Immunotherapy in Lung Cancer

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Objectives

• Describe the recent advances in immunotherapy for patients with lung cancer

• Outline pertinent side effects, management of side effects, and appropriate patient counseling of immune therapy for lung cancer patients receiving treatment

Lung Cancer Epidemiology

• Lung cancer is the leading cause of cancer-related deaths in men and women in the United States
  – Estimated 224,390 cases in 2016
  • 158,080 deaths
• Smoking leads to almost 80% of all lung cancers
• Lung cancer subtypes
  – Non small cell lung cancer (85%)
    • Adenocarcinoma, squamous, large cell
  – Small cell (25%)
The Path to Immunotherapy

- Immune activity plays a crucial step in the destruction of malignant cells
- Historically, lung cancer has not been identified as cancer that is acknowledged by the immune system
- Immunotherapeutic treatment approaches to lung cancer have been disappointing over the past decade
- Advances in manipulation of the immune system instead of stimulation have proven to be more effective

Checkpoint Inhibitors: Mechanism of Action

PD-1 Inhibitors

- Programmed death 1 (PD-1) receptor is an inhibitory T-cell receptor
  - Reacts with PD-L1 (primary ligand) and PD-L2 (secondary ligand) within the tumor cell
  - Negatively regulates the effector phase of T cell response
- By blocking the interaction between PD-1 and PD-L1, cytotoxic results can be achieved without as many immune based adverse reactions
PD-L1 Expression = Biomarker or Not?

- Controversy around PD-L1 expression as a biomarker
  - Many different assays are used
  - Variation in tissue expression
  - What is the best cutoff of expression?
- Tumors with overexpression of PD-L1 have improved outcome
- Tumor with low expression of PD-L1 have also demonstrated long term benefits

There is no clear guideline on the use of PD-L1 expression as a biomarker of response.

Nivolumab Advanced Squamous NSCLCA

- Randomized, open-label, international, phase 3 study
  - Second line in advanced SCC
- Primary endpoint
  - Overall survival
- Randomized
  - Nivolumab 3 mg/kg Q2 weeks (n=135)
  - Docetaxel 75 mg/m² Q3 weeks (n=137)
- More grade 3 and 4 adverse effects with docetaxel (55% vs. 7%)
- PD-L1 status with neither prognostic nor predictive.

<table>
<thead>
<tr>
<th></th>
<th>Overall Survival (Months)</th>
<th>1 year Overall Survival</th>
<th>PFS (Months)</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>9.2</td>
<td>42%</td>
<td>5.5</td>
<td>28%</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>6</td>
<td>24%</td>
<td>2.8</td>
<td>9%</td>
</tr>
</tbody>
</table>

Nivolumab
Advanced Non-Squamous NSCLC
• Randomized, open-label, international, phase 3 study
  – Second line after a platinum-based doublet
• Primary endpoint
  – Overall survival
• Randomized
  – Nivolumab 3 mg/kg Q2 weeks (n=292)
  – Docetaxel 75 mg/m2 Q3 weeks (n=290)
• More grade 3 and 4 adverse effects with docetaxel (54% vs. 10%)
  – Appeared higher levels of PD-L1 correlated with ORR, PFS, and OS

<table>
<thead>
<tr>
<th></th>
<th>Overall survival (Months)</th>
<th>1-Year Survival (%)</th>
<th>18-month Survival (%)</th>
<th>Response rate (%)</th>
</tr>
</thead>
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<tr>
<td>Nivolumab</td>
<td>12.2</td>
<td>52%</td>
<td>39%</td>
<td>29%</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>9.4</td>
<td>38%</td>
<td>23%</td>
<td>19%</td>
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</table>


Pembrolizumab
Advanced Squamous and Non-Squamous NSCLC
• Multi-center, open label multi-cohort (n=280)
  – Second line after progression with a platinum-containing regimen
  – Non-squamous or squamous histology with >50% PD-L1 expression
  – 61 patients
• Primary endpoint
  – Overall response rate
• Randomized
  – Pembrolizumab 2 mg/kg or 10 mg/kg Q2 weeks (n=27) or 3 weeks (n=34)
• Results
  – 41% response rate
  – CR: 0%, PR: 41%


Checkpoint Inhibitors in Advanced NSCLC

Nivolumab
• March 2015 approval was granted for second line treatment of squamous cell
• October 2015 approval was extended to include non-squamous cell
• Both trials looked at PD-L1 expression, but did not require it for use.
  – Approval granted without need for PD-L1 biomarker
• Approved dose 3 mg/kg IV over 1 hr Q2 weeks
  – A flat 240 mg IV Q2 weeks has been recently been approved
  – Short stability 4 hrs
  – Infuse with 0.2 micron filter

Pembrolizumab
• In October 2015, the FDA granted accelerated approval for second line treatment with pembrolizumab in patients with metastatic NSCLC with PD-L1 expression
• Approved dose 2 mg/kg IV over 30 min Q3 weeks
  – Infuse with 0.2 micron filter
**PD-1 Clinical Trial Pearls**

- Around 20% of patients respond to anti-PD-1 therapy
  - Biomarkers remain unclear
- Agents are well tolerated
- Tumor flare phenomena
- A link has been observed between response and current/former smokers
- EGFR mutants do not appear to respond to anti PD-1 therapy

**Pembrolizumab and Nivolumab: Adverse Effects**

- Common
  - Fatigue, rash, pruritis, nausea, diarrhea, decreased appetite, arthralgias
- Immune related adverse effects
  - Pneumonitis (2.9%)
  - Colitis (1%)
  - Hepatitis (1.9%)
  - Hypophysitis (0.5%)
  - Nephritis (0.7%)
  - Hyperthyroidism & hypothyroidism (1.2%)
- Lab Abnormalities
  - Hyperglycemia
  - Hypoponemia
  - Hyponatremia
  - Hypertlyveridemia
  - ↑ AST
- Hypocalcemia
- Anemia

**Immune Related Adverse Effects (irAE’s)**

- **Skin**: Dermatitis, Vitiligo, Toxic epidermal necrolysis, SJS
- **Eye**: Uveitis
- **Pulmonary**: Pneumonitis, ILD
- **Gastrointestinal**: Colitis
- **Neuropathy**: Neuropathy, Gullian-Barré, Myasthenia Gravis
- **Liver**: Hepatitis
- **Renal**: Nephritis
- **Endocrine**: Hyperthyroidism, Hypothyroidism, Adrenal Insufficiency

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*References*


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*Keytruda (pembrolizumab) [Package Insert]. Whitehouse Station, NJ; Merck; Revised September.*
*Opdivo (nivolumab) [Package Insert]. Princeton, NJ; BMS. Revised September.*
**Immune-Related Adverse Effects NSCLC**

- Clinical trials reported up to 60% incidence in irAEs with ipilimumab in melanoma
- irAEs in PD-1 inhibitors are < 5%
- Pneumonitis of greater concern for NSCLC

### Immune-Related Adverse Events from Immune Checkpoint Inhibitors in Patients with NSCLC

<table>
<thead>
<tr>
<th>Immune checkpoint inhibitor</th>
<th>N</th>
<th>Incidence of Grade 3/4 irAEs</th>
<th>Most common Grade 3/4 irAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab (Yokochi 2015)</td>
<td>70</td>
<td>10.3%</td>
<td>Diarrhea (n=8), rash (n=4), hypersensitivity reaction (n=3), pulmonary embolism (n=2), colitis (n=1), increased LFTs (n=2)</td>
</tr>
<tr>
<td>Nivolumab (Brahmer 2015)</td>
<td>116</td>
<td>2%</td>
<td>Tubulointerstitial nephritis (n=1), colitis (n=1), and pneumonitis (n=1)</td>
</tr>
<tr>
<td>Pembrolizumab (Garon 2015)</td>
<td>495</td>
<td>NR</td>
<td>Pneumonitis (n=9 [1.8%]), fatigue (0.8%), elevation in AST (0.6%), and diarrhea (0.6%)</td>
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### irAE Timing

**Know when to expect your irAE’s**

![Graph showing toxicity of irAEs over time](image)

**Fig. 2.** Kinetics of appearance of immune-related adverse events.


### Monitoring and Labs

- Drug interactions...none known!
- Labs
  - Baseline and routine: CBC and CMP
  - TFT’s-baseline, every 6-12 weeks, and for 6 months after therapy
- Beware of non-specific symptoms and fatigue
  - Obtain ACTH and cortisol with fatigue and non-specific symptoms

General Management of Immune-Related Adverse Effects

Grade

1  Supportive Care  (Lomotil, loperamide, topical corticosteroids)

2  Withhold drug, consider re-initiation once symptoms resolved, if symptoms do not resolve consider corticosteroids

3-4  Discontinue drug, High-dose corticosteroids (1-2 mg/kg/day of prednisone or equivalent). Once resolved to grade 1 taper slowly over a month  (Infliximab, mycophenolate, or cyclosporine)  Endocrinopathies may require lifetime hormonal replacement

Patient Counseling

- Patient Counseling
  - New or worsening cough, chest pain or shortness of breath
  - Severe diarrhea or abdominal pain
  - Yellowing of skin
  - Muscle pain
  - Decreased appetite
  - Unusual headaches, extreme weakness, dizziness, fainting, or vision changes
  - Routine blood work including thyroid function tests
  - Contraception

Immunotherapy in Lung Cancer  
Future Directions

- Biomarkers
  - Continued work in progress

- First line therapy
  - Single-agent nivolumab recently failed to meet primary endpoint of PFS for first line therapy

- Adjuvant setting

- Sequencing

- Combination with chemotherapy or other immunotherapy
  - Ipilimumab/carboplatin/paclitaxel untreated squamous NSCLCA underway
  - Ipilimumab/nivolumab combination
  - CTLA-4/PD-L1 inhibitor combination
### Conclusions

- The arrival of immunotherapy into the treatment of lung cancer represents a significant advancement.

- A survival advantage has been observed in a subset of NSCLC patients treated with these therapies.

- Nivolumab and pembrolizumab are well tolerated with few autoimmune adverse effects which, with appropriate patient education and early treatment, can be effectively managed.