Immunotherapy of Lung Cancer

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Disclosures

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Non-Small Cell Lung Cancer Demographics

- Lung cancer is the leading cause of cancer mortality in the United States
- Accounts for more deaths than breast, prostate and colorectal cancer combined
- Histologically and molecularly a very heterogeneous disease
- Unfavorable stage distribution at the time of diagnosis - most cases > 70% of NSCLC are diagnosed at an advanced stage
- Smoking remains the major risk factor but 10-15% of lung cancer diagnoses are in never-smokers
- Historically shrouded by therapeutic nihilism
Current Therapeutic Landscape for NSCLC

- Current treatment strategies in NSCLC
  - Various chemotherapy regimens based on histologic diagnosis
  - Targeted therapy options available for specific molecular mutations
    - Anti-EGFR–targeted therapy for patients with EGFR mutations
    - ALK inhibitors for patients with ALK translocations
- Even with various personalized approaches, the 5-yr survival rate for patients with NSCLC (all stages) is only 17%
- NSCLC is ideal for assessment of novel immunotherapy approaches
Evolution of NSCLC subtyping from histologic to molecular based

Li T et al. JCO 2013;31:1039-1049
Treatment Algorithm for Advanced-Stage NSCLC (2016)

**Proposed Treatment Algorithm**

- **Molecular**
  - Good PS
  - Clinical (PS)
  - Poor PS

- **Histologic**
  - Nonsquamous
  - Squamous

**EGFR mutation positive**
- or ALK, ROS1 positive

**Erlotinib/afatinib/ gefitinib or crizotinib**

**Bevacizumab eligible**
- Platinum/pemetrexed (or other*) ± bevacizumab

**Bevacizumab ineligible**
- Platinum/pemetrexed (or other*)

**End of First-line Chemotherapy**

**First-line**

**Progression**
- If T790M: Osimertinib; ALK+ Ceritinib, Alectinib
- Chemotherapy by algorithm or Nivolumab or Pembrolizumab (PDL-1+)

**Second-line**

- Nivolumab or Pembrolizumab (PDL-1+)
- Nivolumab or Pembrolizumab (PDL-1+)
- Nivolumab or Pembrolizumab (PDL-1+)

**Based on prior therapy**

*With docetaxel, paclitaxel, gemcitabine, vinorelbine, or nab-paclitaxel for SCCA.*
Response Patterns for Immunotherapy Compared With Targeted Therapy

Harnessing the Immune System to Treat Lung Cancer

- Historically, immunotherapy has had minimal success in lung cancer
- The limited success is felt to be attributed to:
  - the belief that lung cancer is not immunogenic
  - the ability of lung cancer to evade immune system: the secretion of immunosuppressive cytokines, loss of major histocompatibility complex antigen expression
  - patients with advanced lung cancer are immune suppressed
    a) documented decrease in peripheral and tumor lymphocyte count
    b) higher levels of regulatory T cells (a subset of lymphocytes known to play a key role in suppressing tumor immune surveillance); Tregs also suppress cytotoxic T lymphocytes that are responsible for killing tumor cells, tumor immune surveillance and immune memory
Cancer Immunoediting: Integrating Immunity's Roles in Cancer Suppression and Promotion

• The immune system plays dual role in cancer:
  a) suppresses growth by destroying cancer cells or inhibits their outgrowth
  b) promotes tumor progression either by selecting for tumor cells that are more fit to survive in an immunocompetent host or by establishing conditions within the tumor microenvironment that facilitate tumor outgrowth

• “Cancer immunoediting” – integrates the immune system’s dual host-protective and tumor-promoting roles
The cancer immunoediting concept

R D Schreiber et al. Science 2011;331:1565-1570
Immunotherapy in lung cancer: Do we finally have a success story?
Immune Checkpoint Inhibitors
Tumor immunology and the PD-L1/PD-1 pathway.

Like CTLA-4 (cytotoxic T-lymphocyte associated antigen-4), the target of the recently approved immunotherapy drug for melanoma, PD-1 and PD-L1 are part of an important molecular pathway that serve primarily to keep immune responses in check. Inhibiting the activity of these molecules can unleash the immune system to attack tumor cells. 

**MHC** – Major histocompatibility complex; **TCR** – T-cell receptor

Image courtesy of the *New England Journal of Medicine* ©2012
CTLA-4 and PD-1/PD-L1 Checkpoint Blockade for Cancer Treatment

- Immune checkpoint blockade includes agents targeting the negative regulators CTLA-4 and PD-1
- CTLA-4 attenuates the early activation of naive and memory T cells in the lymph nodes
  - Agents targeting CTLA-4 include ipilimumab and tremelimumab
- In contrast, PD-1 modulates the effector phase of T cell activity in peripheral tissues via interaction with PD-L1 and PD-L2
  - Agents targeting PD-1 include nivolumab and pembrolizumab
  - Agents targeting PD-L1 include atezolizumab and durvalumab
Phase III Trial: Nivolumab vs. Docetaxel in Squamous-Cell NSCLC (CheckMate 017)

- Primary endpoints: **ORR, OS**
- Secondary endpoints: PFS, ORR, and OS in PD-L1-positive vs. PD-L1-negative subgroups, duration of OR, time to OR, proportion of patients exhibiting disease-related symptom progression as per Lung Cancer Symptom Scale

Stage IIIB/IV or recurrent squamous-cell NSCLC following RT or resection, previous Pt-containing chemotherapy ECOG PS ≤ 1 (N = 272)

- Stratified by previous paclitaxel therapy (yes vs. no) and region

  - **Docetaxel 75 mg/m² IV q3w** (N=135)
  - **Nivolumab 3 mg/kg IV q2w** (N=137)

  Treat until progression or unacceptable toxicity or withdrawal of consent

Efficacy of Nivolumab versus Docetaxel in Patients with Advanced Squamous-Cell Non-Small-Cell Lung Cancer.

- Nivolumab monotherapy as compared with docetaxel, was associated with 41% lower risk of death, a 3.2-month longer median survival, and nearly twice the 1-year survival rate
- Median OS 9.2 vs. 6.0 nivolumab and docetaxel respectively

CheckMate 057: Nivolumab vs. Docetaxel in Previously Treated Nonsquamous NSCLC

Stratified by previous maintenance therapy (yes vs. no) and line of therapy (second vs. third line)

Pts with stage IIIB/IV nonsquamous NSCLC and ECOG PS 0-1 who failed 1 prior platinum doublet chemotherapy ± TKI therapy (N = 582)

Nivolumab 3 mg/kg IV q2w (n = 292)

Docetaxel 75 mg/m² IV q3w (n = 290)

Until disease progression or unacceptable toxicity

- Primary endpoint: OS
- Secondary endpoints: ORR, PFS, efficacy by PD-L1 expression, safety, QoL

Overall Survival, Duration of Response, and Progression-free Survival. CheckMate057

Nivolumab significantly improved efficacy vs. docetaxel in previously treated pts with advanced nonsquamous NSCLC:
- 27% reduction in risk of death (HR: 0.73; P = .0015); OS 12.2 vs. 9.4 months.
- ORR 19% (nivolumab) vs. 12% (docetaxel).
- No improvement in PFS (2.3 vs. 4.2 months).

PD-L1 expression predicted benefit from nivolumab:
- OS, PFS, and ORR significantly greater with higher baseline PD-L1 expression at all thresholds (≥ 1%, ≥ 5%, ≥ 10%).

All-grade and grade 3/4 toxicity reduced in nivolumab arm;

KEYNOTE-010: Pembrolizumab vs. Docetaxel in Previously Treated PD-L1+ NSCLC

Stratified by ECOG PS (0 vs. 1), region (east Asia vs. not), PD-L1 TPS (≥ 50% vs. 1% to 49%)

Pts with advanced NSCLC PD after ≥ 2 cycles of platinum-doublet chemotherapy, PD-L1 TPS ≥ 1%, ECOG PS 0-1, no brain metastases (N = 1034)

- Pembrolizumab 2 mg/kg Q3W for 24 m (n = 345)
- Pembrolizumab 10 mg/kg Q3W for 24 m (n = 346)
- Docetaxel 75 mg/m² Q3W per local guidelines (n = 343)

• Primary endpoints*: PFS, OS
• Secondary endpoints: ORR, DoR, safety

*In both the PD-L1 TPS ≥ 1% and ≥ 50% populations.

KEYNOTE-010: Overall Survival

- All pts experienced OS benefit from pembrolizumab

**PD-L1 TPS ≥ 1%**

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median OS, Mos (95% CI)</th>
<th>1-Yr OS, %</th>
<th>HR vs Docetaxel (95% CI); 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); .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); &lt; .0001</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>8.5 (7.5-9.8)</td>
<td>34.6</td>
<td>–</td>
</tr>
</tbody>
</table>

HR, 2 vs 10 mg/kg: 1.17 (95% CI: 0.94-1.45)

**PD-L1 TPS ≥ 50%**

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median OS, Mos (95% CI)</th>
<th>HR vs Docetaxel (95% CI); P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro 2 mg/kg</td>
<td>14.9 (10.4-NR)</td>
<td>0.54 (0.38-0.77); .0002</td>
</tr>
<tr>
<td>Pembro 10 mg/kg</td>
<td>17.3 (11.8-NR)</td>
<td>0.50 (0.36-0.70); &lt; .0001</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>8.2 (6.4-10.7)</td>
<td>–</td>
</tr>
</tbody>
</table>

HR, 2 vs 10 mg/kg: 1.12 (95% CI: 0.77-1.62)

OAK: Phase III Atezolizumab vs. Docetaxel

- Locally advance/metastatic NSCLC
- Tumor specimen available (FFPE)
- 1-2 Prior lines of chemotherapy including 1 line of platinum chemotherapy
- Any PD-L1 expression status is permitted
- ECOG PS 0-1
  (n=1,225)

Endpoints

1. OS ITT in Primary Population (PP, i.e. the first 850 patients enrolled)
   - OS TC1/2/3 or IC1/2/3 in PP

2. ORR, PFS and DoR (RECIST v 1.1)
   - Safety, tolerability

PD-L1 expression was centrally evaluated on TCs and ICs with the VENTANA SP142 IHC assay
OAK Trial - Results

- Atezolizumab arm demonstrated a statistically significant and clinically relevant improvement in OS – 13.6 m vs. 9.6 m \( (p=0.0003) \) as compared to docetaxel.

- Survival was improved regardless of PDL-1 expression, but more pronounced in TC3 or IC3 patients.

- OS benefit was similar in patients with squamous or nonsquamous histology.
# OAK: Duration of Response (DoR)

<table>
<thead>
<tr>
<th></th>
<th>Atezolizumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ITT Population</strong></td>
<td>(n=58)</td>
<td>(n=57)</td>
</tr>
<tr>
<td>Median DoR, months</td>
<td>16.3</td>
<td>6.2</td>
</tr>
<tr>
<td>Ongoing responses, %</td>
<td>52</td>
<td>18</td>
</tr>
<tr>
<td><strong>TC 1/2/3 or IC 1/2/3 subgroup</strong></td>
<td>(n=43)</td>
<td>(n=36)</td>
</tr>
<tr>
<td>Median DoR, months</td>
<td>16.0</td>
<td>6.2</td>
</tr>
<tr>
<td>Ongoing response, %</td>
<td>47</td>
<td>11</td>
</tr>
<tr>
<td><strong>TC0 and IC0 subgroup</strong></td>
<td>(n=14)</td>
<td>(n=21)</td>
</tr>
<tr>
<td>Median DoR, months</td>
<td>NE</td>
<td>6.2</td>
</tr>
<tr>
<td>Ongoing response, %</td>
<td>71</td>
<td>29</td>
</tr>
</tbody>
</table>
KEYNOTE-024 Pembrolizumab vs. Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer

- Stage IIIB/IV NSCLC (EGFR, ALK-)
- Squamous or Nonsquamous
- No prior treatment
- ECOG PS 0-1
- PDL-1 TPS ≥50% BY IHC

R

pembrolizumab 200mg i.v. q3w (max 35 cycles)

Paclitaxel or pemetrexed or gemcitabine + carboplatin or cisplatin (4-6 cycles)

Optional maintenance pemetrexed

Crossover to pembrolizumab permitted

Endpoints

1. PFS
2. OS, OOR, PFS in patients with any PDL-1 status

KEYNOTE-024 Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer - PFS and OS

CheckMate 026 Nivolumab vs. Chemotherapy for Non-Small-Cell Lung Cancer

- Stage IIIB/IV NSCLC (EGFR, ALK-)
- SQUAMOUS OR NONSQUAMOUS
- No prior treatment
- ECOG PS 0-1
- PDL-1 TS ≥1% BY IHC

Nivolumab 3 mg/kg, IV, q 2 weeks

Paclitaxel or pemetrexed gemcitabine, or pemetrexed or paclitaxel with cisplatin or carboplatin

Optional maintenance pemetrexed

Crossover to nivolumab permitted

Endpoints 1) PFS in patients PDL-1 TS ≥5% and PFS in ITT populations PDL-1 TS ≥1% by IHC
2) OS, ORR, PFS

ESMO 2016
## CheckMate 026 Nivolumab vs. Chemotherapy for Non-Small-Cell Lung Cancer Results

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (&gt;5% PD-L1)</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>4.2 months</td>
<td>5.9 months</td>
</tr>
<tr>
<td>OOS</td>
<td>14.4 months</td>
<td>13.2 months</td>
</tr>
<tr>
<td>Any grade AE</td>
<td>71%</td>
<td>92%</td>
</tr>
<tr>
<td>Grade ¾ AE</td>
<td>18%</td>
<td>51%</td>
</tr>
</tbody>
</table>

ESMO 2016
Why CheckMate 026 and KEYNOTE 024 different outcomes: Potential explanations

- Different PD-L1 cut-point: 5% vs. 50%
- Assay robustness
- Patient selection
- Unbalance between treatment arms
- Study drugs
- Cross-over rate
- Other
Examples of PD-L1 NSCLC Sample
Immunohistochemical Staining*

<table>
<thead>
<tr>
<th>Staining Intensity</th>
<th>PD-L1 Positivity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0+</td>
<td>0</td>
</tr>
<tr>
<td>1+</td>
<td>2</td>
</tr>
<tr>
<td>2+</td>
<td>100</td>
</tr>
<tr>
<td>3+</td>
<td>100</td>
</tr>
</tbody>
</table>

*PD-L1 Negative

*PD-L1 Positive

*Clinical trial assay.

Issues with PD-L1 as a Biomarker

- PD-L1 negativity an unreliable biomarker
  - Assays are technically difficult, imperfect; results may differ depending on the antibody/assay (tumor vs. immune cells)
  - 5% expression, tumor heterogeneity, and inducible gene = sampling error (false negative)
  - Archived tissue different than recent biopsy
- May be more useful in determining which tumors rather than which patients to treat
- PD-L1 expression may be less relevant for combination therapies
- PD-L1 expression might be constitutive (no immune infiltrate)
Expected Effect of the Combinatorial Strategy of Immune-Checkpoint Blockade with Conventional Therapies

First-line immunotherapy plus chemo combination: pembrolizumab plus chemo (KEYNOTE-021, cohort C)

- Stage IIIB/IV NSCLC
- No systemic therapy for recurrent disease
- ECOG PS 0-1
  (n=308 across all cohorts)

Endpoints

1. ORR
2. OS, PFS and DoR

Cohorts A-C are pembrolizumab + platinum doublet chemotherapy: Cohorts D and H are pembrolizumab + ipilimumab; Cohorts E and F are pembrolizumab + EGFR TKI
Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomized, phase 2 cohort of the open-label KEYNOTE-021 study

Best percentage change from baseline in tumor size in the pembrolizumab plus chemotherapy group (n=56; A) and the chemotherapy alone group (n=55B)

Corey J Langer et al. The Lancet Oncology – published on line October 9th, 2016
Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomized, phase 2 cohort of the open-label KEYNOTE-021 study

Kaplan-Meier estimates of progression-free survival (A) and overall survival (B) Progression-free survival assessed per Response Evaluation Criteria In Solid Tumors version 1.1 by masked, independent central radiology review in the intention-to-treat population

Corey J Langer et al. The Lancet Oncology – published on line October 9th, 2016
Immune-Related AEs 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

**Hepatic**
- Hepatitis, autoimmune

**Renal**
- Nephritis, autoimmune
- Renal failure

*If not vigilant, may result in more serious immune-related AEs*
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 months 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

Management of Immune-Related AEs

- All healthcare team members should be educated about potential AEs
- Rapid and timely diagnostic and therapeutic intervention is imperative for optimal control of irAEs
  - Persistent grade 2 irAEs and grade 3/4 irAEs are treated with steroids
  - Early discontinuation of steroids may predispose to relapse
- Reinitiation of treatment may be possible with optimal management
- Approximately 5% of pts experience evidence of enlarging tumor lesions prior to a response
  - Pseudoprogression can be managed by continuing treatment and monitoring closely

Optimal management is attainable through continued communication between all members of the healthcare team and individual pts
Checkpoint Inhibition: Managing Grade 3/4 Treatment-Related AEs

Grade 3/4 pneumonitis, nephritis, enterocolitis, hepatitis, or infusion-related reaction
New or worsening neuropathy
Any life-threatening or grade 4 AE
Any severe or grade 3 recurrent AE

If no improvement in colitis or pneumonitis, infliximab or mycophenolate†

Hepatitis associated with
- AST/ALT > 5 x ULN
- AST/ALT ≥ 50% ↑ from baseline lasting ≥ 1 wk*
- Total bilirubin > 3 x ULN

Permanently discontinue PD-1 treatment

If no improvement in hepatitis, consider mycophenolate; infliximab contraindicated

Grade 4 elevation of pancreatic enzymes

Usually resolves with treatment interruption‡

*In pts with liver metastasis who begin treatment with grade 2 elevation of AST/ALT.
†Pts receiving ipilimumab may tolerate treatment with PD-1/PD-L1 inhibitor alone.
‡Steroids do not appear to accelerate the rate of improvement.

Pembrolizumab adverse reaction management guide.
Nivolumab adverse reaction management guide.
Ipilimumab adverse reaction management guide.
Conclusions

- Available data support the use of high PD-L1 expression as a biomarker for benefit with first-line anti-PD1 monotherapy - a new standard of care in this subgroup of patients
- Anti-PD1/PDL1 therapy is the new standard of care in patients with previously treated NSCLC
  - A significant overall survival benefit can be achieved with PD1/PD-L1 inhibitors vs. docetaxel
  - Clinical data demonstrate that durable responses can be achieved in previously treated patients
- In most studies, patients with higher levels of PD-L1 expression show increased benefit from treatment with PD1/PD-L1 inhibitors, but patients with low or no PD-L1 expression may also derive a benefit
Conclusions

• Anti-PD1/PDL1 therapy chemotherapy appears promising
• Combinations of checkpoint inhibitors are also under investigation
  • Toxicity profiles are still being defined
• There are currently nine phase III studies ongoing
• These studies should help to define the role immunotherapy in this setting within the next five years
Thank you.