Lung Cancer 2017: It’s Complicated

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Lung Cancer—”The Good Old Days”

• Small cell had no changes any time recently
• Histology didn’t matter in NSCLC
• Doublet of choice (usually carboplatinum/paclitaxel in the US) followed by docetaxel followed by gefitinib or erlotinib
• No molecular subtypes of disease
Lung Cancer is Now Complicated

• SCLC—Finally progress?
• Squamous NSCLC
• Nonsquamous NSCLC—Targeted therapy update
• Immunotherapy Update
Small Cell Lung Cancer (SCLC)
SCLC

• Platinum/etoposide is standard initial therapy
• Radiation improves outcomes slightly in limited disease
• Topotecan has modest activity in relapsed/refractory disease but has toxicity issues
• No progress for twenty years, but two promising approaches
Rovalpituzumab tesirine (Rova-T)

• Targets DLL3, a cancer stem cell target
• 74 patient trial relapsed/refractory SCLC reported at ASCO 2016, 60 evaluable
• 68% stable disease, 18% RR
• 12 patients received Rova T 3rd line, with 6 responses
• Durability of responses is encouraging
• Fast track by FDA, should have more data within a year

Rudin et al ASCO 2016
Immunotherapy in SCLC

- Nivolumab and the combination of nivolumab and ipilimumab have been evaluated
- Nivolumab alone has 10% RR with 13% grade ¾ toxicity
- Nivo/Ipi has higher response rates (about 20%) with 18-19% grade ¾ toxicity
- Durable responses occur, larger studies underway
- Should have good combination IO data in SCLC within a year

Antonio et al Lancet Oncology 2016 7:883-95
Not Much Progress in Squamous NSCLC Either

Pemetrexed and bevacizumab contraindicated in SqCLC histology;
No oncogene-directed targeted therapy in squamous histology to date
### Molecular Targets in Squamous NSCLC

<table>
<thead>
<tr>
<th>Reference</th>
<th>Agent</th>
<th>Target</th>
<th>N (squamous)</th>
<th>Study Description</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scagliotti, 2010</td>
<td>Sorafenib</td>
<td>RAF, VEGFR</td>
<td>926 (223)</td>
<td>Phase III advanced NSCLC, including squamous (with paclitaxel/carboplatin) (HR detriment in squamous)</td>
<td>Negative</td>
</tr>
<tr>
<td>Novello, 2014</td>
<td>Motesanib</td>
<td>VEGFR, PDGFR</td>
<td>1450 (360)</td>
<td>Phase III advanced NSCLC, including squamous (with paclitaxel/carboplatin) (unacceptable toxicity in squamous)</td>
<td>Negative</td>
</tr>
<tr>
<td>Laurie, 2014</td>
<td>Cediranib</td>
<td>VEGFR, PDGFR</td>
<td>306 (39)</td>
<td>Phase II/III advanced NSCLC, including squamous (with carboplatin/paclitaxel) (halted for futility)</td>
<td>Negative</td>
</tr>
<tr>
<td>Pirker, 2009</td>
<td>Cetuximab (FLEX Study)</td>
<td>EGFR</td>
<td>1125 (377)</td>
<td>Phase III advanced EGFR+ NSCLC (with vinorelbine/cisplatin) (HR favorable in SCCA)</td>
<td>Positive</td>
</tr>
<tr>
<td>Sanofi, 2013</td>
<td>Iniparib</td>
<td>PARP</td>
<td>780 (780)</td>
<td>Phase III advanced squamous NSCLC (with gemcitabine/carboplatin)</td>
<td>Negative</td>
</tr>
<tr>
<td>Langer, 2014</td>
<td>Figitumumab</td>
<td>IGF1R</td>
<td>681 (584)</td>
<td>Phase III advanced non-adenocarcinoma NSCLC (with paclitaxel/carboplatin)</td>
<td>Negative</td>
</tr>
</tbody>
</table>
SQUIRE Trial

1093 patients
- First-line Stage IV sq- NSCLC
- ECOG PS 0-2

Gem-Cis + NECI (GC+N) (N = 545)

Maximum of 6 cycles

Gem-Cis (GC) N = 548

CR PR SD PD

NECI (N) PD

PD
SQUIRE Results

**GC + N**

<table>
<thead>
<tr>
<th>Stratified HR (95% CI)</th>
<th>0.84 (0.74, 0.96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stratified P value (log-rank)</td>
<td>0.01</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>11.5 (10.4, 12.6)</td>
</tr>
</tbody>
</table>

**GC**

CR, complete response; GC, gemcitabine-cisplatin; N, necitumumab; OS, overall survival; PD, progressive disease; PR, partial response; R, randomization; SD, stable disease

• Necitumumab did not significantly impact practice
• Recently taken out of the NCCN guidelines
• Necitumumab no longer actively marketed
Can We Improve the Value?

**SQUIRE (EGFR FISH+)**

<table>
<thead>
<tr>
<th></th>
<th>GC-N</th>
<th>GC</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>111</td>
<td>147</td>
</tr>
<tr>
<td>Unstrafied HR (95% CI)</td>
<td>0.70 (0.52, 0.96)</td>
<td></td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>12.0 (11.5, 15.9) vs. 12.1</td>
<td></td>
</tr>
</tbody>
</table>

**S0819 (SqCLC-EGFR FISH+)**

- Cetuximab Arm: N = 55, Events = 52, Median in Months = 11.8, 95% Conf. Int. = (8.6 - 13.5)
- Control Arm: N = 56, Events = 50, Median in Months = 8.4, 95% Conf. Int. = (4.2 - 8.7)

FISH, fluorescent in situ hybridization; GC, gemcitabine and cisplatin; N, necitumumab

1. Hirsch et al., WCLC 2015; abstr ORAL32.05
2. Herbst et al., WCLC 2015; abstr PLEN04.01

**FLEX**

<table>
<thead>
<tr>
<th>EGFR IHC High</th>
<th>HR* for OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>0.74 (0.48–1.14)</td>
</tr>
<tr>
<td>Squamous</td>
<td>0.62 (0.43–0.88)</td>
</tr>
</tbody>
</table>

*Chemotherapy + cetuximab vs chemotherapy
A MAP to Progress in Squamous NSCLC?

Multiple phase II-III sub-studies with “rolling opening and closure”

Each sub-study independent of the others
Each sub-study designed for registration of a drug-biomarker combination
Self-sustaining with new sub-studies in planning stages

http://www.lung-map.org/healthcare-providers
MAP In Progress

- Lung-MAP amended to 2nd line therapy & beyond to accommodate Nivolumab approval
- Pre-screening added back
- Eligibility criteria broadened; *Sub-studies in development

http://www.lung-map.org/healthcare-providers
Squamous NSCLC Summary

- Not much progress here either than immunotherapy
- Necitumumab might be considered for younger, motivated patients, particularly if EGFR expressed at high levels, though a confirmatory trial would be helpful
- MAP has not found the road to progress yet, but it continues and is an important effort
- Standard approach is platinum doublet chemotherapy (? With necitumumab in highly selected patients) followed by docetaxel alone or with ramicurimab and then afatinib
- We’ll talk about immunotherapy later!
Nonsquamous NSCLC—Targeted Therapy

• EGFR mutations—use of liquid biopsies
• ALK mutations—standard of care is changing
• We are in a target rich environment
EGFR mutated NSCLC

• Osimertinib is now approved for the T790M mutation
• Rebiopsy has become a standard approach
• Liquid biopsy is specific but not always sensitive, so standard is liquid biopsy at progression with tissue if liquid biopsy is not helpful
• Rb mutations suggest small cell transformation, but not all liquid biopsies include Rb
ALK mutated NSCLC

- EML-ALK mutation was described as a driving mutation in NSCLC in 2007
- Crizotinib was approved in 2011
- There are now three approved ALK inhibitors in the US—crizotinib, ceritinib, and alectinib
J-ALEX

- Randomized trial of alectinib vs crizotinib in ALK inhibitor naïve ALK-positive NSCLC
- Japanese trial of 207 patients closed early by DSMB
- PFS favored alectinib with HR 0.34 (0.17-0.70, p<.0001)
- Median PFS for alectinib not reached vs 10.2 months for crizotinib
- Crizotinib had more grade 3-4 toxicity
- Multinational confirmatory trial (ALEX) will be at ASCO; press release says it is positive
- Alectinib is likely the new standard in ALK positive NSCLC
- Alectinib is much more active in the CNS

Nokihara et al ASCO 2016 abstract 9008
Other Targets in Nonsquamous NSCLC

- ROS 1
- KRAS (so far no drugs for this)
- RET
- BRAF
- MET exon 14 mutations
- More coming—It’s getting complicated!
Targeted Therapy in Nonsquamous NSCLC 2017

• Rebiopsy is important; liquid biopsies are useful but need tissue at times
• Understanding of EGFR resistance mutations is evolving rapidly
• Standard of care in ALK-positive NSCLC changing from crizotinib to alectinib
• New mutations, each of which account for 1-2% of NSCLC, are being identified
Immunotherapy of NSCLC

• State of the art
• Use in first-line metastatic NSCLC
• New approaches in earlier disease
• Theoretical discussion of variability of response
NSCLC Immunotherapy 2017

• Three drugs are approved in the second-line and beyond—pembrolizumab, nivolumab, and atezolizumab
• Use in second-line does not require PD-L1 testing for any of these drugs
• Pembrolizumab is approved in first-line NSCLC for patients with PD-L1 expression >50%
Checkmate 017: Nivolumab vs. Docetaxel

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

Randomization

Nivolumab
3 mg/kg IV Q2W until PD or unacceptable toxicity
n = 135

Docetaxel
75 mg/m² IV Q3W until PD or unacceptable toxicity
n = 137

Primary Endpoint:
- OS

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

Patients stratified by region and prior paclitaxel use

- One pre-planned interim analysis for OS
- At time of DBL (December 15, 2014), 199 deaths were reported (86% of deaths required for final analysis)
- The boundary for declaring superiority for OS at the pre-planned interim analysis was \( P < 0.03 \)

Spigel et al., ASCO 2015; abstr 8009.
Checkmate 017 Results

- Phase III RCT of patients with advanced squamous cell NSCLC in whom disease progressed during or after first-line chemotherapy
- Randomized 272 patients to receive nivolumab 3 mg per kg of body weight every 2 weeks or docetaxel 75 mg/m² every 3 weeks

**Median OS**

- Efficacy of nivolumab was independent of PD-L1 status in this SqCLC trial.
- Treatment-related AEs grade 3 or 4 occurred in 7% in the nivolumab group vs 55% in the docetaxel group
PD-L1 Expression in 017

No apparent prognostic effect of PD-L1 expression. Survival benefit of nivolumab was independent of PDL1 expression levels.
Checkmate 057: Nonsquamous NSCLC

No. of Deaths/Total No. of Patients
- Nivolumab: 190/292
- Docetaxel: 223/290

Median Overall Survival (95% CI)
- Nivolumab: 12.2 (9.7–15.0) mo
- Docetaxel: 9.4 (8.1–10.7) mo

1-Yr Overall Survival Rate (95% CI)
- Nivolumab: 51 (45–56) %
- Docetaxel: 39 (33–45) %

Hazard ratio for death, 0.73 (96% CI, 0.59–0.89); P=0.002

No. of Events/Total No. of Patients
- Nivolumab: 234/292
- Docetaxel: 245/290

Median Progression-free Survival (95% CI)
- Nivolumab: 2.3 (2.2–2.3) mo
- Docetaxel: 4.2 (3.5–4.9) mo

1-Yr Progression-free Survival Rate (95% CI)
- Nivolumab: 19 (14–23) %
- Docetaxel: 8 (5–12) %

Hazard ratio for disease progression or death, 0.92 (95% CI, 0.77–1.11); P=0.39
PD-L1 Expression and Outcome in 057

OS benefit correlates with PD-L1 expression in this Non-SQ trial.
Contrasts with trial 017 in SQ.
It’s complicated!
Outcomes of Subgroups in 057

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Unstratified HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>582</td>
<td>0.75 (0.62, 0.91)</td>
</tr>
<tr>
<td>Age Categorization (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>339</td>
<td>0.81 (0.62, 1.04)</td>
</tr>
<tr>
<td>≥65 and &lt;75</td>
<td>200</td>
<td>0.63 (0.45, 0.89)</td>
</tr>
<tr>
<td>≥75</td>
<td>43</td>
<td>0.90 (0.43, 1.87)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>319</td>
<td>0.73 (0.56, 0.96)</td>
</tr>
<tr>
<td>Female</td>
<td>263</td>
<td>0.78 (0.58, 1.04)</td>
</tr>
<tr>
<td>Baseline ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>179</td>
<td>0.64 (0.44, 0.93)</td>
</tr>
<tr>
<td>≥1</td>
<td>402</td>
<td>0.80 (0.63, 1.00)</td>
</tr>
<tr>
<td>Smoking Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current/Former Smoker</td>
<td>458</td>
<td>0.70 (0.56, 0.86)</td>
</tr>
<tr>
<td>Never Smoked</td>
<td>118</td>
<td>1.02 (0.64, 1.61)</td>
</tr>
<tr>
<td>EGFR Mutation Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>82</td>
<td>1.18 (0.69, 2.00)</td>
</tr>
<tr>
<td>Not Detected</td>
<td>340</td>
<td>0.66 (0.51, 0.86)</td>
</tr>
<tr>
<td>Not Reported</td>
<td>160</td>
<td>0.74 (0.51, 1.06)</td>
</tr>
</tbody>
</table>

Paz-Ares et al., ASCO 2015, abstr LBA109.
Immunotherapy in 2d Line NSCLC

Summary

• Data for nivolumab, pembrolizumab, and atezolizumab are all compelling and fairly similar
• No direct comparisons have been done and likely never will
• There will be some limited data about sequential IO therapy soon
• Doublet therapy will likely make this moot
Keynote 24: Pembrolizumab in 1st-Line NSCLC

Key eligibility criteria
- Untreated stage IV NSCLC
- PD-L1 TPS ≥50%
- No activating EGFR mutation or ALK translocation
- No untreated brain metastases

Primary endpoint
◆ PFS (RECIST v1.1)

Secondary endpoints
◆ OS, ORR, safety

Exploratory endpoint
♦ DOR

Platinum-doublet chemotherapy
(4-6 cycles) (n=151)

Pembrolizumab 200 mg
q3w (35 cycles) (n=154)

PD / toxicity / other

Crossover permitted from chemotherapy to pembrolizumab if PD

Pembrolizumab vs. Chemotherapy in PD-L1 Positive* NSCLC


<table>
<thead>
<tr>
<th>Pembrolizumab</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>45%</td>
</tr>
<tr>
<td>ORR</td>
<td>28%</td>
</tr>
<tr>
<td>mPFS</td>
<td>10.3 mo</td>
</tr>
<tr>
<td>mPFS</td>
<td>6.0 mo</td>
</tr>
<tr>
<td>6-mo OS</td>
<td>80%</td>
</tr>
<tr>
<td>6-mo OS</td>
<td>72%</td>
</tr>
</tbody>
</table>

*PD-L1 expression ≥50%
Incidence of treatment-related AE, any severity, was lower with pembrolizumab compared with chemotherapy (73.4 vs 90.0%, respectively).

Keynote 24 Summary

• For patients with PD-L1 positive (>50%) NSCLC, pembrolizumab improved OS, PFS, and RR compared to chemotherapy
• 44% of chemotherapy patients crossed over to pembrolizumab after disease progression
• Pembrolizumab had fewer adverse events than chemotherapy
Keynote 21: Chemotherapy + Pembrolizumab

**Key patient inclusion criteria**
- Untreated stage IIIB / IV nonsquamous NSCLC
- No EGFR mutation or ALK translocation
- Provision of sample for PD-L1 assessment
- ECOG PS 0–1
- No untreated brain metastases

**Primary endpoint**
- ORR (RECIST) central review

**Secondary endpoints**
- PFS, DOR, OS, safety, relationship between anti-tumor activity and PD-L1 TPS

**Stratification**
- PD-L1 status (TPS ≥1 vs. <1%)

**Pembrolizumab + chemotherapy**
- Pembrolizumab 200 mg q3w (2 years) + carboplatin AUC5 mg/mL/min + pemetrexed 500 mg/m² q3w (4 cycles)* (n=60)

**Chemotherapy**
- Carboplatin AUC5 mg/mL/min + Pemetrexed 500 mg/m² q3w (4 cycles)* (n=63)

**Pembro 200 mg q3w (2 years)**

*Pemetrexed 500 mg/m² q3w permitted as optional indefinite maintenance therapy

Keynote 21: Key Results

- Pembrolizumab + chemotherapy significantly improved the proportion of patients who achieved an ORR compared with chemotherapy alone (estimated treatment difference 26%).

Pembrolizumab + Chemo 55% vs. Chemo Alone 29%

confirmed ORR: 55% vs. 29%


graph: ORR, % (95% CI)

TTR, months median (IQR) 1.5 (1.4–2.8) vs. 2.7 (1.4-2.8)
DoR, months median (IQR) NR (4.2-9.0) vs. NR (3.5-10)
Ongoing response, n (%) 29 (88) vs. 14 (78)

 alive without subsequent disease progression

Keynote 21: Key Results

- PFS was significantly longer with pembrolizumab + chemotherapy (13.0 mo) compared with chemotherapy alone (8.9 mo) (HR 0.53; p=0.010)

Keynote 21: Key Results

80% of patients who had a PD-L1 score of ≥50% achieved ORR with pembrolizumab + chemotherapy.

Horizontal dotted lines represent the ORR in the total population.

Keynote 21: Key Results

Exposure and AE summary

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab + chemotherapy (n=59)</th>
<th>Chemotherapy alone (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exposure, months median (IQR)</strong></td>
<td>8.0 (4.7 to 11.2 mo)</td>
<td>4.9 (2.1 to 7.4 mo)</td>
</tr>
<tr>
<td><strong>Treatment-related AEs, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3–4</td>
<td>55 (93)</td>
<td>56 (90)</td>
</tr>
<tr>
<td>Serious</td>
<td>22 (37)</td>
<td>14 (23)</td>
</tr>
<tr>
<td>Led to discontinuation</td>
<td>16 (27)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Led to death</td>
<td>6 (10)</td>
<td>8 (13)</td>
</tr>
<tr>
<td></td>
<td>1 (2)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

◆ Exposure was 1.6 times longer in the pembrolizumab + chemotherapy group
◆ Most treatment-related AEs were mild and grade 1–2 severity

Keynote 21 Conclusions

• Pembrolizumab in combination with carboplatinum and pemetrexed had better PFS and RR than chemotherapy alone
• OS was similar between two arms, but very immature
• Safety profile was manageable
• Only a randomized phase 2
• Conditional FDA approval may be coming soon
First-line IO Summary

• Pembrolizumab is FDA approved for patients with PD-L1>50%
• The chemo/pembro combination will likely get conditional approval next month
• This may have an impact on PD-L1 testing
• Multiple other chemo/IO combination trials are in progress or have completed accrual, so a wealth of data is coming
And Now For Something Completely Different...
Checkmate 026: Nivolumab 1st-Line NSCLC

Key patient inclusion criteria
- Stage IV or recurrent NSCLC
- No prior systemic therapy for advanced disease
- No EGFR / ALK mutations sensitive to targeted inhibitor therapy
- PD-L1 expression of ≥1%
- CNS mets permitted if adequately trt at least 2 wks prior to randomization
- ECOG PS 0 or 1

Primary endpoint
- PFS (≥5% PD-L1+)

Secondary endpoints
- PFS (≥1% PD-L1+), OS, ORR

Nivolumab 3 mg/kg IV q2w (n=271)
- PD / toxicity

Nivolumab (optional)

Chemotherapy (investigator choice – histology dependent) for 6 cycles (n=270)

Stratification
- PD-L1 expression (<5% vs. ≥5%)
- Histology (squamous vs. nonsquamous)

PD

Checkmate 026: Results

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>mPFS, months</td>
<td>4.2 (95%CI 3.0, 5.6)</td>
<td>5.9 (95%CI 4.4, 6.9)</td>
</tr>
<tr>
<td>1-year PFS rate, %</td>
<td>23.6</td>
<td>23.2</td>
</tr>
</tbody>
</table>

HR 1.15 (95%CI 0.91, 1.45); p=0.2511

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

Checkmate 026: Conclusions

- Nivolumab did not meet the primary endpoint of superior PFS compared with chemotherapy
- Safety results were consistent with the known safety profile of nivolumab; there were fewer treatment-related grade 3–4 AEs in the nivolumab vs. chemotherapy arm
- OS was similar in the nivolumab and chemotherapy arms and both compared favourably with historical controls
  - 60.4% of patients in the chemotherapy arm received subsequent nivolumab

New from AACR 2017

• Impact of Tumor Mutation Burden (TMB) on the Efficacy of First-Line Nivolumab in Stage IV or Recurrent Non-Small Cell Lung Cancer: An Exploratory Analysis of CheckMate 026

Peters et al, AACR 2017
TMB in Checkmate 026

• TMB has been shown to be predictive of outcomes in immuno-oncology (Rizvi et al, Science 2015 348:124-8)

• An exploratory analysis of 026 was done to test the hypothesis that high TMB might predict benefit from nivolumab vs. chemotherapy

• Matched tumor and germline exome sequences were performed for TMB analysis

• 312 patients (58% of population) had matched samples for analysis

• TMB in 026 patients generally similar distribution to that seen in previous report of TCGA

Peters et al AACR 2017
TMB in Checkmate 026

• Analysis of baseline characteristics very similar in overall population and TMB-evaluable (TMB-E) population

• OS AND PFS were similar in each arm for overall and TMB-E

• Patients were divided into three subgroups based on numbers of mutations (<100, 100-242, >243)

Peters et al AACR 2017
PFS by TMB Tertile in Checkmate 026

Nivolumab

<table>
<thead>
<tr>
<th></th>
<th>Low (n = 62)</th>
<th>Medium (n = 49)</th>
<th>High (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>4.2 (1.5, 5.6)</td>
<td>3.6 (2.7, 6.9)</td>
<td>9.7 (5.1, NR)</td>
</tr>
</tbody>
</table>

Chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Low (n = 41)</th>
<th>Medium (n = 53)</th>
<th>High (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>6.9 (5.4, NR)</td>
<td>6.5 (4.3, 8.6)</td>
<td>5.8 (4.2, 8.5)</td>
</tr>
</tbody>
</table>

Peters et al AACR 2017
## PFS and RR by TMB Subgroup in Checkmate 026

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>HIGH</th>
<th>TMB</th>
<th>LOW/MED</th>
<th>TMB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab vs Chemotherapy</td>
<td>Nivolumab</td>
<td>9.7</td>
<td>5.8</td>
<td>4.1</td>
</tr>
<tr>
<td>PFS (months)</td>
<td>9.7</td>
<td>5.8</td>
<td>4.1</td>
<td>6.9</td>
</tr>
<tr>
<td>HR 0.62 (0.38, 1.0)</td>
<td>HR 1.82 (1.3, 2.55)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td>47%</td>
<td>28%</td>
<td>23%</td>
<td>33%</td>
</tr>
</tbody>
</table>

Peters et al AACR 2017
OS and TMB in Checkmate 026

• OS was not impacted by TMB subgroup
  • High TMB Nivo 18.3 v Chemo 18.8 mos (HR 1.1) (68% crossover to nivo)
  • Low/med TMB 12.7 v 13.2 mos (HR 0.99) (55% crossover to nivo)

Peters et al AACR 2017
TMB in Checkmate 026

• Current/former smokers had higher TMB than never-smokers
• There was no association between TMB and PD-L 1 expression

Peters et al AACR 2017
### ORR by TMB subgroup and PD-L1 Expression

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th></th>
<th>Chemotherapy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High TMB</td>
<td>Low/Med TMB</td>
<td>High TMB</td>
<td>Low/Med TMB</td>
</tr>
<tr>
<td>PD-L1 &gt;50%</td>
<td>75%</td>
<td>34%</td>
<td>25%</td>
<td>46%</td>
</tr>
<tr>
<td>PD-L1 1-49%</td>
<td>32%</td>
<td>16%</td>
<td>32%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Peters et al AACR 2017
PFS by TMB and PD-L1 in O26

Peters et al AACR 2017
TMB in Checkmate 026--Summary

• Nivolumab improved RR and PFS vs chemotherapy in patients with high TMB
• PFS was longer in patients with high TMB regardless of PD-L1 status
• Patients with high TMB and PD-L1 >50% benefited the most from nivolumab
• Patients with med/low TMB had greater benefit from chemotherapy
• These subsets are exploratory and numbers are small, so these findings should be viewed cautiously

Peters et al AACR 2017
Neoadjuvant Nivolumab

Study Design & Endpoints

- Newly diagnosed resectable stage I (>2cm)/II/IIIA NSCLC
- Nivolumab 3mg/kg IV on Day-28 & Day-14
- Surgical resection on Day 0
- Standard of care postoperative treatment
- Safety follow up for 30 days after surgery

Forde et al ESMO 2016
Study Endpoints

- **Primary Endpoint:** Safety and feasibility

- **Exploratory Endpoints:** Correlatives in blood and tumor, percent pathologic response, RFS, OS

- **Planned enrollment:** 6 patient safety & feasibility run-in followed by expansion to enroll up to 20 resected patients.

Forde et al ESMO 2016
Treatment-related AEs

<table>
<thead>
<tr>
<th></th>
<th>Any grade N (%)</th>
<th>Grade 3-4 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-related AEs</td>
<td>6 (32%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Events leading to discontinuation</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Delays to surgery</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

- Treatment-related toxicities were consistent with those seen in other studies of nivolumab and there were no treatment-related deaths
- One death occurred during the postoperative safety evaluation period that assessed as unrelated to study treatment

Data is based on a Sept 15, 2016 database lock

Forde et al ESMO 2016
Analysis of Response (Exploratory)

Radiographic response (N=18) RECIST 1.1

<table>
<thead>
<tr>
<th>Response</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Response</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>13 (72)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>

Pathologic downstaging from pre-treatment clinical stage (N=18)

<table>
<thead>
<tr>
<th>Response</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>7 (39)</td>
</tr>
<tr>
<td>No</td>
<td>11 (61)</td>
</tr>
</tbody>
</table>

Tumor pathologic response after neoadjuvant anti-PD-1 (N=17)

- 39% (95% CI 20-61%) of per protocol patients, 7 of 18, had <10% residual viable tumor at resection
- 1 patient had a pathologic complete response

Forde et al ESMO 2016
Neoadjuvant Nivolumab Summary

• Neoadjuvant nivolumab did not interfere with surgery and there were no surprising safety issues
• 39% of patients had a major pathologic response with tumor infiltration by immune cells
• Responses were seen in PD-L1 positive and negative patients
• Very small numbers; Need confirmation in larger studies

Forde et al ESMO 2016
Why Is Immunotherapy Complicated?

• Unchangeable host immune factors such as HLA type
• Changeable host immune factors such as lymphocyte subsets can be influenced by chemotherapy and other treatment
• Tumor immunogenicity can change over time and can be influenced by chemotherapy and other treatment
• Tumor immunogenicity may inherently vary as well (e.g. EGFR mutated tumors in non-smokers with low TMB)
• Concomitant chemotherapy and Immunotherapy may have significant interactions specific to the drugs used
What’s Next for Immunotherapy of NSCLC?

• Combinations are already being evaluated (IO and IO, IO and chemo, IO and antibodies)

• Literally thousands of potential combinations to be studied

• Broad clinical trial participation in the community is vital to making progress!
“When people complain of your complexity, they fail to remember they made fun of your simplicity.”

--Michael Bassey Johnson