ESTADIOS AVANZADOS

Dra. Virginia Calvo
## POSTERS DISCUSSED

<table>
<thead>
<tr>
<th>ID</th>
<th>Lead Author</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>1385PD</td>
<td>Peters et al.</td>
<td>A randomised phase III trial evaluating the addition of denosumab to standard first-line treatment in advanced NSCLC – the ETOP and EORTC SPLENDOUR trial</td>
</tr>
<tr>
<td>LBA64</td>
<td>Spigel et al.</td>
<td>nab-Paclitaxel + Carboplatin induction followed by nab-Paclitaxel maintenance in squamous non-small cell lung cancer (NSCLC): results from the ABOUND sqm study</td>
</tr>
<tr>
<td>LBA65</td>
<td>Socinski et al.</td>
<td>Progression-free survival (PFS) and overall survival (OS) analysis of a randomised Phase III study of atezolizumab + carboplatin + paclitaxel or nab-paclitaxel vs carboplatin + nab-paclitaxel in 1L advanced squamous NSCLC</td>
</tr>
<tr>
<td>1386PD</td>
<td>Reck et al.</td>
<td>IMpower150: clinical safety, tolerability and immune-related adverse events in a Phase III study of atezolizumab (atezo) + chemotherapy (chemo) + bevacizumab (bev) vs chemo + bev in 1L nonsquamous NSCLC</td>
</tr>
</tbody>
</table>
1385PD. A randomised phase III trial evaluating the addition of denosumab to standard first-line treatment in advanced NSCLC - the ETOP and EORTC SPLENDOUR trial

**PETERS ET AL. #1385PD**

**SPLENDOUR design**

**Screening, eligibility and enrolment**
- First-line Stage IV NSCLC
- Stratify:
  - Bone mets
  - Region
  - ECOG PS
  - Histology

**Trial treatment**
- **A**: 4-6 cycle chemotherapy every 3 weeks + BSC
- **B**: Denosumab every 3-4 weeks
- **Open label**
- Primary endpoint: OS
- **Blood**
- **FFPE**

**Progression Follow-up**
- **Blood**
- **FFPE**

**Translational research**
- Bone mets if bone mets
1385PD. A randomised phase III trial evaluating the addition of denosumab to standard first-line treatment in advanced NSCLC - the ETOP and EORTC SPLENDOUR trial

PETERS ET AL. #1385PD
SPLENDOUR outcomes: PFS & OS

Progression-free survival

0.97
(0.81, 1.17)

Overall survival

0.96
(0.78, 1.18)
1385PD. A randomised phase III trial evaluating the addition of denosumab to standard first-line treatment in advanced NSCLC-the ETOP and EORTC SPLENDOUR trial

**PETERS ET AL. #1385PD**

SPLENDOUR outcomes: OS (+/- bone mets)

Contrary to Scagliotti et al post hoc analyses

No obvious strong bone protective effect: CARE, power of dataset & effect of x-over
SO...WHAT DOES SPLENDOUR MEAN IN 2018?

My interpretation

- Trial did not meet the primary endpoint (OS)
- Adding denosumab to 1st line CHEMOTHERAPY ALONE in advanced NSCLC with/without bone mets (the ITT population) does not improve OS.
- The OS suggestion of denosumab in NSCLC (the registration trial) was not identified: population biases.
- A heterogeneous population, ITT difficult to interpret, changing over life of trial.
- A victim of rapid systemic therapy changes in advanced NSCLC.
  - Oncogene addicted patients excluded: those most likely to benefit from long-term denosumab
  - Likely over-representation of PDL1 negative, 1-49%+ TPS patients, unsuitable for ICIs (hidden biases)
- I look forward to translational analyses
LBA64. Nab-Paclitaxel + Carboplatin induction followed by nab-Paclitaxel maintenance in squamous non-small cell lung cancer (NSCLC): results from the ABOUND.sqm study

**SPIEGEL ET AL. #LBA2936**

**ABOUND.sqm study**

- **INDUCTION PHASE**
  - 4 x 21-day cycles
  - nab-P 100 mg/m² d1, 8, and 15 (30-min infusion) + Carbo AUC 6 d1
  - Screen for maintenance

- **MAINTENANCE PHASE**
  - 21-day cycles until progression
  - nab-P 100 mg/m² d1 and 8 (30-min infusion)
  - Best supportive care

**Primary endpoint:**
- PFS

**Secondary endpoints:**
- OS, ORR

**Randomize 2:1**

**Received any anti-cancer Tx (71%)**
- ICI (56%)
- Nivolumab (46%)
- Pembrolizumab (7%)
- Atezolizumab (1%)
- Other (2%)
- Other (15%)

**Anti-Cancer Therapy During Follow-Up:**
- Received any anti-cancer Tx (67%)
  - ICI (58%)
  - Nivolumab (45%)
  - Pembrolizumab (8%)
  - Atezolizumab (2%)
  - Other (3%)
  - Other (9%)

**iDMC declared futility criteria was met at interim analysis of PFS; follow-up continued to final analysis**

**Best supportive care**
- n = 136
- 48%

**n = 66**

**Balanced post PD therapies**
LBA64. Nab-Paclitaxel + Carboplatin induction followed by nab-Paclitaxel maintenance in squamous non-small cell lung cancer (NSCLC): results from the ABOUND.sqm study

SPIEGEL ET AL. #LBA2936

PFS and OS: no statistically significant benefit

- ORR was 69.1% with maintenance nab-P vs 57.6% with BSC alone (RRR 1.20 [95% CI, 0.95-1.52], P = 0.087)

ORR result may be due to lower power than registration trial
LBA64. Nab-Paclitaxel + Carboplatin induction followed by nab-Paclitaxel maintenance in squamous non-small cell lung cancer (NSCLC): results from the ABOUND.sqm study

SPIGEL ET AL. #LBA2936
Differential benefit by subsequent ICI use: hypothesis generating

**Figure 3. OS in Patients With (a) and Without (b) Subsequent ICI Treatment**

Has OS benefit in those receiving ICI confounded by imbalance in PDL1≥50%?
LBA64. Nab-Paclitaxel + Carboplatin induction followed by nab-Paclitaxel maintenance in squamous non-small cell lung cancer (NSCLC): results from the ABOUND.sqm study

SPIEGEL ET AL. #LBA2936
Safety of registration trial

Table 4. Safety

<table>
<thead>
<tr>
<th>Parameter</th>
<th>nab-P + BSC (n = 130)</th>
<th>BSC Alone (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 grade ≥ 3 TEAE, n (%)</td>
<td>109 (83.8)</td>
<td>48 (77.4)</td>
</tr>
<tr>
<td>At least 1 severe TEAE, n (%)</td>
<td>55 (42.3)</td>
<td>22 (35.5)</td>
</tr>
<tr>
<td>Hematologic grade ≥ 3 TEAEs, n (%)</td>
<td>69 (53.1)</td>
<td>20 (32.3)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>43 (33.1)</td>
<td>31 (50.0)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>16 (12.3)</td>
<td>10 (16.1)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>14 (10.6)</td>
<td>9 (14.5)</td>
</tr>
<tr>
<td>Nonhematologic grade ≥ 3 TEAEs, n (%)</td>
<td>18 (13.8)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>6 (6.2)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (6.4)</td>
<td>2 (3.2)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>7 (6.4)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Time to improvement of grade ≥ 3 PN by ≥ 1 grade, median, days</td>
<td>21</td>
<td>NE</td>
</tr>
</tbody>
</table>

Table 3. Most Common Treatment-Related Grade ≥ 3 AEs According to NCI-CTCAE

<table>
<thead>
<tr>
<th>AE</th>
<th>nab-PC (%) (n = 514)</th>
<th>sb-PC (%) (n = 524)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3</td>
<td>Grade 4</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Hematologic AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>33</td>
<td>14</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Anemia</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nonhematologic AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Severity of AEs was graded using CTCAE v4.0. † Throughout entire study. ‡ Occurring in ≥ 5% of patients in either arm.

Much higher neuropathy & neutropenia; likely exposure related

Socinski et al. JCO (2012)
SO...WHAT DOES ABOUND.SQM MEAN IN 2018?

My interpretation

- No PFS benefit (primary endpoint): a negative trial.
- No significant OS benefit (negative); OS benefit identified by PD ICI use, may be confounded PDL1 strata.

AND

- More neutropenia: febrile neutropenia?
- More peripheral neuropathy
- + weekly vs q21 dosing

What will happen when you add ICI to nab-paclitaxel?

Invited Discussant: S. Popat