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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Disclosure

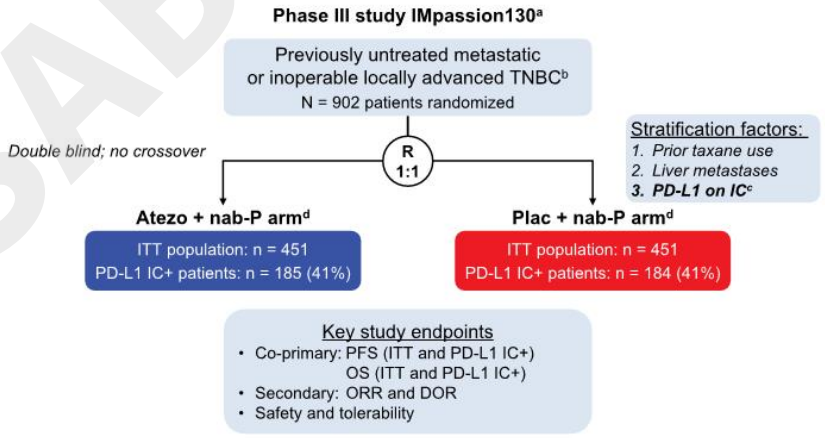
- Dr Emens declares the following financial interests:
  - Consulting and advisory roles for AbbVie, Amgen, Bayer, Celgene, eTHeRNA, Gritstone Oncology, Macrogenics, MedImmune, MolecuVax, Novartis, Peregrine, Replimune, Syndax and Vaccinex
  - Travel, accommodations and expenses support from Bayer, Bristol-Myers Squibb, Corvus, Macrogenics, Novartis, Replimune, Roche/Genentech and Vaccinex
  - Stock and ownership interest in MolecuVax
  - Grants or research support from Aduro Biotech, AstraZeneca, Breast Cancer Research Foundation, Corvus, EMD Serono, Roche/Genentech, MaxCyte and Merck
  - Licensing royalties with Aduro Biotech
- Dr Emens is a member of FDA Advisory Committee on Cell Tissue and Gene Therapies, on the Board of Directors for the Society of Immunotherapy of Cancer, on the Data Safety and Monitoring Board for the TRIO025 trial, and a steering committee member for the IMpassion130 and KATE2 trials
- This study is sponsored by F. Hoffmann-La Roche, Ltd
- Editorial support, funded by the sponsor, was provided by an independent medical writer under the guidance of the authors

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 disease[2,3]
  - Estimates of median OS vary but are generally ≈ 18 months or less[4-6]
- 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 States[7]
  - PARP inhibitors for *BRCA1/2*-mutant, HER2-negative mBC have been approved in several countries[8]
- IMpassion130 is the first Phase III study to demonstrate a benefit with immunotherapy in mTNBC[9]
  - 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 months[9]

PD-L1+: PD-L1 on ≥ 1% of IC (as % of tumor area).
1. den Brok *BCRT* 2017. 2. NCCN 2018. 3. Cardoso *Ann Oncol* 2018. 4. Gobbini *EJC* 2018. 5. Yardley *Ann Oncol* 2018. 6. Miles *Ann Oncol* 2013. 7. AVASTIN SmPC 2017. 8. Lynparza USPI 2018. 9. Schmid *N Engl J Med* 2018.

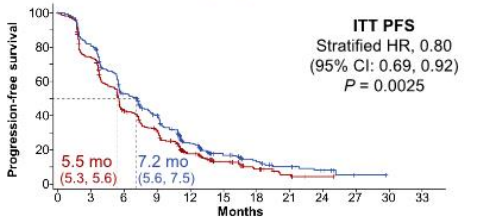
IMpassion130 study design: Prespecified analyses in the ITT and PD-L1 IC+ population

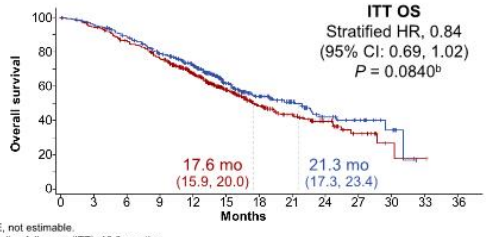


[a] NCT02425891. [b] Locally evaluated per ASCO-CAP guidelines. Prior chemotherapy in the curative setting, including taxanes, allowed if treatment-free interval ≥ 12 mo.
[c] Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status, PD-L1+: PD-L1 on ≥ 1% of IC). [d] Atezolizumab 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. 1. Schmid *N Engl J Med* 2018.

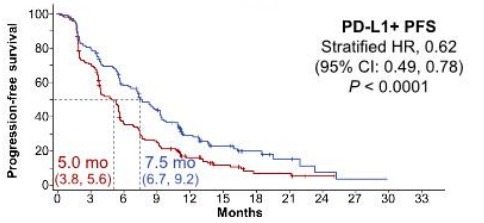
IMpassion130 primary analysis[1,2]: Clinically meaningful PFS and OS benefit in the PD-L1+ population

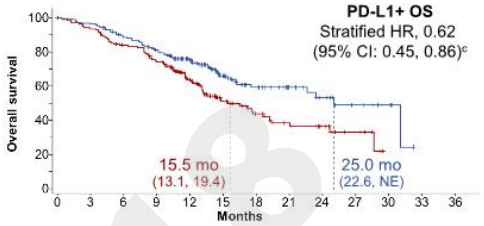
ITT population





PD-L1+ population[a]





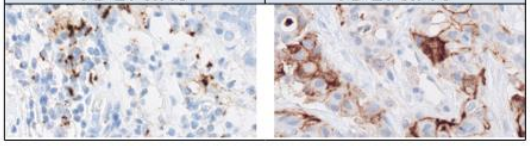
NE, not estimable.
Median follow-up (ITT): 12.9 months.
[a] PD-L1+: PD-L1 in ≥ 1% of IC. [b] Not significant. [c] Not formally tested per hierarchical study design.
1. Schmid *N Engl J Med* 2018. 2. Schmid ESMO 2018 [LBA1_PR].

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-1[1,2]
- 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[a]
  - Intratumoral CD8+ T cells by IHC (Dako clone C8/144B) and stromal TILs by H&E[b]
  - *BRCA1/2* mutation status by FoundationOne assay

PD-L1 IHC (SP142) Assay by Ventana Medical Systems

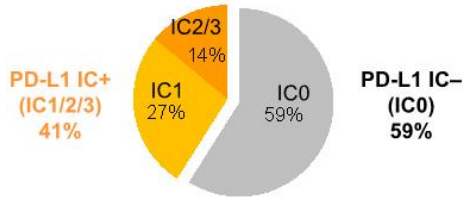
PD-L1 on IC	PD-L1 on TC



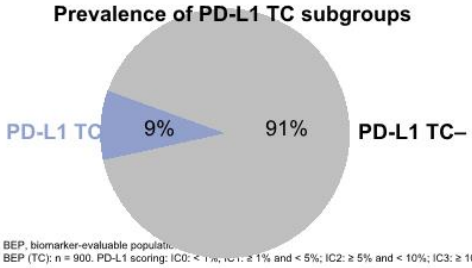
H&E, hematoxylin and eosin staining; IHC, immunohistochemistry.
[a] PD-L1 scoring: IC0: < 1%; IC1: ≥ 1% and < 5%; IC2: ≥ 5% and < 10%; IC3: ≥ 10%; TC–: < 1% PD-L1 on tumor cells; TC+: ≥ 1% PD-L1 on tumor cells.
[b] Pre-specified cutoffs for CD8 IHC and stromal TILs are based on references 1 and 2.
1. Adams *JAMA Oncol* 2018. 2. Denkert *Lancet Oncol* 2018.

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

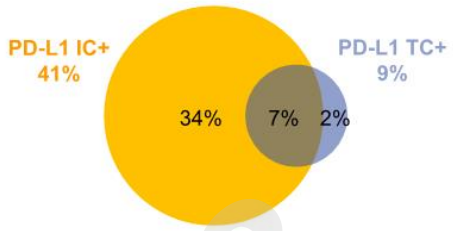
Prevalence of PD-L1 IC subgroups



Prevalence of PD-L1 TC subgroups



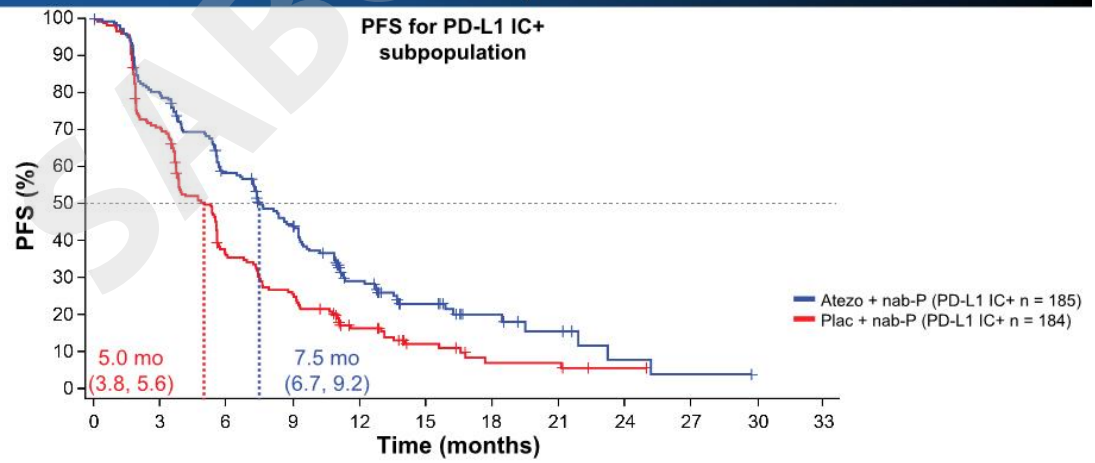
The majority of patients with expression of PD-L1 on TC are included within the PD-L1 IC+ population



BEP, biomarker-evaluable populati...
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.

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

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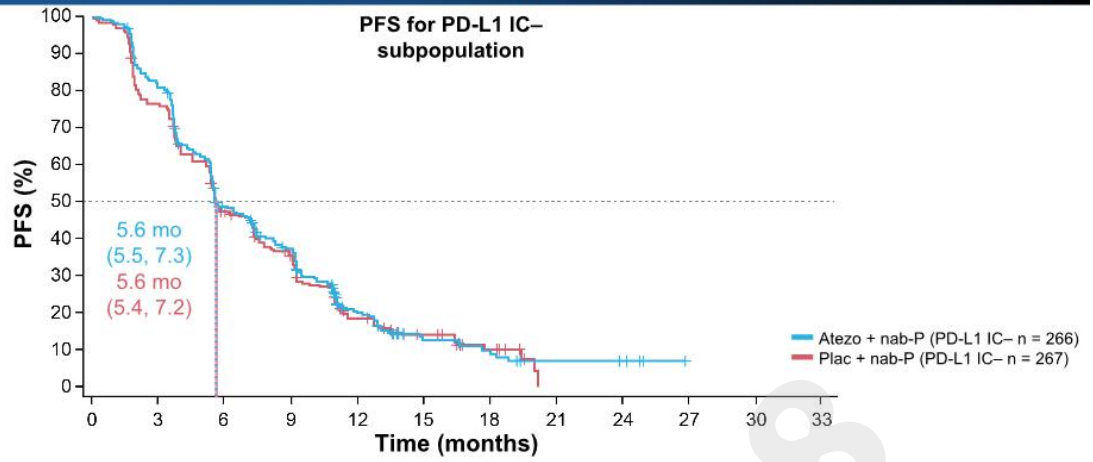

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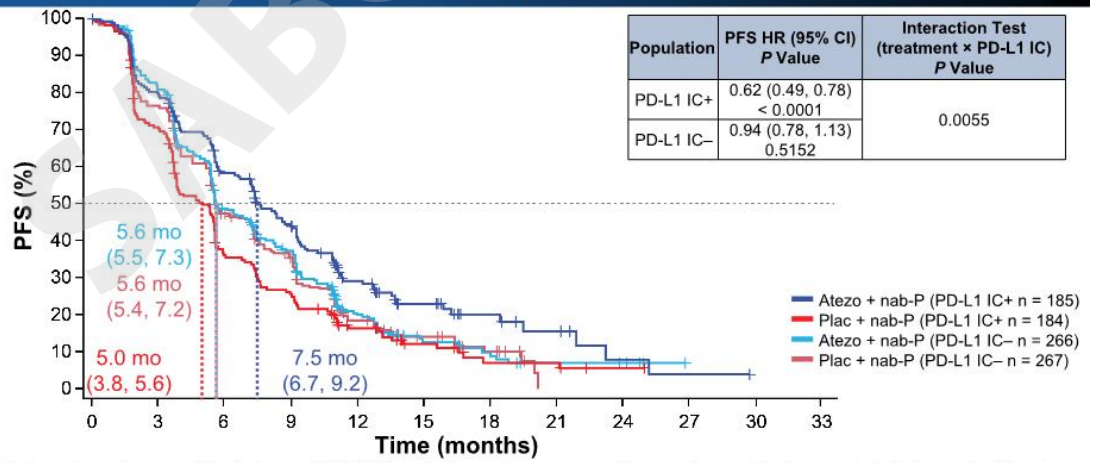
PD-L1 IC status (positive vs negative) predicts PFS benefit with atezolizumab + *nab*-paclitaxel

Population	PFS HR (95% CI) *P* Value	Interaction Test (treatment × PD-L1 IC) *P* Value
PD-L1 IC+	0.62 (0.49, 0.78) < 0.0001	0.0055
PD-L1 IC–	0.94 (0.78, 1.13) 0.5152	

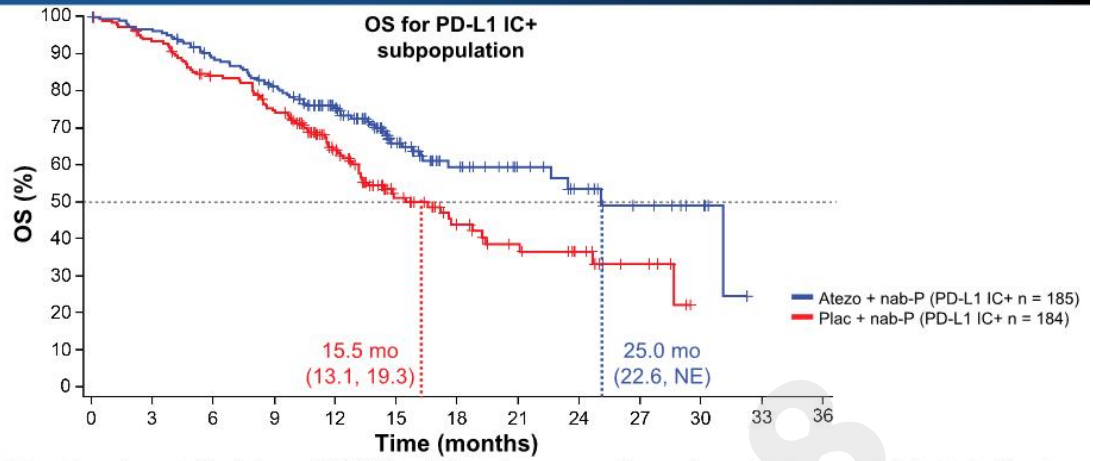


- A trend toward association between PD-L1 IC positivity and poor prognosis was observed but was not statistically significant
- PD-L1 IC positivity was predictive of PFS and OS benefit with atezolizumab + *nab*-paclitaxel

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.

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

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



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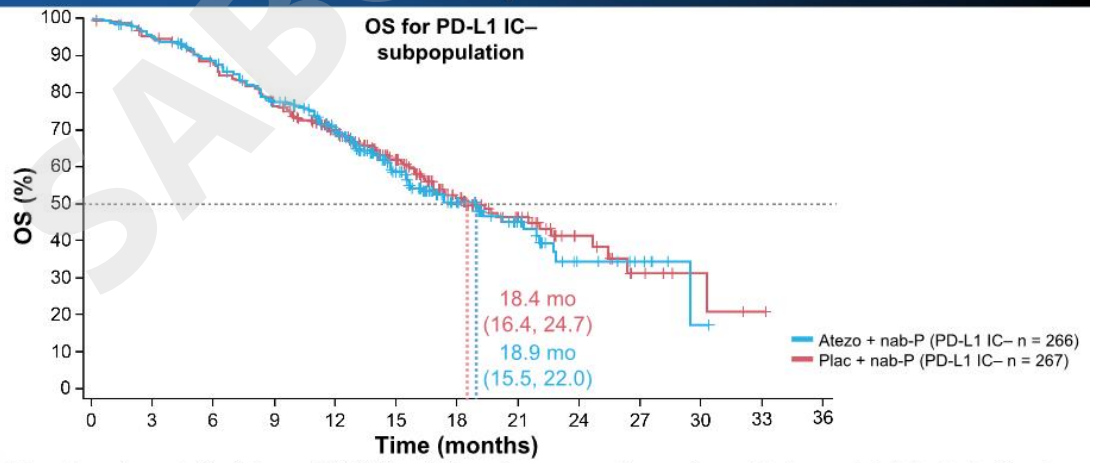

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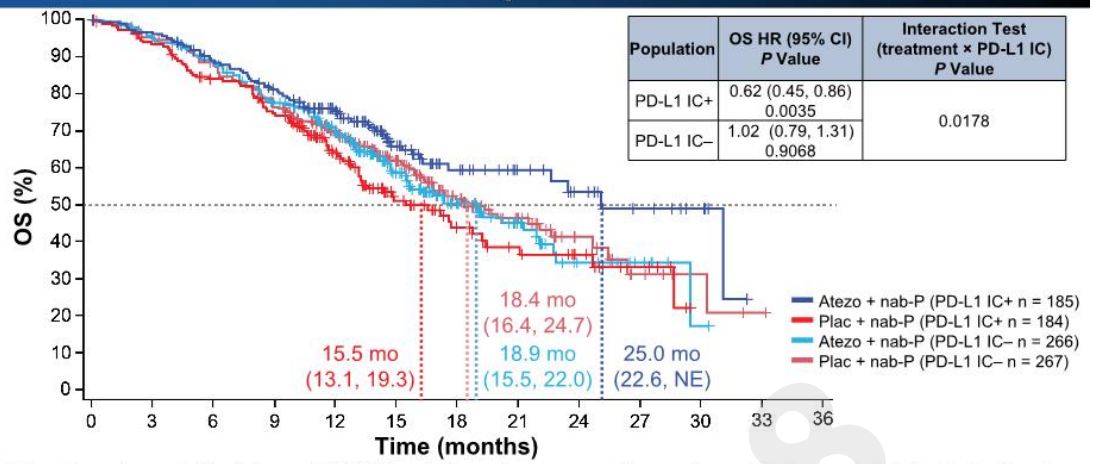

Population	OS HR (95% CI) *P* Value	Interaction Test (treatment × PD-L1 IC) *P* Value
PD-L1 IC+	0.62 (0.45, 0.86) 0.0035	0.0178
PD-L1 IC–	1.02 (0.79, 1.31) 0.9068	

- 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

Median OS durations (and 95% CIs) are indicated on the plot. Stratified HRs are shown. All *P* values are nominal. Data cutoff: April 17, 2018.

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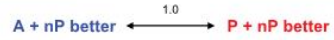
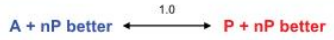
Consistent clinical benefit with atezolizumab + *nab*-paclitaxel was observed across all PD-L1 IC+ subgroups

	PD-L1 IC Status	n	PFS Median, mo A + nP	PFS Median, mo P + nP	PFS HR[a] (95% CI)	PFS *P* value	OS Median, mo A + nP	OS Median, mo P + nP	OS HR[a] (95% CI)	OS *P* value
Neg	IC0	532	5.6	5.6	0.93 (0.77, 1.12)	0.47	18.9	18.4	1.02 (0.79, 1.31)	0.90
Pos	IC1	243	7.4	3.9	0.59 (0.44, 0.78)	≤ 0.005	23.4	14.4	0.56 (0.38, 0.82)	≤ 0.005
Pos	IC2/3	125	9.3	5.7	0.64 (0.42, 0.97)	0.03	25.0	21.1	0.71 (0.39, 1.30)	0.26
	All	900	7.2	5.5	0.79 (0.68, 0.92)	≤ 0.005	21.3	17.6	0.83 (0.68, 1.02)	0.07





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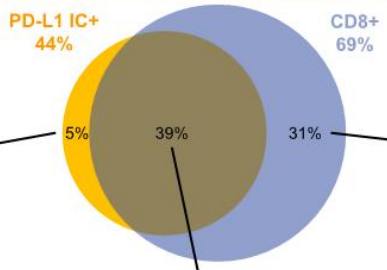
CD8+ IHC has clinical benefit if co-occurring with PD-L1 IC+



CD8–/PD-L1 IC+ (n = 37)

	HR (95% CI)	*P* Value
PFS	0.33 (0.13, 0.87)	0.03
OS	0.25 (0.06, 1.02)	0.05

CD8+/PD-L1 IC– (n = 220)

	HR (95% CI)	*P* Value
PFS	0.89 (0.66, 1.20)	0.45
OS	0.77 (0.50, 1.17)	0.21

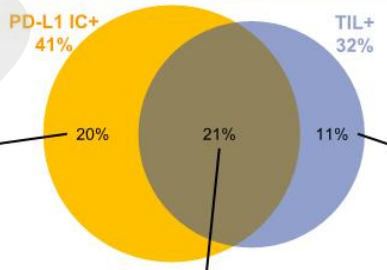
CD8+/PD-L1 IC+ (n = 280)

	HR (95% CI)	*P* Value
PFS	0.61 (0.46, 0.80)	≤ 0.005
OS	0.55 (0.38, 0.80)	≤ 0.005

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

BEP (CD8): n = 720. A CD8+ cutoff of 0.5% was selected based on Phase Ib study in TNBC (Adams *JAMA Oncol* 2018). All *P* values are nominal.
[a] Data derived from contingency table with Fisher exact tests.

Stromal TILs has clinical benefit if co-occurring with PD-L1 IC+



TIL–/PD-L1 IC+ (n = 176)

	HR (95% CI)	*P* Value
PFS	0.74 (0.54, 1.03)	0.07
OS	0.65 (0.41, 1.02)	0.06

TIL+/PD-L1 IC– (n = 94)

	HR (95% CI)	*P* Value
PFS	0.99 (0.62, 1.57)	0.97
OS	1.53 (0.76, 3.08)	0.24

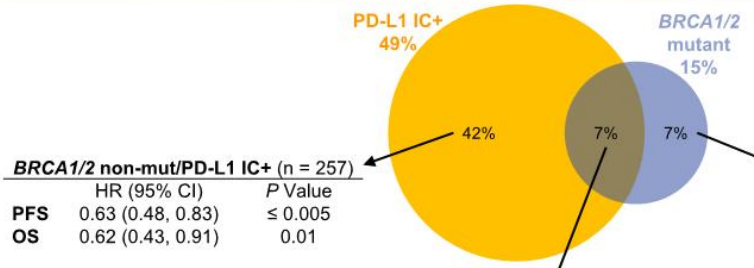
TIL+/PD-L1 IC+ (n = 190)

	HR (95% CI)	*P* Value
PFS	0.53 (0.38, 0.74)	≤ 0.005
OS	0.57 (0.35, 0.92)	0.02

- TIL+ were enriched for PD-L1 IC+ ($P < 0.0001$) but PD-L1 IC+ were not enriched for TIL+ (P = ns)[a]
- ***Patients with TIL+ tumors derived clinical benefit (PFS/OS) only if their tumors were also PD-L1 IC+***

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.
[a] Data derived from contingency table with Fisher exact tests.

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



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

	HR (95% CI)	*P* Value
PFS	0.63 (0.48, 0.83)	≤ 0.005
OS	0.62 (0.43, 0.91)	0.01

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

	HR (95% CI)	*P* Value
PFS	0.45 (0.21, 0.96)	0.04
OS	0.87 (0.26, 2.85)	0.82

***BRCA1/2* mut/PD-L1 IC–** (n = 44)

	HR (95% CI)	*P* Value
PFS	0.77 (0.37, 1.61)	0.49
OS	0.85 (0.29, 2.43)	0.76

- *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]**

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.

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

Acknowledgments

- The patients and their families and caretakers
- Participating study investigators and clinical sites
- The independent Data and Safety Monitoring Board
- This study is sponsored by F. Hoffmann-La Roche, Ltd.
- Medical writing assistance for this presentation was provided by Steffen Biechele, PhD, of Health Interactions and funded by F. Hoffmann-La Roche, Ltd.