Immune-Related Adverse Events With Checkpoint Inhibitors

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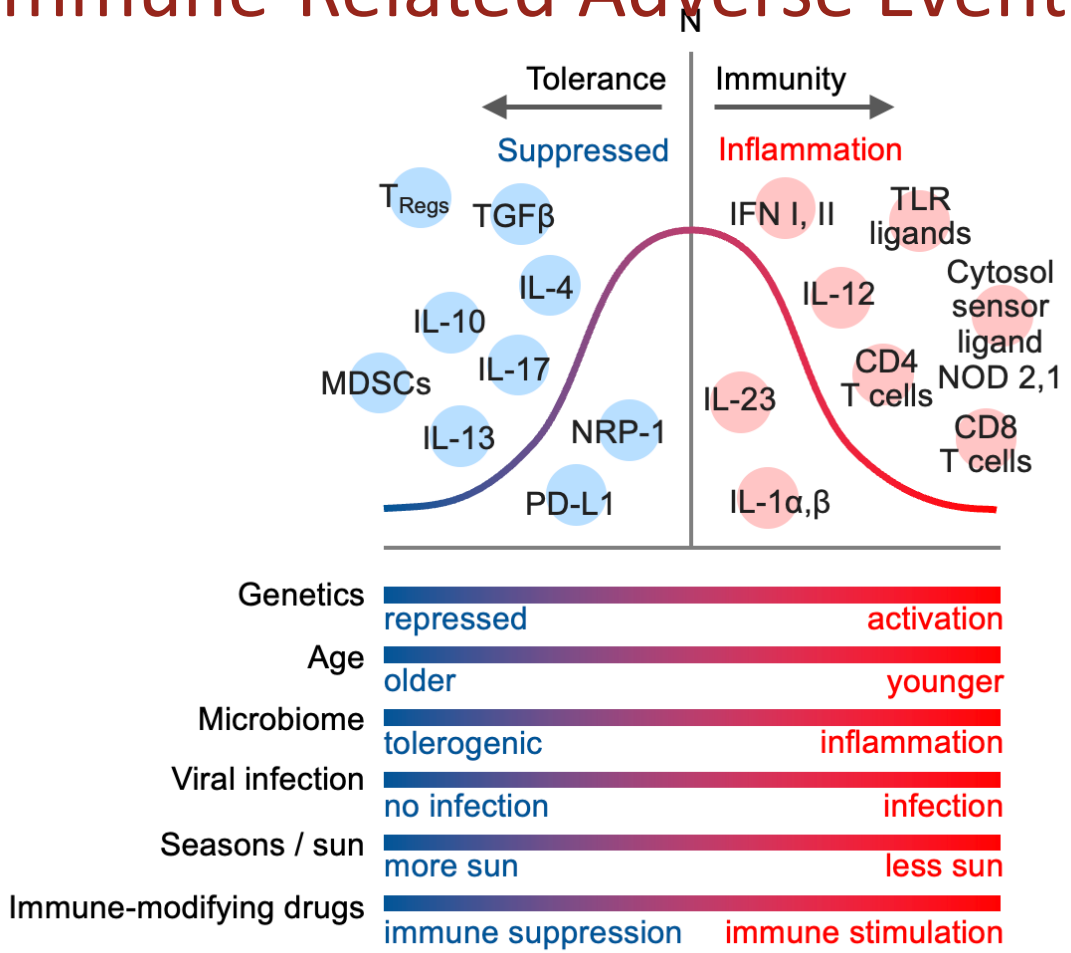
Objectives

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

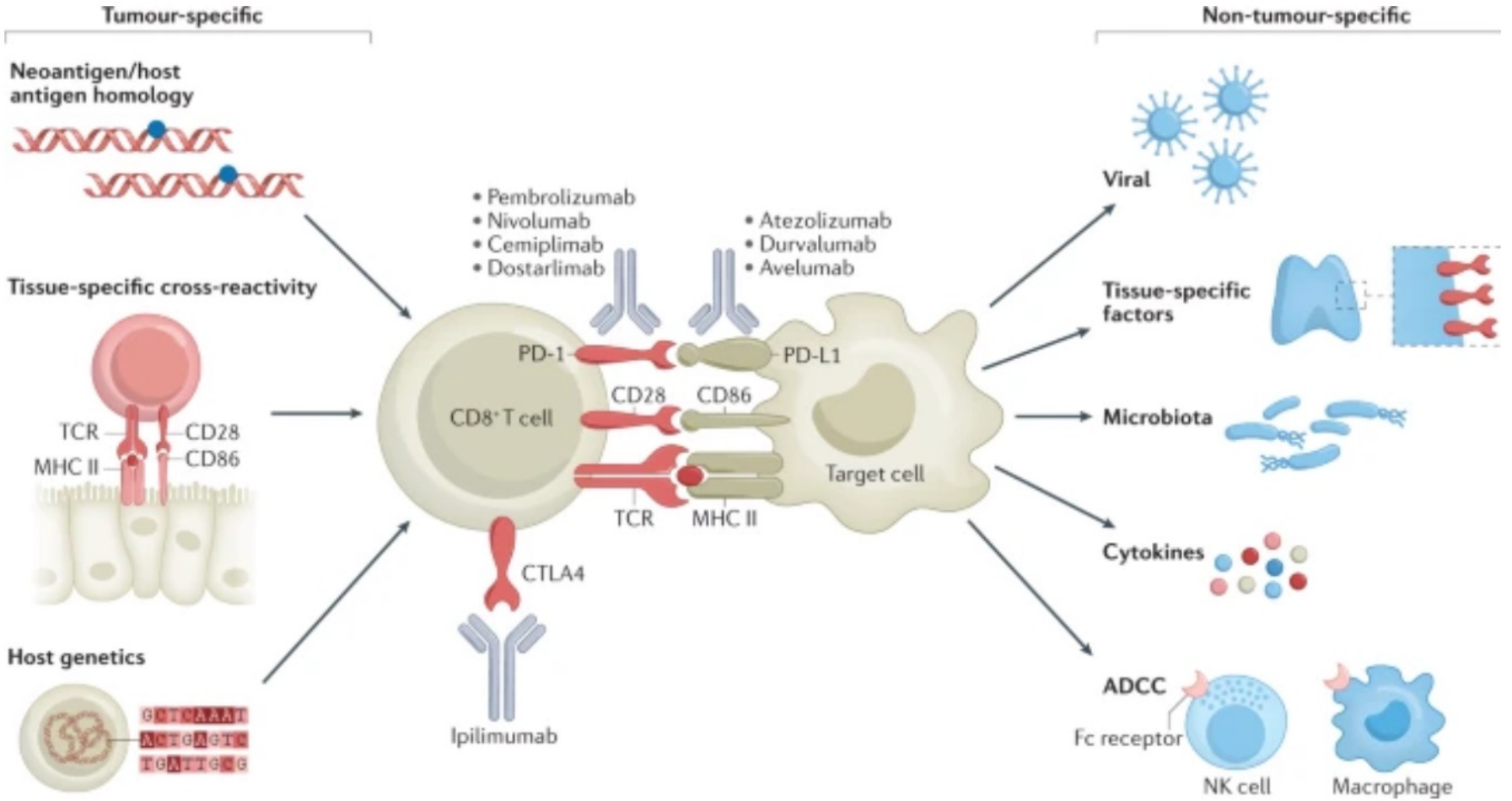
The Cancer–Immune Set Point: Multivariate Factors Influence Tolerance and Immunity Immune-Related Adverse Events With Checkpoint Inhibitors



- 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

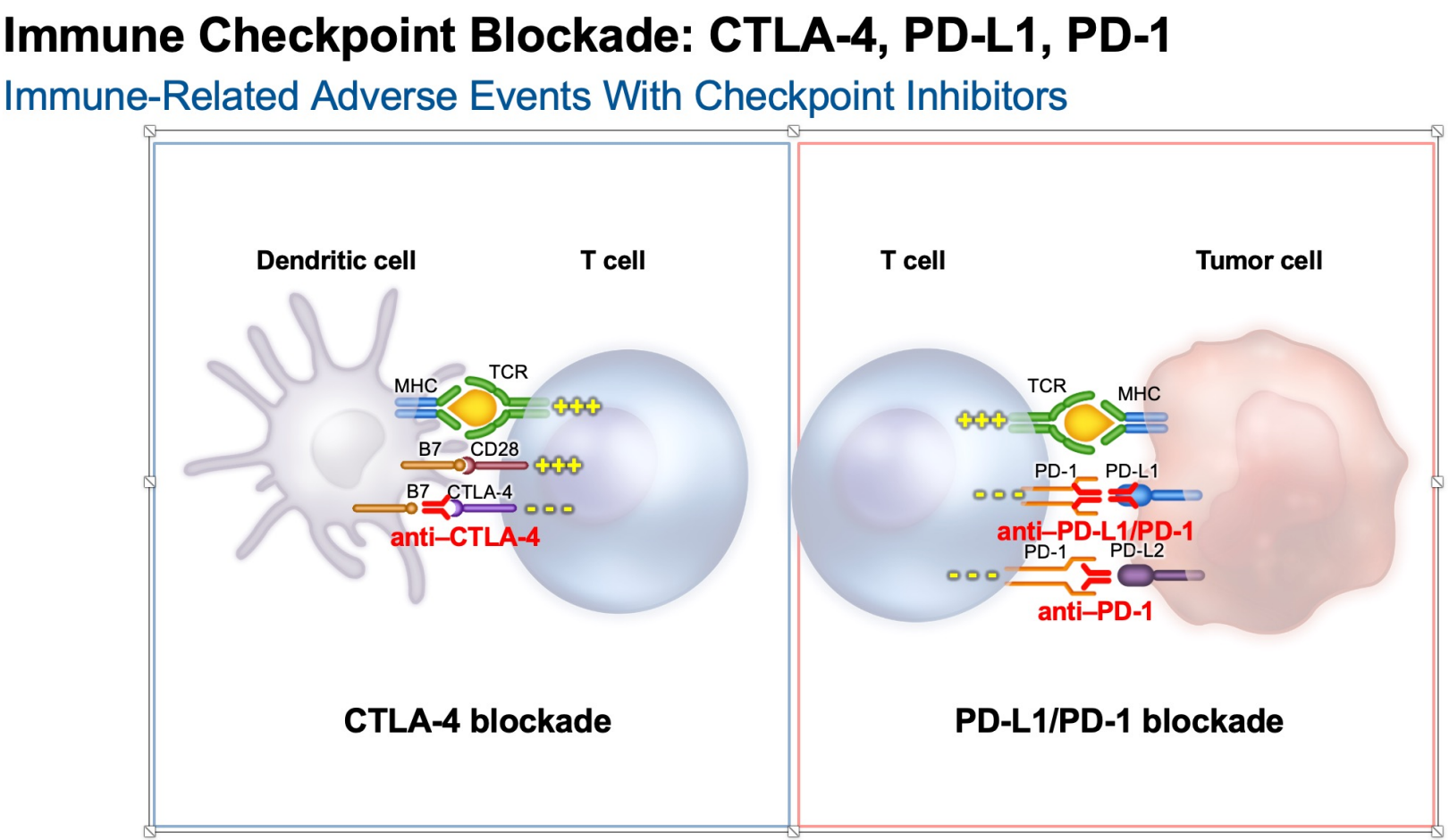
1. Chen DS and Mellman I. *Nature*. 2017;541:321-330

Mechanism of immune-related adverse events



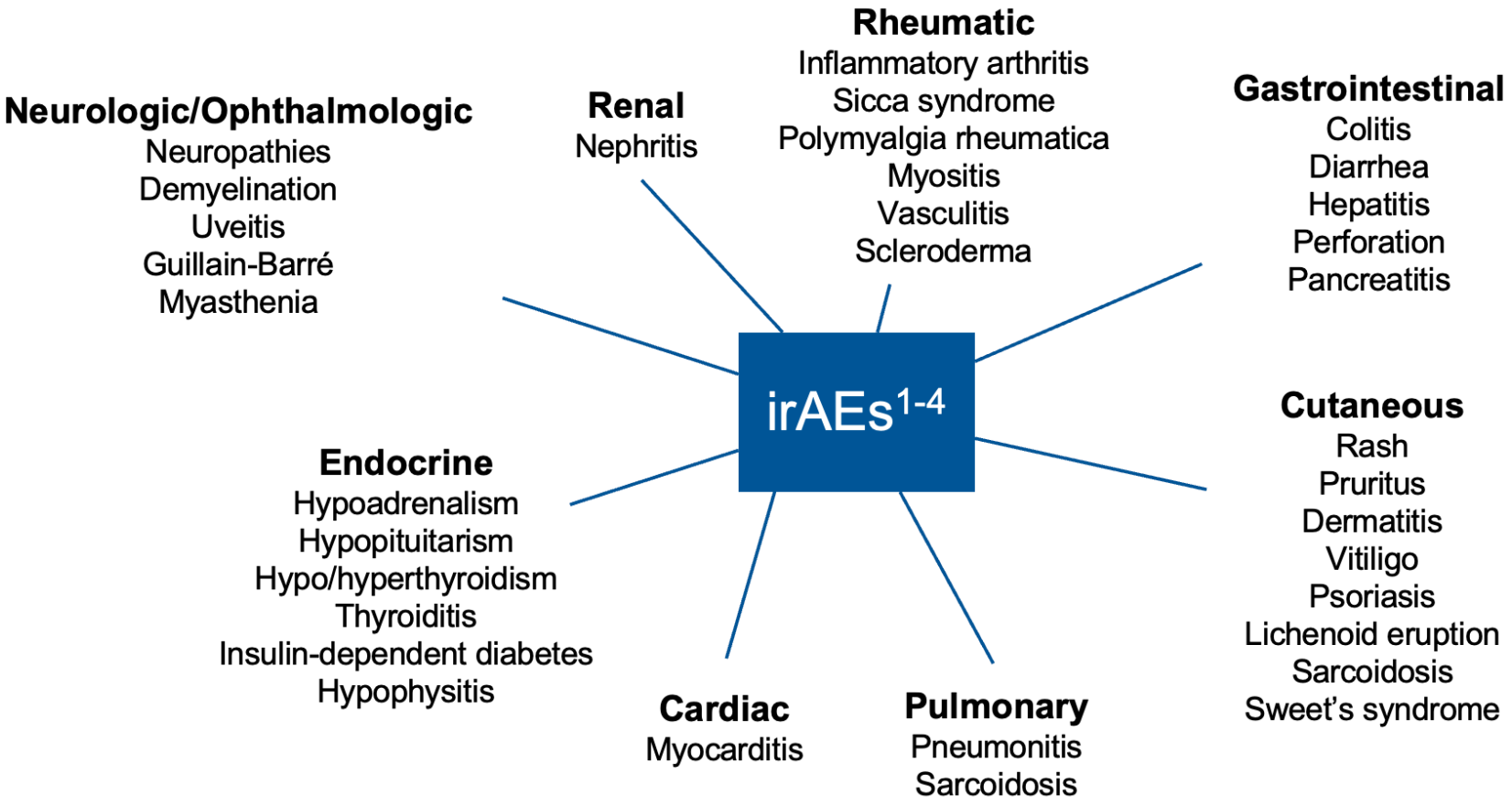
Johnson, D.B., Nebhan, C.A., Moslehi, J.J. *et al.* Immune-checkpoint inhibitors: long-term implications of toxicity. *Nat Rev Clin Oncol* **19**, 254–267 (2022). https://doi.org/10.1038/s41571-022-00600-w

Immune Checkpoint Blockade: CTLA-4, PD-L1, PD-1



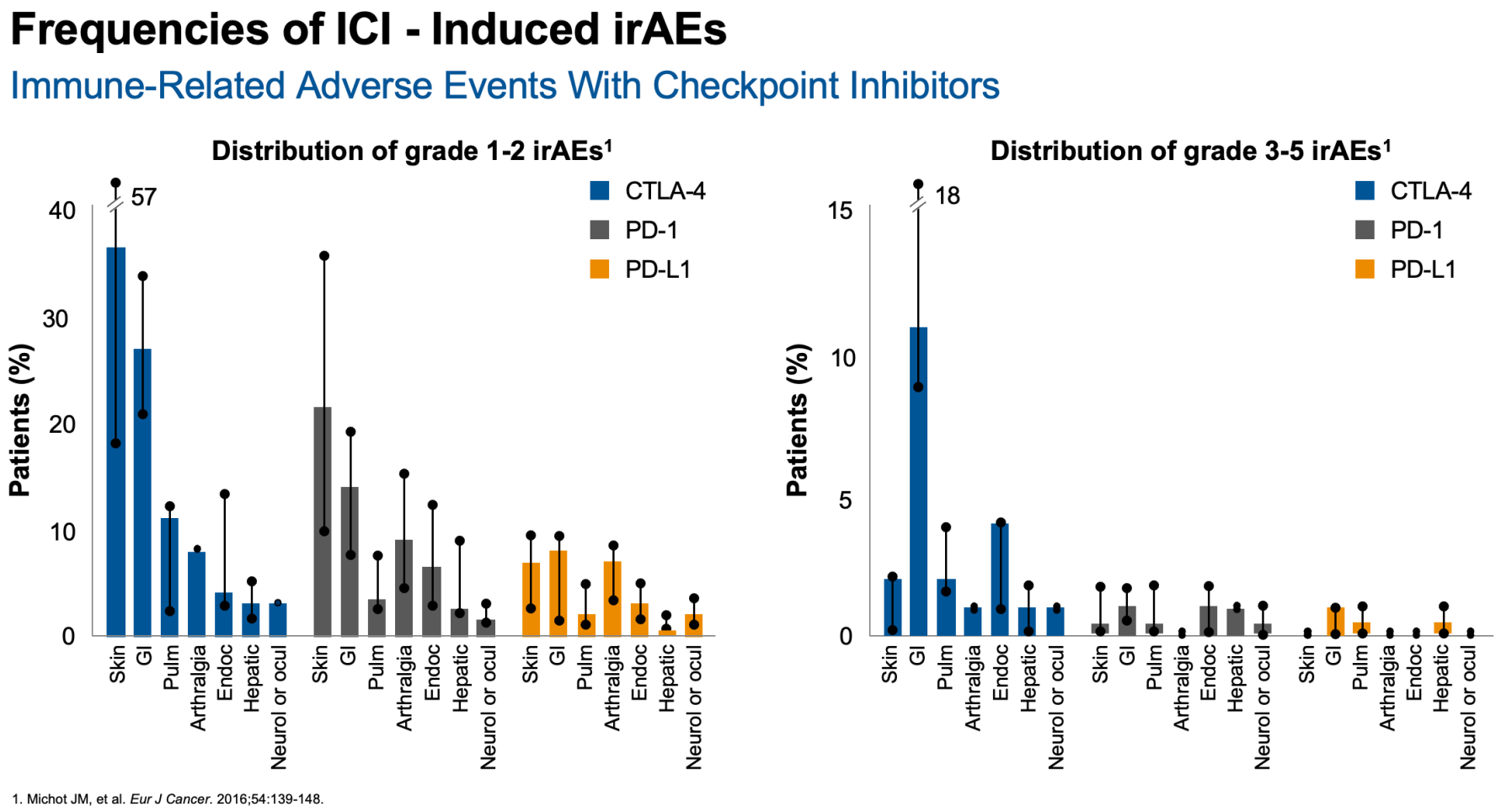
Adapted from Pardoll DM. *Nat Rev Cancer*. 2012;12:252-264 and Merelli B, et al. *Critical Rev Oncol Hematol*. 2014;89:140-165.

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

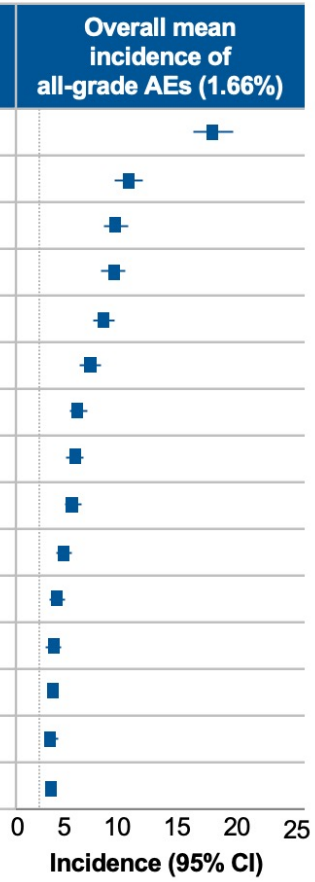


1. Michot JM, et al. *Eur J Cancer*. 2016;54:139-148.

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

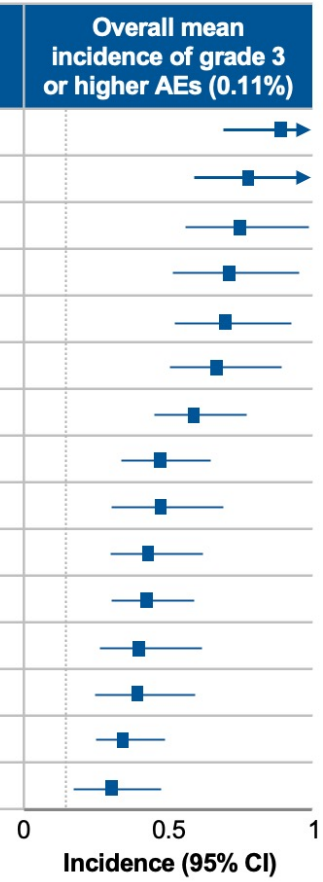
All-grade AEs[1]

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)



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)



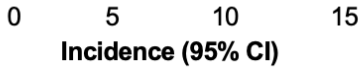
- Systemic review and meta-analysis including 125 clinical trials and 20,128 patients
- Overall AE rates:
  - All-grade: 66.0%
  - ≥ Grade 3: 14.0%
- Overall incidence of treatment-related death was 0.45%

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

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

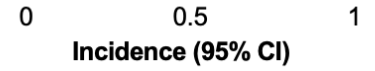
All-grade irAEs[1]

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)



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)

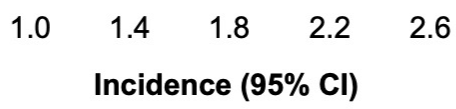


1. Wang Y, et al. *JAMA Oncol*. 2019. doi: 10.1001/jamaoncol.2019.0393.

AEs by Cancer Type

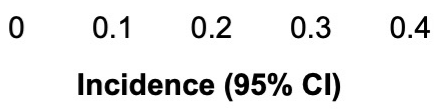
All-grade AEs[1]

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)	



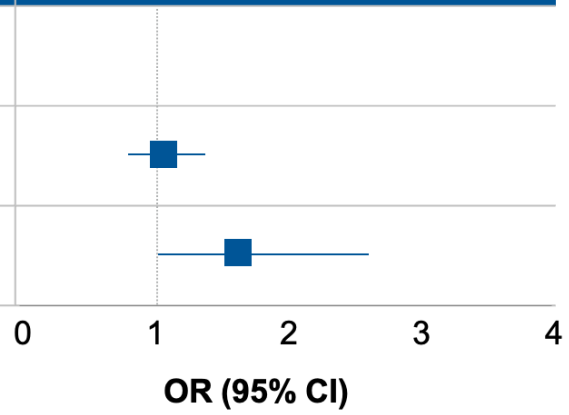
- The overall mean incidence of adverse events were similar across cancer types[1]

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

AEs by Drug Type

- PD-1 inhibitors were associated with a higher mean incidence of grade 3 or higher adverse events than PD-L1 inhibitors[1]

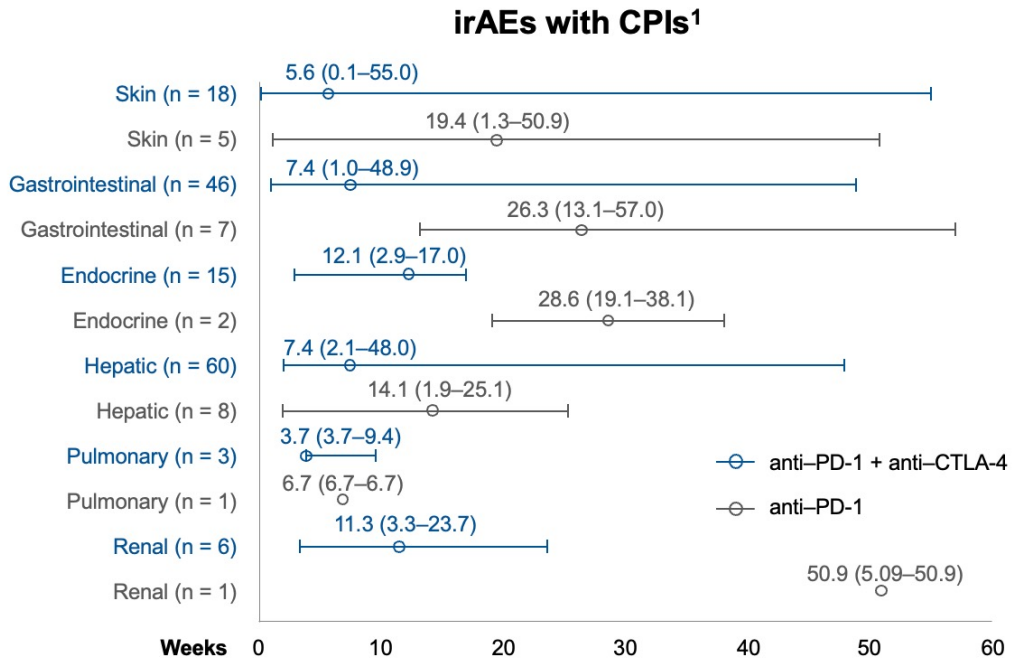
Comparison	PR (OR > 1 | Data)	Odds Ratio (95% CI)	Overall mean incidence of grade 3 or higher AEs (0.11%)
PD-1 vs PD-L1 inhibitors			
All grade	0.51	1.00 (0.78-1.32)	
Grade 3 or higher	0.97	1.58 (1.00-2.54)	



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

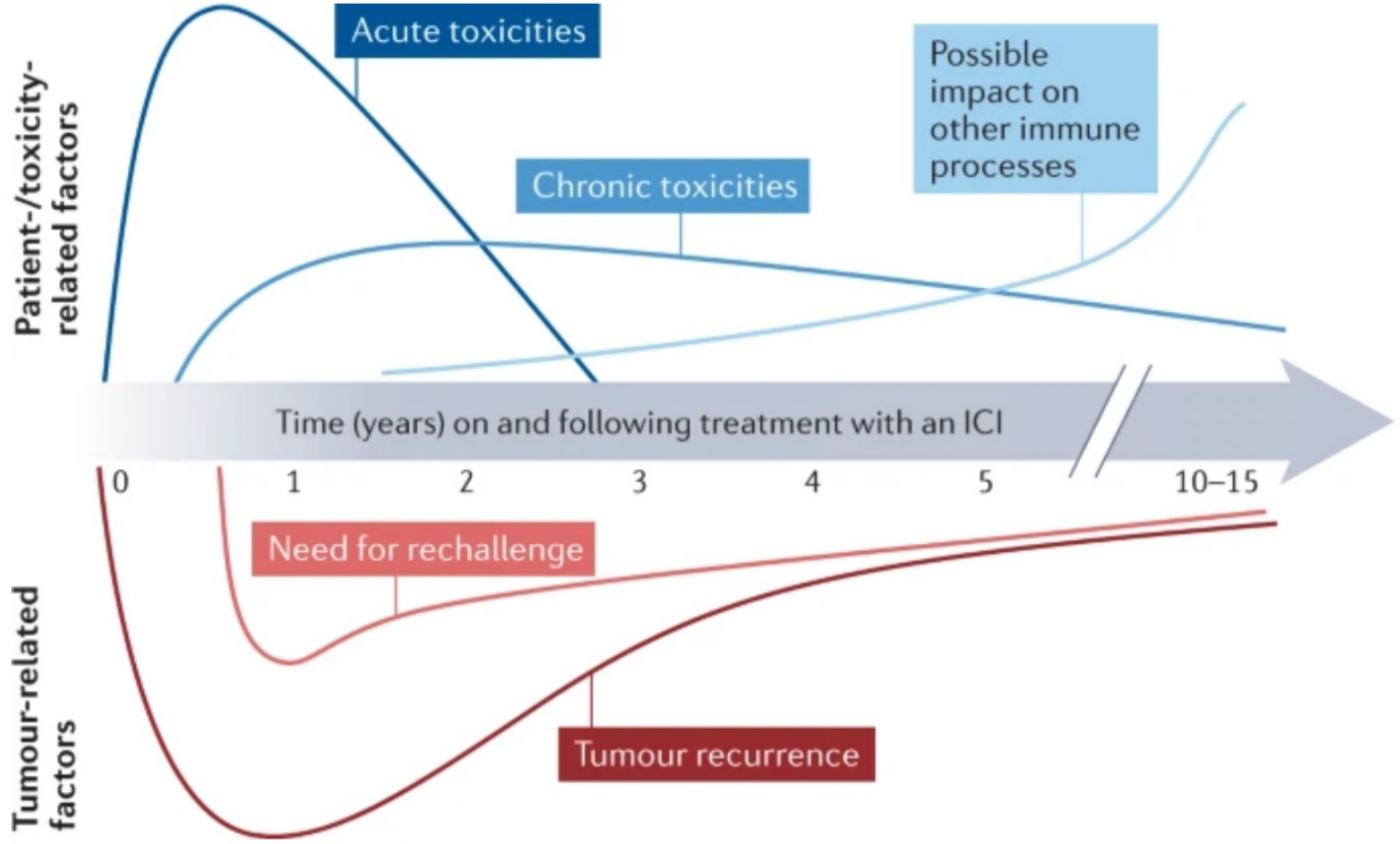
Kinetics of ICI - Induced irAEs

- 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

Time course



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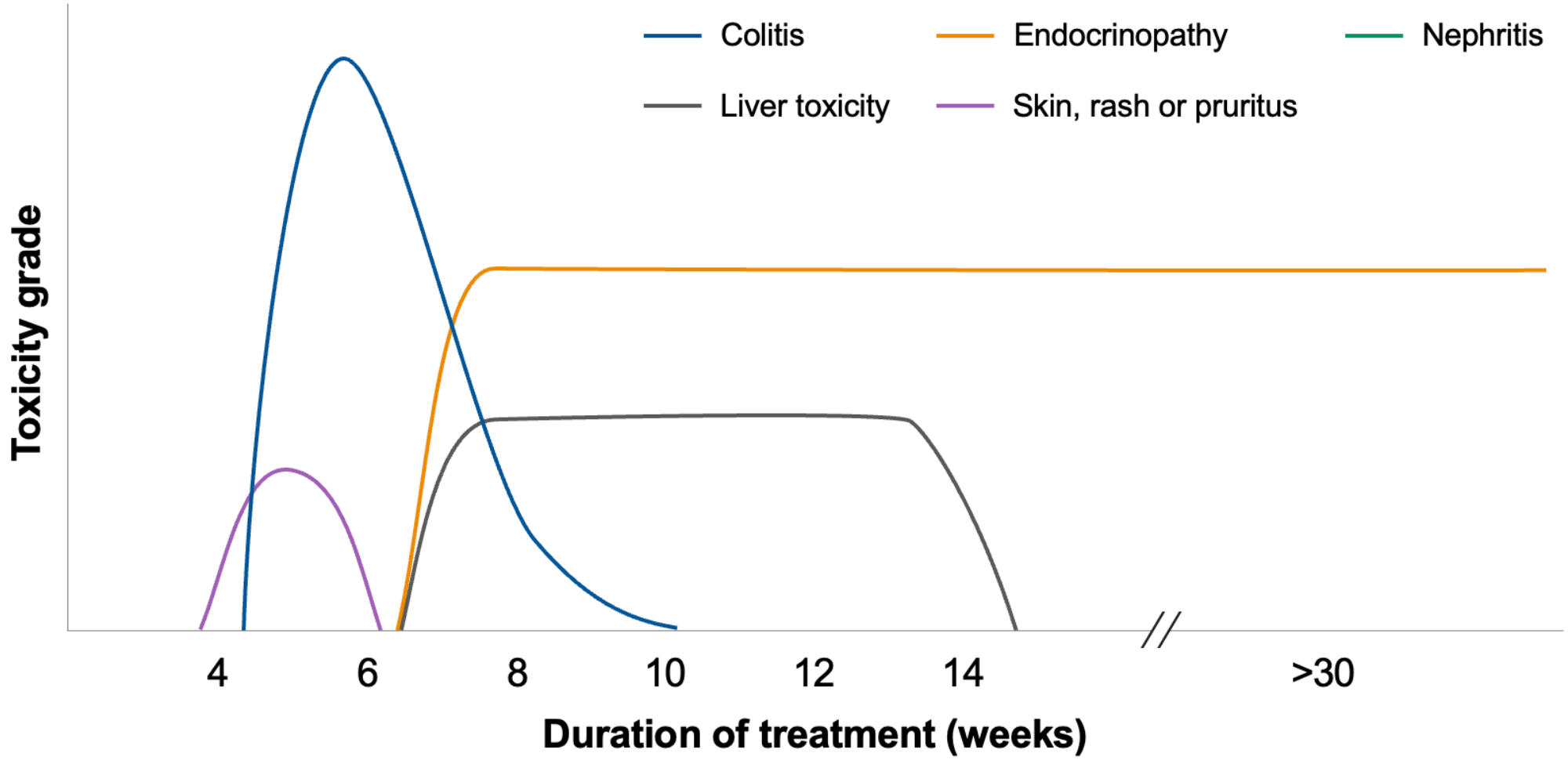
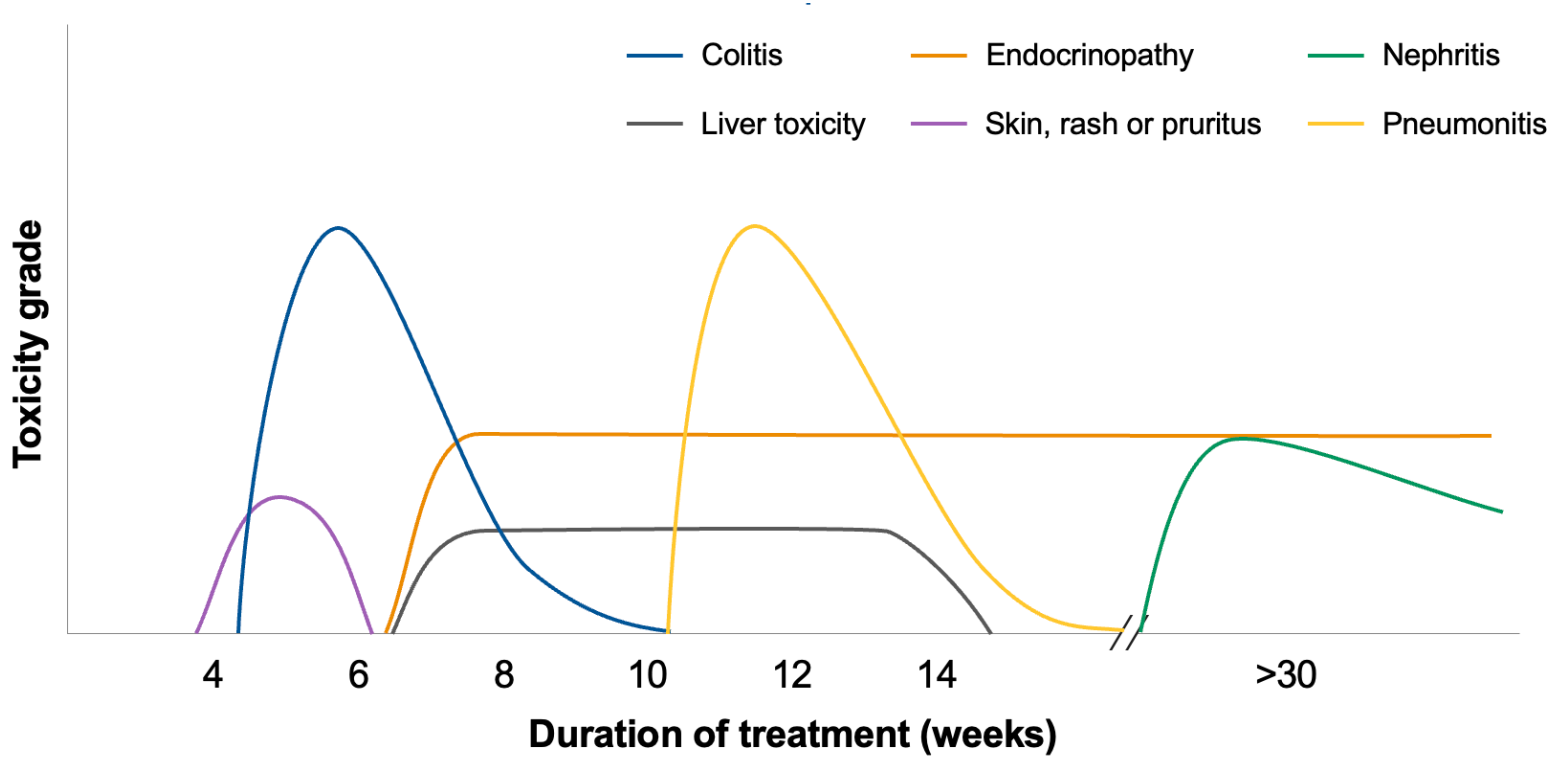
Kinetics of ICI - Induced irAEs – CTLA-4 Antagonists



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

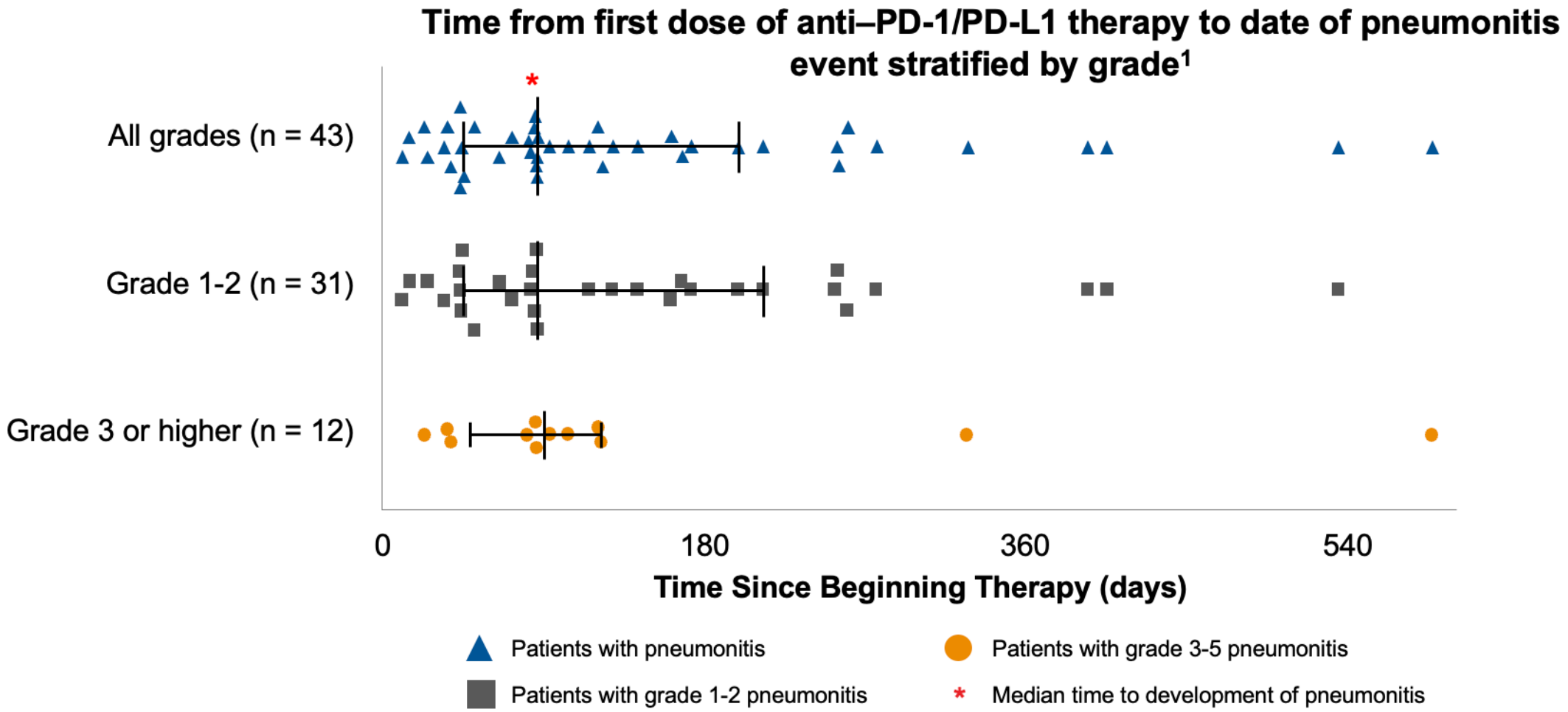
Kinetics of ICI - Induced irAEs – PD-1/PD-L1 Antagonists

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



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

Kinetics of ICI - Induced Pneumonitis



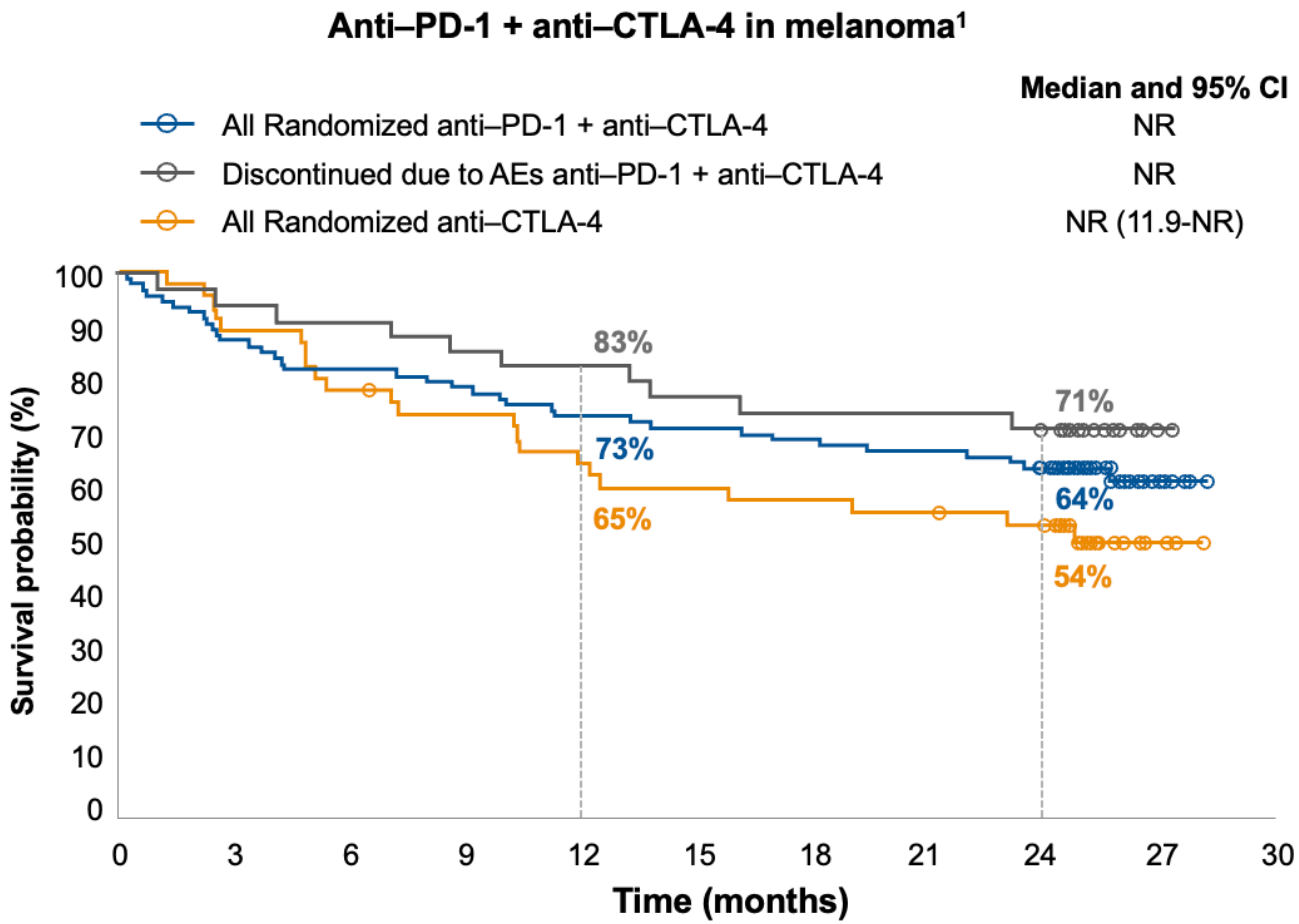
1. Naidoo J, et al. *J Clin Oncol*. 2017;35:709-717.

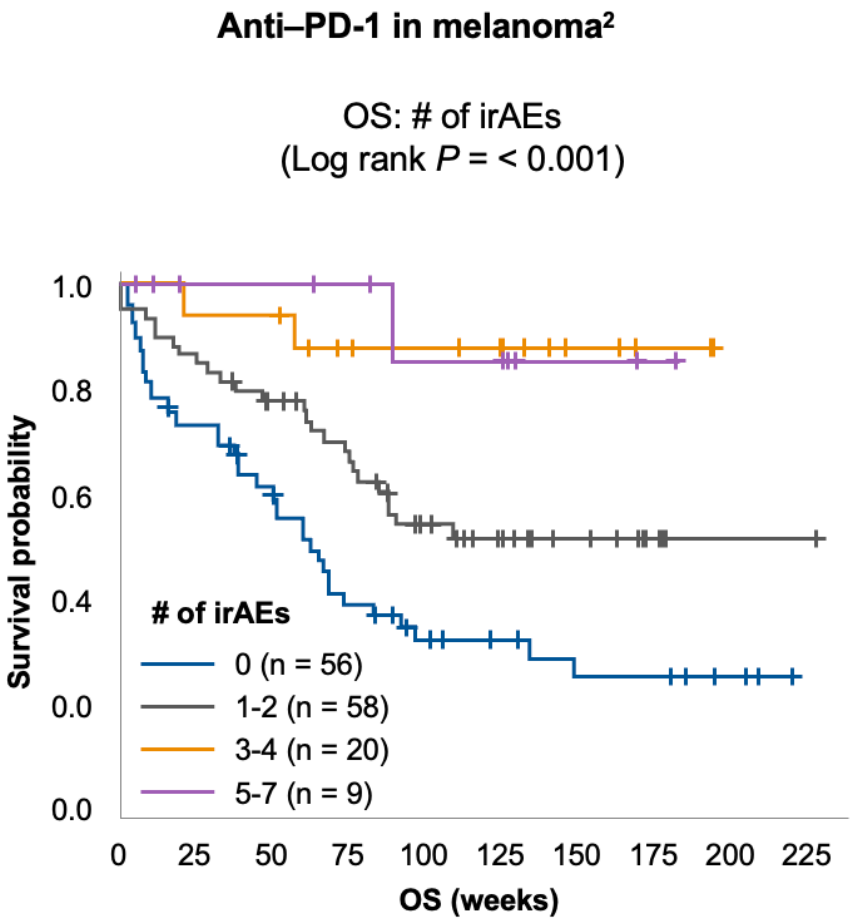
Clinical Course of Pneumonitis With Anti–PD-1/PD-L1 Therapy[1]

- 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 irAEs and Outcomes





1. Adapted from Hodi FS, et al. *Lancet Oncol*. 2016;17:1558-1568 and Hodi FS, et al. Poster. ASCO. 2016 (abstract 9518). 2. Freeman-Keller M, et al. *Clin Cancer Res*. 2016;22:886-894.

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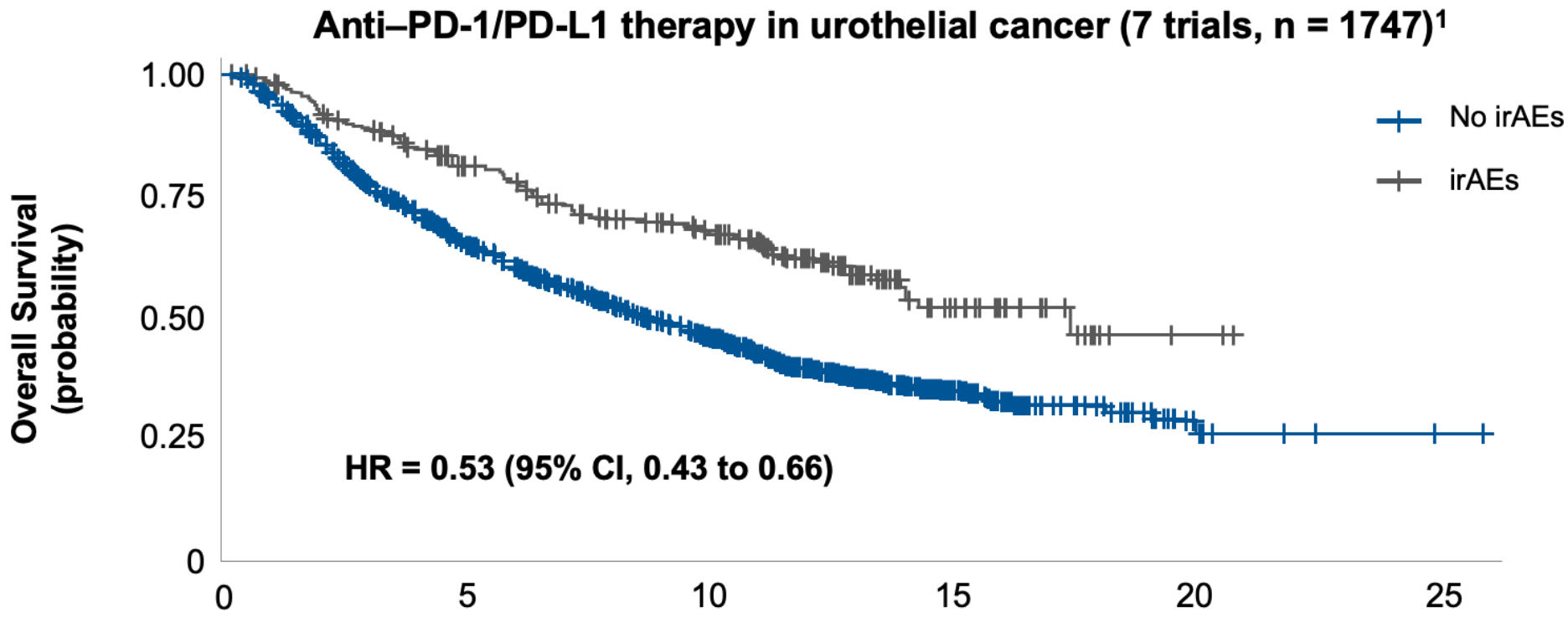
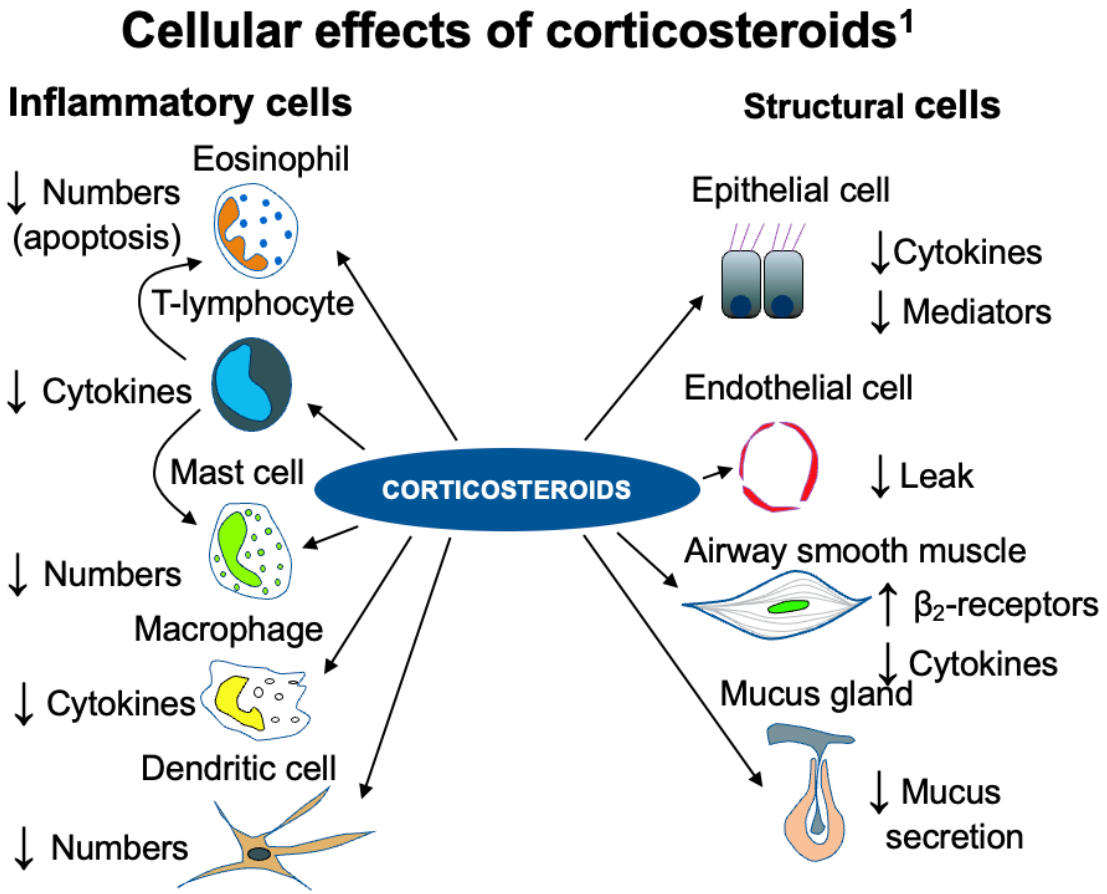


No. at risk (No. censored)						
No irAEs	1479 (0)	814 (136)	461 (287)	111 (560)	8 (653)	1 (660)
irAEs	268 (0)	195 (24)	139 (50)	33 (139)	3 (168)	0 (171)

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

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]

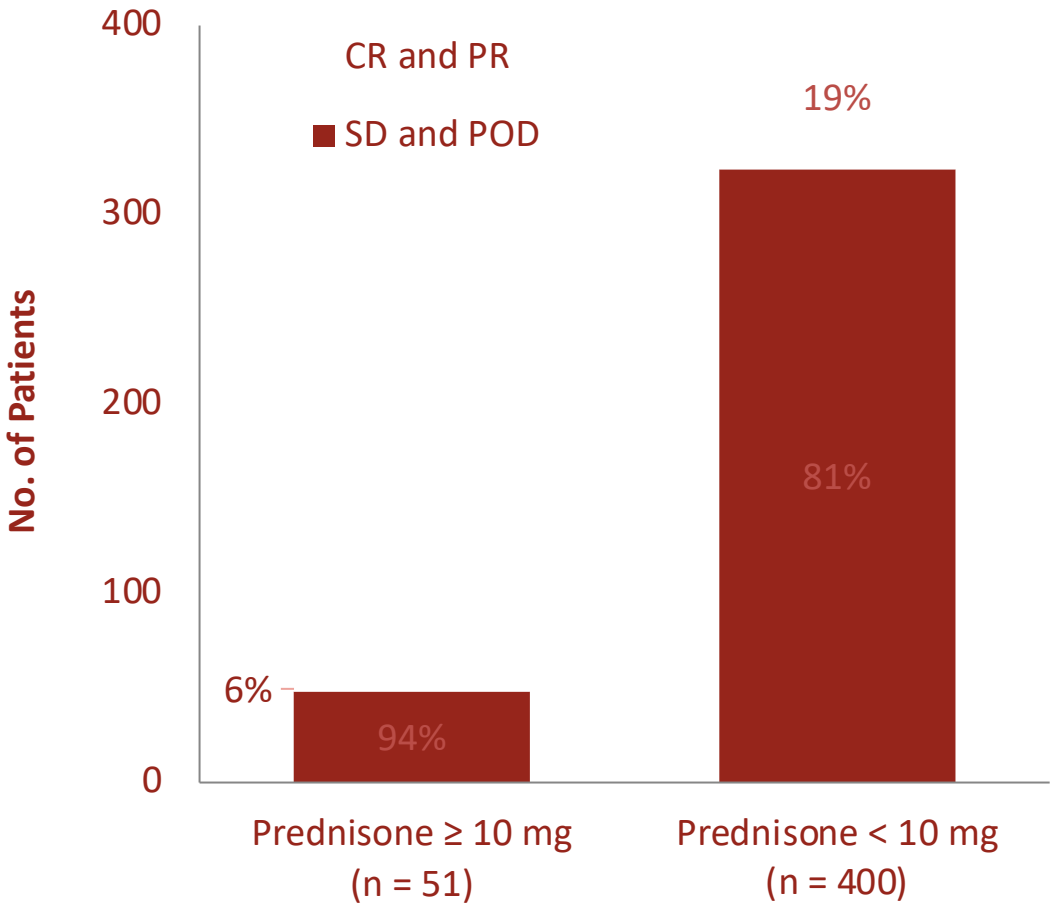
The specific cellular and molecular immune mechanisms underlying toxicity are unlikely to precisely match those that cause tumor rejection e.g. IFN-γ vs TNF-α[7]

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



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.

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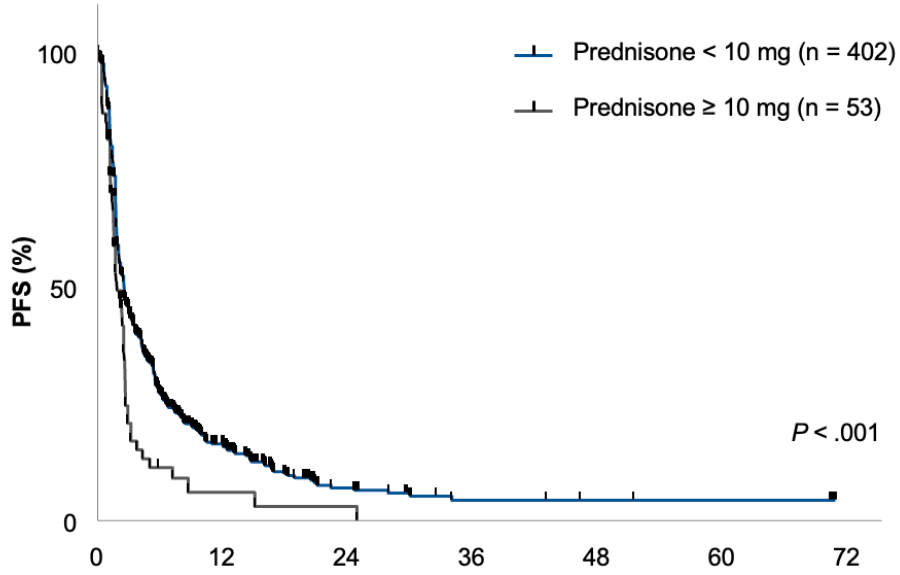

No. at risk:							
< 10 mg:	402	50	13	5	3	2	0
≥ 10 mg:	53	2	1	0	0	0	0

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

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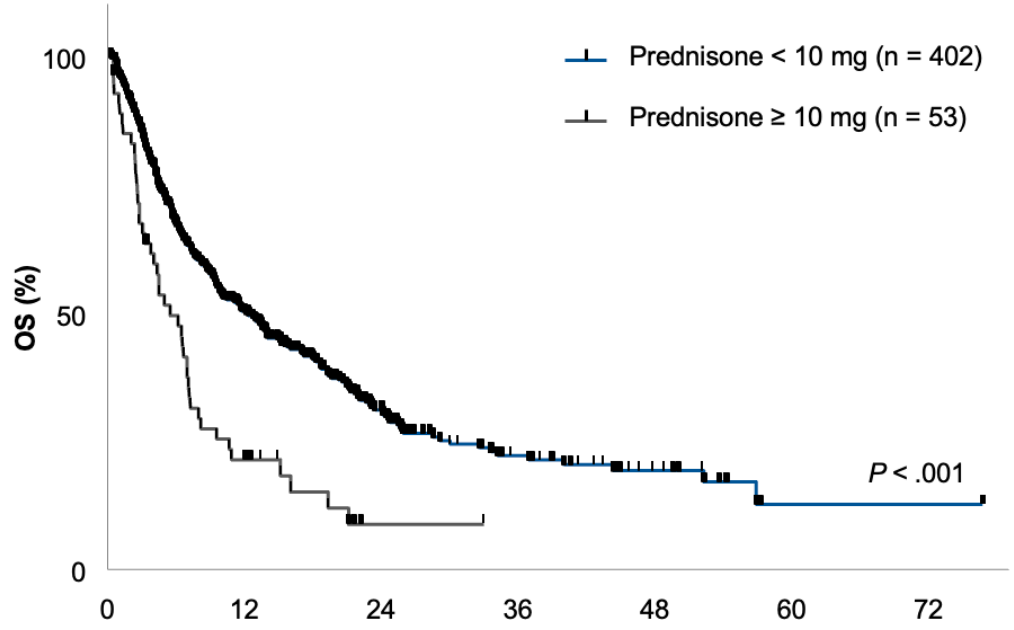

No. at risk:							
< 10 mg:	402	180	67	28	13	2	2
≥ 10 mg:	53	11	1	0	0	0	0

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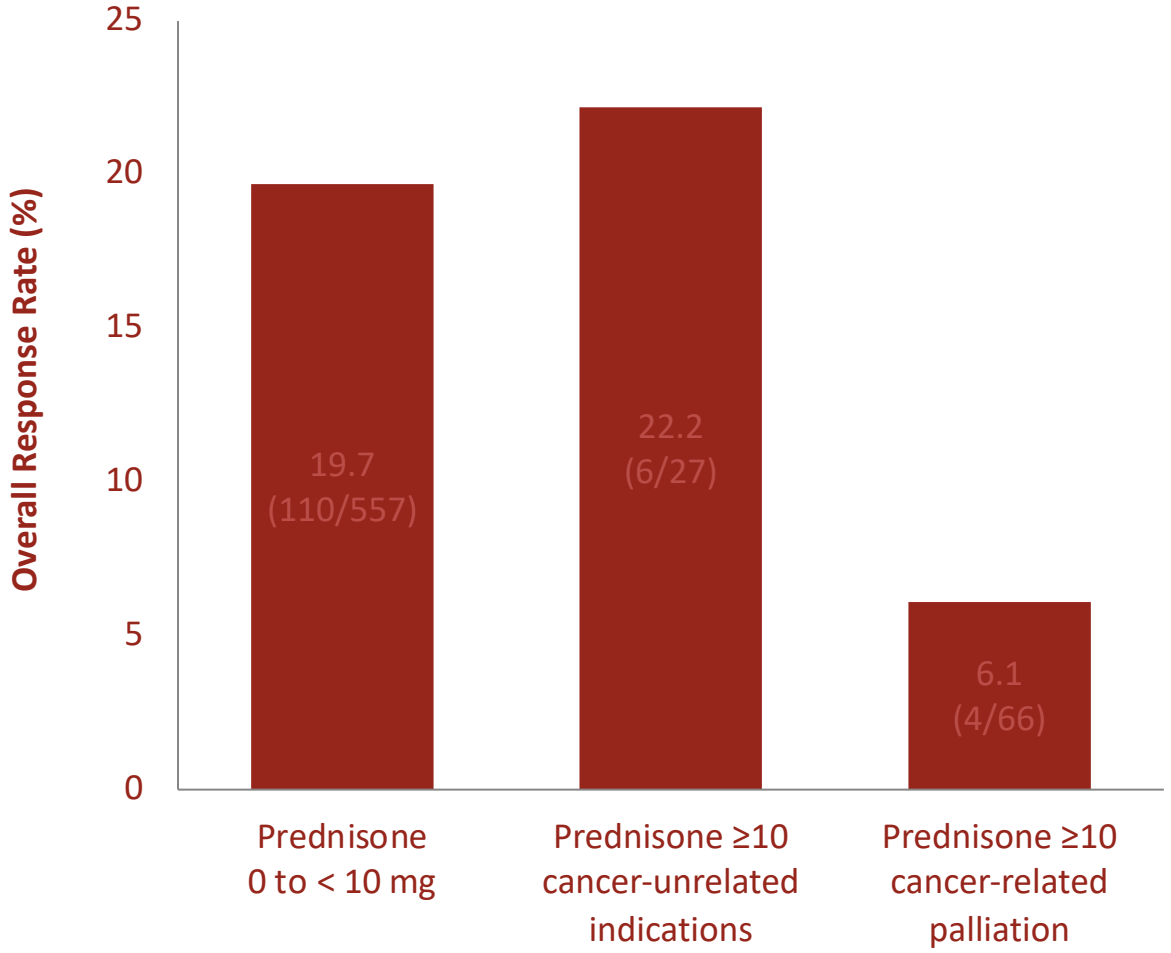
Effect of Baseline Corticosteroid Use on Outcome with ICIs

- 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.

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)
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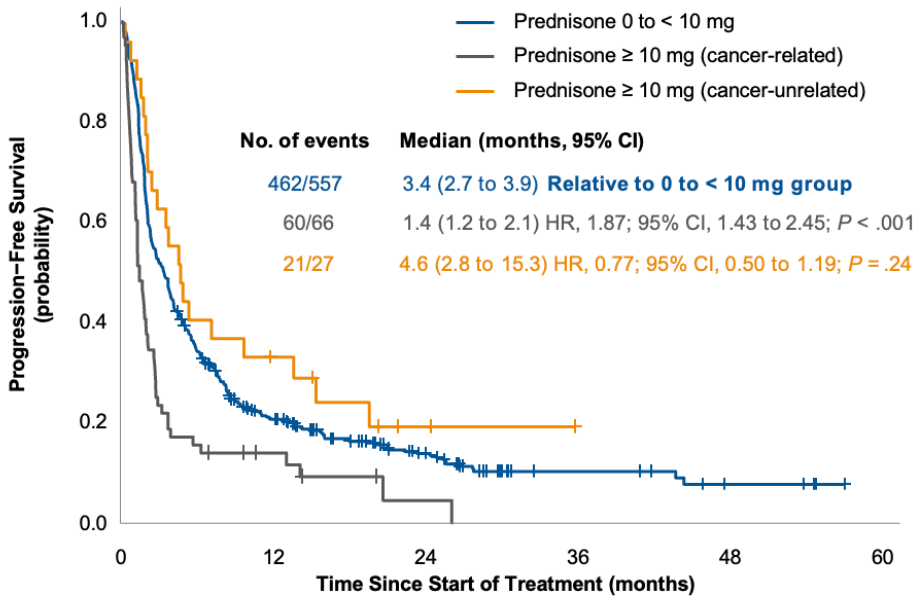

No. at risk:						
Prednisone 0 to < 10 mg	557	91	35	10	4	0
Prednisone ≥ 10 mg (cancer-related)	66	6	1	0	0	0
Prednisone ≥ 10 mg (cancer-unrelated)	27	8	2	0	0	0

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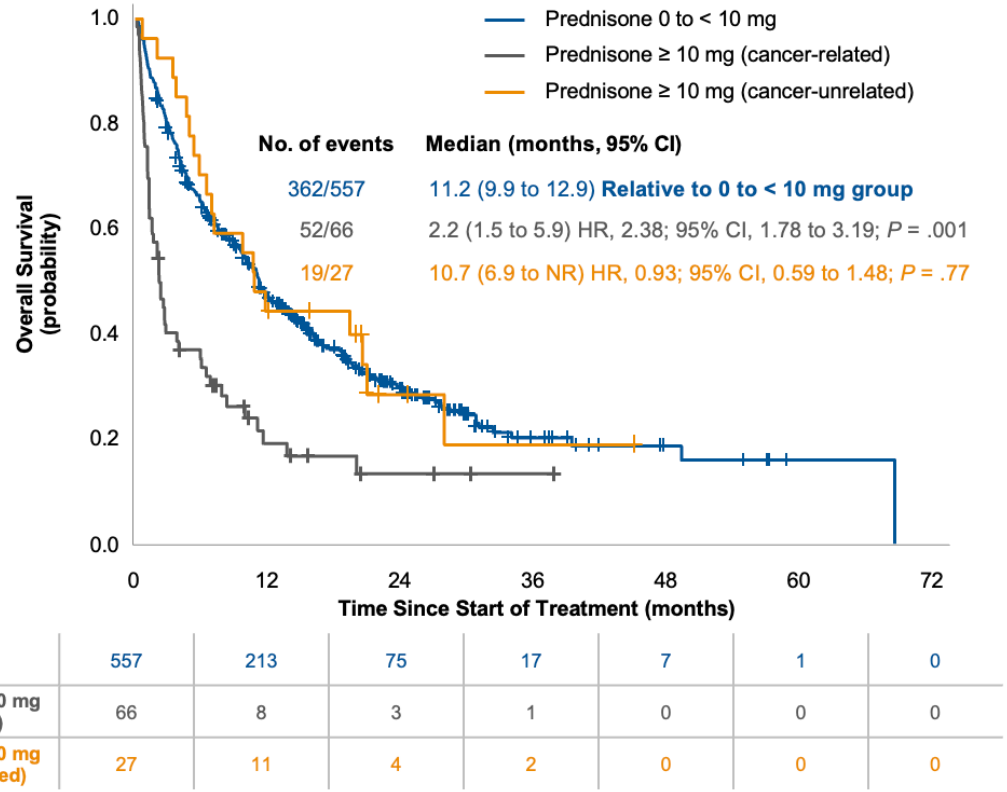

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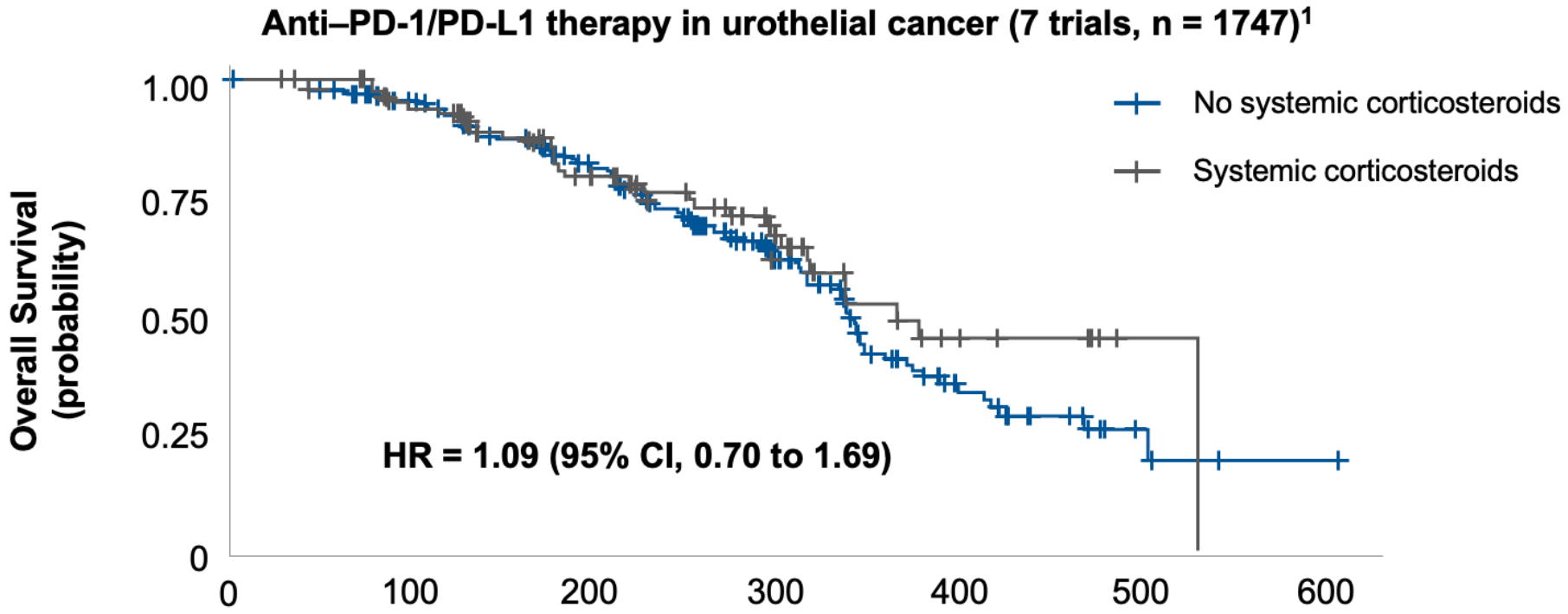
Association Between Use of Corticosteroids and Outcomes



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)

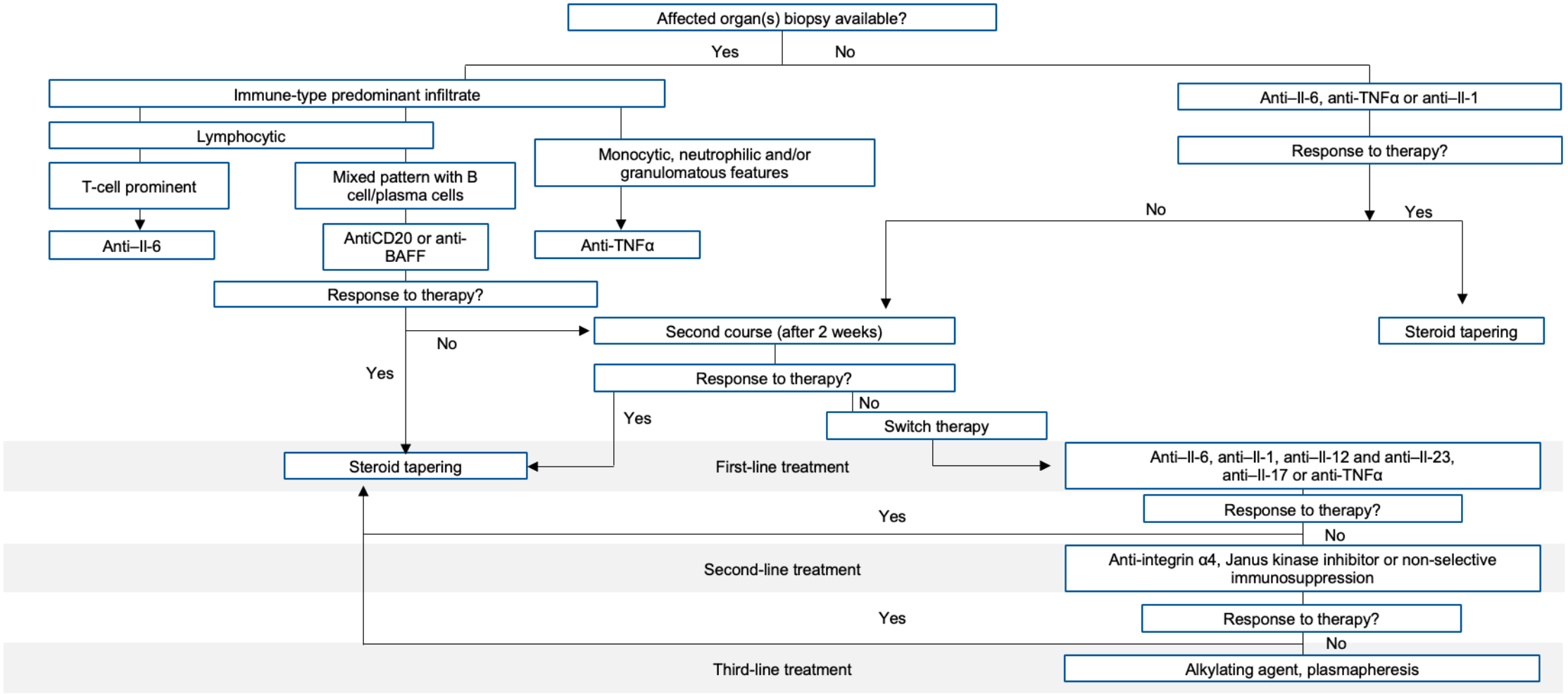
1. Maher VE, et al. *J Clin Oncol.* 2019. doi: 10.1200/JCO.19.00318.

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.

Personalized Treatment of irAEs[1]



1. Adapted from Martins F, et al. *Lancet Oncol*. 2019;20:e54-64.

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