Non–Small Cell Lung Cancer: Immunotherapy
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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
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\%\(^2\)

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

Overview of Lung Cancer

Two major types

Small cell lung cancer (SCLC)
15%

Non–small cell lung cancer (NSCLC)
85%

Squamous

Adenocarcinoma

Large cell

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
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)
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

**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

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

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

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 \textit{EGFR} or \textit{ALK} genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab.\(^2\)

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

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
  - 200-mg fixed dose being utilized in current studies

- **Administration**
  - 30-min infusion every 3 weeks

- **Side effects**
  - Most common side effects in KEYNOTE-001 were fatigue, pruritus, and decreased appetite
  - Immune-related side effects

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
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

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

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

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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

Immunotherapy and Pseudoprogression

- Imaging studies may demonstrate
  - Development of new lesions
  - Inflammatory infiltrates
  - Increase in size of baseline lesions

- Immune-related response criteria (irRC)
  - Takes into account total disease burden, including new measurable lesions
  - Requires confirmatory imaging not less than 4 weeks later

Immunotherapy: Future Directions

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

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

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

Colitis

- Rate: 1%–2%\textsuperscript{1,2}
- Onset: Approximately 2–6 months\textsuperscript{1,2}
- Management
  - Hold treatment for moderate (grade 2) or severe (grade 3)\textsuperscript{1,2}
  - Permanently discontinue for grade 4\textsuperscript{1,2}
  - Administer corticosteroids for grade 2 or greater
  - Grade 3 or 4: 1–2 mg/kg/day prednisone equivalent followed by corticosteroid taper\textsuperscript{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\textsuperscript{1}

\textsuperscript{1} Bristol-Myers Squibb 2015. Opdivo (nivolumab) package insert.
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\(^1\)

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\(^1\)

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\(^1\)

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
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
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
What would you recommend for AB?

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

References (cont)


