Setting lung cancer on fire

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Division of Respiratory Medicine
NCCN Guidelines Version 3.2019
Non-Small Cell Lung Cancer
NCCN Evidence Blocks™

CLINICAL PRESENTATION

Advanced or metastatic Disease

Establish histologic subtype with adequate tissue for molecular testing (consider rebiopsy if appropriate)
Smoking cessation counseling
Integrate palliative care (See NCCN Guidelines for Palliative Care)

TESTING

Molecular testing

EGFR mutation testing (category 1)
ALK testing (category 1)
ROS1 testing
BRAF testing
Testing should be conducted as part of broad molecular profiling
PD-L1 testing (category 1)

TESTING RESULTS

Sensitizing EGFR mutation positive (see NSCL-18)
ALK positive (see NSCL-21)
ROS1 positive (see NSCL-24)
BRAF V600E positive (see NSCL-25)

PD-L1 ≥50% and EGFR, ALK negative or unknown (see NSCL-27)
EGFR, ALK, ROS1, BRAF negative or unknown, PD-L1 <50% or unknown (see NSCL-28)

Sensitizing EGFR mutation positive (see NSCL-18)
ALK positive (see NSCL-21)
ROS1 positive (see NSCL-24)
BRAF V600E positive (see NSCL-25)

PD-L1 ≥50% and EGFR, ALK negative or unknown (see NSCL-27)
EGFR, ALK, ROS1, BRAF, negative or unknown, PD-L1 <50% or unknown (see NSCL-29)
Cancer immunoediting

Immune checkpoints: CTLA-4 and PD-1

Pennell NA. Semin Oncol 2015;42:S3-S10
PD-1/PD-L1 pathway

Dempke WC et al. Anticancer Res 2015;35:574 5-28
Different approaches to targeting the PD-L1/PD-1 pathway

**Anti-PD-L1 Agents**

- Tumor cell
- PD-L1
- PD-L2
- B7.1
- Macrophage

**Anti-PD-1 Agents**

- Tumor cell
- PD-L1
- PD-L2
- B7.1
- Macrophage

*Anti-PDL1 provides dual blockade of co-inhibitory receptors, PD-1 and B7.1, for enhanced T-cell activation and propagation*

*Spares PD-L2/PD-1 interactions, helping to minimize autoimmune reactions in healthy tissue*
Case 1

- M/75
- Ex-chronic smoker (40 pack-yrs, quitted since 2012)
- PMH: GU/gastritis in 2004, HBsAg –ve
- Presented with haemoptysis in Dec 2015
CXR
Case 1

- FOB in Feb 2016: Irregular mucosa at RB1 + EB tumour at lingular segment
- EBBx at lingula: Adenosquamous NSCLC (CK7 & p63 +ve; TTF-1 –ve), EGFR/ALK WT
Case 1

- **PET-CT:**
  - Bilateral parotid nodules SUVmax 2.5 and 4.3)
  - RUL mass (4.1 x 3.8 x 3.7 cm, SUVmax 11.9) with satellite nodules
  - Another speculated mass in lingula (SUVmax 10.1)
  - N3 mediastinal LNs
  - Mucosal lesions at hepatic flexure (SUVmax 7) and proximal ascending colon (SUVmax 5.3)
Case 1

- Colonoscopy: 2 polyps → Tubulovillous adenoma
- R parotic FNA biopsy: Warthin’s tumour
Case 1

- Recruited into KEYNOTE 042 trial (1st line pembrolizumab vs chemotherapy for PD-L1 ≥ 1%)
- On pembrolizumab arm since April 2016
- CT reassessment (Post-cycle 3): PR in June 2016
- CT on 8 Feb 2018: Still in PR
- Completed 2 years of pembrolizumab thus stopped in Apr 2018

<table>
<thead>
<tr>
<th>Date</th>
<th>Tx wks</th>
<th>LUL (mm)</th>
<th>RUL (mm)</th>
<th>Sum of longest diameters (mm)</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apr/16</td>
<td>Baseline</td>
<td>31.9</td>
<td>41.1</td>
<td>109.3</td>
<td></td>
</tr>
<tr>
<td>Jun/16</td>
<td>9</td>
<td>18.2</td>
<td>20.4</td>
<td>60.1</td>
<td>-45.0%</td>
</tr>
<tr>
<td>Jun/17</td>
<td>57</td>
<td>13.1</td>
<td>17.2</td>
<td>48.9</td>
<td>-55.3%</td>
</tr>
<tr>
<td>Feb/18</td>
<td>93</td>
<td>10.2</td>
<td>16</td>
<td>44.5</td>
<td>-59.3%</td>
</tr>
</tbody>
</table>
CT scans

Apr 2016

Feb 2018
CT scans

Apr 2016

Feb 2018
CT scans

Apr 2016

Feb 2018
CT scans

Apr 2016  Feb 2018
CT scans

Apr 2016

Feb 2018
## Case 1

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>C2</th>
<th>C4</th>
<th>C6</th>
<th>C8</th>
<th>C10</th>
<th>C26</th>
<th>C32</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TSH</strong> (N: 0.3-5 mIU/L)</td>
<td>2.608</td>
<td>5.301↑</td>
<td>0.177↓</td>
<td>116.36↑</td>
<td>13.98↑</td>
<td>0.64</td>
<td>0.34</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>fT3</strong> (N: 1.23-3.08 nmol/L)</td>
<td>1.69</td>
<td>1.69</td>
<td>2.00</td>
<td>0.46↓</td>
<td>1.54</td>
<td>1.54</td>
<td>1.39</td>
<td>1.39</td>
</tr>
<tr>
<td><strong>fT4</strong> (N: 9.0-28.4 pmol/L)</td>
<td>10.3</td>
<td>10.3</td>
<td>14.2</td>
<td>2.6↓</td>
<td>12.9</td>
<td>16.8</td>
<td>16.8</td>
<td>18.1</td>
</tr>
<tr>
<td><strong>T4 replacement</strong></td>
<td>100 mcg/d</td>
<td>100 mcg/d</td>
<td>100 mcg/d</td>
<td>100/75 mcg/d alt.day</td>
<td>100/75 mcg/d alt.day</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Case 1

- In May 2017 (Cycle 18)
- On and off vomiting x 1 month
- Progressive weight loss
- Malaise
- Hb 9.8 HcMc (11.6 in Mar 2017)
- Na 140, K 4.0
- Transferrin saturation 36% (normal)
What is the emerging problem?

1. Peptic ulceration
2. Hypothyroidism
3. Autoimmune haemolytic anaemia
4. Adrenal insufficiency
5. Infective complications
Case 1

- Testosterone, GH normal
- Prolactin 382 mIU/L (ULN: 375)
- Cortisol (9AM): <5 nmol/L (N: 130-600)
- ACTH 7.9 pg/ml (N ≤ 46)
- Short synacthen test: cortisol (nmol/L) 10 (pre-), 93 (post-30 min), 81 (post-60 min) → c/w ACTH insufficiency /hypophysitis
- Put on hydrocortisone 10mg BD replacement
MRI pituitary June 2017

- Inhomogeneous contrast enhancement in keeping with chronic inflammation (hypophysitis). Tiny 2mm nodule in posterior part of anterior lobe in keeping with a small microadenoma
Case 1

- CT thorax in Apr 2019: Focal LUL parenchymal density noted, with mild interval decrease at lateral aspect and mildly increased at medial aspect comparing with last private study dated 21.11.2018.
- CT-guided FNA of lingular nodules done on 5 June 2019, result pending
Anti-PD1 monotherapy in 1L Advanced NSCLC

- KEYNOTE 024
- KEYNOTE 042
KEYNOTE-024 Study Design (NCT02142738)

Key Eligibility Criteria
- Untreated stage IV NSCLC
- PD-L1 TPS ≥50%
- ECOG PS 0–1
- No activating EGFR mutation or ALK translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy

R (1:1) N = 305

Pembrolizumab
200 mg IV Q3W
(2 years)

Platinum-Doublet Chemotherapy
(4–6 cycles)

- Pemetrexed + carboplatin
- Pemetrexed + cisplatin
- Paclitaxel + carboplatin
- Gemcitabine + carboplatin
- Gemcitabine + cisplatin

Pembrolizumab
200 mg Q3W
for 2 years

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

Optional pemetrexed maintenance therapy for nonsquamous disease.
Permitted for nonsquamous disease only.
Prior to the DMC recommendation and amendment 6, which permitted those in the chemotherapy arm to be offered pembrolizumab (based on interim analysis 2 data), patients were eligible for crossover when PD was confirmed by blinded, independent central radiology review.
Overall Survival: Updated Analysis

![Graph showing survival rates and hazard ratios for Pembrolizumab and Chemotherapy.]

<table>
<thead>
<tr>
<th></th>
<th>Events, n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab&lt;sup&gt;a&lt;/sup&gt;</td>
<td>73</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.47–0.86)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>96</td>
<td>P = 0.002&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Median (95% CI)**
- Pembrolizumab: 30.0 mo (18.3 mo–NR)
- Chemotherapy: 14.2 mo (9.8 mo–19.0 mo)

**No. at risk**

<table>
<thead>
<tr>
<th></th>
<th>Pembro</th>
<th>Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>154</td>
<td>151</td>
</tr>
<tr>
<td>3</td>
<td>136</td>
<td>123</td>
</tr>
<tr>
<td>6</td>
<td>121</td>
<td>107</td>
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<tr>
<td>9</td>
<td>112</td>
<td>88</td>
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<td>12</td>
<td>106</td>
<td>80</td>
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<td>15</td>
<td>96</td>
<td>70</td>
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<td>18</td>
<td>89</td>
<td>61</td>
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<td>21</td>
<td>83</td>
<td>55</td>
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<td>24</td>
<td>52</td>
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</tr>
<tr>
<td>27</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>30</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>33</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Effective crossover rate from chemotherapy to anti-PD-L1 therapy, 62.3% (82 patients crossed over to pembrolizumab during the study and 12 received anti-PD-L1 therapy outside of crossover). <sup>b</sup>Nominal P value. NR, not reached.

Data cutoff: July 10, 2017.
**KEYNOTE-042 Study Design**

**Key Eligibility Criteria**
- Untreated locally advanced or metastatic NSCLC of any histology
- PD-L1 TPS $\geq$1%
- No sensitizing EGFR or ALK alterations
- ECOG PS 0 or 1
- No untreated or unstable CNS metastases
- No history of pneumonitis that required systemic corticosteroids

**Stratification Factors**
- Region (east Asia vs rest of the world)
- ECOG PS (0 vs 1)
- Histology (squamous vs nonsquamous)
- PD-L1 TPS ($\geq$50% vs 1-49%)

**Randomize 1:1**

- **N = 637**

**Pembrolizumab**
- 200 mg Q3W for up to 35 cycles

**Carboplatin AUC 5 or 6 Q3W + Paclitaxel 200 mg/m² Q3W**
- OR
- Carboplatin AUC 5 or 6 Q3W + Pemetrexed 500 mg/m² Q3W for up to 6 cycles

**End points**
- Primary: OS in PD-L1 TPS $\geq$50%, $\geq$20%, and $\geq$1%
- Secondary: PFS and ORR in TPS $\geq$50%, $\geq$20%, and $\geq$1%; safety in TPS $\geq$1%

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*Pemetrexed maintenance therapy was optional but strongly encouraged for patients with nonsquamous histology.*
Overall Survival: TPS ≥50%

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>157 (52.5%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Chemo</td>
<td>199 (66.3%)</td>
<td>(0.56-0.85)</td>
</tr>
</tbody>
</table>

Median (95% CI)
20.0 mo (15.4-24.9)
12.2 mo (10.4-14.2)

Data cutoff date: Feb 26, 2018.
Overall Survival: TPS ≥1%

**Events** | **HR (95% CI)** | **P**  
--- | --- | ---  
Pembro | 371 (58.2%) | 0.81 | 0.0018  
Chemo | 438 (68.8%) | (0.71-0.93) |  

**Median (95% CI)**  
- Pembro: 16.7 mo (13.9-19.7)  
- Chemo: 12.1 mo (11.3-13.3)  

No. at Risk  
- Months  
  - 0: 637, 637  
  - 6: 463, 485  
  - 12: 365, 316  
  - 18: 214, 166  
  - 24: 112, 88  
  - 30: 35, 24  
  - 36: 2, 1  
  - 42: 0, 0  

Data cutoff date: Feb 26, 2018.
Overall Survival: TPS ≥1-49% (Exploratory Analysis\textsuperscript{a})

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>0.92</td>
</tr>
<tr>
<td>Chemo</td>
<td>(0.77-1.11)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}No alpha allocated to this comparison.

Median (95% CI):
- Pembro: 13.4 mo (10.7-18.2)
- Chemo: 12.1 mo (11.0-14.0)

No. at Risk:
- 338
- 239
- 176
- 107
- 53
- 13
- 0
- 0

Data cutoff date: Feb 26, 2018.
Current 1L treatment algorithm

Advanced lung adenoca/selected squamous cell ca

EGFR/ALK/ROS1/BRAF WT

PD-L1 \( \geq 50\% \) → Pembro

Chemotherapy options
1. pem/platinum (nonsquamous)
2. Bev + chemo (nonsquamous)
3. Gem or taxane/platinum (squamous)

PD-L1 1-49%

Specific TKIs

EGFR/ALK/ROS1/BRAF driven

Based on KEYNOTE 024 data and NCCN guideline
Adverse events from immune checkpoint inhibitors

Table. Selected immune-related adverse events associated with immune checkpoint inhibitors

<table>
<thead>
<tr>
<th>Organ/System</th>
<th>Immune-related Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic</td>
<td>pruritis, rash, psoriasis, vitiligo</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>diarrhoea, colitis, ileitis, hepatitis, pancreatitis, gastritis</td>
</tr>
<tr>
<td>Endocrine</td>
<td>thyroiditis, hypophysitis, adrenal insufficiency, diabetes</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>pneumonitis, pleuritis, granulomatosis</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>arthralgia, arthritis, dermatomyositis</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>myocarditis, pericarditis, vasculitis</td>
</tr>
<tr>
<td>Neurological</td>
<td>Guillain-Barre syndrome, encephalopathy, myasthenia, neuropathy, myelopathy, meningitis</td>
</tr>
<tr>
<td>Kidney</td>
<td>nephritis</td>
</tr>
<tr>
<td>Blood</td>
<td>haemolytic anaemia, thrombocytopenia, neutropenia, haemophilia</td>
</tr>
<tr>
<td>Eyes</td>
<td>uveitis, conjunctivitis, scleritis, episcleritis, blepharitis, retinitis</td>
</tr>
</tbody>
</table>
Case 2

- M/57
- Non-smoker, non-drinker
- HBsAg –ve
- Allergic to aspirin
- Clerical work
- Good past health
Case 2

- Presented with hameoptysis 11/2017
- Mild dyspnoea

- PE
  - GC well
  - No cervical LN
  - CVS/Chest/Abdomen/CNS normal
PET-CT
MRI Brain
Bronchoscopy/EBUS-TBNA

- EBUS-TBNA
  - #11Rs x 1 passes; very good results
  - #7 x 1 passes; very good results
- Right endobronchial lesion - NIL
- Left endobronchial lesion - LB8b lesion
Bronchoscopy/EBUS-TBNA

- Adenocarcinoma
  - Immunostaining: CK7 positive, CK20 focally positive, TTF-1: strongly positive, p63 negative
  - Consistent with adenocarcinoma, primary from lung origin
Bronchoscopy/EBUS-TBNA

- EGFR mutation –ve
- ALK mutation –ve
Treatment

– Palliative chemotherapy with Alimta + Carboplatin (I) since 7/4/18
– 1 episode of non-neutropenic fever, given antibiotic
– SRS to brain metastasis 28/4/18
– Tumour PD-L1 TPS 60%
– NGS: RET fusion (KIF5B-RET)
– Switched to Pembrolizumab on 2/5/2018, given for 3 cycles
Reassessment PET-CT

28 Feb 2018

25 Jun 2018
Treatment

- PET-CT in June 2018: Mixed response (interval ↓ size but ↑ FDG uptake in LLL primary, ↓ mediastinal LNs, but new LLL nodule/L suprahilar LN/abdominal LNs)
- Switched to Pembrolizumab/Alimta/Carboplatin in view of mixed response to Pembrolizumab on 4/7/2018
- CEA Trend: 6.5 → 5.1 → 4.3 → 4.0
- Then continued on Pembrolizumab/Alimta as maintenance therapy
Reassessment PET-CT

28 Feb 2018

22 Jan 2019
Reassessment PET-CT

– The overall pictures are suggestive of primarily stable disease although there are interval slight increase in metabolic activities of the primarily lung tumour and the mediastinal lymph nodes.
Treatment

- RT by tomotherapy to LLL primary tumor on 12/2/19
- Continued on Pembrolizumab/Alimta as maintenance therapy, so far given for 15 cycles
Case 2

PD-L1 +ve Stage IV Adenocarcinoma of lung
Responded to Pembrolizumab + Chemotherapy
Anti-PD1/L1 + CT

- KEYNOTE 189
- KEYNOTE 407
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)

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

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

Pembrolizumab 200 mg Q3W for up to 35 cycles

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

R (2:1)

N = 410

N = 206

*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.
Analysis Populations and End Points

Analysis Populations

- Efficacy
  - Intention-to-treat (ITT)
- Safety
  - All patients who received ≥1 dose of study medication

End Points for Discussion

- Primary
  - Overall survival
  - Progression-free survival
- Secondary
  - Response rate
  - Duration of response
  - Safety
- Exploratory
  - Effect of PD-L1 expression on efficacy
  - Patient-reported outcomes
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</td>
</tr>
<tr>
<td>Placebo/Pem/Plat</td>
<td>52.4%</td>
<td>(0.38-0.64)</td>
</tr>
</tbody>
</table>

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

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

## TPS < 1%
- **Events**
  - Pembrolizumab/Pem/Plat: 38.6%
  - Placebo/Pem/Plat: 55.6%
- **HR (95% CI)**
  - Pembrolizumab/Pem/Plat: 0.59 (0.38-0.92)
- **P**
  - Pembrolizumab/Pem/Plat: 0.0095

## TPS 1-49%
- **Events**
  - Pembrolizumab/Pem/Plat: 28.9%
  - Placebo/Pem/Plat: 48.3%
- **HR (95% CI)**
  - Pembrolizumab/Pem/Plat: 0.55 (0.34-0.90)
- **P**
  - Pembrolizumab/Pem/Plat: 0.0081

## TPS ≥50%
- **Events**
  - Pembrolizumab/Pem/Plat: 25.8%
  - Placebo/Pem/Plat: 51.4%
- **HR (95% CI)**
  - Pembrolizumab/Pem/Plat: 0.42 (0.26-0.68)
- **P**
  - Pembrolizumab/Pem/Plat: 0.0001

### OS Median (95% CI)
- **TPS < 1%**
  - Pembrolizumab/Pem/Plat: 15.2 mo (12.3-NE)
  - Placebo/Pem/Plat: 12.0 mo (7.0-NE)
- **TPS 1-49%**
  - Pembrolizumab/Pem/Plat: NR (NE-NE)
  - Placebo/Pem/Plat: 12.9 mo (8.7-NE)
- **TPS ≥50%**
  - Pembrolizumab/Pem/Plat: NR (NE-NE)
  - Placebo/Pem/Plat: 10.0 mo (7.5-NE)

### No. at Risk
- **TPS < 1%**
  - Pembrolizumab/Pem/Plat: 127, 113, 104, 79, 42, 20, 6, 0
  - Placebo/Pem/Plat: 63, 54, 45, 32, 21, 6, 1, 0

### OS benefit in TPS < 1%

*Nominal and one-sided. Data cutoff date: Nov 8, 2017.*
Overall Survival: Brain Metastases

With Brain Metastases

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events, n (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro/Pem/Plat</td>
<td>42 (57.5)</td>
<td>0.41</td>
</tr>
<tr>
<td>Placebo/Pem/Plat</td>
<td>28 (80.0)</td>
<td>(0.24–0.67)</td>
</tr>
</tbody>
</table>

Without Brain Metastases

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events, n (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro/Pem/Plat</td>
<td>171 (50.7)</td>
<td>0.59</td>
</tr>
<tr>
<td>Placebo/Pem/Plat</td>
<td>116 (67.8)</td>
<td>(0.46–0.75)</td>
</tr>
</tbody>
</table>

Median (95% CI):
- With Brain Metastases: 19.2 mo (15.0–25.9) 7.5 mo (4.6–10.0)
- Without Brain Metastases: 22.4 mo (19.7–25.4) 12.1 mo (9.1–15.0)

Data cutoff date: September 21, 2018.
Immune-Mediated Adverse Events

*Includes 3 grade 5 events. Data cutoff date: Nov 8, 2017.*
KEYNOTE-407 Study Design (NCT02775435)

Key Eligibility Criteria
- Untreated stage IV NSCLC with squamous histology
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- No symptomatic brain metastases
- No pneumonitis requiring systemic steroids

Pembrolizumab 200 mg Q3W + Carboplatin AUC 6 Q3W + Paclitaxel 200 mg/m² Q3W OR nab-Paclitaxel 100 mg/m² Q1W for 4 cycles (each 3 wk)

Placebo (normal saline) Q3W + Carboplatin AUC 6 Q3W + Paclitaxel 200 mg/m² Q3W OR nab-Paclitaxel 100 mg/m² Q1W for 4 cycles (each 3 wk)

Stratification Factors
- PD-L1 expression (TPS³ <1% vs ≥1%)
- Choice of taxane (paclitaxel vs nab-paclitaxel)
- Geographic region (East Asia vs rest of world)

R (1:1)

Optional Crossover
- Pembrolizumab 200 mg Q3W for up to 35 cycles

End points
- Primary: PFS (RECIST v1.1, BICR) and OS
- Secondary: ORR and DOR (RECIST v1.1, BICR), safety

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BICR, blinded independent central radiologic review. ³Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay.
⁴Patients could crossover during combination therapy or monotherapy. To be eligible for crossover, PD must have been verified by BICR and all safety criteria had to be met.
Overall Survival at IA2, ITT

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + Chemo</td>
<td>30.6%</td>
<td>0.64</td>
<td>0.0008</td>
</tr>
<tr>
<td>Placebo + Chemo</td>
<td>42.7%</td>
<td>(0.49-0.85)</td>
<td></td>
</tr>
</tbody>
</table>

Median (95% CI):
- Pembro + Chemo: 15.9 mo (13.2-NE)
- Placebo + Chemo: 11.3 mo (9.5-14.8)

No. at Risk
- Pembro + Chemo: [278 256 188 124 62 17 2 0 281 246 175 93 45 16 4 0]
- Placebo + Chemo: [278 256 188 124 62 17 2 0 281 246 175 93 45 16 4 0]

Data cutoff date: Apr 3, 2018.

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Overall Survival at IA2 by PD-L1 TPS

<table>
<thead>
<tr>
<th>TPS &lt;1%</th>
<th>TPS 1-49%</th>
<th>TPS ≥50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Events</td>
<td>Events</td>
</tr>
<tr>
<td>Pembro + Chemo</td>
<td>30.5%</td>
<td>30.1%</td>
</tr>
<tr>
<td>Placebo + Chemo</td>
<td>44.4%</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.61 (0.38-0.98)</td>
<td>0.57 (0.36-0.90)</td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>15.9 mo (13.1-NE)</td>
<td>14.0 mo (12.8-NE)</td>
</tr>
<tr>
<td></td>
<td>10.2 mo (8.6-13.8)</td>
<td>11.6 mo (8.9-17.2)</td>
</tr>
</tbody>
</table>

Data cutoff date: Apr 3, 2018.

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Case 3
Case 3

- M/84
- Chronic smoker (60 pack-yrs)
- Presented with pneumonic illness in late March/early April 2018 to private hospital
- Initial improvement with antibiotics
- CT thorax: LUL mass
- PET-CT: huge LUL mass (8 x 6 x 6.8cm, SUVmax 20) abutting aortic arch/chest wall, hypermetabolic L SCF LN (5mm, SUVmax 2.7)
PET-CT in Apr 2018
Case 3

- CT-guided L Lung Bx: Adenocarcinoma of lung origin (PD-L1 TPS 95%, EGFR/ALK/ROS1 –ve)
- Seen by thoracic surgeon: deemed unresectable with chest wall invasion + ? shotty mediastinal/L SCF LN involvement
- Given antibiotic cover for febrile/pneumonic illness
- Started pembrolizumab (3-weekly) since 29 Apr 2018
Case 3

- SBRT to LUL tumour since 28 May 2018 x 10 fractions
- Interval improvement on serial PET-CT
- Given a total of 13 cycles of pembrolizumab till 21 Jan 2019, minor skin rash/dry skin only
Serial CXRs

May 2018

Feb 2019
PET-CT in Dec 2018
Case 3

- LU lobectomy in Feb 2019 → No viable tumours seen on resected lung (Only necrotic tissues)
Neoadjuvant PD-1 Blockade in Resectable Lung Cancer


NEJM 2018;378;1976-86
18 years old or older
Stage I, II, or IIIA NSCLC that was deemed to be surgically resectable before enrollment
ECOG 0-1
Normal organ function, adequate pulmonary function

Baseline tumor staging pretreatment biopsy, pathological evaluation of mediastinal lymph nodes
PET–CT
CT or MRI of brain and chest
chest CT repeated within 7 days before surgery

Adjuvant chemotherapy/RT if indicated

Surgery at ~4 weeks after 1st dose

Two doses of intravenous nivolumab (at a dose of 3 mg per kilogram of body weight) every 2 weeks

End points:
Primary: safety and feasibility
Secondary: radiologic and pathological responses to treatment and immunologic, genomic, and pathological correlates of response in blood and tumor
Three patients with recurrence
1. Solitary brain lesion 2 months after surgery—treatment with stereotactic radiation therapy, no further recurrence at more than 16 months
2. Mediastinal lymph-node recurrence—treated with concurrent chemo-RT—no further progression at 12 months
3. Distant metastasis at 12 months—die
• Radiological progression
  ?infiltration of immune cells into tumor
• Pathological response
Major pathological response occurred in both PD-L1–positive and PD-L1–negative tumors
Figure 3. Association between Mutational Burden and Pathological Response to PD-1 Blockade.
Conclusions

- Immunotherapy can be used as a single agent for PD-L1 enriched advanced wild-type (WT) NSCLC in the first-line setting
- Immunotherapy can be combined with chemotherapy for a wide spectrum of metastatic WT NSCLC
- There is a potential role of neoadjuvant anti-PD1 in resectable early-stage NSCLC
- Future direction will focus on transforming an immunologically “cold” to “hot” tumour that allows immunotherapy to take action