



Clinical trial data and emerging immunotherapeutic strategies: hormone receptor-positive, HER2– negative breast cancer

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Abstract

While checkpoint inhibitors have been approved in patients with newly metastatic PDL1-positive triple negative breast cancer, similar clinical benefit with immunotherapy alone or in combination with chemotherapy has not been observed in patients with hormone receptor-positive, HER2– negative breast cancer in the metastatic setting. However, in the ISPY2 trial, an increase in pathologic response has been observed with the addition of immunotherapy (\pm PARP inhibition) to chemotherapy compared to chemotherapy alone in patients with high-risk hormone receptor-positive, HER2– breast cancer. We review strategies to enhance the immunotherapeutic activity in this subtype of breast cancer, including combinations of checkpoint inhibition with chemotherapy, endocrine therapy, PARP inhibitors, HDAC inhibitors, CDK4/6 inhibitors, and radiotherapy. Combinations with agents targeting novel immunotherapeutic targets are also discussed. Though there remains an unmet need for immunotherapy approaches in patients with hormone-receptor positive breast cancer, there are a number of approaches that may lead to increased anti-tumor activity with immunotherapy in this tumor subtype.

Keywords Immunotherapy · Checkpoint inhibitors · Novel immunotherapeutic combinations · Hormone receptor-positive breast cancer

Introduction

Results from the IMpassion130 [1] and KEYNOTE-355 [2] trials have demonstrated that the combination of chemotherapy and immunotherapy improves progression free survival (PFS) in the front-line treatment of patients with PD-L1+metastatic triple negative breast cancer (TNBC), moving immunotherapy into the treatment algorithms for patients with metastatic breast cancer (mBC). On the other hand, patients with hormone receptor -positive, HER2– negative (HR+, HER2–) cancers have lower levels of tumor

infiltrating lymphocytes (TILs) [3] and PD-L1 expression [4] and are traditionally considered immunologically cold tumors. Despite this, a minority of patients will have clinically meaningful responses to immunotherapy and identifying better predictive biomarkers for response and the optimal setting for checkpoint inhibition is imperative. Here, we discuss the current landscape of immunotherapy in HR+, HER2– disease and emerging combination strategies to augment responses to these agents, which are summarized in Fig. 1 and Table 1.

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Strategies in the metastatic setting: immunotherapy alone

Anti-PD-1/PD-L1 monotherapy

The phase Ib KEYNOTE-028 trial evaluated pembrolizumab monotherapy among patients with metastatic PD-L1-positive pretreated solid tumors, including a cohort of patients with HR+, HER2– breast cancer [5]. PD-L1 positivity was defined as tumor combined positive score (CPS \geq 1. Of note, among 261 patients with HR+, HER2– breast cancer

who were screened for tumor PD-L1 expression, only 48 (19.5%) had PD-L1 positive tumors. Among 25 enrolled patients with a median number of prior therapies of 9, the ORR was 12% [all partial responses (PR)], and clinical benefit rate (CBR), defined as complete response (CR) plus PR plus stable disease (SD) for at least 6 months, was 20%. The median duration of response was 12.0 months for the three patients with PR, and one patient had sustained response for 69.3 weeks at time of analysis. Of note, all patients with PR had progressed on at least three lines of therapy in the metastatic setting. Median PFS and overall survival (OS) for the entire cohort were 1.8 months and 8.6 months, respectively. The durable responses observed among those who had at least stable disease highlighted both the potential activity of pembrolizumab in a subgroup of this population and the need to identify additional or alternative predictive biomarkers than PD-L1 status for HR+, HER2– patients.

The PD-L1 inhibitor avelumab has similarly been evaluated as monotherapy in pretreated patients with HR+, HER2– mBC, with mixed success. In the phase Ib JAVELIN Solid Tumor trial, 168 patients with pretreated mBC of all subtypes received avelumab monotherapy, including 72 women with HR+, HER2– cancers [6]. Unlike KEYNOTE-028, JAVELIN did not selectively enroll patients with PD-L1 positive tumors. The ORR for the entire cohort was only 3.0% (five patients), of whom three had TNBC and two had HR+, HER2– disease. The one patient with a CR had TNBC. Disease control rate (DCR), defined as those with response or SD, was 28.0% for the entire cohort, and median PFS and OS were 6.0 weeks and 9.2 months, respectively. While PD-L1 expression on tumor cells was not

associated with a statistically significant difference in clinical efficacy, PD-L1 expression of $\geq 10\%$ tumor-associated immune cells at any intensity was associated with improved ORR (16.7% vs. 1.6%, $p = 0.039$).

In 2020, the United States Food and Drug Administration granted accelerated approval to pembrolizumab monotherapy in previously treated, unresectable/metastatic solid tumors with high tumor mutational burden (TMB), defined as ≥ 10 mutations/Mb, based upon the results of KEYNOTE-158, which showed an ORR of 34.3% among 233 patients with 27 tumor types [7]. Analysis of nearly 4000 tumor samples from women with primary or metastatic breast cancer revealed that HR-positive breast cancers have significantly lower mean TMB compared to TNBC and HER2-positive cancers, but among those with metastatic breast cancer, the frequency of breast cancers with high TMB was similar among tumor subtypes (3.7–3.9%) [8]. While less than 5% of mBCs have high TMB, analysis of TMB can identify a minority of patients who might derive benefit from pembrolizumab, independent of PD-L1 expression.

Immunotherapeutic combinations

Based upon the success of combinations of anti-PD-(L)1 therapies in other solid tumors [9, 10], the combination of nivolumab plus ipilimumab is currently being investigated in patients with pretreated HER2-negative mBC who have high TMB (≥ 10 mutations/Mb) in the NIMBUS trial (NCT03789110) [11]. The combination of durvalumab, an anti-PD-1 monoclonal antibody, with tremelimumab, an anti-CTLA4 monoclonal antibody, was evaluated in a pilot study among 18 women with mBC, and did not show activity in patients with HR+, HER2– tumors [12]. While the ORR was 17% in the overall population, no patient with HR-positive mBC responded.

Maintenance anti-PD-1 after chemotherapy

Immunotherapy has also been evaluated as potential maintenance therapy among patients with HER2-negative mBC who have response to first-line chemotherapy, with the goals of reducing the burden of chemotherapy-related toxicity, as well as potentiating an immune response after chemotherapy. In a substudy of the SAFIR02-IMMUNO trial, 199 patients with metastatic HER2-negative mBC without a targetable mutation and who had SD, PR, or CR after six to eight cycles of chemotherapy were randomized 2:1 to receive maintenance durvalumab at 10 mg/kg every 14 days or maintenance chemotherapy [13]. Overall, maintenance durvalumab did not improve PFS compared with chemotherapy, and in the HR-positive subgroup, chemotherapy provided greater PFS benefit than durvalumab [hazard ratio

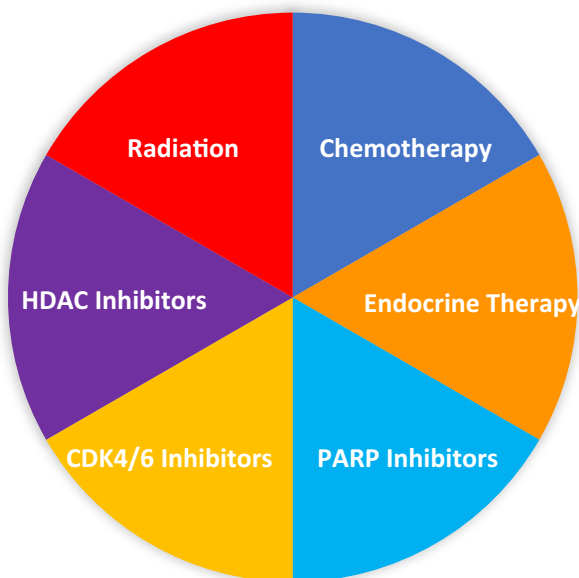


Fig. 1 Therapies combined with checkpoint inhibition

Table 1 Summary of immunotherapeutic strategies in HR+, HER2- breast cancer in the metastatic and localized setting

Trial name	Phase	First-line and/or Pretreated?	Treatment arms	Cohort	ORR	Survival outcomes	Additional outcomes	Notable adverse Events	Biomarker	Comments	Clinicaltrials.gov	Reference(s)
Immunotherapy-only strategies												
KEYNOTE-028	1b	Pretreated: ≥ 1 line of therapy	Pembrolizumab	25 (all HR+/HER2-)	12% (3 patients)	mPFS 1.6mo mOS 8.6mo	CBR 20% DOR 12.0mo	irAEs: 20%	PD-L1 CPS	Only enrolled patients with PD-L1 CPS ≥ 1	NCT02054806	[5]
JAVELIN solid tumor	1b	Pretreated: ≥ 1 but ≤ 3 prior lines of therapy Required prior treatment with taxane and anthracycline	Avelumab	168 (72 HR+/HER2-)	3.0% (including TNBC) *16.7% in those with PD-L1 CPS ≥ 1%	mPFS 6.0 weeks mOS 9.2mo	DCR 28%	irAEs: 10.1% 2 treatment-related deaths (acute liver failure, respiratory failure)	PD-L1 CPS	Did not select based upon PD-L1 expression	NCT01772004	[6]
Santa-Maria CA, et al. (2018)	2	Pretreated: ≥ 1 line of therapy HR+/HER2-; required ≥ 1 prior endocrine therapy	Durvalumab + tremelimumab	18 (11 HR+/HER2-)	0% for HR+/HER2- (43% for TNBC)	mPFS 2.2mo	CBR 19%	Hepatitis, electrolyte abnl, rash	none	Did not move to next phase because of low response rate	NCT02536794	[12]
NIMBUS	2	First line or pretreated: 0–3 prior lines of therapy HR+/HER2-; required 1 + prior endocrine therapy	Nivolumab + ipilimumab	30 (including HR+/HER2- and TNBC)	NR	NR	NR	NR	TMB	Requires TMB ≥ 9mut/Mb	NCT03789110	[11]
SAFIR02-IMMUNO	2	First-line: at least SD after induction chemotherapy	Maintenance durvalumab (durva) vs. chemotherapy (chemo) (2:1)	199 (108 HR+/HER2-)	NR	*for entire population (including TNBC) mPFS: 2.7mo (durva) vs. 4.7mo (chemo) mOS: 21.7mo (durva) vs. 17.9mo(chemo)	NR	8.5% serious treatment-related AEs	PD-L1	Exploratory analysis: PD-L1 CPS ≥ 1 associated with better mOS with durva vs. chemo (25.8mo vs 12.1mo)	NCT02299999	[13]
Combination strategies												
Chemotherapy												
Shah AN, et al. (2020)	2	Pretreated: ≥ 1 prior endocrine therapy	Pembrolizumab + capecitabine	30 (14 HR+/HER2-)	14%	PFS 5.1mo (HR+cohort)* Not statistically better than historical control mOS NR in HR+ group	CBR 28%	Abnl LFTs (50+%), 1 death from immune-mediated hepatitis	PD-L1	PD-L1 positivity did not correlate with response Heavily-pretreated: median prior therapies = 9	NCT03044730	[15]

Table 1 (continued)

Trial name	Phase	First-line and/or Pretreated?	Treatment arms	Cohort	ORR	Survival outcomes	Additional outcomes	Notable adverse Events	Biomarker	Comments	Clinicaltrials.gov	Reference(s)
Tolaney SM, et al. (2020)	2	Pretreated: ≥ 2 prior endocrine therapies, ≤ 3 prior chemotherapy	Eribulin \pm pembrolizumab (E \pm P)	88 (all HR+/HER2-)	27% vs. 34% (E+P vs. E alone)	mPFS: 4.1 mo vs. 4.2 mo (E+P vs. E alone)		2 deaths from immune-related colitis	PD-L1 TMB TILs	37% of patients had PD-L1 CPS ≥ 1 , but not associated with improved PFS	NCT03051659	[16]
Endocrine therapy												
Vonderheide RH, et al. (2010)	1	Pretreated: ≥ 1 line of therapy	Tremelimumab+exemestane	26 (all HR+/HER2-)	SD ≥ 12 weeks in 42% No PR or CR	NR		5 pts had dose-limiting diarrhea, transaminitis 1 pt with severe colitis requiring steroids, infliximab	Circulating CD4+ and CD8+T cells	Most patients with SD had increased ICOS expression on CD4+ and CD8+ T cells	NR	[17]
PARP inhibitors												
MEDIOLA	1b/2	Pretreated: ≥ 1 prior endocrine therapy ≤ 2 prior chemotherapy Must have received prior anthracycline or taxane	Olaparib + durvalumab	34 (16 HR+/HER2-) *all with germline BRCA1/2 mutations	NR	mPFS 8.2 mo mOS 21.5 mo	80% DCR at 12 weeks	Any irAE: 29%	PD-L1 TMB	PD-L1 and TMB did not correlate with response in exploratory analyses	NCT02734004	[28]
JAVELIN PARP Medley	1b/2	≥ 1 prior chemotherapy	Avelumab + talozoparib	NR	NR	NR	NR	NR	PD-L1 TMB		NCT03330405	[29]
CDK4/6 inhibitors												
Rugo HS, et al. (2020)	1b	≥ 1 but ≤ 2 prior systemic therapies *no prior CDK4/6 inhibitors	Cohort 1: pembrolizumab + abemaciclib Cohort 2: Pembrolizumab + abemaciclib + anastrozole	Cohort 1: 28 (all HR+/HER2-)	Cohort 1: 29% Cohort 2: NR	Cohort 1: mPFS 8.9 mo mOS 26.3 mo Cohort 2: NR	DCR 82%	Grade 3/4: neutropenia, abn LFTs, diarrhea	NR		NCT02779751	[37]
WJOG11418B NEWFLAME	2	First-line or Pretreated (≤ 1 prior systemic therapy)	Nivolumab + abemaciclib + letrozole or fulvestrant	17 (all HR+/HER2-) Fulvestrant = 12, letrozole = 5	54.5% (fulvestrant group) 20% (letrozole group)	NR		Grade 3+ irAEs in 40–50% Severe AEs in 50–6% 1 death from interstitial lung disease		Trial closed for safety concerns	NR	[38]

Table 1 (continued)

Trial name	Phase	First-line and/or Pretreated?	Treatment arms	Cohort	ORR	Survival outcomes	Additional outcomes	Notable adverse Events	Biomarker	Comments	Clinicaltrials.gov	Reference(s)
Histone deacetylase (HDAC) inhibitors												
Terranova-Barbero M, et al. (2020)	2	≥ 1 prior endocrine therapy	Tamoxifen + vorinostat + pembrolizumab	34 (all HR+/HER2-)	4%	NR	CBR 19%	Anorexia (24%), nausea (24%), diarrhea (21%)	PD-L1 TILs	Terminated early due to low efficacy Median prior lines of therapy =5	NCT02395627	[41]
Radiation												
Barroso-Sousa R, et al. (2020)	2	No limit	Pembrolizumab + palliative radiation therapy (RT)	8 (all HR+/HER2-)	0%	NR	PD in 5 patients as best response			Closed for futility after no responses	NCT03051672	[42]
Novel immunomodulatory therapies												
Brignone C, et al. (2010)	2	Prior endocrine therapy allowed No prior chemotherapy in metastatic setting	IMP-321 + paclitaxel	30 (most HR+/HER2-)	50%	NR	NR	asthenia neuropathy, allergic reaction and neutropenia	APC, NK, and CD8+ T cell numbers and activity	Increase in # of APCs, and percentage of NK and CD8+ T cells	NCT00349934	[43]
AIPAC	2b		Paclitaxel (T) ± IMP321	227 (all HR+/HER2-)	48.3% vs. 38.4% (T + IMP321 vs. T alone)	mPFS: 7.29mo vs. 7.29mo	At 5mo, 63% vs. 54% were progression free (T + IMP321 vs T alone)	LFT abnlis, injection site reaction, neutropenia		IMP321 increased # of APCs and T cells (CD4 and CD8)	NCT02614833	[44]
Chemotherapy												
KEYNOTE-510	2	≥ 2.5 cm measurable breast tumor	Paclitaxel ± pembrolizumab → ddAC	250 (40 HR+/HER2- patients in the pembro arm)	30% vs. 13% (chemo + pembro vs. chemo alone)	Pts with pCR with pembro had EFS 93% at 3y		6 pts with immunorelated adrenal insufficiency			NCT01042379	[47]
KEYNOTE-756	3	cT1c-T2 (≥ 2.0 cm), cN1-2 cT3-T4, cN0-2 Inflammatory breast cancer allowed	Neoadjuvant: Paclitaxel ± pembrolizumab → ddAC vs. EC ± pembrolizumab Adjuvant: endocrine therapy ± pembrolizumab	1140 (anticipated, only HR +/HER2-)	NR	NR					NCT03725059	[48]

Table 1 (continued)

Trial name	Phase	Eligible stages	Treatment arms	Cohort	pCR	Additional outcomes	Adverse events	Bio-marker	Clinicaltrials.gov	Reference(s)
CheckMate 7FL	3	cT1c-T2 (> 2.0 cm), cN1-2 cT3-T4, cN0-2	Neoadjuvant: Paclitaxel ± nivolumab → ddAC ± nivolumab Adjuvant: endocrine therapy ± nivolumab	1200 (anticipated, all HR+/HER2-)	NR	NR	NR	NR	NCT04109066	[49]
Targeted therapies										
I-SPY2	2	≥ 2.5 cm measurable breast tumor	Olaparib + durvalumab + paclitaxel → ddAC	73 (52 HR+/HER2-)	28%	NR	14% irAEs, including pneumonitis, adrenal insufficiency		NCT01042379	[50]
Checkmate 7A8	2	cT1c-3 (≥ 2.0 cm)	Palbociclib + anastrozole ± nivolumab	136 (anticipated, all HR+/HER2-)	NR	NR	NR		NCT04075604	[51]

AEs = adverse events, *APC* = antigen-presenting cell, *HR* = hormone receptor, *BC* = breast cancer, *CBR* = clinical benefit rate (defined as complete response (CR) plus PR plus stable disease (SD) for at least 6 months), *CPS* = combined positive score, *CR* = complete response, *ddAC* = dose-dense doxorubicin plus cyclophosphamide, *DCR* = disease control rate (CR, PR, or SD), *DOR* = duration of response, *EC* = epirubicin plus cyclophosphamide, *EFS* = event free survival, *irAE* = immune related adverse event, *LFTs* = liver function tests, *mO* = months, *mPFS* = median progression free survival, *mOS* = median overall survival, *NA* = not applicable, *NR* = not reported, *ORR* = overall response rate, *PD* = progressive disease, *PR* = partial response, *SD* = standard disease, *TILs* = tumor infiltrating lymphocytes, *TNBC* = triple negative breast cancer

(HR) = 2.08, 95% confidence interval (CI) = 1.28–3.40; $p = 0.0025$]. While exploratory analyses suggested that patients with PD-L1 positive tumors had improved PFS and OS with durvalumab, the majority of patients with PD-L1-positive tumors had TNBC, with only 14.9% of patients with HR-positive disease having a PD-L1-positive tumor.

Combination strategies in the metastatic setting with chemotherapy, targeted therapies, and/or radiation therapy

Chemotherapy and radiotherapy have the potential to augment responses to immunotherapy, though the degree as to which this happens clinically remains unclear. Chemotherapy and radiotherapy induce immunogenic cell death, resulting in the release of tumor related neoantigens and damage associated molecular patterns which ultimately stimulate cytotoxic T-cells and add to the anti-tumoral potential of immune checkpoint blockade [14]. Additionally, chemotherapy has been shown to have various favorable immunogenic effects on the tumor microenvironment, including reduction in myeloid derived suppressor cells, reduction in regulatory T-cells (Tregs), and promotion of dendritic cell maturation [15, 16].

Clinically, IMpassion130 [1] and KEYNOTE-355 [2] demonstrated that combination chemo-immunotherapy improves PFS in the frontline setting in patients with metastatic, PD-L1 positive TNBC when compared to chemotherapy alone. Success has been seen in other solid tumor types, with combination chemo-immunotherapy approved frontline in the metastatic setting in non-small cell lung cancer [17, 18], small cell lung cancer [19] and PD-L1 positive squamous cell carcinoma of the head and neck [20]. Radiotherapy has also been shown to induce responses at non-irritated sites though the abscopal effect [21] and a variety of trials, predominantly in melanoma and non-small cell lung cancer, have evaluated combinations of immune checkpoint blockade and radiotherapy alone with mixed results [22]. Maintenance immunotherapy is approved after concurrent chemoradiotherapy in both non-small cell lung cancer [23] and esophageal cancer [24]. Given these successful combinations, trials have evaluated the efficacy of these combinations in attempts to improve the response to checkpoint inhibition in HR+, HER2– breast cancer.

Chemotherapy

The combination of pembrolizumab with chemotherapy has been evaluated in patients with HER2-negative breast cancers in a similar approach to IMpassion130 and KEYNOTE-355 without demonstration of a similar survival benefit among patients with HR-positive disease. A single-arm

phase II trial evaluated the efficacy of the combination of pembrolizumab and capecitabine in 30 patients with pre-treated HER2-negative breast cancer, including 14 patients with endocrine-refractory metastatic HR+, HER2– mBC [25]. In a 21-day cycle, patients received pembrolizumab 200 mg every two weeks and capecitabine 1000 mg/m² oral (p.o.) twice daily (BID) on days 1–14. Median PFS for the entire cohort was 4.0 months and for the HR-positive subgroup was 5.1 months, which was not statistically better than a historical control of 3.0 months and therefore did not meet the prespecified endpoint. ORR was 14%, with two PRs observed in the HR-positive subgroup, and 21% of HR-positive patients had disease control for greater than one year. One patient with HR-positive disease died of immune related hepatitis.

A second phase II trial randomized patients with HR+, HER2– breast cancer to eribulin with or without pembrolizumab [26]. Eligible patients must have progressed on at least two prior lines of endocrine therapy, and 0–2 lines of prior chemotherapy in the metastatic setting. Patients were treated with 1.4 mg/m² of eribulin on days 1 and 8 and 200 mg of pembrolizumab on day 1 of a 21-day cycle, and the primary endpoint was PFS. In total, 88 patients were enrolled and 37% were PD-L1 positive, defined as a modified proportion score of at least 1%. The addition of pembrolizumab did not improve PFS compared to eribulin alone in the entire cohort (4.1 months vs 4.2 months) or in the PD-L1 positive subgroup (4.2 vs 4.3 months). OS data was immature at the time of publication. Exploratory analysis of biomarkers for response included PD-L1 status, tumor infiltrating lymphocytes, and TMB, all of which could not identify a population that statistically benefited from the addition of pembrolizumab. Two patients died of immune-related adverse events (irAEs) in the pembrolizumab arm.

Endocrine therapy

While endocrine therapy is the backbone of standard first-line therapies with cyclin-dependent kinases (CDK) 4/6 inhibitors for HR+, HER2– mBC, it has not been frequently investigated in combination with immunotherapy in this population. In theory, endocrine therapy is an attractive combination therapy because it is not immunosuppressive and therefore not likely to blunt anti-tumor T-cell responses to tumor antigens. A phase I trial investigating the combination of tremelimumab and exemestane enrolled 26 women with metastatic HR+, HER2– breast cancer who had progressed on at least one line of systemic therapy in the metastatic setting [27]. While most adverse events were grade 1 or 2, five patients developed dose-limiting toxicities (diarrhea, transaminitis) and one patient had diarrhea refractory to oral steroids and required treatment with infliximab. The best overall response was stable disease in 11 of

26 patients (42%), which was durable for at least 12 weeks, and no patient had PR or CR. While there was no association between clinical response and total circulating CD4+ or CD8+ T-cells, the investigators noted that most patients with SD demonstrated increased co-expression of inducible costimulator (ICOS) on circulating CD4+ and CD8+ T-cells, likely signally immune activation. This combination did not proceed to a phase II trial, but it provided support for the further investigation of endocrine therapy in combination with immunotherapy.

PARP inhibitors

BRCA1 and BRCA2, in conjunction with a variety of other proteins including Chk2, ATM, RAD51 and others, play important roles in the homologous recombination pathway utilized in the repair of DNA double stranded breaks [28]. PARP inhibitors are thus felt to work through “synthetic lethality” in which cells with a deficiency in homologous recombination undergo cell death with PARP inhibition secondary to an inability to maintain genomic stability [29]. Multiple trials have demonstrated the efficacy of PARP inhibition in germline *BRCA1/2*-mutated, HER2-negative breast cancers [30, 31], with ongoing trials such as TBCRC 048 investigating if deficiencies in other components of the homologous recombination pathway also predict benefit with PARP inhibition [32].

Preclinical data suggest potential synergy with combining of PARP inhibition and immune checkpoint blockade. PARP inhibition and double-stranded DNA breaks have both been shown to increase PD-L1 expression in an ATM/ATR/Chk1 dependent manner [33], and the combination of PARP inhibition with checkpoint inhibition was more effective than either agent alone in an EMT6 breast cancer mouse model [34]. Additionally, PARP inhibition has been shown to result in the accumulation of cytosolic DNA with consequent activation of the cGAS-STING pathway and type I IFN production [35, 36], which can be further augmented when combined with checkpoint inhibition [37].

The phase Ib/II MEDIOLA trial evaluated the safety and efficacy of olaparib with durvalumab in patients with advanced solid malignancies, including a cohort of patients with germline *BRCA1/2*-mutated, HER2-negative mBC [38]. Patients with HR+, HER2– mBC were eligible if they had a tumor that had progressed on at least one line of endocrine therapy, had previously received an anthracycline or taxane, and received no more than two lines of prior chemotherapy for metastatic disease. Thirty-four patients with mBC were enrolled, of whom 16 (47%) had HR-positive breast cancer. The most common adverse were fatigue, GI effects, and anemia, and the most common grade 3/4 adverse events were anemia (12%), consistent with known toxicities of PARP inhibition. Overall, the median OS was 21.5 months and

median PFS was 8.2 months with an 80% DCR at 12 weeks. Median OS and PFS in the HR-positive subgroup were 22.4 and 9.9 months respectively, with 8 PRs and no CR. Though not formally calculated, PD-L1 status did not appear to predict benefit. Intrinsic subtype and TMB also did not correlate with outcomes. Additional studies, such as JAVELIN PARP medley [39], are evaluating the combination of checkpoint and PARP inhibition.

CDK4/6 inhibitors

CDK 4/6 regulate the transition from the G1 to S phases of the cell cycle, and alterations in the CDK4/6 pathway are associated with resistance to endocrine therapy [40]. CDK4/6 inhibition with endocrine therapy is now standard of care among patients with HR+, HER2– breast cancer in the first-line metastatic setting, given improved survival outcomes compared to endocrine therapy alone [41–43]. There is preclinical evidence that CDK4/6 inhibitors elicit an anti-tumor immune response through enhanced antigen presentation by tumor cells, reduced proliferation of immunosuppressive Tregs, and stimulation of effector T-cells [44, 45]. In the neoMONARCH study, which randomized postmenopausal women to a two-week run in of neoadjuvant abemaciclib alone, anastrozole alone or the combination of both, post treatment biopsies demonstrated increased gene expression in inflammatory and PD-1 pathways by RNA-seq [46]. In mouse models, the addition of anti-PD-L1 antibody to abemaciclib enhanced tumor regression compared to either agent alone [44].

A multicohort phase Ib study is currently evaluating the efficacy and safety of the combination of pembrolizumab and abemaciclib, including two patient cohorts with HR+, HER2– mBC [47]. Eligible patients must be naïve to CDK4/6 inhibition and have received at least one but not more than two lines of systemic therapy. The first cohort is evaluating the combination of pembrolizumab and abemaciclib alone, and the second cohort is evaluating this combination with anastrozole. Early data from 28 patients in the pembrolizumab and abemaciclib arm, all with tumors which had progressed on endocrine therapy, demonstrated an ORR of 29%, with PR in 8 patients. Median PFS and OS were 8.9 months and 26.3 months, respectively. Adverse events were consistent with known toxicities of immune checkpoint inhibition and CDK4/6 inhibition, and the most common grade 3/4 adverse was neutropenia.

Recently, a non-randomized phase II trial evaluated the combination of nivolumab, abemaciclib, and either fulvestrant or letrozole in the first- or second-line setting among women with HR+, HER2– mBC [48]. In contrast to the combination of pembrolizumab and abemaciclib ± anastrozole, this combination resulted in significant toxicity, with trial closure for safety concerns. Among 17 women who

were enrolled, over half had grade 3 or higher immune-related adverse events, and one died of treatment-related toxicity (interstitial lung disease). While the ORR were 54.5% and 20% among patients who received fulvestrant and letrozole, respectively, the significant toxicity associated with this combination raises concerns.

Histone deacetylase (HDAC) inhibitors

Histone deacetylases (HDAC) are epigenetic modifiers responsible for acetylation modulation which subsequently opens chromatin and allows for transcription of genes and results in cell cycle arrest, differentiation and/or cell death [49]. There are currently four HDAC inhibitors approved for various malignancies, with ongoing investigations evaluating the anti-tumor potential of these agents in breast cancer.

In HR-positive disease, preclinical data have demonstrated that HDAC inhibition in MCF-7 breast cancer models induces estrogen receptor alpha degradation, downregulates estrogen receptor transcription and reduces tumor growth [50]. The combination of checkpoint inhibition with the HDAC inhibitor entinostat in 4T1 bearing mice resulted in greater anti-tumor efficacy than immune checkpoint alone, and while the combination did not increase TILs, the addition of entinostat reduced myeloid-derived stem cells and tumor associated Tregs.

A phase II trial investigated the combination of tamoxifen, vorinostat, and pembrolizumab among 34 women with heavily-pretreated HR+, HER2– mBC [51]. While the ORR was only 4% and CBR only 19%, the combination was well-tolerated without excess toxicity beyond what was expected from endocrine therapy and checkpoint inhibitors. Among the five patients with clinical benefit, increased markers of CD8+ T-cell exhaustion and treatment-induced depletion of Tregs correlated with improved response and prolonged PFS. Of note, only two patients had PD-L1 positive tumors, and both were non-responders to therapy, indicating the need to identify alternative biomarkers of response to these therapies. Ultimately, this study was terminated early due to low efficacy in unselected patients.

Radiation

A phase II study evaluated the efficacy of pembrolizumab with palliative radiation therapy to non-visceral metastases in patients with metastatic HR+, HER2– mBC [52]. Patients received pembrolizumab 200 mg 2–7 days prior to 20 Gy of radiation over five fractions. Eight patients were enrolled at the time of interim analysis, but the trial was closed due to futility after no responses. Five of eight patients had progressive disease as best response, and there were no abscopal responses. Paired biopsies were attempted but only collected in two patients, in which there appeared to be an increase in

stromal TILs. It was hypothesized that fractionation schedule, radiation to bone lesions as opposed to alternative sites, and the overall treatment-refractory population may have contributed to lack of response.

Novel immunomodulatory therapies in the metastatic setting

As the complex interplay between the immune system, stroma and tumor becomes better understood, multiple co-stimulatory and co-inhibitory receptors have been described with the potential to increase responses to immunotherapy in traditionally immunologically “cold” tumor like HR-positive breast cancers. There are preclinical data supporting the anti-tumoral potential of OX40 and GITR agonist antibodies or LAG3, TIM3, and adenosine receptor antagonism in breast cancer, typically in combination with anti-PD1/PD-L1 blockade.

IMP321 is a recombinant soluble LAG3-Ig protein that was originally developed as a LAG3 antagonist but was later determined to be a potent stimulator of major histocompatibility complex class II. This agent was evaluated with single agent paclitaxel in a phase I/II trial in patients with HER2-negative mBC [53]. Patients received IMP321 subcutaneously at various doses every two weeks on days 2 and 16 of a 28-day cycle for up to 12 injections with weekly paclitaxel 80 mg/m² on days 1, 8 and 15. Thirty patients were enrolled, most of whom were HR-positive, and the ORR was 50%, which compared favorably to historical control with weekly paclitaxel alone. IMP321 increased the number of monocytes in a dose dependent manner and additionally increased dendritic cells, activated CD8+ cells and natural killer cells. These results prompted the randomized phase IIb AIPAC trial of paclitaxel alone compared to IMP321 plus paclitaxel in 227 patients with HR+, HER2– mBC [54]. PFS and OS was not improved with the addition of IMP321 with a median PFS of 7.29 months in both arms, though the combination did improve OS in patients younger than 65 years of age with a median OS of 21.9 months vs. 14.8 months in with paclitaxel alone ($p=0.012$).

Multiple ongoing phase I/II trials are evaluating novel immuno-oncology combinations in advanced refractory solid malignancies including breast cancer. While TNBC remains the focus of many of these trials, investigations with combinatorial immunotherapeutic approaches are ongoing in HR-positive disease.

Combination with chemotherapy in the neoadjuvant setting

In early-stage breast cancer, the benefits of neoadjuvant systemic therapy include less morbid breast surgery [55], the ability to assess tumor response to therapy, and evidence that pathologic complete response (pCR) is associated with improved long-term clinical outcomes [56]. However, higher rates of pCR are observed in patients with HER2-positive and triple-negative cancers, with a pCR rate of less than 20% in HR+, HER2– breast cancer. Combinations of chemotherapy with immunotherapy have been increasingly investigated in the neoadjuvant setting.

I-SPY2 is an ongoing multicenter, multicohort trial developed as a platform to evaluate the efficacy of novel agents in conjunction with neoadjuvant chemotherapy for high-risk operable breast cancers. These novel agents are “graduated” if they meet a predefined, subtype specific efficacy threshold. Arms in I-SPY2 are open for patients with high-risk HR+, HER2– tumors, which are defined as tumors at least 2.5 cm with a high risk MammaPrint.

The addition of pembrolizumab to paclitaxel demonstrated efficacy and was the first novel agent graduated in the I-SPY2 trial [57]. Patients with HER2-negative breast cancer were treated with pembrolizumab 200 mg every three weeks for 4 cycles in combination with weekly paclitaxel (T) 80 mg/m² followed by standard dose dense doxorubicin plus cyclophosphamide (AC) alone. Sixty-nine patients were randomized to pembrolizumab and 181 were randomized to control. Forty patients randomized to pembrolizumab group had HR+, HER2– breast cancer. In the HR-positive subgroup, the estimated pCR rate was 30% as compared to 13% in the control group. Adverse events were mostly grade 1–2 and consistent with known adverse events of immunotherapy, though notably six patients developed adrenal insufficiency. KEYNOTE-756 [58] and CheckMate 7FL [59] are ongoing phase III trials incorporating immune checkpoint inhibition with standard neoadjuvant chemotherapy with AC-T followed by continued immune checkpoint inhibition with endocrine therapy.

The combination of olaparib, durvalumab and paclitaxel followed by standard dose dense AC was evaluated in an arm of the I-SPY2 trial and graduated after 13 months [60]. Patients were treated with three cycles of durvalumab 1.5 g every 4 weeks along with olaparib 100 mg p.o. BID for weeks 1–11 and weekly T, followed by dose dense AC. Seventy-three patients were enrolled, 52 of whom had HR+, HER2– breast cancer. The estimated pCR rate was 28% and this combination was generally well tolerated. Future investigations with this combination are ongoing.

Another combination under evaluation in the Checkmate 7A8 randomized phase II trial is neoadjuvant

palbociclib and anastrozole ± nivolumab [61]. Given the toxicity of a similar combination in the metastatic setting, this study will hopefully provide insight into the tolerability and efficacy of the of anti-PD-1 in combination with CDK4/6 inhibition and endocrine therapy.

Conclusions

While checkpoint inhibition alone or with standard chemotherapy has not shown the same clinical efficacy in patients with HR+, HER2– mBC as has been demonstrated in patients with TNBC, novel combinations with targeted therapies, particularly CDK4/6 inhibitors and PARP inhibitors, show promise. Preclinical data suggest synergy with immune checkpoint inhibition and these targeted agents in patients with HR+, HER2– breast cancer, potentially because of alternative mechanisms of enhancing anti-tumor immune response.

There are several challenges to utilizing immunotherapy in HR+, HER2– breast cancer. It is becoming clear that immune checkpoint inhibition is most efficacious when used in early line settings, and with numerous effective agents in HR+, HER2– mBC, early investigations with immunotherapy have been limited to patients often refractory to multiple agents. Additionally, finding a biomarker predictive of response to immunotherapy remains a challenge. The results of immunotherapy-based clinical trials in the HR-positive population call into question the reliability of PD-L1 expression as a biomarker of response and highlight the need to identify other immune signatures that can predict response and identify candidates for novel treatment strategies. Investigations of novel biomarkers in tumor tissue, liquid biopsies and the tumor microenvironment are ongoing.

In the early-stage setting, the innovative I-SPY2 clinical trial design offers an opportunity for the investigation of novel immunotherapy combinations in the neoadjuvant setting, with the potential to lead to further drug development in the advanced/metastatic setting. However, the risk of long-term toxicities with immunotherapy must be weighed against potential benefit in localized disease, particularly in a patient population with better outcomes when compared to their triple negative counterparts. The emerging safety concerns when combining immunotherapy with endocrine therapy reflects the potential for toxicity with immunotherapy combinations despite well described toxicity profiles as monotherapy. Despite these and challenges further advances in the field of immunotherapy in HR+, HER2– disease can be expected in the coming years.

Authors contributions All authors (MK, JEM, KK) contributed equally to this manuscript.

Declarations

Conflict of interest MK and JEM have no disclosures to report. KK declares the following potential conflicts of interest: Medical Advisor—Immunomedics, Pfizer, Novartis, Eisai, Eli-Lilly, Amgen, Immunomedics, Merck, Seattle Genetics, and Astra Zeneca; Institutional Support—Immunomedics, Novartis, Incyte, Genentech/Roche, Eli-Lilly, Pfizer, Calithera Biosciences, Acetylon, Seattle Genetics, Amgen, Zentalis Pharmaceuticals, and CytomX Therapeutics; Speakers Bureau—Eli-Lilly; Spouse—Array Biopharma, Pfizer, Grail.

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