Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Identification and Management of Immune-Related Adverse Events in the Emergency Setting

Matthew N. Graber, MD PhD FAAEM

Chair, Department of Emergency Medicine

Magnolia Regional Health Center

Corinth, MS

Association of Community Cancer Centers

Society for Immunotherapy of Cancer

Disclosures

- No relevant financial relationships to disclose

ADVANCES IN Cancer IMMUNOTHERAPY™

Mechanism CTLA-4 &PD-1

- Involved in maintaining appropriate immune response
- Downregulates & prevents inappropriate activity
- Autoimmune type response
- Thinking “Chemo” will lead down wrong path
- **Think Graft versus Host disease**

ADVANCES IN Cancer IMMUNOTHERAPY™

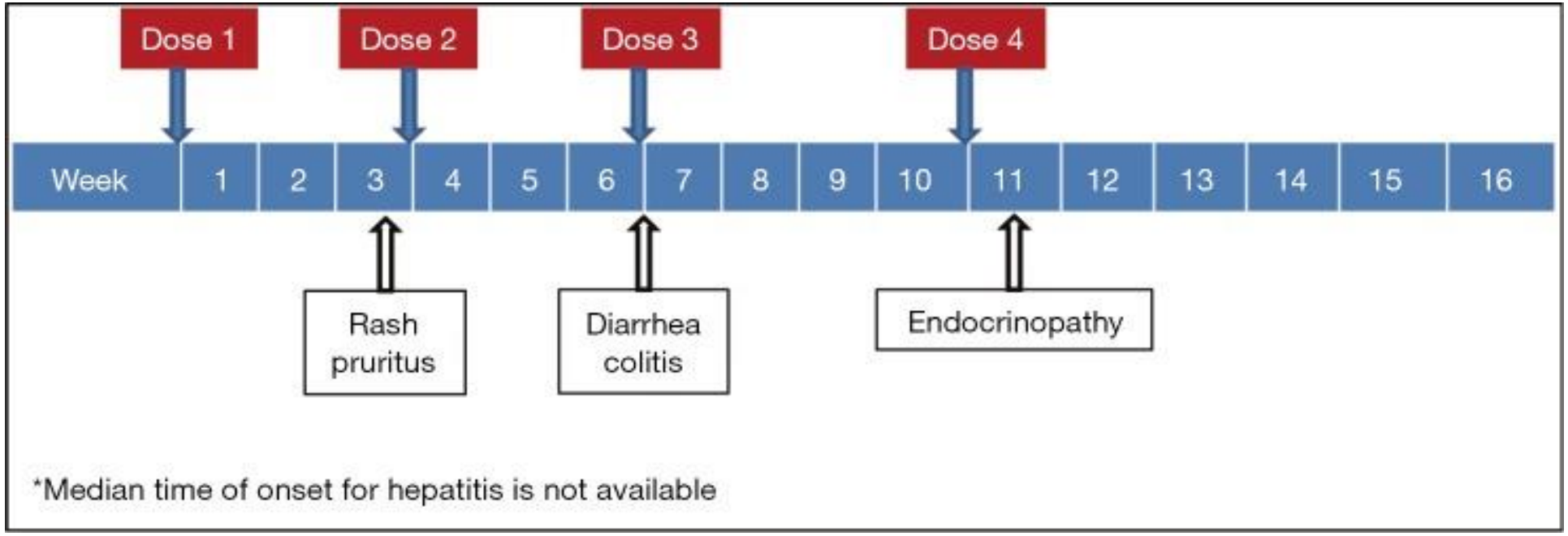
Timing

- Most occur within first 3 months
- May occur after final dose
- Some dose dependent
- Grade 3-4 toxicity 10% overall

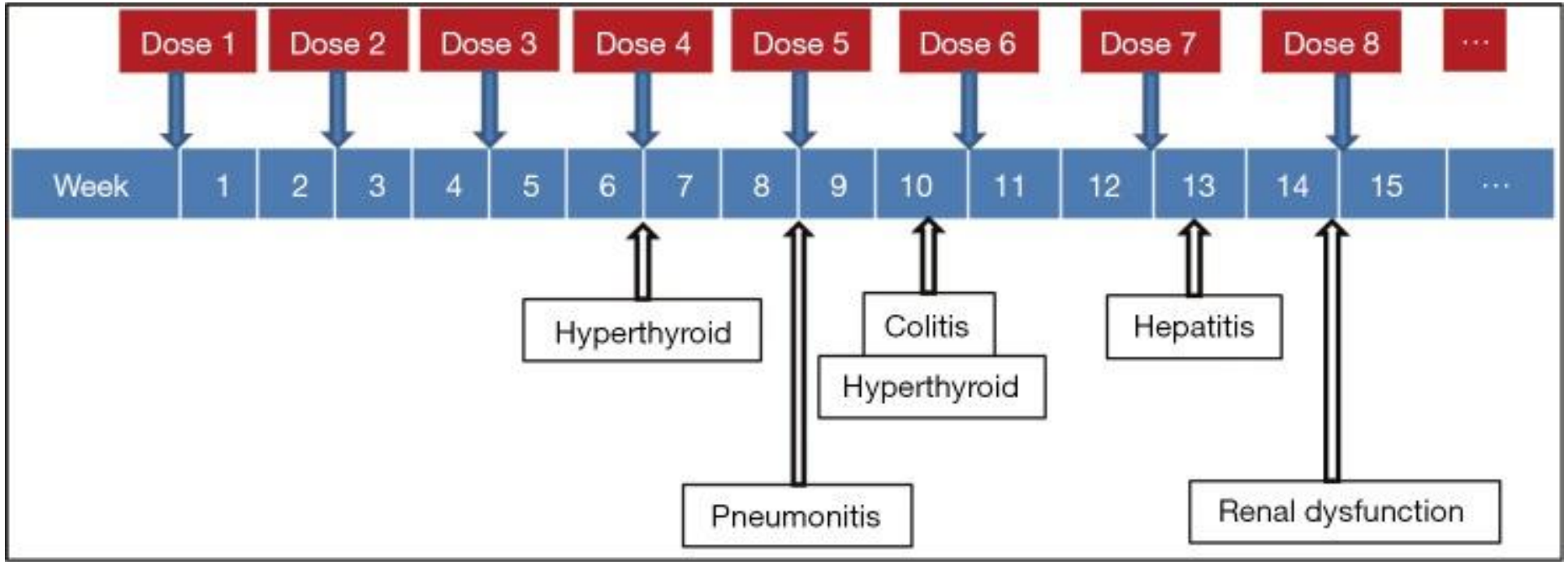
ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Phase III Trial ipilimumab

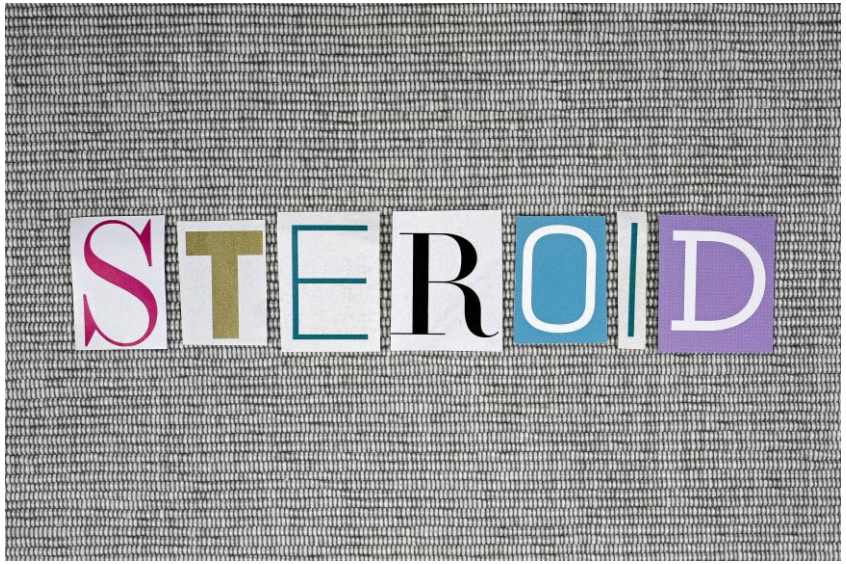


Phase III Trial nivolumab



Common Medications

- Corticosteroids
  - **Prednisone**
  - Dexamethasone
  - Methylprednisolone
  - Hydrocortisone
  - Cortisone
- Mycophenolate mofetil (CellCept)
  - Standard BID
- TNF inhibitors
  - Infliximab
  - Adalimumab
  - Others



ADVANCES IN Cancer IMMUNOTHERAPY™

Dermatologic Toxicity

- Presents three weeks into therapy
- Mild – maculopapular rash with or without symptoms
  - Pruritis, burning, tightness
  - 10%-30% TBSA
  - Limiting ADL's
  - Topical steroids, hydroxyzine, diphenhydramine, famotidine, doxepin
- Moderate – diffuse, non-localizing rash
  - 30-50% TBSA
  - Topical steroids, hydroxyzine, diphenhydramine, famotidine, doxepin
  - Consider systemic corticosteroids if no improvement in one week (0.5-1mg/kg/day)

ADVANCES IN Cancer IMMUNOTHERAPY™

Dermatologic Toxicity

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Severe

- Blisters, dermal ulceration, necrotic, bullous or hemorrhagic
- Systemic corticosteroids 1-2 mg/kg/day prednisone equivalent
- Taper over one month following improvement

Vitiligo

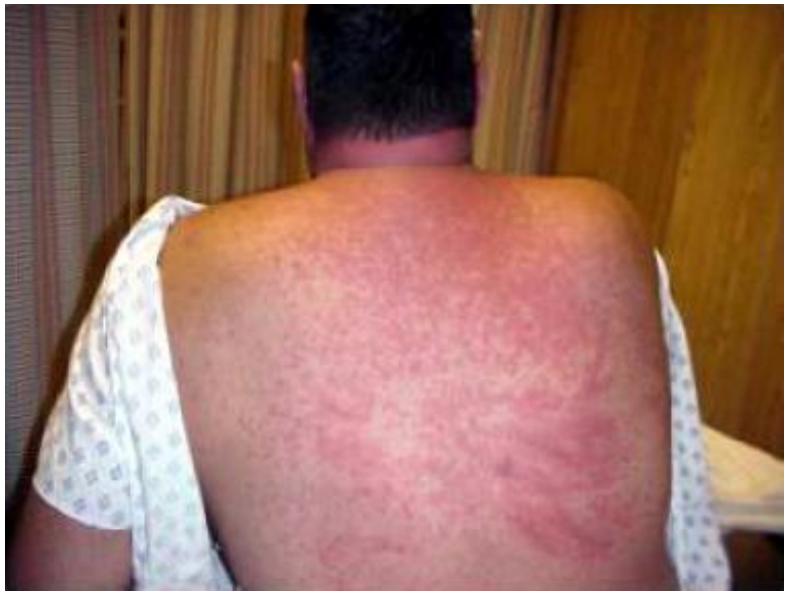
- Most cases permanent
- No treatment
- Intra oral lesions – consider candidiasis.

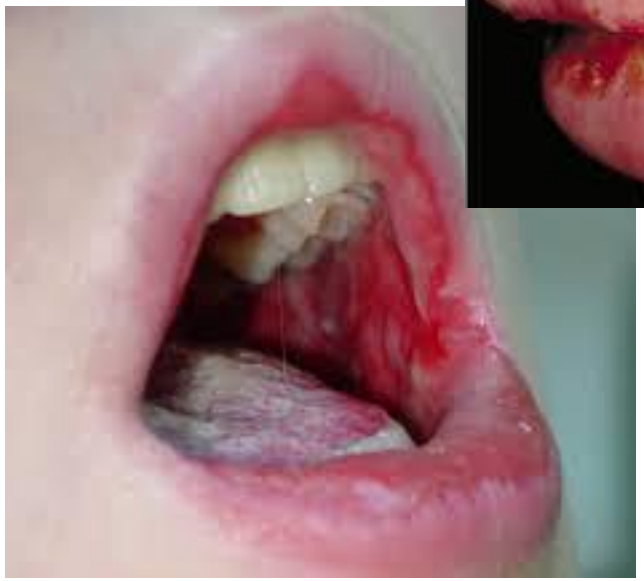
ACCC Association of Community Cancer Centers

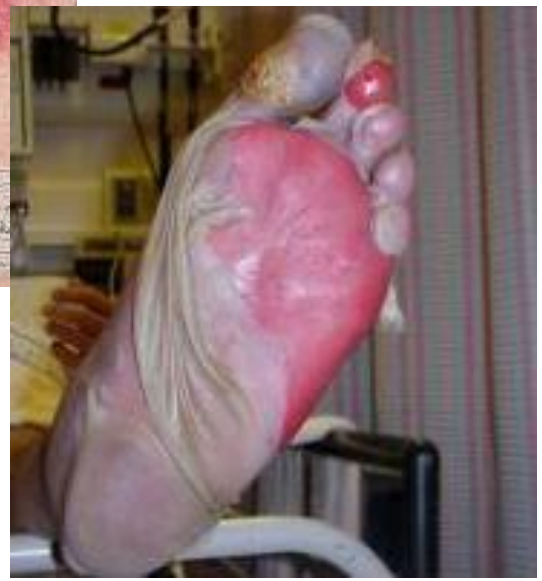
sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Stevens Johnsons Syndrome (SJS) / TEN (Toxic Epidermal Necrolysis)







ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Vitiligo

Association of Community Cancer Centers

Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Patient 1

Association of Community Cancer Centers

Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Association of Community Cancer Centers

Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Association of Community Cancer Centers

Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

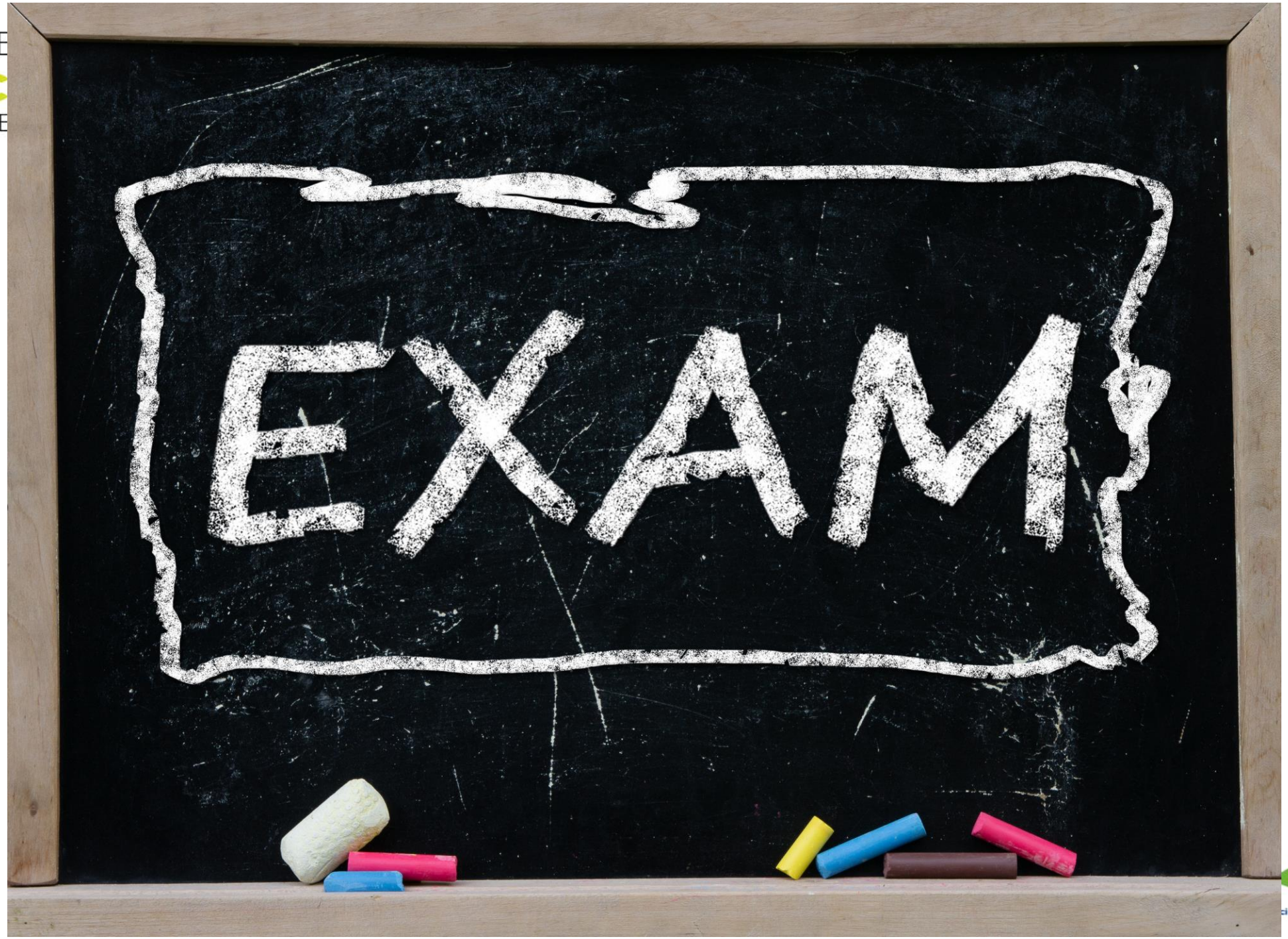
- PMH: Small Cell Lung Cancer, HTN, DM

- Meds: Nivolumab

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

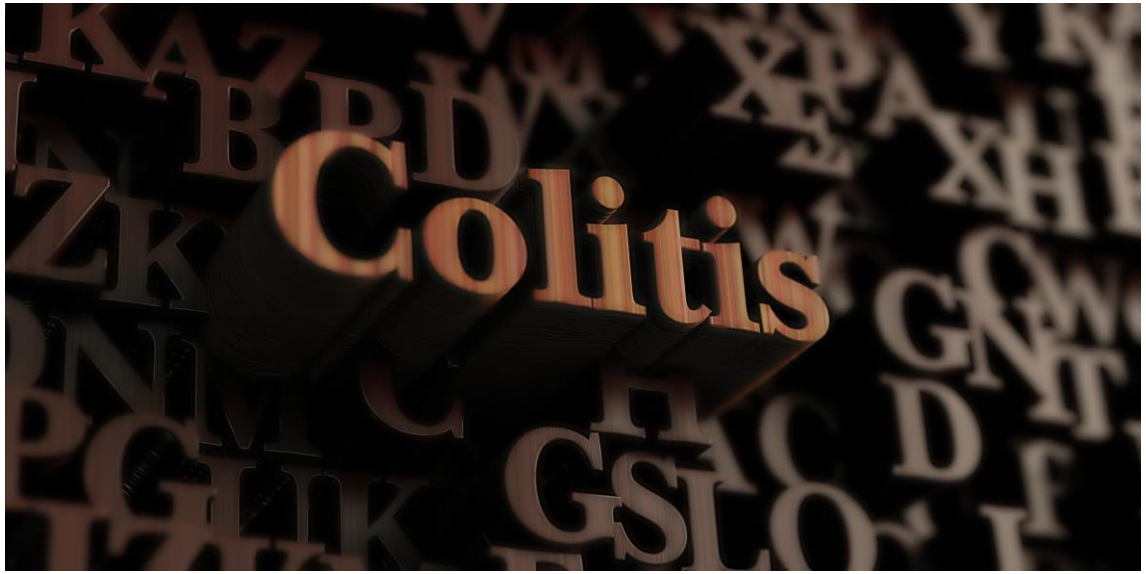
ADVANCE
Canc
IMMUNOTHE



sitc
ciety for Immunotherapy of Cancer

Management

- Fluids & Anagelsia
- Stool Studies
- CT scan
- ABX & steroids



ADVANCES IN Cancer IMMUNOTHERAPY™

Diarrhea / Colitis

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

- Mild - <4 stools above baseline/day
- Testing
- Treatment
  - Symptomatic: oral hydration & bland diet
  - No corticosteroids
  - Avoid meds
  - Budesonide – no significant difference

ADVANCES IN Cancer IMMUNOTHERAPY™

- Moderate – 4-6 stools above daily baseline
- Abdominal pain, blood or mucus in stool
- Testing - C. diff., lactoferrin, O & P, stool Cx
- Systemic corticosteroids 0.5/mg/kg/day equivalent if symptoms > one week

Severe

- 7 stools above baseline/day
- Peritoneal signs, ileus or fever
- Admission
- IV hydration
- Rule out perforation
- Stool studies

ADVANCES IN Cancer IMMUNOTHERAPY™

- Systemic corticosteroids 1-2mg/kg/day equivalent, if no perforation
  - Hold if clinically stable until stool studies available (24hrs)
- Unstable – High dose corticosteroids: methylprednisolone 125 mg IV daily x 3 days to evaluate responsiveness
- Consider empiric antibiotics for fever or leukocytosis
- Infliximab 5 mg/kg if no response to corticosteroids
- Consider mycophenolate mofetil for select patients

Hepatotoxity

- 8-12 weeks after therapy initiation
- Avoid ETOH & acetaminophen

ADVANCES IN Cancer IMMUNOTHERAPY™

Grade 2 toxicity

- 2.5< AST/ALT <5 times ULN
- 1.5< Bilirubin<3 times ULN
- Corticosteroids 0.5-1 mg/kg/day & 1 mo. taper

Grade ≥3 toxicity

- Admission
- Methylprednisolone IV 125mg/day
- Consider mycophenolate mofetil 500mg PO Q12hrs

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Endocrinopathies

- <10%

- Both CTLA &PD-1 inhibitors

Hypophysitis

- Fatigue, headaches, visual field defects
- ACTH, TSH, FSH, LH, GH, prolactin
- Imaging – enlarge pituitary gland
- 1-2 months after initiation of therapy
- Corticosteroids 1 mg/kg/day. Or IV dexamethasone 6 mg Q6hr x 3 days, or methylprednisolone 125 mg daily

Endocrinopathies cont.

- Hypothyroidism
  - 1 wk-19 months onset after therapy initiation
  - Appropriate levothyroxine replacement
- Hyperthyroidism
  - Check TSH level
  - Acute thyroiditis secondary to immune activation
    - Corticosteroids 1 mg/kg for symptomatic patients
- Adrenal Insufficiency
  - Admission
  - Corticosteroids 60-80 mg prednisone or equivalent

ADVANCES IN Cancer IMMUNOTHERAPY™

Pneumonitis

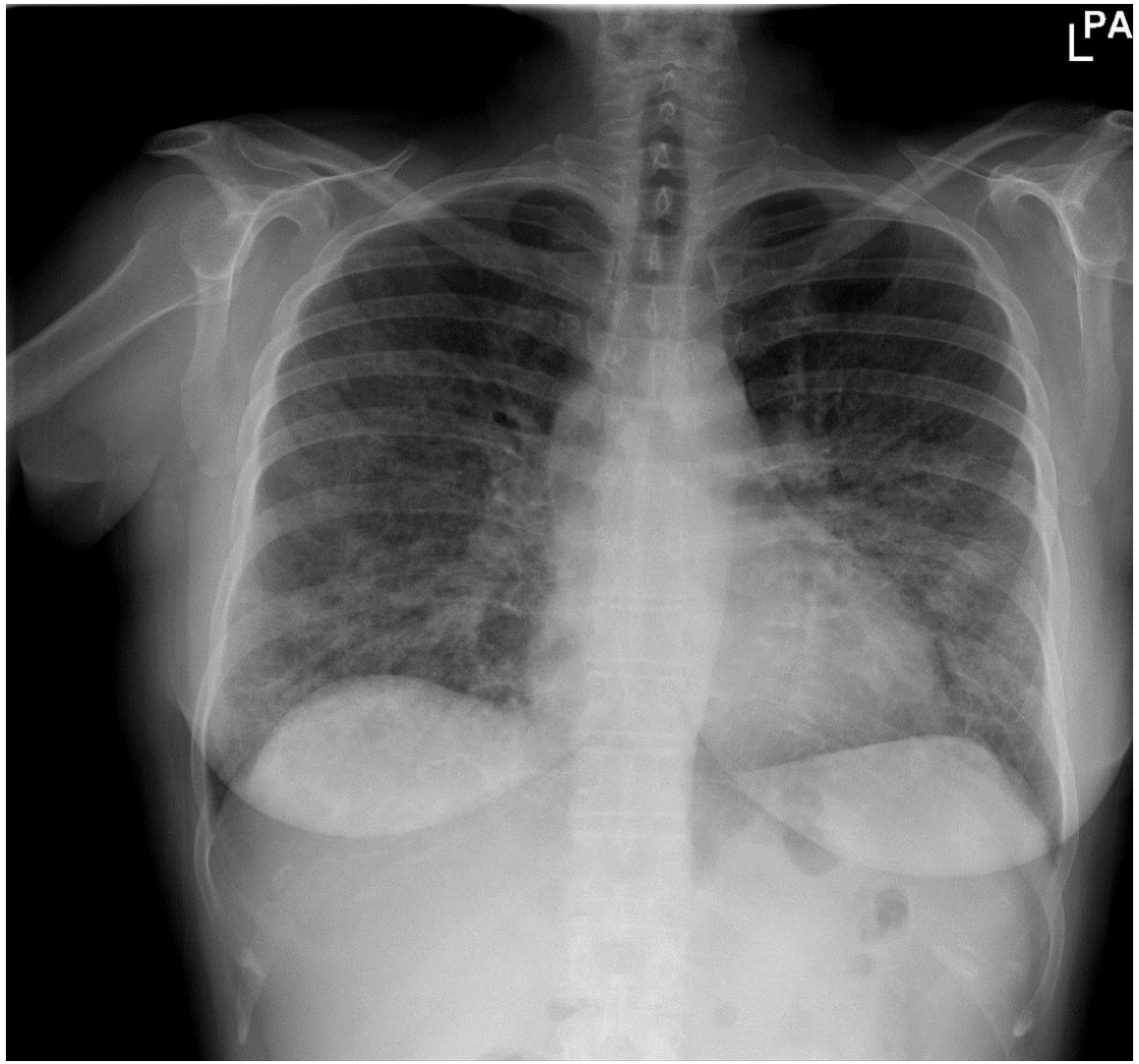
- Occur with CTLA-4 &PD1 inhibitors
- 5 months after treatment initiation
- New cough or dyspnea
- Multiple grades

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Pneumonitis

- Grade 2
  - Admission
  - Prednisone/prednisolone
    - Taper over one month after improvement seen
- Grade 3-4
  - Admission
  - Prednisone/prednisolone
  - Six week taper



Pancreatitis

- Elevation lipase / CT findings
  - With both CTLA-4 &PD1 inhibitors
  - Without overt pancreatitis– monitor
  - Grade 3-4 with symptoms – hold therapy

- New onset diabetes with DKA
  - Normal ED treatment
  - Aggressive treatment of DKA

ADVANCES IN Cancer IMMUNOTHERAPY™

Patient 2

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Association of Community Cancer Centers

Society for Immunotherapy of Cancer


management

ADVANCES IN Cancer IMMUNOTHERAPY™

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Renal Insufficiency

- <1%
- Grade 1: up to 1.5 times above baseline
- Grade 2 to 3: 1.5-6 times baseline
- 10-12 months after initiation of treatment
- Full recovery with high dose corticosteroids. (>40 mg/day)

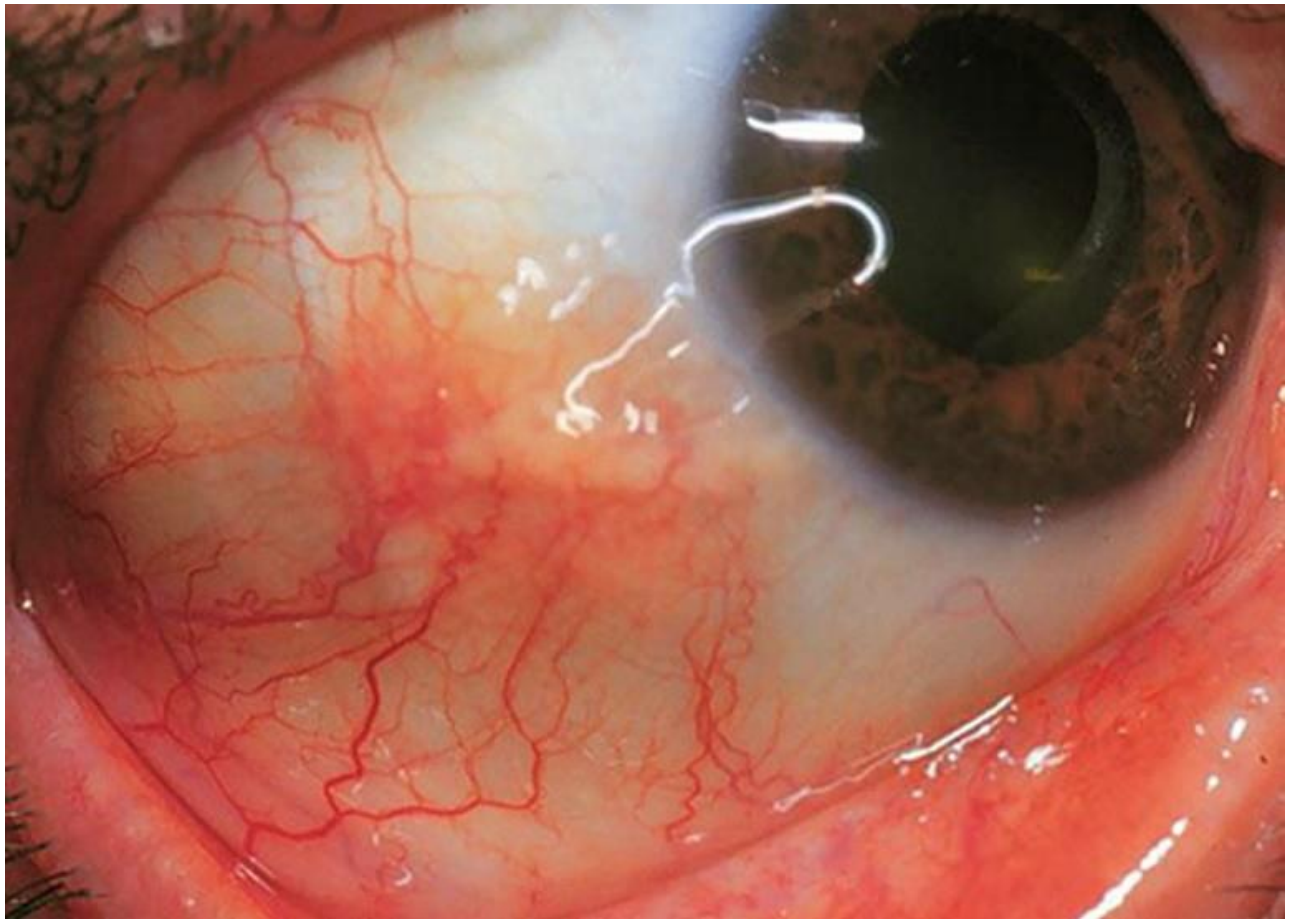
ADVANCES IN Cancer IMMUNOTHERAPY™

Ophthalmologic

- <1%
- Episcleritis
- Uveitis
- Conjunctivitis
- Topical corticosteroids – prednisolone acetate 1%

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer



ADVANCES IN Cancer IMMUNOTHERAPY™

Association of Community Cancer Centers

Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Rare irAEs

- <1%
  - Red cell aplasia
  - Thrombocytopenia
  - Hemophilia A
  - Gullian-Barre syndrome
  - Myasthenia gravis
  - Posterior reversible encephalopathy syndrome
  - Aseptic meningitis
  - Transverse myelitis
  - ??

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Case Study #3: 54-year-old male with NSCLC

- New immunotherapy 8 weeks ago for lung cancer
- Vision is blurry, & glasses don't work anymore
  - Denies eye pain
  - Mild HA "because he reads a lot & his glasses don't work anymore"
- Exam
  - VA w/o correction: 20/25 right eye (OD), 20/125 left eye (OS)
  - IOP: 10 mmHg OD, 12 mmHg OS
  - Pupils: 5 → 3 mm in both eyes (OU)
  - Confrontation visual fields: temporal loss OD, central scotoma OS

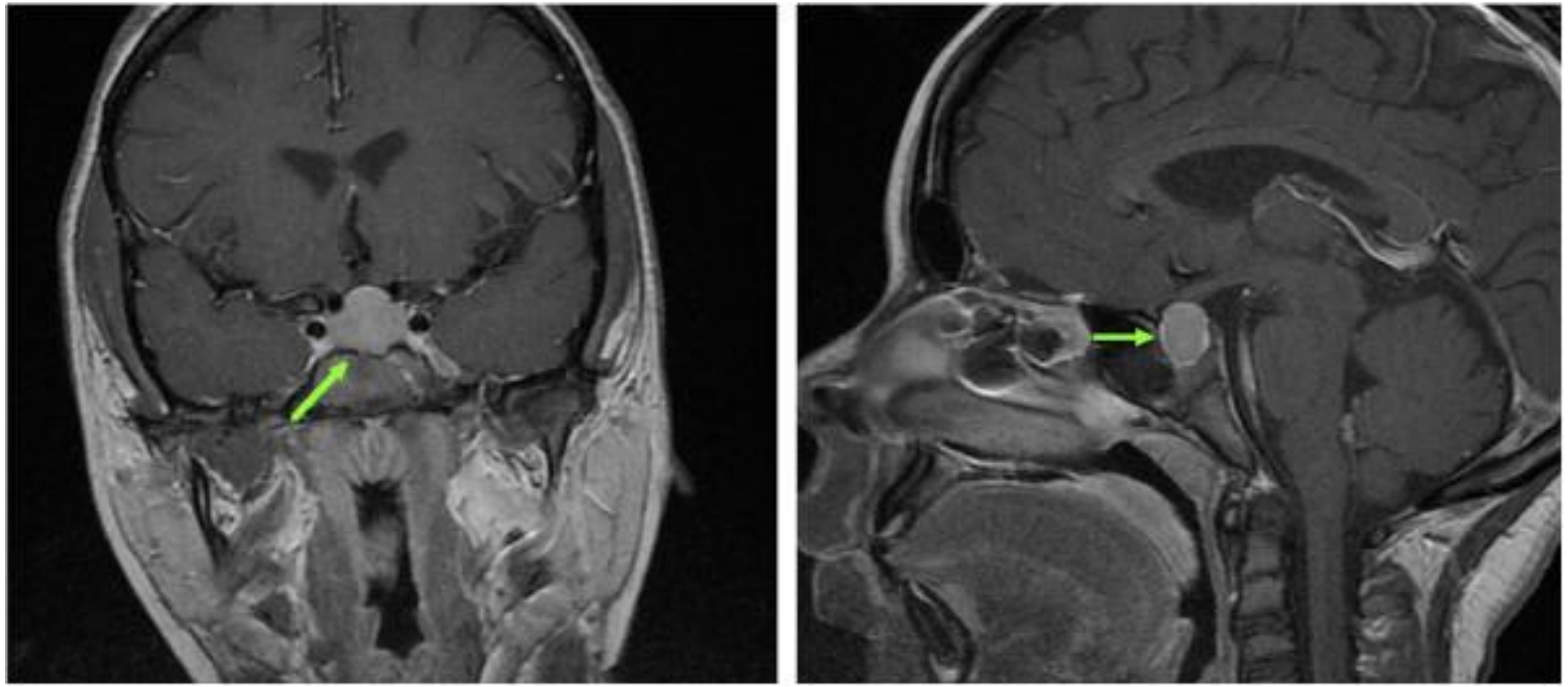
ADVANCES IN Cancer IMMUNOTHERAPY™

Plan

- Imaging?
  - CT/MRI
- Labs?
  - Inpatient: ACTH, TSH, FSH, LH, GH prolactin

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer



ADVANCES IN Cancer IMMUNOTHERAPY™

Treatment

- Corticosteroids 1 mg/kg/day
- IV dexamethasone 6mg Q6hr x 3 days
- Methylprednisolone 125mg daily
- Switch to oral prednisone after improvement 1-2 mg/kg qd
- Contact Hem/Onc

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Bibliography

- Villadolid J, Amin A. Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. *Translational Lung Cancer Research*. 2015;4(5):560-575. doi:10.3978/j.issn.2218-6751.2015.06.06.
- Abdel-Wahab N, Shah M, Suarez-Almazor M. Adverse Events Associated with Immune Checkpoint Blockade in Patients with Cancer: A Systematic Review of Case Reports. *PLOS*. 2016.07.29.
- Jeffrey S. Weber, Katharina C. Kähler, and Axel Hauschild. **Management of Immune-Related Adverse Events and Kinetics of Response With Ipilimumab.** *Journal of Clinical Oncology* 2012 30:21, 2691-2697
- Horvat T, Adel N, et al. Immune-Related Adverse Events, Need for systemic Immunosuppression, and Effects on Survival and Time to Treatment Failure in Patients with Melanoma Treated with Ipilimumab at MSKCC. *Journal of Clinical Oncology* 33, no. 28 (October 2015) 3193-3198.
- Images provided under license by adobe stock