CancerCare Manitoba
UNITING PRIMARY CARE AND ONCOLOGY

CancerCare Manitoba
COMMUNITY ONCOLOGY PROGRAM

The Dark Side of Immunotherapy

5 April 2017

Joel Gingerich, MD, FRCPC
Medical Oncologist
Medical Director, Community Oncology Program
Associate Program Medical Director, WRHA Oncology Program
CancerCare Manitoba
Assistant Professor
University of Manitoba

Presenter Disclosure

- **Faculty:** Joel Gingerich

- **Relationships with commercial interests:**

  N/A

Mitigating Potential Bias

- N/A

Learning Objectives

- Identify common toxicities associated with immune checkpoint inhibitors

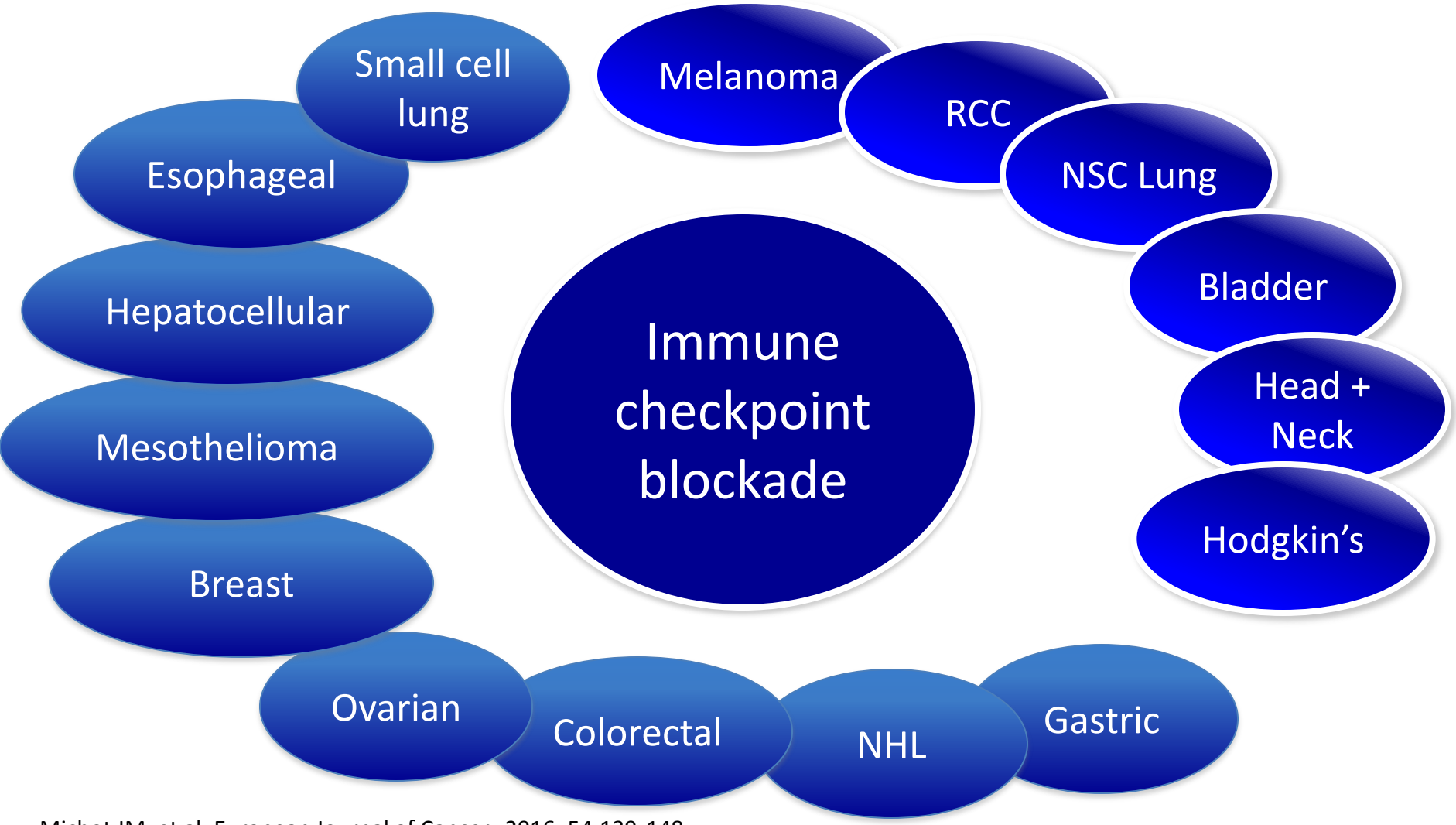
- Recognize and treat potentially life-threatening toxicities associated with immune checkpoint inhibitors

“Chemotherapy” drug classes

Chemotherapy[t]	Targeted therapy[t]	Immuno-oncology
5-fluorouracil Methotrexate Cisplatin Oxaliplatin Doxorubicin Irinotecan Doxetaxel	Bevacizumab Sunitinib Trastuzumab Cetuximab Imatinib Vemurafenib	Immune checkpoint inhibitors ↓ Different toxicities (can be fatal) ↓ Different management strategies

[t] Selected agents shown

Immune Checkpoint inhibitors are active in many types of cancers



Michot JM, et al: European Journal of Cancer. 2016; 54:139-148

Approved immune checkpoint inhibitors as of 4/2017

PD-1 inhibitors

- Pembrolizumab
- Nivolumab

PDL-1 inhibitors

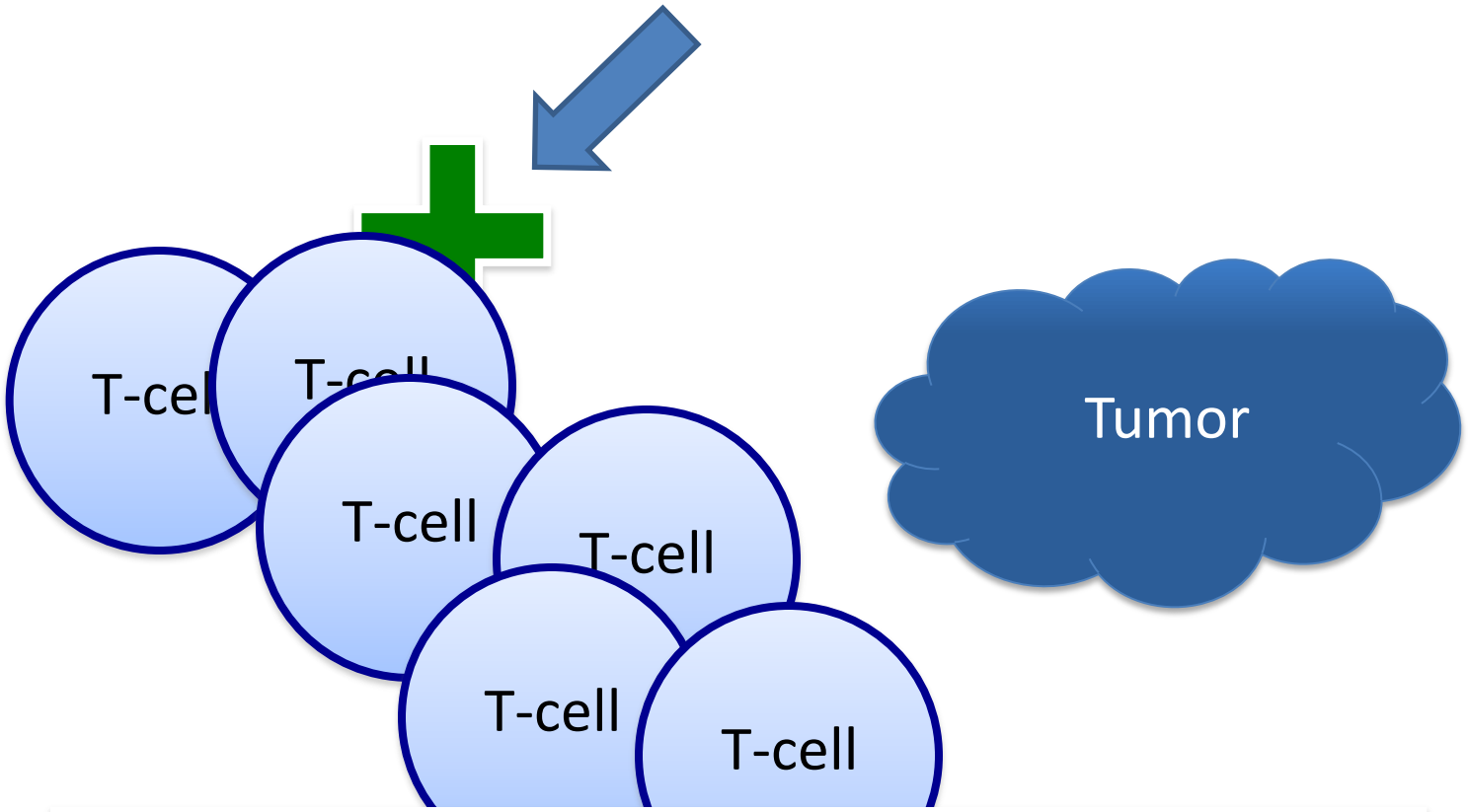
- Atezolizumab
- Avelumab
- Durvalumab

CTLA-4 inhibitor

- Ipilimumab

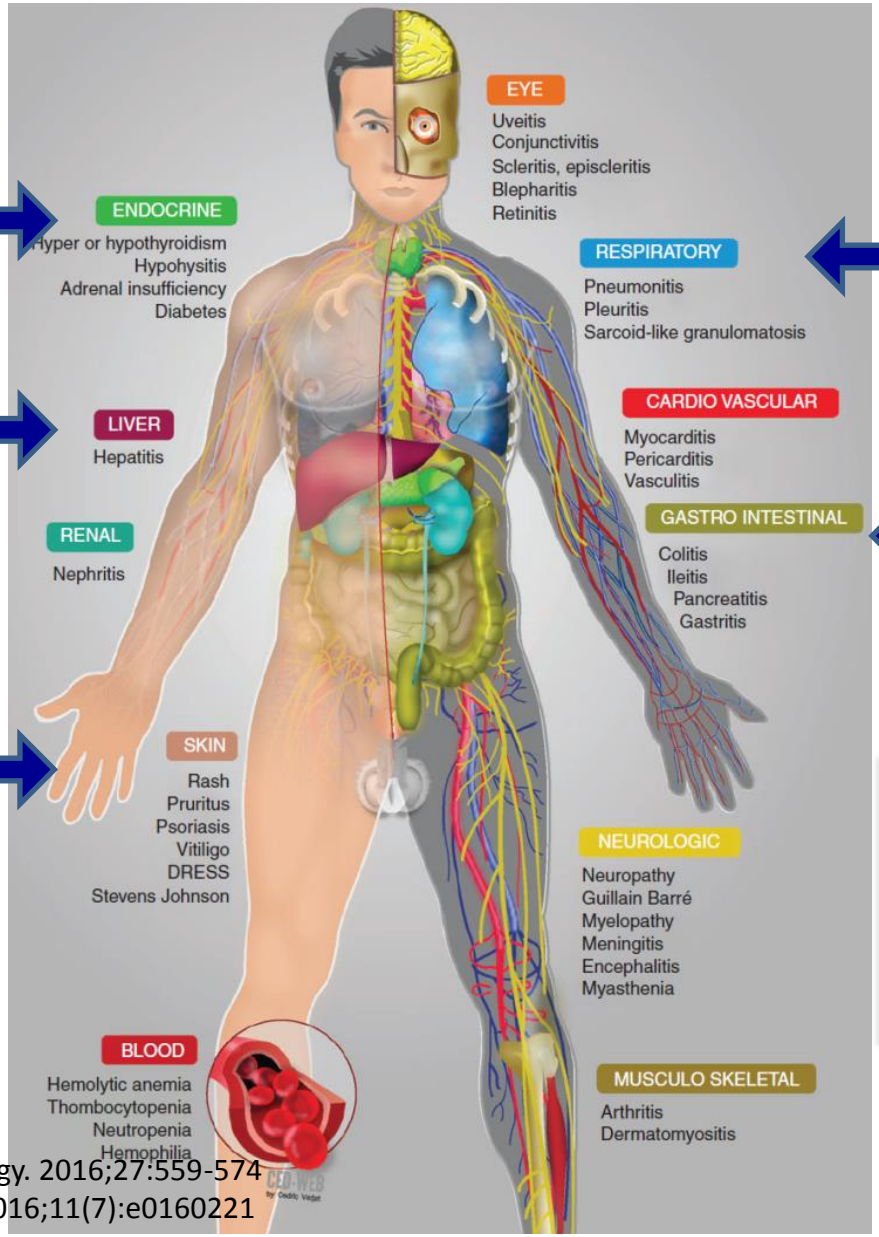
https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/immune-checkpoint-inhibitors.html

Immune checkpoint inhibitors



↑risk for immune related side effects

Immune related adverse events (irAE)



Other reported toxicities:
Polymyalgia rheumatica
Lupus
Celiac disease

Champiat S, et al: Annals of Oncology. 2016;27:559-574
Abdel-Wahab N, et al: PLoS ONE. 2016;11(7):e0160221

How common are irAE's: A meta-analysis

- Included randomized phase II/III trials between 1996-2016
- 21 trials
- N = 11,454

Toxicity	All Grade (%)	Grade 3-4 (%)
Colitis	2.3	1.5
Hepatotoxicity	6.5	1.5
Rash	13.9	1.1
Hypothyroidism	5.1	0.3
Pneumonitis	2.6	1.1

Fatal irAE's occurred in 0.64% of patients

De Velasco G, et al: Cancer Immunol Res. 2017;5(4):213-218

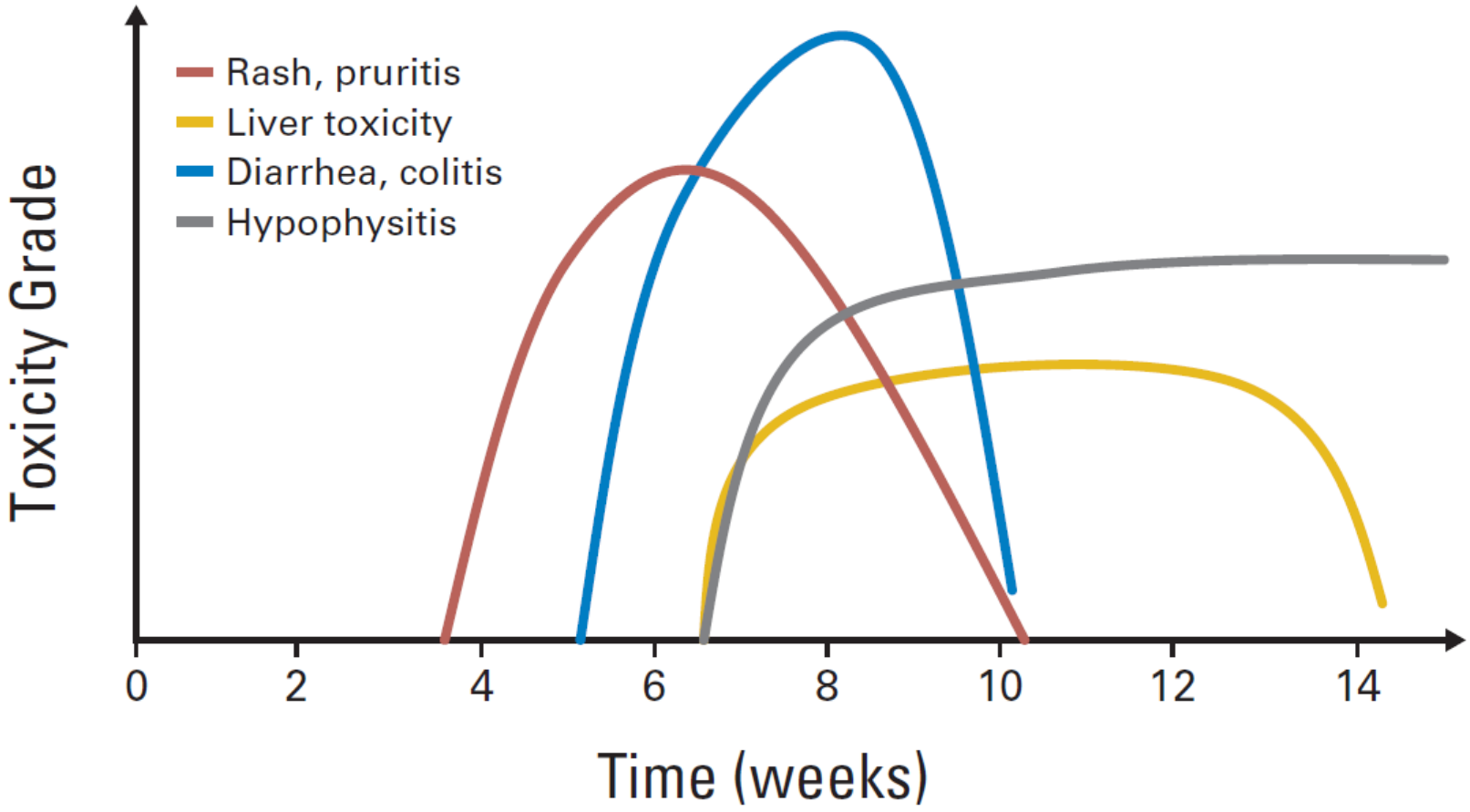
Cumulative incidence of AE's (selected phase III studies)

Class	Grade 3-4 (%)
PD-1/ PDL-1	10-19%
CTLA-4	20-27%
Combined treatment	55%

↑ Colon, liver, skin, endocrine, and lung toxicity vs. chemo

Rpbert C. et al: N Engl J Med. 2015;372(26):2521-2532
Larkin J, et al: N Engl J Med. 2015;373(1):23-34
Motzer RJ, et al: N Engl J Med. 2015;373(19):1803-1813
Ferris RL, et al: N Engl J Med. 2016;375(19):1856-1867
Bellmun J, et al: N Engl J Med. 2017;
De Velasco G, et al: Cancer Immunol Res. 2017;5(4):213-21

When do irAE's occur?

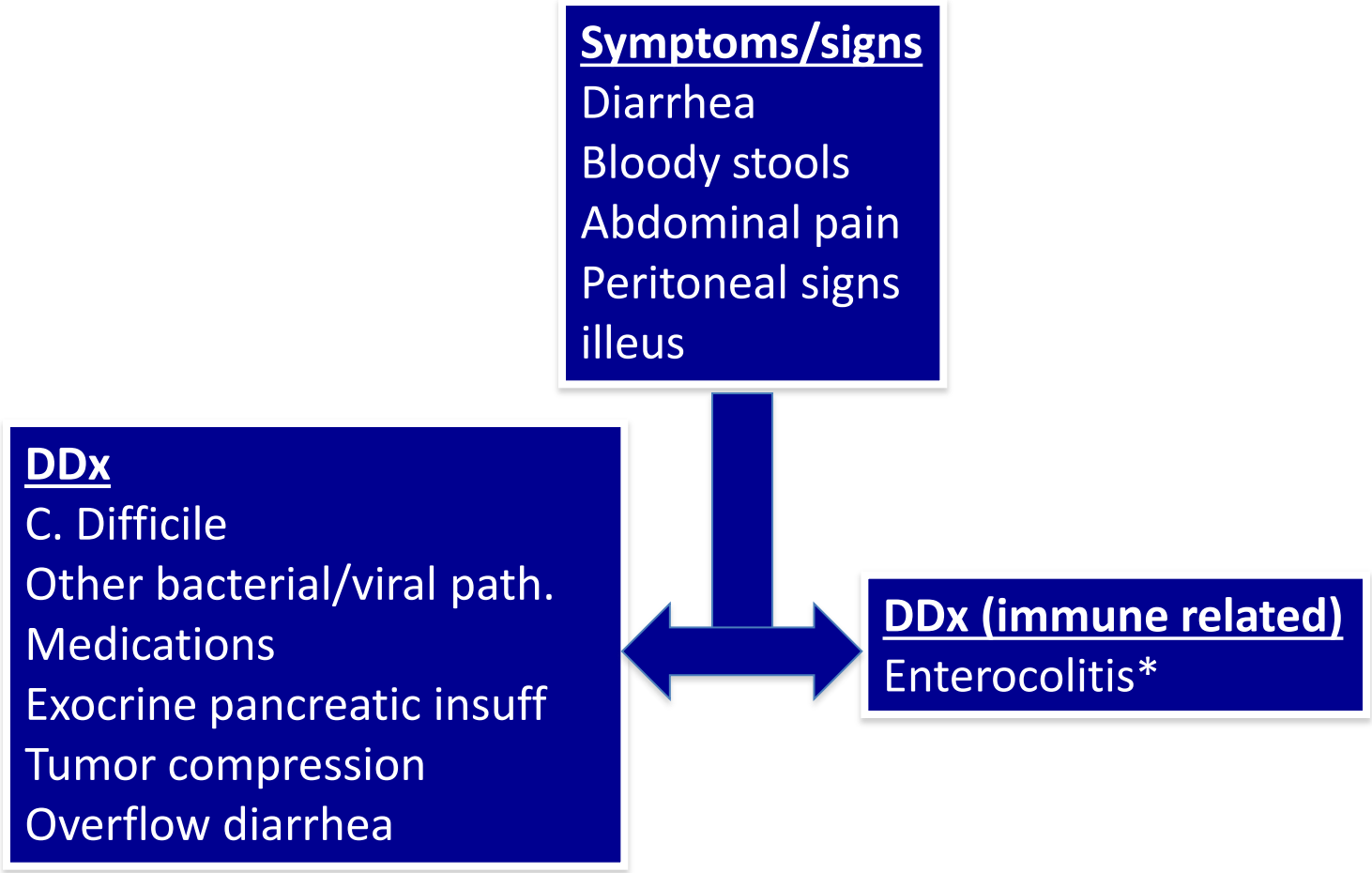


Can occur at anytime during or even after treatment ends

Weber JS, et al: J Clin Oncol. 2012;30:2691-2697

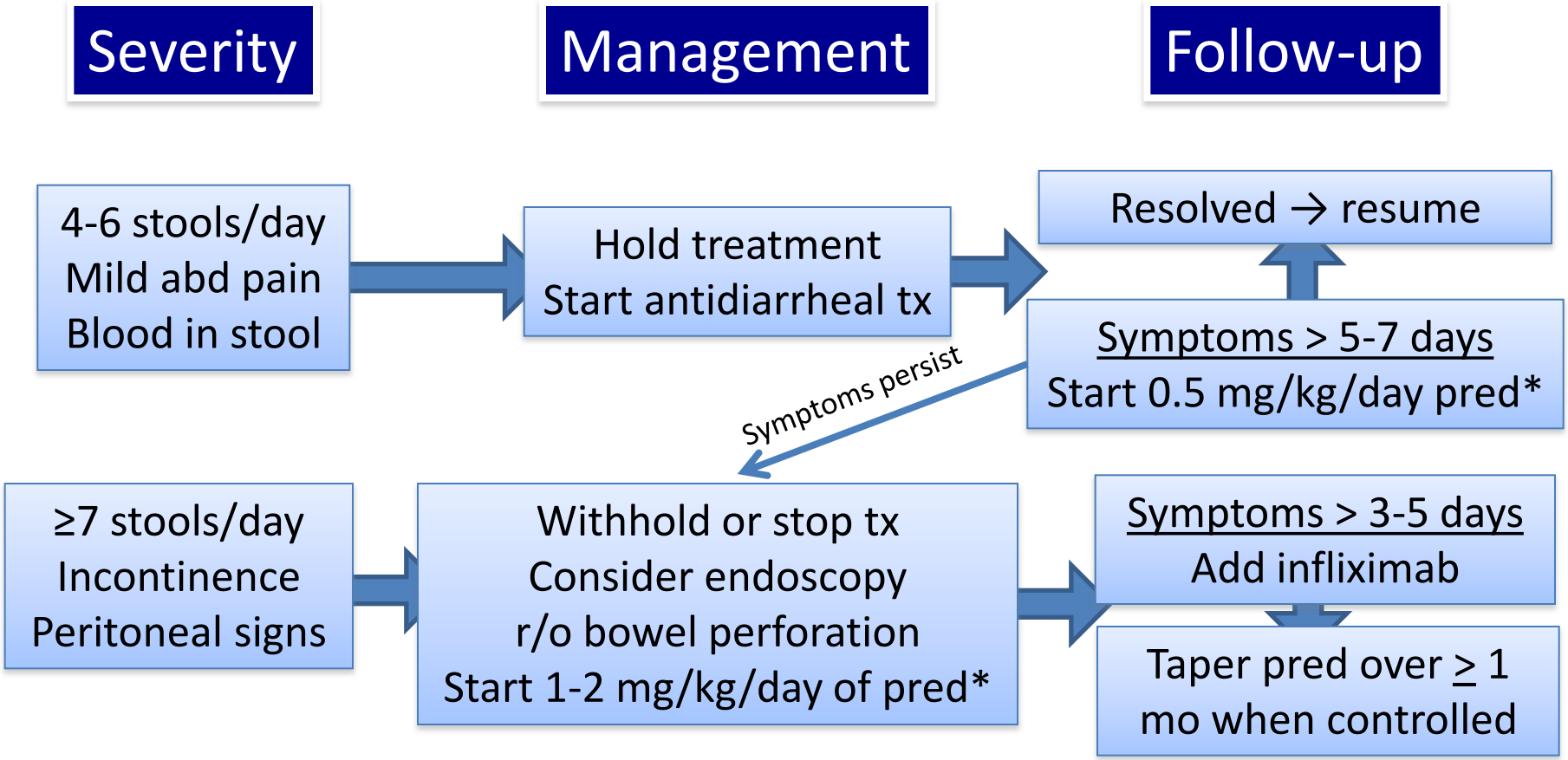
- 55 yo female with advanced melanoma presents to your clinic with a 3 day history of 4 loose BM's per day.
  - She has been on ipilumumab for 6 months.
  - She has not had any fevers or chills.
  - She recently completed a course of antibiotics for a UTI.

irAE: Diarrhea/colitis



Champiat S, et al: Annals of Oncology. 2016;27:559-574

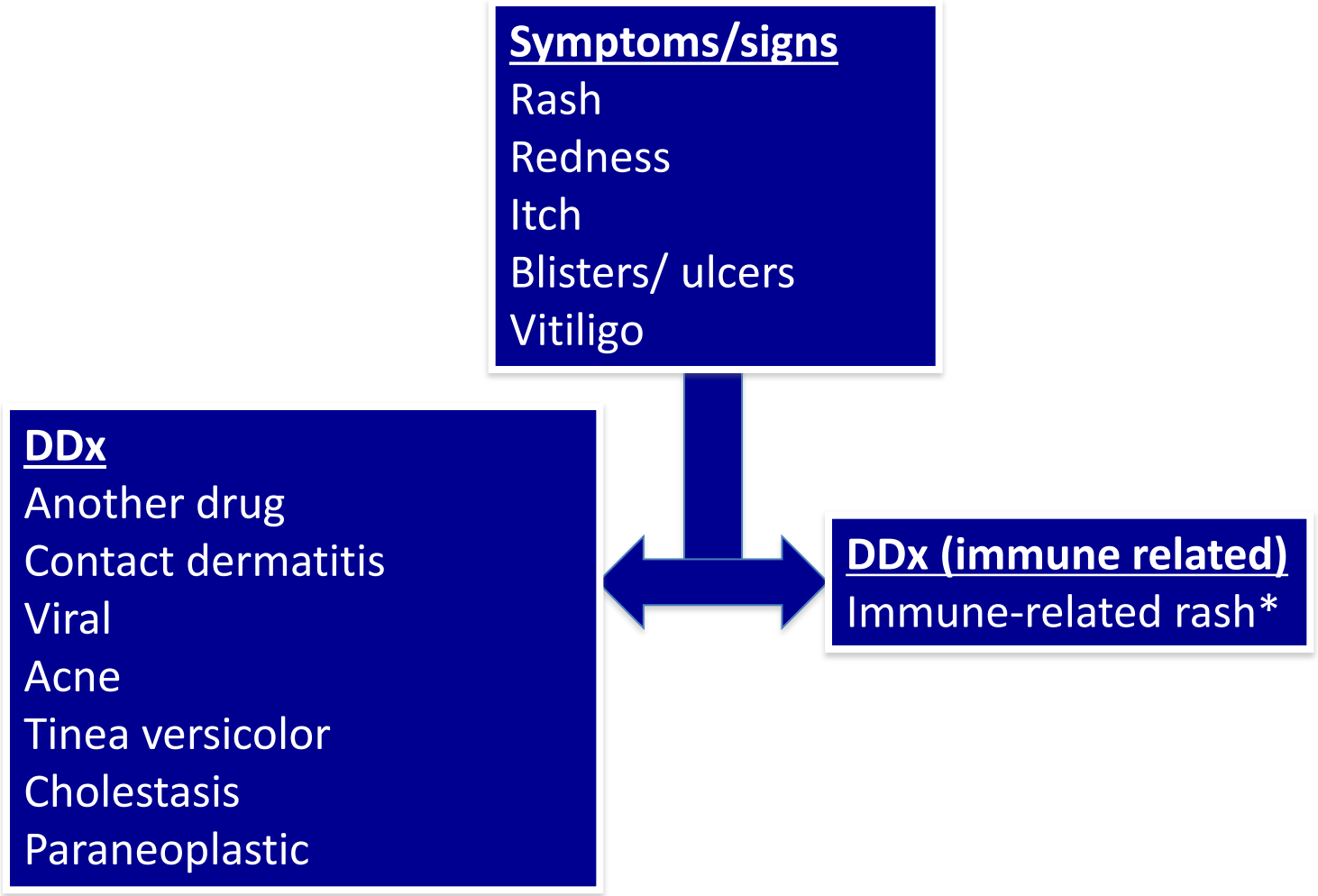
Managing toxicity: Diarrhea



http://www.accessdata.fda.gov/drugsatfda_docs/rems/Yervoy_2012-02-16_Full.pdf
http://www.opdivoyervoyhcp.com/servlet/servlet.FileDownload?file=00Pi000000SRPWfEAP
Naidoo J, et al: Annals of Oncology. 2015;26:2375-2391

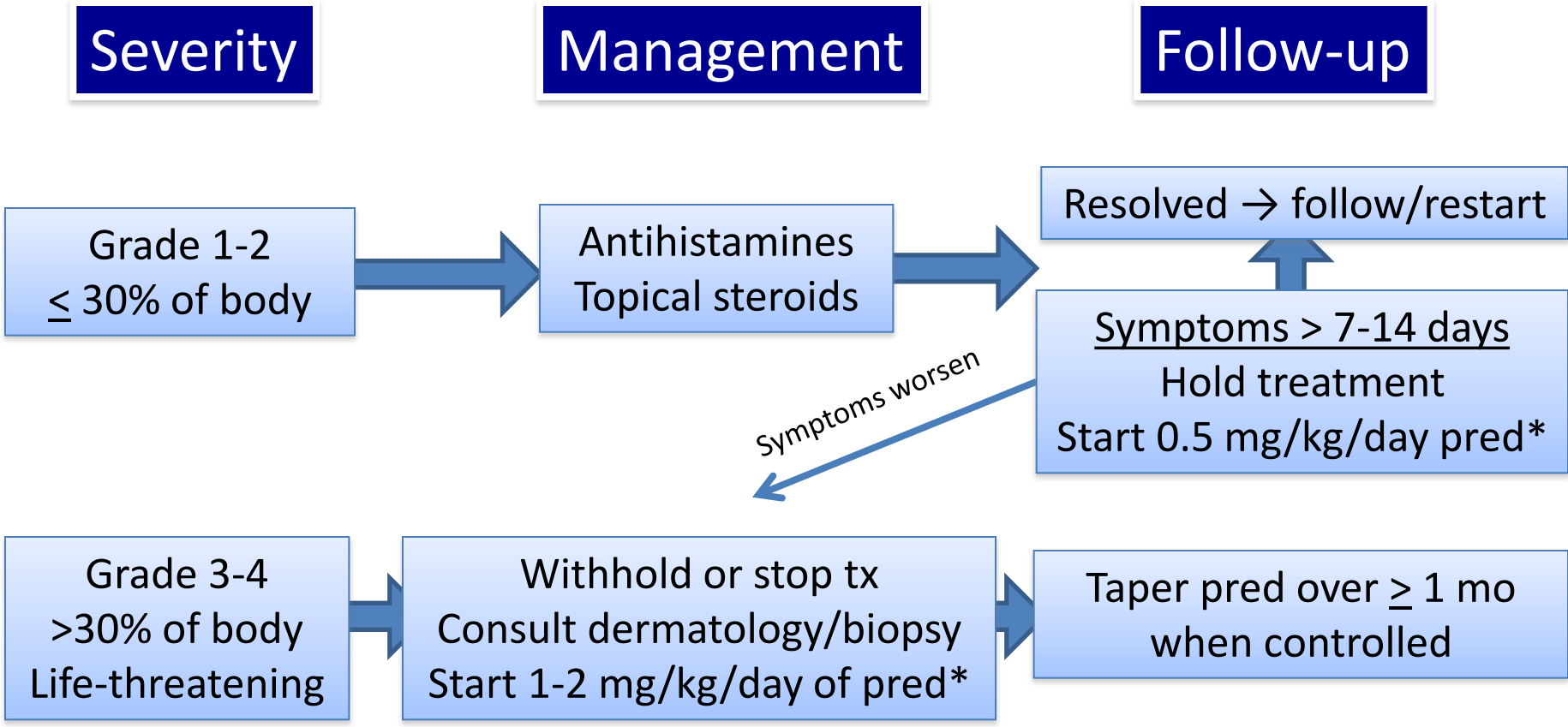
- 65 yo male presents to your urgent care clinic with a 2 day history of a mild erythematous maculo-papular rash.
  - He has mild pruritus
  - The rash involves 40% of his body
  - Blood work shows AST 4x ULN. TB = 1 x ULN
  - He is currently on nivolumab for metastatic kidney cancer (Initially diagnosed 4 years ago)

irAE': Rash and pruritis



Champiat S, et al: Annals of Oncology. 2016;27:559-574

Managing toxicity: Rash



http://www.accessdata.fda.gov/drugsatfda_docs/rems/Yervoy_2012-02-16_Full.pdf
http://www.opdivoyervoyhcp.com/servlet/servlet.FileDownload?file=00Pi000000SRPWfEAP
Naidoo J, et al: Annals of Oncology. 2015;26:2375-2391

irAE: Liver

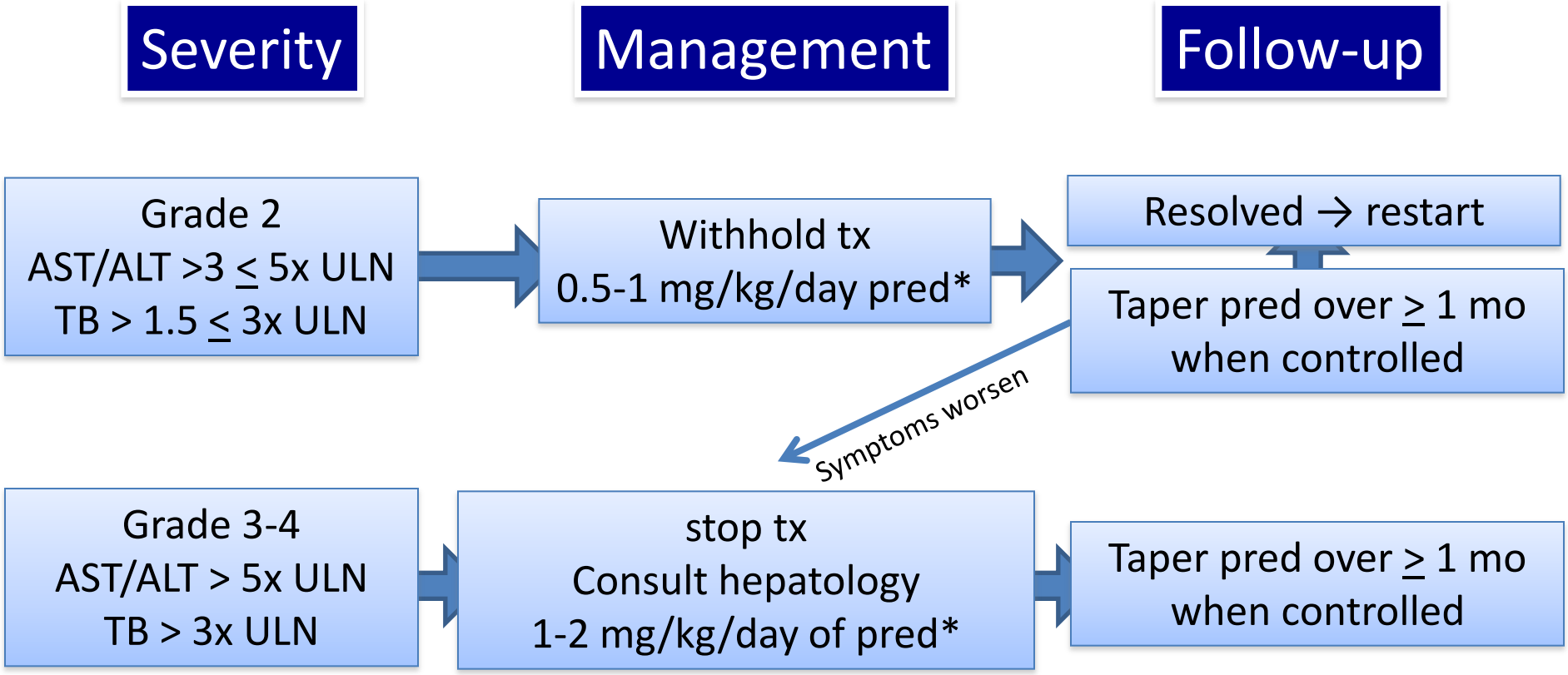
Symptoms/signs/labs
Liver enzyme elevation*
Fever
Jaundice
N/V
Right sided abdominal pain

DDx
Liver metastasis
Medications
ETOH
Cholecystitis
Viral hepatitis
NAFLD
Genetic disorders

DDx (immune related)
Hepatitis*

Champiat S, et al: Annals of Oncology. 2016;27:559-574

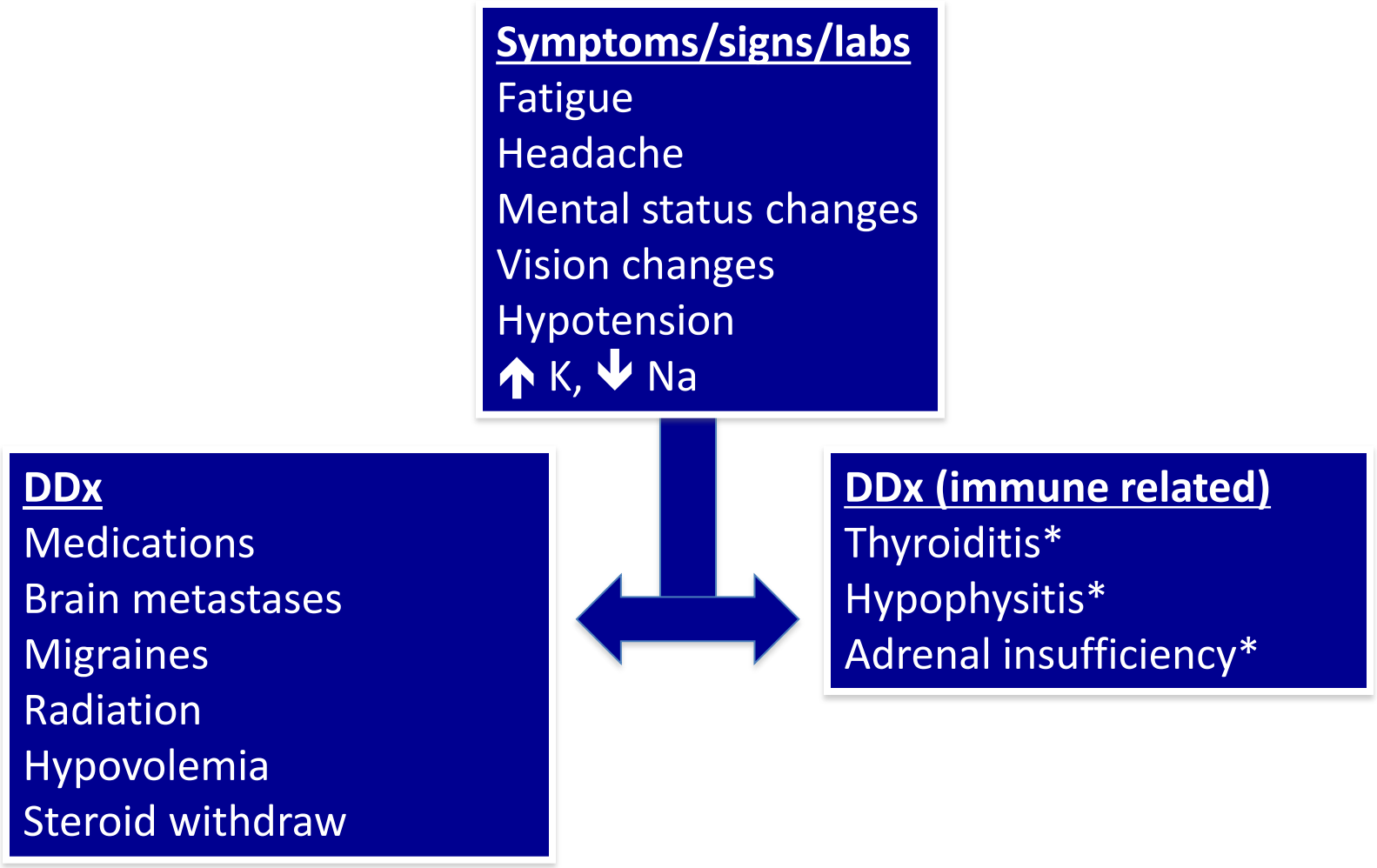
Managing toxicity: Liver



http://www.accessdata.fda.gov/drugsatfda_docs/rems/Yervoy_2012-02-16_Full.pdf
http://www.opdivoyervoyhcp.com/servlet/servlet.FileDownload?file=00Pi000000SRPWfEAP
Naidoo J, et al: Annals of Oncology. 2015;26:2375-2391

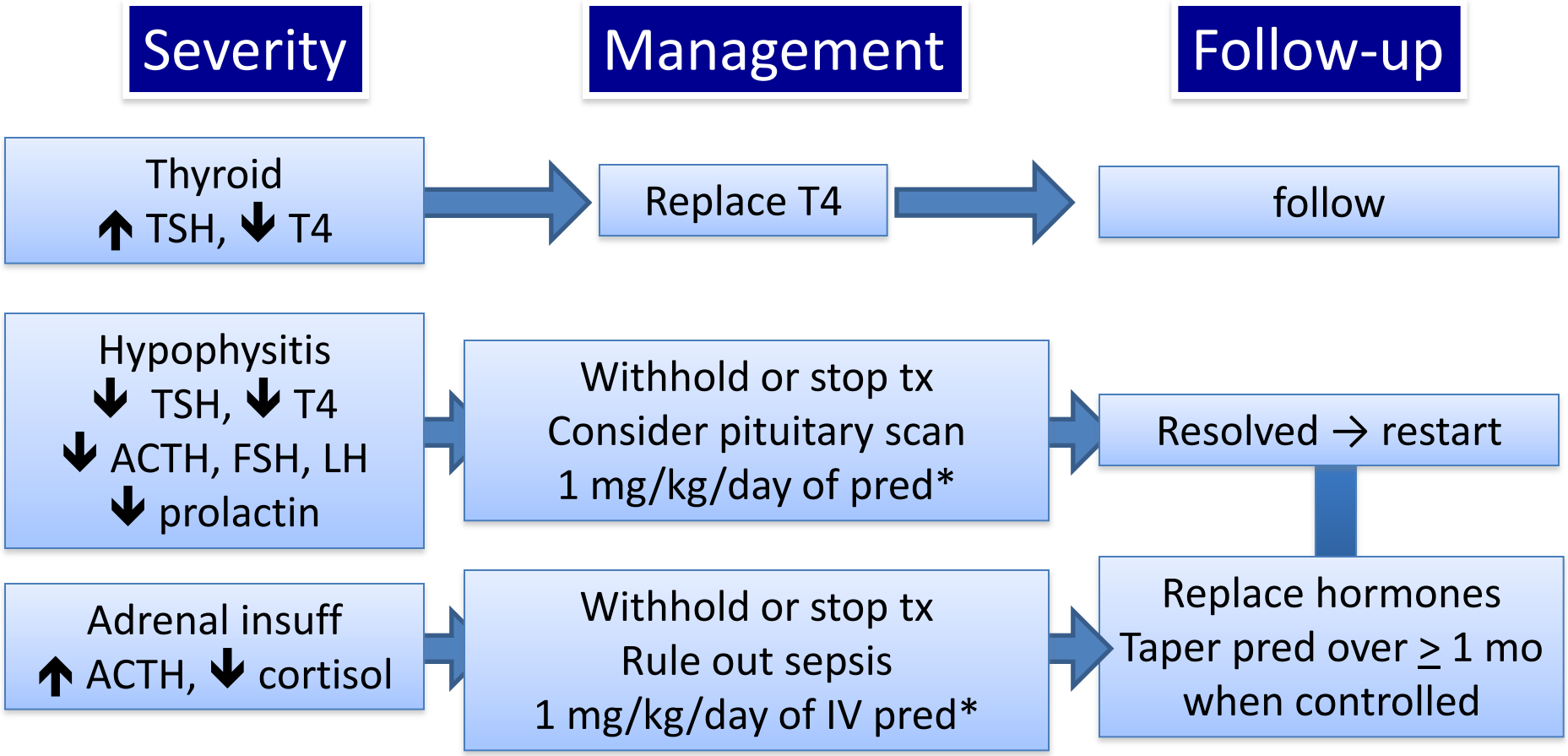
- 60 yo female presents to the ER with new N/V, headache, mild confusion and vision changes.
  - She has metastatic bladder cancer and has been receiving nivolumab x 9 mo

irAE: Endocrine



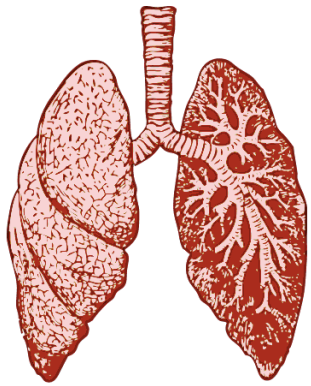
Champiat S, et al: Annals of Oncology. 2016;27:559-574

Managing toxicity: Endocrine

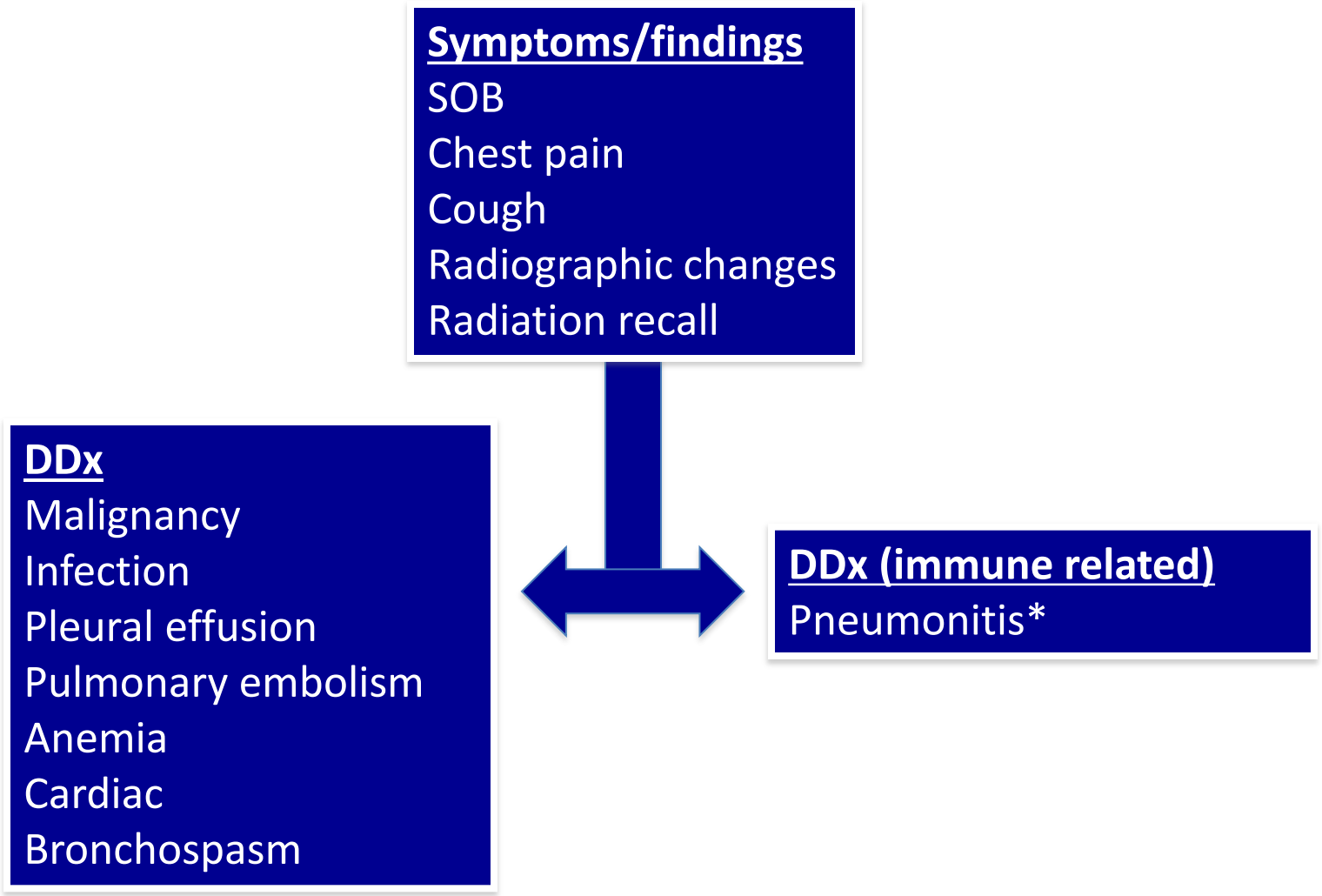


http://www.accessdata.fda.gov/drugsatfda_docs/rems/Yervoy_2012-02-16_Full.pdf
http://www.opdivoyervoyhcp.com/servlet/servlet.FileDownload?file=00Pi000000SRPWfEAP
Naidoo J, et al: Annals of Oncology. 2015;26:2375-2391

- 50 yo male presents to the ER with sob and cough.
  - He has metastatic melanoma that was treated with pembrolizumab for 6 months but stopped it 4 months ago (patient preference).
  - On exam he has mild crackles in the bilateral upper lung fields and has an o2 sat = 89%.

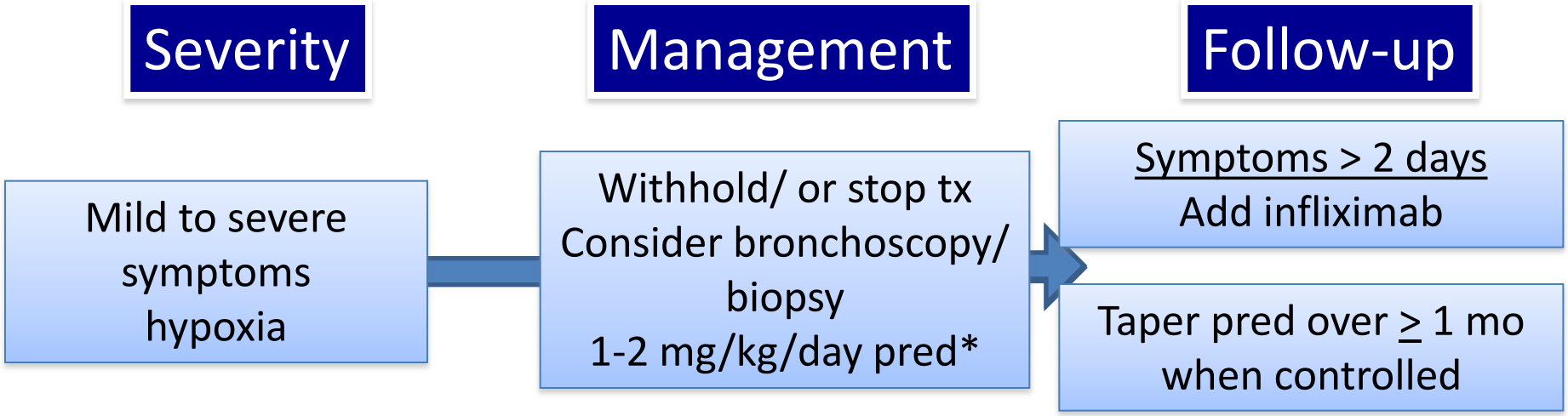


irAE: Pneumonitis



Champiat S, et al: Annals of Oncology. 2016;27:559-574

Managing toxicity: Pneumonitis



http://www.accessdata.fda.gov/drugsatfda_docs/rems/Yervoy_2012-02-16_Full.pdf
http://www.opdivoyervoyhcp.com/servlet/servlet.FileDownload?file=00Pi000000SRPWfEAP
Naidoo J, et al: Annals of Oncology. 2015;26:2375-2391

Optimizing communication

- Patient – physician
  - Pts given card/bracelet to carry with them
    - Drug name and common toxicity

- Physician – physician
  - Please contact us if a patient is reporting symptoms that might be associated with irAE

Considerations

- Pts on prolonged steroids have ↑ risk of opportunistic infections
  - When pred ≥ 20 mg x 4 wks = TMP/SMX double strength 3x week

- For now pts with pre-existing autoimmune disorders have been excluded from clinical trials

https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf
Champiat S, et al: Annals of Oncology. 2016;27:559-574

Conclusions

- Immune checkpoint inhibitors are:
  - A new class of cancer treatment that is rapidly expanding
  - Associated with unique irAE's
  - Side effects are usually mild, but can be life-threatening if not identified and treated promptly
  - Good communication between providers is key