Atezolizumab monotherapy vs docetaxel in 2L/3L non-small cell lung cancer: Primary analysis for efficacy, safety and predictive biomarkers from a randomized Phase II study (POPLAR)

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  - Boehringer Ingelheim
  - Pfizer
Atezolizumab is a Humanized Anti-PDL1 Antibody That Inhibits the Binding of PD-L1 to PD-1 and B7.1

- Inhibiting PD-L1/PD-1 and PD-L1/B7.1 interactions can restore anti-tumor T-cell activity and enhance T-cell priming.
- Targeting PD-L1 leaves the PD-L2/PD-1 interaction intact, thereby potentially preserving peripheral immune homeostasis.
- Atezolizumab (anti-PDL1) has demonstrated promising response rates in NSCLC that correlated with PD-L1 expression on tumor cells (TC) and/or tumor-infiltrating immune cells (IC); (Horn et al., ASCO 2015; Fehrenbacher et al., Lancet 2016)
POPLAR: A Randomized All-comer Phase II Study (NCT01903993)

Primary study objective:
• Estimate OS in ITT and PD-L1 expression subgroups

Secondary study objectives:
• Estimate PFS, ORR and DOR in ITT and PD-L1 expression subgroups
• Evaluate safety

Metastatic or locally advanced NSCLC (2L/3L)
Disease progression on a prior platinum therapy
N = 287

Stratification Factors
• PD-L1 IC expression (0 vs 1 vs 2 vs 3)\(^a\)
• Histology (squamous vs non-squamous)
• Prior chemotherapy regimens (1 vs 2)

Atezolizumab
1200 mg IV q3w until loss of clinical benefit

Docetaxel
75 mg/m\(^2\) IV q3w until disease progression

Primary analysis conducted with 173 events, minimum follow-up 13 months

Interim analysis with 153 events, minimum follow-up 10 months was presented at ASCO 2015 (Spira et al., Abstract 8010)

\(^a\)Archival or new tissue required for pre-dose testing.
## Characteristics of Patients with NSCLC

<table>
<thead>
<tr>
<th>Characteristics of Patients with NSCLC</th>
<th>Atezolizumab (n = 144)</th>
<th>Docetaxel (n = 143)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>≥ 65 y</td>
<td>40%</td>
<td>39%</td>
</tr>
<tr>
<td>Male</td>
<td>65%</td>
<td>53%</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-squamous</td>
<td>66%</td>
<td>66%</td>
</tr>
<tr>
<td>Squamous</td>
<td>34%</td>
<td>34%</td>
</tr>
<tr>
<td>ECOG score, 0 / 1</td>
<td>32% / 68%</td>
<td>32% / 68%</td>
</tr>
<tr>
<td>No. of prior therapies, 1 / 2</td>
<td>65% / 35%</td>
<td>67% / 33%</td>
</tr>
<tr>
<td>History of tobacco use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>19%</td>
<td>20%</td>
</tr>
<tr>
<td>Current</td>
<td>17%</td>
<td>15%</td>
</tr>
<tr>
<td>Previous</td>
<td>64%</td>
<td>65%</td>
</tr>
</tbody>
</table>

Data cut-off May 8, 2015.

Rittmeyer et al., Atezolizumab in NSCLC (POPLAR)
POPLAR: All Patient Efficacy
ITT OS (N = 287)

- Event/patient ratio: 60% (54% for atezolizumab, 66% for docetaxel)

Median 12.6 mo (9.7, 16.4)
Median 9.7 mo (8.6, 12.0)

HR$^a$ = 0.73 (0.53, 0.99)
$P$ value = 0.040

$^a$Stratified HR.
Data cut-off May 8, 2015.
POPLAR: Treatment-related AEs

Safety population includes patients who received any amount of either study treatment. Data cut-off May 8, 2015.

Rittmeyer et al., Atezolizumab in NSCLC (POPLAR)
**POPLAR: Overall Survival by Histology**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n (%)</th>
<th>Median OS (95% CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous</td>
<td>97 (34%)</td>
<td>10.1 (6.7, 14.5)</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>190 (66%)</td>
<td>12.6 (9.7, 16.4)</td>
</tr>
<tr>
<td>ITT</td>
<td>N = 287</td>
<td>12.6 (9.7, 16.4)</td>
</tr>
</tbody>
</table>

- **Event/patient ratio:** Squamous 69% (63% for atezolizumab, 75% for docetaxel)
  Non-squamous 56% (49% for atezolizumab, 62% for docetaxel)

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*a* Unstratified HR for subgroups and stratified HR for ITT.

Data cut-off May 8, 2015.

Rittmeyer et al., Atezolizumab in NSCLC (POPLAR)
PD-L1 Expression on TC and IC is a Potential Predictive Biomarker for Atezolizumab in NSCLC

- SP142 IHC assay is sensitive and specific for PD-L1 expression on both TC and IC
- Distinct TC and IC sub-populations exist at each of four cutoff levels (Gettinger et al., ASCO 2015; Schmid et al., ECC 2015)
- PD-L1 expression on TC and IC was independently predictive of response (Horn et al., ASCO 2015)

**Intrinsic** PD-L1 expression on tumor cells (TC)

**Adaptive** PD-L1 expression on tumor-infiltrating immune cells (IC)

PD-L1 expression levels and TC/IC overlap in POPLAR

TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1 expressing cells;
TC2/3 or IC2/3 = TC or IC ≥ 5% PD-L1 expressing cells;
TC1/2/3 or IC1/2/3 = TC or IC ≥ 1% PD-L1 expressing cells;
TC0 and IC0 = TC and IC < 1% PD-L1 expressing cells, respectively.
POPLAR: Overall Survival by PD-L1 Expression

Subgroup    n (%)    Hazard Ratio
TC3 or IC3  47 (16%)  0.49
TC2/3 or IC2/3 105 (37%)  0.54
TC1/2/3 or IC1/2/3 198 (68%)  0.59
TC0 and IC0  92 (32%)  1.04

ITT        N = 287  0.73

Median OS (95% CI), mo
Atezolizumab n = 144
Docetaxel  n = 143

In favor of atezolizumab  In favor of docetaxel

Rittmeyer et al., Atezolizumab in NSCLC (POPLAR)
POPLAR: Overall Survival by PD-L1 Expression TC0 and IC0 Subgroup (n = 92)

Minimum follow up = 13 months

HR^a = 1.04 (0.62, 1.75)

P value = 0.871

^aUnstratified HR.

Data cut-off May 8, 2015.

Rittmeyer et al., Atezolizumab in NSCLC (POPLAR)
POPLAR: Overall Survival by PD-L1 Expression TC2/3 or IC2/3 Subgroup (n = 105)

HR\textsuperscript{a} = 0.54 (0.33, 0.89)

\( P \text{ value} = 0.014 \)

\( P \text{ value} = 0.014 \)
POPLAR: Overall Survival by PD-L1 Expression TC1/2/3 or IC1/2/3 Subgroup (n = 195)

HR$^a$ = 0.59 (0.40, 0.85)  
$P$ value = 0.005

Minimum follow up = 13 months

Median 15.5 mo (11.0, NE)
Median 9.2 mo (7.3, 12.8)

Minimum follow up = 13 months

Atezolizumab  
Docetaxel

**No. of Patients at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Atezolizumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>102</td>
<td>95</td>
</tr>
<tr>
<td>1</td>
<td>95</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>86</td>
<td>86</td>
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<tr>
<td>3</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>69</td>
<td>69</td>
</tr>
<tr>
<td>5</td>
<td>64</td>
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<tr>
<td>6</td>
<td>61</td>
<td>57</td>
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<tr>
<td>7</td>
<td>57</td>
<td>51</td>
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<tr>
<td>8</td>
<td>51</td>
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<tr>
<td>9</td>
<td>48</td>
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<tr>
<td>10</td>
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<tr>
<td>11</td>
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<tr>
<td>12</td>
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<td>13</td>
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<tr>
<td>14</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>15</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>16</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

$^a$Unstratified HR.  
Data cut-off May 8, 2015.

Rittmeyer et al., Atezolizumab in NSCLC (POPLAR)
POPLAR: Both TC and IC are Independent Predictors of Survival Improvement

<table>
<thead>
<tr>
<th>PD-L1 status</th>
<th>OS HR&lt;sup&gt;b&lt;/sup&gt; (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC1/2/3 and IC0</td>
<td>0.37 (0.12, 1.13)</td>
</tr>
<tr>
<td>IC1/2/3 and TC0</td>
<td>0.63 (0.36, 1.12)</td>
</tr>
<tr>
<td>TC1/2/3 and IC1/2/3</td>
<td>0.60 (0.34, 1.08)</td>
</tr>
<tr>
<td>TC1/2/3 or IC1/2/3</td>
<td>0.59 (0.40, 0.85)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Number of patients within subgroup/total study population; Percentage of total study population.

<sup>b</sup>Unstratified HR.

Data cut-off May 8, 2015.

Rittmeyer et al., Atezolizumab in NSCLC (POPLAR)
Teff/IFNγ signature is defined by expression of CD8A, GZMA, GZMB, IFNγ, EOMES, CXCL9, CXCL10 and TBX21 genes
POPLAR: Overall Survival in T\textsubscript{eff}/IFN\textgamma Signature Subgroups

T\textsubscript{eff}/IFN\textgamma signature defined by expression of CD8A, GZMA, GZMB, IFN\textgamma, EOMES, CXCL9, CXCL10 and TBX21 genes.

aHigh biomarker group defined as gene expression at or above the median level; low biomarker group defined as gene expression below the median level.

bStratified and adjusted HR for survival with atezolizumab vs docetaxel.

Data cut-off May 8, 2015.

Rittmeyer et al., Atezolizumab in NSCLC (POPLAR)
Teff/IFNγ signature defined by expression of CD8A, GZMA, GZMB, IFNγ, EOMES, CXCL9, CXCL10 and TBX21 genes.

aStratified and adjusted HR for survival with atezolizumab vs docetaxel.

Data cut-off May 8, 2015.
• The POPLAR Phase II randomized study demonstrated significant OS improvements for PD-L1–unselected NSCLC patients receiving atezolizumab vs docetaxel ITT: OS HR = 0.73 (P = 0.040)

• Activity was seen in both squamous and non-squamous patients treated with atezolizumab

• PD-L1 expression on TC and IC was independently predictive of survival improvement with atezolizumab

• Higher PD-L1 expression was associated with improved OS with atezolizumab (HR range, 0.49-0.59)

• TC0 and IC0: no difference in OS (HR = 1.04), but overall safety data shows significantly less toxicity with atezolizumab vs docetaxel

• High gene expression of PD-L2, PD-1, B7.1 and the Teff/IFNγ gene signature was associated with improved OS for atezolizumab treatment (HR range, 0.39-0.45)
Future Atezolizumab Development in NSCLC

- Ongoing randomized trials
  - Phase III study of atezolizumab monotherapy in 2L/3L patients (OAK; NCT01846416)
  - Phase III study of atezolizumab monotherapy in PD-L1-selected 1L patients (IMpower110)

- Phase 1b trial of atezolizumab with chemotherapy showed 67% preliminary ORR and tolerable safety in unselected patients with NSCLC (NCT01633970). (Camidge et al., WCLC 2015; Giaccone et al., ECC 2015)

- Multiple Phase III 1L NSCLC studies are underway
  - IMpower130, IMpower131, IMpower132 and IMpower150 studies of chemotherapy + atezolizumab (NCT02367781; NCT02367794; NCT02657434 and NCT02366143)

- IMpower010 study of atezolizumab vs best supportive care in adjuvant setting (NCT02409342)
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