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

Supporters

• This activity is supported by educational grants from Ariad, AstraZeneca, Ethicon, Foundation Medicine, Genentech, Lilly, Novartis Pharmaceuticals Corporation, and Pfizer.
• This activity is supported by independent educational grants from Abbvie and Merck.

Q&A and Technical Support

• Please use the Q&A feature on the right-hand portion of your screen for any clinical questions and logistical concerns you have regarding the session. This is the only online method of communicating questions or concerns. Should you need additional assistance please e-mail education@nccn.org or call 215-690-0300 and ask to be connected with someone in the NCCN Conferences and Meetings Department.

• While NCCN is pleased to respond to as many questions as possible during this webinar, NCCN will not be able to respond to your individual questions of a clinical nature after the webinar has concluded. We are also not able to offer recommendations on patient care regarding specific cases.
Attendance Lists & Registration

• If you are participating with a group of peers, a list of everyone who attended in your group must be submitted within two weeks of the activity in order for the participants to be eligible to receive credit. This list is in addition to individual registration. Attendee lists will not be accepted after two weeks post-activity.

• Lists can be sent to education@nccn.org and should contain full contact information for each participant, including first and last name, credentials, mailing address, phone number, and e-mail address.

• If you have not individually registered, please register at: www.cvent.com/d/dfqty3.

Accreditation Information

Intended Audience
This educational program is designed to meet the educational needs of oncologists, nurses, pharmacists, and other health care professionals who manage patients with breast cancer.

Learning Objectives
Following this program, participants should be able to:
• Describe recent updates regarding the use of immunotherapy as subsequent therapy for patients with metastatic NSCLC.
• Implement the use of biomarkers to identify patients with metastatic NSCLC who may be candidates for immunotherapy.
• Identify the unique side effects that may occur with immunotherapy and describe how to manage the side effects in patients with non-small cell lung cancer.
### Accreditation Information

**Physicians**

National Comprehensive Cancer Network (NCCN) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

National Comprehensive Cancer Network designates this web-based activity for a maximum of 1.0 *AMA PRA Category 1 Credit™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

**Nurses**

National Comprehensive Cancer Network (NCCN) is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center’s (ANCC) Commission on Accreditation. NCCN designates this educational activity for a maximum of 1.0 contact hour. Accreditation as a provider refers to the recognition of educational activities only; accredited status does not imply endorsement by NCCN or ANCC of any commercial products discussed/displayed in conjunction with the educational activity.

Kristina M. Gregory, RN, MSN, OCN, is our lead nurse planner for this educational activity.

### Accreditation Information

**Pharmacists**

**Pharmacy Educational Objective:** After completing this activity, the participant should be able to:

- Provide accurate and appropriate counsel as part of the treatment team.

**Accreditation Statement**

National Comprehensive Cancer Network is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

**Type of Activity:** Knowledge

**UAN:** 0836-0000-16-073-L01-P

**Credit Designation:** National Comprehensive Cancer Network designates this continuing education activity for 1.0 contact hour (0.10 CEUs) of continuing education credit in states that recognize ACPE accredited providers.

Attention Pharmacists: ACPE and NABP have implemented CPE Monitor as a way to electronically track all ACPE-accredited CPE Units. In order to receive credit for this activity, please enter your six-digit NABP e-profile ID and birth date in the format of MMDD as part of the Overall Evaluation. If you have not already done so, please complete your e-profile at http://www.nabp.net to obtain your NABP e-Profile ID.

To comply with ACPE standards, pharmacists must complete all activity requirements within **30 days** of the live event date.
Accreditation Information

How to Claim Credit:

Within 5 business days after this educational program, you will receive an e-mail with information on how to claim credit for this activity. A statement of credit will be issued only upon completion of the activity evaluation form & immediate post-test within 30 days of the activity date. A certificate will be electronically generated immediately upon completion of the evaluation.

All credit claiming must be done online through NCCN’s continuing education portal at http://education.nccn.org/node/79130.

Should you not receive an e-mail within 5 days, please contact us at education@nccn.org.

Accreditation Information

- It is required by the ACCME that all educational activities are designed to change participant competence, performance, or patient outcomes.
- To meet this requirement, NCCN asks that all participants complete the outcomes measures described below:
  - The post-test and evaluation as indicated in e-mail you will receive within 3-5 business days of the conclusion of this activity. This is required to receive credits or your certificate of completion. You must be registered in advance to receive credits or certificate. Certificates will be generated automatically upon successful completion of this step.
    - There will be a separate WebEx evaluation at the conclusion of this program, which is optional and does not go to NCCN.
    - The follow-up post test (to be sent 30 days after the activity has ended to demonstrate an increase in participant competence)
- NCCN greatly appreciates your compliance with completing the aforementioned post-test and surveys. All of these measures will be available by logging into your account at http://education.nccn.org. Reminder e-mails will be sent to the participants via e-mail. If you have any questions or concerns, please e-mail education@nccn.org.
Disclosures

The ACCME/ANCC/ACPE defines “conflict of interest” as when an individual has an opportunity to affect CE content about products or services of a commercial interest with which he/she has a financial relationship.

ACCME, ACPE, and ANCC focuses on financial relationships with commercial interests in the 12-month period preceding the time that the individual is being asked to assume a role controlling content of the CE activity. ACCME, ACPE, and ANCC have not set a minimal dollar amount for relationships to be significant. Inherent in any amount is the incentive to maintain or increase the value of the relationship. The ACCME, ACPE, and ANCC defines “relevant financial relationships” as financial relationships in any amount occurring within the past 12 months that create a conflict of interest.

All faculty for this continuing education activity are competent in the subject matter and qualified by experience, training, and/or preparation to the tasks and methods of delivery.

Faculty Disclosures

Disclosure of Relevant Financial Relationships

All faculty and activity planners participating in NCCN continuing education activities are expected to disclose any relevant financial relationships with a commercial interest as defined by the ACCME’s, ANCC’s, and ACPE’s Standards for Commercial Support. All faculty presentations have been reviewed for adherence to the ACCME’s Criterion 7: The provider develops activities/educational interventions independent of commercial interests (SCS 1, 2, and 6) by experts on the topics. Full disclosure of faculty relationships will be made prior to the activity.

Faculty Disclosures

The faculty listed below have disclosed the following relevant financial relationships:

Leora Horn, MD, MSc
AstraZeneca Pharmaceuticals LP: Grant/Research Support
Bayer HealthCare: Scientific Advisor
Biodesix, Inc.: Product/Speakers Bureau
Boehringer Ingelheim GmbH: Scientific Advisor
Bristol-Myers Squibb Company: Scientific Advisor
Genentech, Inc.: Consulting Fees, Honoraria
Merck & Co., Inc.: Consulting Fees, Honoraria
Xcovery: Scientific Advisor
NCCN Staff Disclosures

NCCN Staff Disclosures
The activity planning staff listed below has no relevant financial relationships to disclose:

Ann Gianola, MA; Mark Geisler; Kristina M. Gregory, RN, MSN, OCN; Kristin Kline Hasson; Rose Joyce; Joan S. McClure, MS; Diane McPherson; Melanie Moletzsky; Deborah Moonan, RN, BSN; Lisa Perfidio; Liz Rieder; Shannon K. Ryan; Kathy Smith; Jennifer McCann Weckesser

The NCCN clinical information team listed below, who have reviewed content, has no relevant financial relationships to disclose:

Ellen Erkess; Kristina M. Gregory, RN, MSN, OCN; Miranda Hughes, PhD

Faculty Biography

Leora Horn, MD, MSc holds multiple positions at Vanderbilt University, including Associate Professor of Medicine in the Department of Hematology and Oncology, Clinical Director of the Thoracic Oncology Research Program, and Assistant Vice Chancellor for Faculty Development.

Dr. Horn received her medical degree from the University of Toronto, where she also completed her postgraduate training in internal medicine and medical oncology. She later completed a fellowship in thoracic oncology at Vanderbilt University, which was funded by an award from the Canadian Association of Medical Oncology.

Dr. Horn’s clinical practice focuses on the care of patients with lung cancer. Her research interests include experimental therapeutics and medical education. She is coauthor of numerous scientific journal articles, book chapters, and manuscripts in this disease state. She also serves as a reviewer for Clinical Lung Cancer, Journal of Clinical Oncology, the Journal of Thoracic Oncology, Annals of Oncology, and The Clinical Teacher.

Dr. Horn has received multiple honors and awards, most recently receiving the NCI Cancer Clinical Investigator Team Leadership Award. She is a member of multiple professional societies, including the American Society of Clinical Oncology, the International Association for the Study of Lung Cancer, and the Royal College of Physicians and Surgeons of Canada.

Dr. Horn is a member of the NCCN Non-Small Cell Lung Cancer/Malignant Pleural Mesothelioma/Thymomas and Thymic Carcinomas Panel. She also contributes to the NCCN Oncology Research Program as a member of the Nintedanib Scientific Review Committee and the Sorafenib Steering Committee.
Immunotherapy in Lung Cancer

Leora Horn, MD, MSc
Associate Professor of Medicine
Clinical Director of Thoracic Oncology Research Program
Vanderbilt Ingram Cancer Center
Nashville, TN

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

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.
Role of PD-1 in Suppressing Antitumor Immunity

[Diagram showing interactions between APC, T cell, MHC-Ag, B7.1, CD28, TCR, Signal 1, Activation (cytokines, lysis, prolif., migration), and Inhibition (anergy, exhaustion, death) with PD-1 and PD-L1 interactions.]


Potential Differences in PD-1 vs. PD-L1 Blockade


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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.

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 I</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\(^4\)


PD-L1 as a Predictive Marker: Response Based on PD-L1 Expression

**PD-L1 Is Broadly Expressed in NSCLC**

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

**Positive PD-L1 staining in NSCLC**

**Adenocarcinoma**

Prevalence of PD-L1 = 45%

**Squamous cell carcinoma**

Prevalence of PD-L1 = 50%

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

**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>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clones</td>
<td>22C3</td>
<td>28-8</td>
<td>SP263</td>
<td>SP142</td>
<td>?</td>
</tr>
<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>Compartment</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%</td>
<td>Strong(+) &gt;50%</td>
<td>PD-L1(+) &gt;1%</td>
<td>Strong(+) &gt;5%</td>
<td>TC / IC (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TC / IC 3(+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TC / IC 2(+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TC / IC 1(+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TC / IC 0(-)</td>
</tr>
</tbody>
</table>

Phase 2: CHECKMATE-063:
Overall Survival (OS) : All Treated Patients

<table>
<thead>
<tr>
<th></th>
<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></td>
<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></td>
<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>

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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>PD-L1 &lt;1%</td>
<td>8.3 (5.6, 15.6)</td>
<td>23/31</td>
</tr>
<tr>
<td>PD-L1 ≥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>

CheckMate 017 (NCT01642004)
- Stage IIIb/IV 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
- 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
- Primary Endpoint: OS
- Additional Endpoints:
  - ORR
  - PFS
  - 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

- **Nivolumab**
  - mOS = 9.2 months (95% CI: 7.33, 12.62)
  - # events = 103
  - 18-month OS rate = 24%
  - 12-month OS rate = 42%

- **Docetaxel**
  - mOS = 6.0 months (95% CI: 5.29, 7.39)
  - # events = 122
  - 18-month OS rate = 13%
  - 12-month OS rate = 28%

**HR** = 0.62 (0.48, 0.81); **P** = 0.0004

Minimum follow-up for survival: 18 months

Reckamp et al., WCLC 2015

Checkmate 057: Overall Survival

- **Nivolumab**
  - mOS = 12.2 months
  - 12-mo OS rate = 51%
  - 18-mo OS rate = 23%
  - No. of patients at risk (12-mo OS) = 292

- **Docetaxel**
  - mOS = 9.4 months
  - 12-mo OS rate = 39%
  - 18-mo OS rate = 39%
  - No. of patients at risk (12-mo OS) = 290

**HR** (95% CI) = 0.72 (0.59, 0.89); **P** = 0.0015

Minimum follow-up for 12-mo OS rate, 13.2 mos; for 18-mo OS rate, 17.1 mos

Horn et al. ESMO
Nivolumab 2 year OS

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

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>Squamous</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR,a % (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>Nonsquamous</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR,a % (n/N)</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

1% PD-L1 Expression level

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 ≥1%</td>
<td>9.3</td>
<td>7.2</td>
</tr>
<tr>
<td>PD-L1 &lt;1%</td>
<td>8.7</td>
<td>5.9</td>
</tr>
</tbody>
</table>

5% PD-L1 Expression level

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 ≥5%</td>
<td>10</td>
<td>6.4</td>
</tr>
<tr>
<td>PD-L1 &lt;5%</td>
<td>8.5</td>
<td>6.1</td>
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</table>

10% PD-L1 Expression level

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 ≥10%</td>
<td>11</td>
<td>7.1</td>
</tr>
<tr>
<td>PD-L1 &lt;10%</td>
<td>8.2</td>
<td>6.1</td>
</tr>
</tbody>
</table>

OS by PD-L1 Expression: Nonsquamous

≥1% PD-L1 expression level

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI) = 0.59 (0.43, 0.82)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<1% PD-L1 expression level

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI) = 0.30 (0.21, 0.48)</td>
<td></td>
<td></td>
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</tbody>
</table>

≥5% PD-L1 expression level

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI) = 0.63 (0.43, 0.89)</td>
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<td></td>
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</tbody>
</table>

<5% PD-L1 expression level

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Docetaxel</th>
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<tbody>
<tr>
<td>HR (95% CI) = 0.43 (0.26, 0.63)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

≥10% PD-L1 expression level

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI) = 0.40 (0.26, 0.59)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<10% PD-L1 expression level

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI) = 1.01 (0.77, 1.34)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Symptoms represent censored observations.

Spigel D et al., ASCO 2015.

Paz-Ares L et al., ASCO 2015.
2-Year OS Rates\textsuperscript{a} Overall and by PD-L1 Expression Level in CheckMate 057 (Non-SQ NSCLC)

\begin{figure}
\centering
\includegraphics[width=\textwidth]{2-year-os-rates.png}
\caption{2-Year OS Rates\textsuperscript{a} Overall and by PD-L1 Expression Level in CheckMate 057 (Non-SQ NSCLC)}
\end{figure}

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

\textsuperscript{a}Kaplan–Meier estimates, with error bars indicating 95% CIs.

\textsuperscript{b}For the comparison of the full Kaplan–Meier survival curves for each treatment group.

Updated Treatment and Safety Summary: Squamous

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
 & Nivolumab n=131 & & Docetaxel n=129 & \\
 & Any grade & Grade 3–5\textsuperscript{a} & Any grade & Grade 3–5 \hline
Treatment-related AEs, % & 59 & 8 & 87 & 58 \hline
Treatment-related AEs leading to discontinuation, % & 5\textsuperscript{b} & 3 & 10\textsuperscript{c} & 7 \hline
Treatment-related deaths, % & 0 & & 2\textsuperscript{d} & \\
\hline
\end{tabular}
\caption{Updated Treatment and Safety Summary: Squamous}
\end{table}

\textbullet{} Median number of doses was 8 (range, 1–56) for nivolumab and 3 (range, 1–29) for docetaxel.

Based on June 2015 DDL. Includes events reported between first dose and 30 days after last dose of study therapy. No grade 3 events were reported with nivolumab. 1% of pts had increased ALT, increased AST, increased lipase, myasthenic syndrome, chest pain, or rash, and 2% of pts had pneumonitis, peripheral neuropathy (2%), and fatigue (2%) were the most frequently reported events (\geq{}2% patients) leading to discontinuation. Transient lung disease, pulmonary hemorrhage, and sepsis (1 pt each).

\textsuperscript{a}Includes any grade 5 events.

\textsuperscript{b}1% of pts had increased ALT, increased AST, increased lipase, myasthenic syndrome, chest pain, or rash.

\textsuperscript{c}Peripheral neuropathy (3%) and fatigue (2%) were the most frequently reported events (\geq{}2% patients).

\textsuperscript{d}Interstitial lung disease, pulmonary hemorrhage, and sepsis (1 pt each).

Reckamp et al., WCLC 2015

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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, 2014d

randomized
(N = 144)
- PD-L1+ tumors
- ≥1 previous therapy
Pembro
10 mg/kg Q3W
Pembro
10 mg/kg Q2W
Nonrandomized
(N = 33)
- PD-L1+ tumors
- ≥2 previous therapies
Pembro
10 mg/kg Q3W
Nonrandomized
(N = 40)
- PD-L1+ tumors
- ≥2 previous therapies
Pembro
10 mg/kg Q2W
Nonrandomized
(N = 4)
- PD-L1+ tumors
- ≥3 previous therapy
Pembro
10 mg/kg Q2W
Nonrandomized
(N = 45)
- PD-L1+ tumors
- Treatment naive
Pembro
2 mg/kg Q3W
Nonrandomized
(N = 45)
- PD-L1+ tumors
- ≥1 previous therapy
Pembro
10 mg/kg Q2W
Nonrandomized
(N = 40)
- PD-L1+ tumors
- ≥3 previous therapy
Pembro
2 mg/kg Q3W

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>n/N (%)</td>
<td>Median, months (95% CI)</td>
<td>n/N (%)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>16/28</td>
<td>14.0 (9.0-NR)</td>
<td>33/54</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>65/108</td>
<td>15.4 (9.9-18.9)</td>
<td>164/248</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current or former</td>
<td>59/108</td>
<td>15.7 (11.1-NR)</td>
<td>136/221</td>
</tr>
<tr>
<td>Never</td>
<td>23/30</td>
<td>8.2 (4.9-17.3)</td>
<td>63/95</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>17/10</td>
<td>8.5 (2.0-13.7)</td>
<td>37/45</td>
</tr>
</tbody>
</table>

**KEYNOTE-010 Study Design**

**Patients**
- Advanced NSCLC
- Confirmed PD after ≥1 line of chemotherapy\(^a\)
- 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\(^b\) (TPS ≥50% vs 1%-49%)

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

---

**ORR (RECIST v1.1, Central Review)**

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

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

\(^a\)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.

\(^b\)Added after 441 patients enrolled based on results from KEYNOTE-001 (Garon EB et al. *N Engl J Med*. 2015;372:2018-28).

\(^d\)Patients received the maximum number of cycles permitted by the local regulatory authority.

---

ClinicalTrials.gov, NCT01905657.

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

#### Table: Progression-Free Survival

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median (95% CI), mo</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro 2 mg/kg</td>
<td>3.9 (3.1, 4.1)</td>
<td>0.88 (0.74, 1.05)</td>
<td>0.07</td>
</tr>
<tr>
<td>Pembro 10 mg/kg</td>
<td>4.0 (2.7, 4.3)</td>
<td>0.79 (0.66, 0.94)</td>
<td>0.004</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>4.0 (3.1, 4.2)</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; PD-L1 = programmed death ligand 1; Pembro = pembrolizumab; PFS = progression-free survival; TPS = tumor proportion score.

---

### Overall Survival at TPS ≥1% and TPS ≥50%

#### Table: Overall Survival

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median (95% CI), mo</th>
<th>OS (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro 2 mg/kg</td>
<td>8.5 (7.5, 9.8)</td>
<td>34.6%</td>
<td>– –</td>
</tr>
<tr>
<td>Pembro 10 mg/kg</td>
<td>10.4 (9.4, 11.9)</td>
<td>43.2%</td>
<td>0.71 (0.58, 0.88)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>8.2 (6.4, 10.7)</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; PD-L1 = programmed death ligand 1; Pembro = pembrolizumab; OS = overall survival; 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</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>53</td>
<td>0.79 (0.61-1.04)</td>
</tr>
<tr>
<td>Pembrolizumab 10 mg/kg</td>
<td>10.8 (9.9-13.3)</td>
<td>58</td>
<td>0.71 (0.53-0.94)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>8.8 (7.8-9.8)</td>
<td>47</td>
<td></td>
</tr>
</tbody>
</table>

Decreased appetite
Fatigue
Nausea
Rash
Diarrhea
Asthenia
Stomatitis
Anemia
Alopecia
Neutropenia

Pembrolizumab 2 mg/kg
Grade 1-2
Grade ≥3

Pembrolizumab 10 mg/kg
Docetaxel

Analysis cut-off date: September 30, 2015.
Garon et al, ASCO 2016

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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)²
• Histology (squamous vs non-squamous)
• Prior chemotherapy regimen (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

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>n MEDIAN OS, Mos</td>
<td>n MEDIAN OS, Mos</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT</td>
<td>144 12.6</td>
<td>143 9.7</td>
<td>0.69 (0.52-0.92)</td>
<td>.011</td>
</tr>
<tr>
<td>TC3 or IC3</td>
<td>24 Not reached</td>
<td>23 11.1</td>
<td>0.45 (0.22-0.95)</td>
<td>.033</td>
</tr>
<tr>
<td>TC2/3 or IC2/3</td>
<td>50 15.1</td>
<td>55 7.4</td>
<td>0.50 (0.31-0.80)</td>
<td>.003</td>
</tr>
<tr>
<td>TC1/2/3 or IC1/2/3</td>
<td>93 15.1</td>
<td>102 9.2</td>
<td>0.59 (0.41-0.83)</td>
<td>.003</td>
</tr>
<tr>
<td>TC0 and IC0</td>
<td>51 9.7</td>
<td>41 9.7</td>
<td>0.88 (0.55-1.42)</td>
<td>.601</td>
</tr>
<tr>
<td>Squamous</td>
<td>49 10.1</td>
<td>48 8.6</td>
<td>0.66 (0.41-1.05)</td>
<td>.075</td>
</tr>
<tr>
<td>Nonsquamous</td>
<td>95 14.8</td>
<td>95 10.9</td>
<td>0.69 (0.49-0.98)</td>
<td>.039</td>
</tr>
</tbody>
</table>

Dry skin, stomatitis and nail disorder were additional AEs with ≥ 5% higher frequency in docetaxel.

Safety population includes patients who received any amount of either study treatment.

Data cut-off Jan 30, 2015.

POPLAR: All-cause AEs

- 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%)

For atezolizumab, other immune-mediated AEs (any grade) included:
- Asthenia (21%)
- Hypothyroidism (12%)
- Increased transaminases (9%)
- Hypothyroidism (13%)
- Hypothyroidism (5%)

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

- 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

Stage IIIB/IV NSCLC (any histology), no prior chemotherapy for advanced disease, ECOG PS 0 or 1

Previous cohorts:
- Nivo 1 Q2W + Ipi 1 Q6W
- Nivo 3 Q2W + Ipi 1 Q6W
- Nivo 3 Q2W until disease progression

Nivo 3 Q2W until disease progression or unacceptable toxicity

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

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

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Confirmed ORR, % (95% CI)</th>
<th>Median duration of response, mo (95% CI)</th>
<th>Median length of follow-up, mo (range)</th>
<th>Best overall response, %</th>
<th>Median PFS, mo (95% CI)</th>
<th>1-year OS rate, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivo 3 Q2W + Ipi 1 Q12W</td>
<td>47 (31, 64)</td>
<td>NR (11.3, NR)</td>
<td>12.9 (0.9–18.0)</td>
<td>0</td>
<td>8.1 (5.6, 13.6)</td>
<td>NC</td>
</tr>
<tr>
<td>(n = 38)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivo 3 Q2W + Ipi 1 Q6W</td>
<td>39 (23, 55)</td>
<td>NR (8.4, NR)</td>
<td>11.8 (1.1–18.2)</td>
<td>0</td>
<td>3.9 (2.6, 13.2)</td>
<td>69 (52, 81)</td>
</tr>
<tr>
<td>(n = 39)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivo 3 Q2W (n = 52)</td>
<td>23 (13, 37)</td>
<td>NR (5.7, NR)</td>
<td>14.3 (0.2–30.1)</td>
<td>0</td>
<td>3.6 (2.3, 6.6)</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><strong>ORR, % (n/N)</strong></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><strong>Median PFS (95% CI), mo</strong></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><strong>1-year OS rate (95% CI), %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1% PD-L1</td>
<td>NC</td>
<td>NC</td>
<td>79 (47, 93)</td>
</tr>
<tr>
<td>≥1% PD-L1</td>
<td>90 (66, 97)</td>
<td>83 (60, 93)</td>
<td>69 (50, 82)</td>
</tr>
<tr>
<td>≥50% PD-L1</td>
<td>NC</td>
<td>100 (100, 100)</td>
<td>83 (48, 96)</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><strong>Treatment-related AEs, %</strong></td>
<td>82</td>
<td>72</td>
<td>71</td>
</tr>
<tr>
<td>Any grade</td>
<td>37</td>
<td>33</td>
<td>19</td>
</tr>
<tr>
<td>Grade 3–4</td>
<td>72</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td><strong>Treatment-related AEs leading to discontinuation, %</strong></td>
<td>11</td>
<td>10</td>
<td>10</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 Immune Checkpoint Blockade

<table>
<thead>
<tr>
<th>Nivolumab + Ipilimumab</th>
<th>MEDI4736 + TREME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td></td>
</tr>
<tr>
<td>SCLC</td>
<td></td>
</tr>
<tr>
<td>NSCLC</td>
<td></td>
</tr>
<tr>
<td><strong>ORR, %</strong></td>
<td>57.6% 29-39% 32% 31-39% 23%</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td>11.5 months 8 months</td>
</tr>
<tr>
<td><strong>Cut Off</strong></td>
<td>5% 1% 25%</td>
</tr>
<tr>
<td><strong>ORR in PD-L1 +</strong></td>
<td>72.1% 48% 22%</td>
</tr>
<tr>
<td><strong>ORR in PD-L1 -</strong></td>
<td>57.5% 0-22% 29%</td>
</tr>
</tbody>
</table>


### Select Ongoing Phase III Studies of PD-1/PD-L1 Inhibitors:

#### I-O Monotherapy in 1L Advanced NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary Endpoints</th>
<th>Treatment Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>CheckMate 227</td>
<td></td>
<td>Nivolumab</td>
</tr>
<tr>
<td>CheckMate 026</td>
<td>PFS</td>
<td>Nivolumab + ipilimumab</td>
</tr>
<tr>
<td>Pembrolizumab KEYNOTE-024</td>
<td>PFS</td>
<td>Pembrolizumab</td>
</tr>
<tr>
<td>KEYNOTE-042</td>
<td>OS</td>
<td>Pembrolizumab + platinum-based chemotherapy</td>
</tr>
<tr>
<td>MYSTIC</td>
<td></td>
<td>Durvalumab</td>
</tr>
<tr>
<td>MYSTIC</td>
<td>OS, PFS</td>
<td>Durvalumab + tremelimumab</td>
</tr>
<tr>
<td>IMpower 110</td>
<td>PFS</td>
<td>Atezolizumab</td>
</tr>
<tr>
<td>IMpower 111</td>
<td>PFS</td>
<td>Atezolizumab</td>
</tr>
<tr>
<td>JAVELIN Lung 100</td>
<td>PFS</td>
<td>Avelumab</td>
</tr>
</tbody>
</table>

irAEs with Immunotherapy

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

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/colitis
  - 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)


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
Q&A SESSION

Please use the Q&A feature on the right-hand portion of your screen to submit clinical questions to the speakers.

• An e-mail will be sent within 5-7 business days with instructions on how to login to complete post-test and evaluation. These must be completed in order to receive a CE certificate. Contact education@nccn.org should you not receive this e-mail within 5 business days.

• If you participated with a group of peers, a list of everyone who attended in your group must be submitted to education@nccn.org within the next two weeks.

• If you have not individually registered, please register at: http://www.cvent.com/d/dfqty3.

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UPCOMING WEBINARS

• Sequencing Targeted Therapy for Patients with Metastatic Non-Small Cell Lung Cancer
  Wednesday, July 20 at 2:00 PM [EDT]
  David S. Ettinger, MD
  The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

• Minimizing Risk from Lung Cancer Screening
  Friday, July 22 at 2:00 PM [EDT]
  Douglas E. Wood, MD
  Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

• Treatment of Older Adult Patients with Non-Small Cell Lung Cancer
  Tuesday, July 26 at 1:30 PM [EDT]
  Neelesh Sharma, MD, PhD, Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Register at NCCN.org/events

Thank you for your participation in today’s program!