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COMPREHENSIVE CANCER CENTER

Clinical Toxicities of Immunotherapies

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NCI CCC *A Comprehensive Cancer Center Designated by the National Cancer Institute*

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Disclosures/ Potential Conflicts

Consultant:

BMS, Merck, Array, Novartis, Genentech/Roche, Pfizer, Nektar, Celldex, Agenus, Aduro, Galactone

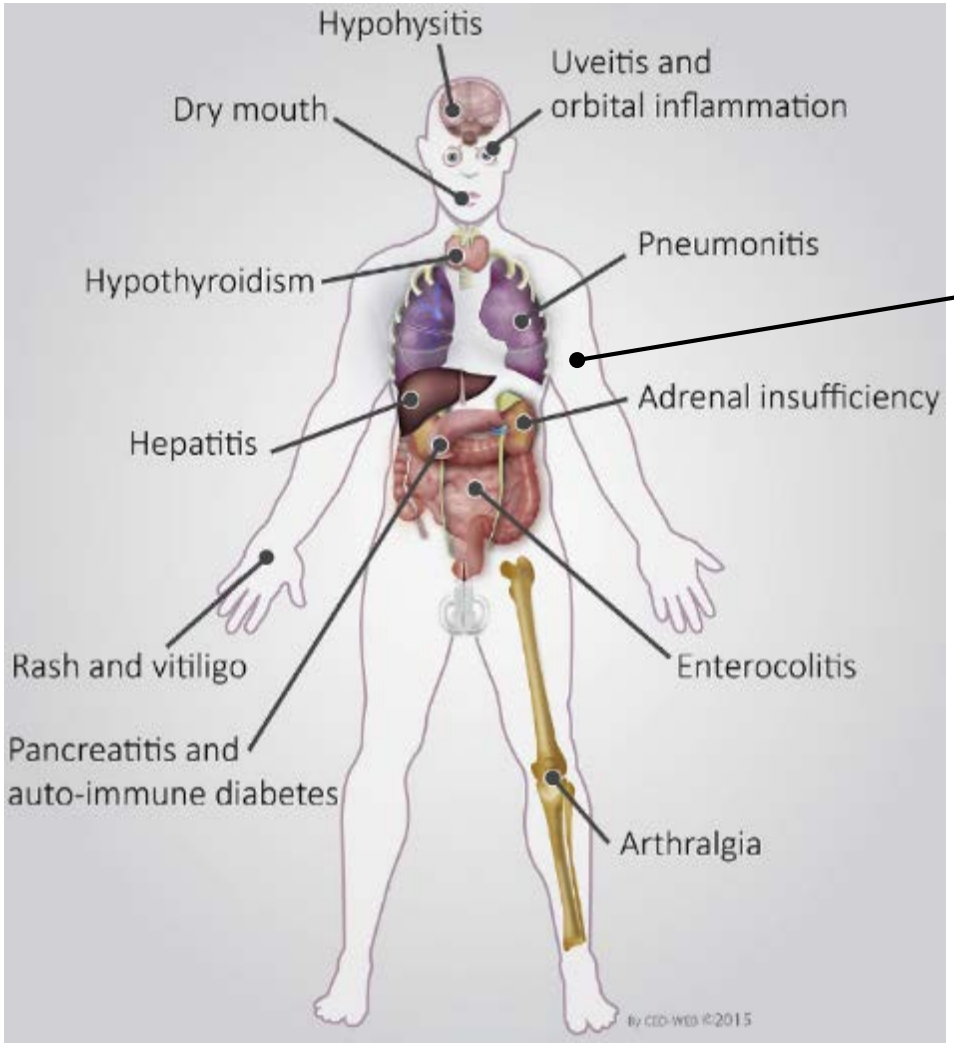
Advisory Board:

Merck, Pfizer, Genentech/Roche, Novartis

Adverse Events from Immune Checkpoint Inhibitors

- Generally do not induce cytokine like effects
- Autoimmunity can affect any organ system
  - But skin, GI, liver, and endocrine organs most common
  - Multiple organ systems can be affected (concurrently or serially)
- Incidence/severity anti-CTLA-4 > PD-1/PD-L1 antagonists
- Dose-relationship for anti-CTLA-4; not evident for active range of anti-PD-1/PD-L1
- Re-challenge with same agent often (but not always) leads to recurrent toxicity
- High grade AE to one class does not preclude safe administration of the other class
- Vast majority of events (except endocrine) completely reversible over time

Immune-Related Adverse Events: *Clinical Spectrum*



Immune checkpoint inhibitors also have an apparent effect on muscle tissue

Immune-Mediated ADVERSE REACTIONS

Pneumonitis[1]	Gastrointestinal events[1]	Skin[1]	Hepatic events[1]	Renal events[1]
• Non-infectious lung inflammation • Dry, unproductive cough • Tachypnea/dyspnea • Tachycardia • Cyanosis • Fatigue	• Diarrhea • Abdominal pain • Fever • Anal pain • Rectal bleeding • Weight loss • Nausea/vomiting Rule out alternative etiologies (progressive disease or infection)	• Pruritus • Rash • Dermatitis • Erythema • Photosensitivity • Toxic epidermal necrolysis • Urticaria • Vitiligo	Hepatic drug-related adverse events can present with asymptomatic increased liver function tests, including: • AST • ALT • GGT • Bilirubin (rare)	• Nephritis is the most inherent cause leading to renal toxicity • Renal failure may have no early clinical signs but can lead to: • Oliguria • Edema • Anuria • Electrolyte disorders

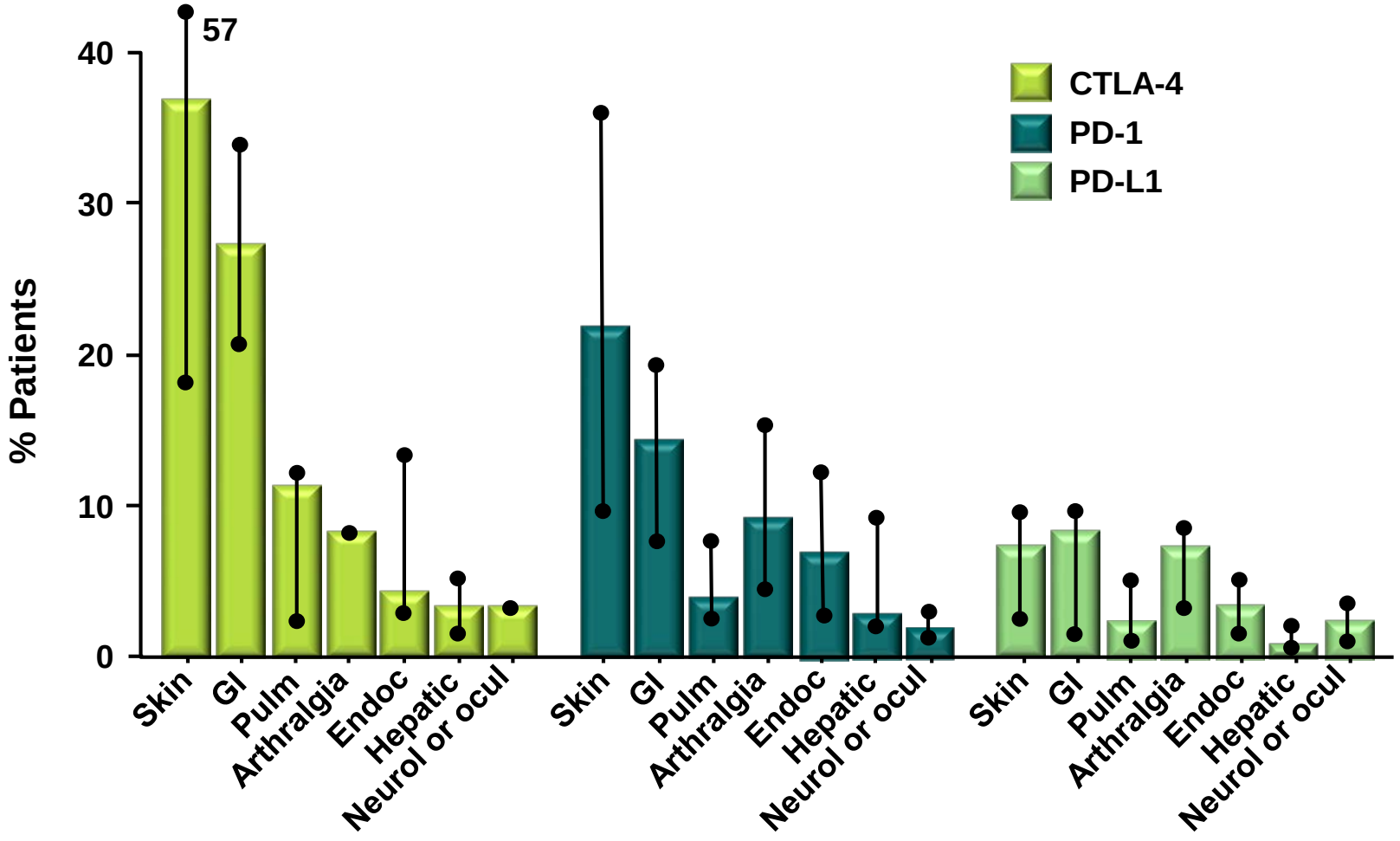
Endocrine events[1]	Carditis[2]	Neurological[3]	Eye[3]
Endocrine toxicities commonly manifest as: • Hypothyroidism • Hyperthyroidism Symptoms may include: • Unusual headaches • Extreme tiredness • Mood/behavior changes • Weight changes	Myocarditis can present as a broad spectrum of symptoms, from asymptomatic to signs of myocardial infarction to cardiogenic shock • Chest pain • Cardiac arrhythmias • Acute or chronic heart failure	• Myasthenia gravis • Guillain-Barré syndrome • Bell's palsy • Leukoencephalopathy • Radiculoneuropathy • Aseptic meningitis	• Uveitis • Conjunctivitis • Iritis • Grave's ophthalmopathy

ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase.

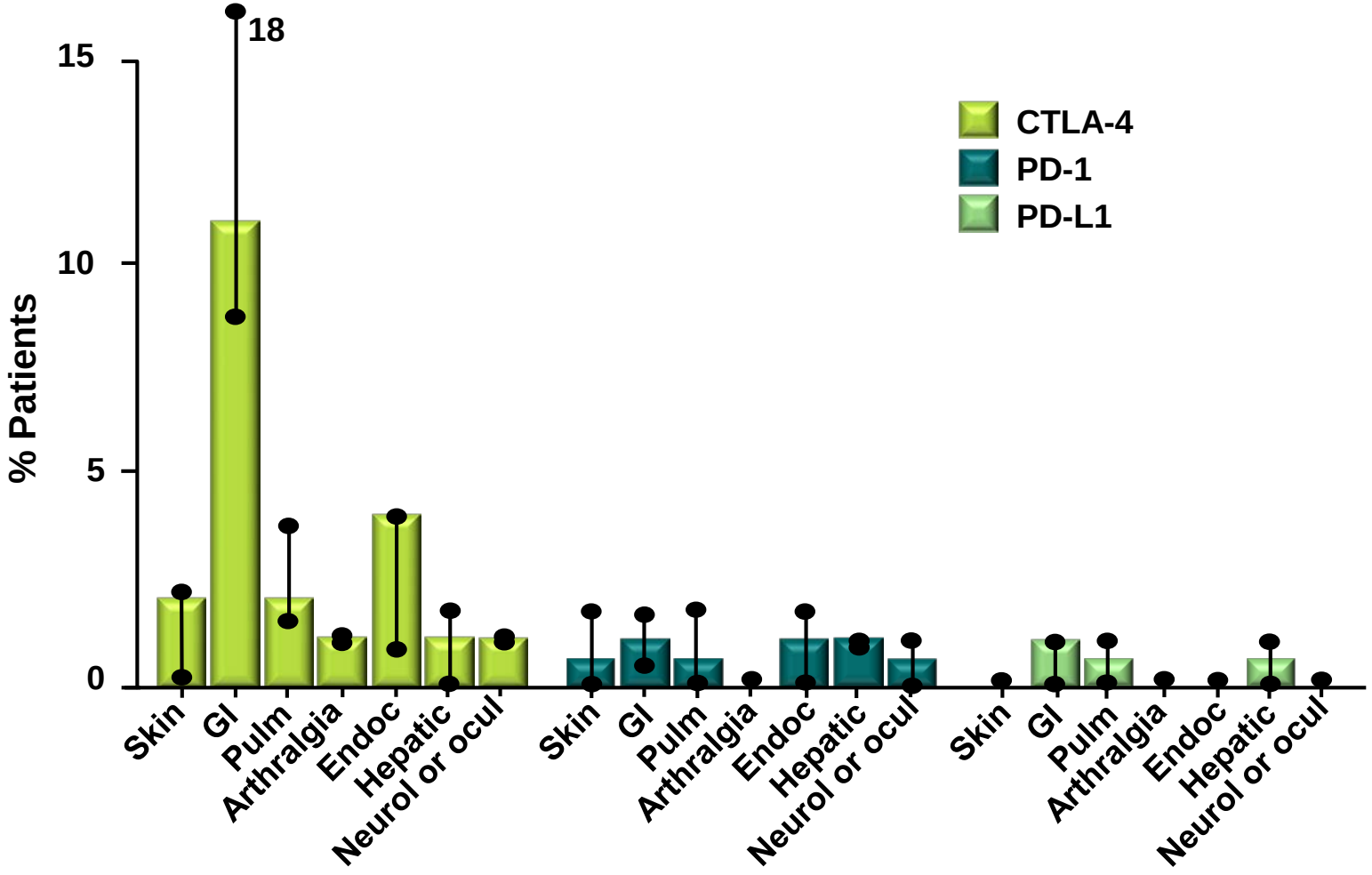
1. Eigentler TK et al. *Cancer Treatment Rev*. 2016;45:7-18. 2. Kindermann I et al. *J Amer Coll Cardio*l. 2012;59(9):770-792 3. Spain L et al. *Cancer Treatment Rev*. 2016;44:51-60.

CTLA-4 and PD-1/PD-L1 Blockade

Distribution of Grade 1-2 irAEs

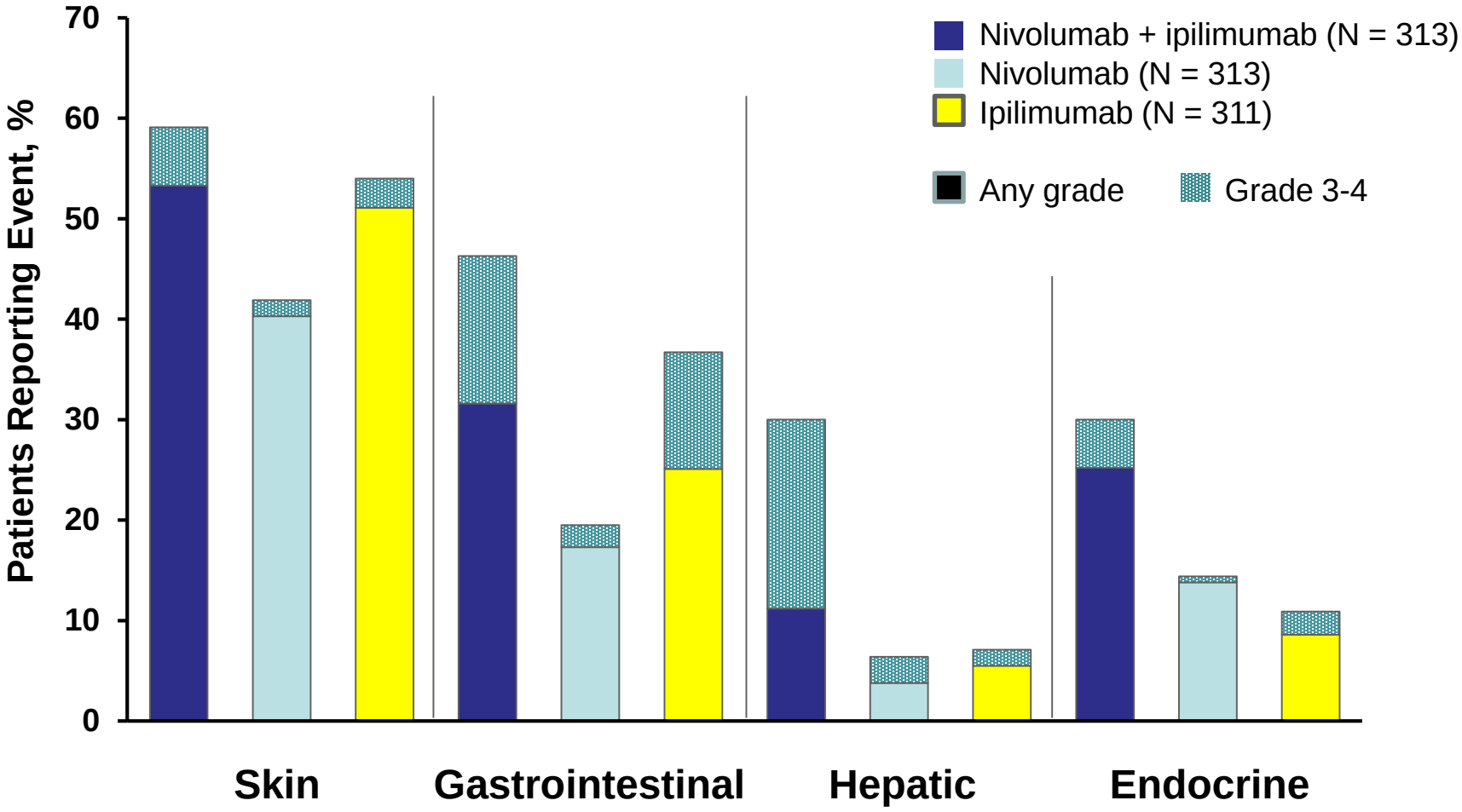


CTLA-4 and PD-1/PD-L1 Blockade
Distribution of Grade 3-5 irAEs



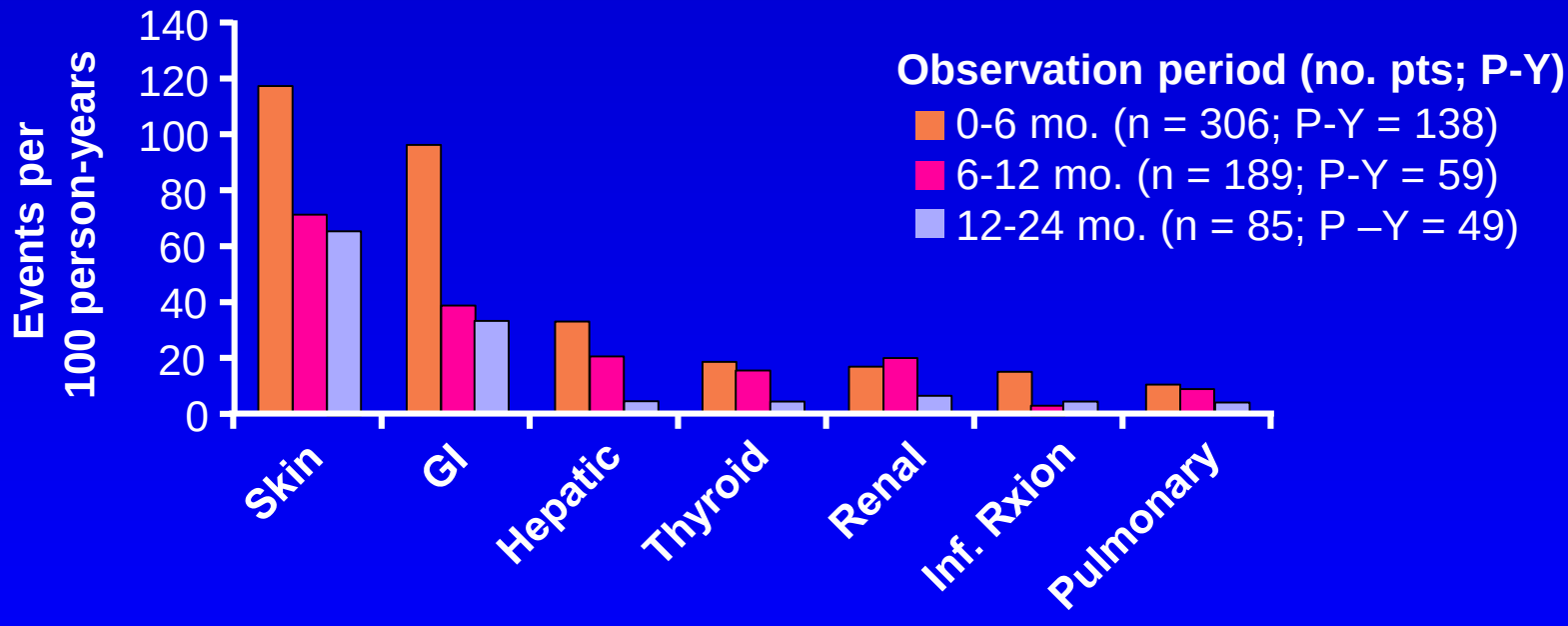
Ipilimumab Versus Nivolumab Versus Combination

irAEs Reported in ≥10% of Patients



Wolchok J et al. Presented at ASCO 2015; abstract LBA1.

Nivolumab Exposure-adjusted irAEs: Toxicity Is Not Cumulative

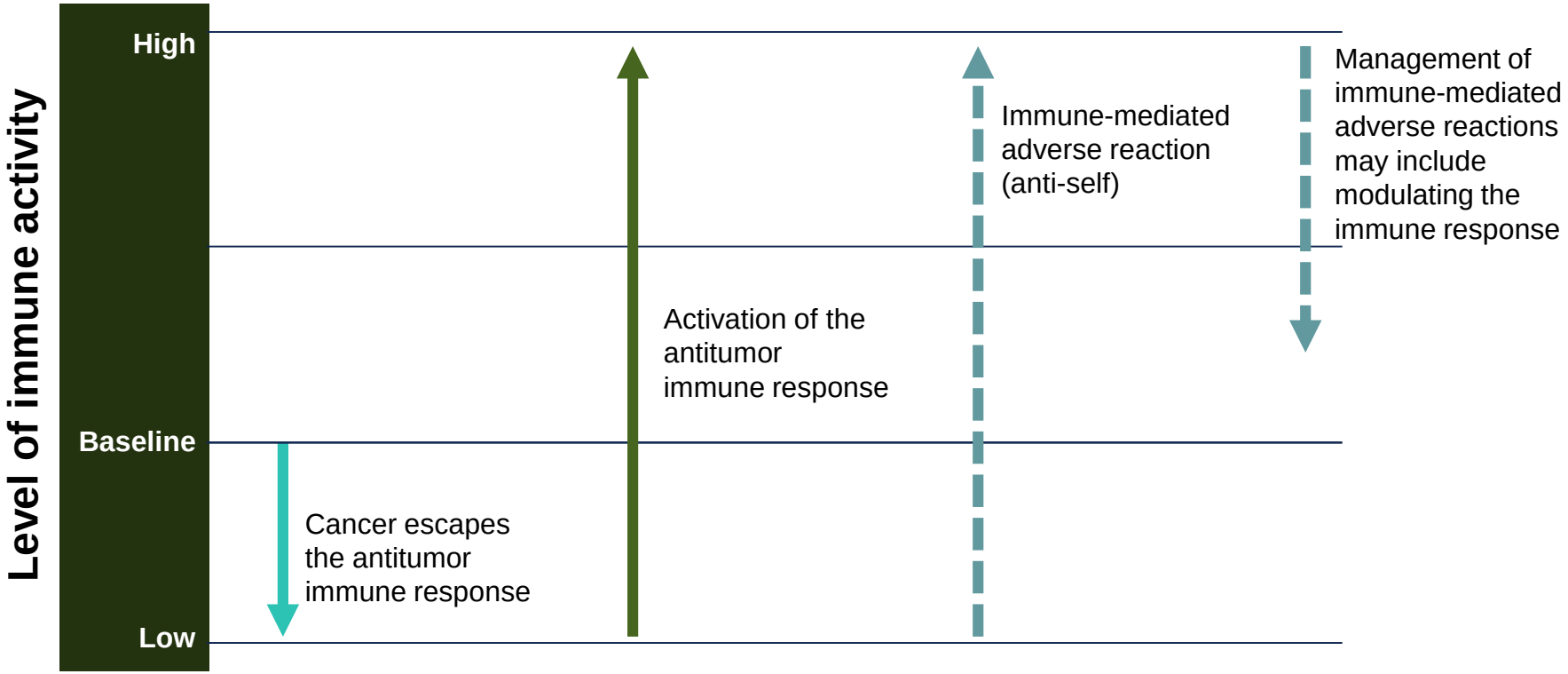


- Multiple occurrences of all-cause select AEs in individual pts are included in this exposure-adjusted analysis.
- Late arthritis-not included here

Topalian SL, et al. J Clin Oncol. 2014;32:1020-1030.

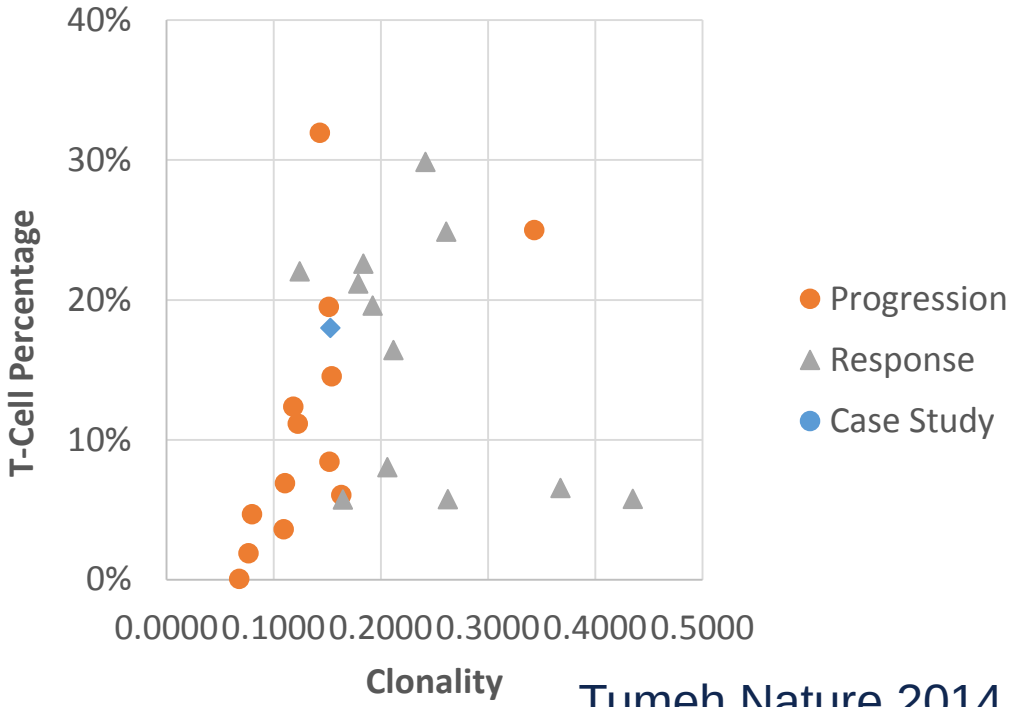
Immune-mediated adverse reactions

- Activating the immune response to attack tumors (nonself) may also result in attack of healthy cells (self)[1]
- The likelihood of an immune-mediated adverse reaction may be influenced by[2,3]
  - Type of immune cell being modulated
  - Type of antigen being targeted
- Median time to onset can range from days to years[4]



1. Amos SM et al. *Blood*. 2011;118(3):499-509. 2. Nishimura H et al. *Science*. 2001;291(5502):319-322. 3. Mellman I et al. *Nature*. 2011; 480(7378):480-490. 4. Eigentler TK et al. *Cancer Treatment Rev*. 2016;45:7-18.

TCR Clonality Study- Uveal Melanoma Case



Tumeh Nature 2014

Amino Acid Sequence	Rank of Metastatic Tumor Frequency	Rank of Whole Blood Frequency	Rank of Duodenal Frequency	Rank of Primary Tumor Frequency
CASRVTSGGYNEQFF	1	1	1	4
CASSPGDSHASNTGELFF	2	16	250	148
CSAGEEGYEQYF	3	30	-	60
CASSQNALGLAGTDTQYF	4	214	-	3
CASSSRRDNTGELFF	5	39	759	-
CASSGQPNSPLHF	6	-	-	-
CASSPIPNSPLHF	7	666	5473	18
CASTLGDRGTEAFF	8	98	51	29
CASSRTGYYNEQFF	9	78	61	-
CASSLIGITEAFF	10	325	-	-
CASSDVGSGLYEQYF	73	2	16	26
CASSQALAGAHEQFF	-	3	801	-

Cancer site, Co-morbidities, paraneoplastic syndromes might influence toxicity

- More vitiligo in melanoma patients
- More pneumonitis in lung cancer patients
- Neuropathy in patients with small cell lung cancer (Eaton Lambert)
- Hemolytic anemia in a patient with CLL

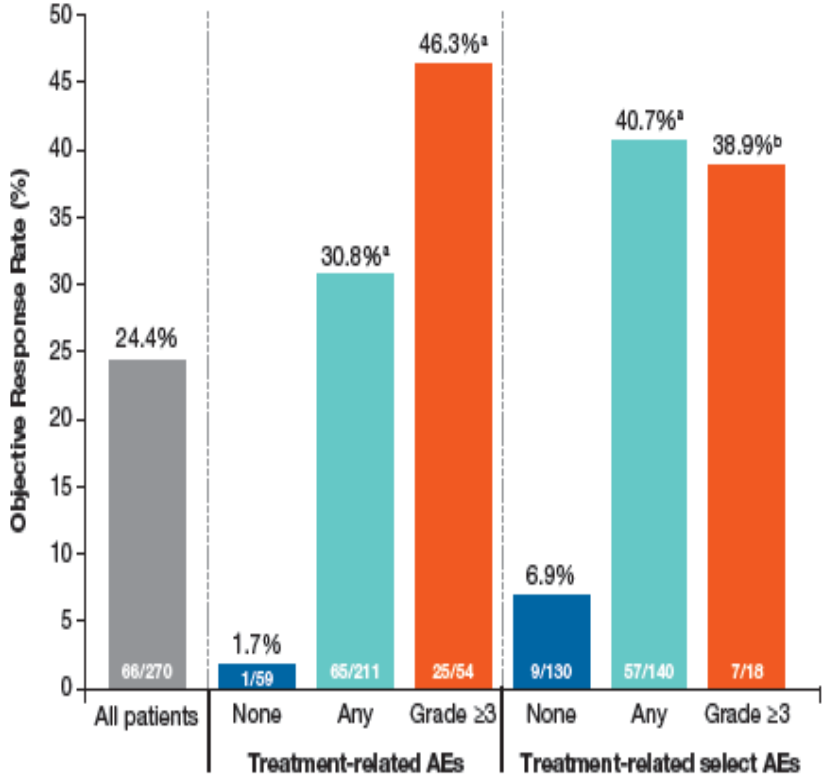
- Will likely see more of these going forward as patients get treated off protocol
  - patient selection important

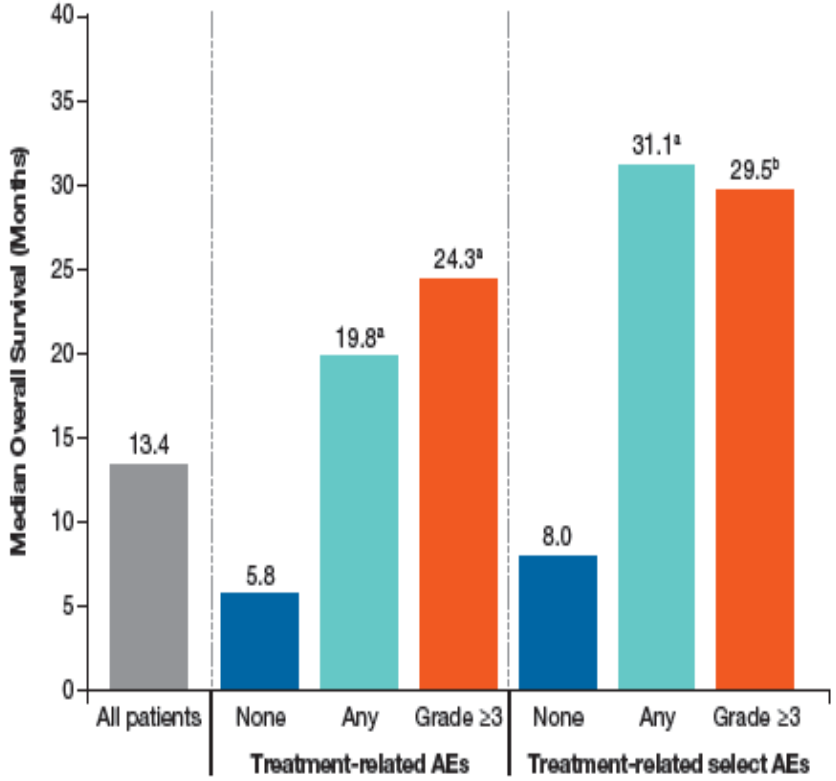
Mixed Combinations Might exacerbate toxicity of Non-IO Agent

- VEGFR TKIs
  - Increased fatigue with sunitinib
  - Increased LFTs with pazopanib
  - ? Increased cardiac toxicity
- Increased proteinuria with Bevacizumab
- Increased fever with dabrafenib
- Increased rash with vemu or MEKis
- Increased edema with SRS

- Toxicity might occur after IO stopped, if used in sequence

irAEs are associated with tumor response and survival





Topalian, Atkins et al, SITC 2017- Long Term Survival in Mel, rCC or NSCLCa, Treated with Nivo

Management of irAEs
Based on CTCAE Severity Grade

Severity CTCAE Grade	Type of Patient Care	Steroids	Other Immunosuppressive Drugs	Immunotherapy and Subsequent Approach
1	Ambulatory	Not recommended	Not recommended	Continue
2	Ambulatory	Topical steroids or systemic steroids oral 0.5-1 mg/kg/d	Not recommended	Suspend* temporarily
3	Hospitalization	Systemic steroids oral or IV 1-2 mg/kg/d for 3 d then reduce to 1 mg/kg/d	To be considered for patients with unresolved symptoms after 3-5 days of steroid course Organ specialist advised	Suspend and discuss resumption based on risk/benefit ratio with patient
4	Hospitalization consider the intensive care unit	Systemic steroids IV methylprednisolone 1-2 mg/kg/d for 3 d and then reduce to 1 mg/kg/d	To be considered for patients with unresolved symptoms after 3-5 days of steroid course Organ specialist advised	Discontinue permanently

[a]Outside skin or endocrine disorders, where immunotherapy can be maintained.

Michot JM et al. *Eur J Cancer.* 2016.

Take Home Messages

- Side effects from immune checkpoint inhibitors are distinct from those from conventional therapies
  - Grade 3 SAEs are uncommon with PD1 pathway blockers
  - Toxicity of Nivo/ipi combo is largely ipi like
- iRAEs can affect any organ system (renal, neuro, pneumo and pancreas more common with PD1pathway blockers than with ipi); pt variables may contribute
- Pt complaints and lab / radiographic abnormalities are auto-immune and drug-related until proven otherwise
  - R/O infections, metabolic causes, tumor effects, etc.
- Immunotherapy could impact toxicity of concurrent or subsequent treatment; change management
- Early recognition, evaluation and treatment are critical; holding CPI should never be an issue
- Patient and caretaker education is critical