Lung cancer
Immunotherapy
2018 update

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Financial Disclosures: None
Objectives

• How does immunotherapy work.
• Updates on trials for advanced non-small cell and small cell lung cancers.
• Predictors for response.
• Promising results for earlier stages.
• Managing side effects.
Case study

• 68 yo with HTN and COPD smoked 2 ppd for 35 years.
• Presented with dyspnea and cough/ mild hemoptysis. CXR showed left hilar mass.
• Bronchoscopy and mediastinoscopy confirmed lung squamous cell carcinoma.
• PET scan showed large left upper lobe lung mass with invasion of upper lobe bronchus, mediastinum. Hypermetabolic mediastinal, bilateral hilar, bilateral internal mammary chains. Biopsy from the latter showed squamous cell carcinoma. PD-L1 100%. Stage IV.

• He underwent radiation to LUL (part of clinical trial) and started on pembrolizumab.
Case study
Immunotherapy: A breakthrough in cancer therapy

“I was like, ‘Oh my God, it happened,’” Allison says to TIME. “I’m just in shock, I guess.”
The journey
Taking the brakes off

**CHECKPOINT INHIBITOR DRUGS**

‘Checkpoint’ proteins block T-cell activity. Inhibitor drugs can release the brakes on T cells at different stages.

The CTLA-4 checkpoint protein prevents dendritic cells from priming T cells to recognize tumours. Inhibitor drugs block the checkpoint.

The PD-1 checkpoint protein prevents T cells from attacking cancer cells. The inhibitor drug allows T cells to act.
Lung Cancer by Histology

- Non-small cell lung cancer (NSCLC) 85%
  - Adenocarcinoma (40%)
  - Squamous (30%)
  - Other (15%)

- Small cell lung cancer (SCLC) 15%
Lung cancer treatment: Overview

Stage I
- Surgery +/- chemo for high risk patients
- Localized radiation if can’t have surgery

Stage II
- Surgery then platinum doublet chemo

Stage III
- IIIA Chemo-radiation --> surgery
- IIIB and IIIC: Definitive chemo-radiation --> Immunotherapy (IO)

Stage IV
- Depending on biomarkers
  - Biologics, Immunotherapy, Platinum doublet, or combination

SCLC

Limited Stage
- Chemoradiation: (Platinum+etoposide)

Extensive disease
- Chemo alone: (Platinum+etoposide)
Metastatic NSCLC treatment

Stage IV (metastatic, recurrent)

Non-squamous

Biochemical targets (ex. EGFR, ALK etc.)

<50% PD-L1

Oral TKI

Another TKI or chemo

>50% PD-L1

Chemo + Pembrolizumab or chemo

IO (Nivo, Pembro, Atezo)

Squamous

>50% PD-L1

Pembrolizumab

Chemo

<50% PD-L1

Pembrolizumab

Chemo

IO (Pembro, Nivo, Atezo)
### Nonsquamous cell

**Targetable driver mutation present?**

<table>
<thead>
<tr>
<th>EGFRm</th>
<th>ALK rearrangement</th>
<th>ROS1 rearrangement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment: 1st line</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib/</td>
<td>Osimertinib</td>
<td></td>
</tr>
<tr>
<td>gefitinib/</td>
<td>or</td>
<td></td>
</tr>
<tr>
<td>afatinib</td>
<td>or</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2nd line</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osimertinib (if T790M resistance develops)</td>
<td>Platinum doublet with pemetrexed ± bevacizumab</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3rd-generation ALK inhibitor clinical trial; or platinum doublet with pemetrexed ± bevacizumab</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alectinib; orbrigatinib; or ceritinib</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2nd-generation ROS1 inhibitor clinical trial; or platinum doublet with pemetrexed ± bevacizumab</td>
<td></td>
</tr>
<tr>
<td><strong>3rd line</strong></td>
<td></td>
<td></td>
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<tr>
<td>Platinum doublet with pemetrexed ± bevacizumab</td>
<td>Docetaxel ± ramucirumab; or gemcitabine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Platinum doublet with pemetrexed ± bevacizumab (if not received as 2nd line); or docetaxel ± ramucirumab; or gemcitabine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3rd-generation ALK inhibitor clinical trial; or platinum doublet with pemetrexed ± bevacizumab</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Platinum doublet with pemetrexed ± bevacizumab (if not received as 2nd line); or docetaxel ± ramucirumab; or gemcitabine</td>
<td></td>
</tr>
</tbody>
</table>

**Measure PD-L1 expression level**

<table>
<thead>
<tr>
<th>PD-L1 ≥ 50%</th>
<th>PD-L1 &lt;50%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PD-L1 ≥ 50%</strong></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Platinum doublet with pemetrexed or bevacizumab</td>
</tr>
<tr>
<td></td>
<td>Carboplatin/pemetrexed/pembrolizumab</td>
</tr>
<tr>
<td><strong>PD-L1 &lt;50%</strong></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Platinum doublet</td>
</tr>
<tr>
<td></td>
<td>Immunotherapy (nivolumab, pembrolizumab, or atezolizumab)</td>
</tr>
<tr>
<td></td>
<td>Docetaxel ± ramucirumab; or gemcitabine</td>
</tr>
<tr>
<td></td>
<td>Platinum doublet</td>
</tr>
<tr>
<td></td>
<td>Immunotherapy (nivolumab, pembrolizumab, or atezolizumab)</td>
</tr>
</tbody>
</table>

Consider clinical trial options from time of diagnosis and throughout treatment.

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**Abbreviations:** PD-L1, programmed cell death 1 ligand 1; EGFRm, EGFR mutated.

*Carboplatin/pemetrexed/pembrolizumab is also FDA approved in this setting.

*If crizotinib treatment was started prior to FDA approval of alectinib for 1st-line treatment.

*Pembrolizumab use requires PD-L1 >1%.
Current immunotherapy FDA approvals

Non-small cell lung cancer

• 1st line Pembrolizumab PD-L1 > 50%
• 1st line Pembrolizumab + pemetrexed/carboplatin in non-squamous NSCLC

• 2nd line Pembrolizumab PD-L1 > 1%
• 2nd line Nivolumab
• 2nd line Atezolizumab

• Stage III: Maintenance Durvalumab after chemo-radiation

Small cell lung cancer

• 3rd line Nivolumab
Major Clinical Trials presented in 2018

• **NSCLC**
  - 1st line chemo + immunotherapy combination in squamous? *Keynote 407*
  - 1st line immunotherapy alone for PD-L1 < 50%? *Keynote 042*
  - Other Biomarkers beside PD-L1 (i.e. TMB)? *CheckMate 227*
  - Immunotherapy + VEGF based combinations? *IMPower 150*
  - Update on previously reported trials. *POPLAR, PACIFIC*

• **SCLC**
  - 1st line immunotherapy + chemo in SCLC. *IMpower 133*
Keynote 407

- 559 pts
- Chemo: carboplatin and paclitaxel or nab-paclitaxel [Abraxane]
- Stratified by PD-L1 status, Geographic location, and Type of chemo
- Crossover allowed (42.5%)
- ORR 59.4% vs 38%,
- Median OS 15.9 vs 11.3 mo
### Subgroup Analysis of Progression-free Survival

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Events/No. of Patients</th>
<th>Hazard Ratio for Disease Progression or Death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>349/559</td>
<td>0.56 (0.45–0.70)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>162/254</td>
<td>0.50 (0.37–0.69)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>187/305</td>
<td>0.63 (0.47–0.84)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>284/455</td>
<td>0.58 (0.46–0.73)</td>
</tr>
<tr>
<td>Female</td>
<td>65/104</td>
<td>0.49 (0.30–0.81)</td>
</tr>
<tr>
<td>ECOG performance-status score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>96/163</td>
<td>0.45 (0.29–0.68)</td>
</tr>
<tr>
<td>1</td>
<td>253/396</td>
<td>0.61 (0.48–0.78)</td>
</tr>
<tr>
<td>Region of enrollment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>East Asia</td>
<td>61/106</td>
<td>0.49 (0.30–0.82)</td>
</tr>
<tr>
<td>Rest of the world</td>
<td>288/453</td>
<td>0.58 (0.46–0.73)</td>
</tr>
<tr>
<td>PD-L1 tumor proportion score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1%</td>
<td>122/194</td>
<td>0.68 (0.47–0.98)</td>
</tr>
<tr>
<td>≥1%</td>
<td>221/353</td>
<td>0.49 (0.38–0.65)</td>
</tr>
<tr>
<td>1–49%</td>
<td>127/207</td>
<td>0.56 (0.39–0.80)</td>
</tr>
<tr>
<td>≥50%</td>
<td>94/146</td>
<td>0.37 (0.24–0.58)</td>
</tr>
<tr>
<td>Taxane-based drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>231/336</td>
<td>0.52 (0.40–0.68)</td>
</tr>
<tr>
<td>Nab-paclitaxel</td>
<td>118/223</td>
<td>0.65 (0.45–0.94)</td>
</tr>
</tbody>
</table>
Keynote 042

1st line/ Non-squamous or squamous NSCLC

Pembrolizumab

Platinum doublet

• 1,274 pts
• PD-L1 >1%
• Chemo (Taxol/ carbo) or (pemetrexed plus carbo) depending on histology

<table>
<thead>
<tr>
<th>PD-L1 TPS</th>
<th>≤50%</th>
<th>≤20%</th>
<th>≤1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrol N = 299</td>
<td>0.69 (0.56-0.85)</td>
<td>0.77 (0.64-0.92)</td>
<td>0.81 (0.71-0.93)</td>
</tr>
<tr>
<td>Chemo N = 309</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrol N = 413</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemo N = 406</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrol N = 637</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemo N = 637</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR (95% CI) | 0.69 (0.56-0.85) | 0.77 (0.64-0.92) | 0.81 (0.71-0.93) |

P | .0003 | .0020 | .0018 |

Median (95% CI), mo | 20.0 | 12.2 | 17.7 | 13.0 | 16.7 | 12.1 |

| Pembrol N = 299 | (15.4-24.9) | (11.6-15.3) | (13.9-14.2) |
| Chemo N = 309 | (10.4-14.2) | (11.6-15.3) | (13.9-14.2) |
| Pembrol N = 413 | (15.3-22.1) | (15.3-19.7) |
| Chemo N = 406 | (11.6-15.3) | (13.9-19.7) |
| Pembrol N = 637 | | | |
| Chemo N = 637 | | | |

ASCO 2018 abstract LBA4
CheckMate 227

1st line/ squamous and non-squamous NSCLC

Nivolumab plus Ipilimumab

Platinum based Chemo doublet

- Exploratory analysis Pts with PD-L1 <1 % and high tumor mutational burden TMB (>10 mutations per megabase)

Hazard ratio for disease progression or death, 0.58 (97.5% CI, 0.41–0.81)
P<0.001

Hellmann NEJM May 2018
IMpower 150

1st line Non-squamous NSCLC

- Atezolizumab + carbo + Taxol (ACP)
- Bevacizumab + carbo + Taxol (BCP)
- Atezo + BCP (ABCP)

- 356 pts ABCP and 336 BCP

Socinski NEJM June 2018
POPLAR

2nd line squamous and non-squamous NSCLC

• Atezolizumab
• Docetaxel

- 287 pts
- Median duration of response 22.3 months vs 7.2 months.
- Long term survivors

Mazieres ELCC 2018
Stage III NSCLC After finishing definitive chemo-radiation

- 713 pts (473 durvalumab and 236 placebo).
- Median follow-up 25.2 months
- Previously reported PFS 17.2 vs 5.6 months

**PACIFIC**

Durvalumab for 12 months

Placebo

- 12-Mo Overall Survival Rate (95% CI) %
  - Durvalumab: 81.1 (79.4–86.2)
  - Placebo: 75.3 (69.2–80.4)

- 24-Mo Overall Survival Rate (95% CI) %
  - Durvalumab: 66.3 (61.7–70.4)
  - Placebo: 55.6 (48.9–61.8)

Stratified hazard ratio for death, 0.68 (99.73% CI, 0.47–0.997)
Two-sided P=0.0025

Antonia S et al. NEJM Sep 2018.
SCLC
CheckMate 032

- **SCLC**
- Progressed after 2 or more chemo

**Nivolumab**

- 109 pts
- Progressed on platinum based chemo and one more chemo
- Regardless of PD-L1

**Graph**
- Median OS, mo: 5.6 (95% CI: 3.1–6.8)
- 12-mo OS = 28.3%
- 18-mo OS = 20.0%
- 3L+ Nivolumab

IMpower133

- 403 pts
- Induction with 4 cycles of platinum/etoposide +/- Atezolizumab followed by maintenance with atezo or placebo

Horn et al. NEJM Sep 2018.
### IMpower133

#### Overall Survival According to Baseline Characteristics

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients (%)</th>
<th>Median Overall Survival (mo)</th>
<th>Hazard Ratio for Death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>261 (65)</td>
<td>12.3</td>
<td>0.74 (0.54–1.02)</td>
</tr>
<tr>
<td>Female</td>
<td>142 (35)</td>
<td>12.5</td>
<td>0.65 (0.42–1.00)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>217 (54)</td>
<td>12.1</td>
<td>0.92 (0.64–1.32)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>186 (46)</td>
<td>12.5</td>
<td>0.53 (0.36–0.77)</td>
</tr>
<tr>
<td>ECOG score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>140 (35)</td>
<td>16.6</td>
<td>0.79 (0.49–1.27)</td>
</tr>
<tr>
<td>1</td>
<td>263 (65)</td>
<td>11.4</td>
<td>0.68 (0.50–0.93)</td>
</tr>
<tr>
<td>Brain metastases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>35 (9)</td>
<td>8.5</td>
<td>1.07 (0.47–2.43)</td>
</tr>
<tr>
<td>No</td>
<td>368 (91)</td>
<td>12.6</td>
<td>0.68 (0.52–0.89)</td>
</tr>
<tr>
<td>Liver metastases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>149 (37)</td>
<td>9.3</td>
<td>0.81 (0.55–1.20)</td>
</tr>
<tr>
<td>No</td>
<td>254 (63)</td>
<td>16.8</td>
<td>0.64 (0.45–0.90)</td>
</tr>
<tr>
<td>Tumor mutational burden</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 mutations/Mb</td>
<td>139 (34)</td>
<td>11.8</td>
<td>0.70 (0.45–1.07)</td>
</tr>
<tr>
<td>≥10 mutations/Mb</td>
<td>212 (53)</td>
<td>14.6</td>
<td>0.68 (0.47–0.97)</td>
</tr>
<tr>
<td>&lt;16 mutations/Mb</td>
<td>271 (67)</td>
<td>12.5</td>
<td>0.71 (0.52–0.98)</td>
</tr>
<tr>
<td>≥16 mutations/Mb</td>
<td>80 (20)</td>
<td>17.8</td>
<td>0.63 (0.35–1.15)</td>
</tr>
<tr>
<td>Intention to treat population</td>
<td>405 (100)</td>
<td>12.5</td>
<td>0.70 (0.54–0.91)</td>
</tr>
</tbody>
</table>

Horn et al. NEJM Sep 2018.
Bristol-Myers Squibb Announces Phase 3 CheckMate 331 Study Does Not Meet Primary Endpoint of Overall Survival with Opdivo Versus Chemotherapy in Patients with Previously Treated Relapsed Small Cell Lung Cancer

The New York Times

Wednesday, October 17, 2018
Possible near future immunotherapy approvals

**Non-small cell lung cancer**

- 1st line Pembrolizumab PD-L1 > 50% (? Anyone with PD-L1>1%)
- 1st line Pembrolizumab + pemetrexed/ carboplatin in non-squamous NSCLC
  (? 1st line chemo + Pembrolizumab in squamous)
- ?1st line Nivolumab + Ipilimumab in high TMB
- ?1st line Chemo/Bevacizumab with Atezolizumab.

- 2nd line Pembrolizumab PD-L1 > 1 %
- 2nd line Nivolumab
- 2nd line Atezolizumab

- Maintenance Durvalumab after chemo-radiation

**Small cell lung cancer**

- ?1st line Chemo+ Atezolizumab
- 3rd line Nivolumab
Neoadjuvant immunotherapy

• Safety and feasibility of neoadjuvant immunotherapy for resectable stage I-III NSCLC.

• Nivolumab every 2 weeks, with surgery 4 weeks after the first dose.

• Major pathologic response (<10% viable residual tumor) in 45% (9 of 20) with no delays in surgical resection.

• Of the 9 patients with a major pathologic response, only 2 had a partial response on preoperative imaging.

• High correlation between pre-treatment tumor mutational burden (TMB) and major pathologic response to nivolumab (more than tumor PD-L1 expression).

Forde et al. NEJM May 2018.
HyperProgressive Disease (HPD)

- Retrospective French study. 406 pts treated with PD-1/PD-L1 inhibitors in second or later line treatment.

- HyperProgressive Disease (HPD) was defined as disease progression on the first CT scan during treatment with an absolute increase in Tumor Growth Rate exceeding 50%.

- 13.8% of pts vs 5.1 % historical chemo control group.

- Associated with more than two metastatic sites prior to treatment.

Ferrara et al. JAMA Oncol. Sep 2018
Adverse events

<table>
<thead>
<tr>
<th>Table</th>
<th>Recognizing the Side Effects of Immune Checkpoint Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body system/side effect</td>
<td>Nervous system events</td>
</tr>
<tr>
<td>Dermatologic events</td>
<td>Bullous dermatitis</td>
</tr>
</tbody>
</table>


Brahmer JCO June 2018
NCCN.com
Adverse Events
Adverse events

Management of Immunotherapy-Related Toxicities
(Immune Checkpoint Inhibitor-Related Toxicities)
Example 1: Rash

<table>
<thead>
<tr>
<th>Dermatologic Adverse Event(s)</th>
<th>Assessment/Grading</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maculopapular rash (^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body skin exam, including mucosa</td>
<td>Assess for history of prior inflammatory dermatologic diseases</td>
<td>Consider holding immunotherapy (^l)</td>
</tr>
<tr>
<td>Consider biopsy if unusual features</td>
<td></td>
<td>Treatment with high potency topical steroids AND/OR Prednisone 0.5–1 mg/kg/day (^g)</td>
</tr>
<tr>
<td></td>
<td>Mild (G1) (^d)</td>
<td>Oral antihistamine</td>
</tr>
<tr>
<td></td>
<td>Moderate (G2) (^b)</td>
<td>Topical emollient</td>
</tr>
<tr>
<td></td>
<td>Severe (G3–4) (^f)</td>
<td></td>
</tr>
</tbody>
</table>

- Continue immunotherapy
- Treatment with moderate potency topical steroids
- Oral antihistamine
- Topical emollient

NCCN.com
Example 2: Diarrhea/Colitis

GASTROINTESTINAL ADVERSE EVENT(S)  

**Mild (G1)**
- Diarrhea
- Colitis

**Moderate (G2)** or Severe (G3–4)
- Stool evaluation to rule out infectious etiology
  - Culture
  - C. difficile
  - Ova & parasites
  - Based on institutional availability, consider lactoferrin/calprotectin
  - Abdominal/pelvic CT with contrast
  - GI consultation
  - Colonoscopy ± esophagogastroduodenoscopy (EGD) with biopsy

**Management**
- Consider holding immunotherapy
- Loperamide
- Hydration
- Close monitoring

- **Moderate (G2)**
  - Hold immunotherapy
  - IV methylprednisolone (1 mg/kg/day)
  - No response in 2–3 days:
    - Increase dose to 2 mg/kg/day
    - Consider infliximab
    - If infliximab-refractory, consider vedolizumab

- **Severe (G3–4)**
  - G3: Discontinue anti-CTLA-4; consider resuming anti-PD-1/PD-L1 after resolution of toxicity
  - G4: Permanently discontinue immunotherapy
  - Consider inpatient care for provision of supportive care
  - IV methylprednisolone (2 mg/kg/day)
    - No response in 2 days:
      - Consider infliximab
      - If infliximab-refractory, consider vedolizumab

NCCN.com
Conclusions

- Immunotherapy therapeutic indications are expanding rapidly in the treatment of advanced lung cancer and have even replaced chemotherapy as first line therapy in many areas.

- PD-L1 expression and TMB are independent predictors of response to immunotherapy.

- It’s important to recognize and treat adverse reactions to immunotherapy promptly.

- Immunotherapy will likely play an important role in earlier stages of lung cancer.
Thank you

Questions???