November 5-8, 2015
JW Marriott Desert Ridge
Phoenix, Arizona

Non–Small Cell Lung Cancer: Immunotherapy

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Non–Small Cell Lung Cancer: Immunotherapy

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Financial Disclosure

Ms. Walker has served on speakers bureaus for Celgene.

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Learning Objectives

1. Discuss basic science behind the human immune response
2. Describe how the checkpoint inhibitors alter the body's immune response to non–small cell lung cancer (NSCLC) cells
3. Describe potential toxicities associated with checkpoint inhibitors, including etiology of these toxicities and management and/or prophylaxis
4. Explain how checkpoint inhibitors differ from other available treatment options for metastatic NSCLC, including kinase inhibitors and cytotoxic chemotherapy
5. Identify FDA-approved checkpoint inhibitors and their indications, including relevant aspects of patient selection

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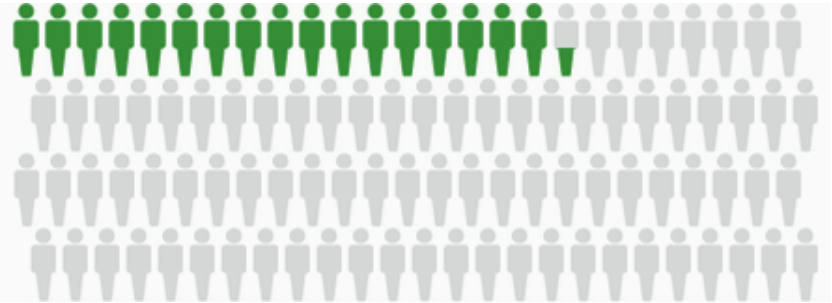
Overview of Lung Cancer

- More than 200,000 new cases anticipated in 2015[1]
- Leading cause of cancer death in both men and women[1]
- More than one-quarter of all cancer deaths[1]
- Higher mortality than breast, prostate, and colorectal cancers combined[1]
- Five-year survival < 20%[2]



[1]American Cancer Society. Cancer Facts & Figures 2015. Atlanta: American Cancer Society: 2015.

[2]SEER Cancer Statistics Factsheets: Lung and bronchus cancer. National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/statfacts/html/lungb.html.

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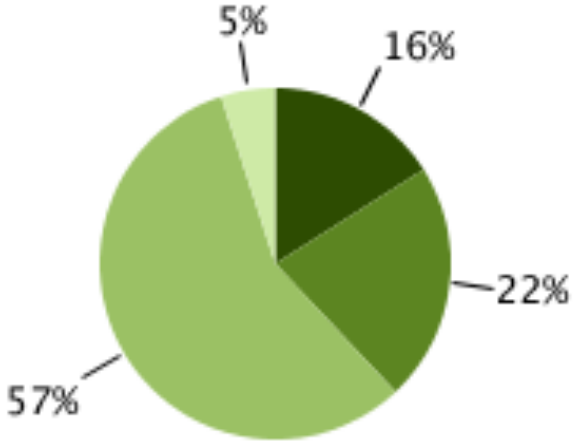
Percentage of Cases by Stage

- **Localized** (16%)
  Confined to primary site
- **Regional** (22%)
  Spread to regional lymph nodes
- **Distant** (57%)
  Cancer has metastasized
- **Unknown** (5%)
  Unstaged



SEER Cancer Statistics Factsheets: Lung and bronchus cancer. National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/statfacts/html/lungb.html.

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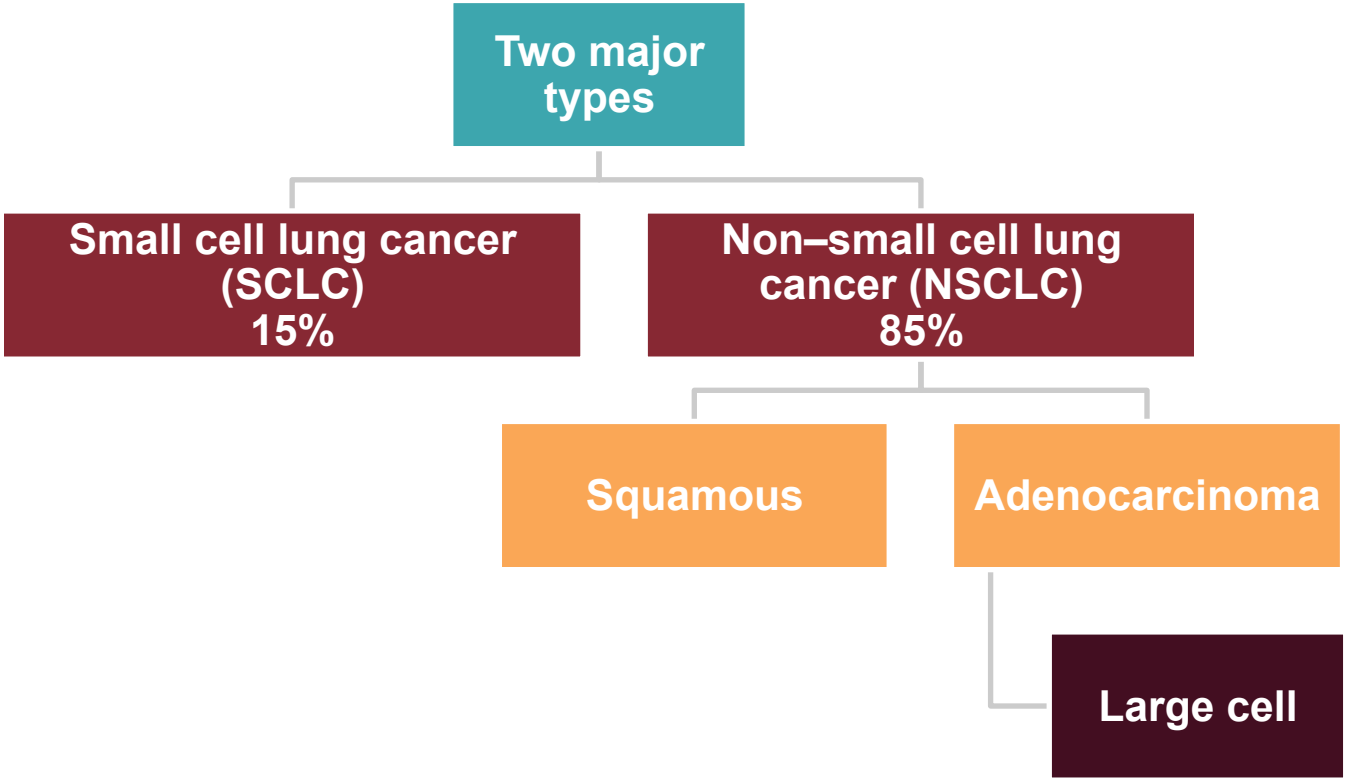
Overview of Lung Cancer



SEER Cancer Statistics Review 1975-2012.
http://seer.cancer.gov/csr/1975_2012/browse_csr.php?sectionSEL=15&pageSEL=sect_15_table.13.html
http://seer.cancer.gov/csr/1975_2012/browse_csr.php?sectionSEL=15&pageSEL=sect_15_table.14.html

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Lung Cancer Treatment: Changing Paradigm

- Chemotherapy
  - Impacts all rapidly dividing cells
- Targeted therapy
  - Focuses on individual molecular targets
- Immunotherapy
  - Works on specific receptors to modulate immune system function

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Immune System 101

- Cancers avoid detection by the immune system
- Immunotherapy enhances the ability to detect and destroy malignant cells
- Immunotherapy activates the immune system
- Provides stimulatory signals (step on the gas)
- Removes the inhibitory signals (lift off the brake)

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PD-1

Programmed cell death protein 1 (PD-1)

- Immunosuppressive molecule that is expressed on many T cells
- Activated when it binds to its ligand, PD-L1
- Activation leads to impaired T-cell function

Gatalica Z, et al. *Cancer Epidemiol Biomarkers Prev. 2014;23*:2965-2970.

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PD-L1

Programmed cell death ligand 1 (PD-L1)

- Ligand that binds to and activates PD-1
- PD-L1 is expressed on many cancer cells

Gatalica Z, et al. *Cancer Epidemiol Biomarkers Prev. 2014;23*:2965-2970.

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T-Cell Immunity

- T lymphocytes are produced in hematopoietic tissue and differentiate and mature in the thymus
- Important component of cell-mediated immunity
- Reliant on antigen-presenting cells to “prime” the antigen for recognition
- Several mechanisms of action
  - Direct cytotoxicity through cell lysis by conversion to cytotoxic T lymphocytes (CTLs)
  - Secretion of cytokines that are directly cytotoxic or through recruitment of other immune-system cells
  - Facilitation of B-cell activity

Paul WE. The immune system. In Paul WE (Ed.), *Fundamental immunology* (7th ed.). Philadelphia, PA: Lippincott, Williams, & Wilkins; 2013.

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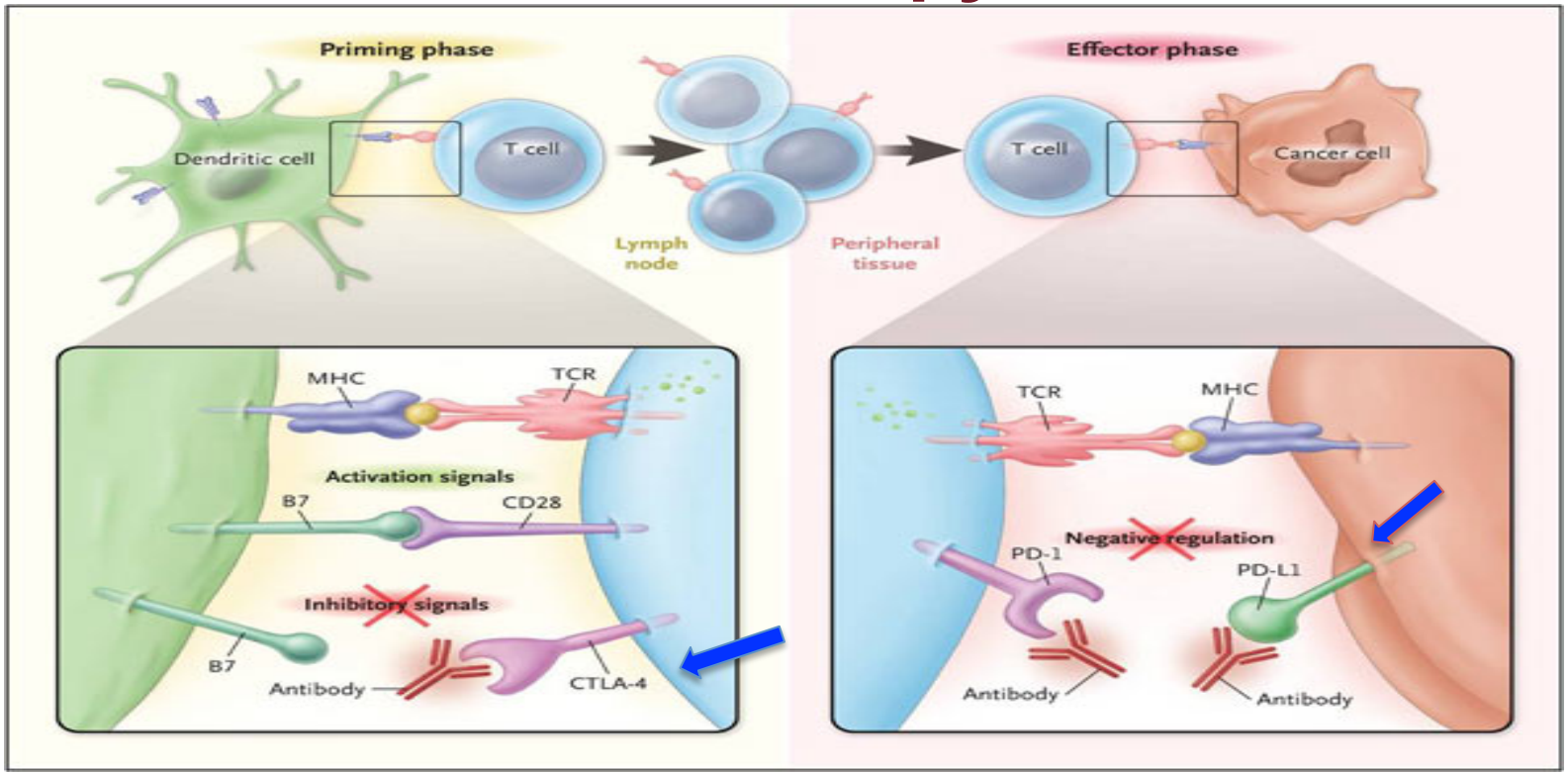
Blockade of PD-1 or CTLA-4 Signaling in Tumor Immunotherapy



From Ribas A. *N Engl J Med*. 2012;366:2517-2519. Copyright © 2012 Massachusetts Medical Society.
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Immunotherapy Agents in NSCLC: Pembrolizumab

- Humanized monoclonal IgG4 kappa antibody against PD-1[1]
- Inhibits the interaction between PD-1 and its ligands, PD-L1 and PD-L2[2]
- FDA approved for patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab.[2]

1. Garon EB, et al. *N Engl J Med*. 2015;372:2018-2028.
2. Merck 2014-2015. Keytruda (pembrolizumab) package insert.

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Pembrolizumab

- KEYNOTE-001 trial
- Phase IB study
- 495 patients with advanced NSCLC
- PD-L1 expression assessed using immunohistochemistry
- 81% squamous and 17% nonsquamous
- More than 80% had prior therapy
- Median overall survival: 12 months

Garon EB, et al. *N Engl J Med*. 2015;372:2018-2028.

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Pembrolizumab (cont)

- Dosing
  - Various dosing schedules have been studied
  - 2 mg/kg, 10 mg/kg, fixed 200-mg dose
  - 2 mg/kg is the package insert dose for melanoma[1]
  - 200-mg fixed dose being utilized in current studies[2,3]
- Administration
  - 30-min infusion every 3 weeks[1]
- Side effects
  - Most common side effects in KEYNOTE-001 were fatigue, pruritus, and decreased appetite[4]
  - Immune-related side effects

1. Merck 2014-2015. Keytruda (pembrolizumab) package insert.
2. Mok T, et al. *J Clin Oncol*. 2015;33 (suppl; abstract TPS8105).
3. Brahmer JR, et al. *J Clin Oncol.* 2015;33 (suppl; abstract TPS8103).
4. Garon EB, et al. *N Engl J Med*. 2015;372:2018-2028.

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Nivolumab

- Human IgG4 monoclonal antibody that binds to the PD-1 receptor
- Inhibits PD-1 receptor interaction with PD-L1 and PD-L2
- FDA approved for metastatic squamous NSCLC with progression on or after platinum-based chemotherapy
- FDA approved for treatment of patients with metastatic NSCLC with progression on or after platinum-based chemotherapy; patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab

Bristol-Myers Squibb 2015. Opdivo (nivolumab) package insert.

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Nivolumab (cont)

CHECKMATE-017

- A phase III study of nivolumab vs. docetaxel in previously treated advanced or metastatic squamous cell NSCLC
- 272 previously treated patients
- Overall survival 9.2 vs. 6 months favoring nivolumab
- Grade 3 or 4 adverse events only 7% of nivolumab patients vs. 55% in docetaxel arm

Brahmer J, et al. *N Engl J Med.* 2015;373:123-125.

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Nivolumab (cont)

CHECKMATE-057

- Phase III randomized trial of nivolumab vs. docetaxel in advanced nonsquamous NSCLC
- 582 patients who had received prior platin-based doublet and a tyrosine kinase inhibitor if eligible
- Overall survival 12.2 vs. 9.4 months favoring nivolumab
- Efficacy across subtypes

Paz-Ares L. *J Clin Oncol*. 2015;33 (suppl; abstract LBA109).

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Nivolumab (cont)

- Dosing and administration
  - 3 mg/kg over 60 minutes every 2 weeks[1]
- Side effects
  - Most common side effects in CHECKMATE-017 were fatigue, decreased appetite, and asthenia[2]
  - Immune-related side effects

1. Bristol-Myers Squibb 2015. Opdivo (nivolumab) package insert.
2. Brahmer J, et al. *N Engl J Med.* 2015;373:123-125.

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Role of PD-L1 Staining

- PD-L1+ status
  - May or may not be predictive and/or prognostic
  - No difference in response rates or survival with nivolumab in CHECKMATE-017[1]
  - Better response rates and survival with nivolumab in CHECKMATE-057 and with pembrolizumab in KEYNOTE-001[2,3]
- Multiple assays and tumor heterogeneity an issue
- Utility is still to be determined

1. Brahmer J, et al. *N Engl J Med.* 2015;373:123-125.
2. Paz-Ares L. *J Clin Oncol*. 2015;33 (suppl; abstract LBA109).
3. Garon EB, et al. *N Engl J Med*. 2015;372:2018-2028.

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Immunotherapy and Pseudoprogression

- Imaging studies may demonstrate[1]
  - Development of new lesions
  - Inflammatory infiltrates
  - Increase in size of baseline lesions
- Immune-related response criteria (irRC)[2]
  - Takes into account total disease burden, including new measurable lesions
  - Requires confirmatory imaging not less than 4 weeks later

1. Chiou VL, Burotto M. *J Clin Oncol.* 2015;Aug 10.
2. Wolchok JD, et al. *Clin Cancer Res*. 2009;15:7412-7420.

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Immunotherapy: Future Directions

- Adjuvant setting
- Oligometastatic disease
- Small cell lung cancer
- In combination with radiation
- In combination with other immunotherapy and targeted agents

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Immune-Mediated Side Effects

- Pneumonitis
- Colitis
- Nephritis/renal dysfunction
- Endocrine dysfunction
- Hepatitis
- Miscellaneous

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Pneumonitis

- Rate: 2%–6%[1,2]
- Onset: Median 2–5 months[1,2]
- Often reversible
- Management
  - Hold treatment and administer corticosteroids for moderate grade 2)[1,2]
  - 1–2 mg/kg/day prednisone equivalent followed by corticosteroid taper[1]
  - Permanently discontinue for severe (grade 3) or life-threatening (grade 4)[1,2]

1. Bristol-Myers Squibb 2015. Opdivo (nivolumab) package insert.
2. Merck 2014-2015. Keytruda (pembrolizumab) package insert.

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Colitis

- Rate: 1%–2%[1,2]
- Onset: Approximately 2–6 months[1,2]
- Management
  - Hold treatment for moderate (grade 2) or severe (grade 3)[1,2]
  - Permanently discontinue for grade 4[1,2]
  - Administer corticosteroids for grade 2 or greater
  - Grade 3 or 4: 1–2 mg/kg/day prednisone equivalent followed by corticosteroid taper[1]
  - Grade 2 if > 5 days' duration: 0.5–1 mg/kg/day prednisone equivalent followed by corticosteroid taper; can increase to 1–2 mg/kg/day if worsening or no improvement[1]

1. Bristol-Myers Squibb 2015. Opdivo (nivolumab) package insert.
2. Merck 2014-2015. Keytruda (pembrolizumab) package insert.

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Nephritis/Renal Dysfunction

- Incidence: < 1%[1,2]
- Onset: Variable; weeks to months[1,2]
- Management
  - Withhold for grade 2 or 3[1]
  - Permanently discontinue for grade 4[1,2]
  - For grade 2 or 3 serum creatinine elevation: Corticosteroids at a dose of 0.5–1 mg/kg/day prednisone equivalent followed by corticosteroid taper; if worsening or no improvement occurs, increase dose of corticosteroids to 1–2 mg/kg/day prednisone equivalent[1]
  - For grade 4: corticosteroids at a dose of 1–2 mg/kg/day prednisone equivalent followed by corticosteroid taper[1]

1. Bristol-Myers Squibb 2015. Opdivo (nivolumab) package insert.
2. Merck 2014-2015. Keytruda (pembrolizumab) package insert.

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Thyroid Dysfunction

- Incidence
  - Hypothyroidism: 4%–8%[1,2]
  - Hyperthyroidism: 1%–3%[1,2]
- Onset: 1.5–5 months[1,2]
- Management
  - Hypothyroidism
    - Administer hormone replacement therapy[1,2]
  - Hyperthyroidism
    - Initiate medical management[1]
    - Administer corticosteroids for grade 3 or greater hyperthyroidism[2]
    - Withhold treatment for grade 3 and permanently discontinue for grade 4 hyperthyroidism with pembrolizumab[2]
  - There are no recommended dose adjustments of nivolumab for hypothyroidism or hyperthyroidism[1]

1. Bristol-Myers Squibb 2015. Opdivo (nivolumab) package insert.
2. Merck 2014-2015. Keytruda (pembrolizumab) package insert.

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Hepatitis

- Incidence: 0–1%[1,2]
- Onset: Weeks to months[1,2]
- Management
  - Hold treatment and administer corticosteroids for moderate (grade 2)[1,2]
  - Discontinue for grade 3 or 4[1]
  - Corticosteroid dosing: 1–2 mg/kg/day prednisone equivalent[1]

1. Bristol-Myers Squibb 2015. Opdivo (nivolumab) package insert.
2. Merck 2014-2015. Keytruda (pembrolizumab) package insert.

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Case 1

- AB is a 55-year-old male with a history of stage IIIA squamous cell NSCLC
- Initially treated with concurrent chemoradiotherapy with weekly paclitaxel and carboplatin
- Three months after completion of chemoradiotherapy, he developed new pulmonary metastases

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Audience Response Question

What is the best treatment option for AB at this point?

A. Docetaxel **JL192**
B. Nivolumab **JL193**
C. Erlotinib **JL194**
D. Gemcitabine **JL195**

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Case 1 (cont)

- AB begins treatment with nivolumab 3 mg/kg every 2 weeks
- After the 4th cycle, he presents to the office with complaints of diarrhea 2 to 3 times a day for the past 3 days

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Audience Response Question

What would you recommend for AB?

A. Continue nivolumab and add an antidiarrheal agent such as loperamide **JL196**
B. Continue nivolumab and add prednisone 0.5–1 mg/kg **JL197**
C. Hold nivolumab and add prednisone 0.5–1 mg/kg **JL198**
D. Hold nivolumab and add prednisone 1–2 mg/kg **JL199**

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NCI Common Terminology Criteria for Adverse Events v.4.0: Diarrhea

- Grade 1: Increase of < 4 stools per day over baseline
- Grade 2: Increase of 4–6 stools per day over baseline
- Grade 3: Increase of > 7 stools per day over baseline; incontinence; hospitalization indicated
- Grade 4: Life-threatening consequences; urgent intervention indicated

NCI CTCAE v.4.03, 2010.

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Case 1 (cont)

- AB is treated with loperamide, and nivolumab is continued
- One week later, he presents to the office with diarrhea up to 10 times over the past 24 hours and is found to have renal failure
- He is urgently admitted to the hospital

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Audience Response Question

What recommendations would you have for the general medicine hospital team caring for AB?

A. Administer octreotide at a dose of 1 mg/kg **JL200**
B. Administer prednisone 0.5–1 mg/kg **JL201**
C. Administer diphenoxylate-atropine every 4 hours **JL202**
D. Administer prednisone 1–2 mg/kg **JL203**

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Case 2

- JM is a 70-year-old female with metastatic squamous NSCLC with bone and hepatic involvement
- She developed progressive disease after 3 cycles of paclitaxel and carboplatin
- Her oncology team begins second-line treatment with nivolumab

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Case 2 (cont)

- JM begins treatment with nivolumab and completes 6 cycles, with stable disease noted on CT scan
- Following the 8th cycle, she develops a progressive cough and shortness of breath when walking around her house
- She is evaluated by the APRN, who recommends obtaining a chest CT
- The chest CT scan shows patchy infiltrates consistent with an inflammatory process

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Audience Response Question

What should the advanced practitioner recommend for JM?

A. Continue nivolumab and begin prednisone 1–2 mg/kg **JL204**
B. Hold nivolumab and begin prednisone 1–2 mg/mg **JL205**
C. Permanently discontinue nivolumab and begin prednisone 1–2 mg/kg **JL206**
D. Continue nivolumab and begin levofloxacin for presumed pneumonia **JL207**

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NCI Common Terminology Criteria for Adverse Events v.4.0: Pneumonitis

- Grade 1: Asymptomatic; clinical or diagnostic observations only
- Grade 2: Symptomatic; medical; intervention indicated; instrumental activities of daily living (ADLs) limited
- Grade 3: Severe symptoms; self-care ADLs limited; oxygen indicated
- Grade 4: Life-threatening respiratory compromise; urgent intervention indicated

NCI CTCAE v.4.03, 2010.

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