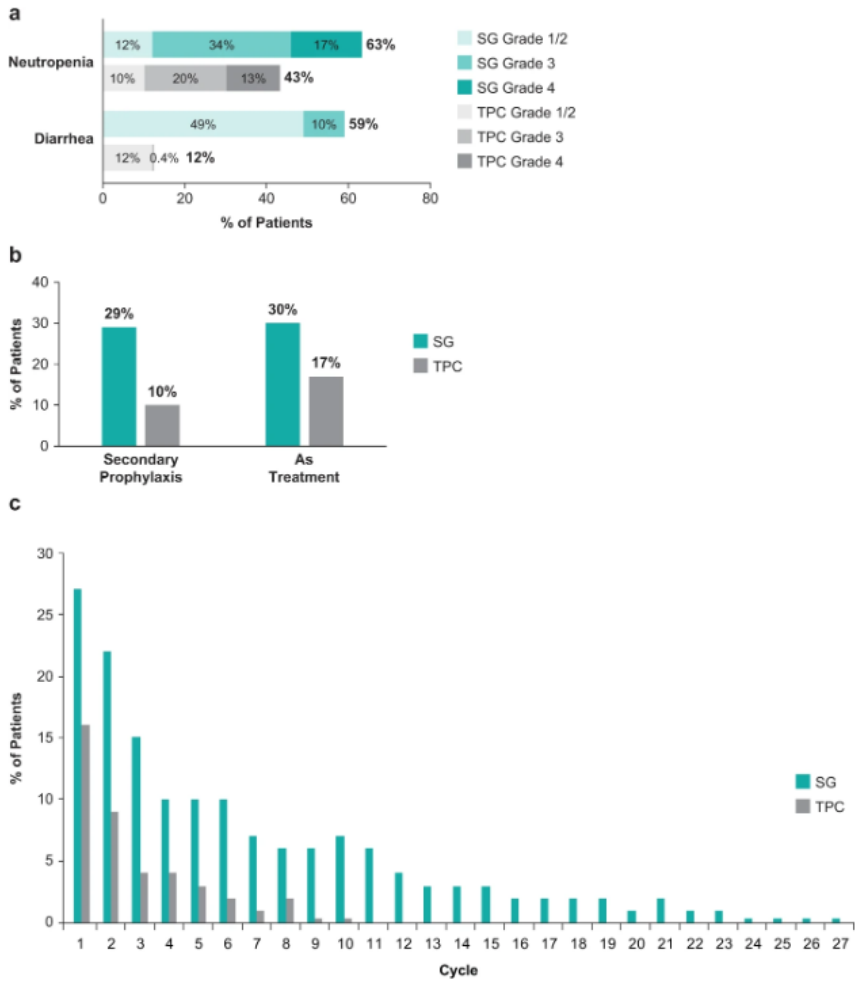
Bardia et al. NEJM. 2021

ASCENT Trial

Table 3. Summary of Treatment-Related Adverse Events in the Safety Population.*

Adverse Event	Sacituzumab Govitecan (N=258)			Chemotherapy (N=224)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	252 (98)	117 (45)	48 (19)	192 (86)	71 (32)	33 (15)
Hematologic event						
Neutropenia†	163 (63)	88 (34)	44 (17)	96 (43)	45 (20)	29 (13)
Anemia‡	89 (34)	20 (8)	0	54 (24)	11 (5)	0
Leukopenia§	41 (16)	23 (9)	3 (1)	25 (11)	10 (4)	2 (1)
Thrombocytopenia¶	14 (5)	2 (1)	2 (1)	25 (11)	3 (1)	0
Febrile neutropenia	15 (6)	12 (5)	3 (1)	5 (2)	4 (2)	1 (<1)
Gastrointestinal event						
Diarrhea	153 (59)	27 (10)	0	27 (12)	1 (<1)	0
Nausea	147 (57)	6 (2)	1 (<1)	59 (26)	1 (<1)	0
Vomiting	75 (29)	2 (1)	1 (<1)	23 (10)	1 (<1)	0
Constipation	44 (17)	0	0	32 (14)	0	0
Abdominal pain	29 (11)	3 (1)	0	9 (4)	1 (<1)	0
General disorders and administration-site conditions						
Fatigue	115 (45)	8 (3)	0	68 (30)	12 (5)	0
Asthenia	31 (12)	2 (1)	0	23 (10)	3 (1)	0
Skin and subcutaneous disorders: alopecia‖	119 (46)	0	0	35 (16)	0	0
Metabolism and nutrition disorders: decreased appetite	51 (20)	4 (2)	0	32 (14)	1 (<1)	0
Nervous system disorders**††	64 (25)	1 (<1)	0	53 (24)	5 (2)	0
Respiratory, thoracic, and mediastinal disorders††	41 (16)	5 (2)‡‡	0	17 (8)	1 (<1)	0
Musculoskeletal and connective-tissue disorders††	32 (12)	0	0	28 (12)	3 (1)	0
Infections and infestations††	30 (12)	6 (2)	1 (<1)	22 (10)	4 (2)	3 (1)

Bardia et al. NEJM. 2021



Rugo et al. Nature. 2022

Management of Toxicities

- Bone Marrow Suppression – Neutropenia & Febrile Neutropenia
  - Homozygous for UGT1A1*28 allele
  - Withhold if ANC <1,500/mm3 or neutropenic fever
  - Consider G-CSF for secondary prophylaxis
  - Initiate anti-infective treatment in patients with febrile neutropenia without delay
- GI toxicity - diarrhea
  - Withhold treatment until diarrhea resolved to grade 1 or dose reduction (may add anti-diarrheal if not infectious)
  - If nausea or vomiting – withhold treatment and resume with supportive measures when resolved to ≤ grade 1
  - If not controlled, may require dose reduction/discontinuation
- Hypersensitivity
  - Requires permanent discontinuation

Fam-trastuzumab deruxtecan

- Commonly used in breast cancer, colorectal cancer, gastric cancer and non-small cell lung cancer
- Used in locally advanced or metastatic disease
- Targets HER-2
- Common adverse events include bone marrow suppression, cardiotoxicity, GI effects and pulmonary toxicity

DESTINY-Lung 02 Trial

Trastuzumab Deruxtecan in Patients With *HER2*-Mutant Metastatic Non–Small-Cell Lung Cancer: Primary Results From the Randomized, Phase II DESTINY-Lung02 Trial

Authors: Koichi Goto, MD, PhD, Yasushi Goto, MD, PhD, Toshio Kubo, MD, PhD, Kiichiro Ninomiya, MD, PhD, Sang-We Kim, MD, PhD, David Planchard, MD, PhD, Myung-Ju Ahn, MD, PhD, ... SHOW ALL ..., and Pasi A. Jänne, MD, PhD | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 41, Number 31 • https://doi.org/10.1200/JCO.23.01361

19,211 / 5 PDF

TABLE 3. Most Common (≥20% of patients) Treatment-Emergent Adverse Events in Patients With Human Epidermal Growth Factor Receptor 2–Mutant Metastatic Non–Small-Cell Lung Cancer Treated With T-DXd

	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 101),[a] No. (%)		T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 50),[a] No. (%)	
Preferred Term	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Nausea	68 (67.3)	4 (4.0)	41 (82.0)	3 (6.0)
Neutropenia[b]	43 (42.6)	19 (18.8)	28 (56.0)	18 (36.0)
Fatigue[b]	45 (44.6)	8 (7.9)	25 (50.0)	5 (10.0)
Decreased appetite	40 (39.6)	2 (2.0)	25 (50.0)	2 (4.0)
Anemia[b]	37 (36.6)	11 (10.9)	26 (52.0)	8 (16.0)
Vomiting	32 (31.7)	3 (3.0)	22 (44.0)	1 (2.0)
Constipation	37 (36.6)	1 (1.0)	16 (32.0)	0
Leukopenia[b]	29 (28.7)	5 (5.0)	17 (34.0)	8 (16.0)
Thrombocytopenia[b]	28 (27.7)	6 (5.9)	14 (28.0)	5 (10.0)
Diarrhea	23 (22.8)	1 (1.0)	18 (36.0)	2 (4.0)
Alopecia	22 (21.8)	0	17 (34.0)	0
Transaminases increased[b]	22 (21.8)	3 (3.0)	10 (20.0)	0

NOTE. Data for adjudicated drug-related interstitial lung disease are presented separately.
Abbreviation: T-DXd, trastuzumab deruxtecan.
[a]The safety analysis set includes all randomly assigned patients who received ≥1 dose of study drug.
[b]Grouped terms include neutropenia (neutrophil count decreased, neutropenia), fatigue (fatigue, asthenia, malaise, lethargy), anemia (hemoglobin decreased, RBC decreased, anemia, hematocrit decreased), leukopenia (WBC decreased, leukopenia), thrombocytopenia (platelet count decreased, thrombocytopenia), and transaminases increased (transaminases increased, AST increased, ALT increased, gamma-glutamyl transferase increased, liver function test abnormal, hepatic function test abnormal, liver function test increased, hypertransaminasemia).

- Blinded, multicenter, phase II study
- Trastuzumab deruxtecan 5.4 mg/kg q3 vs. 6.4 mg/kg q3 weeks in patients with mNSCLC previously treated with platinum containing therapy
- Primary end-point was ORR

Goto et al. JCO. 2023

DESTINY-Lung 02 Trial

Type of AE	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 101),[a] No. (%)	T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 50),[a] No. (%)
Any-grade TEAEs	101 (100.0)	50 (100.0)
Drug-related	97 (96.0)	50 (100.0)
Grade ≥ 3 TEAEs	53 (52.5)	33 (66.0)
Drug-related	39 (38.6)	29 (58.0)
Serious TEAEs	37 (36.6)	20 (40.0)
Drug-related	14 (13.9)	12 (24.0)
TEAEs associated with drug discontinuation	15 (14.9)	13 (26.0)
Drug-related	14 (13.9)	10 (20.0)
TEAEs associated with dose reduction	18 (17.8)	16 (32.0)
Drug-related	17 (16.8)	16 (32.0)
TEAEs associated with drug interruption	45 (44.6)	31 (62.0)
Drug-related	27 (26.7)	24 (48.0)
TEAEs associated with an outcome of death	6 (5.9)[b]	2 (4.0)[c]
Drug-related	1 (1.0)	1 (2.0)
Adjudicated drug-related ILD[d]		
Grade 1	4 (4.0)	4 (8.0)
Grade 2	7 (6.9)	9 (18.0)
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	1 (1.0)	1 (2.0)
Total (95% CI)	13 (12.9) (7.0 to 21.0)	14 (28.0) (16.2 to 42.5)

Adjudicated Drug-Related ILD in Patients With Prior Anti–PD-(L)1 Therapy	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 74), No. (%)	T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 39), No. (%)
Grade 1	4 (5.4)	2 (5.1)
Grade 2	5 (6.8)	9 (23.1)
Grade 3	1 (1.4)	0
Grade 4	0	0
Grade 5	1 (1.4)	0
Total	11 (14.9)	11 (28.2)

150 patients were randomly assigned 2:1 T-DXd 5.4 or 6.4 mg/kg q3 weeks dosing

ORR 49% in 5.4 mg/kg dosing and 56% in the 6.4 mg/kg dosing

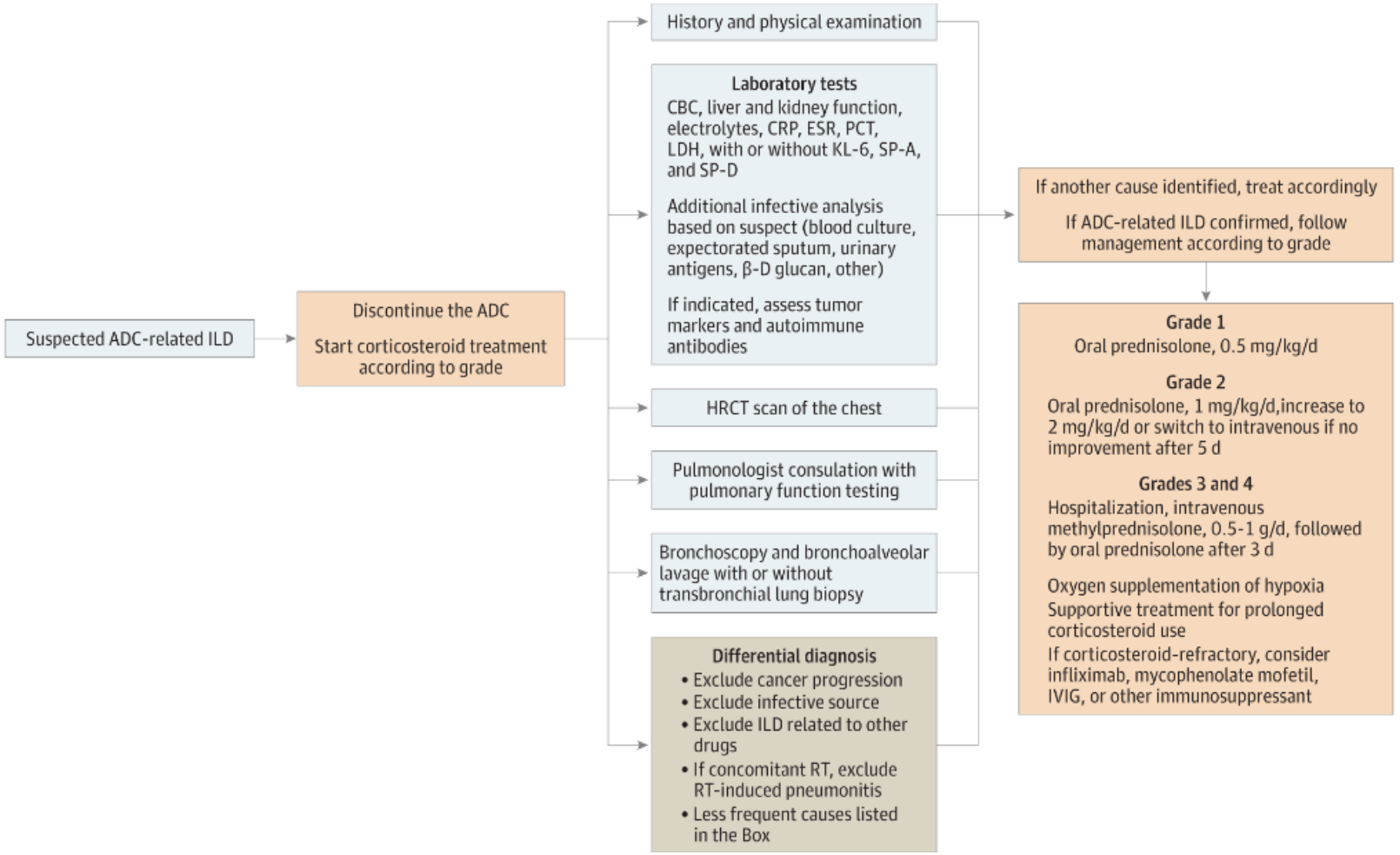
Grade ≥ 3 drug-related treatment-emergent adverse events occurred in 39 of 101 (38.6%) and 29 of 50 (58.0%) patients with 5.4 and 6.4 mg/kg.

13 of 101 (12.9%) and 14 of 50 (28.0%) patients had adjudicated drug-related interstitial lung disease (2.0% grade ≥ 3 in each arm) with 5.4 and 6.4 mg/kg.

Result: 5.4 mg/k q3 weeks was approved

Goto et al. JCO. 2023

Evaluation and Management



Tarantino et al. JAMA. 2021.

Trastuzumab emtansine

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer

Cortés J et al. DOI: 10.1056/NEJMoa2115022

- A phase 3, multicenter, open label, randomized controlled trial comparing trastuzumab deruxtecan with standard 2nd line treatment, trastuzumab emtansine in patients with HER-2 positive breast cancer
- Incidence of drug-related adverse events was higher with trastuzumab deruxtecan than with trastuzumab emtansine in particular ILD and pneumonitis.

Cortes et al. NEJM. 2022.

Adverse Events

Event	Trastuzumab Deruxtecan (N = 257)		Trastuzumab Emtansine (N = 261)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Most common drug-related adverse events				
Blood and lymphatic system disorders				
Neutropenia*	110 (42.8)	49 (19.1)	29 (11.1)	8 (3.1)
Anemia†	78 (30.4)	15 (5.8)	37 (14.2)	11 (4.2)
Leukopenia‡	77 (30.0)	17 (6.6)	20 (7.7)	1 (0.4)
Thrombocytopenia§	64 (24.9)	18 (7.0)	135 (51.7)	65 (24.9)
Gastrointestinal disorders				
Nausea	187 (72.8)	17 (6.6)	72 (27.6)	1 (0.4)
Vomiting	113 (44.0)	4 (1.6)	15 (5.7)	1 (0.4)
Diarrhea	61 (23.7)	1 (0.4)	10 (3.8)	1 (0.4)
Constipation	58 (22.6)	0	25 (9.6)	0
General disorders				
Fatigue¶	115 (44.7)	13 (5.1)	77 (29.5)	2 (0.8)
Investigations				
Aspartate aminotransferase increased	60 (23.3)	2 (0.8)	97 (37.2)	13 (5.0)
Alanine aminotransferase increased	50 (19.5)	4 (1.6)	71 (27.2)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	67 (26.1)	3 (1.2)	33 (12.6)	0
Skin and subcutaneous tissue disorders				
Alopecia‖	93 (36.2)	1 (0.4)	6 (2.3)	0
Adjudicated drug-related interstitial lung disease or pneumonitis**	27 (10.5)	2 (0.8)	5 (1.9)	0

		T-DXd	TDM1
General	alopecia	++	
	Fatigue	+++	++
haematological	Neutropenia	+++	+
	Anaemia	++	+
GI	Vomiting	+++	
	Constipation	+	
	Nausea	+++	++
	Diarrhea	+	
Liver	transaminitis	+	++

Cortes et al. NEJM. 2022.
Powles ASCO 2023

What happens to toxicity when we combine ADCs with other drugs?

Enfortumab + pembrolizumab vs. enfortumab vedotin

TRAEs **Any Grades** by Preferred Term **≥20% of Patients**	EV+P (N=76) n (%)		EV Mono (N=73) n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Overall	76 (100.0)	48 (63.2)	68 (93.2)	35 (47.9)
Fatigue	43 (56.6)	7 (9.2)	29 (39.7)	6 (8.2)
Peripheral sensory neuropathy	39 (51.3)	1 (1.3)	32 (43.8)	2 (2.7)
Rash maculo-papular	35 (46.1)	13 (17.1)	21 (28.8)	1 (1.4)
Pruritus	30 (39.5)	3 (3.9)	19 (26.0)	1 (1.4)
Weight decreased	23 (30.3)	3 (3.9)	21 (28.8)	1 (1.4)
Diarrhea	22 (28.9)	5 (6.6)	20 (27.4)	4 (5.5)
Nausea	19 (25.0)	0	25 (34.2)	1 (1.4)
Dry eye	15 (19.7)	0	8 (11.0)	0

Same when tox is related to one agent

Worse when tox is common for both

Rosenberg et al. ESMO 2022
Powles ASCO 2023

Conclusions

- Adverse events are dose limiting for ADCs
- Adverse events are commonly associated with significant grade toxicity causing delays, dose reduction and cessation of therapy
- Multiple independent factors are associated with toxicity, including the antibody target, the linker and the payload.
- Classes of similar mode of action have similar adverse events but the linker molecule remains relevant
- Treatment monitoring is important