Developmental Therapeutics in Lung Cancer

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April 20, 2018
Gleecher Center, University of Chicago
Disclosure Information

23rd Annual Developmental Therapeutics Symposium

Jyoti D. Patel, MD

• I have the following financial relationships to disclose:
  Consultant for: AbbVie, Astra Zeneca, Roche, Takeda, BMS
  Grant/Research support from: BMS
Learning Objectives

• To understand the role of molecular diagnostics and biomarker testing in advanced lung cancer

• To describe the effects of targeting particular oncogenes on clinical outcome in lung cancer

• To understand the role of immunotherapy in the treatment of advanced lung cancer

• To understand current research opportunities in lung cancer
Lung Cancer

- Lung cancers account for over 25% of cancer deaths in the US each year
  
  222,500 new cases in 2017\textsuperscript{1}
  
  155,879 deaths in 2017

- Major lung cancer histologies are:
  lung adenocarcinoma (60%)
  squamous cell lung carcinoma (25%)
  small cell lung carcinoma (10%)

- While lung cancer is generally associated with smoking, lung adenocarcinoma uniquely often occurs in non-smokers
  15-20% of all cases worldwide\textsuperscript{2}

\textsuperscript{1} Siegel, CA, Jan 2017
\textsuperscript{2} Subramanian, Oncology, 2010
## Gene Alterations in NSCLC

<table>
<thead>
<tr>
<th>Genetic abnormality (references)</th>
<th>Gene location</th>
<th>SCC</th>
<th>Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53 (36, 71)</td>
<td>17p13.1</td>
<td>51%</td>
<td>36%</td>
</tr>
<tr>
<td>PI3KCA amplification (51, 52, 54)</td>
<td>3q26.3</td>
<td>33%</td>
<td>6%</td>
</tr>
<tr>
<td>SOX2 amplification (23, 24)</td>
<td>3q26.3-q27</td>
<td>23%</td>
<td>Very rare</td>
</tr>
<tr>
<td>FGFR1 amplification (24, 25)</td>
<td>8p12</td>
<td>22%</td>
<td>1%</td>
</tr>
<tr>
<td>PTEN mutation (36, 61)</td>
<td>10q23.3</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>MET amplification (34, 35)</td>
<td>7q31.1</td>
<td>3%–21%</td>
<td>3%–21%</td>
</tr>
<tr>
<td>PTEN loss (59, 62)</td>
<td>10q23.3</td>
<td>8%–20%</td>
<td>8%–20%</td>
</tr>
<tr>
<td>KRAS mutation (36)</td>
<td>12p12.1</td>
<td>6%</td>
<td>21%</td>
</tr>
<tr>
<td>Variant III mutation (36)</td>
<td>7p12</td>
<td>5%</td>
<td>Very rare</td>
</tr>
<tr>
<td>LKB1 mutation (70)</td>
<td>19p13.3</td>
<td>5%</td>
<td>23%</td>
</tr>
<tr>
<td>DDR2 mutation (30)</td>
<td>1q23.3</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>HER2 overexpression (39–42)</td>
<td>17q11.2-q12, 17q21</td>
<td>3%–5%</td>
<td>5%–9%</td>
</tr>
<tr>
<td>PI3KCA mutation (50–52)</td>
<td>3q26.3</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>BRAF mutation (36, 64)</td>
<td>7p34</td>
<td>2%</td>
<td>1%–3%</td>
</tr>
<tr>
<td>EGFR mutation (36)</td>
<td>7p12</td>
<td>&lt;5%</td>
<td>10%–15%</td>
</tr>
<tr>
<td>AKT1 mutation (56)</td>
<td>14q32.32</td>
<td>1%</td>
<td>Very rare</td>
</tr>
<tr>
<td>MET mutation (36)</td>
<td>7q31.1</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>HER2 mutation (46, 48, 49)</td>
<td>17q11.2-q12, 17q21</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>EML4-ALK fusion (66, 67)</td>
<td>2p21, 2p23</td>
<td>1%</td>
<td>2%–7%</td>
</tr>
</tbody>
</table>
Targeted Therapy Options Are Expanding Beyond EGFR, ALK, ROS1, and BRAF


* Testing for MET and HER2 should include: MET exon14 skipping mutation and MET amplification; HER2 mutation and HER2 amplification
Oncoscreen Performance
• Reflex NGS testing
• Reflex PDL1
• FNA service adjudicates adequacy of tissue
• Testing all EGFR, ALK at progression
Endpoints

- **Primary endpoint:** PFS based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing a 29% improvement in median PFS from 10 months to 14.1 months) at a 2-sided alpha-level of 5%

- **Secondary endpoints:** objective response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety
Tumor response to Osimertinib, Front Line EGFR mut+ NSCLC

Best percentage change in target lesion size is the maximum reduction from baseline or the minimum increase. *Represents imputed values: if it is known that the patient has died, has new lesions or progression of assessments, best change will be imputed as 20%.

Ramalingam, Proc ESMO 2017

FLAURA data cut-off: 12 June 2017
Best percentage change in target lesion size is the maximum reduction from baseline or the minimum increase. *Represents imputed values: if it is known that the patient has died, has new lesions or progression of assessments, best change will be imputed as 20%.

*By investigator assessment; CI, confidence interval; SD, standard deviation; SoC, standard-of-care
FLAURA: Overall Survival Interim Analysis

- **Median Overall Survival**
  - Osimertinib: Not reached
  - SoC: Not reached

- **Number of patients at risk**
  - **Osimertinib**: 279, 276, 269, 253, 243, 232, 154, 87, 29, 4, 0
  - **SoC**: 277, 263, 252, 237, 218, 200, 126, 64, 24, 1, 0

- **HR**: 0.63 (95% CI 0.45, 0.88)
  - **P = .0068‡**

  ‡A P value of <.0015 was required for statistical significance at current maturity

Mechanisms of Acquired Resistance

Resistance after 1\textsuperscript{st}/2\textsuperscript{nd} generation TKIs

- MET amplification: 3%
- Small cell + MET: 1%
- Small cell: 1%
- Small cell + T790M: 2%
- MET + T790M: 3%
- Unknown: 18%
- HER2: 8%
- HER2 + T790M: 4%
- T790M: 60%

Resistance after 3\textsuperscript{rd} generation TKIs

- T790M "loss": 29%
- T790M "maintained": 23%
- C797S/T790M-positive: 9%
- SCLC/T790-wild-type: 3%
- MET amp/T790-wild-type: 3%
- HER2 amp/T790-wild-type: 3%

Mechanisms of resistance to osimertinib and rociletinib, third-generation EGFR tyrosine kinase inhibitors have been described in several studies. amp indicates amplification; HER2, human epidermal growth factor receptor 2; MET, MET proto-oncogene; SCLC, small cell lung cancer; TKI, tyrosine kinase inhibitor.
Lessons from patients…

Diane and her twin sister, 2014
EGFR Resistance-Personalized Therapy

- 30 year old never smoker, presented with DVT, developed hemoptysis and found to have EGFR mut+, del 19 stage IIIB NSCLC
- Due to extent of disease, started on afatinib
- 4 weeks, minimal response, so started cddp/pemetrexed + RT
- Progression in cervical node and bone, restarted on erlotinib while awaiting NGS
- NGS with high level MET amplification + EGFR del 19
- Phase 1 clinical trial of MET TKI (savolitinib) + EGFR TKI (osimertinib) → near CR x 36 weeks → progression
- Repeat NGS with MET amplification, EGFR del19 + MET kinase domain mut
- Trial of 1: erlotinib + cabozatinib → near CR x 1 year
March 2016 to Dec 2017 → 2 TKIS-off
label: Cabozatinib + Erlotinib
The story continues...

• Dec 2017, progression in Abd Nodes
• NGS: MET Amp, EGFR del 19, 2 MET kinase mut
• Started on ABBV-399 (c-MET ADC) + erlotinib → almost CR > 4 months
Broad Molecular Testing in NSCLC

- FDA Approvals in \textit{EGFR/ALK/ROS1/BRAF V600E}
- UCCCCC Trials in discrete populations
  - Tepotinib in \textit{METex14}
  - \textit{MET AMP-ABBV-399}
  - \textit{LOXO 101 in NTRK fusion positive}
  - \textit{LOXO 292 in RET translocations}
  - \textit{TAK-788 in exon 20 EGFR and HER2 activating mutations}
  - \textit{Lorlatinib in ALK resistant}
### Management of Advanced NSCLC

<table>
<thead>
<tr>
<th>EGFRmt (1st line)</th>
<th>ALK rearrangement</th>
<th>ROS1 rearrangement</th>
<th>PD-L1 expression level</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib/gemcitabine</td>
<td></td>
<td></td>
<td>PD-L1 ≥50%</td>
<td>Pembrolizumab</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>Alectinib</td>
<td>Crizotinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osimertinib (if T790M resistance develops)</td>
<td>Platinum doublet with pemetrexed ± bevacizumab</td>
<td>3rd-generation ALK inhibitor clinical trial; or platinum doublet with pemetrexed ± bevacizumab</td>
<td>PD-L1 &lt;50%</td>
<td>Platinum doublet with pemetrexed ± bevacizumab</td>
</tr>
<tr>
<td>Platinum doublet with pemetrexed ± bevacizumab</td>
<td>Docetaxel ± ramucirumab; or gemcitabine</td>
<td>3rd-generation ALK inhibitor clinical trial; or platinum doublet with pemetrexed ± bevacizumab</td>
<td>Docetaxel ± ramucirumab; or gemcitabine</td>
<td></td>
</tr>
</tbody>
</table>

**2nd line**

<table>
<thead>
<tr>
<th>EGFRmt (if T790M resistance develops)</th>
<th>ALK rearrangement</th>
<th>ROS1 rearrangement</th>
<th>PD-L1 expression level</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib</td>
<td>Alectinib</td>
<td>Crizotinib</td>
<td>PD-L1 ≥50%</td>
<td>Pembrolizumab</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>Alectinib; or brigatinib; or ceritinib</td>
<td>2nd-generation ROS1 inhibitor clinical trial; or platinum doublet with pemetrexed ± bevacizumab</td>
<td>PD-L1 &lt;50%</td>
<td>Immunootherapy (nivolumab, pembrolizumab, or atezolizumab)</td>
</tr>
<tr>
<td>Platinum doublet with pemetrexed ± bevacizumab</td>
<td>Docetaxel ± ramucirumab; or gemcitabine</td>
<td>Platinum doublet with pemetrexed ± bevacizumab (if not received as 2nd line); or docetaxel ± ramucirumab; or gemcitabine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**3rd line**

<table>
<thead>
<tr>
<th>EGFRmt (if T790M resistance develops)</th>
<th>ALK rearrangement</th>
<th>ROS1 rearrangement</th>
<th>PD-L1 expression level</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platinum doublet with pemetrexed ± bevacizumab</td>
<td>Docetaxel ± ramucirumab; or gemcitabine</td>
<td>3rd-generation ALK inhibitor clinical trial; or platinum doublet with pemetrexed ± bevacizumab</td>
<td>Docetaxel ± ramucirumab; or gemcitabine</td>
<td></td>
</tr>
</tbody>
</table>

**Consider clinical trial options from time of diagnosis and throughout treatment.**

**Abbreviations:** PD-L1, programmed cell death 1 ligand; EGFRmt, EGFR mutated.

*If crizotinib treatment was started prior to FDA approval of alectinib for 1st-line treatment.

*bCarboplatin/pemetrexed/pembrolizumab is also FDA approved in this setting.

*cPembrolizumab use requires PD-L1 >1%.

Doroshow, JAMA Onc, 2018
Front Line: IO only

KEYNOTE-024 Study Design (NCT02142738)

- Key Eligibility Criteria:
  - Untreated stage IV NSCLC
  - PD-L1 TF8 25%
  - ECOG PS 0-1
  - No activating EGFR mutation or ALK translocation
  - No untreated brain metastases
  - No active autoimmune disease requiring systemic therapy

- Pembrolizumab 200 mg IV Q2W (2 years)

- Platinum-Douplet Chemotherapy (4-6 cycles)

- Key End Points:
  - Primary: PFS (RECISt v1.1 per blinded, independent central review)
  - Secondary: OS, ORR, safety
  - Exploratory: DOR

CheckMate-026

- Key eligibility criteria:
  - Stage IV or recurrent NSCLC
  - No prior systemic therapy for advanced disease
  - No EGFR/ALK mutations sensitive to available targeted inhibitor therapy
  - ≥1% PD-L1 expression
  - CNS metastases permitted if adequately treated at least 2 weeks prior to randomization

- Nivolumab 3 mg/kg IV Q2W
  - Randomize 1:1
  - n = 271
  - Disease progression or unacceptable toxicity

- Chemotherapy (histology dependent)
  - Maximum of 6 cycles
  - n = 270
  - Tumor scans Q6W until wk 48 then Q12W
  - Disease progression
  - Crossover nivolumab (optional)
Tale of Two Studies

Keynote-024

CheckMate-026

Overall Survival

<table>
<thead>
<tr>
<th>Events,</th>
<th>Median,</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>44</td>
<td>NR</td>
<td>0.60 (0.41-0.89)</td>
</tr>
<tr>
<td>Chemo</td>
<td>64</td>
<td>NR</td>
<td>0.45 (0.30-0.69)</td>
</tr>
</tbody>
</table>

Nivolumab n = 211
Chemotherapy n = 212

Median OS, months (95% CI)
- Nivolumab: 14.4 (11.7, 17.4)
- Chemotherapy: 13.2 (10.7, 17.1)

1-year OS rate, %
- Nivolumab: 56.3
- Chemotherapy: 53.6

No. of patients at risk:
- Nivolumab: 211
  - 186
  - 156
  - 133
  - 118
  - 98
  - 49
  - 14
  - 0
- Chemotherapy: 212
  - 186
  - 156
  - 133
  - 118
  - 98
  - 49
  - 14
  - 3
  - 1
  - 0

Data cut-off: May 9, 2016.
Can PD-L1 select appropriate patients for IO?

- Multiple issues
  - Is PD-L1 IHC the way to measure PD-L1 and its importance?
  - What about PD-L2 or other markers?
  - Functional activation markers and gene signatures?
  - Mutation of antigen presentation pathway as a negative selection factor
  - Mutation burden assessment
  - Predicted neo-epitopes among the predicted substitutions
Rationale for Immunotherapy/Chemotherapy Combination

Preclinical and clinical data have suggested that there is rationale in support of combining chemotherapy with immunotherapy.¹

- Increasing the release of antigens and damage associated molecular patterns (DAMPs).¹
- Reducing the number of myeloid-derived suppressor cells, MDSCs (gemcitabine).¹
- Depletion of circulating regulatory T-cells (Tregs) (cyclophosphamide).¹

In a genetically engineered mouse model of lung adenocarcinoma, a combination of oxaliplatin and cyclophosphamide rendered the tumors, which lacked T cell infiltrates, sensitive to treatment with PD-1 and CTLA-4 antibodies.³

Keynote-189: Phase III Pembrolizumab vs Placebo Plus Platin + Pemetrexed in Advanced NS-NSCLC
Gandhi et al, NEJM, April 2018

KEYNOTE-189 Study Design (NCT02578680)

Key Eligibility Criteria
- Untreated stage IV nonsquamous NSCLC
- No sensitizing EGFR or ALK alteration
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- No symptomatic brain metastases
- No pneumonitis requiring systemic steroids

Stratification Factors
- PD-L1 expression (TPS<1% vs ≥1%)
- Platinum (cisplatin vs carboplatin)
- Smoking history (never vs former/current)

N = 410
R (2:1)
N = 206

Pembrolizumab 200 mg + Pemetrexed 500 mg/m² + Carboplatin AUC 5 OR Cisplatin 75 mg/m² Q3W for 4 cycles

Pembrolizumab 200 mg Q3W for up to 31 cycles
+ Pemetrexed 500 mg/m² Q3W

Placebo (normal saline) + Pemetrexed 500 mg/m² + Carboplatin AUC 5 OR Cisplatin 75 mg/m² Q3W for 4 cycles

Placebo (normal saline) for up to 31 cycles
+ Pemetrexed 500 mg/m² Q3W

Pembrolizumab 200 mg Q3W for up to 35 cycles

*Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDX assay. **Patients could crossover during the induction or maintenance phases.
To be eligible for crossover, PD must have been verified by blinded, independent central radiologic review and all safety criteria had to be met.
Overall Survival, ITT

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro/Pem/Plat</td>
<td>31.0%</td>
<td>0.49 (0.38-0.64)</td>
</tr>
<tr>
<td>Placebo/Pem/Plat</td>
<td>52.4%</td>
<td></td>
</tr>
</tbody>
</table>

Overall Survival, ITT

Median (95% CI)
NR (NE-NE)
11.3 mo (8.7-15.1)

Data cutoff date: Nov 8, 2017.
Overall Survival in Key Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Deaths/No. of Patients</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>235/616</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>133/312</td>
<td></td>
</tr>
<tr>
<td>≥65 yr</td>
<td>102/304</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>143/363</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>92/253</td>
<td></td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>74/266</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>159/346</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current/former</td>
<td>211/543</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>24/73</td>
<td></td>
</tr>
<tr>
<td>Platinum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>59/171</td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
<td>176/445</td>
<td></td>
</tr>
<tr>
<td>PD-L1 TPS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1%</td>
<td>84/190</td>
<td></td>
</tr>
<tr>
<td>≥1%</td>
<td>135/388</td>
<td></td>
</tr>
<tr>
<td>1-49%</td>
<td>65/186</td>
<td></td>
</tr>
<tr>
<td>≥50%</td>
<td>70/202</td>
<td></td>
</tr>
</tbody>
</table>

Data cutoff date: Nov 8, 2017.
Overall Survival by PD-L1 TPS

<table>
<thead>
<tr>
<th>TPS &lt;1%</th>
<th>HR (95% CI)</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Events</td>
<td></td>
</tr>
<tr>
<td>Pembro/Pem/Plat</td>
<td>38.6%</td>
<td>0.59 (0.38-0.92)</td>
</tr>
<tr>
<td>Placebo/Pem/Plat</td>
<td>55.6%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TPS 1-49%</th>
<th>HR (95% CI)</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Events</td>
<td></td>
</tr>
<tr>
<td>Pembro/Pem/Plat</td>
<td>28.9%</td>
<td>0.55 (0.34-0.90)</td>
</tr>
<tr>
<td>Placebo/Pem/Plat</td>
<td>48.3%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TPS ≥50%</th>
<th>HR (95% CI)</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Events</td>
<td></td>
</tr>
<tr>
<td>Placebo/Pem/Plat</td>
<td>25.8%</td>
<td>0.42 (0.26-0.68)</td>
</tr>
</tbody>
</table>

Nominal and one-sided. Data cutoff date: Nov 8, 2017.
Primary PFS and safety analyses of a randomised Phase III study of carboplatin + paclitaxel +/− bevacizumab, with or without atezolizumab in 1L non-squamous metastatic NSCLC (IMpower150)

Martin Reck,¹ Mark A. Socinski,² Federico Cappuzzo,³ Francisco Orlandi,⁴ Daniil Stroyakovskii,⁵ Naoyuki Nogami,⁶ Delvys Rodríguez-Abreu,⁷ Denis Moro-Sibilot,⁸ Christian A. Thomas,⁹ Fabrice Barlesi,¹⁰ Gene Finley,¹¹ Claudia Kelsch,¹² Anthony Lee,¹² Shelley Coleman,¹² Yijing Shen,¹² Marcin Kowanetz,¹² Ariel Lopez-Chavez,¹² Alan Sandler,¹² Robert Jotte¹³

¹Lung Clinic Grosshansdorf, Airway Research Center North, German Center of Lung Research, Grosshansdorf, Germany; ²Florida Hospital Cancer Institute, Orlando, FL, USA; ³Azienda Unità Sanitaria Locale della Romagna, Ravenna, Italy; ⁴Instituto Nacional del Torax, Santiago, Chile; ⁵Moscow City Oncology Hospital, Moscow, Russia; ⁶National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan; ⁷Hospital Universitario Insular de Gran Canaria, Las Palmas, Spain; ⁸Centre Hospitalier Universitaire de Grenoble Alpes, Grenoble, France; ⁹New England Cancer Specialists, Scarborough, ME, USA; ¹⁰Aix Marseille University, Assistance Publique Hôpitaux de Marseille, Marseille, France; ¹¹Allegheny Cancer Center, Pittsburgh, PA, USA; ¹²Genentech, Inc., South San Francisco, CA, USA; ¹³Rocky Mountain Cancer Centers, Denver, CO, USA
**Rationale for combining atezolizumab + bevacizumab**

- In addition to its known anti-angiogenic effects\(^1\), bevacizumab’s inhibition of VEGF has immune modulatory effects.
- Atezolizumab’s T-cell mediated cancer cell killing may be enhanced through bevacizumab’s reversal of VEGF-mediated immunosuppression.

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Figure adapted from Chen DS, Mellman I. *Immunity*, 2013.
IMpower150 Demonstrated PFS Benefit in Arm B vs C in the ITT-WT

- OS positivity has since been reached (March 2018) and will be presented at an upcoming meeting.

Atezo, atezolizumab; bev, bevacizumab; CP, carboplatin + paclitaxel.
* Stratified HR.
Data cutoff: September 15, 2017

Kowanetz M, Socinski M, et al. AACR 2018
IMpower150: Efficacy Across Subgroups

---

Atezo + Bev + CP: 356 332 311 298 290 265 232 210 186 151 124 111 87 77 75 58 55 42 39 27 24 16 12 9 7 6 3 2 2 2
Bev + CP: 336 321 292 261 243 215 179 147 125 91 69 55 39 32 21 18 12 9 7 6 3 2 1 1
T-Cell Immune Checkpoints as Therapeutic Targets

Activating receptors
- CD28
- OX40
- GITR
- CD137
- CD27

Inhibitory receptors
- CTLA-4
- PD-1
- B7-1
- TIM-3
- BTTLA
- VISTA
- LAG-3

T cell stimulation

Blocking antibodies

TARGETED THERAPY

CHEMOTHERAPY

CELL THERAPY

VACCINES

Agonistic antibodies

UChicago Medicine

Mellman et al. Nature. 2011
Nivolumab + Ipilimumab vs Platinum-Doublet Chemotherapy as First-line Treatment for Advanced NSCLC

Co-primary Endpoint: PFS With Nivolumab + Ipilimumab vs Chemotherapy in Patients With High TMB (≥10 mut/Mb)\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>Nivo +ipi (n = 139)</th>
<th>Chemo (n = 160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mo</td>
<td>7.2</td>
<td>5.4</td>
</tr>
<tr>
<td>HR</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>97.5% CI</td>
<td>0.41, 0.81</td>
<td></td>
</tr>
</tbody>
</table>

\(P = 0.0002\)

- In patients with TMB <10 mut/Mb treated with nivo + ipi vs chemo, the HR was 1.07 (95% CI: 0.84, 1.35)\(^d\)

\(^a\)Per blinded independent central review (BICR); median (range) of follow-up in the co-primary analysis population was 13.6 mo (0.4, 25.1) for nivo + ipi and 13.2 mo (0.2, 26.0) for chemo;

\(^b\)95% CI: nivo + ipi (5.5, 13.2 mo), chemo (4.4, 5.8 mo);

\(^c\)95% CI: 0.43, 0.77 mo;

\(^d\)The \(P\)-value for the treatment interaction was 0.0018
CheckMate 227: Nivo + Ipi in 1L NSCLC With High TMB (≥10 mut/Mb)

Best Change in Target Lesion Tumor Burden From Baseline in Patients With High TMB (≥10 mut/Mb)

Horizontal line indicates 30% reduction consistent with a RECIST 1.1 response; Asterisk (*): Responder per RECIST1.1 criteria, confirmation of response required.

Waterfall plots show patients with baseline and at least one on-treatment tumor assessment per BICR treated with nivolumab + ipilimumab (n = 119) or chemotherapy (n = 145). Percentages of deep response were calculated based on all randomized patients with baseline TMB ≥10 mut/Mb; *Negative/positive value means maximum tumor reduction/minimum tumor increase.
CheckMate 227: Nivo + ipi in 1L NSCLC With High TMB (≥10 mut/Mb)

Treatment-Related Select AEs in Patients Treated With Nivolumab + Ipilimumab\textsuperscript{a,b}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{chart.png}
\caption{Treatment-Related Select AEs in Patients Treated With Nivolumab + Ipilimumab.}
\end{figure}

\textsuperscript{a, b} Select AEs are those with potential immunologic etiology that require frequent monitoring/intervention; \textsuperscript{c} Includes events reported between first dose and 30 days after last dose of study drug.
Summary: Nivolumab + Ipilimumab in First-line NSCLC With High TMB (≥10 mut/Mb)

- In first-line TMB high metastatic NSCLC, nivolumab + ipilimumab prolonged PFS vs chemotherapy
  - PFS HR = 0.58 (97.5% CI: 0.41, 0.81); \( P = 0.0002 \)
  - Durable benefit: 1-y PFS: 43% vs 13%; 68% vs 25% of responses lasting ≥1 y
  - Benefit independent of PD-L1, histology, and observed across nearly all subgroups
  - Nivolumab + ipilimumab improved PFS vs nivolumab (HR = 0.75; 1-y PFS: 42% vs 29%)\(^a\)
- Early analysis of OS is encouraging
- Safety was manageable and consistent with previous reports of nivolumab + low-dose ipilimumab in NSCLC
- Results from CheckMate 227 may introduce 2 new standards of care for first-line NSCLC
  - Introduces nivolumab + ipilimumab as a new option for first-line NSCLC with TMB ≥10 mut/Mb
    - Durable benefit while sparing first-line chemotherapy and preserving effective second-line options
  - Validates TMB as an important and independent biomarker to be routinely tested in treatment-naive, advanced NSCLC

\(^a\)In patients with ≥1% tumor PD-L1 expression and high TMB (≥10 mut/Mb)
# 1L NSCLC Summary (Post-AACR 2018)

<table>
<thead>
<tr>
<th></th>
<th>KN-024 PDL1≥50%</th>
<th>KN-189 (NSq) PDL1≥50%</th>
<th>KN-189 (Nsq) All PD-L1</th>
<th>IMPower 150 (NSq)</th>
<th>CM-227 (TMB &gt; 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS PFS @ 12 m</td>
<td>10.6 vs 6.0</td>
<td>9.4 vs 4.7</td>
<td>8.8 vs 4.9</td>
<td>8.3 vs 6.8</td>
<td>7.2 vs 5.4</td>
</tr>
<tr>
<td>PFS HR p value</td>
<td>48% vs 15%</td>
<td>45% vs 15%</td>
<td>34% vs 17%</td>
<td>37% vs 18%</td>
<td>43% vs 13%</td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>0.36</td>
<td>0.52</td>
<td>0.62</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.00001</td>
<td>&lt;0.00001</td>
<td>&lt;0.0001</td>
<td>0.0002</td>
</tr>
<tr>
<td>mOS OS @ 12 mo</td>
<td>30.0 vs 14.2</td>
<td>NR vs 10.0</td>
<td>NR vs 11.3</td>
<td>19.2 vs 14.4</td>
<td>23.0 vs 16.4</td>
</tr>
<tr>
<td>OS @ 24 mo OS HR p value</td>
<td>70% vs 55%</td>
<td>73% vs 48%</td>
<td>69% vs 49%</td>
<td>67% vs 60%</td>
<td>67% vs 58%</td>
</tr>
<tr>
<td></td>
<td>52% 35%</td>
<td>0.63</td>
<td>0.42</td>
<td>0.775</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>0.035</td>
<td>0.002</td>
<td>0.001</td>
<td>0.0262</td>
<td>NA</td>
</tr>
<tr>
<td>RR</td>
<td>45% vs 28%</td>
<td>61% vs 23%</td>
<td>48% vs 19%</td>
<td>64% vs 48%</td>
<td>45% vs 27%</td>
</tr>
</tbody>
</table>
Immunomodulatory Properties of RT

Kalbasi et al. 2013 J Clin Invest
An Iterative Process

The T cell-inflamed tumor microenvironment is characterized by high expression of immune-inhibitory pathways, including FoxP3+ Tregs, PD-L1, and IDO.

- CD8+ T cell-derived INF-γ upregulates PD-L1 and IDO, and CCL22 recruits Tregs

Metastatic NSCLC naive to immunotherapy regardless of PD-L1 expression

RANDOMIZE
Biospecimen collection

SEQUENTIAL ARM (I)

SBRT to 2-4 metastases

Biospecimen collection + Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W

Imaging with cycle 2 and every other cycle afterwards until discontinuation from trial

CONCURRENT ARM (II)

Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W + SBRT to 2-4 metastases

Biospecimen collection
Predictive Biomarkers

- Mutational burden
- Molecular profile of tumor microenvironment
- Expression of inflammatory genes
- Clonal T-cell expansion
- Clonal B-cell expansion
- Microbiome profile
Modern Therapy for Lung Cancer

• Newly diagnosed patients need adequate pathologic assessment to personalize therapy
• The success of immunotherapy has generated new clinical questions:
  use of immunotherapy in earlier stage disease
  optimizing dose, schedule and duration of therapy
  best biomarkers for patient selection
  development of novel surrogate endpoints
  Super responders and super progressors

Effective immunotherapy of cancer is likely to be a multifaceted and multilayered process.
Thank You

Presented by: JD Patel