MANAGEMENT OF IMMUNOTHERAPY RELATED TOXICITIES

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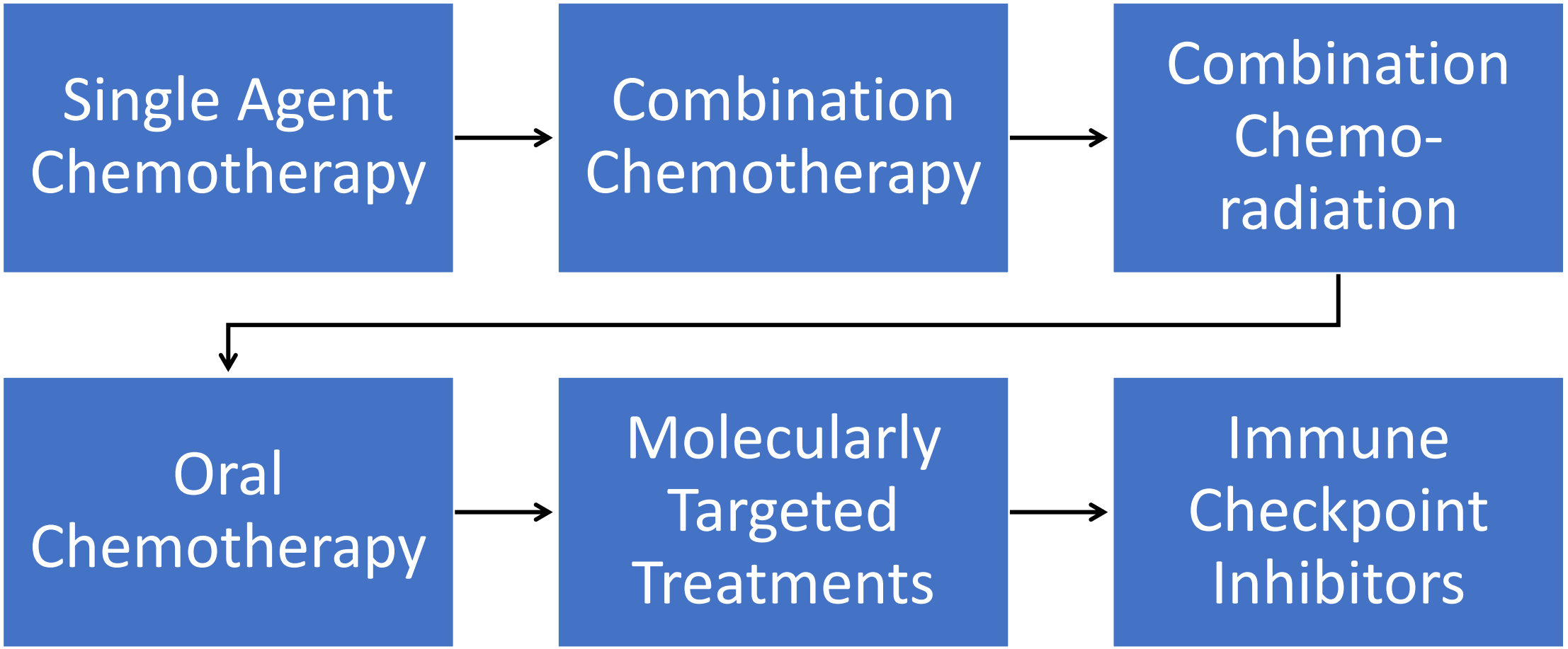
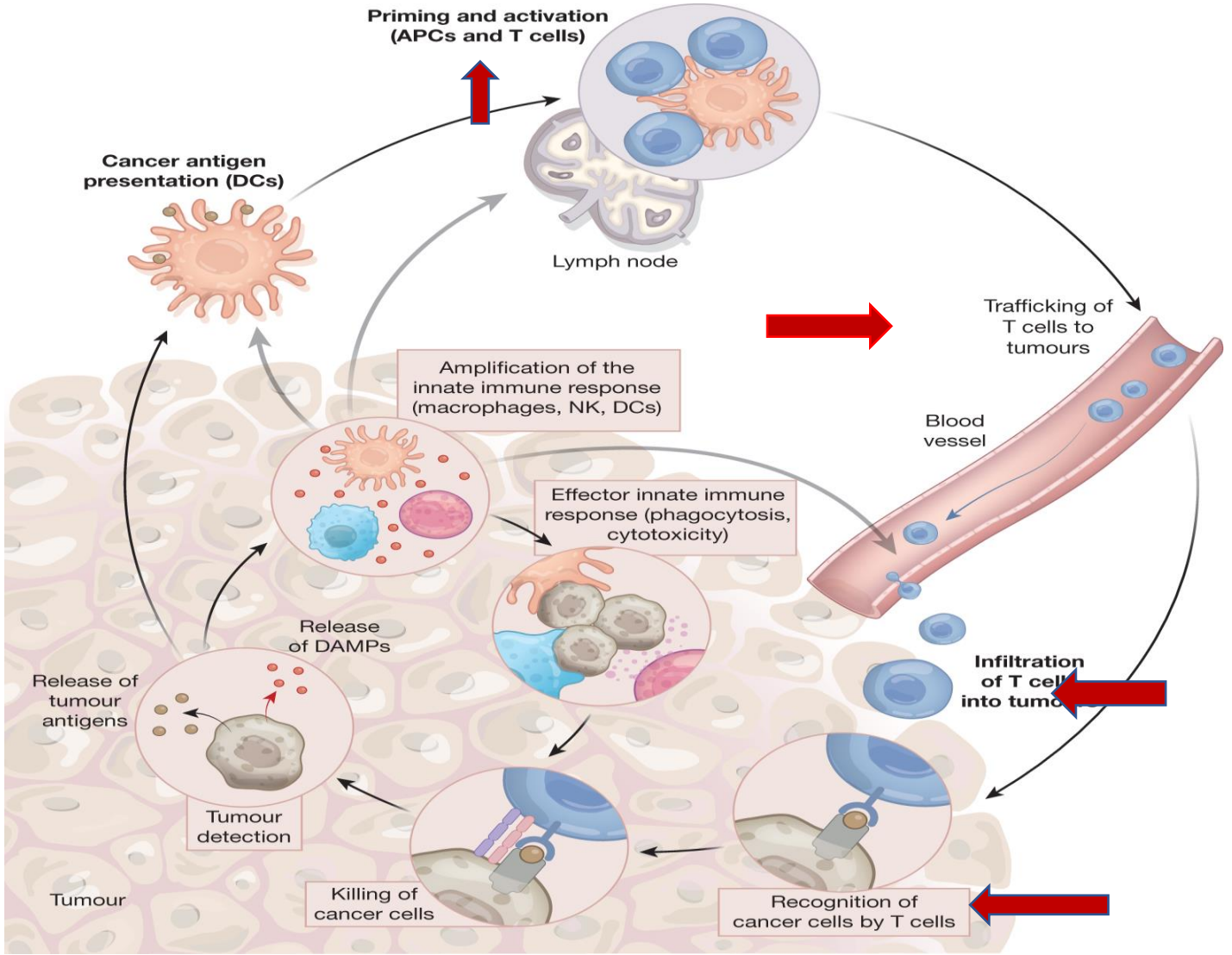
Disclosures

- Consultant for Pfizer, and Seattle Genetics.

Evolution of Cancer treatment



Cancer Immune Cycle: role of T-cells



Demaria O, Cornen S, Daëron M, Morel Y, Medzhitov R, Vivier E. *Nature*. 2019;574(7776):45-56.

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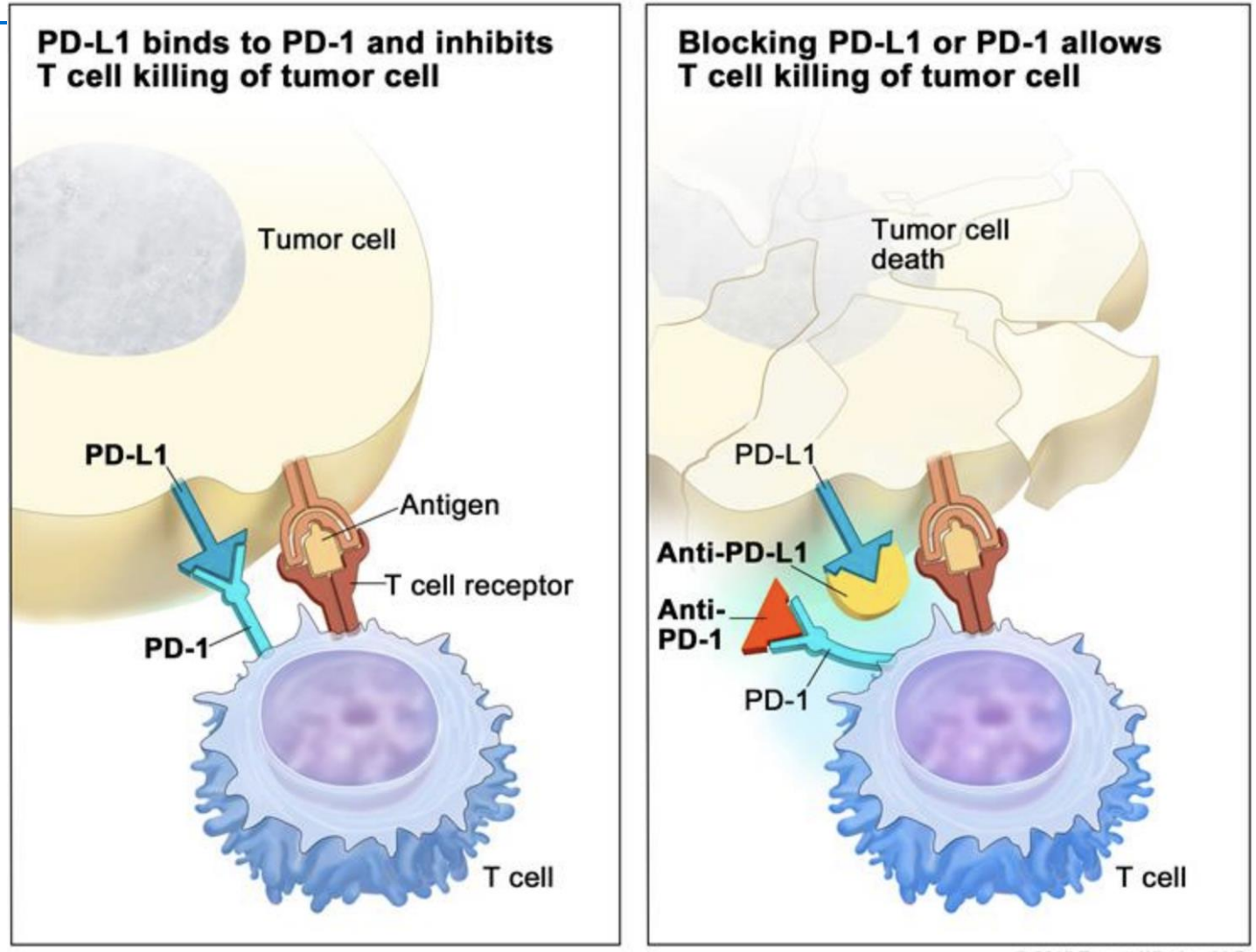
MoA of PD-1/PD-L1 inhibitor

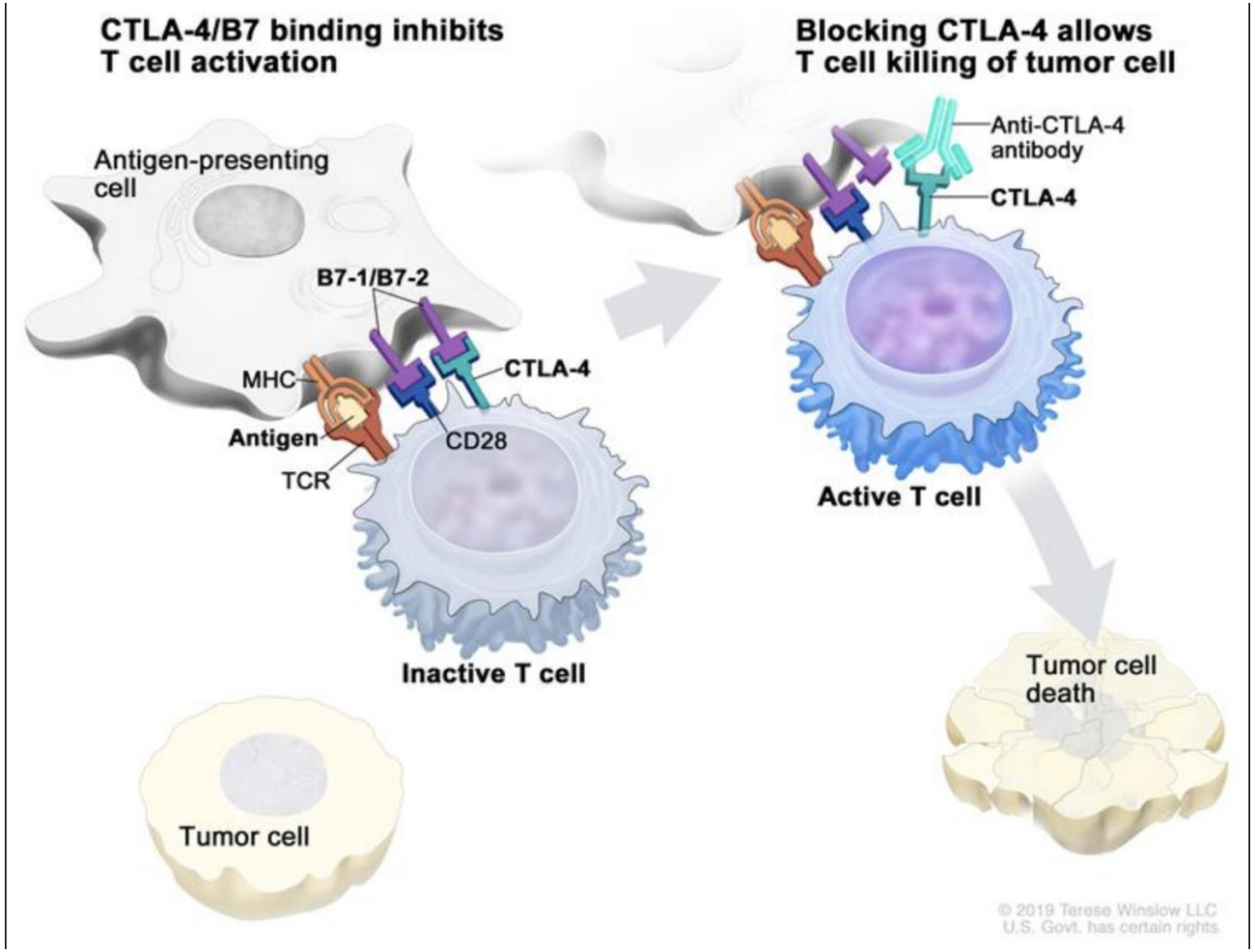
- Checkpoint proteins, such as PD-L1 on tumor cells and PD-1 on T cells, help keep immune responses in check.
- Activation of PD-L1 to PD-1 prevents T cells from killing tumor cells
- Inhibition of the binding of PD-L1 to PD-1 with an immune checkpoint inhibitor (anti-PD-L1 or anti-PD-1) allows the T cells to kill tumor cells



NCI Dictionary of Cancer Terms. (n.d.). Retrieved May 2020, from https://www.cancer.gov/publications/dictionaries/cancer-terms/def/immune-checkpoint-inhibitor

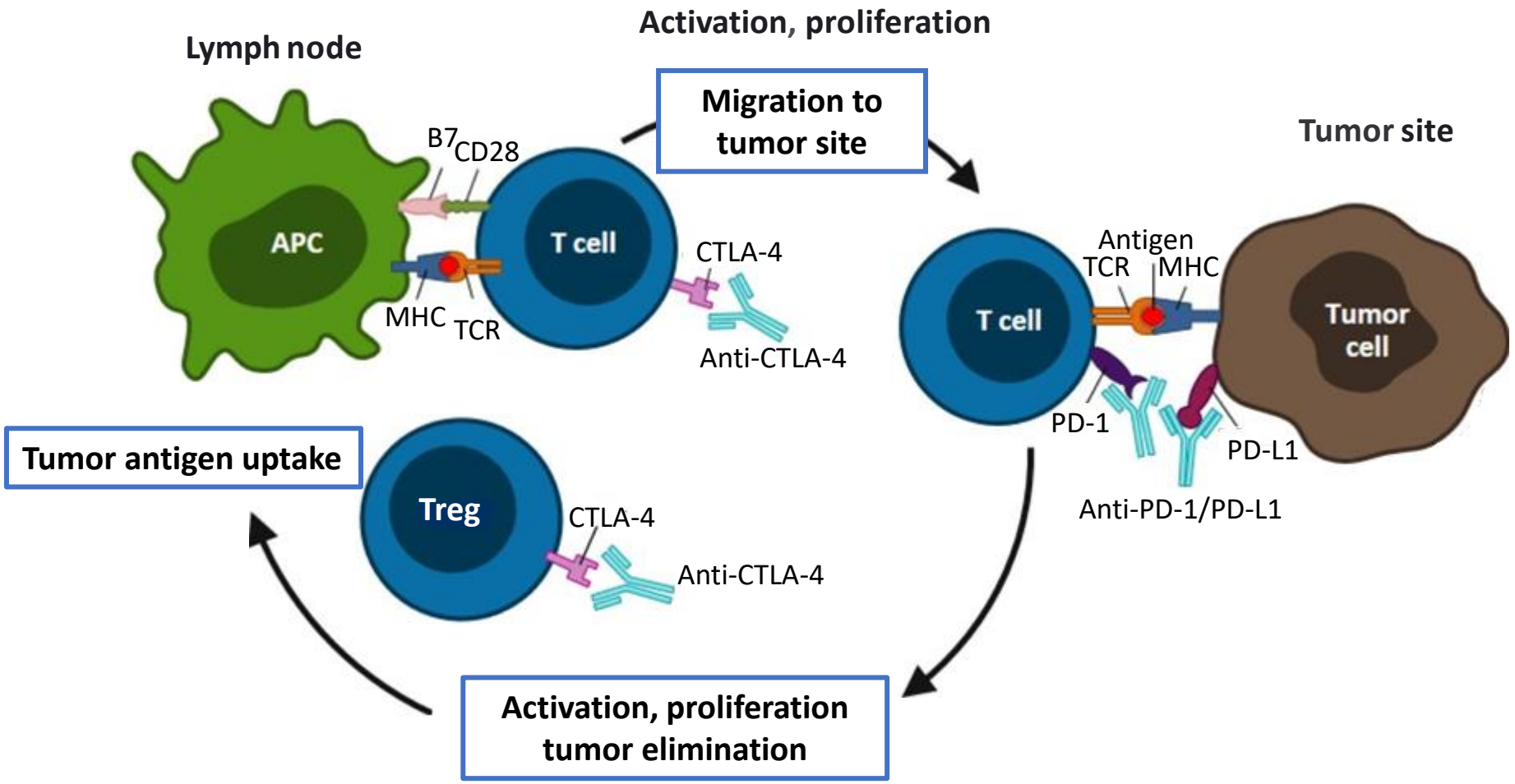
MoA of CTLA-4 inhibitor

- Checkpoint proteins, such as B7-1/B7-2 on antigen presenting cells and CTLA-4 on T cells, help keep immune responses in check
- Activation of B7-1/B7-2 to CTLA-4 keeps the T cells in the inactive state so they are not able to kill tumor cells
- Inhibition of B7-1/B7-2 to CTLA-4 with an immune checkpoint inhibitor (anti-CTLA-4 antibody) allows the T cells to be active and to kill tumor cells (right panel).



NCI Dictionary of Cancer Terms. (n.d.). Retrieved May 2020, from https://www.cancer.gov/publications/dictionaries/cancer-terms/def/immune-checkpoint-inhibitor

ICI Mechanism of action



Anti-CTLA-4
- ipilimumab

Anti-PDL1
- Atezolizumab
- Avelumab
- Durvalumab

Anti-PD1
- Nivolumab
- Pembrolizumab

Ref: Buchbinder EI, Desai A. *Am J Clin Oncol*. 2016;39(1):98-106.

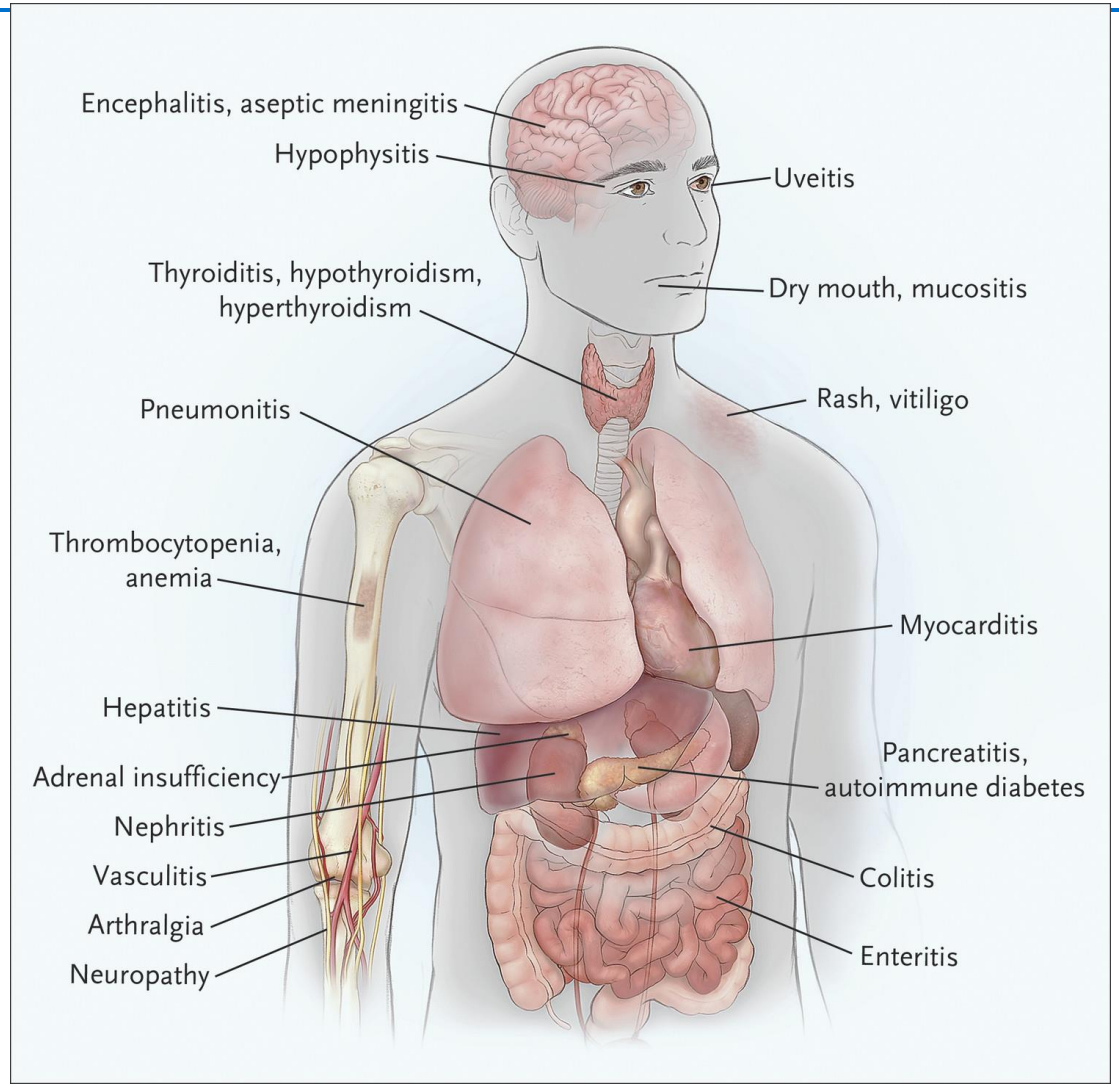
Wide use of ICIs across many malignancies

Drug	Indications
Atezolizumab	NSCLC, SCLC, breast CA (TNBC)
Avelumab	Merkel cell carcinoma, urothelial carcinoma, advanced RCC
Durvalumab	NSCLC, urothelial carcinoma
Nivolumab	Metastatic NSCLC, Metastatic Melanoma, Advanced RCC, Small Cell Lung CA, Recurrent or Metastatic SCC of the Head and Neck, HCC, Locally Advanced or Metastatic Urothelial Carcinoma, MSI-H/dMMR Metastatic Colorectal CA, Relapsed or Progressed cHL
Pembrolizumab	Advanced NSCLC, NMIBC, MSI-H cancer, Advanced gastric CA, Primary mediastinal B-cell lymphoma, Advanced Merkel cell carcinoma, Melanoma, Advanced kidney cancer, cHL, Advanced cervical cancer, Advanced liver cancer, Advanced esophageal SCC, Head and neck SCC, Advanced gastric cancer
Cemiplimab-rwlc	advanced cutaneous SCC
Ipilimumab	Melanoma, RCC, MSI-H/dMMR colorectal CA, HCC

CA, cancer; dMMR, mismatch repair deficient; IV, intravenously; MSI-H, microsatellite instability-high; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; TNBC, triple-negative breast cancer; RCC: Renal Cell Carcinoma; SCC,Squamous Cell Carcinoma; HCC,Hepatocellular Carcinoma; NMIBC, High-risk non-muscle invasive bladder cancer , cHL, classical Hodgkin lymphoma

Bavencio [prescribing information]; Rockland, Md.: EMD Serano; 2019.;
Imflinzi [prescribing information]; Wilmington, Del.: AstraZeneca Pharmaceuticals; 2020.;
Keytruda [prescribing information]; Whitehouse Station, NJ: Merck & Co., Inc.;2020.;
Libtayo [prescribing information]; Tarrytown, NY: Regeneron Pharmaceuticals and Sanofi-Aventis;2018.;
Opdivo [prescribing information]; Princeton, NJ: Bristol-Myers Squibb;2020.;
Tecentriq [prescribing information]; South San Francisco, CA: Genentech;2019.;
Yervoy [prescribing information]; Princeton, NJ: Bristol-Myers Squibb;2020.

Immune checkpoint inhibitors (ICI) adverse effects



<u>Use of ICI can affect any organ in the body</u>

- Relatively well tolerated with majority of patients only having mild/moderate AE

Most common
- Colitis
- Fatigue – thyroid, hypophysitis
- Pneumonitis

Most lethal
- Myocarditis
- hepatitis

ASCO Guidelines on irAE management

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICL

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Julie R. Brahmer, Christina Lacchetti, Bryan J. Schneider, Michael B. Atkins, Kelly J. Brassil, Jeffrey M. Caterino, Ian Chau, Marc S. Ernstoff, Jennifer M. Gardner, Pamela Ginex, Sigrun Hallmeyer, Jennifer Holter Chakrabarty, Natasha B. Leighl, Jennifer S. Mammen, David F. McDermott, Aung Naing, Loretta J. Nastoupil, Tanyanika Phillips, Laura D. Porter, Igor Puzanov, Cristina A. Reichner, Bianca D. Santomasso, Carole Seigel, Alexander Spira, Maria E. Suarez-Almazor, Yinghong Wang, Jeffrey S. Weber, Jedd D. Wolchok, and John A. Thompson in collaboration with the National Comprehensive Cancer Network

ASCO Guidelines on management of irAEs

- In general, ICI therapy should be continued with close monitoring for grade 1 toxicities, with the exception of some neurologic, hematologic, and cardiac toxicities.
- Hold ICIs for most grade 2 toxicities and consider resuming when symptoms and/or laboratory values revert to grade 1 or less. Corticosteroids (initial dose of 0.5 to 1 mg/kg/d of prednisone or equivalent) may be administered.
- Hold ICIs for grade 3 toxicities and initiate high-dose corticosteroids (prednisone 1 to 2 mg/kg/d or methylprednisolone IV 1 to 2 mg/kg/d). Corticosteroids should be tapered over the course of at least 4 to 6 weeks. If symptoms do not improve with 48 to 72 hours of high-dose corticosteroid, infliximab may be offered for some toxicities.
- When symptoms and/or laboratory values revert to grade 1 or less, rechallenging with ICIs may be offered; however caution is advised, especially in those patients with early-onset irAEs. Dose adjustments are not recommended.
- In general, grade 4 toxicities warrant permanent discontinuation of ICIs, with the exception of endocrinopathies that have been controlled by hormone replacement.

Brahmer et al. JCO 2018

Management of immune related AE - Diarrhea

- Colitis/Diarrhea as an example (50% of pts receiving ipi/nivo)
- Rule out infection (c. diff)
  - Gr 1: 4 stools/day - symptomatic management (loperamide)
  - Gr 2: 4-6 stools/day – steroids (prednisone < 10 mg/day)
  - Gr 3: 7 stools/day – stop ICI. Prednisone 1-2 mg/kg/day
  - Gr 4: life threatening – permanently DC ICI. Admit pt.
    - Methylprednisolone 1-2 mg/kg/day
    - Consider infliximab infusion

Management of immune related AE - Dermatitis

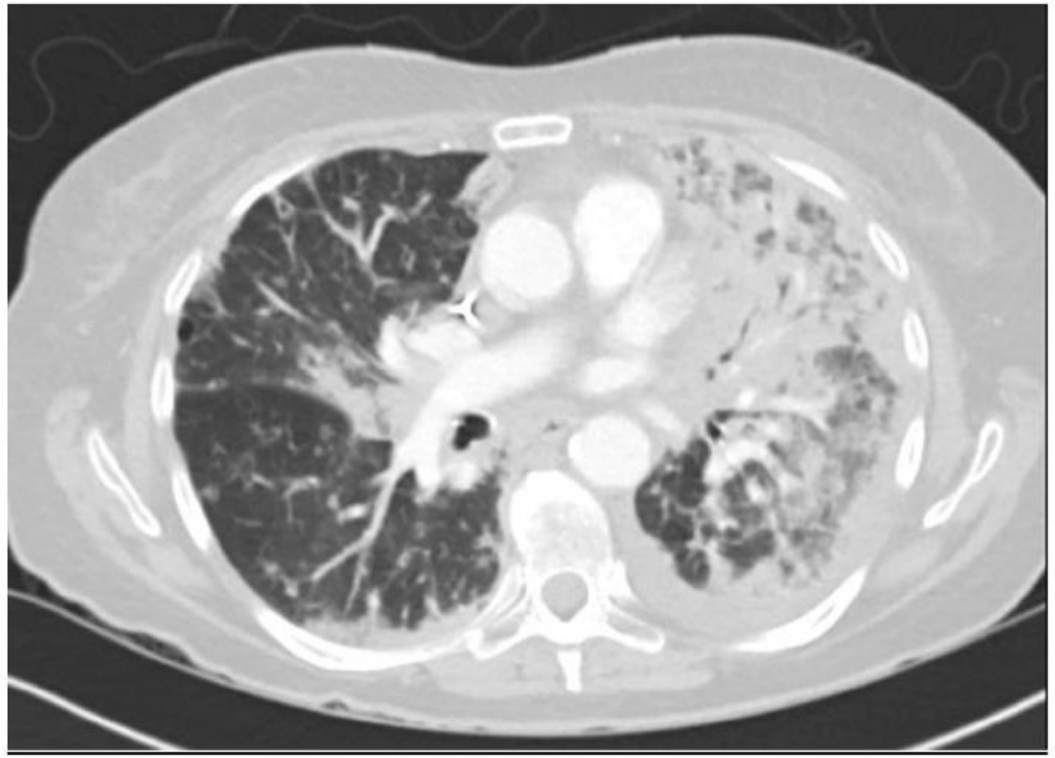
- All grades - For SJS or mucus membrane involvement hold ICI and monitor closely. Consider Dermatology consult.
- Gr 1: not affecting QoL- topical corticosteroids, cont. ICI
- Gr 2: affects quality of life – consider holding ICI and prednisone 1 mg/kg with taper over 4 weeks.
- Gr 3: As G2 but failure to respond to prednisone: Hold ICI and consult derm. Methylprednisolone 1-2 mg/kg
- Gr4: All severe rashes unresponsive to above tx and intolerable: Admit patient and consult derm. Methylprednisolone 2 mg/kg.

Management of immune related AE

- irAEs requiring special attention
  - Pneumonitis
  - Endocrinopathies
  - Cardiomyopathy

Management of immune related AE - pneumonitis

- Presents with cough, dyspnea
  - Rule out infectious causes – pneumonia, COVID-19
  - Incidence – PD-1/PD-L1 3%). CTLA-4 + PD-1 (10%)
  - grade 1 (intervention not needed)– hold ICI 2-3 weeks
  - Grade 2 (affects ADLs) – hold ICI 2-3 weeks and give prednisone (1 mg/kg)
  - Grade 3 (oxygen needed) – hold ICI, glucocorticoids, consider admission for close monitoring



Naidoo et. al JCO 2016

Petri et. al Respiratory Medicine Case Reports 2019

Management of immune related AE - endocrinopathies

- Symptoms
  - Fatigue, hypotension, headaches, pre-syncope, syncope
- Autoimmune hypothyroidism – fatigue, weight gain
  - Check thyroid function with each infusion, prescribe thyroid replacement if necessary
- Hypophysitis – sx of fatigue and headache
  - Replace deficient hormones – levothyroxine, hydrocortisone
- Adrenal insufficiency – nausea/vomiting, hypotension, fatigue, hyponatremia
  - Check serum cortisol levels with each infusion
  - If adrenal crisis then admit patient. If more indolent then replace adrenal hormones with hydrocortisone.

Management of immune related AE - myocarditis

- Presents with acute coronary syndrome after ICI infusion – sx acute chest pain, dyspnea, diaphoresis, elevated troponins and other cardiac enzymes
- Incidence is rare – est. 0.27% during ipi/nivo combination
- Low threshold for admission and cardiology consult. If needed CCU admission
- High dose steroids – methylprednisolone 2 mg/kg
- If unresponsive escalate to cardiac transplant rejection meds infliximab, mycophenolate, abatacept

Johnson DB et al. NEJM 2016

Summary – irAE management (ASCO guidelines)

- The use of immune checkpoint inhibitors in cancer treatment is rapidly expanding.
- As a result there are more incidences of immune related adverse effects (irAEs).
- Patient and caregivers should receive timely and current education on possible irAEs so they can report any symptoms.
- ICI therapy should be continued with close monitoring and symptomatic treatment for grade 1 toxicities. The exception is for some neurologic, hematologic, and cardiac toxicities.
- Grade 4 toxicities warrant permanent discontinuation of ICIs, with the exception of endocrinopathies that have been controlled by hormone replacement.
- Hold ICIs for grade 3 toxicities and initiate high-dose corticosteroids (prednisone 1 to 2 mg/kg/d or methylprednisoloneIV 1 to 2 mg/kg/d). Corticosteroids should be tapered over the course of at least 4 to 6 weeks.

Case 1

- A 74 year old female patient with metastatic urothelial carcinoma who was treated with cisplatin/gemcitabine and is now on maintenance avelumab presents to your clinic for her routine follow up. She has been getting four cycles of maintenance avelumab but now reports having new onset diarrhea with 3 loose stools a day. You do an infectious disease work up for her diarrhea and determine this is an immune related adverse effect. How would you manage her immune checkpopint inhibitor treatment?

- A. Continue the immune check point inhibitor and treat symptomatically with loperamide.

- B. Hold the immune checkpoint inhibitor temporarily until symptoms resolve

- C. Continue the immune checkpoint inhibitor and start prednisone 1 mg/kg daily with a 4 week taper

- D. Discontinue the immune checkpoint inhibitor permanently

Management of immune related AE - Diarrhea

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  - Gr 4: life threatening – permanently DC ICI. Admit pt.
    - Methylprednisolone 1-2 mg/kg/day
    - Consider infliximab infusion

Case 1

- **Answer is (A).** Patient is having grade 1 diarrhea. Per ASCO guidelines on irAE management recommendation is to continue the immune checkpoint inhibitor and treat symptomatically with loperamide or other anti-diarrheal agents if possible.

- Ref: ASCO Guidelines on immune related adverse effents. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, Chau I, Ernstoff MS, Gardner JM, Ginex P, Hallmeyer S, Holter Chakrabarty J, Leighl NB, Mammen JS, McDermott DF, Naing A, Nastoupil LJ, Phillips T, Porter LD, Puzanov I, Reichner CA, Santomasso BD, Seigel C, Spira A, Suarez-Almazor ME, Wang Y, Weber JS, Wolchok JD, Thompson JA; National Comprehensive Cancer Network. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018 Jun 10;36(17):1714-1768. doi: 10.1200/JCO.2017.77.6385. Epub 2018 Feb 14. PMID: 29442540; PMCID: PMC6481621.

Case 2

- A 60 year old male patient with newly diagnosed metastatic renal cell carcinoma is started on ipilimumab/nivolumab treatment. One week after his first infusion he calls the clinic reporting symptoms of severe fatigue, nausea/vomiting, and light headedness when trying to stand up. You see the patient that day urgently in the clinic and find that he is hypotensive with BP of 80/50, HR 62. His general demeaner shows severe malaise. On labs he has hyponatremia, normal TSH, and low serum cortisol. What would be next best step for clinical management?

- A. Prescribe levothyroxine and follow up in 2 weeks.

- B. Give NS IV hydration and ondansetron in the infusion center and follow up in 2 weeks.

- C. Admit patient to the hospital for possible adrenal insufficiency and consult endocrinology.

- D. Prescribe prednisone 1 mg/kg with a taper over 4 weeks and follow up in clinic after taper is finished.

Management of immune related AE - endocrinopathies

- Symptoms
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  - Check serum cortisol levels with each infusion
  - If adrenal crisis then admit patient. If more indolent then replace adrenal hormones with hydrocortisone.

Case 2

- **Answer is C**. Patient may have adrenal insufficency/crisis as an irAE of ipi/nivo. As a result he will need inpatient admission for both diagnostic work up and treatment with replacement steroids (glucocorticoids and mineralocorticoid replacement).

- Ref: ASCO Guidelines on immune related adverse effents. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, Chau I, Ernstoff MS, Gardner JM, Ginex P, Hallmeyer S, Holter Chakrabarty J, Leighl NB, Mammen JS, McDermott DF, Naing A, Nastoupil LJ, Phillips T, Porter LD, Puzanov I, Reichner CA, Santomasso BD, Seigel C, Spira A, Suarez-Almazor ME, Wang Y, Weber JS, Wolchok JD, Thompson JA; National Comprehensive Cancer Network. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018 Jun 10;36(17):1714-1768. doi: 10.1200/JCO.2017.77.6385. Epub 2018 Feb 14. PMID: 29442540; PMCID: PMC6481621.

Thank you!

- <u>City of Hope/Beckman Research Institute</u>
  - Tanya Dorff, MD (Section Chief, GU Oncology)
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