Non-Small Cell Lung Cancer Webinar

Thursday, September 13, 2018
1–2 p.m. EDT
The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of non-small cell lung cancer (NSCLC)

Julie R. Brahmer¹, Ramaswamy Govindan², Robert A. Anders³, Scott J. Antonia⁴, Sarah Sagorsky⁵, Marianne J. Davies⁶, Steven M. Dubinett⁷, Andrea Ferris⁸, Leena Gandhi⁹, Edward B. Garon¹⁰, Matthew D. Hellmann¹¹, Fred R. Hirsch¹², Shakuntala Malik¹³, Joel W. Neal¹⁴, Vassiliki A. Papadimitrakopoulou¹⁵, David L. Rimm¹⁶, Lawrence H. Schwartz¹⁷, Boris Sepesi¹⁸, Beow Yong Yeap¹⁹, Naiyer A. Rizvi²⁰ and Roy S. Herbst²¹*
Webinar Faculty

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Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Patrick Forde, MD
Johns Hopkins University

Scott N. Gettinger, MD
Yale Cancer Center

Roy S. Herbst, MD, PhD
Yale Cancer Center
Webinar Agenda

1:00–1:05 p.m. EDT  Welcome and Introductions
1:05–1:40 p.m. EDT  Review of SITC Cancer Immunotherapy Guideline – NSCLC
1:40–1:55 p.m. EDT  Question and Answer Session
1:55–2:00 p.m. EDT  Closing Remarks
To Submit a Question

Computer

Mobile Phone

Q: Has the webinar started?
A: Yes, thank you for joining today!
FDA-approved Checkpoint Inhibitors in NSCLC

2008
Nivolumab trials initiated

2012
Pembrolizumab trials initiated

2015
Nivolumab approved for 2nd line sq NSCLC
Nivolumab approved for 2nd line non-sq NSCLC
Pembrolizumab approved for 2nd line NSCLC (PD-L1 ≥ 50%)

2016
Pembrolizumab approved for 1st line NSCLC (PD-L1 ≥ 50%)
Pembrolizumab approved for 2nd line NSCLC (PD-L1 ≥ 1%)
Atezolizumab approved for 2nd line NSCLC

2017
Pembrolizumab + Pemetrexed and Carboplatin approved for 1st line NSCLC
Durvalumab approved for Stage III NSCLC after chemoradiation

In Development
Pembrolizumab + carboplatin/(nab-)paclitaxel for 1st line sq NSCLC
Atezolizumab/bevacizumab/chemotherapy for non-sq NSCLC
Atezolizumab + chemotherapy for non-sq NSCLC
Nivolumab + ipilimumab for TMB-high non-sq NSCLC
First-Line: Phase III KEYNOTE-024 Trial
Pembrolizumab vs Platinum Doublet Chemotherapy for PD-L1 ≥ 50% NSCLC (without EGFRm/ALKr)

Primary Endpoint: PFS

<table>
<thead>
<tr>
<th>Events, n</th>
<th>Median, mo</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>73</td>
<td>10.3</td>
<td>0.50 (0.37-0.68)</td>
</tr>
<tr>
<td>Chemo</td>
<td>116</td>
<td>6.0</td>
<td></td>
</tr>
</tbody>
</table>

Crossover to Pembrolizumab N = 82

<table>
<thead>
<tr>
<th>Objective Response, n</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>20.7 (12.6–31.1)</td>
</tr>
<tr>
<td>Median Time to Response, mo (range)</td>
<td>2.0 (1.1–8.4)</td>
</tr>
<tr>
<td>Censored duration of response, n</td>
<td>12</td>
</tr>
</tbody>
</table>
First-Line: Phase III KEYNOTE-042 Trial
Pembrolizumab vs Platinum Doublet Chemotherapy for PD-L1 ≥ 1% NSCLC (without EGFRm/ALKr)

1º Endpt: OS in PD-L1 TPS > 50%, > 20%, > 1%

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

Median (95% CI)

- Pembrolizumab: 16.7 mo (13.9-19.7) ORR 27.3
- Platinum Doublet Chemotherapy: 12.1 mo (11.3-13.3) ORR 26.5

ORR (%): 27.3 vs 26.5
DOR (m): 20.2 vs 8.3

Lopes et al. ASCO 2018
First-Line: Phase III KEYNOTE-042 Trial
Pembrolizumab vs Platinum Doublet Chemotherapy for PD-L1 ≥ 1% NSCLC (without EGFRm/ALKr)

<table>
<thead>
<tr>
<th>PD-L1 TPS</th>
<th>≥ 1%</th>
<th>≥ 20%</th>
<th>≥ 50%</th>
<th>1-49%</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (P/ Chemo)</td>
<td>637/ 637</td>
<td>413/ 415</td>
<td>299/ 300</td>
<td>338/ 337</td>
</tr>
<tr>
<td>OS HR (95% CI)</td>
<td><strong>0.81</strong> (0.71-0.93)</td>
<td><strong>0.77</strong> (0.64-0.92)</td>
<td><strong>0.69</strong> (0.56-0.85)</td>
<td><strong>0.92</strong> (0.77-1.11)</td>
</tr>
<tr>
<td>OS (mos) Median (95% CI)</td>
<td><strong>16.7-12.1</strong> (13.9-19.7) (11.3-13.3)</td>
<td><strong>17.7/ 13</strong> (15.3-22.1) (11.6-15.3)</td>
<td><strong>20.2/ 12.2</strong> (15.4-24.9) (10.4-14.2)</td>
<td><strong>13.4/ 12.1</strong> (10.7-18.2) (11-14)</td>
</tr>
<tr>
<td>2yr OS %</td>
<td><strong>39.3/ 28</strong></td>
<td><strong>40.5/ 29.6</strong></td>
<td><strong>44.7/ 30.1</strong></td>
<td><strong>34.6/ 26.5</strong></td>
</tr>
<tr>
<td>PFS HR (95% CI)</td>
<td><strong>1.07</strong> (0.94-1.21)</td>
<td><strong>0.94</strong> (0.8-1.11)</td>
<td><strong>0.81</strong> (0.67-.99)</td>
<td></td>
</tr>
<tr>
<td>PFS (mos) Median (95% CI)</td>
<td><strong>5.4/ 6.5</strong> (4.3-6.2) (6.3-7)</td>
<td><strong>6.2/ 6.6</strong> (5.1-7.8) (6.2-7.3)</td>
<td><strong>7.1/ 6.4</strong> (5.9-9) (6.1-6.9)</td>
<td></td>
</tr>
<tr>
<td>1yr PFS %</td>
<td><strong>28/ 26.6</strong></td>
<td><strong>32.4/ 28.8</strong></td>
<td><strong>37.4/ 27.3</strong></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td><strong>27.3/ 26.5</strong></td>
<td><strong>33.4/ 28.9</strong></td>
<td><strong>39.5/ 32</strong></td>
<td></td>
</tr>
</tbody>
</table>

Lopes et al. ASCO 2018
First-Line: Phase III KEYNOTE-189 Trial
Carboplatin/ Cisplatin with Pemetrexed +/- Pembrolizumab for Advanced, Non-squamous NSCLC (without EGFRm/ALKr)

Primary Endpoints: PFS & OS

OS:
- HR 0.49 [95% CI: 0.38-0.64]; p <0.00001
- Median (95% CI): NR (NE-NE)
  - 11.3 mo (8.7-15.1)

PFS:
- HR 0.52 [95% CI: 0.43-0.64]; p <0.00001
- Median (95% CI):
  - 4.9 mo (4.7-5.5)
  - 8.8 mo (7.6-9.2)

By PD-L1 TPS

<table>
<thead>
<tr>
<th></th>
<th>&lt;1%</th>
<th>1-49%</th>
<th>&gt; 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS HR (95% CI)</td>
<td>0.59 (0.38-0.92)</td>
<td>0.55 (0.34-0.90)</td>
<td>0.42 (0.26-0.68)</td>
</tr>
<tr>
<td>OS (mos)</td>
<td>15.2/12 (12.3-NE)</td>
<td>NR/12.9 (7.0-NE)</td>
<td>NR/10 (NE-NE)</td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>11.3 (7.0-NE)</td>
<td>11.3 (8.7-NE)</td>
<td>11.3 (7.5-NE)</td>
</tr>
<tr>
<td>1yr OS %</td>
<td>61.7/52.2</td>
<td>71.5/50.9</td>
<td>73/48.1</td>
</tr>
<tr>
<td>PFS HR (95% CI)</td>
<td>0.75 (0.53-1.05)</td>
<td>0.55 (0.37-0.81)</td>
<td>0.36 (0.25-0.52)</td>
</tr>
<tr>
<td>PFS (mos)</td>
<td>6.1/5.1 (4.9-7.6)</td>
<td>9/4.9 (7.1-11.3)</td>
<td>9.4/4.7 (9-13.8)</td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>6.1 (4.5-6.9)</td>
<td>9 (4.6-6.9)</td>
<td>9.4 (3.1-6)</td>
</tr>
<tr>
<td>1yr PFS %</td>
<td>19.1/15.7</td>
<td>37.5/19.6</td>
<td>44.9/15.4</td>
</tr>
<tr>
<td>ORR</td>
<td>32.3/14.3</td>
<td>48.4/20.7</td>
<td>61.4/22.9</td>
</tr>
</tbody>
</table>

Gandhi et al. NEJM 2018
First-Line: Phase III KEYNOTE-407 Trial
Carboplatin with Paclitaxel/ (nab-)Paclitaxel +/- Pembrolizumab for Advanced, Squamous NSCLC

Primary Endpoints: PFS & OS

<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>

**OS (mos)**

- **Median (95% CI)**
  - Pembro + Chemo: 15.9 mo (13.2-NE)
  - Placebo + Chemo: 11.3 mo (9.5-14.8)

**PFS (mos)**

- **Median (95% CI)**
  - Pembro + Chemo: 6.3 mo (6.1-6.5)
  - Placebo + Chemo: 4.8 mo (4.3-5.7)

**ORR**

- **59%**
  - Pembro + Chemo: 54.7%
  - Placebo + Chemo: 70.1%

*By PD-L1 TPS*

<table>
<thead>
<tr>
<th>OS HR (95% CI)</th>
<th>&lt;1%</th>
<th>1-49%</th>
<th>&gt; 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (mos)</td>
<td>15.9/ 10.2 (13.1-6NE)</td>
<td>14.0/ 11.6 (12.8-NE)</td>
<td>NR/ NR (11.3-NE)</td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>15.9 mo (13.2-NE)</td>
<td>14.0 mo (12.8-NE)</td>
<td>NR/ NR (11.3-NE)</td>
</tr>
</tbody>
</table>

**PFS HR (95% CI)**

- **0.68** (0.47-0.98)
- **0.56** (0.39-0.80)
- **0.37** (0.24-0.58)

**PFS (mos)**

- **6.3/ 5.3** (6.1-6.5) | **7.2/ 5.2** (6-11.4) | **8/ 4.2** (6.1-10.3) |

*Paz Ares et al. ASCO 2018*
Efficacy of Anti-PD-1/PD-L1 by EGFR/ALK & PD-L1 Status

**Pembrolizumab (EGFRm and wt)**

<table>
<thead>
<tr>
<th>ORR</th>
<th>TPS 0-24%</th>
<th>TPS 1-49%</th>
<th>TPS &lt;1%</th>
<th>Total*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>ORR, %</td>
<td>n</td>
<td>ORR, %</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td></td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>144</td>
<td>38.2 (30.2-46.7)</td>
<td>185</td>
<td>11.9 (7.6-17.4)</td>
</tr>
<tr>
<td>EGFR wild type</td>
<td>113</td>
<td>39.8 (30.7-49.5)</td>
<td>156</td>
<td>12.2 (7.5-18.4)</td>
</tr>
<tr>
<td>EGFR mutant</td>
<td>20</td>
<td>20.0 (5.7-43.7)</td>
<td>23</td>
<td>8.7 (1.1-28.0)</td>
</tr>
</tbody>
</table>

**OS**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>TPS ≥25%</th>
<th>TPS ≥1%</th>
<th>TPS &lt;1%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>nN³</td>
<td>Median, months (95% CI)</td>
<td>nN³</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR mutation status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wild type</td>
<td>60/109</td>
<td>15.7 (11.1-NR)</td>
<td>152/245</td>
</tr>
<tr>
<td>Mutant</td>
<td>17/19</td>
<td>6.5 (2.0-13.7)</td>
<td>37/45</td>
</tr>
</tbody>
</table>

**Durvalumab (EGFRm/ALKr)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Weight</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR wild-type</td>
<td>26.0%</td>
<td>0.68 [0.51, 0.86]</td>
</tr>
<tr>
<td>Checkmate 057</td>
<td>52.0%</td>
<td>0.66 [0.55, 0.80]</td>
</tr>
<tr>
<td>Keynote 010</td>
<td>11.0%</td>
<td>0.70 [0.47, 1.04]</td>
</tr>
<tr>
<td>POPLAR</td>
<td>89.0%</td>
<td>0.60 [0.38, 0.97]</td>
</tr>
</tbody>
</table>

| EGFR mutant               | 6.0%   | 1.18 [0.69, 2.00]     |
| Checkmate 057             | 3.8%   | 0.88 [0.45, 1.70]     |
| Keynote 010               | 11.1%  | 0.60 [0.29, 1.40]     |
| POPLAR                     | 11.0%  | 1.05 [0.79, 1.39]     |

| Total (95% CI)            | 100.0% | 0.70 [0.61, 0.80]     |

**Similar meta-analysis (4 studies) done by Huang et al. (OncoImmunology, 2017)**

- **OS HR 1.09 (95% CI: 0.84-1.41)**
- **PFS HR 1.44 (95% CI: 1.05-1.98, p=0.02)**

Lee et al, JTO 2016

Hui et al, KEYNOTE 001 ASCO 2016

Garassino et al, ATLANTIC ESMO 2016

Hellman et al, KEYNOTE 001 WCLC 2015
Efficacy of Anti-PD-1 in Advanced EGFRmutant NSCLC

Nivolumab + erlotinib in advanced TKI treated EGFRmutant NSCLC (TKI last Tx)*

Gettinger et al, Cm-012 JTO 2018

Pembrolizumab in Advanced TKI naïve EGFRmutant NSCLC

Lisberg et al, Cm-012 JTO 2018

Nivolumab + Ipilimumab in Advanced EGFRmutant NSCLC

Hellman et al, ASCO 2016, Lancet Oncol 2017
Consensus Recommendations for Advanced NSCLC

**Diagnostic Workup**
- Clinical history, patient characteristics, and tumor data reviewed by a multidisciplinary team
- Workup should include imaging, pathology to determine histological subtype, molecular testing using a broad-based panel, and immunohistochemistry to determine PD-L1 status

**Squamous Cell**
- PD-L1 TPS ≥ 50%
  - Pembrolizumab
  - Pembrolizumab + carboplatin/(nab-)paclitaxel

**Non-Squamous Cell**
- PD-L1 TPS < 50%
  - EGFR, ALK, or ROS1 +
    - Targeted therapy
  - EGFR, ALK, or ROS1 -
    - PD-L1 TPS < 50%
      - Chemotherapy
      - Atezolizumab / Nivolumab / Pembrolizumab (TPS ≥ 1%)
    - PD-L1 TPS ≥ 50%
      - Pembrolizumab + pemetrexed/carboplatin

**Treatment Recommendations**
- Treatment until response, progression, or unacceptable toxicities
Second-Line: Phase III Trials
Improved OS with PD-1 Axis Inhibitors vs Docetaxel for Advanced NSCLC

CHECKMATE 017  (Brahmer et al, NEJM 2015)

CHECKMATE 057  (Borghaei et al, NEJM 2015)

KEYNOTE 010  (TPS ≥ 1%)  (Herbst et al, Lancet 2016)

OAK  (Rittmeyer et al, Lancet 2017)
Stage III NSCLC: Phase III PACIFIC Trial
Durvalumab After Chemoradiotherapy

- OS primary endpoint met in May, 2018
In Development: IMPOWER 131 Trial
Carboplatin/(nab-)Paclitaxel +/- Atezolizumab in Advanced Squamous NSCLC

Arm B: Atezo + CnP
Arm C: CnP

<table>
<thead>
<tr>
<th>Median PFS (95% CI), mo</th>
<th>6.3 (5.7, 7.1)</th>
<th>5.6 (5.5, 5.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR(^a) (95% CI) P value</td>
<td>0.71 (0.60, 0.85)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Minimum follow-up, 9.8 mo
Median follow-up, 17.1 mo

In Development: Atezolizumab/Carboplatin/nab-paclitaxel in advanced non-squamous NSCLC
- Phase III IMpower 130 met PFS & OS co-primary endpoints (May 2018)
In Development: IMPOWER 150 Trial
Carboplatin/Paclitaxel/Bevacizumab
+/- Atezolizumab in Advanced Non-squamous NSCLC

- Improved PFS and OS with addition of atezolizumab to carboplatin/paclitaxel/bevacizumab
Tumor Mutational Burden (TMB) may Determine Sensitivity to PD-1 Blockade in NSCLC

Patients whose tumors have higher numbers of mutations are more likely to benefit from PD-1 blockade
In Development: CheckMate 227 Trial
Ipilimumab + Nivolumab vs Chemotherapy in TMB-high NSCLC

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

Hazard ratio for disease progression or death, 0.62 (95% CI, 0.44–0.88)

Hazard ratio for disease progression or death, 0.48 (95% CI, 0.27–0.85)

Hellmann et al. NEJM 2018
• Unanimous agreement that PD-L1 testing should be performed for all newly diagnosed patients with metastatic disease
  • Including those tested for EGFR/ALK/ROS1 mutations
  • 100% of Subcommittee members reported experience with PD-L1 testing of patients with newly diagnosed metastatic NSCLC

• 100% of Subcommittee members reported waiting for PD-L1 test results before initiating first-line treatment

• 72% of Subcommittee members did not retest PD-L1-negative patients after disease progression on first-line therapy

• The Subcommittee recognizes TMB testing may be necessary/appropriate for treatment decisions in the near future
### Summary of First-line Immunotherapies for Advanced NSCLC

<table>
<thead>
<tr>
<th>Trial</th>
<th>PFS / OS (months)</th>
<th>PFS HR in PD-L1 neg.</th>
<th>Toxicities Grade 3-5</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KEYNOTE-024</strong></td>
<td></td>
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</tr>
<tr>
<td>PD-L1≥50%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pembro</td>
<td>10.3</td>
<td></td>
<td>30</td>
<td>NA</td>
</tr>
<tr>
<td>Plat/Pem or Gem or Pacli</td>
<td>6</td>
<td>14.2</td>
<td></td>
<td>27 vs 53%</td>
</tr>
<tr>
<td><strong>KEYNOTE-042</strong></td>
<td></td>
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<tr>
<td>PD-L1≥1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembro</td>
<td>5.4</td>
<td></td>
<td>16.7</td>
<td>NA</td>
</tr>
<tr>
<td>Plat/Pem or Pacli</td>
<td>6.5</td>
<td>12.1</td>
<td></td>
<td>18 vs 41%</td>
</tr>
<tr>
<td><strong>IMPower150</strong></td>
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<tr>
<td>Non-squamous</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Atezo + Beva + Plat/Pacl</td>
<td>8.3</td>
<td>19.2</td>
<td></td>
<td>0.72</td>
</tr>
<tr>
<td>Plat/Pacl</td>
<td>6.8</td>
<td>14.4</td>
<td></td>
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<tr>
<td><strong>KEYNOTE-189</strong></td>
<td></td>
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<tr>
<td>Non-squamous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembro + Plat/Pem</td>
<td>8.8</td>
<td>21.5</td>
<td></td>
<td>0.59</td>
</tr>
<tr>
<td>Plat/Pem</td>
<td>4.9</td>
<td>11.3</td>
<td></td>
<td></td>
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<tr>
<td><strong>KEYNOTE-407</strong></td>
<td></td>
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<tr>
<td>Squamous</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pembro + Plat/Pacl or NabPacli</td>
<td>6.4</td>
<td>15.9</td>
<td></td>
<td>0.68</td>
</tr>
<tr>
<td>Plat/Pacl or NabPacli</td>
<td>4.8</td>
<td>11.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CheckMate 227</strong></td>
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<td></td>
<td></td>
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<tr>
<td>TMB≥10mut/Mb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivo + Ipi</td>
<td>7.2</td>
<td>23</td>
<td></td>
<td>0.48</td>
</tr>
<tr>
<td>Plat/Pem or Gem</td>
<td>5.4</td>
<td>16.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Solange Peters, ASCO 2018
Immune-related Adverse Events (irAEs)

- **Eye**
  - Uveitis
  - Scleritis
  - Retinitis

- **Pituitary**
  - Hypophysitis

- **Lung**
  - Pneumonitis
  - Pleuritis

- **Liver**
  - Hepatitis

- **Adrenal**
  - Adrenalitis

- **Kidney**
  - Nephritis

- **Muscle**
  - Myositis

- **Rheumatological**
  - Vasculitis
  - Arthritis

- **Nervous system**
  - Guillain-Barré syndrome
  - Myasthenia gravis
  - Encephalitis
  - Meningitis
  - Neuropathy

- **Thyroid**
  - Hypothyroidism

- **Heart**
  - Myocarditis

- **Pancreas**
  - Type1 Diabetes
  - Pancreatitis

- **Stomach**
  - Gastritis

- **Gastrointestinal**
  - Colitis

- **Skin**
  - Vitiligo
  - Alopecia
  - Psoriasis
  - DRESS syndrome
  - Rush / Pruritus

- **Blood**
  - Thrombocytopenia
  - haemolytic anaemia
  - Neutropaenia
# Single-agent Toxicities in 2/3L for NSCLC

<table>
<thead>
<tr>
<th></th>
<th>Atezolizumab OAK</th>
<th>Nivolumab SQ: CM 017 (updated OS; 2L)</th>
<th>Nivolumab NSQ:CM 057 (updated OS; 2/3L)</th>
<th>Pembrolizumab KEYNOTE-010</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Related Grade 3-5 AEs</strong></td>
<td>15%</td>
<td>8%</td>
<td>11%</td>
<td>13-16%</td>
</tr>
<tr>
<td><strong>Discontinuation due to related AEs</strong></td>
<td>5%</td>
<td>6%</td>
<td>6%</td>
<td>4-5%</td>
</tr>
<tr>
<td><strong>Pneumonitis incidence</strong></td>
<td>1%</td>
<td>5%</td>
<td>3%</td>
<td>4-5%</td>
</tr>
</tbody>
</table>

Rittmeyer et al. Lancet 2017  
Brahmer et al. NEJM 2015  
Borghaei et al. NEJM 2015  
Herbst et al. Lancet 2015
First-Line: Phase III KEYNOTE-407 Trial
Carboplatin/(nab-)Paclitaxel +/- Pembrolizumab for Advanced, Squamous NSCLC

Paz-Ares et al. ASCO 2018
First-Line: Phase III KEYNOTE-189 Trial
Carboplatin/Pemetrexed +/- Pembrolizumab for Advanced, Non-squamous NSCLC (without EGFRm/ALKr)

<table>
<thead>
<tr>
<th>Event</th>
<th>Pembrolizumab Combination (N = 405)</th>
<th>Placebo Combination (N = 202)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Any Grade</td>
</tr>
<tr>
<td></td>
<td>Grade 3, 4, or 5</td>
<td>Grade 3, 4, or 5</td>
</tr>
<tr>
<td>Any</td>
<td>92 (22.7)</td>
<td>24 (11.9)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>27 (6.7)</td>
<td>5 (2.5)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>18 (4.4)</td>
<td>5 (2.5)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>16 (4.0)</td>
<td>6 (3.0)</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>10 (2.5)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Colitis</td>
<td>9 (2.2)</td>
<td>0</td>
</tr>
<tr>
<td>Severe skin reaction</td>
<td>8 (2.0)</td>
<td>5 (2.5)</td>
</tr>
<tr>
<td>Nephritis</td>
<td>7 (1.7)</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>5 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>3 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>3 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>1 (0.2)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Myositis</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
</tbody>
</table>

Ghandi et al. NEJM 2018
In Development: CheckMate 227 Trial
Ipilimumab + Nivolumab vs Chemotherapy in TMB-high NSCLC

<table>
<thead>
<tr>
<th>TRAE, a %</th>
<th>Nivolumab + ipilimumab (n = 576)</th>
<th>Chemotherapy (n = 570)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3–4</td>
</tr>
<tr>
<td>Any TRAE</td>
<td>75</td>
<td>31</td>
</tr>
<tr>
<td>TRAE leading to discontinuation b</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Most frequent TRAEs (≥15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>13</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Constipation</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-related deaths c</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Hellmann et al. AACR 2018
Hellmann et al. NEJM 2018
Consensus Recommendations for Treatment and Management of irAEs In NSCLC

• Recommend close monitoring and cross-collaboration with disease specialists
  • Subcommittee members reported past collaborations with
    • Radiologists (79%)
    • Pulmonologists (71%)
    • Dermatologists (71%)
    • Rheumatologists (71%)
    • Endocrinologists (71%)

• ≥50% of Subcommittee members routinely use the following tests to monitor patients treated with immune checkpoint inhibitors
  • Thyroid function studies (93%)
  • Liver function tests (93%)
  • Blood urea nitrogen (BUN) and creatinine (86%)
  • Whole body imaging (71%)
  • Closely monitoring patients’ oxygen saturation at rest and on ambulation was also noted

• The Subcommittee recommends patient monitoring and education of pneumonitis
  • All patients with radiographic and/or clinical evidence of pneumonitis should be referred to a pulmonary specialist
  • Grade 2 pneumonitis: immunotherapy should be withheld and steroids administered
  • Grade 3/4 pneumonitis: permanently discontinue immunotherapy and initiate treatment with steroids, including consideration of IV steroids and hospitalization
Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group

I. Puzanov\textsuperscript{1}, A. Diab\textsuperscript{2}, K. Abdallah\textsuperscript{3}, C. O. Bingham III\textsuperscript{4}, C. Brogdon\textsuperscript{5}, R. Dadu\textsuperscript{2}, L. Hamad\textsuperscript{1}, S. Kim\textsuperscript{2}, M. E. Lacouture\textsuperscript{6}, N. R. LeBoeuf\textsuperscript{7}, D. Lenihan\textsuperscript{8}, C. Onofrei\textsuperscript{9}, V. Shannon\textsuperscript{2}, R. Sharma\textsuperscript{1}, A. W. Silk\textsuperscript{12}, D. Skondra\textsuperscript{10}, M. E. Suarez-Almazor\textsuperscript{2}, Y. Wang\textsuperscript{2}, K. Wiley\textsuperscript{11}, H. L. Kaufman\textsuperscript{12}, M. S. Emstoff\textsuperscript{11} and on behalf of the Society for Immunotherapy of Cancer Toxicity Management Working Group
Immunotherapies in Development

1. **Release of cancer cell antigens**
   - Vaccines
   - Anti-CD40 (agonist)
   - TLR agonists
   - HDAC inhibitors

2. **Cancer antigen presentation**
   - Chemotherapy
   - Radiation therapy
   - Targeted therapy

3. **Priming and activation**
   - Anti-CTLA4
   - Anti-CD137 (agonist)
   - Anti-OX40 (agonist)
   - Anti-CD27 (agonist)
   - IL-2
   - IL-12

4. **Trafficking of T cells to tumors**

5. **Infiltration of T cells into tumors**
   - Anti-VEGF

6. **Recognition of cancer cells by T cells**
   - CAR Ts

7. **Killing of cancer cells**
   - Anti-PD-L1
   - Anti-PD-1
   - IDO inhibitors
   - Other Checkpoints

Chen et al. Immunity 2013
Courtesy of Dr. Michael Atkins
Consensus Recommendations for Advanced NSCLC

- Clinical history, patient characteristics, and tumor data reviewed by a multidisciplinary team
- Workup should include imaging, pathology to determine histological subtype, molecular testing using a broad-based panel, and immunohistochemistry to determine PD-L1 status

**Diagnostic Workup**

- **Squamous Cell**
  - PD-L1 TPS ≥ 50%
  - PD-L1 TPS < 50%
  - Pembrolizumab or Pembrolizumab + carboplatin/(nab-)-paclitaxel

- **Non-Squamous Cell**
  - EGFR, ALK, or ROS1 +
  - EGFR, ALK, or ROS1 -
  - PD-L1 TPS < 50%
  - PD-L1 TPS ≥ 50%

**Treatment Recommendations for Squamous Cell**

1. Pembrolizumab
2. Pembrolizumab + carboplatin/(nab-)-paclitaxel

**Treatment Recommendations for Non-Squamous Cell**

1. Pembrolizumab
2. Pembrolizumab + pemetrexed/carboplatin

**Treatment Cessation**

- Treatment until response, progression, or unacceptable toxicities
Case Study

Background:
• 58 year-old male, non-smoker
• 3 month history of cough and shortness of breath, not resolved after two courses of antibiotics
• 20 lb. weight loss, night sweats, several bouts of hemoptysis
• CT scan: Bilateral lung metastases
• Biopsy
  • Adenocarcinoma
  • KRAS/p53 mutation positive
  • PD-L1 is 1%
  • TMB-intermediate of 8 mutations/MB
• Brain MRI negative for intraparenchymal metastasis
Case Study

For this specific patient, which regimen would be most appropriate for improved survival?

A. Pembrolizmab
B. Pembrolizumab + Carboplatin/Pemetrexed
C. Carboplatin/Pemetrexed
D. Atezolizumab with Carboplatin/Paclitaxel/Bevacizumab
E. Ipilimumab/Nivolumab
Case Study

**Conclusion/take-away:** The upfront treatment of advanced NSCLC patients without an actionable mutation has evolved drastically with the incorporation of immunotherapy to platinum doublet chemotherapy. While single-agent pembrolizumab still remains the standard of care of patients whose tumor PD-L1 is greater than 50% (non-EGFR and/or ALK mutated), those patients whose TPS is between 1 and 50% should be considered for triplet therapy with Carboplatin/Pemetrexed/Pembrolizumab based on the landmark KEYNOTE-189 study. While dual checkpoint blockade with Ipilimumab/Nivolumab remains promising it has only been investigated in patients with TMB-high tumors.
To Submit a Question

Computer

Mobile Phone

Q: Has the webinar started?
A: Yes, thank you for joining today!
Additional Resources from SITC

Cancer Immunotherapy Guidelines:
www.sitcancer.org/cancer-immunotherapy-guidelines
• Expert consensus recommendations
• On-demand webinars

Resources for healthcare providers:
www.sitcancer.org/clinicians
• Educational programs
• Online courses
• Free resources
Continuing Education Credits are offered for physicians, PA’s, NP’s, RN’s and pharmacists.

You will receive an email following the webinar with instructions on how to claim credit.

Questions and comments: connectED@sitcancer.org

Thank you for attending the NSCLC Webinar!