KEYNOTE-189: Updated Overall Survival and Progression After the Next Line of Therapy With Pembrolizumab plus Chemotherapy With Pemetrexed and Platinum vs Placebo plus Chemotherapy for Metastatic Nonsquamous Non–Small-Cell Lung Cancer
Study Design, Participants and Treatment

**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)

**R (2:1)**

- **N = 410**
  - Pembrolizumab 200 mg + Pemetrexed 500 mg/m² + Carboplatin AUC 5 OR Cisplatin 75 mg/m² Q3W for 4 cycles

- **N = 206**
  - Placebo (normal saline) + Pemetrexed 500 mg/m² + Carboplatin AUC 5 OR Cisplatin 75 mg/m² Q3W for 4 cycles

**PD<sup>b</sup>**

- Pembrolizumab 200 mg Q3W for up to 35 cycles

AUC, area under the concentration–time curve; ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease; Q3W, every 3 weeks; R, randomized.

<sup>a</sup>Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay.

<sup>b</sup>Patients could cross over 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.
Kaplan-Meier Estimates of OS in the Total Population (ITT)

**12-mo rate**
- Pembrolizumab/pemetrexed/platinum: 70.0%
- Placebo/pemetrexed/platinum: 48.1%

**24-mo rate**
- Pembrolizumab/pemetrexed/platinum: 45.5%
- Placebo/pemetrexed/platinum: 29.9%

**Median (95% CI)**
- Pembrolizumab/pemetrexed/platinum: 22.0 mo (19.5–25.2)
- Placebo/pemetrexed/platinum: 10.7 mo (8.7–13.6)

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>HR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Pembrolizumab/pemetrexed/platinum</td>
<td>52.0%</td>
<td>0.56 (0.45–0.70)</td>
</tr>
<tr>
<td>Placebo/pemetrexed/platinum</td>
<td>69.9%</td>
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**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>410</th>
<th>377</th>
<th>346</th>
<th>316</th>
<th>283</th>
<th>256</th>
<th>234</th>
<th>144</th>
<th>79</th>
<th>28</th>
<th>2</th>
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<tbody>
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<td>206</td>
<td>183</td>
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<td>26</td>
<td>10</td>
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Kaplan-Meier Estimates of PFS2 in the Total Population and PD-L1 TPS Subgroups (ITT)

- **Total Population**
  - 12-mo rate: 63.6%, 41.3%
  - 24-mo rate: 38.4%, 13.8%
  - Median (95% CI): 17.0 mo (15.1-19.4), 9.0 mo (7.6-10.4)

- **Events**
  - Pembrolizumab/pembrolizumab/placebo (Pembro/pem/plat): 59.5%, HR (95% CI): 0.49 (0.40-0.59)
  - Placebo/pembrolizumab/placebo (Placebo/pem/plat): 83.0%

- **No. at Risk**
  - 410, 377, 336, 294, 253, 217, 185, 115, 67, 26, 2, 0
# Safety

## Summary of Adverse Events in the Total Population (ASaT)a

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>All-Cause</th>
<th>Immune-Mediated and Infusion Reactionsb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pembro/Pem/Plat n = 405</td>
<td>Placebo/Pem/Plat n = 202</td>
</tr>
<tr>
<td>Any grade</td>
<td>404 (99.8)</td>
<td>200 (99.0)</td>
</tr>
<tr>
<td>Grade 3-5</td>
<td>291 (71.9)</td>
<td>135 (66.8)</td>
</tr>
<tr>
<td>Led to deathc</td>
<td>29 (7.2)</td>
<td>14 (6.9)</td>
</tr>
<tr>
<td>Led to discontinuation of any treatment component</td>
<td>136 (33.6)</td>
<td>33 (16.3)</td>
</tr>
</tbody>
</table>

ASaT, all participants who received ≥1 dose of study treatment.

aMedian (range) duration of exposure to initially allocated study treatment was 7.2 mo (0.03-30.4) in the pembrolizumab plus pemetrexed and platinum arm and 4.2 mo (0.03-25.0) in the placebo plus pemetrexed and platinum arm.

bEvents were based on a list from the sponsor and considered regardless of attribution to treatment or immune relatedness by the investigator.

cEight (2.0%) participants in the pembrolizumab plus pemetrexed and platinum group and 2 (1.0%) participants in the placebo plus pemetrexed and platinum group died from AEs attributed to study treatment by the investigator.
Summary and conclusions

- Pembrolizumab plus pemetrexed and a platinum continued to show a substantial survival benefit versus placebo plus pemetrexed and a platinum.
- PFS2 was substantially improved for participants treated with pembrolizumab plus pemetrexed and platinum.
- Median OS, PFS, and PFS2 were approximately doubled in the pembrolizumab plus pemetrexed and platinum arm.
- Benefit for pembrolizumab plus pemetrexed and a platinum was observed
  - In both PD-L1-expressing and PD-L1-non-expressing disease.
  - Despite 54% of participants in the placebo plus pemetrexed and platinum arm receiving a subsequent PD-1 or PD-L1 inhibitor, including 41% who crossed over in-study to receive pembrolizumab monotherapy.
- Safety and tolerability remained manageable.
- Data confirm that pembrolizumab should be given as part of first-line therapy to maximize outcomes in both PD-L1-expressing and PD-L1-non-expressing, metastatic nonsquamous NSCLC.