Managing Toxicity in Patients Receiving Immune Therapy

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2017 Winter Lung Meeting

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Case Study 1

- A 65-year-old man current smoker with *KRAS* mutation-positive advanced adenocarcinoma of the lung, involving liver and bone.
- He receives treatment with combination pemetrexed and carboplatin with partial response after 4 cycles; he is then put on maintenance treatment with pemetrexed alone.
- However, after 6 cycles of maintenance treatment, his tumor starts to progress, with enlarging lung lesions and a new supraclavicular node.
- Prior tissue has been depleted.

Case 1 — Continued

- A supraclavicular node biopsy shows progressive adenocarcinoma, *KRAS* mutant-positive and 70% positive for PD-L1 expression on IHC.

- He is randomized on clinical trial to a PD1 MAb monotherapy and sustains a striking partial response, with resolution of supraclavicular node, liver metastases, and 80% reduction of lung lesions.

- However, after 6 months, updated CT scans show new ground-glass changes around the tumor in the left lung; the patient starts to complain of dyspnea on exertion and cough, with pulse ox desaturating to 86% on exertion.

Case 1 — Continued

- Within 4 weeks, after withholding treatment and institution of steroids, CT changes have resolved, and the patient's PS has improved to "0" from "2." He is no longer dyspneic. There is no symptomatic evidence of PD.

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Disclosures

Advisory Committee	Abbott Laboratories, AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, EMD Serono Inc, Genentech BioOncology, GlaxoSmithKline, ImClone Systems, a wholly owned subsidiary of Eli Lilly and Company, Lilly, Merck, Novartis Pharmaceuticals Corporation, Pfizer Inc
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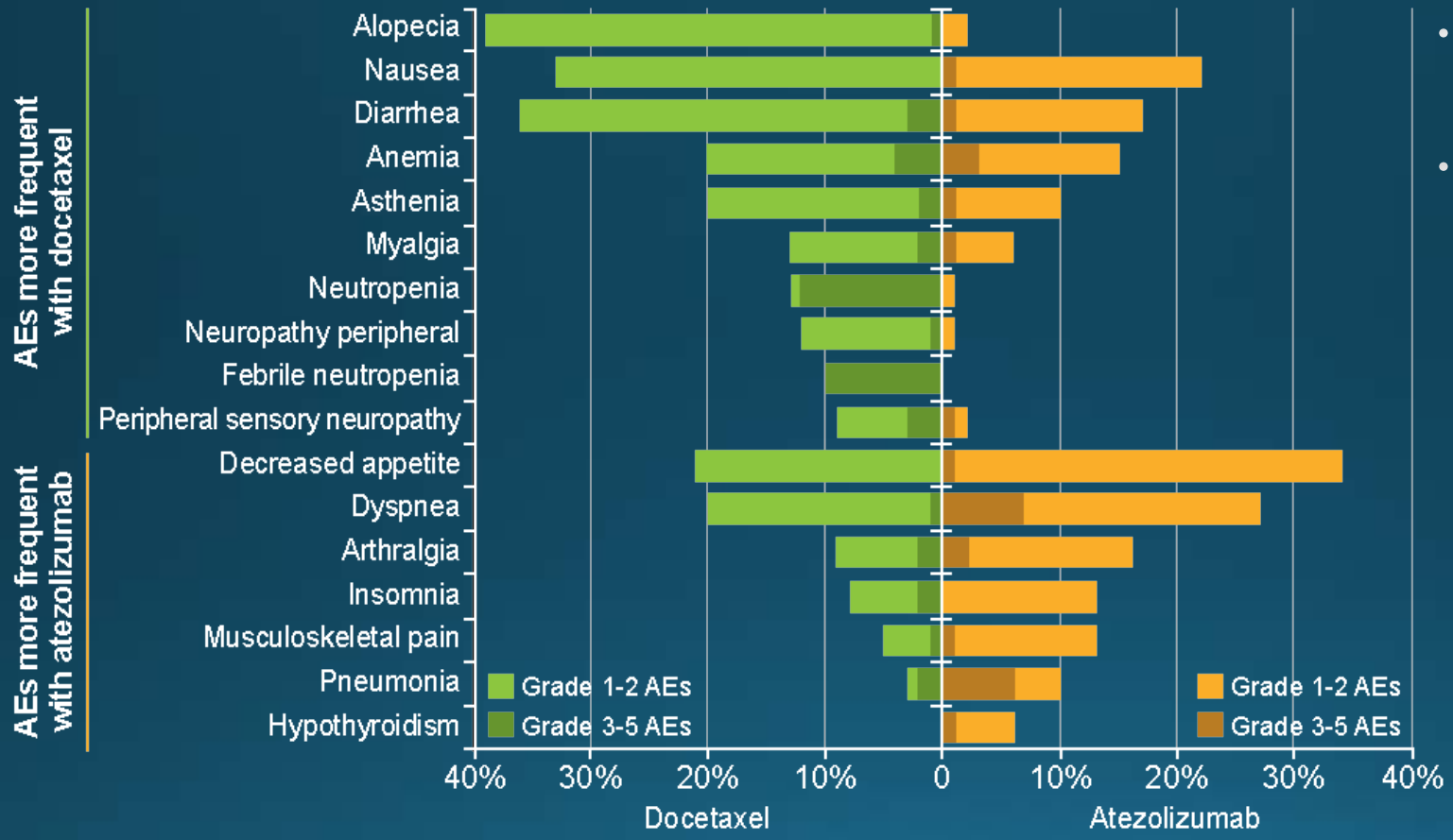
Data and Safety Monitoring Board	Abbott Laboratories, Amgen Inc, Lilly, Peregrine Pharmaceuticals Inc, Synta Pharmaceuticals Corp

Comparison of Checkpoint Inhibitors (eg, Atezolizumab) to Standard Chemotherapy in Advanced NSCLC



- AE profiles consistent with previous studies
- For atezolizumab, other immune-mediated AEs (any grade) included:
  - AST increase (4%)
  - ALT increase (4%)
  - Pneumonitis (2%)
  - Colitis (1%)
  - Hepatitis (1%)

Dry skin, stomatitis and nail disorder were additional AEs with ≥5% higher frequency in docetaxel.

Safety population includes patients who received any amount of either study treatment.

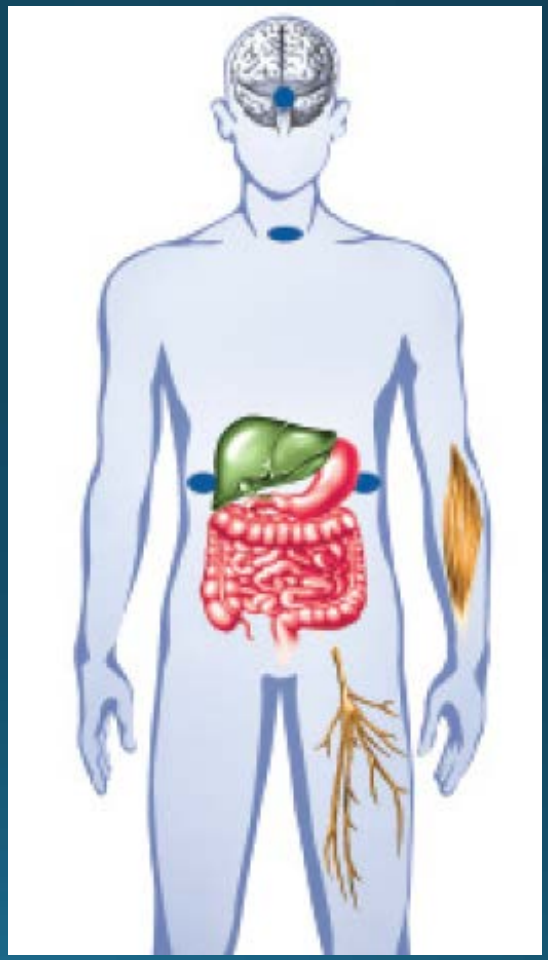
Data cutoff Jan 30, 2015

Spira AI et al. *Proc ASCO* 2015;Abstract 8010.

Immune-Related Adverse Events (IRAEs) Associated with Immune Checkpoint Inhibitors

Occasional (5-20%) irAEs
Grade 3/4 Uncommon

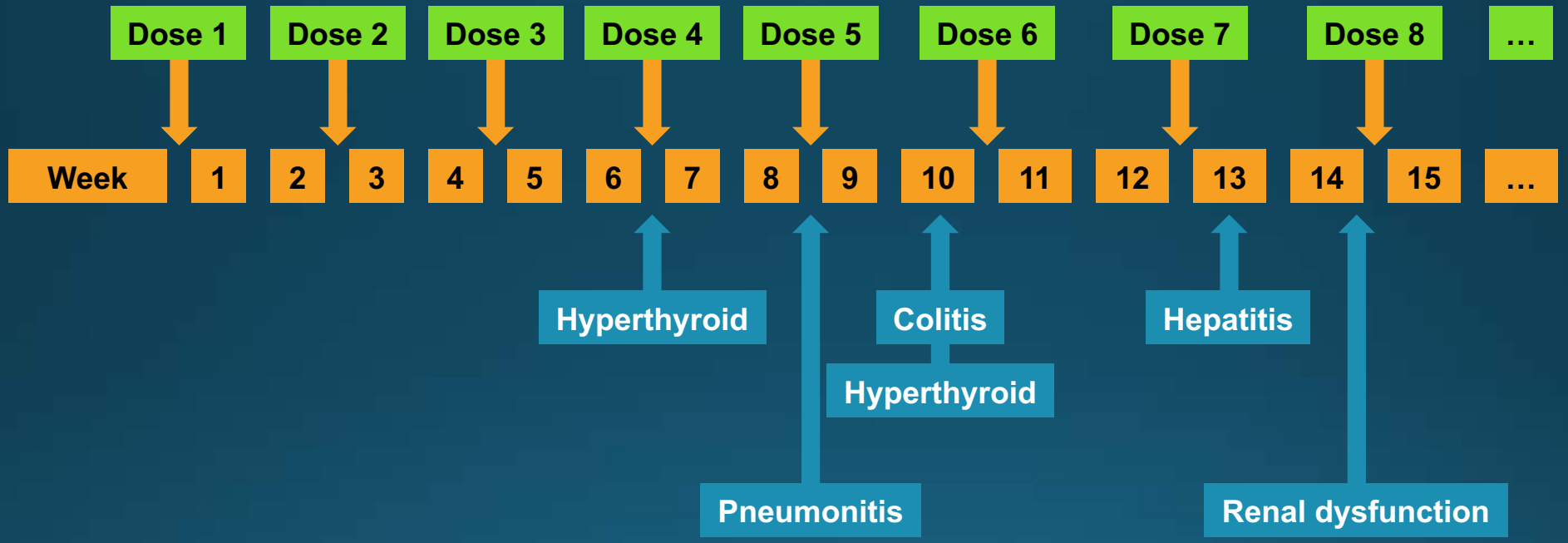
- Hypophysitis
- Thyroiditis
- Adrenal insufficiency
- Colitis
- Dermatitis
- Pneumonitis
- Hepatitis
- Pancreatitis
- Motor and sensory neuropathies
- Arthritis



Less common: hematologic; cardiovascular; ocular; renal

Courtesy of Julie R Brahmer, MD.

Median Time to Appearance of irAEs



Villadolid J, Amin A. *Transl Lung Cancer Res* 2015;4(5):560-75.

Managing immune therapy side effects

- Patient education
- Patients should be evaluated before each dose
  - Labs (TSH, LFTs), H&P
- General treatment approach
  - Mild irAE: Supportive care, increase monitoring
  - Moderate irAE: Hold treatment, consider steroids
  - Severe irAE: Start steroids; Permanently discontinue Tx

Weber JCO 2012
Gangadhar Nature Rev Clin Oncol 2014

Rash and pruritus

- Patients should immediately report symptoms
- Treatment
  - Mild: Supportive care, increase monitoring
    - Antihistamines, topical non-Rx strength steroids
  - Moderate: Hold treatment, consider steroids (oral)
  - Severe: Permanently discontinue, start steroids

Diarrhea and colitis

- Symptoms occur after an average of 6-7 weeks
  - Diarrhea, abdominal pain, mucus/blood in stool
  - Peritoneal signs, bowel perforation, ileus
- Patients should immediately report BM changes
- Rule out infectious/alternative causes

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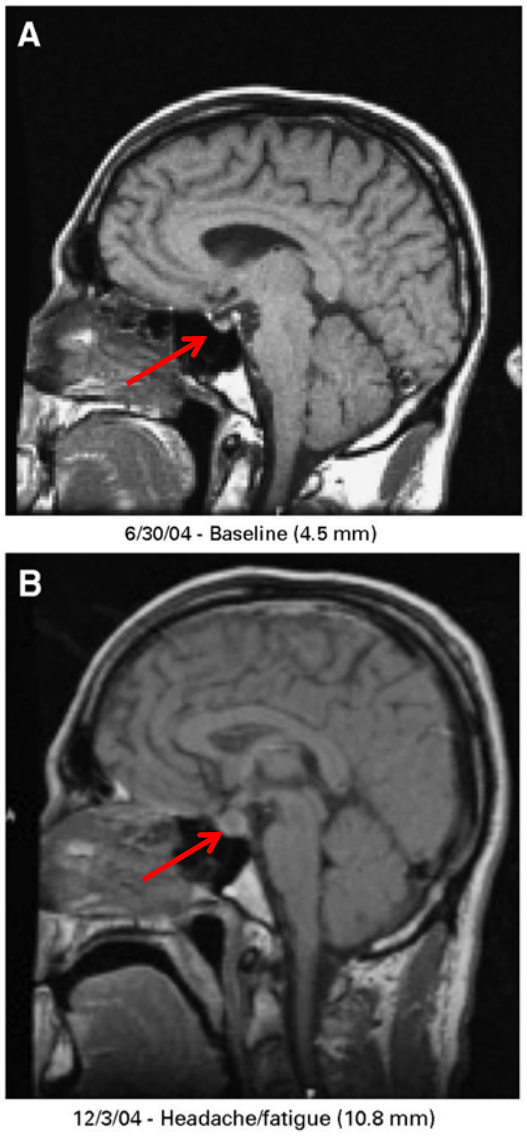
- Patients should immediately report BM changes
- Rule out infectious/alternative causes
- Treatment
  - Mild: Supportive care (paregoric; immodium), increase monitoring
  - Moderate: Hold treatment, consider steroids
  - Severe: Permanently discontinue, start steroids
    - Consider infliximab, GI consultation
    - Taper steroids slowly over at least several weeks and consider opportunistic infectious prophylaxis

Hypophysitis and endocrinopathies



- Can present with severe HA
- Differential includes CNS mets
- MRI with pituitary cuts
- Pituitary dysfunction may be reversible or permanent
  - Adrenal insufficiency
  - Hypothyroid

Weber JCO 2012

Adrenal insufficiency

- Non-specific complaints
  - Fatigue, fevers, nausea
- Consider endocrinopathies early, especially with fatigue
  - Risk of adrenal crisis
- Check TSH, cortisol, ACTH, consider others
  - Initiate replacement therapy, referrals
- Patient education
  - Stress dosing, communication to providers

Liver toxicity

- Monitor liver function tests before each dose
- Rule out viral hepatitis, disease progression
- Treatment of mild elevation
  - Increase frequency of monitoring
- AST/ALT > 2.5-5x ULN or Bilirubin > 1.5-3x ULN
  - Hold treatment, increase monitoring
- ASLT/ALT > 5x ULN or Bilirubin > 3x ULN
  - Permanently discontinue, start steroids

Pneumonitis

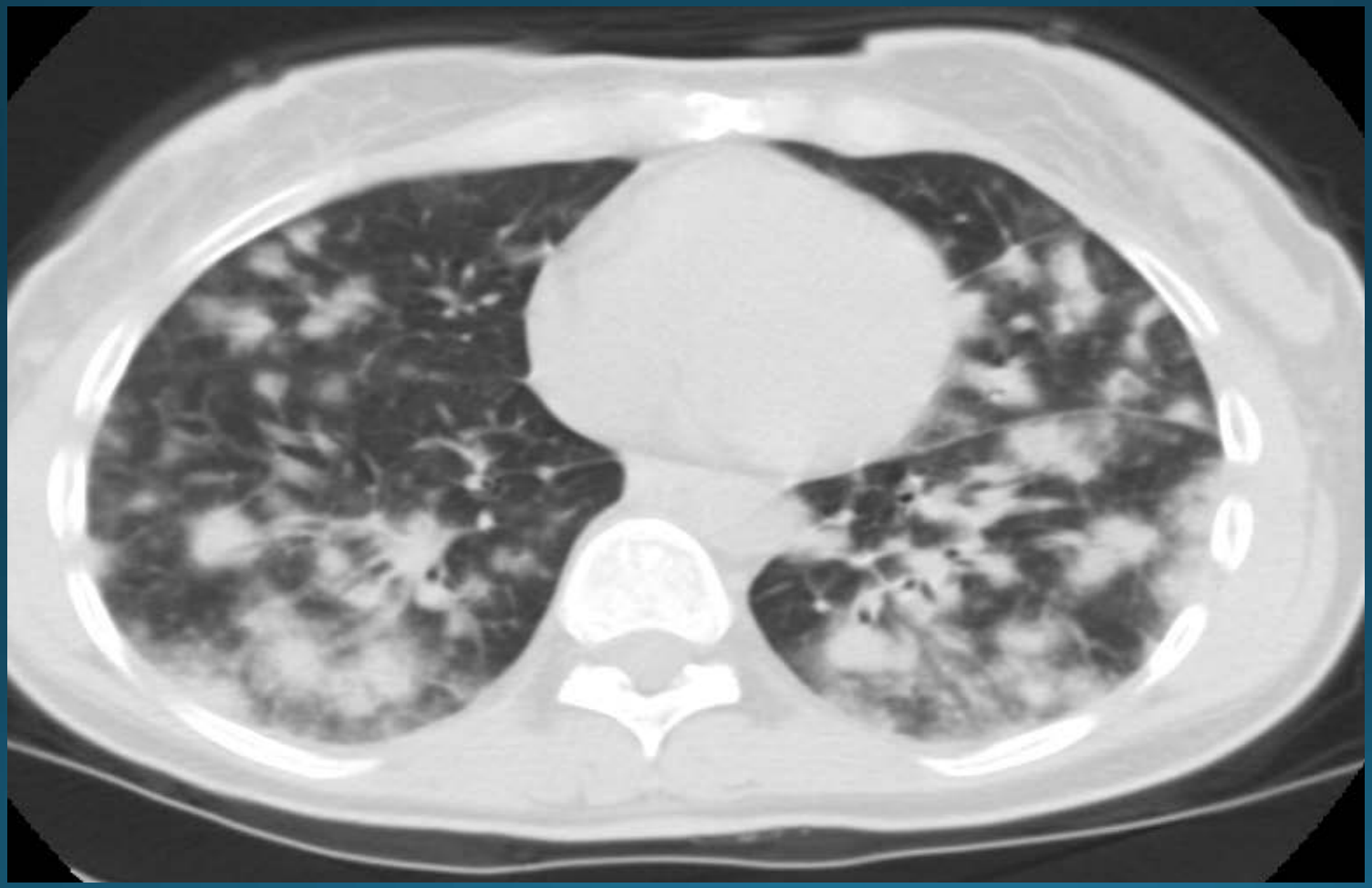
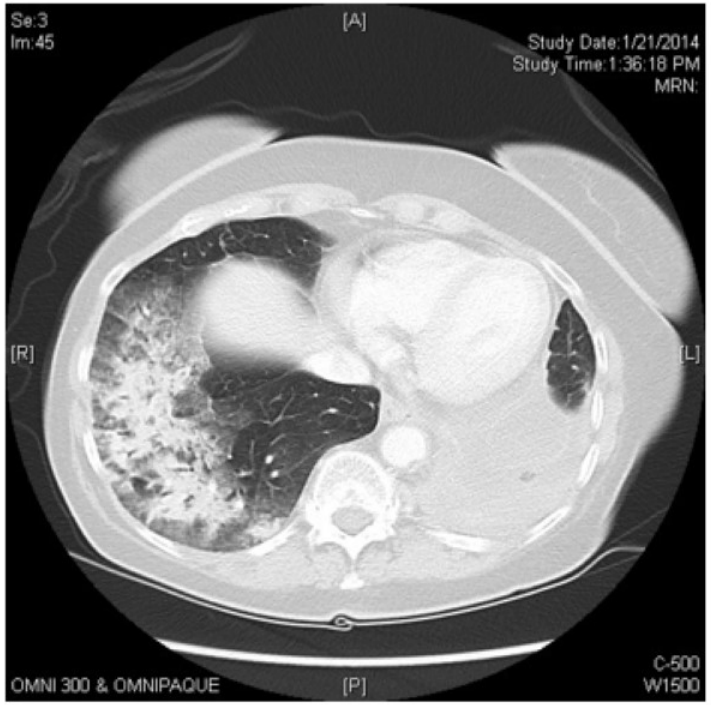


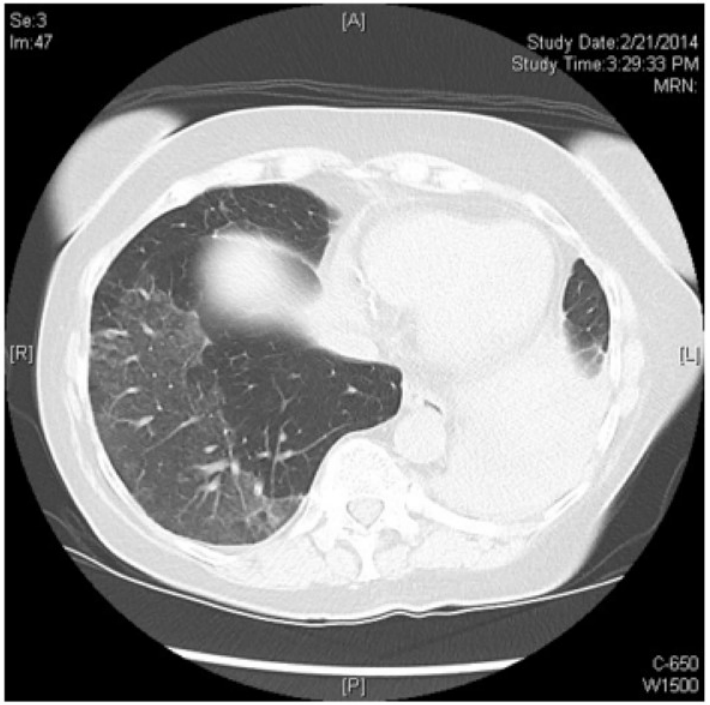
Image from Mike Postow

Pneumonitis

New SOB, cough, hypoxia (90% RA, 85% with exertion)

- CT: new RLL consolidation/GGO concerning for pneumonitis. Admitted -- methylprednisolone 60 mg twice daily
- Improved with steroids; tapered over 6 weeks





Images courtesy of Naiyer Rizvi, MD.

Pneumonitis Management

1. Radiographic changes: monitor

2. Mild to moderate symptoms: high dose prednisone, consider hospitalization/pulmonary eval

3. Severe symptoms or hypoxia: high dose steroid, hospitalize, pulmonary eval, bronchoscopy

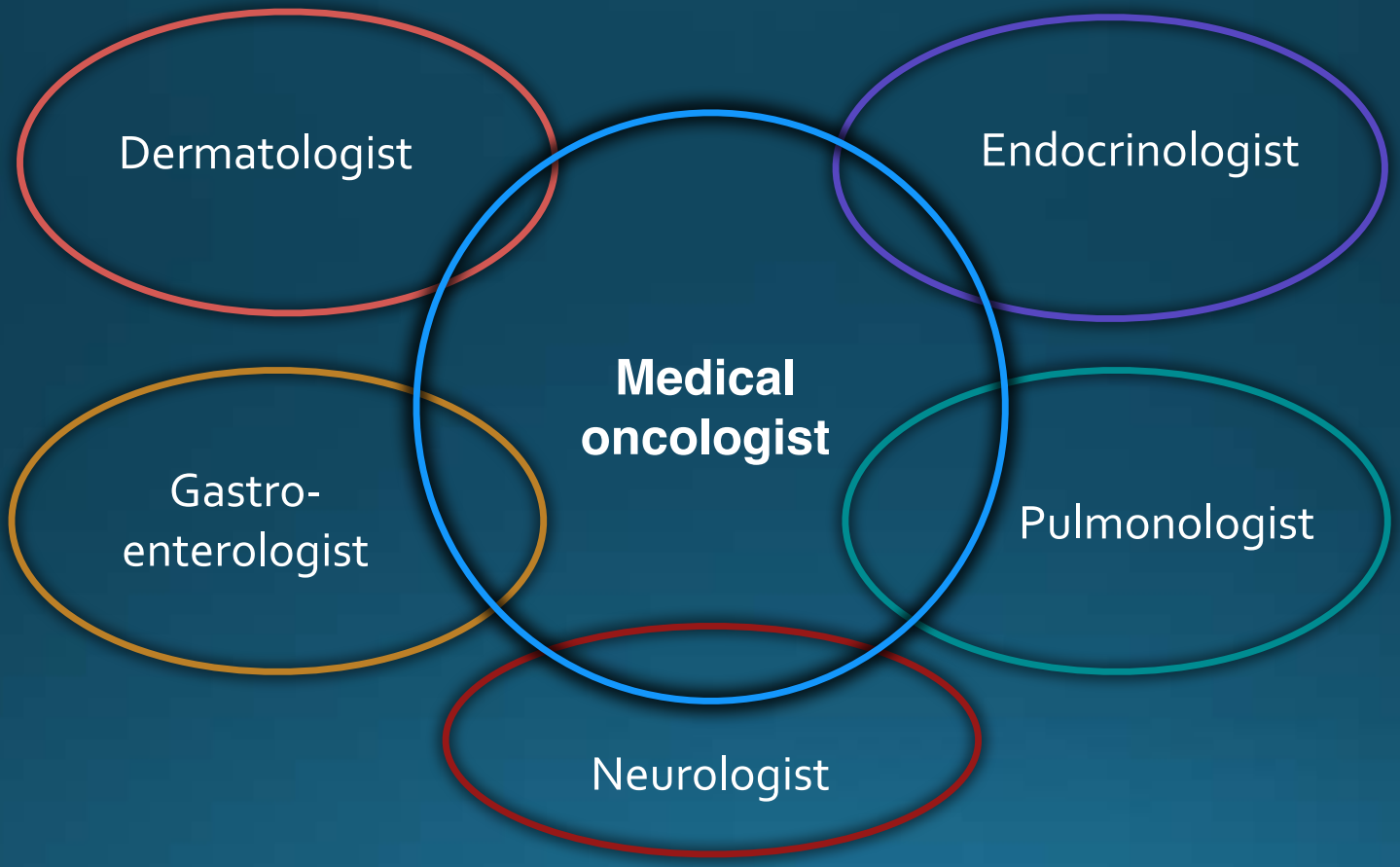
Taper steroids slowly over at least several weeks and consider opportunistic infectious prophylaxis

IrAEs- Honorable mention

- Episcleritis/ uveitis
- Pancreatitis
- Nephritis
- Neuropathies, Guillain-Barre, myasthenia gravis
- Lymphadenopathy (sarcoid)
- Thrombocytopenia, anemia
- Pneumonitis
- Myocarditis, pericarditis, vasculitis

Management of Immune Checkpoint Toxicity

Multidisciplinary approach



Conclusions

- Indications for immune therapy are increasing in advanced NSCLC
  - Broad 2nd line indication for Nivo, Pembro, Atezo
  - FDA approval of Pembro in 1st line in PDL1 (+) > 50%
- Familiarity with agents and their toxicities is critical
  - Rash > GI > Endocrine > Arthritic >Other
- Patient education and monitoring for delayed toxicity is essential
- Combination immune therapies may pose special challenges wrt heightened clinical toxicity