Immunotherapy in Lung Cancer

3/29/19
Kathryn C. Arbour, MD
Thoracic Oncology Service
www.MSKCC.org
Disclosures

- I have served as a paid consultant to AstraZeneca

- MSKCC has received money for research support conducted by me from:
  - Novartis
  - Merck
  - Takeda
Agenda

• Rationale for immunotherapy in lung cancer

• Current lung cancer treatment landscape
  – Role in metastatic NSCLC
  – Role in Stage III NSCLC
  – Role in SCLC

• Potential toxicities of immunotherapy and management
Diagnosis of Lung Cancer in 2019

Histology

NSCLC

PD-L1

Molecular

Squamous Cell Carcinoma

Adenocarcinoma

Other

Adenocarcinoma

Squamous

Non-Squamous

Memorial Sloan Kettering Cancer Center
Treatment of Stage IV Lung Cancer in 2019

NSCLC Diagnosis

Non-Squamous

Histology

Squamous

(Consider testing, particularly if no significant smoking history)

Molecular Testing

No Actionable Drivers

PD-L1 Testing

OSIMERTINIB

ALECTINIB or BRIGATINIB

CRIZOTINIB

DABRAFENIB+ TRAMETINIB

EGFR

ALK

ROS1

BRAF

PD-L1 ≥50%

Pembrolizumab

or

Chemotherapy + Immune Checkpoint Inhibitor

PD-L1 <50%

Chemotherapy + Immune Checkpoint Inhibitor

Memorial Sloan Kettering Cancer Center
Immune Checkpoint Inhibitors

Adapted from Intelkofer and Thompson, TLB, 2015 & Callahan and Wolchok, TLB, 2013
Somatic Mutation Burden in Cancer

Memorial Sloan Kettering Cancer Center
Tumor Mutation Burden Associated with Response to PD-1 Inhibition

* Durable Clinical Benefit (6 month PFS)

Rizvi et al. Science. 2015
Not All Biomarkers are Created Equal…

Biomarkers to predict response to Immune Checkpoint Inhibitors

Biomarkers to predict response to targeted therapy

Not All Biomarkers are Created Equal…

EGFR Mutation  
PD-L1 IHC  
Biomarker Challenges in Immunotherapy
- PD-L1 expression variable within tissue?
- Ideal cutoff to use?
- Potential differences between assays
- TMB and PD-L1 are independent variables

- Response rate to EGFR TKI in patients with EGFR mutation: 80%
- Response rate to PD-1 Inhibitor in patients with “high” PD-L1: 45%

• Nivolumab approved in the 2nd line setting, all patients, regardless of PD-L1
• Pembrolizumab approved in the 2nd line setting, PD-L1 >1%
• Atezolizumab approved in the 2nd line settings, all patients, regardless of PD-L1
Pembrolizumab is Superior to Platinum-based Chemo in Patients with PD-L1 ≥50% (KEYNOTE-024)

Key Eligibility Criteria
- Metastatic NSCLC (any histology)
- PD-L1 TPS ≥50%
- EGFR and ALK negative
- No untreated or unstable CNS metastases

Randomize 1:1

Pembrolizumab Q3W
Carboplatin + Paclitaxel Q3W
OR
Carboplatin + Pemetrexed Q3W

Reck et al, NEJM 2016

Median OS 30 vs 14.2 months
Randomized Trial of Pembrolizumab and Platinum-based Chemotherapy in Patients with PD-L1 ≥1%

Key Eligibility Criteria
- Metastatic NSCLC (any histology)
- PD-L1 TPS ≥1%
- EGFR and ALK negative

• Pembrolizumab
  - 200 mg Q3W

• Carboplatin AUC 5 or 6 Q3W + Paclitaxel 200 mg/m² Q3W
  OR
  Carboplatin AUC 5 or 6 Q3W + Pemetrexed 500 mg/m² Q3W

N = 637

Gilberto Lopes ASCO 2018
Pembrolizumab vs Platinum-based Chemo in Patients with PD-L1 ≥1%

- TPS 1-19%:
  - Pembrolizumab: 35.2%
  - Chemotherapy: 36.4%

- TPS 20-49%:
  - Pembrolizumab: 17.9%
  - Chemotherapy: 16.5%

- TPS ≥50%:
  - Pembrolizumab: 46.9%
  - Chemotherapy: 47.1%

Gilberto Lopes ASCO 2018
Pembrolizumab vs Platinum-based Chemo in Patients with PD-L1 ≥50%

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>157 (52.5%)</td>
<td>0.69 (0.56-0.85)</td>
</tr>
<tr>
<td>Chemo</td>
<td>199 (66.3%)</td>
<td></td>
</tr>
</tbody>
</table>

Median OS (95% CI)

- Pembrolizumab: 20.0 mo (15.4-24.9)
- Platinum-based Chemo: 12.2 mo (10.4-14.2)

Gilberto Lopes ASCO 2018
Pembrolizumab vs Platinum-based Chemo in Patients with PD-L1 ≥20%

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>230 (55.7%)</td>
<td>0.77 (0.64-0.92)</td>
</tr>
<tr>
<td>Chemo</td>
<td>266 (65.7%)</td>
<td></td>
</tr>
</tbody>
</table>

Median OS (95% CI)
- Pembrolizumab: 17.7 mo (15.3-22.1)
- Platinum-based Chemo: 13.0 mo (11.6-15.3)

Gilberto Lopes ASCO 2018
Pembrolizumab vs Platinum-based Chemo in Patients with PD-L1 ≥1%

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro 371 (58.2%)</td>
<td>0.81 (0.71-0.93)</td>
<td>0.0018</td>
</tr>
<tr>
<td>Chemo 438 (68.8%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median OS (95% CI)
- Pembrolizumab: 16.7 mo (13.9-19.7)
- Platinum-based Chemo: 12.1 mo (11.3-13.3)

Gilberto Lopes ASCO 2018
Pembrolizumab vs Platinum-based Chemotherapy: PD-L1 ≥1-49%

Events  | HR (95% CI)  
--- | ---  
Pembro 214 (63.3%)  | 0.92  
(0.77-1.11)  
Chemo 239 (70.9%)  |  

Median OS (95% CI)  
13.4 mo (10.7-18.2)  
12.1 mo (11.0-14.0)  

Gilberto Lopes ASCO 2018
Chemo + IO rationale in Lung Cancer

- Chemotherapy may:
  - Increase antigen cross presentation after tumor cell death
  - Inhibition of MDSCs
  - Increase ratio of cytotoxic T-cells to regulatory T-cells

→ Enabling immune checkpoint inhibitors to work better
→ Many patients do not receive 2nd line therapy

Galluzzi et al. Cancer Cell. 2015
Chemotherapy + Pembrolizumab in Metastatic Non-squamous NSCLC

Key Eligibility Criteria
- Untreated stage IV nonsquamous NSCLC
- EGFR and ALK negative
- Provision of a sample for PD-L1 assessment
- No symptomatic brain metastases
- No hx pneumonitis requiring systemic steroids

N=410

Pembrolizumab 200 mg + Pemetrexed 500mg/m² + Carboplatin AUC 5 OR Cisplatin 75 mg/m² for 4 cycles (each 3 wk)

N=206

Placebo (normal saline) + Pemetrexed 500mg/m² + Carboplatin AUC 5 OR Cisplatin 75 mg/m² for 4 cycles (each 3 wk)

Optional Crossover
- Pembrolizumab 200 mg Q3W for up to 35 cycles

Memorial Sloan Kettering Cancer Center
Chemotherapy + Pembrolizumab in Metastatic Non-squamous NSCLC

**Progression-free Survival**

- 12 month PFS 34% vs 17%
- median PFS 8.8 vs 4.9 months
- ORR 47% vs 19%

**Overall Survival**

- 12 month OS 69% vs 49%
- mOS NR vs 11.3 months
- Median follow up 10.5 months

Gandhi et al. NEJM 2018
Chemo + Atezolizumab + Bevacizumab in Non-squamous Lung Cancer

**Arm A**
Atezolizumab + Carboplatin + Paclitaxel
4 or 6 cycles

- Treated with Atezolizumab
- Stage IV
- Nonsquamous NSCLC
- Chemotherapy-naive
- Any PD-L1 IHC status
- Stratification factors:
  - Sex
  - PD-L1 IHC expression
  - Liver metastases
- N = 1202

**Arm B**
Atezolizumab + Carboplatin + Paclitaxel + Bevacizumab
4 or 6 cycles

- Treated with Atezolizumab and Bevacizumab
- Treated with bevacizumab until PD by RECIST v1.1 or loss of clinical benefit AND/OR

**Arm C (control)**
Carboplatin + Paclitaxel + Bevacizumab
4 or 6 cycles

- Treated with bevacizumab until PD by RECIST v1.1

Socinski et al, ASCO 2018
### Chemo + Atezolizumab + Bevacizumab in Non-squamous Lung Cancer

<table>
<thead>
<tr>
<th>Landmark OS, %</th>
<th>Arm B: atezo + bev + CP</th>
<th>Arm C: bev + CP</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-month</td>
<td>68%</td>
<td>61%</td>
</tr>
<tr>
<td>18-month</td>
<td>54%</td>
<td>42%</td>
</tr>
<tr>
<td>24-month</td>
<td>45%</td>
<td>36%</td>
</tr>
</tbody>
</table>

**HR, 0.77**  
(95% CI: 0.63, 0.93)

Socinski et al, ASCO 2018
Pembrolizumab with Carboplatin and Taxane in Squamous NSCLC

Key Eligibility Criteria
- Stage IV NSCLC with squamous histology
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- No symptomatic brain metastases

End points
- Primary: PFS (RECIST v1.1, BICR) and OS
- Secondary: ORR and DOR (RECIST v1.1, BICR), safety

Paz-Ares ASCO 2018
Pembrolizumab with Carboplatin and Taxane in Squamous NSCLC

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + Chemo</td>
<td>30.6%</td>
<td>0.64 (0.49-0.85)</td>
</tr>
<tr>
<td>Placebo + Chemo</td>
<td>42.7%</td>
<td></td>
</tr>
</tbody>
</table>

Median OS (95% CI)
- 15.9 mo (13.2-NE)
- 11.3 mo (9.5-14.8)

Similar chemo+ atezolizumab study showed PFS benefit but not OS in preliminary analysis

Luis Paz-Ares. NEJM 2018
First Line Treatment Algorithm

NSCLC Diagnosis

Non-Squamous

Histology

Squamous

(Consider testing, particularly if no significant smoking history)

Molecular Testing

No Actionable Drivers

PD-L1 Testing

PD-L1 ≥50%

Pembrolizumab

or

Chemotherapy + Immune Checkpoint Inhibitor

PD-L1 <50%

Chemotherapy + Immune Checkpoint Inhibitor

Osimertinib

Alectinib or Brigatinib

Crizotinib

Dabrafenib + Trametinib

EGFR

ALK

ROS1

BRAF

Memorial Sloan Kettering Cancer Center
Immunotherapy in Stage III disease

**Key Eligibility Criteria**
- Stage III or locally advanced unresectable NSCLC
- Treated with ≥ 2 cycles platinum based chemo with concurrent RT
- Any level PD-L1 expression

Randomize 2:1

Durvalumab Q2W for 12 months

Placebo

Primary Endpoints: Progression free survival and Overall Survival
Immunotherapy in Stage III disease

- Risk of pneumonitis: 33.9% of pts on durvalumab and 24.8% on placebo
- No clear benefit if PD-L1 negative -> not approved in Europe for PD-L1 neg patients

Antonia et al. NEJM. 2018
Extensive Stage Small Cell Lung Cancer

- Standard of care 1L treatment SCLC has been platinum/etoposide chemotherapy for over 20 years
  - Initial responses are robust, recurrent disease often rapid
- Topotecan is the only FDA approved therapy at time of progression (limited efficacy)
- Immunotherapy has demonstrated (minimal) benefit in the 2nd line setting
  - In practice patients most patients received Ipi/Nivo
- Many SCLC patients have rapid decline and may not receive 2nd line therapy
Chemo + IO in Small Cell Lung Cancer

Patients with (N = 403):
- Measurable ES-SCLC (RECIST v1.1)
- ECOG PS 0 or 1
- No prior systemic treatment for ES-SCLC
- Patients with treated asymptomatic brain metastases were eligible

Stratification:
- Sex (male vs. female)
- ECOG PS (0 vs. 1)
- Brain metastases (yes vs. no)

Induction (4 x 21-day cycles):
- Atezolizumab (1200 mg IV, Day 1) + carboplatin + etoposide
- Placebo + carboplatin + etoposide
  - Carboplatin: AUC 5 mg/mL/min IV, Day 1
  - Etoposide: 100 mg/m² IV, Days 1–3

Maintenance:
- Atezolizumab
- Placebo
  - PCI per local standard of care

Co-primary end points:
- Overall survival
- Investigator-assessed PFS

Key secondary end points:
- Objective response rate
- Duration of response
- Safety

Survival follow-up:

Liu et al. WCLC. 2018
Recently FDA approved, quickly adopted as standard of care

Horn et al. NEJM. 2018
Contraindications to Immunotherapy

Are there any lung cancer patients that should not receive immunotherapy in the first line setting?

• Patients with targetable oncogenic drivers (EGFR, ALK, ROS1, BRAF)
  – Immunotherapy less effective in these patients, even if high PD-L1
  – May have increased toxicity if TKI used after IO (e.g. osimertinib)

• Patients with known autoimmune conditions who may be at increased risk of toxicity
Immune Related Adverse Events (irAE)

- Toxicities of immunotherapy most likely to occur in initial weeks/months of treatment (but can happen at any time)

- Organ specific toxicities different in PD-1 vs CTLA-4
  - More colitis with anti-CTLA-4
  - More pneumonitis with anti-PD-1

- Patients with preexisting autoimmune conditions may be at higher risk

Sidlow, Hellmann, and Postow. NEJM. 2018
Immunotherapy Toxicities: Pneumonitis

Risk of pneumonitis (all grades): ~5%
Risk of Grade 3-5 pneumonitis: ~ 1%
Risk higher with combination therapy (PD-1+CTLA-4)

Naidoo et al. JCO 2016.
Multiple potential radiographic patterns of pneumonitis related to immunotherapy

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Description</th>
<th>Images</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptogenic organizing pneumonia-like</td>
<td>(n = 5, 19%)</td>
<td><img src="image1.png" alt="Radiograph" /></td>
</tr>
<tr>
<td>Ground glass opacities</td>
<td>(n = 10, 37%)</td>
<td><img src="image2.png" alt="Radiograph" /></td>
</tr>
<tr>
<td>Interstitial</td>
<td>(n = 6, 22%)</td>
<td><img src="image3.png" alt="Radiograph" /></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>(n = 2, 7%)</td>
<td><img src="image4.png" alt="Radiograph" /></td>
</tr>
<tr>
<td>Pneumonitis not otherwise specified</td>
<td>(n = 4, 15%)</td>
<td><img src="image5.png" alt="Radiograph" /></td>
</tr>
</tbody>
</table>

Naidoo et al. JCO 2016.
Management of irAEs: Pneumonitis

Consensus Guidelines from ASCO (no prospective trials to guide management)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Management Recommendations</th>
</tr>
</thead>
</table>
| G1: Asymptomatic; confined to one lobe of the lung or <25% of lung parenchyma; clinical or diagnostic observations only. | • Hold treatment, repeat CT in 3-4 weeks  
• May resume ICPI with radiographic evidence of improvement  
• If no improvement, should treat as G2 (with steroids) | |
| G2: Symptomatic; involves more than one lobe of the lung or 25 to 50% of lung parenchyma; medical intervention indicated; limiting instrumental ADL. | • Hold until resolution to G1 or less.  
• Prednisone 1 to 2 mg/kg/day and taper by 5 to 10 mg/week over 4-6 weeks.  
• Consider bronchoscopy with BAL.  
• Consider empirical antibiotics. | |
| G3: Severe symptoms; hospitalization required; involves all lung lobes or >50% of lung parenchyma; limiting self-care ADL; oxygen indicated. | • Permanently discontinue immunotherapy  
• Empiric antibiotics; methylpred IV 1 to 2 mg/kg/day  
• If no improvement after 48 hours, consider infliximab or mycophenolate mofetil or IVIG or cyclophosphamide, taper corticosteroids over 4-6 weeks  
• Bronchoscopy with BAL ± transbronchial biopsy. | |
| G4: Life-threatening respiratory compromise; urgent intervention indicated (intubation) | | |
Immunotherapy Toxicities

- Rates of irAEs are higher in patients with response to treatment
- Prompt initiation of steroids is important
- Treatment with steroids for irAEs does not reduce efficacy of treatment
- If Grade 3-4 toxicity occurs, agents should be permanently discontinued
  - Responses can be maintained off therapy
  - Current practice is often to restart other treatments only with clear clinical/radiographic signs of progressive cancer
Impact of Baseline Steroids on PD-(L)1 Efficacy: Lower Overall Response Rate

Indications for steroids in lung cancer treatment:
- Brain metastases
- Dyspnea
- Fatigue
- Anorexia
- Pain

Best Overall Response

<table>
<thead>
<tr>
<th>Condition</th>
<th>Steroids (n=51)</th>
<th>No steroids (n=400)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR+PR</td>
<td>94%</td>
<td>81%</td>
</tr>
<tr>
<td>SD+POD</td>
<td>6%</td>
<td>19%</td>
</tr>
</tbody>
</table>

Arbour et al. JCO 2018
Impact of Baseline Steroids on PD-(L)1 Efficacy: Inferior PFS and OS

**Progression Free Survival**

- No steroids (n=402)
- Steroids (n=53)

HR 1.7, p<0.0001

**Overall Survival**

- No steroids (n=402)
- Steroids (n=53)

HR 2.1, p<0.0001

Arbour et al. ASCO 2018
Conclusions

• PD-1 and PD-L1 inhibitors have dramatically changed the treatment landscape of metastatic NSCLC and SCLC

• PD-L1 staining is most established biomarker, though TMB being increasingly recognized

• Immunotherapy offers the promise of durable disease control for patients with lung cancer

• irAEs can develop in patients treated with PD-1/L1 inhibitors, including pneumonitis
  - Prompt initiation of steroids is the mainstay of management