

Practical Management Pearls for Immunotherapy for the Treatment of Melanoma

December 7, 2023

1:00 p.m. – 2:00 p.m. EST



The Practical Management Pearls and Case Studies Webinars are part of the Cancer Immunotherapy Clinical Practice Guidelines Advanced Webinar Series supported, in part, by grants from Amgen and Merck & Co., Inc. (as of 9/7/2023)

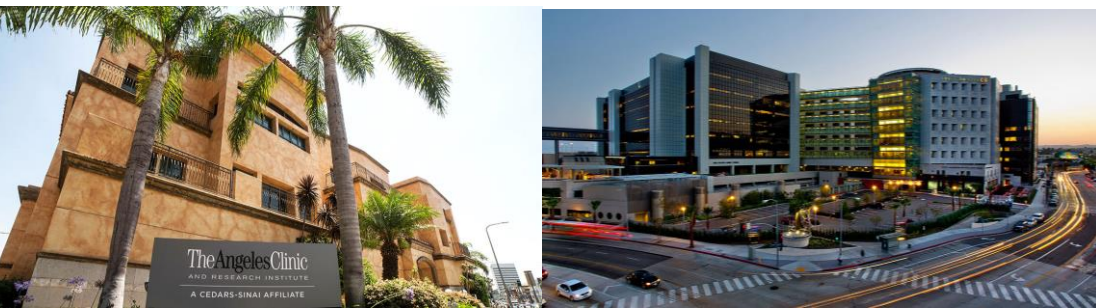
SITC Clinical Practice Guideline Webinar – Practical Management Pearls for Immunotherapy for the Treatment of Melanoma

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Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of melanoma, version 3.0

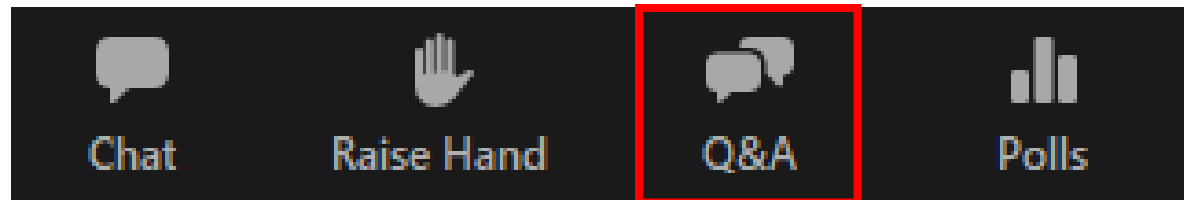
Anna C Pavlick ,¹ Charlotte E Ariyan,² Elizabeth I Buchbinder,³
Diwakar Davar ,⁴ Geoffrey T Gibney ,⁵ Omid Hamid,⁶ Tina J Hieken,⁷
Benjamin Izar ,⁸ Douglas B Johnson,⁹ Rajan P Kulkarni ,^{10,11}
Jason J Luke ,¹² Tara C Mitchell,¹³ Meghan J Mooradian ,¹⁴ Krista M Rubin,¹⁴
April KS Salama,¹⁵ Keisuke Shirai,¹⁶ Janis M Taube,¹⁷ Hussein A Tawbi ,¹⁸
J Keith Tolley,¹⁹ Caressa Valdueza,²⁰ Sarah A Weiss,²¹ Michael K Wong ,¹⁹
Ryan J Sullivan ¹⁴

Webinar Agenda

Welcome and Introductions	Omid Hamid, MD
GI Effects: Colitis, Pancreatitis, Duodenitis	Charlotte Ariyan, MD, PhD
Endocrine, Hypoadrenalism	Krista Rubin, MS, FNP-BC
Neuromuscular AEs, Triple M Syndrome	Shaheer Khan, DO
Q&A Session and Round-table Discussion	All
Closing Remarks	Omid Hamid, MD

How to Submit Questions

- Click the “Q&A” icon located on at the bottom of your Zoom control panel
- Type your question in the Q&A box, then click “Send”
- Questions will be answered in the Question & Answer session at the end of the webinar (as time permits)



Question and Answer

Welcome to Q&A
Questions you ask the host and panelists will show up here.

Type your question here...

☐ Send anonymously

Cancel Send

Omid Hamid, MD, has a financial interest/relationship or affiliation in the form of:

Contracted Research For Institution:

Arcus; Aduro; Akeso; Amgen; Bioatla; BMS; CytomX; Exelixis; Roche Genentech; GSK; Immunocore; Idera; Incyte; Iovance; Merck; Moderna; Merck-Serono; NextCure; Novartis; Pfizer; Sanofi Regeneron; Seagen; Taiga; Torque; Zelluna

Speakers Bureau participant with:

BMS; Novartis; Pfizer; Sanofi Regeneron

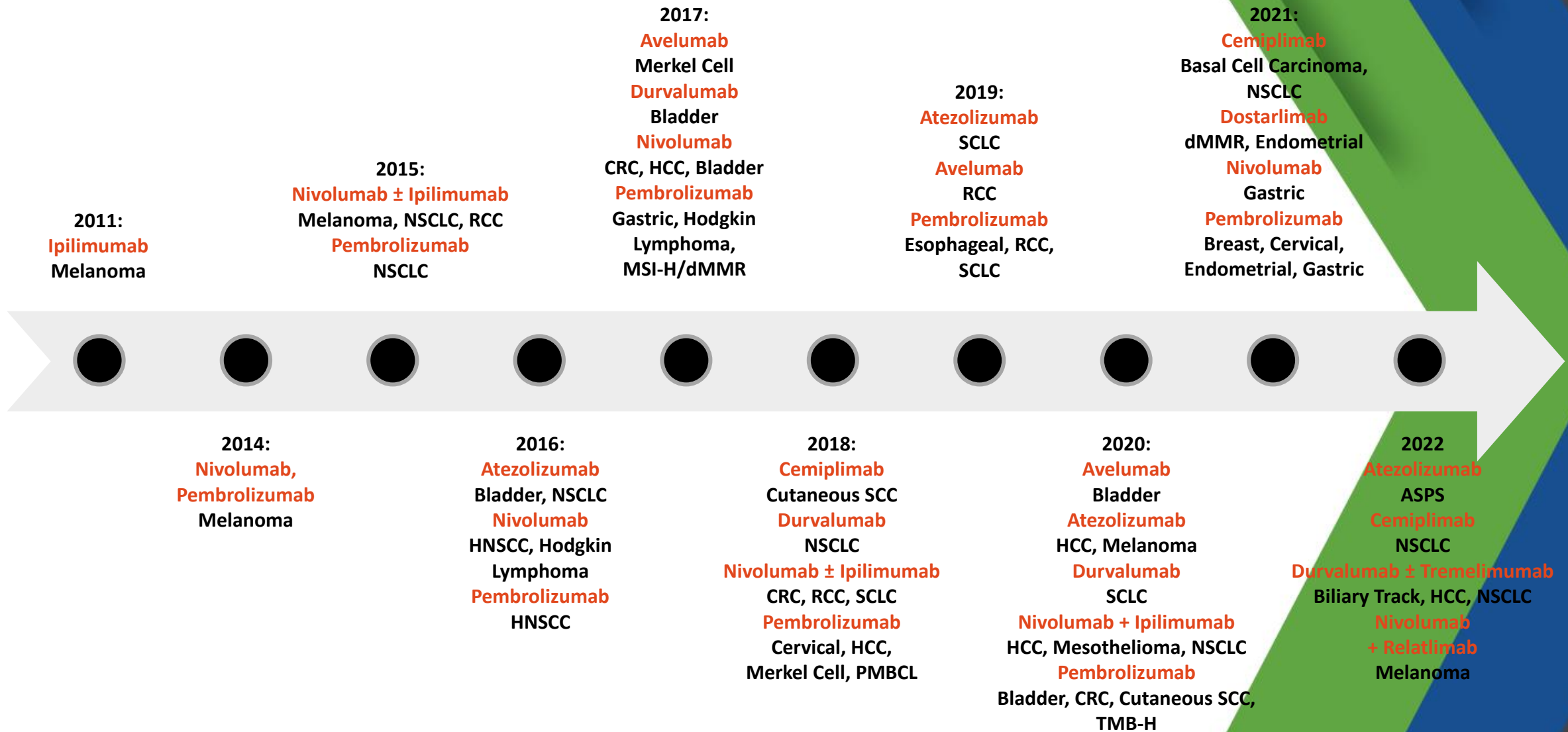
Advisory Board For:

Aduro; Alkermes; Akeso; Amgen; Beigene; Bioatla; BMS; Roche Genentech; Gigagen; GSK; Immunocore; Idera; Incyte; Janssen; Merck; NextCure; Novartis; Partner Therapeutics; Pfizer; Sanofi Regeneron; Seagen; Tempus; Zelluna

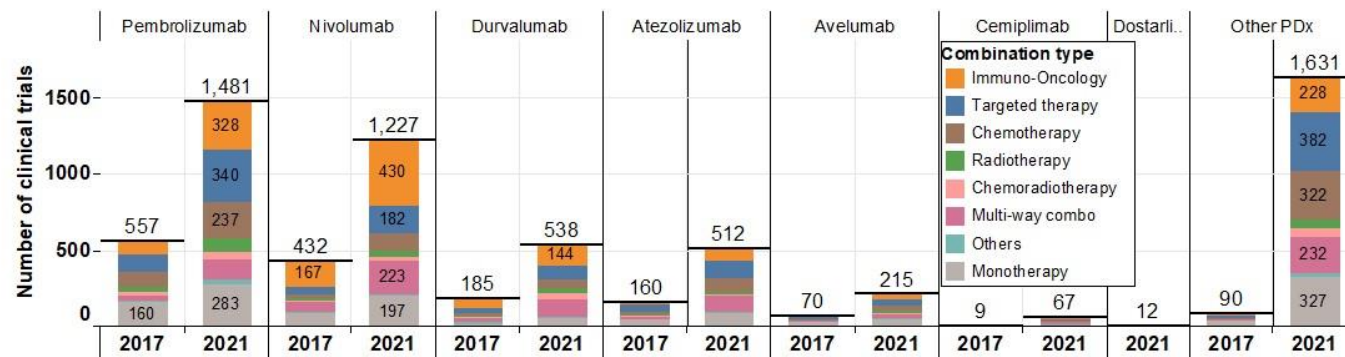
Omid Hamid, MD, does intend to discuss either non-FDA-approved or investigational use for the following products/devices: pembrolizumab as adjuvant therapy in high-risk stage II melanoma; various combination strategies with checkpoint inhibitors and vaccine-based approaches/targeted agents.



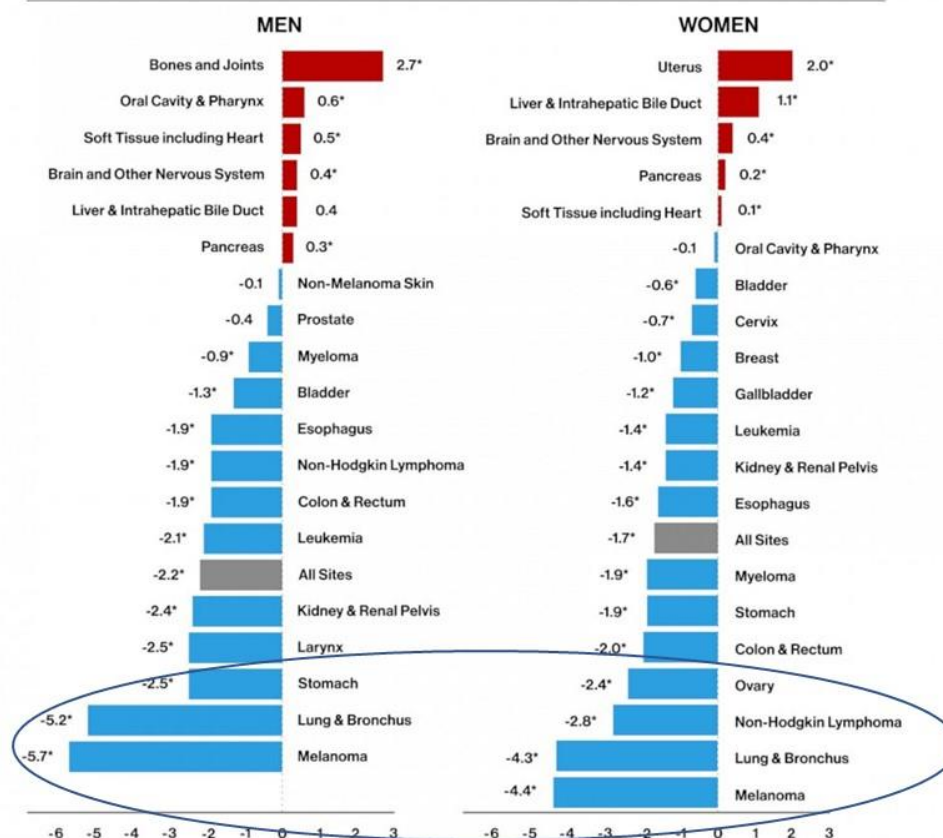
Timeline of Select FDA Approvals of ICI



ICI use in cancers is increasing significantly; and is dramatically altering death rates (in some cancers)



National Trends in Cancer Death Rates (2014-2018)

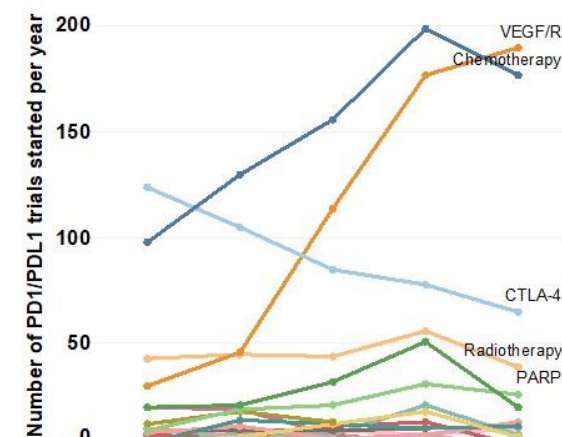


* AAPC is significantly different from zero ($p < 0.5$)

SOURCE: ANNUAL REPORT TO THE NATION

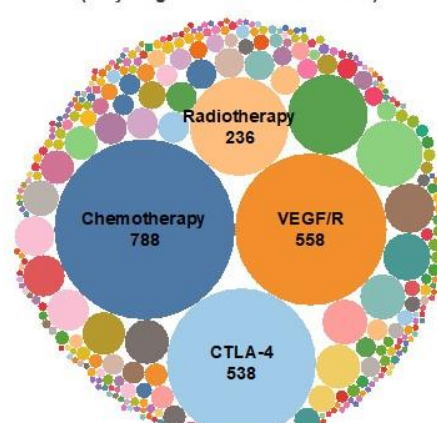
abc NEWS

Evolution of Top 20 Targets in 2021



4,652 combination trials using ~300 targets

(Only targets with > 5 trials shown)



NEUROLOGIC

- Posterior Reversible Encephalopathy
- Neuropathy
- Guillian-Barre Syndrome
- Myelopathy
- Autoimmune Encephalitis
- Aseptic Meningitis
- Myasthenia gravis
- Transverse Myelitis
- Non-specific symptoms: headache, tremor, lethargy, memory disturbance, seizure

RESPIRATORY

- Cough/dyspnea
- Laryngitis
- Pneumonitis
- Bronchitis
- Pleuritis
- Sarcoid-like granulomatosis

RENAL



- Tubulointerstitial nephritis
- Acute renal failure
- Lupus nephritis
- Granulomatous lesions
- Thrombotic microangiopathy

HEMATOLOGIC

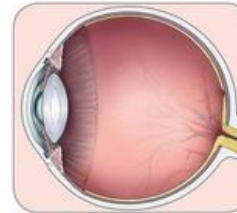
- Autoimmune hemolytic anemia
- Red cell aplasia
- Thrombocytopenia
- Leukopenia/Neutropenia
- Acquired hemophilia
- Myelodysplasia

DERMATOLOGIC

- Rash/Pruritis
- Mucositis
- Psoriasis
- Vitiligo
- Bullous pemphigoid
- Steven-Johnson syndrome
- DRESS syndrome



OCULAR



- Uveitis
- Conjunctivitis
- Scleritis, episcleritis
- Optic neuritis
- Blepharitis
- Retinitis
- Peripheral ulcerative keratitis
- Vogt-Koyanagi-Harada

CARDIOVASCULAR

- Myocarditis
- Pericarditis
- Pericardial effusion
- Arrhythmia
- Hypertension
- Congestive heart failure

ENDOCRINE

- Hyper or hypothyroidism
- Hypophysitis
- Adrenal insufficiency
- Diabetes

GASTROINTESTINAL

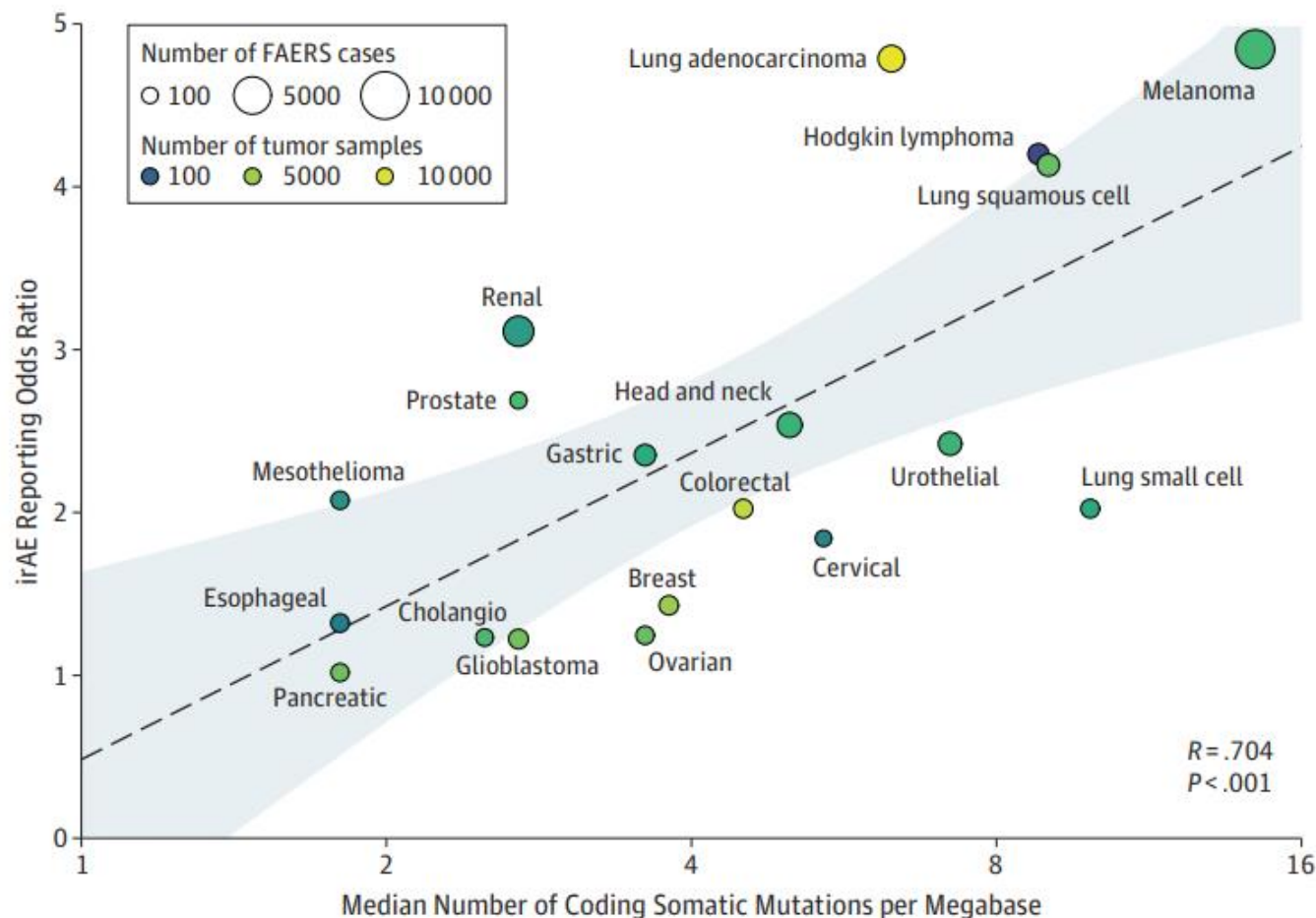
- Diarrhea
- Gastritis
- Colitis
- Ileitis
- Pancreatitis
- Hepatitis

RHEUMATOLOGIC

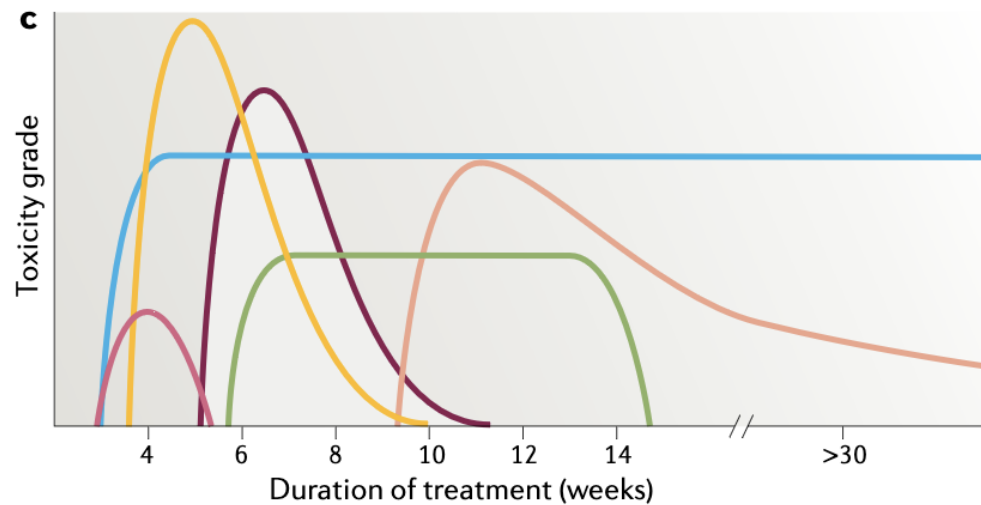
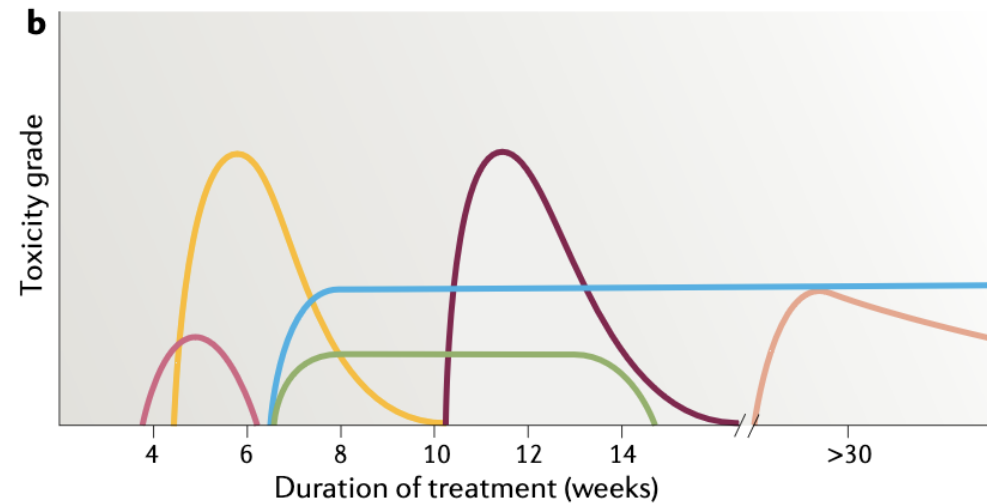
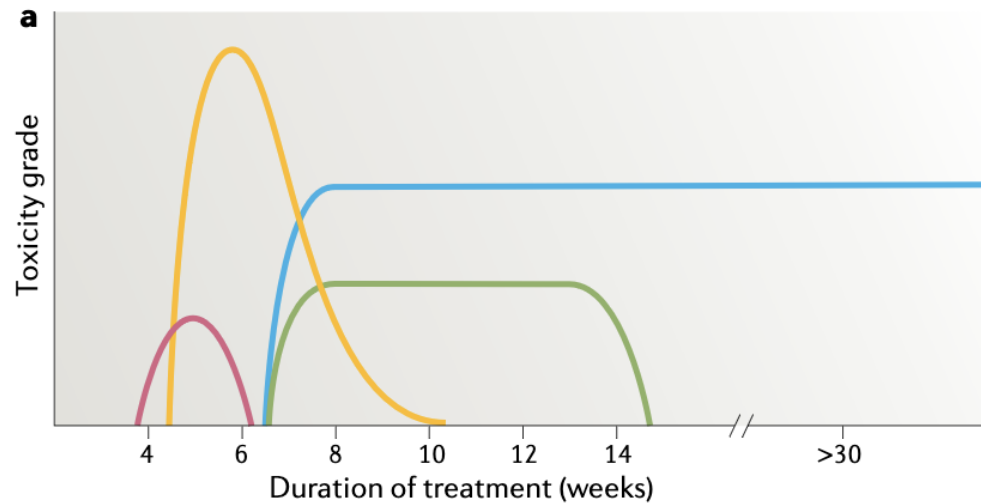
- Arthralgias/Myalgias
- Inflammatory Polyarthritis
- PMR-like
- Psoriatic Arthritis
- Oligoarthritis
- Vasculitis
- Sicca Syndrome
- Sarcoidosis
- Inflammatory myositis
- Resorptive bone lesions and fractures

Cross-antigen recognition

Figure. Association of Tumor Mutational Burden With Immune-Related Adverse Events During Anti-PD-1 Therapy Across Multiple Cancers



Kinetics of main irAEs.



Colitis	Endocrinopathy	Nephritis
Liver toxicity	Skin, rash or pruritus	Pneumonitis

Martins, F., Sofiya, L. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nature Reviews Clinical Oncology* 16, 563–580..

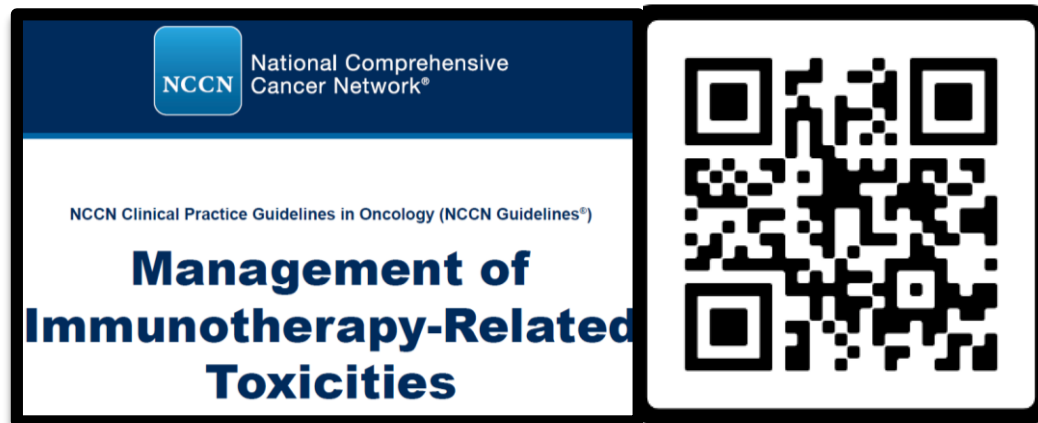
Management Guidelines



Haanen J et al. *Ann Oncol.* 2022;33(12):1217-1238.



Schneider BJ et al. *J Clin Oncol.* 2021;39(36):4073-4126.



NCCN. Clinical Practice Guidelines in Oncology. **Management of Immunotherapy-Related Toxicities, version 2.2023**. Accessed May 10, 2023. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf



Brahmer JR et al. *J Immunother Cancer.* 2021;9(6):e002435.

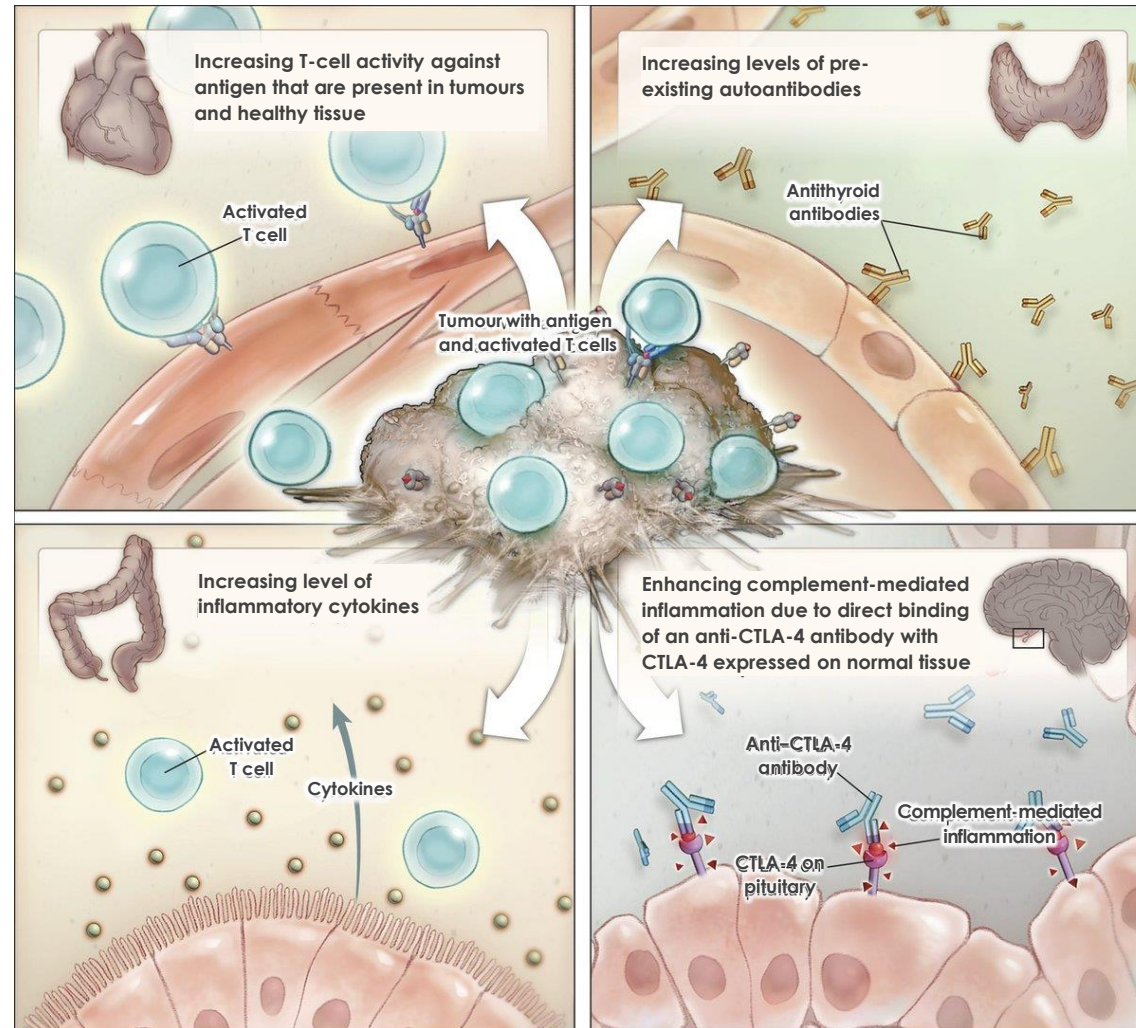
irAEs Result from Increased or Excessive Immune Activity, but the Immunomodulatory Cause May Vary

T-cells reacting to antigens in healthy tissue

- Myocarditis
- Vitiligo

Cytokine-mediated

- Colitis
- Arthritis
- Skin: psoriasis, eczema



Antibody-mediated

- Thyroiditis
- Hemolytic anemia
- Skin – Bullous pemphigoid
- Neurologic (myasthenia gravis, transverse myelitis, autoimmune encephalitis)

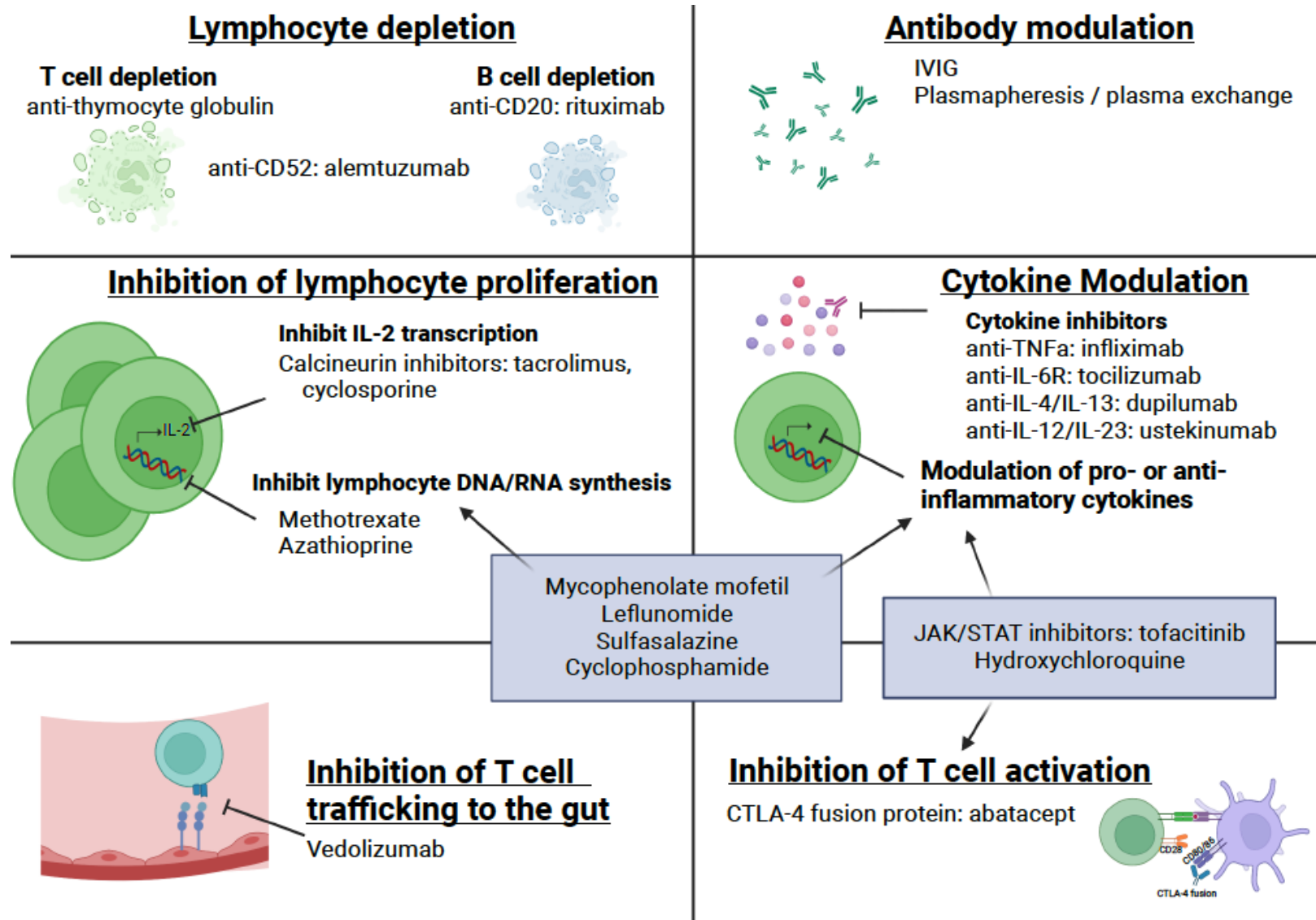
Expression of target (e.g., CTLA-4) in normal tissue

- Pituitary toxicity (Hypophysitis)

Immunomodulatory Agents to Manage irAEs

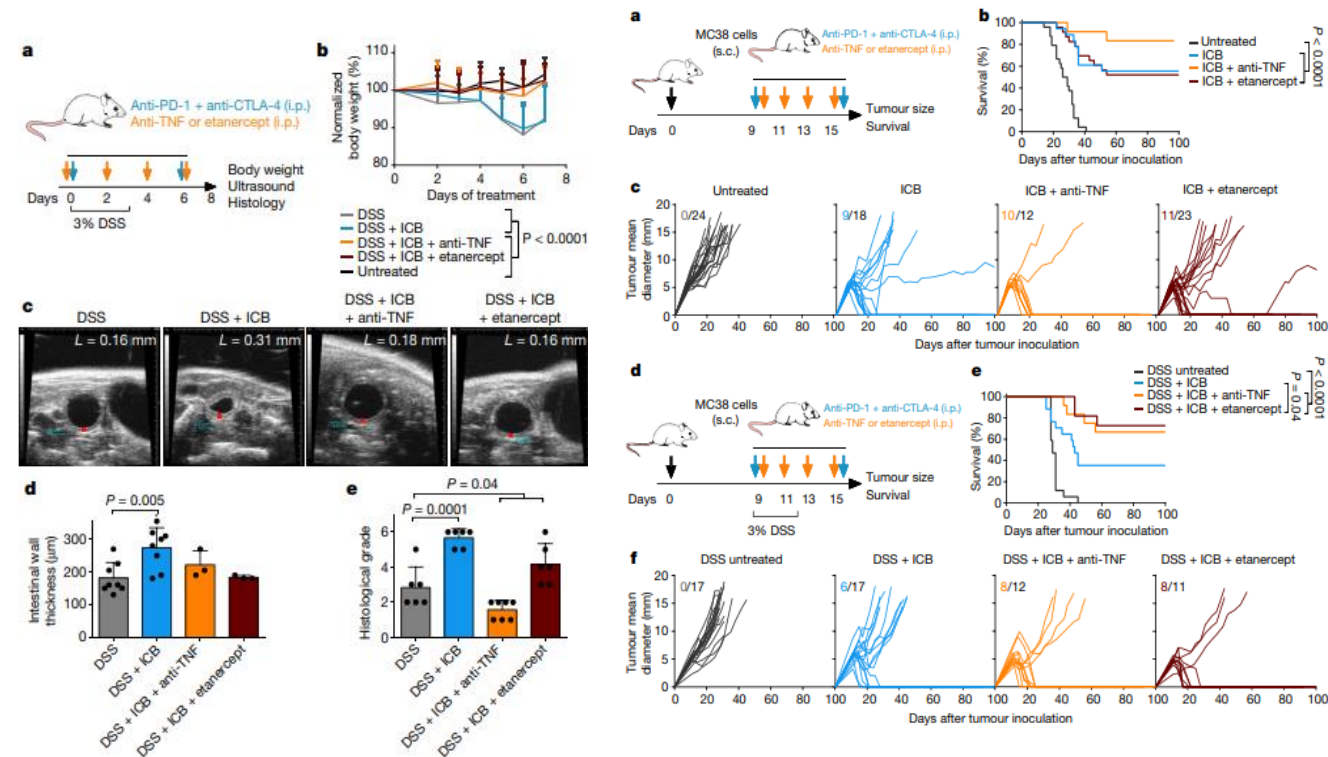
- Steroids (prednisone, methylprednisolone): nonspecific anti-inflammatory
- Mycophenolate: relatively selective inhibition of T-cells and B-cells (blocks inosine monophosphate dehydrogenase to prevent purine production)
- Biologic agents
 - Abatacept: targets CTLA-4 (T-cells)
 - Rituximab: targets CD20 (B-cells)
 - Infliximab: targets TNF- α
 - Tocilizumab: targets IL-6
 - Vedolizumab: $\alpha 4\beta 7$ integrin inhibitor

Our tools to treat toxicity are very crude?



Prophylactic TNF blockade uncouples efficacy and toxicity in dual CTLA-4 and PD-1 immunotherapy

Elisabeth Perez-Ruiz^{1,2,3,4,5}, Luna Minute^{1,2}, Itziar Otano^{1,2}, Maite Alvarez^{1,2}, Maria Carmen Ochoa^{1,2,6}, Virginia Belsue^{1,2}, Carlos de Andrea^{2,7}, Maria Esperanza Rodriguez-Ruiz^{1,3}, Jose Luis Perez-Gracia^{2,3,6}, Ivan Marquez-Rodas^{6,8}, Casilda Llacer⁹, Martina Alvarez^{5,10,11}, Vanesa de Luque^{5,10}, Carmen Molina^{1,2}, Alvaro Teijeira^{1,2,6}, Pedro Berraondo^{1,2,6,13*} &



A Phase II Study of the Interleukin-6 Receptor Blocking Antibody Sarilumab in Combination with Ipilimumab, Nivolumab and Relatlimab in Patients with Unresectable Stage III or Stage IV Melanoma

Abbreviations: C = cycle, D= day; FU = follow-up; Ipi = ipilimumab; Nivo = nivolumab; PD = progressive disease;.

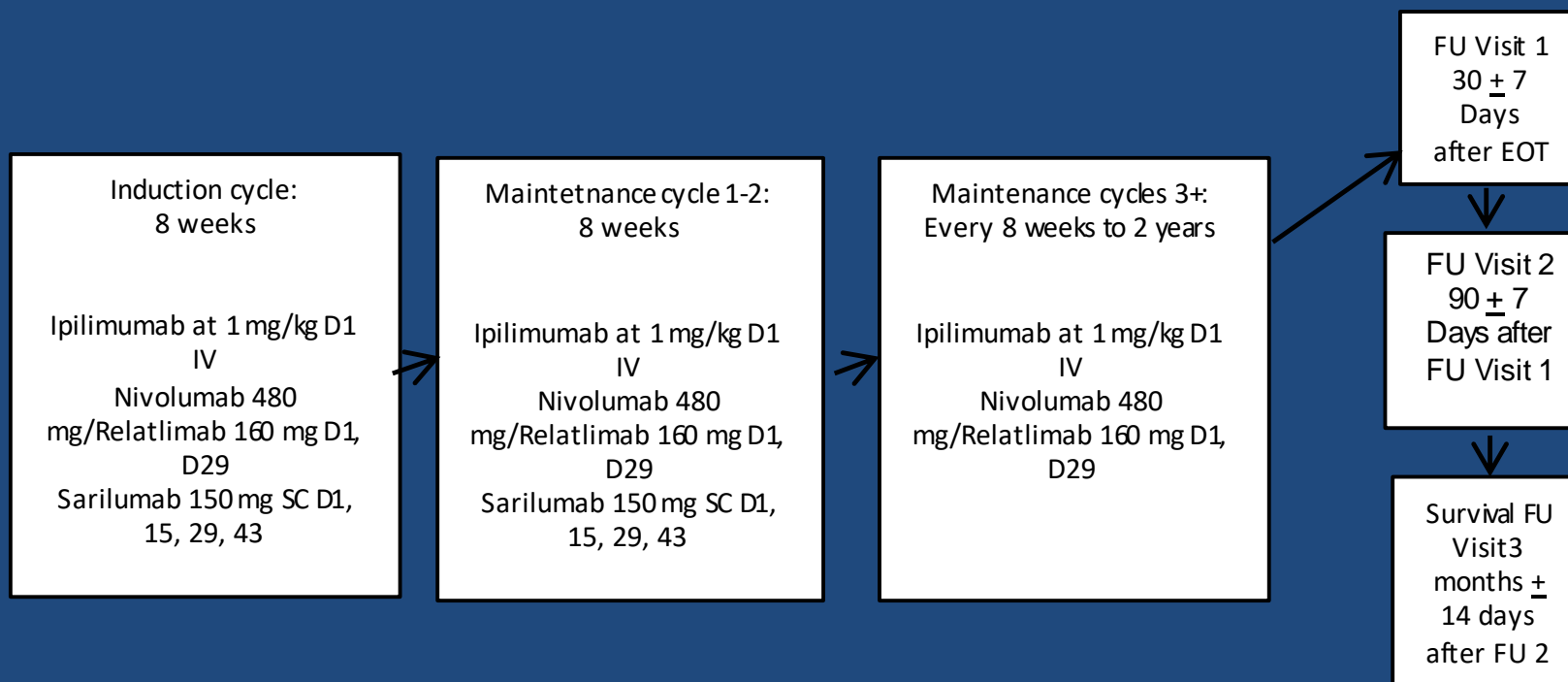


TABLE 3 Ancillary management recommendations for oral mucosal and salivary irAEs

Topical agents ^a	When to prescribe	How to prescribe ^b
Class I steroid		
<ul style="list-style-type: none">• Clobetasol propionate 0.05% gel/ointment/solution^c• Betamethasone dipropionate 0.05% gel/ointment	Gel is preferred for focal intra-oral mucosal lesions	Dry affected area and apply gel or ointment
Class II steroid		OR
<ul style="list-style-type: none">• Dexamethasone solution 0.5 mg/5 ml• Fluocinonide 0.05% gel/ointment• Betamethasone dipropionate 0.05% ointment	Solution is preferred for diffuse oral mucosal lesions; clobetasol solution is preferred for grade ≥ 3 oral irAEs	Saturate a strip of gauze with gel and apply to affected site for 10 min
Class III steroid		OR
<ul style="list-style-type: none">• Triamcinolone 0.1% dental paste	Ointment is preferred for lip vermilion lesions (Note: only use Class V or lower steroid or tacrolimus ointment on the vermilion if expecting long-term (>2 week) use due to risk of atrophy)	Place gel in gingival stent and apply for 10 min
Class IV or V steroid		OR
<ul style="list-style-type: none">• Fluocinolone acetonide 0.025% ointment• Desonide 0.05% ointment		Swish 5 ml of solution for 5 min and spit out
Non-steroidal agent		
<ul style="list-style-type: none">• Tacrolimus 0.1% ointment/solution^c		
Analgesics		
<ul style="list-style-type: none">• Viscous lidocaine 2%• Aluminum-magnesium-simethicone-diphenhydramine-lidocaine 1:1:1 solution	As needed/tolerated	Swish 5–15 ml and spit out
Sialagogues		
Pilocarpine	Consider for any grade salivary irAE	5 mg 3 times daily
Cevimeline		30 mg 3 times daily

Note: Adapted with permission from Oral Pathology: A Comprehensive Text and Atlas, 2nd ed (p. 505) by SB Woo, 2017, Elsevier.

^aWhile specific topical steroids are provided, others of equivalent class may be considered.

^bTopical therapies may be applied up to four times daily depending on severity and treatment response. No food or drink for 20 min following application.

^cSolution requires compounding.

Management:

Increase hydration

Avoid Caffeine/Smoking

Biotene, Xylimelts, sugar-free gum

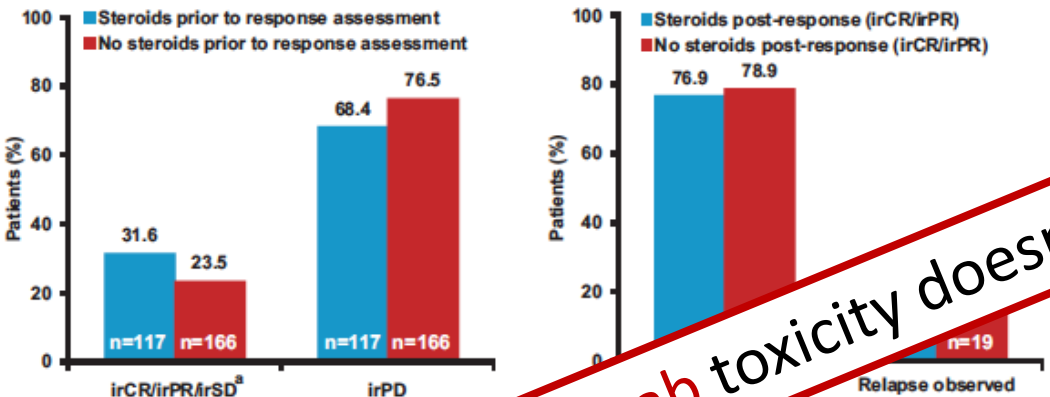
Pilocarpine

Topical fluoride

Very severe – consider steroids/hold ICI

Does irAE treatment mitigate benefit?

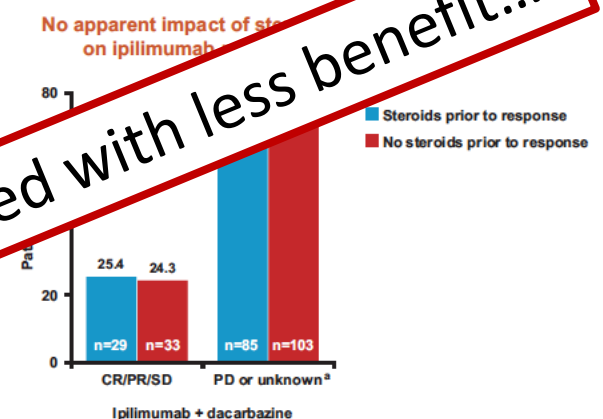
Clinical Response Was Not Affected by Use of Corticosteroids in Phase II Trials



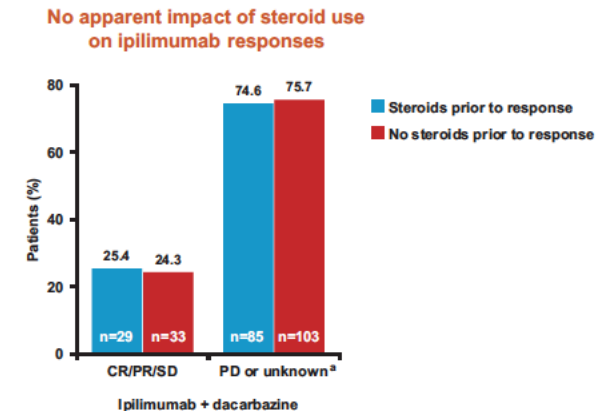
^aExcluding patients who had...
irCR=immune-related...
irPR=immune-related...
irSD=immune-related stable disease;
Amin... May 29-June 2, 2009; Orlando, FL.



No Impact of Systemic Corticosteroids on Clinical Response in Phase III Study CA184-024

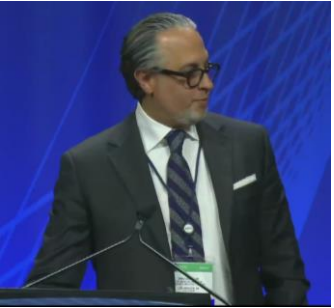


No Impact of Systemic Corticosteroids on Clinical Response in Phase III Study CA184-024



^aIncluding patients who had SD followed by PD.
CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease
Baurain et al. Presented at: ASCO Annual Meeting; June 1-5, 2012; Chicago, IL.





Key Takeaways: Impact on Practice

Education leads to Identification and Appropriate Therapies

Awareness is the key

Guidelines

Early ID, Slow tapers

DDx: irAE

Look for them as they may travel in bunches

Educate your colleagues

.....