Hypes and Hopes: progress and controversies in lung cancer 2016/17

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University of Colorado Cancer Center
Disclosures (DRC)

- Employment or leadership Position: None
- **Advisory Role: Ad Hoc Advisory Boards/Consultations (most recent contact last 3 years):**
  - 2017: Genoptix
  - 2016: G1 Therapeutics (DSMB), Orion, Clovis, Ariad, Celgene, Novartis
  - 2015: Ariad, Array, Eli Lilly, Novartis, Celgene, Abbvie, Clovis
- Stock Ownership: None
- **Honoraria: Seminar/Talks to Industry (most recent contact last 3 years).**
  - 2015: AstraZeneca, Clovis
- **Research Funding:**
  - 2013 (ongoing): Ariad
- Speakers Bureau/Talks for Industry: None
- Expert Testimony: None
- Other Remuneration: None
Agenda: Highlights and Lowlights of recent ASCO/ESMO/WCLC/Publications

• NSCLC
  – EGFR
  – ALK
  – IO
Standard management stage IV NSCLC: USA

1st line:
- EGFR Sensitizing Mt: 1st/2nd gen EGFR TKI
- ALK rearranged: 1st gen ALK TKI
- ROS1 rearranged: 1st gen ROS1 TKI
- NOS NSCLC: Platinum-doublet chemotherapy +/- bev +/- pem continuation (depending on histology)

Other personalizable therapy plans based on specific molecular subtypes?
- BRAF, MET exon 14, MET amp
EGFR developments?
Acquired Resistance: Biological

- **Altered drug target**
  - Driver A
  - Driver A
  - Driver A
  - Driver A

- **Gene copy number gain of drug target**
  - Driver A
  - Driver A
  - Driver A

- **Bypass tracks**
  - Coincident in same cell (second drivers)
  - Emergence of distinct clone (separate driver)

- **Not shown:**
  - Phenotypic change
  - Manipulation of downstream signalling pathways
3rd generation EGFR TKIs: Activity of Rociletinib and Osimertinib in tissue T790M Positive Patients

Rociletinib
ORR in T790M+ Patients: ~60 %

Updated ORR ~30%, QTc and hyperglycemia issues
Denied FDA accelerated approval ODAC April 2016

Osimertinib (AZD 9291)
ORR in T790M+ Patients: ~60 %

FDA accelerated approval 2015

Janne et al. NEJM 2015;372: 1689-99. (FIG 2B); Sequist et al., NEJM 2015
Epidermal growth factor receptor genotyping of matched urine, plasma and tumor tissue from non-small cell lung cancer patients treated with rociletinib

Heather Wakelee,1 Shirish Gadgeel,2 Jonathan Goldman,3 Karen Reckamp,4 Chris Karlovich,5 Vlada Melnikova,6 Jean-Charles Soria,7 Helena Yu,8 Benjamin Solomon,9 Maurice Pérol,10 Joel Neal,1 Stephen Liu,11 Mitch Raponi,5 Darrin Despain,5 Mark Erlander,6 Shannon Matheny,5 Sergey Yurasov,5 D. Ross Camidge,12 Lecia Sequist13

1Stanford University Medical Center, Stanford, CA, USA; 2Barbara Karmanos Cancer Institute, Detroit, MI, USA; 3UCLA Medical Center, Santa Monica, CA, USA; 4City of Hope Comprehensive Cancer Center, Duarte, CA, USA; 5Clovis Oncology, Inc., Boulder, CO, USA; 6Trovagene, Inc., San Diego, CA, USA; 7Gustave Roussy Cancer Center, Villejuif, France; 8Memorial Sloan Kettering Cancer Center, New York, NY, USA; 9Peter MacCallum Cancer Centre, Melbourne, Australia; 10Leon Bérard Cancer Center, Lyon, France; 11Georgetown University Medical Center, Washington DC, USA; 12University of Colorado, Aurora, CO, USA; 13Massachusetts General Hospital, Boston, MA, USA

Abstract 9001
Presented by: Heather A. Wakelee
Plasma, Tissue, and Urine Identify Unique and Overlapping Subsets of T790M-Positive Patients

- 181 samples had matched pretreatment T790M results in plasma, tissue, and urine
  - 7 were T790M-negative or inadequate by all 3 sample types (4%)
  - 174 were T790M-positive by at least 1 sample type (96%)

**T790M-Positive Cases**

- Total positive by tissue: 146 of 181
- Total positive by plasma: 145 of 181
- Total positive by urine: 144 of 181

104 (57%) were positive by all 3 sample types

Proportion of patients in diagram not to scale.

Abstract 9001
Presented by: Heather A. Wakelee
Investigator-Assessed Confirmed Response Rate Is Similar for T790M-Positive Patients Identified by Plasma, Tissue, and Urine Test

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>n</th>
<th>Objective Response Rate,* % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue</td>
<td>443</td>
<td>33.9 (29.5–38.5)</td>
</tr>
<tr>
<td>Plasma</td>
<td>374</td>
<td>32.1 (27.4–37.1)</td>
</tr>
<tr>
<td>Urine</td>
<td>169</td>
<td>36.7 (29.4–44.4)</td>
</tr>
</tbody>
</table>

*Investigator-assessed confirmed objective response rate (RECIST v1.1).
Detection of T790M in Liquid Biopsies of Patients with Distant Metastatic vs Intrathoracic Disease

<table>
<thead>
<tr>
<th>Sample Matrix</th>
<th>Disease Classification</th>
<th>Total Patients with Mutation Detected</th>
<th>Subset with Mutation in Liquid Biopsy</th>
<th>Percentage</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine</td>
<td>M1a/M0</td>
<td>61</td>
<td>45</td>
<td>73.8%</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>M1b</td>
<td>141</td>
<td>118</td>
<td>83.7%</td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>M1a/M0</td>
<td>132</td>
<td>75</td>
<td>56.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>M1b</td>
<td>329</td>
<td>291</td>
<td>88.4%</td>
<td></td>
</tr>
</tbody>
</table>

- T790M is more readily detected in liquid biopsies of patients with distant metastatic (M1b) vs intrathoracic (M1a/M0) disease

Abstract 9001
Presented by: Heather A. Wakelee
Plasma, Tissue, and Urine Identify Unique and Overlapping Subsets of T790M-positive Patients

- 181 samples had matched pretreatment T790M results in plasma, tissue, and urine
  - 7 were T790M-negative or inadequate by all three sample types (4%)
  - 174 were T790M-positive by at least one sample type (96%)

T790M-positive cases

- Total positive by tissue: 146 of 181
- Total positive by plasma: 145 of 181
- Total positive by urine: 144 of 181

The ‘dominance’ of different negatives remains to be determined

A positive is usually a positive

Abstract 9001
Presented by: Heather A. Wakelee
Similar situation with osimertinib

Plasma T790M+ ORR 63%
Tumor T790M+ ORR 62%
Acquired resistance to EGFR TKI

All pts undergo biopsy, FDA-approved FFPE assay for T790M

T790M+ → Third gen. EGFR TKI
T790M- → Chemotherapy

Acquired resistance to EGFR TKI

FDA-approved plasma assay for T790M and sensitizing mutations

T790M+ → Skip biopsy, start third gen. EGFR TKI
T790M- → Biopsy, FDA approved FFPE assay for T790M

T790M+ → Third gen. EGFR TKI
T790M- → Chemotherapy
AURA 1 Osimertinib trial

402 pts total

216 pts had matched tumor and plasma

Results

18 pts T790M pos plasma and negative in tumor (blue bars, panel B)

Looks more like Panel D?

Oxnard et al, JCO 2016
Plasma T790M+, PFS by tumor T790M status

Discrepant results tell us something about dominant biology?
Inform frequency/type of surveillance??
ALK developments?
### ALK progression within brain on Crizotinib

<table>
<thead>
<tr>
<th>Study</th>
<th>Brain metastases on treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weickhardt et al, JTO 2012</td>
<td>46% as site of first progression, (85% of whom had CNS as sole site of first progression)</td>
</tr>
<tr>
<td>Costa et al, JCO 2011</td>
<td>At CNS progression: CSF:plasma ratio = 0.0026 (i.e. &lt;0.3% gets into brain)</td>
</tr>
<tr>
<td>Costa et al, JCO 2015</td>
<td>18% ORR in untreated measurable CNS lesions (53% systemically); median duration of response 26.4 weeks (47.9 weeks systemically); median CNS TTP 7 months (12.5 months systemically); 72% had CNS as first site of progression</td>
</tr>
</tbody>
</table>
90 ALK+ patients with brain metastases across 6 institutions

30% present at baseline

Median OS > 4 years from time of CNS mets
Figure 1 Treatment options for baseline parenchymal CNS metastases in ALK-Positive NSCLC with respect to 1st line crizotinib use.
**Figure 2** | Mechanisms of biological acquired resistance. 

**a** | *EGFR*-mutant NSCLC resistant to erlotinib and gefitinib. Note that frequencies are approximate, and data are compiled from multiple series. \(^{31,36,37,39-41,46,49-51,55,56}\)

**b** | ALK-rearranged NSCLC resistant to crizotinib. Note that frequencies are approximate, and data are compiled from two studies. \(^{43,44}\)
PROFILE 1014: First line PFS of crizotinib vs pemetrexed-based platinum doublet chemotherapy (up to 6 cycles without continuation maintenance pemetrexed)

Crizotinib (N=172) vs Chemotherapy (N=171)

- Events, n (%): 100 (58) vs 137 (80)
- Median, months: 10.9 vs 7.0
- HR (95% CI): 0.45 (0.35–0.60)
- \( P < 0.0001 \)

PFS probability (%)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Crizotinib (N=172)</th>
<th>Chemotherapy (N=171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100 (58)</td>
<td>137 (80)</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
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<tr>
<td>15</td>
<td></td>
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<tr>
<td>20</td>
<td></td>
<td></td>
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<tr>
<td>25</td>
<td></td>
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<tr>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No. at risk
- Crizotinib: 172, 120, 65, 38, 19, 7, 1, 0
- Chemotherapy: 171, 105, 36, 12, 2, 1, 0

Mok T, et al. ASCO 2014
Solomon et al, NEJM 2014
ORR and mPFS post crizotinib: An indirect comparison

PFS differs, despite same ORR
Differ in control of disease in CNS?
Differ in suppression of spectrum of acquired resistance clones not dominant at baseline?

Primary Endpoint: PFS by BIRC

Ceritinib Demonstrated an Estimated 45% Risk Reduction Vs Chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Ceritinib (N=189)</th>
<th>Chemotherapy (N=187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>89 (47.1)</td>
<td>113 (60.4)</td>
</tr>
<tr>
<td>Median (95% CI), months</td>
<td>16.6 (12.6, 27.2)</td>
<td>8.1 (5.8, 11.1)</td>
</tr>
</tbody>
</table>

Hazard ratio (95% CI) = 0.55 (0.42, 0.73)
Stratified Log-rank p-value < 0.001
## Forest Plot for PFS by Subgroup (BIRC)

**Ceritinib Demonstrated PFS Benefit Vs Chemotherapy Across Majority of Predefined Subgroups**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients (%)</th>
<th>Hazard ratio (HR) and 95% CI</th>
<th>HR 95% CI</th>
<th>Median PFS (95% CI), months</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>376</td>
<td></td>
<td>0.55 (0.42, 0.73)</td>
<td>16.6 (12.6, 27.2) 8.1 (5.8, 11.1)</td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South America</td>
<td>18 (4.8)</td>
<td>0.65 (0.17, 2.54)</td>
<td>7.0 (1.1, NE)</td>
<td>5.0 (1.4, 11.2)</td>
</tr>
<tr>
<td>Europe</td>
<td>199 (52.9)</td>
<td>0.54 (0.37, 0.80)</td>
<td>17.1 (11.7, 27.7)</td>
<td>7.1 (4.8, 11.1)</td>
</tr>
<tr>
<td>Asia Pacific</td>
<td>159 (42.3)</td>
<td>0.60 (0.38, 0.96)</td>
<td>26.3 (11.0, NE)</td>
<td>9.7 (5.8, 13.9)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65 Years</td>
<td>295 (78.5)</td>
<td>0.58 (0.42, 0.80)</td>
<td>17.1 (12.5, 27.7)</td>
<td>8.1 (5.8, 12.4)</td>
</tr>
<tr>
<td>≥ 65 Years</td>
<td>81 (21.5)</td>
<td>0.45 (0.24, 0.86)</td>
<td>14.0 (8.3, NE)</td>
<td>6.8 (4.2, 12.8)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>160 (42.6)</td>
<td>0.41 (0.27, 0.63)</td>
<td>15.2 (11.0, NE)</td>
<td>4.3 (3.3, 7.1)</td>
</tr>
<tr>
<td>Female</td>
<td>216 (57.4)</td>
<td>0.63 (0.43, 0.93)</td>
<td>25.2 (11.0, 27.7)</td>
<td>10.6 (7.6, 14.5)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>202 (53.7)</td>
<td>0.44 (0.30, 0.66)</td>
<td>16.4 (12.1, 27.7)</td>
<td>7.0 (4.3, 8.5)</td>
</tr>
<tr>
<td>Asian</td>
<td>158 (42.0)</td>
<td>0.66 (0.41, 1.06)</td>
<td>26.3 (8.6, NE)</td>
<td>10.6 (6.7, 15.0)</td>
</tr>
<tr>
<td><strong>Brain metastases at screening</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>255 (67.8)</td>
<td>0.48 (0.34, 0.69)</td>
<td>26.3 (15.4, 27.7)</td>
<td>8.3 (6.0, 13.7)</td>
</tr>
<tr>
<td>Presence</td>
<td>121 (32.2)</td>
<td>0.70 (0.44, 1.12)</td>
<td>10.7 (8.1, 16.4)</td>
<td>6.7 (4.1, 10.6)</td>
</tr>
<tr>
<td>WHO status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>139 (37.0)</td>
<td>0.59 (0.37, 0.96)</td>
<td>17.1 (11.3, NE)</td>
<td>9.7 (7.0, 14.2)</td>
</tr>
<tr>
<td>≥ 1</td>
<td>236 (62.0)</td>
<td>0.52 (0.37, 0.74)</td>
<td>16.6 (10.9, 27.7)</td>
<td>6.7 (4.3, 8.5)</td>
</tr>
<tr>
<td>Prior adjuvant chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19 (5.1)</td>
<td>1.41 (0.12, 15.84)</td>
<td>NE (6.9, NE)</td>
<td>NE (14.5, NE)</td>
</tr>
<tr>
<td>No</td>
<td>357 (94.9)</td>
<td>0.55 (0.41, 0.73)</td>
<td>16.4 (12.1, 27.2)</td>
<td>7.5 (5.7, 9.7)</td>
</tr>
<tr>
<td>Disease burden per BIRC assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline SOD for target lesions &lt; median SOD for target lesions</td>
<td>177 (47.1)</td>
<td>0.51 (0.32, 0.80)</td>
<td>26.3 (14.0, NE)</td>
<td>10.6 (7.0, 14.5)</td>
</tr>
<tr>
<td>baseline SOD for target lesions &gt;= median SOD for target lesions</td>
<td>184 (48.9)</td>
<td>0.53 (0.36, 0.79)</td>
<td>13.9 (9.5, 27.2)</td>
<td>5.6 (4.1, 8.1)</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>230 (61.2)</td>
<td>0.56 (0.38, 0.80)</td>
<td>16.6 (11.7, 27.7)</td>
<td>8.3 (7.0, 12.5)</td>
</tr>
<tr>
<td>Ex-smoker or Current smoker</td>
<td>146 (38.8)</td>
<td>0.48 (0.30, 0.77)</td>
<td>15.7 (9.7, 26.3)</td>
<td>5.8 (4.1, 12.4)</td>
</tr>
</tbody>
</table>
J-ALEX: Interim analysis. Primary Endpoint: PFS by IRF (ITT Population)

<table>
<thead>
<tr>
<th></th>
<th>Alectinib (N=103)</th>
<th>Crizotinib (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>25 (24.3%)</td>
<td>58 (55.8%)</td>
</tr>
<tr>
<td>Median, mo [95% CI]</td>
<td>NR [20.3 - NR]</td>
<td>10.2 [8.2 - 12.0]</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>HR [99.6826% CI]</td>
<td>0.34 [0.17 - 0.71]</td>
<td></td>
</tr>
</tbody>
</table>

Progression-free survival rate (%)

Presented by: Hiroshi Nokihara
Alectinib phase III studies

- ALK+
- Stage IIIb/IV or recurrent NSCLC
- ≤1 prior chemotherapy
- ECOG PS 0–2

Inc interim analyses

R 1:1

Alectinib 300 mg b.i.d. (n=100)
Crizotinib 250 mg b.i.d. (n=100)

Alectinib 600 mg b.i.d. (n=143)
Crizotinib 250 mg b.i.d. (n=143)

Primary endpoint: PFS
Secondary endpoints include CNS TTP
IO NSCLC developments?
"The world is full of obvious things which nobody by any chance ever observes."

*Sherlock Holmes, The Hound of the Baskervilles*
Checkmate 017: Squamous NSCLC 2nd line Nivolumab (PD1) vs docetaxel: Primary Endpoint = Overall Survival

FDA licensed March 2015

Number of Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>135</td>
<td>137</td>
</tr>
<tr>
<td># events</td>
<td>86</td>
<td>113</td>
</tr>
</tbody>
</table>

OS (%)

Time (months)

mOS mo, (95% CI)

Nivolumab: 9.2 (7.3, 13.3)
Docetaxel: 6.0 (5.1, 7.3)

HR = 0.59 (95% CI: 0.44, 0.79), P = 0.00025

Symbols represent censored observations

Spigel et al, ASCO 2015

ORR: 20 vs 9%
mDoR: NR vs 8.4m
mPFS: 3.5 vs 2.8mo
### Checkmate 057: non-Squamous NSCLC 2nd line Nivolumab (PD1) vs docetaxel: Primary Endpoint = Overall survival

<table>
<thead>
<tr>
<th>Number of Patients at Risk</th>
<th>Time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>292</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>290</td>
</tr>
</tbody>
</table>

Symbols represent censored observations.

**FDA licensed October 2015**

- **mOS, mo**
  - Nivolumab (n = 292): 12.2
  - Docetaxel (n = 290): 9.4
  - HR = 0.73 (96% CI: 0.59, 0.89); \( P = 0.0015 \)

- **1-yr OS rate**
  - Nivolumab: 51%
  - Docetaxel: 39%

- **ORR**: 19 vs 12%
- **mDoR**: 17.2 vs 5.6 mo
- **mPFS**: 2.3 vs 4.2 mo

Paz-Ares et al, ASCO 2015
**KEYNOTE-010**

≥1% Proportion score for PD-L1
Second line NSCLC

Pembro at 2 or 10mg/kg
Docetaxel 75mg/m2

Primary endpoints OS, PFS
in overall and in PS ≥ 50%
~70% non-squamous
~8% EGFR mt (~8% unknown)
~1% ALK+ (~10% unknown)

**In total pop:**
mOS: 10.4, 12.7, 8.5 months
HR vs doc: 0.71, 0.61

**In ≥50% PS:**
mOS: 14.9, 17.3, 8.2 months
HR vs doc: 0.54, 0.5

Herbst et al, Lancet 2016
In total pop:

mPFS: 3.9, 4, 4 months
HR vs doc: 0.88, 0.79 (NS)
ORR 18, 18.5, 9.3%

In ≥50% PS:

mPFS: 5, 5.2, 4.1 months
HR vs doc: 0.59, 0.59
ORR 30, 29, 8%

Herbst et al, Lancet 2016
1st line PD-1 trials
1st line enrichment options for PD1 monotherapy vs chemo

• **Maximal enrichment**
  (size of benefit versus chemo) to ensure individual likely to really benefit, but smaller absolute size of group?

Maximal population benefit vs maximum tolerable dilution of effect?

• **Minimal necessary enrichment** to beat chemo giving largest absolute size of group?
In Checkmate 057/017 (2nd line non-Sq/Sq 5% PD-L1 rate was 36-41%)
Primary Endpoint (PFS per IRRC in ≥5% PD-L1+)
CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab n = 211</th>
<th>Chemotherapy n = 212</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>4.2 (3.0, 5.6)</td>
<td>5.9 (5.4, 6.9)</td>
</tr>
<tr>
<td>1-year PFS rate, %</td>
<td>23.6</td>
<td>23.2</td>
</tr>
<tr>
<td>HR = 1.15 (95% CI: 0.91, 1.45), P = 0.2511</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No. of patients at risk:
Nivolumab 211 104 71 49 35 24 6 3 1 0
Chemotherapy 212 144 74 47 28 21 8 1 0 0

All randomized patients (≥1% PD-L1+): HR = 1.17 (95% CI: 0.95, 1.43)
OS (≥5% PD-L1+)

CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC

- Median OS, months
  - Nivolumab: 14.4 (11.7, 17.4)
  - Chemotherapy: 13.2 (10.7, 17.1)
- 1-year OS rate, %
  - Nivolumab: 56.3
  - Chemotherapy: 53.6
- HR = 1.02 (95% CI: 0.80, 1.30)

60.4% in the chemotherapy arm had subsequent nivolumab therapy
43.6% in the nivolumab arm had subsequent systemic therapy

No. of patients at risk:
- Nivolumab: 211 186 156 133 118 98 49 14 4 0 0
- Chemotherapy: 212 186 153 137 112 91 50 15 3 1 0

All randomized patients (≥1% PD-L1+): HR = 1.07 (95% CI: 0.86, 1.33)
# Summary of Response (≥5% PD-L1+)

**CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC**

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 211)</th>
<th>Chemotherapy (n = 212)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, % (95% CI)</strong></td>
<td>26.1 (20.3, 32.5)</td>
<td>33.5 (27.2, 40.3)</td>
</tr>
<tr>
<td><strong>Best overall response, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>1.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Partial response</td>
<td>24.2</td>
<td>33.0</td>
</tr>
<tr>
<td>Stable disease</td>
<td>38.4</td>
<td>47.2</td>
</tr>
<tr>
<td><strong>Progressive disease</strong></td>
<td>27.5</td>
<td>9.9</td>
</tr>
<tr>
<td>Could not be determined</td>
<td>8.1</td>
<td>9.4</td>
</tr>
<tr>
<td><strong>Median time to response, months (range)</strong></td>
<td>2.8 (1.2, 13.2)</td>
<td>2.6 (1.2, 9.8)</td>
</tr>
<tr>
<td><strong>Median duration of response, months (95% CI)</strong></td>
<td>12.1 (8.8, NE)</td>
<td>5.7 (4.2, 8.5)</td>
</tr>
</tbody>
</table>
**Key End Points**

Primary: PFS (RECIST v1.1 per blinded, independent central review)
Secondary: OS, ORR, safety
Exploratory: DOR

---

*To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.*
PD-L1 Screening

1934 patients entered screening

1729 submitted samples for PD-L1 assessment

1653 samples evaluable for PD-L1

500 TPS ≥50% (30%)

1153 TPS <50%
Progression-Free Survival

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

Assessed per RECIST v1.1 by blinded, independent central review.
Data cut-off: May 9, 2016.
DMC recommended stopping the trial because of superior efficacy observed with pembrolizumab.
Confirmed Objective Response Rate

Assessed per RECIST v1.1 by blinded, independent central review.
Data cut-off: May 9, 2016.

- **Pembrolizumab**
  - CR: n = 6
  - PR: n = 63
  - ORR: 45% (95% CI)
  - TTR, mo median (range): 2.2 (1.4-8.2)
  - DOR, mo median (range): NR (1.9+ to 14.5+)

- **Chemotherapy**
  - CR: n = 1
  - PR: n = 41
  - ORR: 28% (95% CI)
  - TTR, mo median (range): 2.2 (1.8-12.2)
  - DOR, mo median (range): 6.3 (2.1+ to 12.6+)

△17% P = 0.0011

Assessed per RECIST v1.1 by blinded, independent central review.
Data cut-off: May 9, 2016.
PD1 first line: Summary

- **Checkmate 026 (nivo)**
  - Unclear percent pos of overall population (≥1% ~50%; ≥5% ~40% in 2nd line trials with same assay)
  - Among ≥1% 77% ≥ 5%+ (balanced); 39% ≥ 50% + (imbalance towards chemo arm)
  - No improvement ORR, PFS or OS

- **Keynote 024 (pembro)**
  - 30% positive on PDL1 assay (unclear balance within this)
  - Improved ORR, PFS, and OS

Both exclude ALK and EGFR, squamous balanced, optional cross-over included
## Baseline Characteristics (All Randomized Patients)
**CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC**

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 271)</th>
<th>Chemotherapy (n = 270)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median time from diagnosis to randomization (range), months</strong></td>
<td>1.9 (0.3, 214.9)</td>
<td>2.0 (0.5, 107.3)</td>
</tr>
<tr>
<td>&lt;3 months, %</td>
<td>75.6</td>
<td>71.9</td>
</tr>
<tr>
<td><strong>Tumor histology, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>24.4</td>
<td>23.7</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>75.6</td>
<td>76.3</td>
</tr>
<tr>
<td><strong>Selected sites of metastases (lesions), %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>12.2</td>
<td>13.3</td>
</tr>
<tr>
<td>Liver</td>
<td>19.9</td>
<td>13.3</td>
</tr>
<tr>
<td><strong>Median sum of target lesion diameters, mm (range)</strong></td>
<td>82.5 (14, 218)</td>
<td>68.0 (15, 272)</td>
</tr>
<tr>
<td><strong>PD-L1 expression, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥5%</td>
<td>76.8</td>
<td>77.8</td>
</tr>
<tr>
<td>≥25%</td>
<td>48.7</td>
<td>60.7</td>
</tr>
<tr>
<td>≥50%</td>
<td>32.5</td>
<td>46.7</td>
</tr>
<tr>
<td>≥75%</td>
<td>20.7</td>
<td>27.4</td>
</tr>
</tbody>
</table>
**PFS and OS Subgroup Analyses (All Randomized Patients)**

*CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC*

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Patients, n</th>
<th>Unstratified HR</th>
<th>Unstratified HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivolumab</td>
<td>Chemotherapy</td>
<td>PFS</td>
</tr>
<tr>
<td>Overall</td>
<td>271</td>
<td>270</td>
<td>1.19</td>
</tr>
<tr>
<td>≥65 years</td>
<td>123</td>
<td>137</td>
<td>1.21</td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>148</td>
<td>133</td>
<td>1.17</td>
</tr>
<tr>
<td>Male</td>
<td>184</td>
<td>148</td>
<td>1.05</td>
</tr>
<tr>
<td>Female</td>
<td>87</td>
<td>122</td>
<td>1.36</td>
</tr>
<tr>
<td>ECOG PS = 0</td>
<td>85</td>
<td>93</td>
<td>1.69</td>
</tr>
<tr>
<td>ECOG PS ≥1</td>
<td>185</td>
<td>177</td>
<td>1.01</td>
</tr>
<tr>
<td>Squamous</td>
<td>65</td>
<td>64</td>
<td>0.83</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>206</td>
<td>206</td>
<td>1.29</td>
</tr>
<tr>
<td>Never smoker</td>
<td>30</td>
<td>29</td>
<td>2.51</td>
</tr>
<tr>
<td>Former smoker</td>
<td>186</td>
<td>182</td>
<td>1.14</td>
</tr>
<tr>
<td>Current smoker</td>
<td>52</td>
<td>55</td>
<td>1.03</td>
</tr>
<tr>
<td>≥50% PD-L1+</td>
<td>88</td>
<td>126</td>
<td>1.07</td>
</tr>
</tbody>
</table>

![Graph showing HR values for different subgroups]
## Subsequent Systemic Therapy (≥5% PD-L1+)

**CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC**

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Nivolumab&lt;sup&gt;a&lt;/sup&gt; (n = 211)</th>
<th>Chemotherapy&lt;sup&gt;b&lt;/sup&gt; (n = 212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any subsequent systemic therapy, &lt;sup&gt;c&lt;/sup&gt; %</td>
<td>43.6</td>
<td>64.2</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>1.4</td>
<td>60.4</td>
</tr>
<tr>
<td>Crossover nivolumab (on study)</td>
<td>0</td>
<td>57.5</td>
</tr>
<tr>
<td>Post-study nivolumab</td>
<td>0.9</td>
<td>3.3</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>ALK/EGFR tyrosine kinase inhibitors</td>
<td>5.7</td>
<td>2.8</td>
</tr>
<tr>
<td>Experimental therapy</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Chemotherapy and other systemic anticancer agents</td>
<td>41.7</td>
<td>14.2</td>
</tr>
</tbody>
</table>

<sup>a</sup>18.7% of treated patients (n = 209) remained on randomized study treatment

<sup>b</sup>5.3% of treated patients (n = 206) remained on randomized study treatment

<sup>c</sup>Patients could receive >1 subsequent systemic therapy
PD1 first line: Summary

- **Checkmate 026 (nivo)**
  - Unclear percent pos of overall population
  - Among $\geq 1\%$ 77% $\geq 5\%+$ (balanced); 39% $\geq 50\%+$ (imbalance towards chemo arm)
  - $\sim 40\%$ pem regimens
  - 12-13% CNS mets
  - **Permitted PS2 (few reported $\sim 1\%$)**
  - **38% prior XRT**
  - No improvement ORR, PFS or OS

- **Keynote 024 (pembro)**
  - 30% positive on PDL1 assay (unclear balance within this)
  - 65% pem regimens
  - 7-12% CNS mets all treated
  - Permitted PS0-1 only
  - Improved ORR, PFS, and OS

Both exclude ALK and EGFR, squamous balanced, optional cross-over included
Standard management stage IV NSCLC: USA

**EGFR Sensitizing Mt**
- 1\(^{st}/2\(^{nd}\) gen EGFR TKI

**ALK rearranged**
- 1\(^{st}\) gen ALK TKI

**ROS1 rearranged**
- 1\(^{st}\) gen ROS1 TKI

**NOS NSCLC**
- Platinum-doublet chemotherapy +/- bev +/- pem continuation (depending on histology)

**Other personalizable therapy plans based on specific molecular subtypes?**
- BRAF, MET exon 14, MET amp

**PD1/PDL1 monotherapy Group**
PD1/PD-L1 combination therapy being explored without preselection in 1st line?

- Platinum doublet +/- PD1/PD-L1
- Immune combination (PD1/CTLA4) vs plt doublet
CAFÉ in LONDON

QUESTIONS?

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University of Colorado
Anschutz Medical Campus