LIVE WEBINARS

Immunotherapy in Patients with Non-Small Cell Lung Cancer

Presented by:
Leora Horn, MD, MSc
Vanderbilt-Ingram Cancer Center

July 14, 2016

Moderated by Rose K. Joyce
NCCN, Conferences and Meetings Department

Cancer Immunotherapy

- Cancer cells may express tumor-specific antigens due to the presence of mutations
- These antigens may induce an immune response
- Up-regulation of PD-L1 in the tumor microenvironment enables cancers to evade T-cell–mediated killing
- Inhibition of the PD-L1/PD-1 and PD-L1/B7.1 interaction may restore antitumor T-cell activity


Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.
Cancer cells may express tumor-specific antigens due to the presence of mutations.

• These antigens may induce an immune response.

• Up-regulation of PD-L1 in the tumor microenvironment enables cancers to evade T-cell–mediated killing.

• Inhibition of the PD-L1/PD-1 and PD-L1/B7.1 interaction may restore antitumor T-cell activity.
Potential Differences in PD-1 vs. PD-L1 Blockade


Hypothetical Goals of Immunotherapies

Hypothetical slide illustrating a scientific concept that is beyond data available so far. These charts are not intended to predict what may actually be observed in clinical studies.

TKI = tyrosine kinase inhibitor.

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.
Clinical Development of Immune Checkpoint Inhibitors

<table>
<thead>
<tr>
<th>Target</th>
<th>Antibody</th>
<th>Molecule</th>
<th>Development stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTLA-4</td>
<td>Ipilimumab</td>
<td>Human IgG1</td>
<td>Approved in Melanoma</td>
</tr>
<tr>
<td></td>
<td>Tremelimumab</td>
<td>Human IgG2</td>
<td>Phase 3</td>
</tr>
<tr>
<td>PD-1</td>
<td>Nivolumab</td>
<td>Human IgG4</td>
<td>MEL, NSCLC, RCC</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td>Humanized IgG4</td>
<td>MEL, PD-L1 + NSCLC</td>
</tr>
<tr>
<td></td>
<td>PDR001</td>
<td>Humanized IgG4</td>
<td>Phase 1</td>
</tr>
<tr>
<td></td>
<td>REGN2810</td>
<td>Human IgG4</td>
<td>Phase 1</td>
</tr>
<tr>
<td>PD-L1</td>
<td>Durvalumab</td>
<td>Engineered human IgG1</td>
<td>Phase 3</td>
</tr>
<tr>
<td></td>
<td>Atezolizumab</td>
<td>Engineered human IgG1</td>
<td>Approved in Bladder Cancer</td>
</tr>
<tr>
<td></td>
<td>Avelumab</td>
<td>Human IgG1</td>
<td>Phase 3</td>
</tr>
</tbody>
</table>

PD-L1 Testing Is Controversial

- Different assays have not been compared
- Each assay has different cut point that defines PD-L1 positive
- What is better: archival tissue or fresh tissue?
- Where do you biopsy: the primary tumor or metastatic site?
- Is tissue from a core the only way to evaluate for expression?
Comparison of Response by PD-L1 Status: Phase I Data

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>RR</th>
<th>PDL1+/PDL-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>PD-1</td>
<td>17%</td>
<td>15%/14%</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>22%</td>
<td>17%-37%/10%</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>PD-L1</td>
<td>23%</td>
<td>31%/14%</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>PD-L1</td>
<td>16%</td>
<td>25%/10%</td>
</tr>
<tr>
<td>Avelumab</td>
<td>PD-L1</td>
<td>12%</td>
<td>14%/10%</td>
</tr>
</tbody>
</table>

PD-L1 as a Prognostic Marker

- PD-L1 expression has been identified as a negative prognostic marker
  - Increased risk of metastases and death in renal cell cancer\(^1\)
  - More aggressive phenotype in melanoma\(^2\)
  - Increased risk of metastases and death in lung cancer\(^3\)
  - Increased risk of metastatic disease in gastric cancer\(^4\)

---


Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.
PD-L1 as a Predictive Marker: Response Based on PD-L1 Expression

Response Status | PD-L1 Positive | PD-L1 Negative | Total
--- | --- | --- | ---
Objective response | 9 (36) | 0 | 9 (36)
No objective response | 36 (94) | 17 (100) | 53 (76)
All | 45 | 17 | 62

P=0.006 for association by Fisher’s exact test

RCC = renal cell cancer

Koeppen H. and Kowanetz M., Proprietary assay PD-L1 IHC

Positive PD-L1 staining in NSCLC

Adenocarcinoma
Prevalence of PD-L1 = 45%

Squamous cell carcinoma
Prevalence of PD-L1 = 50%

High sensitivity and specificity in formalin-fixed, paraffin-embedded (FFPE) samples

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.
**PD-L1 expression on TCs and ICs**

<table>
<thead>
<tr>
<th>IC Score</th>
<th>PD-L1 IC staining</th>
<th>TC Score</th>
<th>PD-L1 TC staining</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC3</td>
<td>IC ≥ 10%</td>
<td>TC3</td>
<td>TC ≥ 50%</td>
</tr>
<tr>
<td>IC2</td>
<td>IC ≥ 5% and &lt; 10%</td>
<td>TC2</td>
<td>TC ≥ 5% and &lt; 50%</td>
</tr>
<tr>
<td>IC1</td>
<td>IC ≥ 1% and &lt; 5%</td>
<td>TC1</td>
<td>TC ≥ 1% and &lt; 5%</td>
</tr>
<tr>
<td>IC0</td>
<td>IC &lt; 1%</td>
<td>TC0</td>
<td>TC &lt; 1%</td>
</tr>
</tbody>
</table>

IC = tumor-infiltrating immune cell; TC = tumor cell


---

**What assay do we use?**

LDT or FDA approved assay? Cut off?

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Machines Utilized</td>
<td>Link 48</td>
<td>Link 48</td>
<td>BenchMark ULTRA</td>
<td>BenchMark ULTRA</td>
<td></td>
</tr>
<tr>
<td>Compartments</td>
<td>TM</td>
<td>TM</td>
<td>TM</td>
<td>TC/IC</td>
<td></td>
</tr>
<tr>
<td>Variables</td>
<td>% of cells</td>
<td>% of cells</td>
<td>% of cells</td>
<td>% of cells</td>
<td></td>
</tr>
<tr>
<td>Definition of positive</td>
<td>PD-L1(+) &gt;1% Strong(+) &gt;50%</td>
<td>PD-L1(+) &gt;1% Strong(+) &gt;5%</td>
<td>PD-L1(+) &gt;25%</td>
<td>TC / IC 3(+)</td>
<td>TC / IC 2(+)</td>
</tr>
</tbody>
</table>
Phase 2: CHECKMATE-063: Overall Survival (OS): All Treated Patients

<table>
<thead>
<tr>
<th>DBL</th>
<th>Median follow-up, mos (range)</th>
<th>Median OS, mos (95% CI)</th>
<th>1-yr OS rate, % (95% CI)</th>
<th>18-mo OS rate, % (95% CI)</th>
<th>Events, n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>July 2014</td>
<td>8.0 (0.0, 17.3)</td>
<td>8.2 (6.1, 10.9)</td>
<td>41 (32, 50)</td>
<td>–</td>
<td>72/117</td>
</tr>
<tr>
<td>June 2015</td>
<td>8.0 (0.0, 26.8)</td>
<td>8.1 (6.1, 10.9)</td>
<td>39 (30, 48)</td>
<td>27 (19, 35)</td>
<td>90/117</td>
</tr>
</tbody>
</table>

Number of patients at risk:
- July 2014 DBL: 117 68 51 28 5 0 0 0 0
- June 2015 DBL: 117 69 45 30 69 34 38 24 0

Overall Survival by PD-L1 Expression

<table>
<thead>
<tr>
<th>PD-L1 Expression</th>
<th>Median OS, mos (95% CI)</th>
<th>Events, n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1%</td>
<td>8.3 (5.6, 15.6)</td>
<td>23/31</td>
</tr>
<tr>
<td>≥1%</td>
<td>10.1 (5.5, 16.8)</td>
<td>32/45</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>13.0 (1.1, 20.8)</td>
<td>8/10</td>
</tr>
</tbody>
</table>

Horn et al., WCLC 2015
CheckMate 017 (NCT01642004)

- Stage IIIb/IV SQ NSCLC
- 1 prior platinum doublet-based chemotherapy
- ECOG PS 0–1
- Pre-treatment (archival or fresh) tumor samples required for PD-L1 analysis
  \[ N = 272 \]

Randomize 1:1

- Nivolumab 3 mg/kg IV Q2W until PD or unacceptable toxicity  \[ n = 135 \]
- Docetaxel 75 mg/m² IV Q3W until PD or unacceptable toxicity  \[ n = 137 \]

- Primary Endpoint:
  - OS

- Additional Endpoints:
  - Investigator-assessed ORR
  - Investigator-assessed PFS
  - Correlation between PD-L1 expression and efficacy
  - Safety
  - Quality of life (LCSS)

CheckMate 057 (NCT01673867)

- Stage IIIb/IV non-SQ NSCLC
- Pre-treatment (archival or recent) tumor samples required for PD-L1
- ECOG PS 0–1
- Failed 1 prior platinum doublet
- Prior maintenance therapy allowed
- Prior TKI therapy allowed for known ALK translocation or EGFR mutation
  \[ N = 582 \]

Randomize 1:1

- Nivolumab 3 mg/kg IV Q2W until PD or unacceptable toxicity  \[ n = 292 \]
- Docetaxel 75 mg/m² IV Q3W until PD or unacceptable toxicity  \[ n = 290 \]

- Primary Endpoint
  - OS

- Additional Endpoints
  - OS\(^a\)
  - PFS\(^b\)
  - Safety
  - Efficacy by tumor PD-L1 expression
  - Quality of life (LCSS)

Patients stratified by prior maintenance therapy and line of therapy (second- vs third-line)

Checkmate 017: Overall Survival

- 12-month OS rate=42%
- 18-month OS rate=28%
- Nivolumab
- Docetaxel

Based on August 2015 DBL.

Symbols refer to censored observations.

Minimum follow-up for survival: 18 months

Reckamp et al., WCLC 2015

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.
Checkmate 057: Overall Survival

**12-mo OS**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events (n=392)</th>
<th>Deaths (n=392)</th>
<th>1-yr OS rate, %</th>
<th>18-mo OS rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>32</td>
<td>25</td>
<td>53</td>
<td>39</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>30</td>
<td>27</td>
<td>61</td>
<td>51</td>
</tr>
</tbody>
</table>

**18-mo OS**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events (n=290)</th>
<th>Deaths (n=290)</th>
<th>1-yr OS rate, %</th>
<th>18-mo OS rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>28</td>
<td>23</td>
<td>56</td>
<td>39</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>26</td>
<td>23</td>
<td>60</td>
<td>53</td>
</tr>
</tbody>
</table>

No. of patients at risk (12-mo OS): Nivolumab 292, Docetaxel 290; 18-mo OS: Nivolumab 292, Docetaxel 290.

HR (95% CI) = 0.73 (0.59, 0.89); P = 0.0015

HR (95% CI) = 0.72 (0.60, 0.88); P = 0.0009

HR (95% CI) for post-hoc testing on July 2, 2015: P = 0.0009

Symbols represent censored observations.

* Based on a March 18, 2015, DBL.
* Based on a July 2, 2015, DBL.

**Nivolumab 2 year OS**

Figure 4. Kaplan–Meier estimates of OS (2 years minimum follow-up)


Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.
**ORR to Nivolumab by PD-L1 Expression**

<table>
<thead>
<tr>
<th>PD-L1 Expression Level</th>
<th>≥1%</th>
<th>&lt;1%</th>
<th>≥5%</th>
<th>&lt;5%</th>
<th>≥10%</th>
<th>&lt;10%</th>
<th>Not quantifiable*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Squamous</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR,* % (n/N)</td>
<td>18</td>
<td>17</td>
<td>21</td>
<td>15</td>
<td>19</td>
<td>16</td>
<td>39</td>
</tr>
<tr>
<td><strong>Nonsquamous</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR,* %</td>
<td>30.9</td>
<td>9.3</td>
<td>35.8</td>
<td>10.3</td>
<td>37.2</td>
<td>11.0</td>
<td>13.1</td>
</tr>
</tbody>
</table>

Reckamp et al., WCLC 2015; Horn et al., ESMO 2015

**OS by PD-L1 Expression: Squamous**

Reckamp et al., WCLC 2015; Horn et al., ESMO 2015

Spigel D et al., ASCO 2015.

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.
**OS by PD-L1 Expression: Nonsquamous**

Symbols represent censored observations.

**2-Year OS Rates**
Overall and by PD-L1 Expression Level in CheckMate 057 (Non-SQ NSCLC)

<table>
<thead>
<tr>
<th>PD-L1 Expression Level</th>
<th>OS (% at 2 Years)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>29/252</td>
<td>25/101</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>18/290</td>
<td>18/101</td>
</tr>
<tr>
<td>≥1%</td>
<td>16/252</td>
<td>16/101</td>
</tr>
<tr>
<td>≥2%</td>
<td>18/252</td>
<td>18/101</td>
</tr>
<tr>
<td>≥10%</td>
<td>18/252</td>
<td>18/101</td>
</tr>
</tbody>
</table>

HR = Hazard Ratio, CI = Confidence Interval

In CheckMate 057, consistent with the primary analysis, PD-L1 expression level was associated with the magnitude of OS benefit at 2 years starting at the lowest level studied (1%)


---

*Kaplan–Meier estimates, with error bars indicating 95% CIs
*For the comparison of the full Kaplan–Meier survival curves for each treatment group

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.
Updated Treatment and Safety Summary: Squamous

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n=131)</th>
<th>Docetaxel (n=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-related AEs, %</td>
<td>Any grade</td>
<td>Grade 3–5*</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>8</td>
</tr>
<tr>
<td>Treatment-related AEs leading to discontinuation, %</td>
<td>5*</td>
<td>3</td>
</tr>
<tr>
<td>Treatment-related deaths, %</td>
<td>0</td>
<td>2d</td>
</tr>
</tbody>
</table>

* Median number of doses was 8 (range, 1–56) for nivolumab and 3 (range, 1–29) for docetaxel

Based on June 2015 DBL. Includes events reported between first dose and 30 days after last dose of study therapy. No grade 5 events were reported with nivolumab. 1% of pts had increased ALT, increased AST, increased lipase, myasthenic syndrome, sepsis, or rash, and 2% of pts had pneumonia. 5% for nivolumab. 1% of pts had increased ALT, increased AST, increased lipase, myasthenic syndrome, colitis, or rash, and 2% of pts had pneumonitis. 5% for docetaxel. Peripheral neuropathy (3%) and fatigue (2%) were the most frequently reported events (>2% patients) leading to discontinuation. Interstitial lung disease, pulmonary hemorrhage, and sepsis (1 pt each) were the most frequently reported events (>2% patients) leading to discontinuation. 2% were the most frequently reported events (>2% patients) leading to discontinuation.

Reckamp et al., WCLC 2015

KEYNOTE-001 Study: Pembrolizumab (MK3475) in NSCLC Expansion Cohorts (N = 550)

- Response assessment
  - Primary measure: ORR by RECIST v1.1\* per independent central review
  - Secondary measure: immune-related response criteria (irRC)\* per investigator assessment
  - Pembrolizumab was given until disease progression, unacceptable toxicity, or death
  - Analysis cut-off date: March 3, 2014\*

* Tumor PD-L1 expression was determined by a prototype assay to inform enrollment. Samples were independently reanalyzed using a clinical trial IHC assay.

\* Including 2 therapy platinum-containing doublet. "First 31 patients randomized to 2 mg/kg Q3W and 10 mg/kg Q2W. The remaining 34 patients were randomized to 10 mg/kg Q2W and 10 mg/kg Q3W."


Hellman et al., WCLC 2015

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.
Keynote-001 Pembrolizumab Response


Keynote-001 Pembrolizumab OS

**Keynote-001 Pembrolizumab OS in Key Subgroups**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>TPS ≥50%</th>
<th>TPS ≥1%</th>
<th>TPS &lt;1%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>nN</td>
<td>Median, months (95% CI)</td>
<td>nN</td>
</tr>
<tr>
<td>Squamous</td>
<td>16/28</td>
<td>14.5 (8.0-19.6)</td>
<td>33/54</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>65/108</td>
<td>15.4 (9.0-18.9)</td>
<td>164/248</td>
</tr>
</tbody>
</table>

**Smoking history**
- Current or former: 59/108 | 15.7 (11.1-NR) | 136/221 | 13.2 (9.4-15.6) | 47/66 | 8.6 (4.9-13.3) |
- Never: 23/30 | 9.2 (4.9-17.3) | 65/85 | 7.3 (5.1-13.7) | 17/24 | 9.1 (4.2-21.3) |

**EGFR mutation status**
- Wild type: 60/109 | 15.7 (11.1-NR) | 152/245 | 13.2 (9.2-15.4) | 51/71 | 9.1 (5.8-13.8) |
- Mutant: 17/19 | 6.5 (2.0-13.7) | 37/45 | 6.5 (4.4-12.6) | 11/17 | 5.7 (2.2-NR) |


---

**KEYNOTE-010 Study Design**

- **Patients**
  - Advanced NSCLC
  - Confirmed PD after ≥1 line of chemotherapy
  - No active brain metastases
  - ECOG PS 0-1
  - PD-L1 TPS ≥1%
  - No serious autoimmune disease
  - No ILD or pneumonitis requiring systemic steroids

- **Stratification factors**
  - ECOG PS (0 vs 1)
  - Region (East Asia vs non-East Asia)
  - PD-L1 status (TPS ≥50% vs 1%-49%)

- **Randomization** 1:1:1

- **Treatments**
  - Pembrolizumab 2 mg/kg IV Q3W for 24 months
  - Pembrolizumab 10 mg/kg IV Q3W for 24 months
  - Docetaxel 75 mg/m² Q3W per local guidelines

- **End points in the TPS ≥50% stratum and TPS ≥1% population**
  - Primary: PFS and OS
  - Secondary: ORR, duration of response, safety

ClinicalTrials.gov, NCT01905657.

*Prior therapy must have included ≥2 cycles of platinum-doublet chemotherapy. An appropriate tyrosine kinase inhibitor was required for patients whose tumors had an EGFR sensitizing mutation or an ALK translocation.


*Patients received the maximum number of cycles permitted by the local regulatory authority.
ORR (RECIST v1.1, Central Review)

<table>
<thead>
<tr>
<th>PD-L1 TPS ≥50%</th>
<th>Pembro 2 mg/kg n = 139</th>
<th>Pembro 10 mg/kg n = 151</th>
<th>Docetaxel n = 152</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>30 (23-39)</td>
<td>29 (22-37)</td>
<td>8 (4-13)</td>
</tr>
<tr>
<td></td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Analysis cut-off date: September 30, 2015.

Herbst RS et al. Oral presentation at ESMO Asia 2015

<Comparison of pembrolizumab vs docetaxel.>

Progression-Free Survival at TPS ≥1% and TPS ≥50%

<table>
<thead>
<tr>
<th>PD-L1 TPS ≥1%</th>
<th>Pembro 2 mg/kg n = 344</th>
<th>Pembro 10 mg/kg n = 346</th>
<th>Docetaxel n = 343</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>18 (14-22)</td>
<td>18 (14-23)</td>
<td>9 (6-13)</td>
</tr>
<tr>
<td></td>
<td>P = 0.0005</td>
<td>P = 0.0002</td>
<td></td>
</tr>
</tbody>
</table>

Analysis cut-off date: September 30, 2015.

Herbst RS et al. Oral presentation at ESMO Asia 2015

<Comparison of pembrolizumab vs docetaxel.>
**Overall Survival at TPS ≥1% and TPS ≥50%**

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median (95% CI), mo</th>
<th>Rate at 1-yr</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro 2 mg/kg</td>
<td>10.4 (9.4, 11.9)</td>
<td>43.2%</td>
<td>0.71 (0.58, 0.88)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Pembro 10 mg/kg</td>
<td>12.7 (10.0, 17.3)</td>
<td>52.3%</td>
<td>0.61 (0.49, 0.75)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>8.5 (7.5, 9.8)</td>
<td>34.6%</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Comparison of pembrolizumab vs docetaxel. Analysis cut-off date: September 30, 2015. HR = hazard ratio; mos = months; NR = not reached; OS = overall survival; PD-L1 = programmed death ligand 1; Pembro = pembrolizumab; TPS = tumor proportion score.*


**Keynote-010**

**Figure 2. Kaplan-Meier estimates of OS in the PD-L1 TPS 1%-49% stratum.**

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median, mo (95% CI)</th>
<th>9-mo Rate, %</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab 2 mg/kg</td>
<td>9.4 (8.7-10.5)</td>
<td>93</td>
<td>0.78 (0.61-0.94)</td>
</tr>
<tr>
<td>Pembrolizumab 10 mg/kg</td>
<td>10.8 (8.5-13.3)</td>
<td>98</td>
<td>0.71 (0.53-0.94)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>8.5 (7.8-9.9)</td>
<td>47</td>
<td>–</td>
</tr>
</tbody>
</table>

Garon et al, ASCO 2016
Treatment-Related AEs With Incidence ≥10% in Any Arm, TPS ≥1%

- Decreased appetite
- Fatigue
- Nausea
- Rash
- Diarrhea
- Asthenia
- Stomatitis
- Anemia
- Alopecia
- Neutropenia

POPLAR: A Randomized All-comer Phase II Study

- Metastatic or locally advanced NSCLC (2L/3L)
- Disease progression on a prior platinum therapy
  - N = 287

Stratification Factors

- PD-L1 IC expression (0 vs 1 vs 2 vs 3)a
- Histology (squamous vs non-squamous)
- Prior chemotherapy regimens (1 vs 2)

Primary study objective:

- Estimate OS by PD-L1 expression

Secondary study objectives:

- Estimate PFS, ORR and DOR by PD-L1 expression
- Evaluate safety

Atezolizumab

- 1200 mg IV q3w until loss of clinical benefit

Docetaxel

- 75 mg/m² IV q3w until disease progression

Interim analysis is based on 153 events with a minimum follow-up 10 months.

POPLAR: Atezolizumab vs Docetaxel in NSCLC
Updated OS, Biomarker analyses

<table>
<thead>
<tr>
<th></th>
<th>Atezolizumab</th>
<th>Docetaxel</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>n</td>
<td>Median OS, Mos</td>
<td>n</td>
<td>Median OS, Mos</td>
</tr>
<tr>
<td>TC3 or IC3</td>
<td>24</td>
<td>Not reached</td>
<td>23</td>
<td>11.1</td>
</tr>
<tr>
<td>TC2/3 or IC2/3</td>
<td>50</td>
<td>15.1</td>
<td>55</td>
<td>7.4</td>
</tr>
<tr>
<td>TC1/2/3 or IC1/2/3</td>
<td>93</td>
<td>15.1</td>
<td>102</td>
<td>9.2</td>
</tr>
<tr>
<td>TC0 and IC0</td>
<td>51</td>
<td>9.7</td>
<td>41</td>
<td>9.7</td>
</tr>
<tr>
<td>Squamous</td>
<td>49</td>
<td>10.1</td>
<td>48</td>
<td>8.6</td>
</tr>
<tr>
<td>Nonsquamous</td>
<td>95</td>
<td>14.8</td>
<td>95</td>
<td>10.9</td>
</tr>
</tbody>
</table>


POPLAR: All-cause AEs
(≥ 5% difference between arms)

• AE profiles consistent with previous studies
• For atezolizumab, other immune-mediated AEs (any grade) included:
  • AST increased (4%)
  • ALT increased (4%)
  • Pneumonitis (2%)
  • Colitis (1%)
  • Hepatitis (1%)

Dry skin, stomatitis, and nail disorder were additional AEs with a 3% higher frequency in docetaxel.
Safety population includes patients who received any amount of either study treatment.
Data cut-off Jan 30, 2016.

Adapted from Spira AI, et al: Presented at ASCO 2015; Oral Presentation #8010.
First Line Therapy

JAVELIN: Phase Ib Trial of First-line Avelumab in NSCLC

- Open-label, dose-escalation phase Ib trial of avelumab (10 mg/kg Q2W) in advanced NSCLC not previously treated for metastatic disease

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>N = 75</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>18.7</td>
</tr>
<tr>
<td>DCR</td>
<td>64.0</td>
</tr>
<tr>
<td>CR</td>
<td>1.3</td>
</tr>
<tr>
<td>PR</td>
<td>17.3</td>
</tr>
<tr>
<td>SD</td>
<td>45.3</td>
</tr>
<tr>
<td>Median PFS</td>
<td>11.6 wks</td>
</tr>
</tbody>
</table>

- Well tolerated, low rate of grade 3/4 AEs
- Tx-related AEs: 56.6% (9% grade 3/4)
- No tx-related deaths

Phase I/II Trial of Durvalumab in Treatment-Naive Advanced NSCLC

- Dose-escalation/dose-expansion phase I/II trial of durvalumab (10 mg/kg Q2W) in pts with treatment-naive PD-L1+ NSCLC
- **ORR:** 27% (N = 59); 29% for PD-L1 high (n = 49); 11% for PD-L1 low or negative (n = 9)


Phase 1 CheckMate 012 Study Design: Nivolumab Plus Ipilimumab in First-line NSCLC

- Stage IIIB/IV NSCLC (any histology), no prior chemotherapy for advanced disease, ECOG PS 0 or 1
- **Primary endpoint:** safety and tolerability
- **Secondary endpoints:** ORR (RECIST v1.1) and PFS rate at 24 weeks
- **Exploratory endpoints:** OS, efficacy by PD-L1 expression

- The safety and tolerability of the nivolumab-ipilimumab combination was improved with less frequent ipilimumab dosing
- Schedules with nivolumab 3 mg/kg also showed increased clinical efficacy in a previous analysis
- Here, we report longer follow-up on nivolumab 3 mg/kg plus ipilimumab schedules

*Patients tolerating study treatment permitted to continue treatment beyond RECIST v1.1-defined progression if considered to be deriving clinical benefit for February 2016 database lock
- Ipilimumab and nivolumab dosing are shown in mg/kg IV (eg, Nivo 3 = nivolumab 1 mg/kg IV)

### Nivolumab Plus Ipilimumab in First-line NSCLC: Summary of Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Nivo 3 Q2W + Ipi 1 Q12W (n = 38)</th>
<th>Nivo 3 Q2W + Ipi 1 Q6W (n = 39)</th>
<th>Nivo 3 Q2W (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR, % (95% CI)</td>
<td>47 (31, 64)</td>
<td>39 (23, 55)</td>
<td>23 (13, 37)</td>
</tr>
<tr>
<td>Median duration of response, mo (95% CI)</td>
<td>NR (11.3, NR)</td>
<td>NR (8.4, NR)</td>
<td>NR (5.7, NR)</td>
</tr>
<tr>
<td>Median length of follow-up, mo (range)</td>
<td>12.9 (0.9–18.0)</td>
<td>11.8 (1.1–18.2)</td>
<td>14.3 (0.2–30.1)</td>
</tr>
<tr>
<td>Best overall response, %</td>
<td>Complete response</td>
<td>Partial response</td>
<td>Stable disease</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>47</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>39</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>8.1 (5.6, 13.6)</td>
<td>3.9 (2.6, 13.2)</td>
<td>3.6 (2.3, 6.6)</td>
</tr>
<tr>
<td>1-year OS rate, % (95% CI)</td>
<td>NC</td>
<td>69 (52, 81)</td>
<td>73 (59, 83)</td>
</tr>
</tbody>
</table>

NC = not calculated (when >25% of patients are censored); NR = not reached.
Combination data based on a February 2016 database lock; monotherapy data based on a March 2015 database lock except for OS data, which are based on an August 2015 database lock.


### Nivolumab Plus Ipilimumab in First-line NSCLC: Efficacy by Tumor PD-L1 Expression

<table>
<thead>
<tr>
<th></th>
<th>Nivo 3 Q2W + Ipi 1 Q12W</th>
<th>Nivo 3 Q2W + Ipi 1 Q6W</th>
<th>Nivo 3 Q2W</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (n/N)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1% PD-L1</td>
<td>30 (3/10)</td>
<td>0 (0/7)</td>
<td>14 (2/14)</td>
</tr>
<tr>
<td>≥1% PD-L1</td>
<td>57 (12/21)</td>
<td>57 (13/23)</td>
<td>28 (9/32)</td>
</tr>
<tr>
<td>≥50% PD-L1</td>
<td>100 (6/6)</td>
<td>86 (6/7)</td>
<td>50 (6/12)</td>
</tr>
<tr>
<td>Median PFS (95% CI), mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1% PD-L1</td>
<td>4.7 (0.9, NR)</td>
<td>2.4 (1.7, 2.9)</td>
<td>6.6 (2.0, 11.2)</td>
</tr>
<tr>
<td>≥1% PD-L1</td>
<td>8.1 (5.6, NR)</td>
<td>10.6 (3.6, NR)</td>
<td>3.5 (2.2, 6.6)</td>
</tr>
<tr>
<td>≥50% PD-L1</td>
<td>13.6 (6.4, NR)</td>
<td>NR (7.8, NR)</td>
<td>8.4 (2.2, NR)</td>
</tr>
<tr>
<td>1-year OS rate (95% CI), %</td>
<td>NC</td>
<td>NC</td>
<td>79 (47, 93)</td>
</tr>
<tr>
<td>&lt;1% PD-L1</td>
<td>90 (66, 97)</td>
<td>83 (60, 93)</td>
<td>69 (50, 82)</td>
</tr>
<tr>
<td>≥1% PD-L1</td>
<td>NC</td>
<td>100 (100, 100)</td>
<td>83 (48, 96)</td>
</tr>
<tr>
<td>≥50% PD-L1</td>
<td>NC</td>
<td>NC</td>
<td></td>
</tr>
</tbody>
</table>

NC = not calculated (when >25% of patients are censored); NR = not reached due to high percentage of ongoing response.
Combination data based on a February 2016 database lock; monotherapy data based on a March 2015 database lock except for OS data, which are based on an August 2015 database lock.

Nivolumab Plus Ipilimumab in First-line NSCLC:
Safety Summary

<table>
<thead>
<tr>
<th></th>
<th>Nivo 3 Q2W + Ipi 1 Q12W (n = 38)</th>
<th>Nivo 3 Q2W + Ipi 1 Q6W (n = 39)</th>
<th>Nivo 3 Q2W (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-related AEs, %</td>
<td>Any grade 82</td>
<td>Grade 3–4 37</td>
<td></td>
</tr>
<tr>
<td>Treatment-related AEs leading to discontinuation, %</td>
<td>Any grade 11</td>
<td>Grade 3–4 5</td>
<td></td>
</tr>
</tbody>
</table>

- There were no treatment-related deaths
- Treatment-related grade 3–4 AEs led to discontinuation at a third of the rate seen with older combination arms using higher or more frequent doses of ipilimumab

Combination data based on a February 2016 database lock; monotherapy data based on a March 2015 database lock.

Combination Immune Checkpoint Blockade

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab + Ipilimumab</th>
<th>MEDI4736 + TREME</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Melanoma</td>
<td>Renal</td>
</tr>
<tr>
<td>ORR, %</td>
<td>57.6%</td>
<td>29-39%</td>
</tr>
<tr>
<td>PFS</td>
<td>11.5 months</td>
<td>8 months</td>
</tr>
<tr>
<td>Cut Off</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>ORR in PD-L1 +</td>
<td>72.1%</td>
<td>48%</td>
</tr>
<tr>
<td>ORR in PD-L1 -</td>
<td>57.5%</td>
<td>0-22%</td>
</tr>
</tbody>
</table>

Select Ongoing Phase III Studies of PD-1/PD-L1 Inhibitors: I-O Monotherapy in 1L Advanced NSCLC

**Anti-PD-1**
- **Nivolumab**
  - CheckMate 227: Stage IV or recurrent NSCLC N=1980
- **Pembrolizumab**
  - KEYNOTE-024: PD-L1+ NSCLC N=535
  - KEYNOTE-042: PD-L1+ NSCLC N=300
- **Durvalumab**
  - MYSTIC: Advanced NSCLC N=4875
- **Atezolizumab**
  - IMpower 110: Stage IV non-squamous PD-L1+ NSCLC N=400
  - IMpower 111: Stage IV squamous PD-L1+ NSCLC N=400
- **Avelumab**
  - JAVELIN Lung 100: Stage IV or recurrent PD-L1+ NSCLC N=420

**Anti-PD-L1**
- **Pembrolizumab**
  - Keynote-024: Platinum-based chemotherapy
- **Atezolizumab**
  - IMpower 110/111: Gemcitabine + cisplatin or carboplatin

**Primary Endpoints**
- OS, PFS


**irAEs with Immunotherapy**

- **Skin**: Dermatitis exfoliative, Erythema multiforme, Stevens Johnson Syndrome, Toxic Epidermal Necrolysis, Vitiligo, Alopecia
- **Eye**: Uveitis, Iritis
- **Endocrine**: Hypothyroidism, Hyperthyroidism, Adrenal insufficiency, Hypophysitis
- **Pulmonary**: Pneumonitis, Interstitial lung disease, Acute interstitial pneumonitis
- **Neurologic**: Autoimmune neuropathy, Demyelinating Polyneuropathy, Guillain-Barré, Myasthenia Gravis like syndrome
- **Gastrointestinal (GI)**: Colitis, Enterocolitis, Necrotizing colitis, GI perforation
- **Renal**: Nephritis, autoimmune, Renal failure
- **Hepatic**: Hepatitis, autoimmune

*If not vigilant, may result in more serious immune-related adverse events.*

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.
Summary of PD-1/PD-L1 Blockade
Immune-Mediated Toxicities

Onset:
Average is 6-12 wks after initiation of therapy
Can occur within days of the first dose, after several mos of treatment, and after
discontinuation of therapy

Occasional (5% to 20%)
• Fatigue, headache, arthralgia, fevers, chills, lethargy
• Rash: maculopapular, pruritus, vitiligo
  – Topical treatments
• Diarrhea/colic
  – Initiate steroids early, taper slowly
• Hepatitis, liver/pancreatic enzyme abnormalities

• Infusion reactions
• Endocrinopathies: thyroid, adrenal, hypophysitis
  Rare (< 5%)
• Pneumonitis
  – Grade 3/4 toxicities uncommon
  – Low grade reversible with steroids and discontinuation
• Anemia


Toxicity Guidelines for
Immune Checkpoint Inhibitors

• TFTs, CBCs, LFTs and metabolic panels should be obtained at each
treatment and q6-12 wks for 6 mos posttreatment in all pts
receiving checkpoint protein antibodies
• ACTH, cortisol should also be checked in pts with fatigue and
nonspecific symptoms, plus testosterone in men
• Frequency of follow-up testing should be adjusted to individual
response and AEs that occur
• Corticosteroids can reverse nearly all toxicities associated with
these agents, but should be reserved for grade 3/4, or prolonged
grade 2, infusion-related AEs (IrAEs)


Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this
publication may be reproduced or transmitted in any other form or by any means, electronic or
mechanical, without first obtaining written permission from NCCN®.
Summary

- Anti-PD1 and PD-L1 antibodies have demonstrated promising results as second line therapy in patients with NSCLC
  - Nivolumab is FDA approved as second line therapy in squamous and nonsquamous NSCLC
  - Pembrolizumab is FDA approved as second line therapy in patients with NSCLC with tumors that are PD-L1 positive ≥ 50%
  - Atezolizumab phase II data show similar results
- PD-L1 expression predicts for response
  - But responses are seen in patients with PD-L1 negative tumors and not all patients with PD-L1 positive tumors are responding
- PD-1 and PD-L1 inhibitors are currently being evaluated as first line therapy for NSCLC, in combination with immunotherapy or chemotherapy; PD-1 and PD-L1 inhibitors are also being evaluated in small cell lung cancer
- Toxicity profile is different than chemotherapy and requires close evaluation

NCCN Member Institutions

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.