

Lessons learned at SABCS 2019 and to-dos from immunotherapy in breast cancer



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In 2018, an important paradigm shift in the treatment of patients with breast cancer (BC) has begun: immunotherapy was shown to improve the outcomes of patients with metastatic triple negative breast cancer (TNBC), with a possible survival benefit for those with programmed death ligand 1 (PD-L1) positivity, as first-line treatment combined with chemotherapy in the IMpassion130 trial.¹ This trial, however positive, has provided a glimpse of immunotherapy's somewhat restricted, but ever growing place in the treatment armamentarium against BC, and this has been further outlined by studies presented at the San Antonio Breast Cancer Symposium (SABCS) 2019.

In SAFIRO2-Immuno, 199 patients with metastatic or locally advanced, inoperable HER2-negative BC and no targetable molecular alteration were randomised to either durvalumab, an anti-PD-L1 antibody, or to maintenance chemotherapy.² Eligible patients had to have at minimum stable disease following 6–8 cycles of chemotherapy and be in their first or second line of chemotherapy. SAFIRO2-Immuno was powered to show an increment in median progression-free survival (mPFS) of durvalumab over chemotherapy. mPFS attained with durvalumab was 2.7 months versus 4.6 months with chemotherapy (HR 1.40 (95% CI, 1.00 to 1.96)), at the expense of an increment in the incidence of serious adverse events (SAEs). No subgroup seemed to benefit from immunotherapy. Yet, overall survival was numerically higher with durvalumab (21.7 vs 17.9 months with chemotherapy), possibly boosted by the TNBC and PD-L1-positive subpopulations who benefited more from durvalumab in the exploratory subgroup analyses.

In the early setting, yet another drawback for immunotherapy was presented at SABCS. NeoTRIPaPDL1 compared the addition of atezolizumab with neoadjuvant carboplatin and nab-paclitaxel versus the same

chemotherapy backbone alone, in 280 TNBC patients.³ NeoTRIPaPDL1 was powered to show a benefit in event-free survival (EFS) rate in favour of neoadjuvant atezolizumab. Nonetheless, in this first analysis, data were presented on the rates of pathological complete response (pCR) in the breast/axilla, a key secondary end point. At surgery, pCR rates were 43.5% with atezolizumab/chemotherapy versus 40.8% with chemotherapy alone, for an OR of 1.11 (95% CI, 0.69 to 1.79), also with an increment in the incidence of SAEs. Curiously, despite PD-L1 expression correlating with higher pCR rates in both treatment arms, it had no predictive value, at this stage, for better outcomes with atezolizumab.

Quite on the opposite direction, key subgroup analyses of KEYNOTE-522 were presented. As in NeoTRIPaPDL1, 602 patients with non-metastatic TNBC were randomised to an optimised neoadjuvant chemotherapy backbone (carboplatin/paclitaxel followed by anthracyclines/cyclophosphamide) with either the anti-PD-1 pembrolizumab or placebo, to be continued after surgery according to the arm of assignment.⁴ Co-primary end points were pCR and EFS, for which the former has already been shown in the first interim analysis to favour immunotherapy. In this exploratory analysis, results were suggestive of a stronger role of immunotherapy in higher disease stages, insofar as the Δ pCR was 11.0% (62.1% with placebo vs 73.1% with pembrolizumab) in stage IIA, increasing to 25.6% (23.1% vs 48.6%) in stage IIIB, as well as Δ pCR increased from 6.3% (58.6% vs 64.9%) in node-negative disease to 20.6% (44.1% vs 64.8%) in node-positive. Again, PD-L1 expression was not predictive for immunotherapy effect. [Table 1](#) provide more details on these trials.

Following these important but somewhat divergent results, it comes to questioning: who are the BC patients likely to benefit from

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Table 1 Summary of key trials testing immunotherapy in breast cancer patients

Study/design/pop	Arms	Pop (N)	N+ (%)	PD-L1+ (%)	Assay	EP	Results	Comments
Early-stage breast cancer								
NeoTRIPaPDL1; Open-label, randomised (1:1), phase III; TNBC ³	Carbo+Nab-pacl ¹ × 8 (control); Carbo+Nab-pacl ¹ +Atezolizumab × 8 (exp); adj A or E/C × 4 for all patients	280	88	56	Ventana SP142 IHC (1+, 2+ or 3+ on immune cells)	EFS at 5 y (primary EP); pCR rates (key-secondary EP)	pCR rates: Exp: 43.5%; Control: 40.8%	Primary EP not yet reported; pCR OR of exp/control (95% CI): 1.1 (0.7–1.8); pCR OR of PD-L1+/PD-L1– (95% CI): 2.1 (1.6–2.7)
KEYNOTE-522; Placebo-controlled, randomised (2:1), phase III; TNBC ⁴	Carbo+pacl ¹ × 4 → A or E/C × 4, all w/ placebo; Carbo+pacl ¹ × 4 → A or E/C × 4, all w/ pembro (exp); adj placebo or pembro × 9 according to assigned arm	602	52	83	PharmDx 22C3 IHC (combined positive score 1+, 2+ or 3+)	Co-primaries: pCR and EFS rates	pCR rates: Exp: 65%; Placebo: 51%; EFS rates at 18 mo: Exp: 91.3%; Placebo: 85.3%	P<0.003 for ΔpCR; stronger benefit w/ pembro in stage III and NR; ΔpCR benefit w/ pembro regardless of PD-L1 expression; EFS analysis immature
Metastatic breast cancer								
SAFIR02-Immuno; Open-label, randomised (2:1), phase II; all-comers ²	After clinical benefit w/ chemotherapy; maintenance chemotherapy (control) or switch to durvalumab (exp)	199	NE	33	Ventana SP142 IHC (≥1% on immune cells)	mPFS (primary EP); mOS (secondary EP)	mPFS: Exp: 2.7 mo; Control: 4.6 mo; mOS: Exp: 21.7 mo; Control: 17.9 mo	Key population features: 56% ER+, 10% second line; mPFS HR of exp/control (95% CI): 1.4 (1.0–2.0); mOS HR of exp/control (95% CI): 0.8 (0.5–1.3) Potential OS benefit in TNBC population as mOS were 14 and 21 mo, for a HR of exp/control (95% CI) of 0.5 (0.3–1.0)
IMpassion130; Double-blind, placebo-controlled, randomised (1:1), phase III; first-line TNBC ¹	Atezolizumab+nab-pacl ¹ (exp); Atezolizumab+placebo (control)	902	NE	41	Ventana SP142 IHC (≥1% on immune cells)	Co-primaries: mPFS and mOS in the ITT and PD-L1+ population	ITT mPFS: Exp: 7.2 mo; Placebo: 5.5 mo; ITT mOS: Exp: 21.0 mo; Placebo: 18.7 mo	ITT mPFS HR of exp/control (95% CI): 0.8 (0.7–0.9); PDL1 +mPFS HR of exp/control (95% CI): 0.6 (0.5–0.8); OS benefit w/ atezolizumab only in PD-L1 +population (HR (95% CI): 0.7(0.5–0.9))

A, doxorubicin; adj, adjuvant; C, cyclophosphamide; carbo, carboplatin; E, epirubicin; EFS, event-free survival; EP, end point; exp, experimental; IHC, immunohistochemistry; ITT, intention-to-treat; mo, months; mPFS, median progression-free survival; NE, non-evaluable; OS, overall survival; pacl¹, paclitaxel; PD-L1, programmed death ligand 1; pembro, pembrolizumab; TNBC, triple negative breast cancer; y, year.

immunotherapy? Moreover, how does one reconcile the divergent results from SAFIRO2-Immuno with those of IMpassion130, and again, from NeoTRIPaPDL1 with KEYNOTE-522?

Unlike with melanoma and other tumours, it takes more for immunotherapy to kick-in in BC, and while several reasons for this have been identified, much ends up funnelling into the intrinsically unfavourable immune phenotype of the most common BC subtype (ie, oestrogen receptor (ER)-positive BC).⁵ Unleashing the immune system response with anti-PD-(L)1 drugs alone against ER-positive BC may be more difficult than we think: these tumours have been shown to have comparative lower concentration of tumour-infiltrating lymphocytes,⁶ PD-L1 expression⁷ and accumulation of non-synonymous mutations,⁸ in comparison with HER2-positive and TNBC.⁹ Likewise, ER-positive BC is frequently immune-excluded, without T-cell infiltration in their parenchyma or stroma, which precludes anti-tumour T-cell activity regardless of their stimulation.¹⁰ Moreover, the poor response rates to single-agent anti-PD-(L)1 reported thus far, especially when given at latter lines,^{11–15} underscore the need to make BC susceptible to activated T-cell infiltration, i.e. to turn a ‘cold’ tumour into a ‘hot’ one. In this sense, chemotherapy has been shown effective, especially by promoting tumour lysis and antigen recognition by T-cells.⁵ Therefore, those may be the ultimate reasons why SAFIRO2-Immuno could not prove maintenance durvalumab beneficial, as too many patients with ER-positive disease were enrolled, some were treated beyond first line and they were not given concomitant chemotherapy to better prime their immune system. Despite all the constraints of cross-trial comparisons, this was quite the opposite of IMpassion130 patients, all of whom had TNBC, were receiving first-line therapy, and were concomitantly treated with nab-paclitaxel.

Still, despite the closely related population of untreated non-metastatic TNBC patients, and similar trials design, why has KEYNOTE-522 succeeded where NeoTRIPaPDL1 has failed? Although pCR rate was not statistically improved with atezolizumab, NeoTRIPaPDL1 was not powered to show such a difference and, despite the strong correlation between pCR and EFS in TNBC,¹⁶ it is yet to be reported the trial’s primary outcome of EFS. Yet, the absence of an anthracycline in NeoTRIPaPDL1’s neoadjuvant backbone may have jeopardised further priming of T-cytotoxic activity and subsequent tumour clearance from the breast and lymph nodes. However, a smaller phase II trial with durvalumab was reported negative, despite the use of neoadjuvant epirubicin.¹⁷ Quite more patients had PD-L1-positive tumours in KEYNOTE-522 than in NeoTRIPaPDL1 which may have contributed to a stronger effect of immunotherapy in the former trial, although this inter-trial population difference may relate to the differently used assays.¹⁸ In fact, the most accurate method for PD-L1 assessment is yet to be elucidated, since most anti-PD-(L)1 drug manufacturers have validated their own companion immunohistochemistry assay, with

variations between antibodies, methods of PD-L1 positivity scoring and predictive values for anti-PD(L)1 efficacy, which can change according to disease and stage.¹⁹

As of today, therefore, patients with metastatic disease can expect to derive a considerable benefit of immunotherapy if they have PD-L1-positive TNBC and are treated upfront with immunotherapy plus chemotherapy. New strategies to further prime the immune system are being tested to extend the benefit of anti-PD-(L)1 drugs to patients with ER-positive BC, such as combined checkpoint inhibition, CDK4/6 inhibition, anti-angiogenic agents and other targeted therapies, radiation and manipulation of the tumour microenvironment, among others. The goal is also to extend immunotherapy to HER2-positive disease and improve outcomes similarly to that observed in TNBC. Besides, improved patient selection may be achieved by the combined assessment of PD-L1 and tumour-infiltrating lymphocytes,²⁰ by biomarkers in tumour and blood,²¹ as well as by immune-gene signatures (eg, Th1),²² though prospective validation is lacking.

Although it is prudent to wait for the definitive analysis of EFS in KEYNOTE-522, patients with non-metastatic TNBC, especially when locally advanced or node positive, merit consideration for neoadjuvant pembrolizumab plus optimised chemotherapy, whereas anti-PD-L1 drugs are yet to prove their benefit in this setting. For the time being, front-line combination of atezolizumab with nab-paclitaxel is considered as one of the standards of care for PD-L1-positive metastatic TNBC.

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