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EDITORIAL

Defining the immunogram of breast cancer: a focus on clinical trials

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ABSTRACT

In phase III ImPassion130 trial, the addition of immunotherapy to chemotherapy improved overall survival in metastatic triple-negative breast cancer patients. This benefit was significant only in patients harboring PD-L1-positive tumors, suggesting that stratification according to response biomarkers is needed to achieve consistent responses. Besides PD-L1 expression, a variety of potential biomarkers are under investigation for predicting immunotherapy efficacy in breast cancer, such as tumor-infiltrating lymphocytes, gene signatures, tumor mutational burden, microsatellite instability, and gut microbiome. Enriching future trials through these biomarkers could help identifying the population of responders, realizing what has been called precision immunotherapy.

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The results of the recently published phase III ImPassion130 trial bring breast cancer (BC) in the immunotherapy era. Schmid and colleagues demonstrated a substantial overall survival (OS) gain in PD-L1-positive metastatic triple-negative breast cancer (mTNBC) patients by the addition of the anti-PD-L1 agent atezolizumab to first-line chemotherapy with nab-paclitaxel [1]. Median OS was prolonged by nearly 10 months compared to chemotherapy arm. Results from this trial led to the recent FDA approval of atezolizumab for adult patients with advanced TNBC whose tumors express PD-L1 [2].

According to these data, is immunotherapy transformative for metastatic TNBC? Many open questions arise from the trial. How best to test the tumor for PD-L1 expression since this subgroup of patients derived benefit from atezolizumab? Is nab-paclitaxel the ideal partner for an immune checkpoint inhibitor? Did we miss an atezolizumab monotherapy arm that might be a good option for a subset of patients? Should we be more focused on OS rather than PFS? What can we learn from the neoadjuvant setting?

Such a positive result was achieved by stratifying patients according to PD-L1 expression, which allowed to identify a population deriving greater benefit from immunotherapy. Stratifying patients based on predictive markers allows to increase benefit from experimental treatments. Therefore, the definition of an 'immunogram' of patients with BC will be key for the design of future clinical trials.

Besides PD-L1 expression, a variety of potential biomarkers are under investigation for predicting immunotherapy efficacy in BC. A conceptualization of the comprehensive view of immunotherapy in cancer treatment has been proposed earlier, included in the framework of the *cancer immunogram* [3]. Since then, interesting evidence has emerged from BC immunotherapy trials regarding predictive biomarkers, and a specific *breast cancer immunogram* can be proposed. The presence of tumor-infiltrating lymphocytes (TILs), a known prognostic factor in early TNBC, showed a predictive value in TNBC patients treated with immune-checkpoint-inhibitors (ICI) monotherapy [4] and is now being implemented as a stratification factor in BC immunotherapy trials. Interestingly, in the ImPassion130 trial, TILs were predictive of ICI efficacy only in PD-L1-positive tumors, showing that a multidimensional immunogram has a better predictive potential compared with a single factor [5]. In fact, since tumoral PD-L1 expression is induced by IFN-γ [6], TILs found in PD-L1-negative tumors are not expected to be secreting IFN-γ, thus most likely not exerting antitumoral activity. Indeed, a recent characterization of BC TILs suggested that a significant part of these should be considered bystander T cells, explaining the lower activity of ICI in this population compared with more immunogenic tumors [7].

Together with TILs, multiple gene signatures have been studied as a surrogate of BC immunogenicity, including the recent proposal of classifying BC into four categories (immunologic constant of rejection, ICR1-4) according to their immune-related gene expression, classes which have been shown to correlate with survival in a retrospective *in-silico* simulation [8]. Nonetheless, the presence of TILs and immune signatures does not seem to guarantee the existence of an immune response, which also requires the presence of immunogenic tumor-associated antigens and neo-antigens to be efficient. As an estimate of neo-antigen expression, tumor mutational burden was recently proved to identify those patients across BC subtypes with more chance to derive benefit from ICI therapy [9]; however, a prospective confirmation is still awaited. One particular condition producing genetic instability and increased neo-antigen formation is the case of microsatellite-unstable tumors, which account for a small percentage of BC, but which predict response to ICI [10]. Lastly, the evidence is arising regarding the effect of the gut

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microbiome in ICI response, although more studies are needed to define its role in clinical practice [11].

The abovementioned biomarkers should not be interpreted as interchangeable, but complementary, since each describes a feature of the complex cancer–immune interaction. They could, therefore, help in enriching study populations, providing the rationale and the tools to design *precision immunotherapy trials* (Figure 1).

IO: immunotherapeutical agent; CT: chemotherapy; AbDC: antibody–drug conjugate; PARP-i: poly-ADP-ribose-polymerase inhibitor.

Expert opinion: In the scenario of BC immune-oncology trials (Table 1), the multiplicity of BC subtypes and disease settings constitute both a matter of complexity and opportunity.

As previously mentioned, immunogenicity differs between BC subtypes, with TNBC generally being more immunogenic than HER2+ and luminal cancers; nevertheless, each subtype provides specific treatment modalities to be potentially combined with ICI to boost their activity. In HER2+ BC, a variety of anti-HER2 agents are currently administered in each disease setting, providing the rationale for immuno-anti HER2 combination therapies. And indeed, some recent data show that adding ICI to anti-HER2 could revert resistance to targeted therapy and induce promising responses [12]. Moreover, in analogy with other oncogene-driven tumors, HER2 amplification was found to reduce tumor immunogenicity by interfering with antigen presentation [13]; thus, anti-HER2 treatment could support ICI efficacy. Therefore, ICI and anti-HER2 agents could prove synergistic in the treatment of these tumors. Luminal cancers, on the other hand, typically benefit of endocrine therapy and are less responsive to ICI; nonetheless, strategies are being studied to improve ICI efficacy in this context, by patient enrichment and by priming the tumor with immune attractants [14]. In both cases, finding the most promising combinations and identifying responders through biomarker enrichment remain the preeminent challenges for immune-oncology trials.

LA: locally advanced; NACT: neoadjuvant chemotherapy; ACT: adjuvant chemotherapy.

Table 1. Examples of ongoing randomized immunotherapy trials in breast cancer.

Setting	Phase	Regimen	Population	Trial
Neoadjuvant	III	Doxorubicin + cyclophosphamide nab-paclitaxel ± *atezolizumab*	TNBC	NCT03197935
Neoadjuvant	III	Carboplatin + paclitaxel + (anthracycline) + cyclophosphamide ± *pembrolizumab*	TNBC	NCT03036488
Neoadjuvant	II	Nab-paclitaxel + epirubicin + cyclophosphamide ± *durvalumab*	TNBC	NCT02685059
Adjuvant	III	Paclitaxel + doxorubicin + cyclophosphamide ± *atezolizumab*	TNBC	NCT03498716
Adjuvant	III	*Pembrolizumab*	TNBC with residual disease after NACT	NCT02954874
Adjuvant	III	Avelumab	High-risk TNBC (after NACT or standard ACT)	NCT02926196
Metastatic/ LA	III	Paclitaxel ± *atezolizumab*	TNBC (first line)	NCT03125902
Metastatic/ LA	III	(Chemotherapy) + *pembrolizumab*	TNBC (first line)	NCT02819518
Metastatic/ LA	III	Paxlitaxel + trastuzumab+ pertuzumab ± *atezolizumab*	HER2+ BC (first line)	NCT03199885
Metastatic/ LA	II	Eribulin ± *pembrolizumab*	HR+ HER2- BC (late line)	NCT03051659
Metastatic/ LA	II	Olaparib ± *atezolizumab*	BRCA-mut HER2- BC (late line)	NCT02849496

Regarding the disease setting, each bears its peculiarities and each could potentially benefit from ICI addition. The metastatic setting was the first to be explored, and some lessons were learned by phase I trials: first, that ICI should be combined with other agents in order to improve benefit for most of the patients; second, that immunotherapy should be

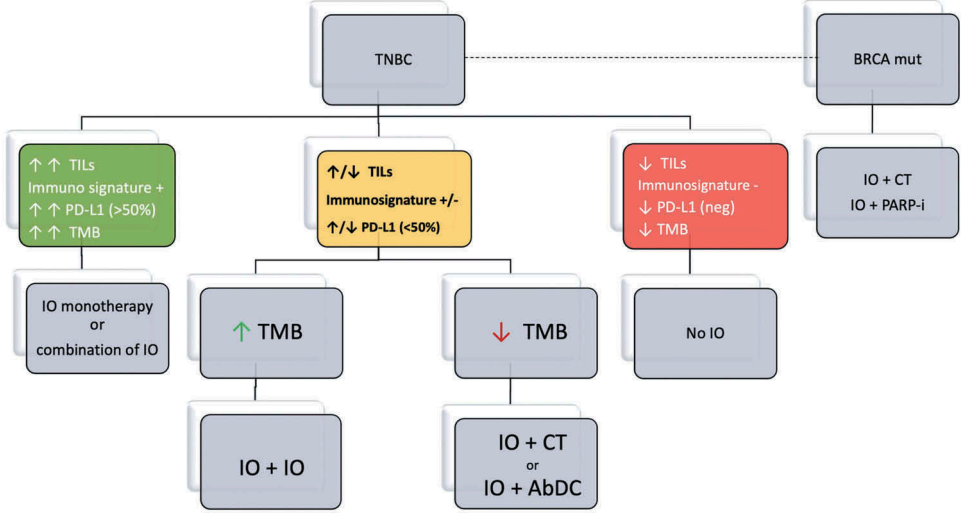

Figure 1. Proposal for a precision immunotherapy trial strategy in mTNBC.

implemented in the first line of metastatic treatment to improve response rates; third, that patients should be stratified according to specific biomarkers. Early BC setting appears to be even more appealing for ICI introduction, both in the neoadjuvant and adjuvant setting, since primary tumors seem to be more immunogenic than metastasis [15]. In the adjuvant setting, we believe that patients at high risk for relapse, less likely to be cured by current standard treatments, are the ones who could potentially benefit the most by ICI addition. For instance, TNBC patients not achieving pCR after neoadjuvant chemotherapy are known to have a worse prognosis, and capecitabine administration is the only standard of care for these patients [16]. ICI addition could improve cure rates in this setting, and some trials (eg. A-BRAVE trial [17]) are exploring this possibility. Combining the risk profile with immune response biomarkers promises to precisely define the population for early BC immunotherapy trials.

Overall, it is an exciting time for breast oncology. Results are awaited from immune-oncology trials studying various combinations and strategies, including a whole new upcoming generation of immune checkpoint inhibitors [18]. These trials will hopefully shed light on BC immuno-response biomarkers and define if a multidimensional immunogram could be better in predicting efficacy than the current PD-L1-based unidimensional immunogram. The expanding knowledge on BC immune landscape might soon help tailoring immunotherapy, enabling us to unleash the power of these agents in selected patients more likely to respond and get long-lasting benefit, leading to a new era of precision BC immunotherapy.

Declaration of interest

G Curigliano is a member of expert advisory boards from Roche, Novartis and Lilly. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer Disclosures

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