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EDITORIAL

Immunotherapy in the treatment landscape of hormone receptor-positive (HR+) early breast cancer: is new data clinical practice changing?

The management of hormone receptor-positive (HR+) early breast cancers (EBC) is based on a risk-adapted optimization strategy escalating adjuvant endocrine treatment (ET) with the addition of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors (CDK4/6i) in high-risk patients.[1] HR+ BC have generally been considered not-immunogenic, and poorly responsive to neoadjuvant treatments, and therefore not amenable to approaches such as combined neoadjuvant chemotherapy (NAC) plus immunotherapy that is used in high-risk HR− EBC.

We now, however, have greater appreciation for HR+ BC heterogeneity with implications for prognosis and immunogenicity.

Recently, the results of two phase III placebo-controlled randomized trials shed new light on the use of immune checkpoint inhibitor (ICI) therapy in high-risk HR+ EBC, bringing into question whether they should be included as standard of care. The checkmate 7FL (CK7FL) and Keynote (KN) 756 trials investigated the addition of nivolumab (CK7FL) and pembrolizumab (KN756) to neoadjuvant anthracycline/taxane-based chemotherapy followed by adjuvant ET. The ICI-containing arm of both trials achieved significantly higher pathologic complete response (pCR) rate than the placebo arm (pCR delta of 10.5% and 8.5% with nivolumab and pembrolizumab, respectively) both trials meeting their primary endpoint.[2,3]

The high-risk target population of both trials was similar, identifying as grade (G)3, nodal (N) positive or T3-4 cN0 HR+ EBC. CK7FL also allowed G2, estrogen receptor (ER) low (1%-10%) BC. These eligibility criteria are different from previous ICI clinical trials in HR+ EBC. For example, the phase II, single-arm, Giada trial enrolled patients with EBC with ER $\geq$10% and/or progesteron receptor $\geq$10% by immunohistochemistry (IHC) along with G3 and/or Ki67 proliferative index $>$20%. This trial, investigating sequential anthracycline-based NAC followed by nivolumab plus ET, did not meet the prespecified hypothesis of the trial (pCR of 25%), demonstrating a pCR of 16% in G3 Luminal B-like HR+ EBC.[4] Half of the EBC achieving pCR with nivolumab-based treatment were basal-like intrinsic molecular subtype by PAM50 assay, supporting the key role of tumor biology on ICI response. Moreover, recently the results of the pembrolizumab arm of the phase II adaptively randomized I-SPY2 trial were presented, which enrolled patients with MammaPrint high-risk, any ER-status/HER2− EBC. Patients received four cycles of paclitaxel plus pembrolizumab or plus placebo followed by four cycles of anthracycline plus cyclophosphamide. The estimated pCR rate achieved in the pembrolizumab arm among 40 patients with HR+/HER2− and 29 with triple negative EBC was 30% and 60% compared with 13% and 22% of the control arm without pembrolizumab, respectively.[5] Among these few patients, and with a short median follow-up, similar event-free survival (EFS) was observed between the two groups. From whole transcriptome microarray of the pre-treatment EBC biopsies, a signature of 53 genes (ImPrint) mostly related to immune-related functions, seemed helpful to predict pCR to pembrolizumab with $>$80% and 85% of sensitivity and specificity, respectively, in the HR+/HER2− EBC subgroup.[6]

IMMUNOGRAM OF HR+ BC

The results of these trials suggest that among HR+ BC, a subset of immunoreactive tumors can benefit from ICI. For this reason, it would be useful to consider a comprehensive portrait of immune vulnerabilities in HR+ BC, including intrinsic characteristics of the tumor and microenvironment (TME), in order to understand sensitivity to ICI and other immune-directed agents (Figure 1).

Immune cells in TME

Conflicting data are published on the role of tumor infiltrate lymphocytes (TILs) in HR+ BC underlying the different interaction of the immune system with HR+ breast cancer tumor. In a big pooled analysis of EBC, a high number of TILs (identified as $\geq$60%) in Luminal/HER2− EBC biopsy was associated with an increase in pCR rate following NAC, but in the meantime, TILs showed a negative prognostic role in overall survival.[7] It was observed in a metanalysis that high TILs did not affect pCR achievement and disease-free survival (DFS) results, but it confirmed the negative prognostic role.[8] Results of other studies could suggest that TILs might have different impact if analyzed in pre- or post-neoadjuvant treatment samples. Elevated TILs, which are generally considered to represent T lymphocytes, in NAC-naive HR+ BC predicted response to NAC.[9] Interestingly, baseline TILs also were associated with poorer long-term outcomes in HR+ BC with low Ki-67 proliferative index,

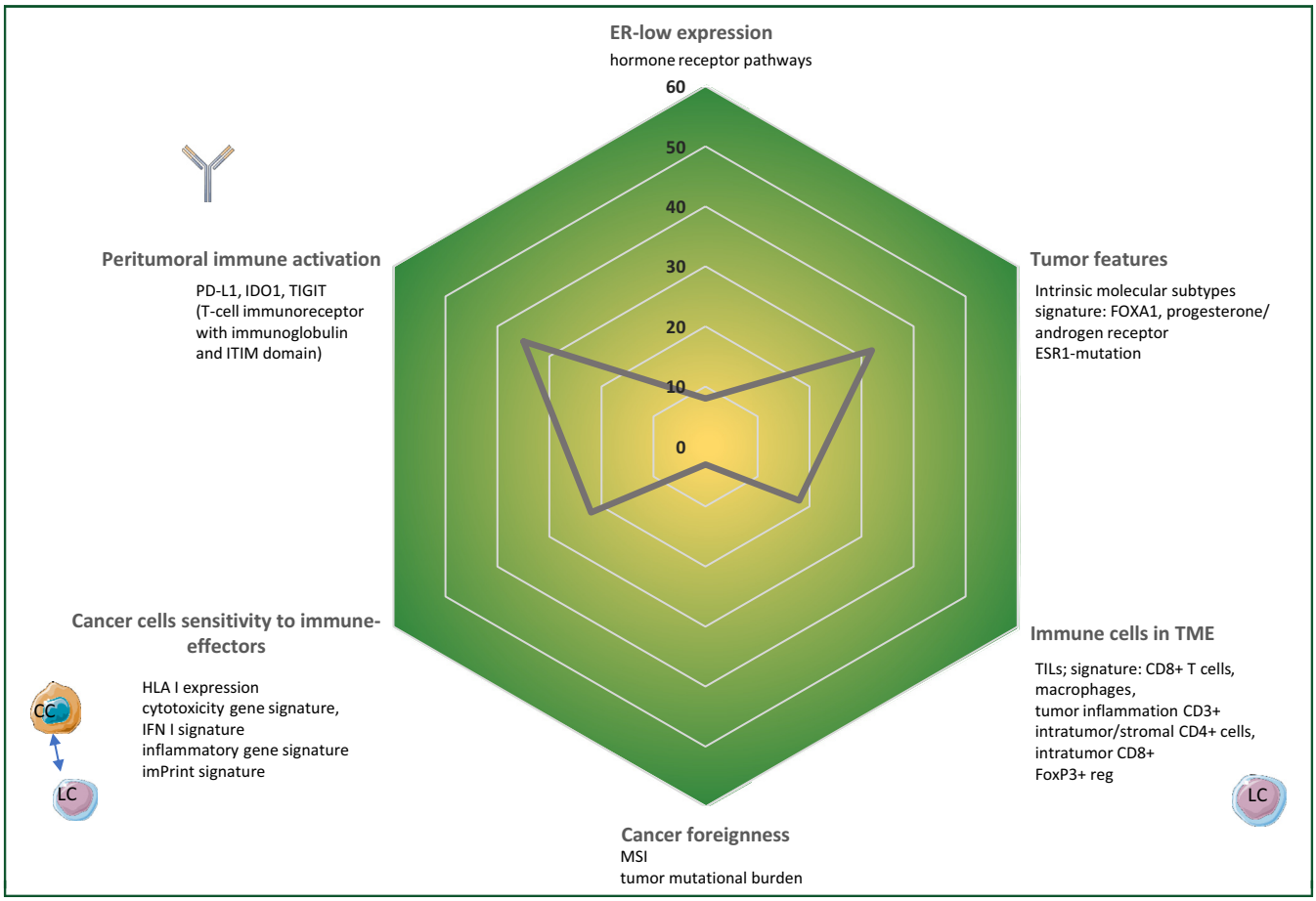

Figure 1. Immunogram of HR+ BC. Radar plot showing six characteristics, including immune and intrinsic tumor features, that may be integrated potential biomarkers to tailor immunotherapy in HR+ BC. Each ring represents a 10% of frequency. The center of the immunogram identifies 0% of frequency of the six characteristics. The grey line connects the percentage frequency of each characteristic described in literature among HR+ BC considering luminal-B/basal-like PAM50 subtype in the tumor features group (upper-right point). (One example: cancer foreignness characteristic is frequent ≤5% among hormone receptor-positive breast cancer and the grey line is in the center between 0% and 10%).
BC, breast cancer; CC, cancer cell; ER, estrogen receptor; HR, hormone receptor; IDO1, indoleamine 2,3-dioxygenase 1; ITIM, immunoreceptor tyrosine-based inhibitory motif; LC, lymphocyte cell; MSI, microsatellite instability; PD-L1, programmed death-ligand 1; TIGIT, T cell immunoreceptor with Ig and ITIM domains; TILs, tumor infiltrating lymphocytes; TMB, tumor mutational burden; TME, tumor microenvironment.

but a better prognosis in high Ki-67 tumors.[9,10] Low TILs analyzed in post-NAC tumor tissue from HR+ BC (instead of NAC-naive), were associated with better outcome.[11] Moreover, high CD8+ and low FOXP3+ TILs in post-NAC tumors were associated with better prognosis, whereas high FOXP3 Treg in treatment-naive biopsies indicated poor prognosis.[12]

Cancer cells sensitivity to immune effectors

The sensitivity of cancer cells to immune effectors is multifactorial. Primary tumors are usually less immunosuppressed than pre-treated cancer[13] and combination of immunotherapy with other types of treatments, like chemotherapy or radiotherapy, may improve the sensitivity of tumor cells to immune regimens. Inflammatory features (e.g. high interferon-γ expression) may reflect higher immune response. In this context, both immune and tumor signatures may help to better identify higher versus lower immune-responder tumors. In the ISPY2 adaptive neoadjuvant trial, higher ICI responsiveness in HR+ EBC was associated with positive ImPrint immune signature and, in the GIADA trial with higher interferon 1, cytotoxicity, macrophage, and inflammation gene signatures.[6]

Peritumoral immune activation

Programmed death-ligand 1 (PD-L1) along with TILs is one of the most used immuno-oncology (IO) biomarkers in clinical practice with conflicting data published in HR+ BC. Immunoreactive TME in HR+ BC is complex and related to enrichment in intratumoral and stromal CD4+ T cells, intratumor CD8+ T cells and stromal macrophages as well as higher immune checkpoints like PD-L1, indoleamine 2,3-dioxygenase and T cell immunoreceptor with Ig and ITIM domains expression.

Various assays are available to assess PD-L1 expression and it should be noted that those used in the two trials for PD-L1 evaluation by IHC were different.

Ventana SP142 and combined positive score (CPS) Dako 28-8 assays were used in CK7FL, whereas KN756 used the Dako 22C3 assay. Each assay uses different antibodies assessing PD-L1 only in immune cells infiltration for the Ventana SP142 assay and in both cancer and immune cells

for the CPS assay. This is one of the reasons behind the different sensitivity and specificity of each assay to determine PD-L1 expression.

The sub-analysis of CK7FL, however, showed 70%-80% of concordance between the two different assays (SP142 and Dako 28-8) with stromal TILs by hematoxylin—eosin (H&E) staining, demonstrating similar pCR delta in favor of nivolumab with different PD-L1 cut-off (PD-L1 $\geq$1% and $\geq$3% by the SP142 and 28-8 CPS assays, respectively). Different assays for PD-L1 expression lead to difficult homogenization of the results and hinder defining the role and the potential cut-off of this immune biomarker to predict immunotherapy benefit.

Moreover, in CK7FL, an increased benefit from the addiction of ICI was observed in tumors with high TILs, but it remains an open question whether the benefit of nivolumab seen in these patients with TILs >1% is related to more immunogenic TME, different tumor features, or both.

We currently lack information about several other putative predictive immune biomarkers in HR+ EBC, for example the immune- and tumor-based gene signatures that were reported in the ICI arm of the I-SPY2 and GIADA trials, as well as other tumor-related features.[4,6]

Tumor features

Reduction of expression of FOXA1, as well as progesterone and androgen receptor gene signatures, may increase ICI responsiveness of HR+ BC.[4] Additionally, estrogen pathway gene expression can modulate TME composition and immune signatures in BC, for example higher hormone receptors expression was inversely correlated with tumor macrophage-related gene signatures.

Negative correlations were found between ESR1, ER and HLA gene expressions in The Cancer Genome Atlas (TCGA) and Cancer Cell Line Encyclopedia (CCLE) data that may explain differential immune response among HR+ BC related to the impact of HLA expression in antigen presentation to lymphocytes and in promoting natural killer cell activation.[14]

Cancer foreignness

Moreover, BC in general, especially the HR+ BC subtype, is typically identified as having relatively low responsiveness to immunotherapy based on the low mutational load with low levels of neoantigens compared with more immunogenic tumors. While uncommon (2%), however, some BC have mismatch repair (MMR) deficiency that increases the 'foreignness' of cancer cells to the immune system, inducing higher response to immunotherapy.[15]

The Luminal B and basal-like intrinsic molecular subtypes within HR+ BC have more immunogenic features, with higher macrophage infiltration associated with higher Ki67, grade and ER loss.

In the CK7FL and KN756 trials, ICI benefit was demonstrated regardless of disease stage and nodal involvement. Beyond the clinical characteristics, in both trials the magnitude of benefit was higher in PD-L1-positive HR+ BC, especially with higher PD-L1 scores.

It is well established that different intrinsic molecular subtypes result in different pCR rates with the same chemotherapy in HR+ BC, with the highest pCR rates in basal-like and the lowest in Luminal A by PAM50 assay.[16] Most HR+ BCs (>50%) are Luminal A.[17] It is also true that pCR is the least associated with long-term outcome in HR+ BC compared with other more aggressive BC subtypes.[18] Given that pCR is uncommon and less prognostic, it is in general less valuable as an intermediate biomarker in HR+ BC, however, there may be subgroups within HR+ EBC based on intrinsic molecular subtype, immune gene signatures, ER expression and IO biomarkers in whom pCR is an appropriate intermediate endpoint for immunotherapy benefit and long-term outcomes.

ER-low BC

In both the CK7FL and KN756 trials, the ICI demonstrated higher pCR rate in centrally-confirmed ER-low BC, typically defined as ER staining 1%-9%, which was true in ER <50% in CK7FL as well. It has been demonstrated that ER-low/HER2− BCs are molecularly heterogeneous, with most being non-luminal,[19,20] share similar behavior to triple-negative breast cancer (TNBC), and are often also treated with NAC and immunotherapy. These tumors have different TMEs to other ER+ BC, with similar TILs levels as TNBC.[21] TILs $\geq$30% have been associated with better EFS in ER-low BC but not in BC with ER expression of 10%-50%, again illustrating ER+ BC heterogeneity within the same clinical subtype.[21] In the CK7FL trial, ICI benefit was seen in ER <50% or in ER $\geq$10% with progesteron receptor expression $\leq$10%, but few ER-low ER+ BC patients were enrolled. In KN756, 6% of the population enrolled in the pembrolizumab arm had ER-low BC; the biggest pCR rate difference (25.6%) was demonstrated in this population. No adjusted analyses in these trials were presented to determine the best biomarker(s) to predict ICI benefit in ER+ EBC. PD-L1-positive and ER-low BC achieved higher pCR rates with pembrolizumab than placebo (24.3% difference, 57.6% versus 33.3%), while among ER >10% BC the pCR difference was 9.2% and 4.4% in PD-L1-positive and -negative, respectively. As already reported, the negative GIADA trial enrolled only EBC with ER >10%. Whether these different results (Table 1) can be explained only by distinct TME or biology is still unknown.

NEXT STEPS

The data from KN756 and CK7FL suggest both that there is a role for ICI in HR+ BC, but also that the importance of identifying predictive biomarkers is crucial. It is possible that integrating immune and tumor features will be helpful to select HR+ BC that may benefit from immunotherapy, but this will require concerted and collaborative efforts.

No data are mature about the impact of ICI on EFS and whether the significant pCR benefit will translate into an improvement in long-term outcome in HR+ HER2− disease.

Table 1. pCR rates achieved in trials using immune checkpoint inhibitor-based treatments.

Delta pCR		Checkmate 7FL	Keynote 756		I-SPY2[a]	GIADA (single arm)
		Paclitaxel (12 weeks) + nivolumab versus paclitaxel + placebo −AC × 4 + nivolumab versus AC × 4 + placebo → surgery → ET + nivolumab versus ET+ placebo	Paclitaxel (12 weeks) + pembrolizumab versus paclitaxel + placebo −AC × 4 + pembrolizumab versus AC × 4 + placebo → surgery → ET+ pembrolizumab versus ET + placebo		Paclitaxel (12 weeks) + pembrolizumab versus paclitaxel (12 weeks) − AC × 4 → surgery	EC × 3— exmestane + nivolumab × 8 → surgery
Overall		10.5%	8.5%		17%[c]	16.3%[b]
In PD-L1 >1%		24.1%	9.8%			
In PD-L1 <1%		3.6%	4.5%			
In ER <50%		29%	NA			
In ER <10%		27%	25.6%			Not enrolled
ER <10% and PD-L1 >1%	ER <10% and PD-L1 <1%		24.2%	NA		
ER >10%		9.2%	8%			
ER >10% and PD-L1 >1%	ER >10% and PD-L1 <1%	NA	9.2%	4.6%		

AC, anthracycline + cyclophosphamide; EC, epirubicin plus cyclophosphamide; ER, estrogen receptor; ET, endocrine therapy; HR, hormone receptor; pCR, pathologic complete response; PD-L1, programmed death-ligand 1.
[a] All enrolled patients were MammaPrint high risk.
[b] pCR rate of single arm, not delta.
[c] Estimated pathological complete response rate in HR+ subgroup.

Long-term outcome in HR+ BC is also more complex, since unlike HR− BC, late recurrences are a common element of prognosis. If demonstrated to have an impact on relapse and survival outweighing cost and toxicity concerns, there are practical considerations since the ICI was given adjuvantly for 6 months in KN756 and 7 months in CK7FL, and CDK4/6i were not included in this high-risk population.

We conclude that these studies provide support that ICI have real potential in the management of high-risk HR+ EBC. We await the EFS results, which were a primary endpoint in KN756 and secondary in CK7FL, before considering these drugs in routine use in high-risk HR+ BC. Regardless, these trials have made clear that, like TNBC, we badly need predictive biomarkers for ICI use in HR+ disease. The immunogram or other approach to integrated analyses of predictive factors for immunotherapy responsiveness may be a useful approach to balancing between risk and benefit of ICI.

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pharmaceutical combinations of a Pi3k inhibitor and a microtubule destabilizing agent. Javier Cortés Castán, Alejandro Piris Giménez, Violeta Serra Elizalde. WO 2014/ 199294 A. ISSUED Her2 as a predictor of response to dual HER2 blockade in the absence of cytotoxic therapy. Aleix Prat, Antonio Llombart, Javier Cortés. US 2019/ 0338368 A1. LICENSED. All COI outside the submitted work. GC reported personal fees (advisory board) from Roche, Daichii Sankyo, Lilly, Novartis, Pfizer, Menarini, and Gilead outside the submitted work. All other authors have declared no conflicts of interest.

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