Case Based approach to Managing Patients With Immune Mediated Toxicities

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Disclosures

- Maria Czupryn
  - Honoraria, consulting or advisory role, speakers' bureau, and travel, accommodation, or expenses: Merck and Novartis .

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Objectives

Utilize patient case studies to highlight the following:

- Incidence and Importance of early recognition of common Immune- mediated toxicities.
- Identify serious and uncommon toxicities of immunotherapy
- Treatment algorithms for immune-mediated adverse events.

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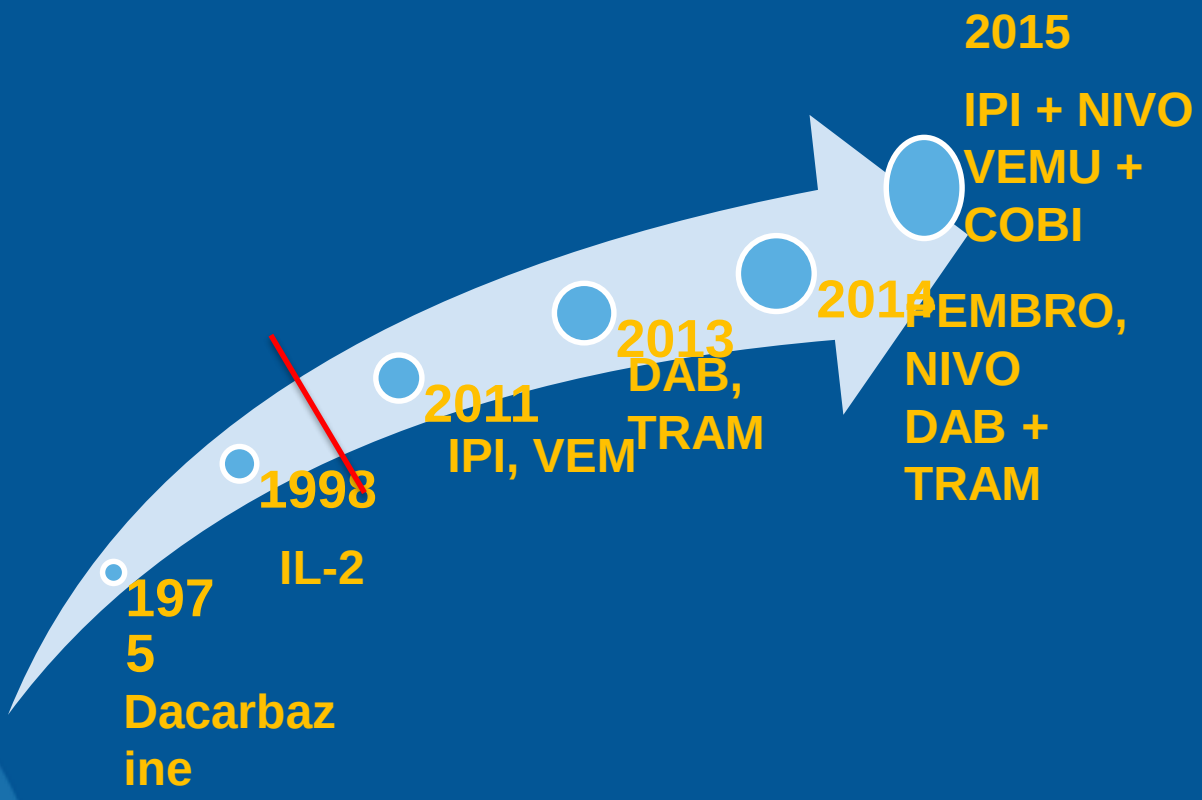
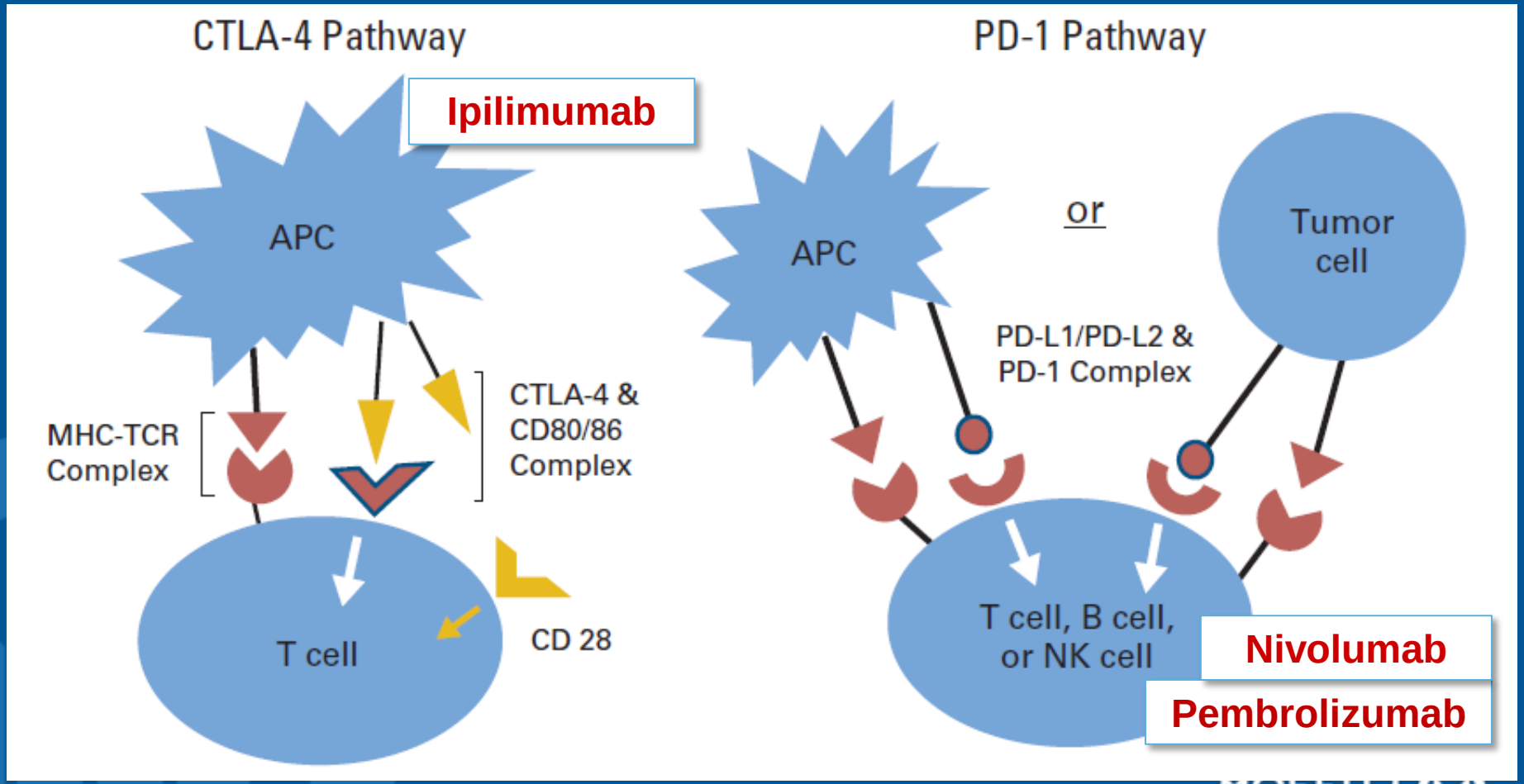
Therapeutic Timeline



CTLA-4 and PD-1 Pathways



Brahmer JR. *J Clin Oncol.* 2013; 31:1021-28.

Case Study

Mr. M.C is a 65 yr old male with a recent diagnoses of stage IV melanoma to the lung. Patient has consented to start Pembrolizumab at 2mg/kg every 3 wks.

- Mr. M.C and family would like to know what are the most common adverse events with this immunotherapy?

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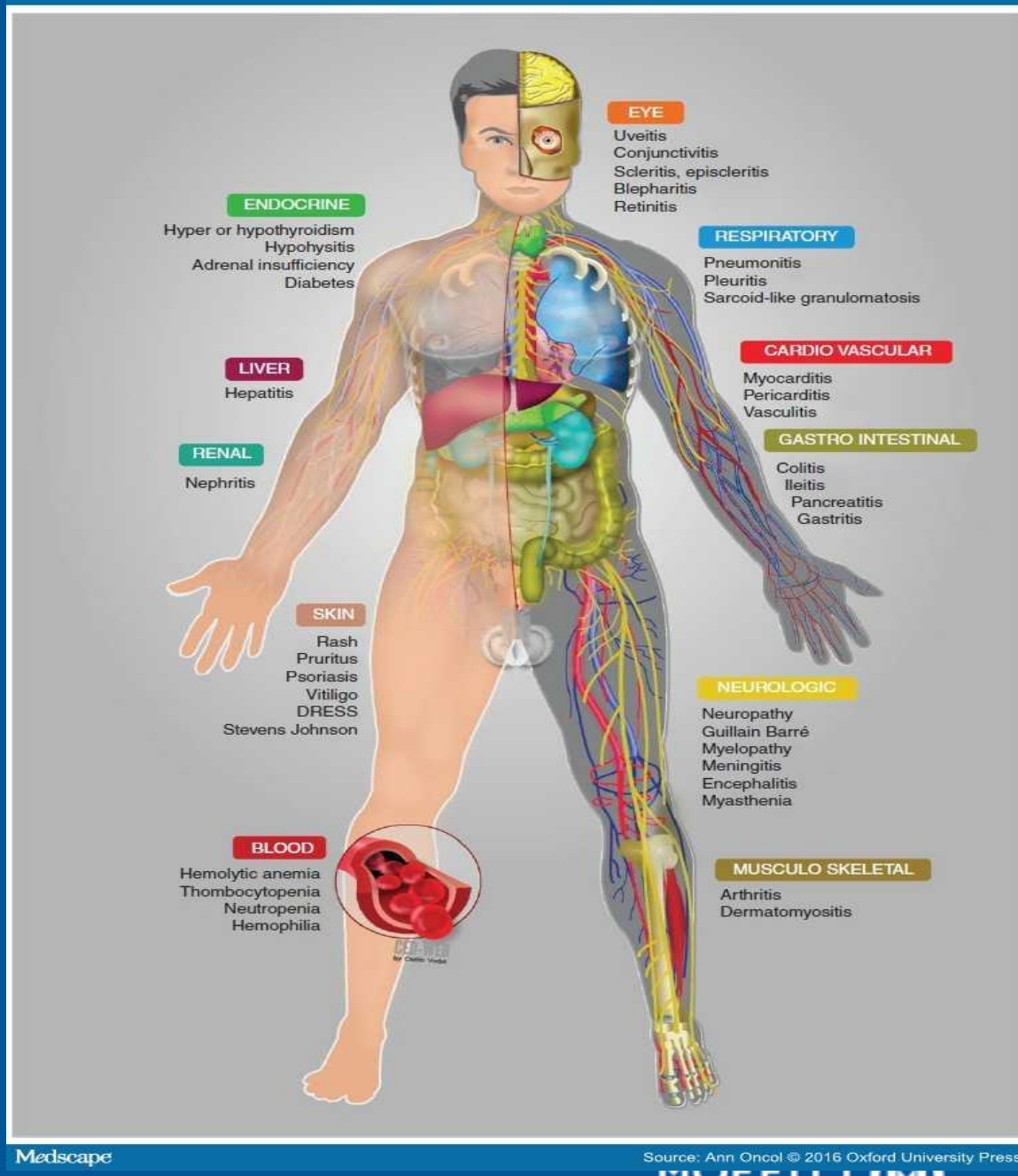
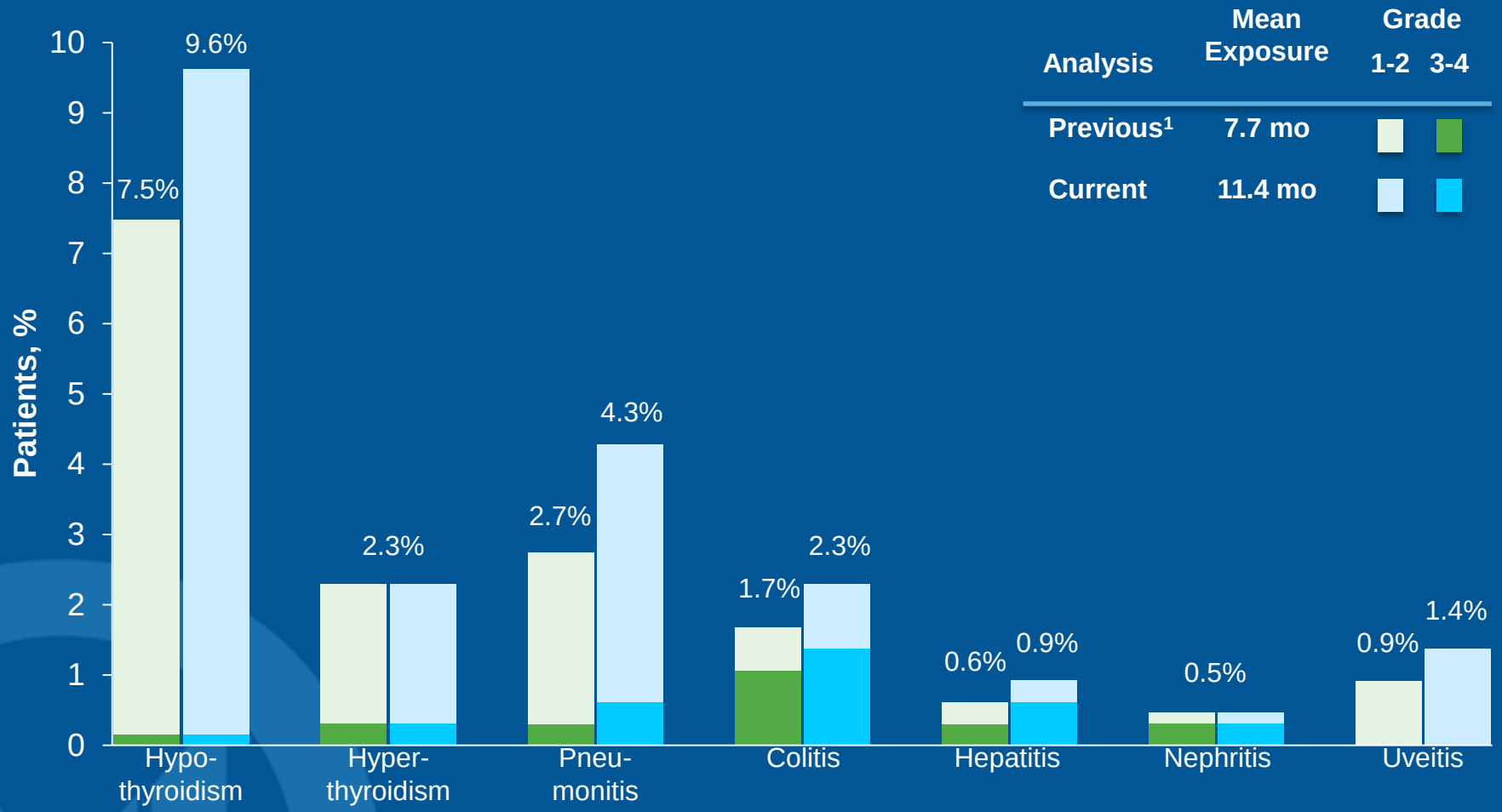
Spectrum of toxicities of immune checkpoint blockade agents

Champiat S, et al, Ann Oncol, 2016



Incidence of Immune-Mediated Aes[a]

Pembrolizumab



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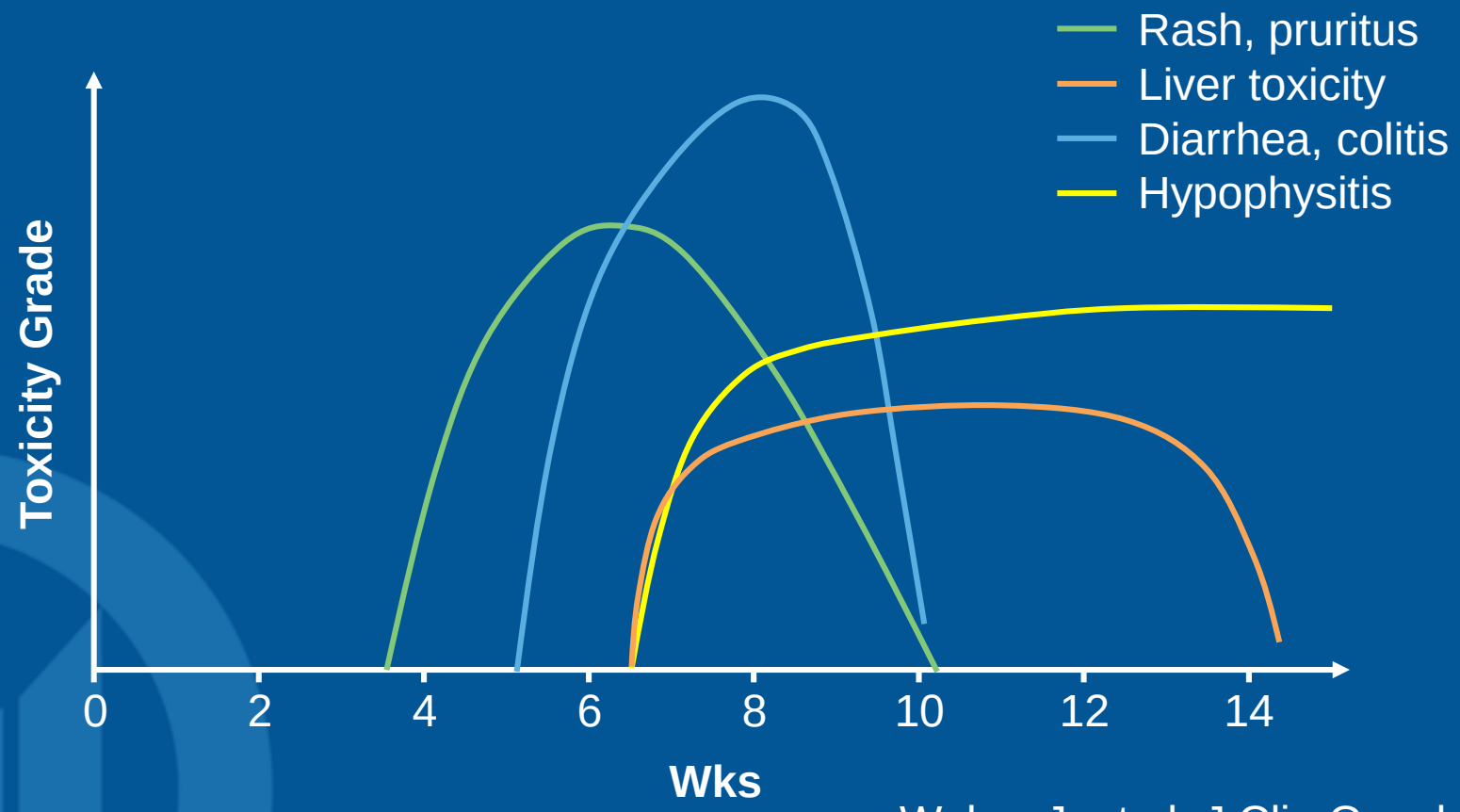
1. Ribas A et al. *JAMA* 2016;315:1600-9.

[a]Based on a list determined by the sponsor and regardless of attribution by the investigator.

Kinetics of Appearance of irAEs with Ipilimumab



Weber J, et al, J Clin Oncol. 2012

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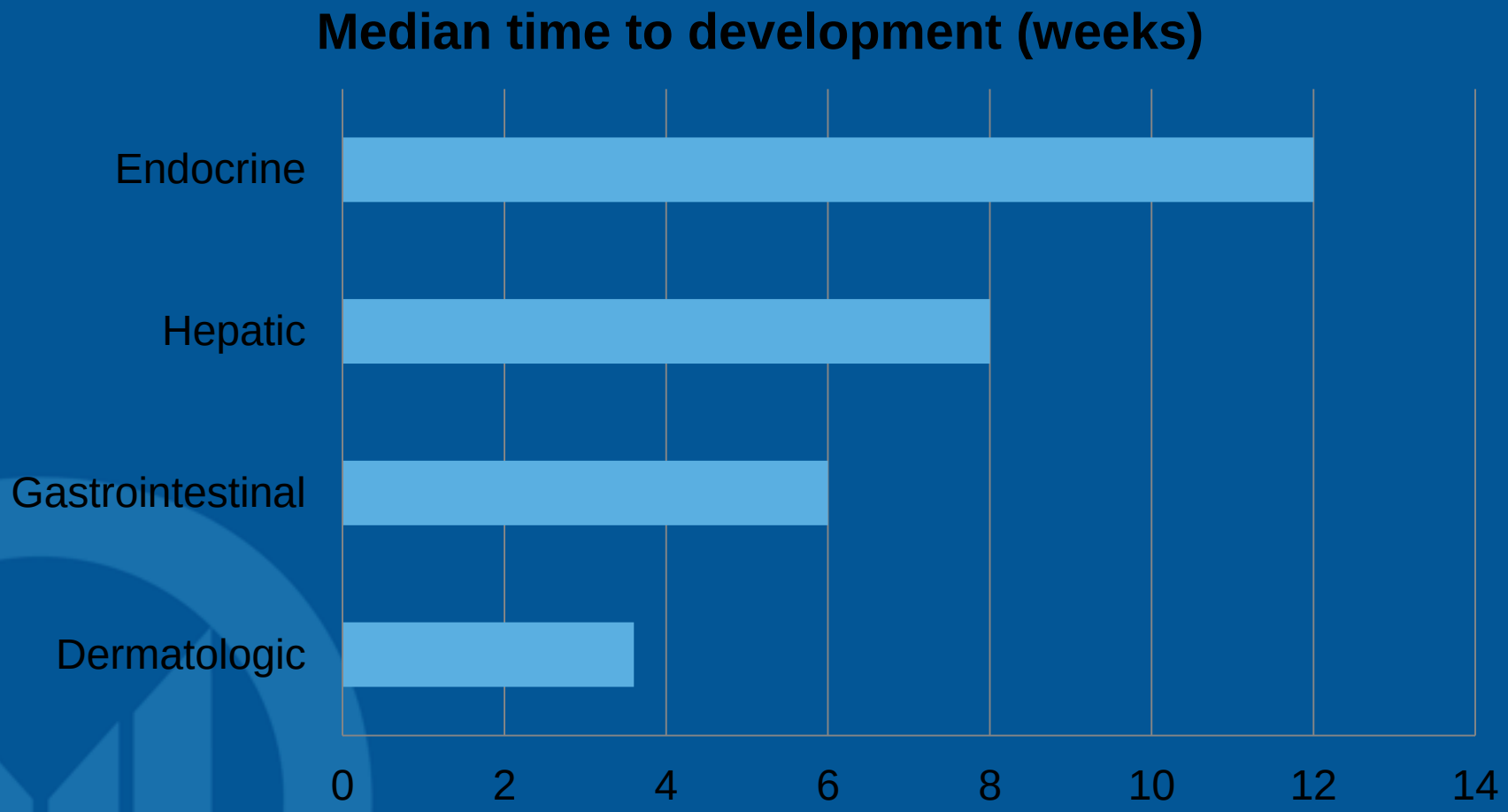
Immune checkpoint inhibitors- irAE's



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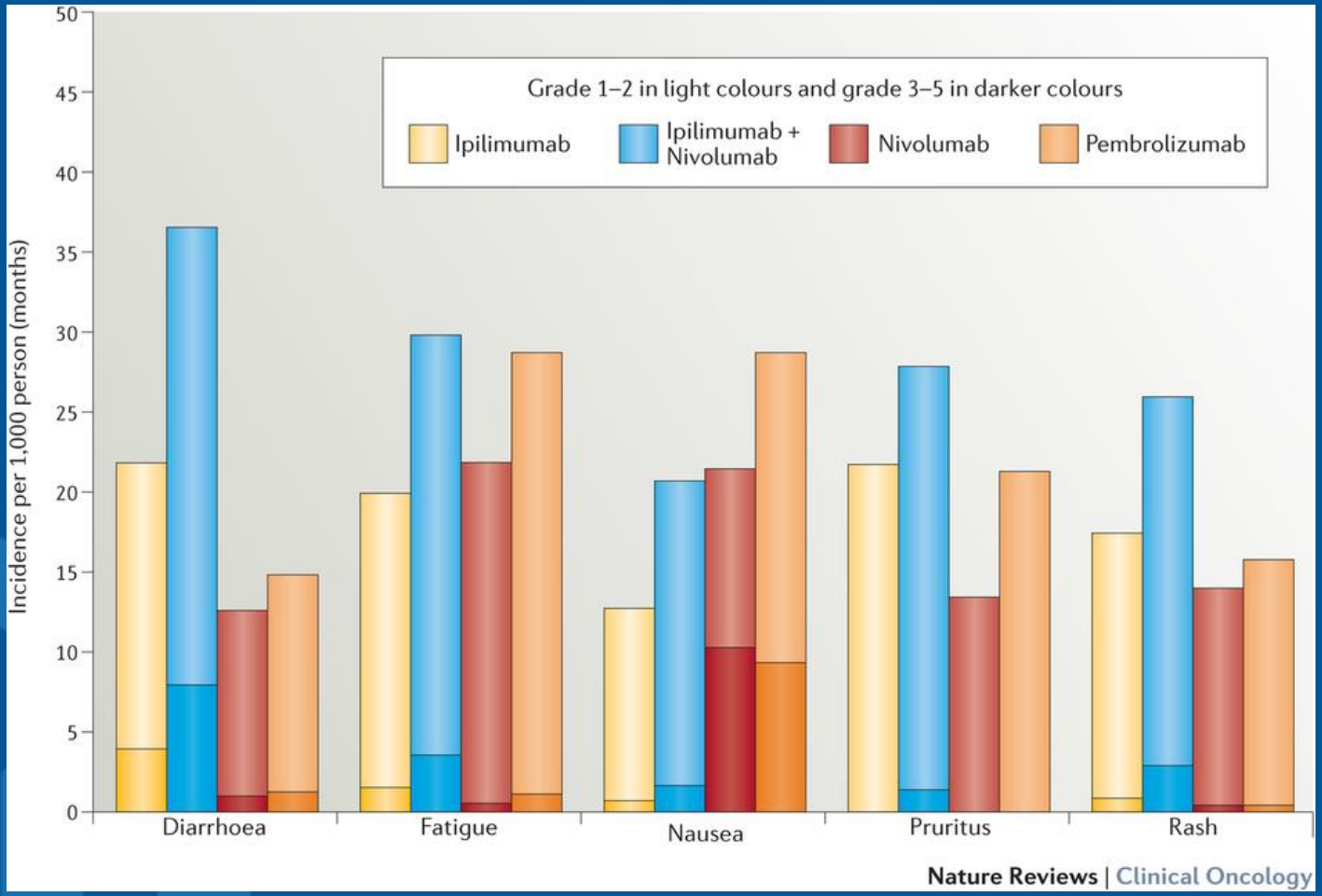
Incidence of AEs with immune check-point inhibitors



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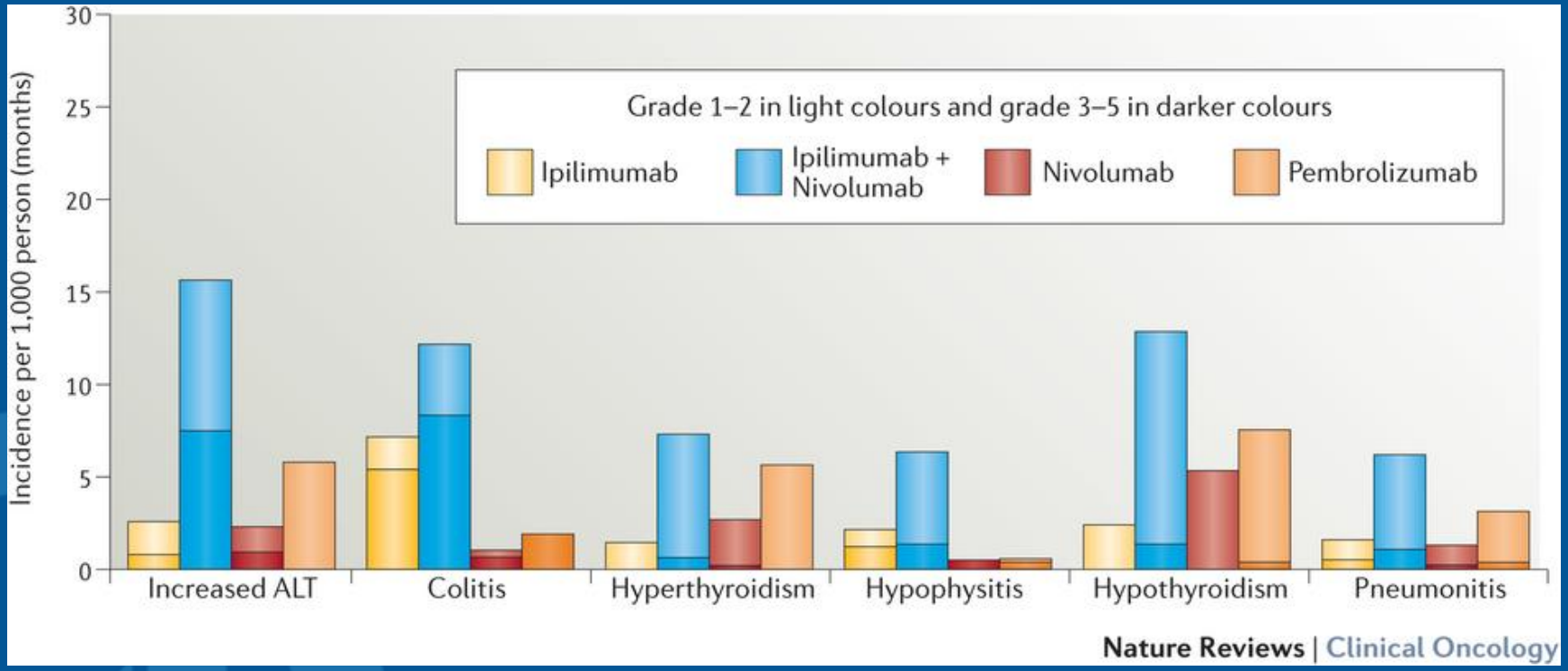
Incidence of Adverse events with immune check-point inhibitors



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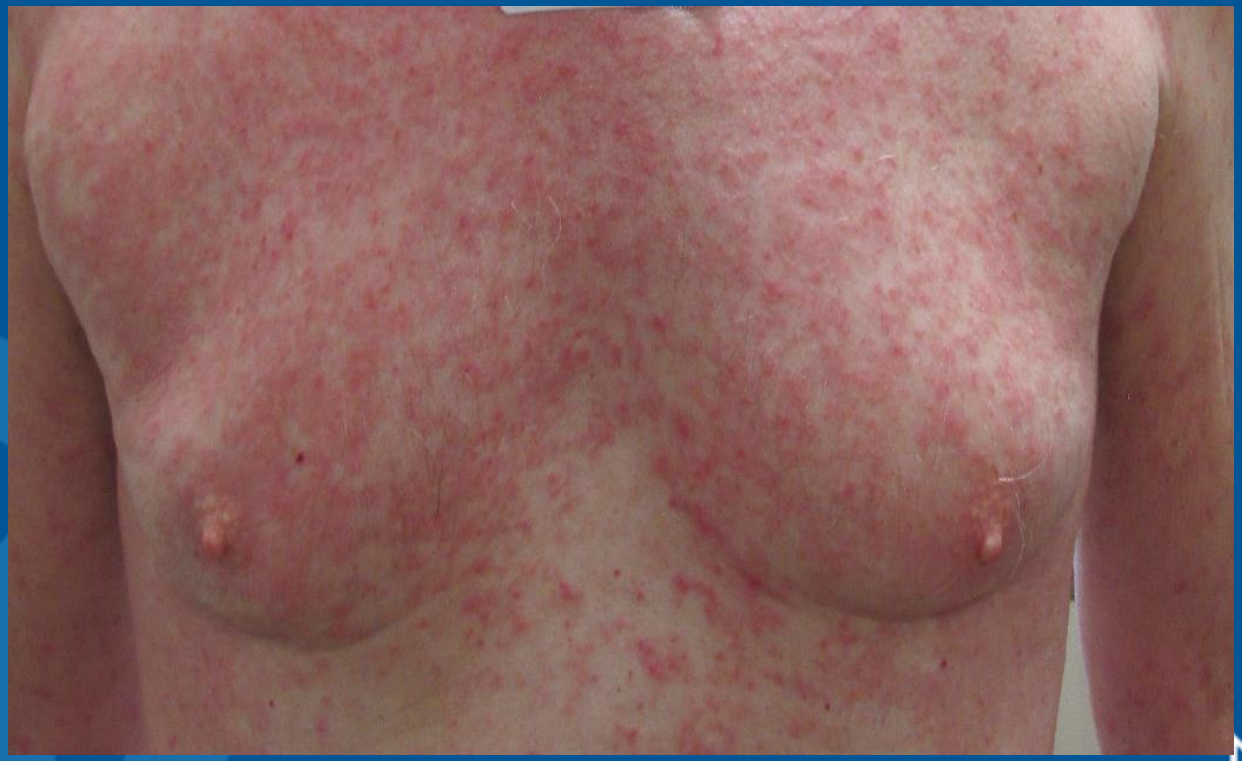
Case Study

Mr. M.C returns to clinic for evaluation prior to dose #4 of Pembrolizumab.

- He reports that for the past week he has had a pruritic rash on his chest, abdomen and arms.



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Immune checkpoint inhibitors- irAE's

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Skin	Covering <10% body surface area (BSA)	Covering 10-30% BSA	Covering >30% BSA	More severe symptoms, requiring IV antibiotics, burn unit admission	
Diarrhea	Increase of <4 stools over baseline	Increase of 4-6 stools over baseline	Increase of ≥7 stools over baseline, hospitalization indicated, incontinence	Life-threatening consequences, urgent intervention indicated	
Hepatotoxicity	AST or ALT >ULN- 3 x ULN or T. bili >ULN–1.5xULN	AST or ALT > 3-5 x ULN or T. bili >1.5–3xULN	AST or ALT >5-20 x ULN or T. bili >3–10xULN	AST or ALT >20 x ULN or T. bili >10xULN	
Endocrine, pneumonitis	Asymptomatic	Symptomatic	Severe symptoms, hospitalization indicated	Life-threatening consequences, urgent intervention indicated	

CTCAE Common Terminology Criteria for Adverse Events v4.03
June 14, 2010

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Managing irAEs

Table 4. Typical management of irAEs

Severity—CTCAE gr	Ambulatory versus	Corticosteroids	Other immunosuppressive drugs	Immunotherapy
1				
2				
3				ion based atient
4	care unit	1–2 mg/kg/day for 3 days then reduce to 1 mg/kg/day	of steroid course Organ specialist referral advised	

Principles of Managing irAEs:

- **Hold immunotherapy for grade ≥ 2**
- **Initiate corticosteroids (e.g.,1–2 mg/kg of prednisone)**
- **Consider infliximab (if gastrointestinal toxicity) or mycophenolate (if hepatotoxicity) if no improvement with corticosteroids**

CTCAE = Common Terminology Criteria for Adverse Events

Champiat S, et al, Ann Oncol, 2016

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Immune checkpoint inhibitors-irAE's

- Dermatologic
  - 47-65% of patients will develop a diffuse, maculopapular rash
  - Usually manageable with topical glucocorticosteroids
  - Hold dose if persistent Grade 2 and Gr 3
    - Give oral corticosteroids 1mg/kg of prednisone equivalent daily
    - Restart when Grade 1 or less
    - Permanently discontinue for Grade 4 or persistent grade 3 skin toxicity

Case Study

- Mrs. L.C is a 46 year old female with metastatic melanoma to the lung. Due to disease progression she consented to start combination Ipilimumab/Nivolumab every 3 wks for 4 doses, followed by Nivolumab maintenance every 2 wks. She is in clinic today for evaluation prior to dose #3 of combination therapy with new onset of 4-6 bloody loose stools for the past 4 days . She was taking Imodium. However, it has not helped. She also reports moderate abdominal cramping.

Immune checkpoint inhibitors- irAE's

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Skin	Covering <10% body surface area (BSA)	Covering 10-30% BSA	Covering >30% BSA	More severe symptoms, requiring IV antibiotics, burn unit admission	
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CTCAE Common Terminology Criteria for Adverse Events v4.03
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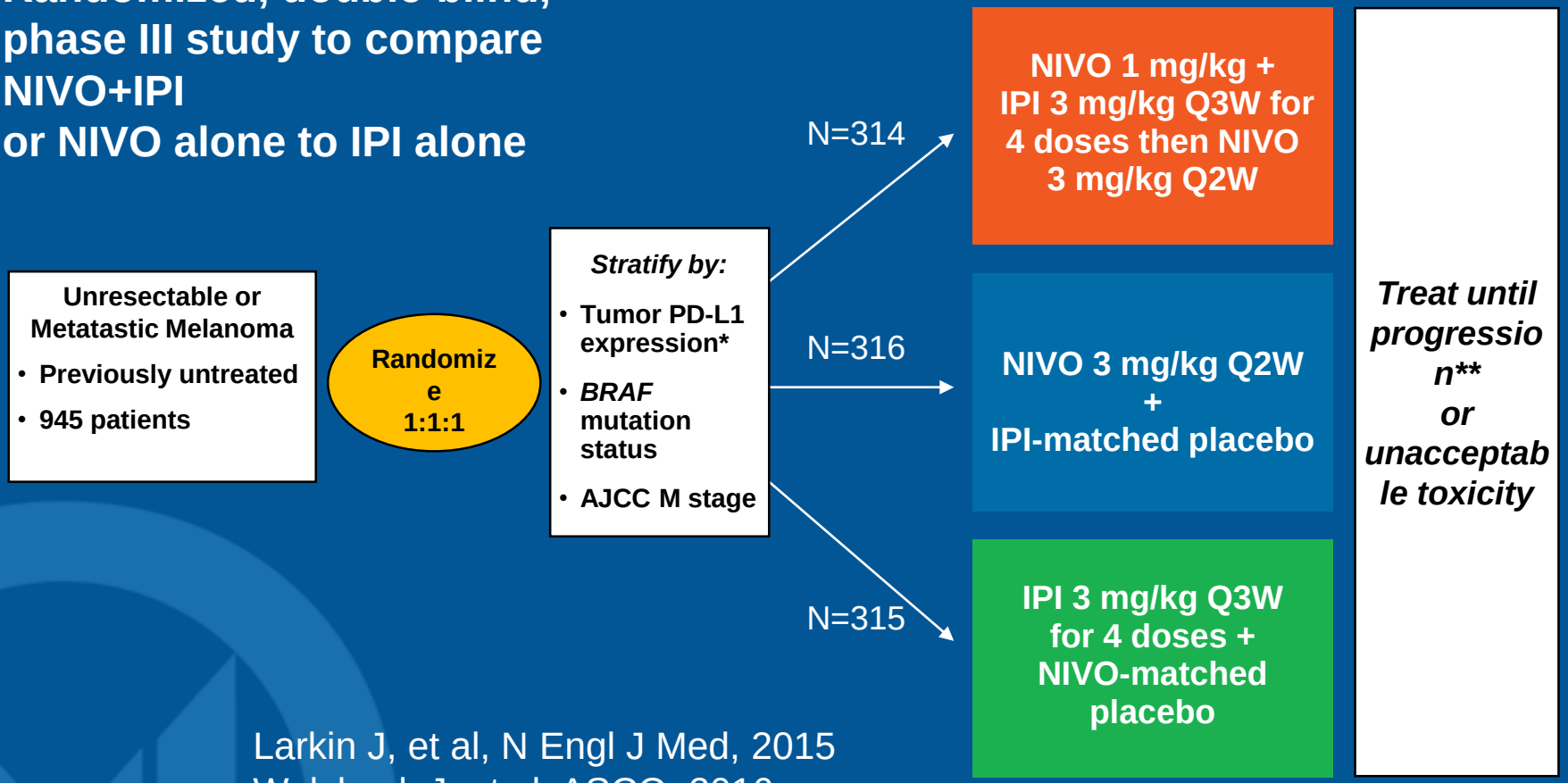
Checkmate 067: Study Design

Randomized, double-blind, phase III study to compare NIVO+IPI or NIVO alone to IPI alone



Larkin J, et al, N Engl J Med, 2015
Wolchock J, et al, ASCO, 2016

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Checkmate 067: TRAEs by Organ System

Updated from Wolchock J, et al, ASCO ,2016

	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All AEs %	95.8	56.5	84.0	19.8	85.9	27.0
Skin AEs, %	60.4	5.8	43.8	2.2	54.7	2.9
Rash	28.4	2.9	22.7	0.3	21.2	1.6
Pruritus	35.1	1.9	20.4	0.3	36.3	0.3
Gastrointestinal AEs, %	47.6	15.3	21.7	2.9	37.3	11.6
Diarrhea	45.4	9.6	20.8	2.2	33.8	6.1
Colitis	11.5	8.0	2.2	1.0	11.3	8.0
Endocrine AEs, %	32.3	5.8	15.7	1.6	11.6	2.6
Hypothyroidism	16.0	0.3	9.3	0	4.5	0
Hyperthyroidism	10.2	1.0	4.5	0	1.0	0
Hepatic AEs, %	31.6	19.8	7.3	2.6	7.4	1.6
Elevated ALT	17.9	8.6	3.8	1.0	3.9	1.6
Elevated AST	15.7	6.1	4.2	1.0	3.9	0.6
Pulmonary AEs, %	7.3	1.0	1.6	0.3	1.9	0.3
Pneumonitis	6.7	1.0	1.3	0.3	1.6	0.3
Renal AEs, %	6.4	1.9	1.0	0.3	2.6	0.3
Elevated creatinine	4.2	0.3	0.6	0.3	1.6	0
Death from irAE						

Database lock Nov 2015

Safety Summary

- Updated safety information with 9 additional months of follow-up were consistent with the initial report

	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
Patients reporting event, %	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related adverse event (AE)	95.8	56.5	84.0	19.8	85.9	27.0
Treatment-related AE leading to discontinuation	38.7	30.7	10.5	7.3	15.4	13.5
Treatment-related death*	0		0.3		0.3	

- 68.8% of patients who discontinued NIVO+IPI due to treatment-related AEs achieved a response

*One reported in the NIVO group (neutropenia) and one in the IPI group (colon perforation)

Database lock Nov 2015

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CTCAE = Common Terminology Criteria for Adverse Events

Champiat S, et al, Ann Oncol, 2016

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Immune checkpoint inhibitors-irAE's

- Gastrointestinal
  - Diarrhea can be seen in up to 48% of patients
    - Grade 1-Symptomatic treatment with hydration, loperamide, bland diet
    - Grade 2-Oral diphenoxylate/atropine QID, oral budesonide, stool studies (including *C. difficile* titer), possible sigmoidoscopy or colonoscopy. If persistent, start steroid taper.
    - Grade 3/4- Discontinue agent, give IV steroids. Then, convert to oral steroids and taper for at least 4 weeks
    - If steroids are not effective after 48-72 hours, give infliximab 5mg/kg q 2 weeks

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Case study

- B.C is 56-year old female with a diagnosis of Stage IV melanoma. She is now on Nivolumab 240mg every two weeks. Today she reports that for the past 5 days she has had SOB, cough and DOE
- O2 saturations at RA 95% and 90% during ambulation

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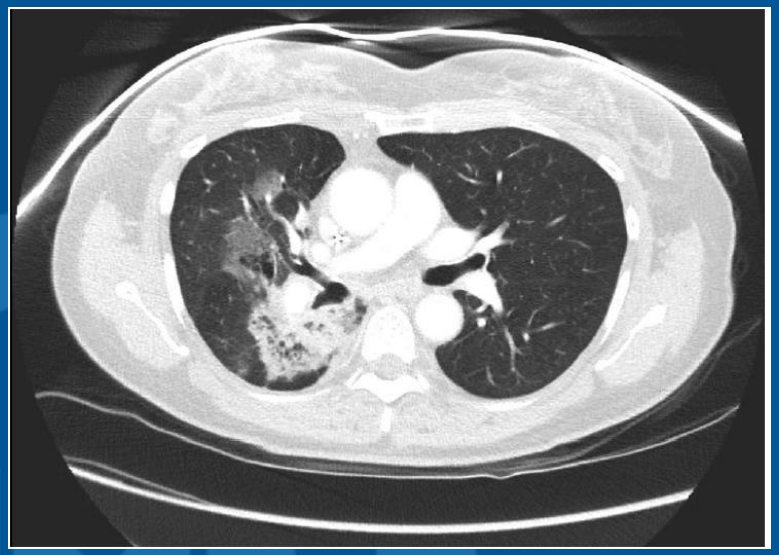
Pneumonitis is more common with anti-PD1/CTLA-4 combination therapy

- Important to address respiratory symptoms and check oxygen saturations at each visit
- On any patients where pneumonitis is suspected based on H&P or clinical exam, hold treatment and order a CT scan of the chest.
- Specific management is necessary for grade 2 or greater pneumonitis.



Grade 2 pneumonitis

↓

Hold treatment and administer steroids;

Taper steroids over 4-5 weeks

Resume if:	**Discontinue if:**
Improved to grade 0 or 1	Not improved to < grade 2

Chow LQM, ASCO Educational Book, 2013.

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Case study

- J.C is a 75 yr old male currently on Nivolumab/Ipilimumab combination therapy. He reports that for the past 5 days he has had
- Moderate Headaches, severe fatigue, weakness, and nausea.
- Endocrine labs revealed low cortisol, ACTH and low testosterone levels. Free T4 and TSH were normal.

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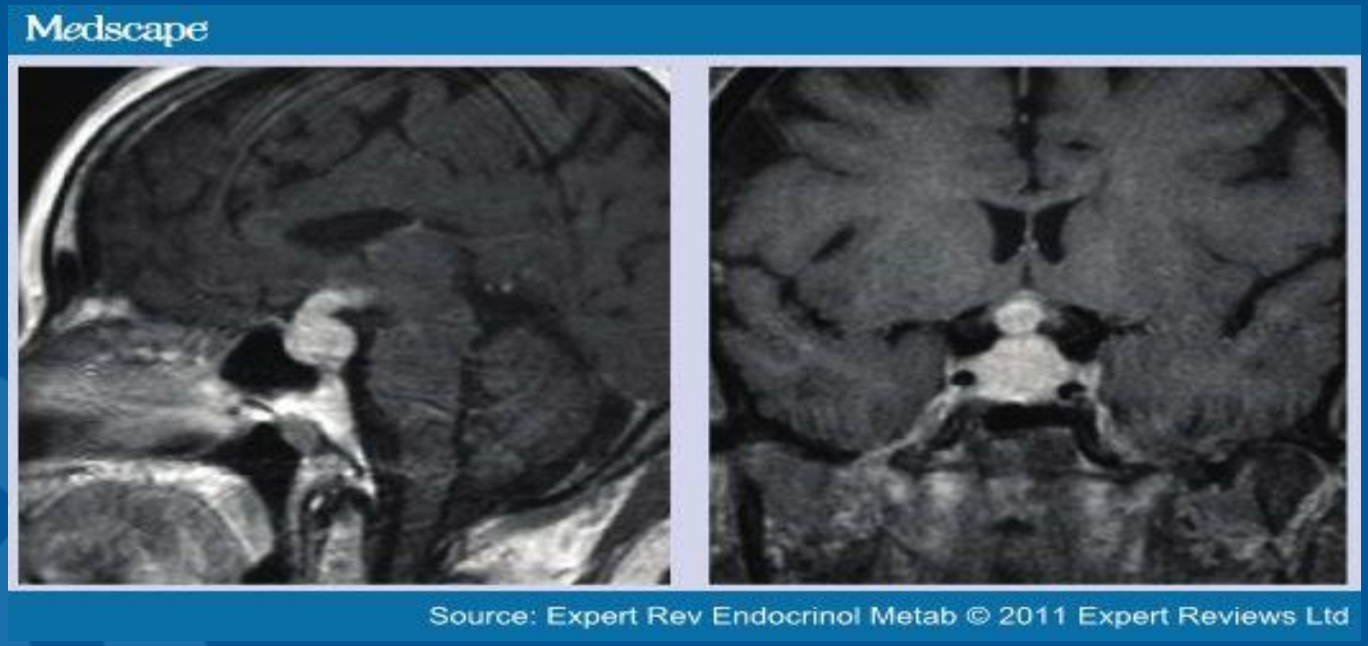
Case study

- MRI of the brain shows inflammation of the pituitary gland. Hypophysitis



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Immune checkpoint inhibitors- irAE's

- Endocrine
  - More common with anti-PD-1 than anti CTLA-4
  - **Hypophysitis**- with Nivo/ipi median time to onset was about 2.7 months. All grades 9%
  - Adrenal insufficiency
    - Rule out brain metastasis
    - Hold for symptoms and/or any Grade 3/4
    - Give steroids (IV followed by PO 1-2mg/kg) tapered over 4 weeks and replace appropriate hormones
      - Hormone replacement may be required for life in ~50% of patients
  - Hypothyroidism
  - Hyperthyroidism

Robert C et al. NEJM 2015

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Immune checkpoint inhibitors-irAE's

- Rare toxicities
  - Type I and II diabetes mellitus
  - Pancreatitis-usually asymptomatic amylase/lipase elevations (hold for symptomatic persistent G2 or G 3/4)
  - Renal toxicity (acute interstitial nephritis)
  - Autoimmune myocarditis
  - Bullous pemphigoid

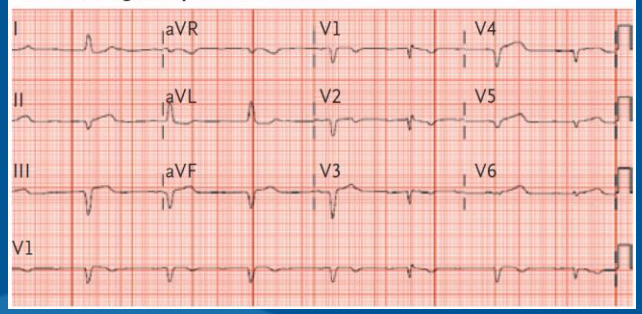
The New York Times | http://nyti.ms/2e3gTtm

HEALTH

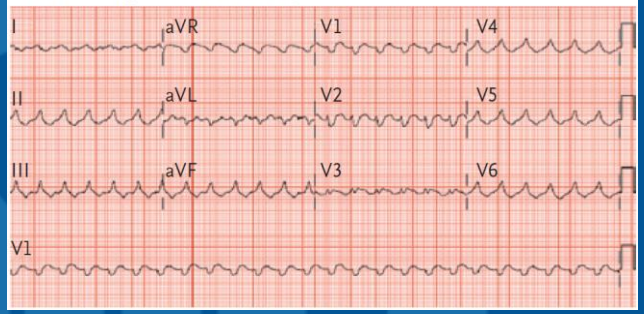
Lifesaving Cancer Drugs May in Rare Cases Threaten the Heart

By DENISE GRADY NOV. 2, 2016

ECG Showing Complete Heart Block



ECG Showing Ventricular Tachycardia



Infiltrate with CD8+ T Cells

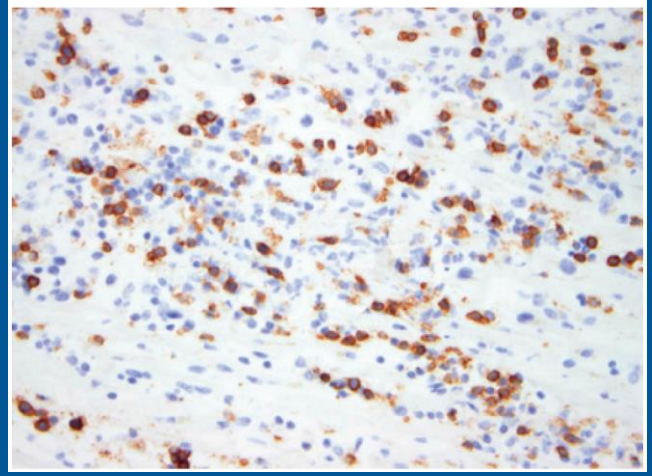


Table 1. Incidence of Myocarditis and Myositis in Patients Receiving Nivolumab or Ipilimumab plus Nivolumab.

Characteristic	Nivolumab (N=17,620)	Nivolumab plus Ipilimumab (N=2974)
	no. (%)	
Myocarditis		
Any*	10 (0.06)	8 (0.27)
Fatal events	1 (<0.01)	5 (0.17)
Myositis		
Any	27 (0.15)	7 (0.24)
Fatal events	2 (0.01)	1 (0.03)

Johnson DB, et al, N Engl J Med, 2016

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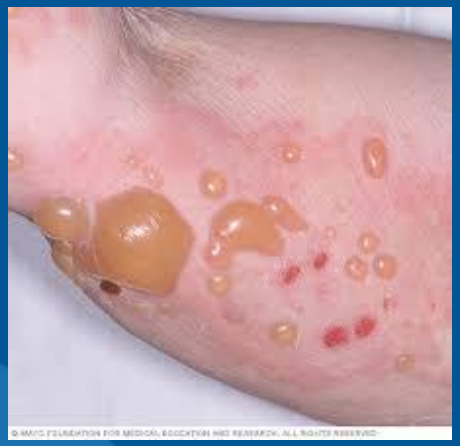
Immune checkpoint inhibitors irAE's

- Rare toxicities
  - Bullous pemphigoid



  - Myasthenia-like syndrome-motor paralysis, intravenous immune globulins
  - Optic neuritis-photophobia, pain, blurred vision
  - Sarcoidosis-lymphadenopathy, increased angiotensin converting-enzyme level, biopsy is granulomata, PET positive
  - Hematologic

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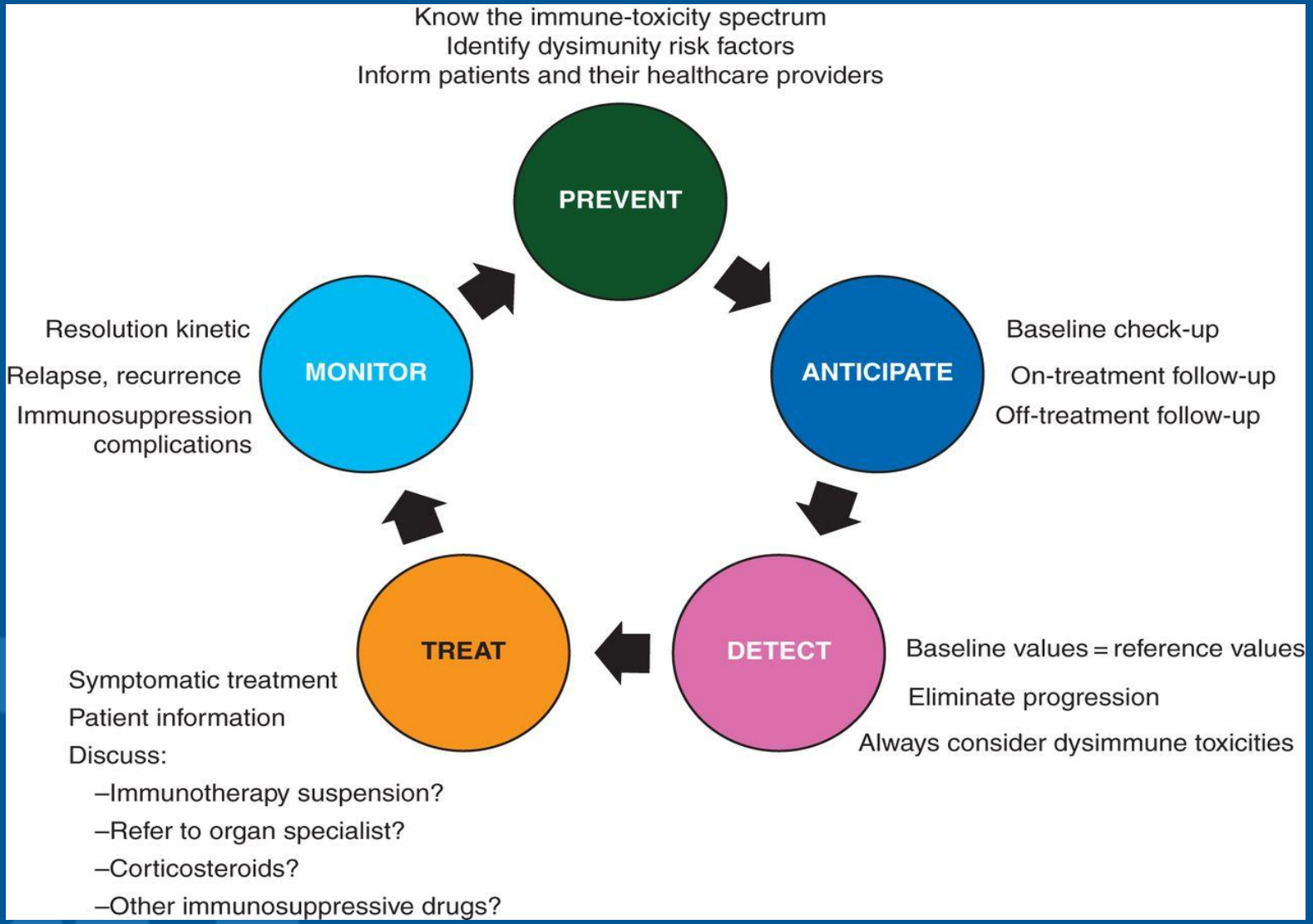
Immune checkpoint inhibitors- irAE's

- General principles of toxicity management
  - Reversible toxicities when recognized quickly and treated appropriately
  - Treatment may include dose delay, omission, or discontinuation, corticosteroids, tumor necrosis alfa (TNF-α) antagonists, and mycophenolate mofetil
  - Corticosteroids may require a long tapering duration to prevent recurrence of symptoms
    - Rechallenge with checkpoint inhibitor may only be done, if clinically appropriate, once a patient is receiving 10mg of oral prednisone or equivalent or less
    - Prolonged use of steroids predisposes patients to systemic infection so prophylaxis may be indicated

Villadolid J and Amin A. *Transl Lung Cancer Res* 2015; 4 (5): 560-575

The five pillars of immunotherapy toxicity management.



S. Champiat et al. Ann Oncol 2016;27:559-574

Annals of Oncology

Conclusions

- irAEs grade 2 and above usually require drug hold/discontinuation and corticosteroids.
- Combination anti-PD-1/CTLA-4 immunotherapy significantly increases the grade 3-4 AE rate.
- Close monitoring for irAEs is imperative for prevention of serious adverse events
- As immunotherapies indications broaden, our understanding of toxicity identification and management is essential to make the risk benefit ratio favorable

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THANK YOU !

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