IMpassion130: Efficacy in immune biomarker subgroups from the global, randomized, double-blind, placebo-controlled, Phase III study of atezolizumab + nab-paclitaxel in patients with treatment-naive, locally advanced or metastatic triple-negative breast cancer

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Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)
TNBC background

- TNBC has the worst breast cancer subtype–specific outcomes,¹ and single-agent taxane or anthracycline chemotherapy remains the typical 1L treatment for advanced disease²³
  - Estimates of median OS vary but are generally ≈ 18 months or less⁴⁻⁶

- No targeted agents have demonstrated definitive OS benefit
  - Bevacizumab in combination with chemotherapy is an approved treatment for mBC in several countries outside the United States⁷
  - PARP inhibitors for BRCA1/2-mutant, HER2-negative mBC have been approved in several countries⁸

- IMpassion130 is the first Phase III study to demonstrate a benefit with immunotherapy in mTNBC⁹
  - Atezolizumab + nab-paclitaxel (vs placebo + nab-paclitaxel) resulted in a statistically significant PFS benefit in the ITT and PD-L1+ populations (ITT HR, 0.80 [95% CI: 0.69, 0.92] and PD-L1+ HR, 0.62 [95% CI: 0.49, 0.78])
  - At this first interim OS analysis, clinically meaningful improvement in OS with atezolizumab + nab-paclitaxel was observed in the PD-L1+ population, with an HR of 0.62 [95% CI: 0.45, 0.86] and a median OS improvement from 15.5 to 25.0 months⁹

IMPASSION130 study design:
Prespecified analyses in the ITT and PD-L1 IC+ population

**Phase III study IMPASSION130**

<table>
<thead>
<tr>
<th>Arm</th>
<th>ITT population: n = 451</th>
<th>PD-L1 IC+ patients: n = 185 (41%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezo + nab-P arm</td>
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<tr>
<td>Plac + nab-P arm</td>
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</table>

**Stratification factors:**
- 1. Prior taxane use
- 2. Liver metastases
- 3. PD-L1 on IC

**Double blind; no crossover**

**Key study endpoints**
- Co-primary: PFS (ITT and PD-L1 IC+)
- OS (ITT and PD-L1 IC+)
- Secondary: ORR and DOR
- Safety and tolerability

**Notes:**
- NCT02425891.
- Locally evaluated per ASCO-CAP guidelines.
- Prior chemotherapy in the curative setting, including taxanes, allowed if treatment-free interval ≥ 12 mo.
- Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status, PD-L1: PD-L1 on ≥ 1% of IC).
- Atezolizumab or placebo 840 mg IV on days 1 and 15 + nab-paclitaxel 100 mg/m² IV on days 1, 8 and 15 of 28-day cycle until RECIST v1.1 PD.

**References:**
- Emens LA, et al. IMPASSION130 biomarkers. SABCS 2018 (program #GS1-04)
IMpassion130 primary analysis¹,²: Clinically meaningful PFS and OS benefit in the PD-L1+ population

**ITT population**

**ITT PFS**
- Stratified HR, 0.80 (95% CI: 0.69, 0.92)
- \( P = 0.0025 \)

**ITT OS**
- Stratified HR, 0.84 (95% CI: 0.69, 1.02)
- \( P = 0.0840^b \)

**PD-L1+ population^a**

**PD-L1+ PFS**
- Stratified HR, 0.62 (95% CI: 0.49, 0.78)
- \( P < 0.0001 \)

**PD-L1+ OS**
- Stratified HR, 0.62 (95% CI: 0.45, 0.86)^c

NE, not estimable.

Median follow-up (ITT): 12.9 months.

^a PD-L1+: PD-L1 in ≥ 1% of IC.

^b Not significant.

^c Not formally tested per hierarchical study design.

2. Schmid ESMO 2018 [LBA1_PR].

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IMpassion130 biomarker analyses

- Pre-existing immune biology, including PD-L1 expression on TC, CD8+ T cells and stromal TILs, has also been associated with clinical benefit from anti-PD-L1/PD-11,2

- In this exploratory analysis, we sought to evaluate whether this immune biology and BRCA1/2 mutation status were associated with clinical benefit from atezolizumab + nab-paclitaxel

- Biomarkers were centrally analyzed in pre-treatment biopsies
  - PD-L1 on IC and TC by VENTANA SP142 IHC assay
  - Intratumoral CD8+ T cells by IHC (Dako clone C8/144B) and stromal TILs by H&E
  - BRCA1/2 mutation status by FoundationOne assay

<table>
<thead>
<tr>
<th>PD-L1 IHC (SP142) Assay by Ventana Medical Systems</th>
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</thead>
<tbody>
<tr>
<td>PD-L1 on IC</td>
</tr>
</tbody>
</table>

H&E, hematoxylin and eosin staining; IHC, immunohistochemistry.

a PD-L1 scoring: IC0: < 1%; IC1: ≥ 1% and < 5%; IC2: ≥ 5% and < 10%; IC3: ≥ 10%; TC+: < 1% PD-L1 on tumor cells; TC+: ≥ 1% PD-L1 on tumor cells.

b Pre-specified cutoffs for CD8 IHC and stromal TILs are based on references 1 and 2.

In IMpassion130, PD-L1 in TNBC is expressed mainly on tumor-infiltrating immune cells.

**Prevalence of PD-L1 IC subgroups**
- PD-L1 IC+ (IC1/2/3): 41%
- PD-L1 IC0 (IC0): 59%
- IC1: 27%
- IC2/3: 14%

The majority of patients with expression of PD-L1 on TC are included within the PD-L1 IC+ population.

**Prevalence of PD-L1 TC subgroups**
- PD-L1 TC+: 9%
- PD-L1 TC+: 91%

**BEP, biomarker-evaluable population.**
BEP (TC): n = 900. PD-L1 scoring: IC0: < 1%; IC1: ≥ 1% and < 5%; IC2: ≥ 5% and < 10%; IC3: ≥ 10%; TC+: < 1% PD-L1 on tumor cells; TC+: ≥ 1% PD-L1 on tumor cells.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)
PD-L1 IC status (positive vs negative) predicts PFS benefit with atezolizumab + nab-paclitaxel

Median PFS durations (and 95% CIs) are indicated on the plot. Stratified HRs are shown. All P values except for PD-L1 IC+ PFS are nominal P values. Data cutoff: April 17, 2018.

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PD-L1 IC status (positive vs negative) predicts PFS benefit with atezolizumab + nab-paclitaxel

- A trend toward association between PD-L1 IC positivity and poor prognosis was observed but was not statistically significant.
- PD-L1 IC positivity was predictive of PFS and OS benefit with atezolizumab + nab-paclitaxel.

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A trend toward association between PD-L1 IC positivity and poor prognosis was observed but was not statistically significant.

PD-L1 IC positivity was predictive of PFS and OS benefit with atezolizumab + nab-paclitaxel.
Consistent clinical benefit with atezolizumab + nab-paclitaxel was observed across all PD-L1 IC+ subgroups

<table>
<thead>
<tr>
<th>PD-L1 IC Status</th>
<th>n</th>
<th>Median, mo</th>
<th>HRa (95% CI)</th>
<th>P value</th>
<th>HRa (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IC0</td>
<td>532</td>
<td>5.6</td>
<td>0.93</td>
<td>0.47</td>
<td>1.02</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.6</td>
<td>(0.77, 1.12)</td>
<td></td>
<td>(0.79, 1.31)</td>
<td></td>
</tr>
<tr>
<td>Pos</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IC1</td>
<td>243</td>
<td>7.4</td>
<td>0.59</td>
<td>≤ 0.005</td>
<td>0.56</td>
<td>≤ 0.005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.9</td>
<td>(0.44, 0.78)</td>
<td></td>
<td>(0.38, 0.82)</td>
<td></td>
</tr>
<tr>
<td>IC2/3</td>
<td>125</td>
<td>9.3</td>
<td>0.64</td>
<td>0.03</td>
<td>0.71</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.7</td>
<td>(0.42, 0.97)</td>
<td></td>
<td>(0.39, 1.30)</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>900</td>
<td>7.2</td>
<td>0.79</td>
<td>≤ 0.005</td>
<td>0.83</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.5</td>
<td>(0.68, 0.92)</td>
<td></td>
<td>(0.68, 1.02)</td>
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</tbody>
</table>

*Adjusted for prior taxane treatment and liver metastases.

A multivariate analysis was performed to account for imbalances in baseline characteristics between PD-L1 IC–expressing subgroups (IC1, IC2 and IC3).

IC0: < 1% PD-L1; IC1: ≥ 1% and < 5% PD-L1; IC2/3: ≥ 5% PD-L1. All P values are nominal. Data cutoff: April 17, 2018.

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CD8+ IHC has clinical benefit if co-occurring with PD-L1 IC+

- PD-L1 IC+ are enriched in CD8+ ($P < 0.0001$) and CD8+ are enriched in PD-L1 IC+ ($P < 0.0001$)\(^\text{a}\)
- **Patients with CD8+ tumors derived clinical benefit (PFS/OS) only if their tumors were also PD-L1 IC+**

<table>
<thead>
<tr>
<th>CD8+/PD-L1 IC+ (n = 37)</th>
<th>HR (95% CI)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>0.33 (0.13, 0.87)</td>
<td>0.03</td>
</tr>
<tr>
<td>OS</td>
<td>0.25 (0.06, 1.02)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CD8+/PD-L1 IC+ (n = 280)</th>
<th>HR (95% CI)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>0.61 (0.46, 0.80)</td>
<td>$\leq 0.005$</td>
</tr>
<tr>
<td>OS</td>
<td>0.55 (0.38, 0.80)</td>
<td>$\leq 0.005$</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>CD8+/PD-L1 IC– (n = 220)</th>
<th>HR (95% CI)</th>
<th>$P$ Value</th>
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</thead>
<tbody>
<tr>
<td>PFS</td>
<td>0.89 (0.66, 1.20)</td>
<td>0.45</td>
</tr>
<tr>
<td>OS</td>
<td>0.77 (0.50, 1.17)</td>
<td>0.21</td>
</tr>
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Stromal TILs has clinical benefit if co-occurring with PD-L1 IC+

- TIL+ were enriched for PD-L1 IC+ ($P < 0.0001$) but PD-L1 IC+ were not enriched for TIL+ ($P = \text{ns}$)

- **Patients with TIL+ tumors derived clinical benefit (PFS/OS) only if their tumors were also PD-L1 IC+**

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**Table:**

<table>
<thead>
<tr>
<th>Group</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIL+/PD-L1 IC+ (n = 190)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td>0.53 (0.38, 0.74)</td>
<td>$\leq 0.005$</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>0.57 (0.35, 0.92)</td>
<td>0.02</td>
</tr>
<tr>
<td>TIL–/PD-L1 IC+ (n = 176)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td>0.74 (0.54, 1.03)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>0.65 (0.41, 1.02)</td>
<td>0.06</td>
</tr>
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</table>

**Table:**

<table>
<thead>
<tr>
<th>Group</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIL+/PD-L1 IC– (n = 94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td>0.99 (0.62, 1.57)</td>
<td>0.97</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>1.53 (0.76, 3.08)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

BEP (TILs): n = 893. Cutoff of 10% was used to distinguish low vs intermediate/high levels of TILs (Denkert Lancet Oncol 2018). All P values are nominal.

* Data derived from contingency table with Fisher exact tests.

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The clinical benefit derived by PD-L1 IC+ patients was independent of their BRCA1/2 mutation status

- BRCA1/2 mutants and PD-L1 IC+ are independent from each other (P = ns)a
- Patients with BRCA1/2-mutant tumors derived clinical benefit (PFS/OS) only if their tumors were also PD-L1 IC+b

**BRCA1/2 non-mut/PD-L1 IC+ (n = 257)**

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>PFS</td>
<td>0.63 (0.48, 0.83)</td>
<td>≤ 0.005</td>
</tr>
<tr>
<td>OS</td>
<td>0.62 (0.43, 0.91)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**BRCA1/2 mut/PD-L1 IC+ (n = 45)**

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>0.45 (0.21, 0.96)</td>
<td>0.04</td>
</tr>
<tr>
<td>OS</td>
<td>0.87 (0.26, 2.85)</td>
<td>0.82</td>
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</tbody>
</table>

**BRCA1/2 mut/PD-L1 IC– (n = 44)**

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>PFS</td>
<td>0.77 (0.37, 1.61)</td>
<td>0.49</td>
</tr>
<tr>
<td>OS</td>
<td>0.85 (0.29, 2.43)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

*BEP (BRCA1/2): n = 612. Per FoundationOne BRCA1/2 testing. BRCA1/2 mutant: known and likely mutations. All P values are nominal.

a Data derived from contingency table with Fisher exact tests. b Data interpretation limited by small number of BRCA1/2-mutant patients.

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Conclusions

- In the Phase III IMpassion130 study, PD-L1 expression on IC is a predictive biomarker for selecting patients who clinically benefit from first-line atezolizumab + nab-paclitaxel treatment for mTNBC
  - PFS and OS benefit was observed in patients with a PD-L1 IC of ≥ 1% (by VENTANA SP142 IHC assay)
  - A treatment effect was not seen for adding atezolizumab to chemotherapy in the PD-L1–negative subgroup
- PD-L1 expression on TC did not provide additional information beyond PD-L1 IC status
  - Prevalence of tumor-cell PD-L1 expression was low, and the majority of these tumors were also PD-L1 IC+
- PD-L1 IC expression was the best predictor of clinical benefit as the patient subgroups with tumor-infiltrating immune cells (stromal TILs+) or cytotoxic T cells (CD8+) derived clinical benefit with atezolizumab + nab-paclitaxel if their tumors were also PD-L1 IC+
- PFS and OS results were consistent regardless of BRCA1/2 mutation status
- Patients with newly diagnosed metastatic and unresectable locally advanced TNBC should be routinely tested for PD-L1 IC status to determine whether they might benefit from atezolizumab + nab-paclitaxel

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