The Tumor Microenvironment and Atezolizumab + nab-Paclitaxel Activity in Metastatic Triple-Negative Breast Cancer: IMpassion130

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Background

- In the Phase III IMpassion130 study in 1L mTNBC, atezolizumab (A; anti–PD-L1) + nab-paclitaxel (nP) demonstrated statistically significant PFS benefit and clinically meaningful OS benefit in the PD-L1 IC+ population\textsuperscript{1,\textperiodcentered}.

- Exploratory analyses from IMpassion130\textsuperscript{2-4} have also demonstrated that the improved clinical outcomes observed with A + nP in patients with richer tumor-immune microenvironments (TME) or higher tumor mutational burden (TMB) were limited to patients with PD-L1 IC+ tumors\textsuperscript{2,3}.

- In a large Phase I study of single-agent atezolizumab in mTNBC, higher ORR and longer OS were observed in patients with the basal-like immune-activated (BLIA) molecular subtype, compared with other TNBC subtypes\textsuperscript{5}.
  - However, the predictive vs prognostic nature of TNBC subtypes could not be confirmed in this single-arm study.

- In this exploratory analysis from IMpassion130, we further characterize the TME and its association with A + nP clinical outcomes.

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Phase III IMpassion130 study\textsuperscript{a}

1L mTNBC (N=902)

\textbf{R\textsuperscript{b}}

\textbf{1:1}

Atezolizumab + \textit{nab}-paclitaxel (A + nP)

Placebo + \textit{nab}-paclitaxel (A + nP)

Co-primary endpoints:
- PFS (tested in parallel in the ITT and PD-L1 IC+ populations\textsuperscript{c})
- OS (hierarchically tested in ITT and PD-L1 IC+ populations)

\textsuperscript{a} ClinicalTrials.gov: NCT02425891. \textsuperscript{b} Stratification factors: liver metastases, prior taxanes, PD-L1 IC status (VENTANA SP142 IHC assay). \textsuperscript{c} PD-L1–expressing immune cells covering ≥1% of the tumor area.


\textbf{PD-L1 IC+ population}

Primary PFS analysis\textsuperscript{1}

Stratified HR=0.62 (95% CI: 0.49, 0.78) \(P<0.0001\)

\begin{itemize}
  \item Median PFS (95% CI):
    \begin{itemize}
      \item 5.0 mo (3.8, 5.6)
      \item 7.5 mo (6.7, 9.2)
    \end{itemize}
\end{itemize}

\textbf{PD-L1 IC+ population}

Final OS analysis\textsuperscript{2}

Stratified HR=0.67 (95% CI: 0.53, 0.86)

\begin{itemize}
  \item Median OS (95% CI):
    \begin{itemize}
      \item 17.9 mo (13.6, 20.3)
      \item 25.4 mo (19.6, 30.7)
    \end{itemize}
\end{itemize}
TME evaluation in IMpassion130

Immune phenotypes assessed according to the location of tumor/stroma CD8 by IHC

ITT population (N=902)
- PD-L1 IHC^{1,2}
- sTILs^{1}
- CD8 IHC^{1} (n=802)
- RNA-Seq (n=836)

Molecular subtypes were assessed with RNA-seq, using Burstein classification^{5}

- GSEA hallmark pathways
- Cellular deconvolution

GSEA, gene set enrichment analysis.
Global gene expression landscape in IMpassion130

- Gene expression variation is best explained by TNBC molecular subtypes
- PD-L1 IC+ cases can be found in all TNBC molecular subtypes

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Biological pathways characteristic of PD-L1 IC+ tumors

PD-L1 IC+: Immune, proliferation and DNA damage repair, IL-2/TNF/PI3K signaling

PD-L1 IC–: Myogenesis, TGF-β signaling

* PD-L1–expressing immune cells covering ≥1% of the tumor area (VENTANA SP142 assay).
Immune phenotypes in IMpassion130

Phenotype distribution in IMpassion130 (n=802)

- Immune inflamed: 36%
- Immune excluded: 48%
- Immune desert: 16%

PD-L1 status within immune phenotypes

- Inflamed: 63%
- Excluded: 41%
- Desert: 8%

- PD-L1 IC+: 63%
- PD-L1 IC−: 37%

Expression

- Development
- Immune
- Metabolic
- Proliferation
- Pathway
- Signaling

Category

- Inflamed: Immune, IL-2/TNF signaling
- Excluded: Proliferation, cholesterol homeostasis, intermediate immune
- Desert: Lipid metabolism, oxidative phosphorylation, myogenesis and EMT

EMT, epithelial to mesenchymal transition.

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PFS by immune phenotypes

Inflamed (36%)
- A + nP (n=141)
- P + nP (n=150)

Survival probability (%)
HR=0.63 (0.49, 0.81)

Excluded (47%)
- A + nP (n=196)
- P + nP (n=183)

Survival probability (%)
HR=0.76 (0.61, 0.95)

Desert (16%)
- A + nP (n=71)
- P + nP (n=60)

Survival probability (%)
HR=1.1 (0.79, 1.6)

HRs adjusted for liver metastases and prior taxanes.

In the P + nP arm, no difference in PFS prognosis was observed based on immune phenotype.

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OS by immune phenotypes

Inflamed (36%)

Survival probability (%)

Time (months)


P D - L 1 I C +

Inflamed (n=183)
Excluded (n=157)
Desert (n=11)

HR=0.61 (0.42, 0.88)
HR=0.72 (0.50, 1.10)
HR=0.14 (0.02, 0.99)

Favors A + nP
Favors P + nP

PD-L1 IC−

Inflamed (n=108)
Excluded (n=223)
Desert (n=120)

HR=0.94 (0.60, 1.50)
HR=0.97 (0.71, 1.30)
HR=1.10 (0.76, 1.70)

Favors A + nP
Favors P + nP

Survival probability (%)

Time (months)

Excluded (47%)

Survival probability (%)

Time (months)

Desert (16%)

Survival probability (%)

Time (months)

HRs adjusted for liver metastases and prior taxanes.

*In the P + nP arm, no difference in OS prognosis was observed based on immune phenotype.

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TNBC molecular subtypes

**Subtype distribution in IMpassion130 (n=836)**

- **MES**: 5%
- **BLIA**: 27%
- **LAR**: 26%
- **BLIS**: 42%

**PD-L1 status within molecular subtypes**

- **BLIA**
  - PD-L1 IC+: 74%
  - PD-L1 IC−: 26%
- **BLIS**
  - PD-L1 IC+: 32%
  - PD-L1 IC−: 68%
- **LAR**
  - PD-L1 IC+: 31%
  - PD-L1 IC−: 69%
- **MES**
  - PD-L1 IC+: 28%
  - PD-L1 IC−: 72%

**Pathways**

1. **INTERFERON_ALPHA_RESPONSE**
2. **INTERFERON_GAMMA_RESPONSE**
3. **ALLOGRAFT_REJECTION**
4. **INFLAMMATORY_RESPONSE**
5. **IL6_JAK_STAT3_SIGNALING**
6. **TNFA_SIGNALING_VIA_NFKB**
7. **COMPLEMENT**
8. **IL2_STAT3_SIGNALING**
9. **MYC_TARGETS_V1**
10. **E2F_TARGETS**
11. **MYC_TARGETS_V2**
12. **G2M_CHECKPOINT**
13. **MITOTIC_SPINDLE**
14. **DNA_REPAIR**
15. **SPERMATOGENESIS**
16. **UNFOLDED_PROTEIN_RESPONSE**
17. **PI3K_AKT_MTOR_SIGNALING**
18. **OXIDATIVE_PHOSPHORYLATION**
19. **WNT_BETA_CATENIN_SIGNALING**
20. **GLYOXYLOSIS**
21. **PEROXISOME**
22. **FATTY_ACID_METABOLISM**
23. **ADIPIONESIS**
24. **CHOLESTEROL_HOMEOSTASIS**
25. **PROTEIN_SECRETION**
26. **REACTIVE_OXYGEN_SPECIES_PATHWAY**
27. **ESTROGENRESPONSE_EARLY**
28. **ESTROGENRESPONSE_LATE**
29. **BAX_APOPTOSIS**
30. **BCL2_APOPTOSIS**
31. **APICAL_JUNCTION**
32. **HEDGEHOG_SIGNALING**
33. **EPITHELIAL_MESENCHYMAL_TRANSITION**
34. **KRAS_SIGNALING_UP**

**Expression**

- High in immune signatures and proliferation; low in lipid metabolism and ER/AR response
- High in proliferation and glycolysis; low in immune, lipid metabolism and ER/AR response
- High in ER/AR response, lipid metabolism; low in proliferation and intermediate immune response
- Most enriched in EMT signaling, Hedgehog signaling, angiogenesis, myogenesis, ER/AR response, TGF-β signaling, fibroblasts and endothelial cells

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PFS by molecular subtype

**BLIA (27%)**
- A + nP (n=106)
- P + nP (n=121)
- Survival probability (%)
  - HR=0.54 (0.40, 0.72)

**BLIS (42%)**
- A + nP (n=183)
- P + nP (n=163)
- Survival probability (%)
  - HR=0.85 (0.68, 1.10)

**LAR (26%)**
- A + nP (n=110)
- P + nP (n=109)
- Survival probability (%)
  - HR=0.86 (0.64, 1.20)

**MES (5%)**
- A + nP (n=24)
- P + nP (n=19)
- Survival probability (%)
  - HR=1.10 (0.58, 2.20)

**PD-L1 IC+**
- BLIA (n=167)
- BLIS (n=111)
- LAR (n=67)
- MES (n=12)
- HRs adjusted for liver metastases and prior taxanes. In the P + nP arm, BLIA and BLIS had poor PFS vs LAR subgroups.

**PD-L1 IC−**
- HR=0.49 (0.34, 0.69)
- HR=0.66 (0.44, 0.98)
- HR=0.91 (0.53, 1.60)
- HR=3.40 (0.66, 18.00)
- HR=0.59 (0.31, 1.10)
- HR=0.98 (0.74, 1.30)
- HR=0.86 (0.60, 1.20)
- HR=0.93 (0.42, 2.00)

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OS by molecular subtype

- BLIA (27%)
  - Survival probability: HR=0.61 (0.44, 0.85)
  - Median survival: Time (months)
  - 74% survival probability after 50 months

- BLIS (42%)
  - Survival probability: HR=0.99 (0.78, 1.20)
  - Median survival: Time (months)
  - 32% survival probability after 50 months

- LAR (26%)
  - Survival probability: HR=0.90 (0.66, 1.20)
  - Median survival: Time (months)
  - 31% survival probability after 50 months

- MES (5%)
  - Survival probability: HR=1.00 (0.49, 2.10)
  - Median survival: Time (months)
  - 28% survival probability after 50 months

**PD-L1 IC+**

- BLIA (n=167)
  - HR=0.54 (0.36, 0.80)

- BLIS (n=111)
  - HR=0.92 (0.60, 1.40)

- LAR (n=67)
  - HR=0.75 (0.39, 1.40)

- MES (n=12)
  - HR=0.70 (0.17, 2.80)

**PD-L1 IC−**

- BLIA (n=60)
  - HR=0.91 (0.46, 1.80)

- BLIS (n=236)
  - HR=1.00 (0.76, 1.40)

- LAR (n=152)
  - HR=1.00 (0.70, 1.50)

- MES (n=31)
  - HR=0.98 (0.38, 2.50)

HRs adjusted for liver metastases and prior taxanes. a In the P + nP arm, BLIA and BLIS had poor OS vs LAR subgroups.

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TME pathways associated with A + nP PFS outcome

- Biological pathway activity and association with A + nP clinical outcomes was assessed using the MSigDB Hallmark gene sets (50 pathways)\(^1\)
- Pathways linked to differential A + nP (vs P + nP) PFS outcomes in patients with PD-L1 IC+ tumors were:
  - **Negative**: Angiogenesis, apoptosis, estrogen response, EMT and protein secretion
  - **Positive**: Proliferation, DNA repair

*False discovery rate <0.2. Pathways marked by an asterisk were considered to have interaction tests HRs that were statistically significant. Multivariate analysis adjusted for liver metastases and prior taxanes. 1. Liberzon A. Cell Syst 2015.*
Select features linked to A + nP PFS outcome

- A + nP treatment improved PFS in patients whose PD-L1 IC+ tumors expressed biomarkers associated with A + nP poor prognosis

HR and P value shown on each plot derived from biomarker interaction test.
Summary

- This exploratory analysis from IMpassion130 reports a detailed molecular pathway characterization of TNBC tumors based on immune phenotypes and molecular subtypes and their relationships with clinical outcomes with A + nP
- Improved clinical outcomes with A + nP were observed in PD-L1 IC+ subgroups
  - PFS: immune-inflamed (followed by immune-excluded) phenotype; BLIA and BLIS molecular subtypes; tumors with increased proliferative/DNA repair pathways
  - OS: immune-inflamed phenotype; BLIA molecular subtype
- Potential mechanisms of resistance to A + nP were observed in PD-L1 IC+ subgroups
  - PFS: LAR molecular subtype; tumors with increased angiogenesis, EMT, Hedgehog pathway, estrogen response and tumor necrosis factor signaling pathways
  - OS: BLIS and LAR molecular subtypes
- These data are hypothesis generating and require validation using an independent dataset
TME features associated with A + nP clinical outcomes in patients with PD-L1 IC+ mTNBC

- No features associated with outcomes in patients with PD-L1 IC– tumors were identified
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