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Breast Cancer (EA Comen, Section Editor)

Checkpoint Blockade Strategies in the Treatment of Breast Cancer: Where We Are and Where We Are Heading

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Opinion Statement

Immunotherapy has become one of the greatest advances in medical oncology over the last century; however, the optimal application for the treatment of breast cancer remains an active area of investigation. Modern immunotherapy strategies augment the immune system and ideally, permit durable tumor-specific immune memory. In fact, several monoclonal antibodies that mediate the immune checkpoint receptors have provided the most clinically meaningful improvement for breast cancer patients to date, particularly for the triple negative subtype. Checkpoint blockade as monotherapy has demonstrated some encouraging results, although some combination strategies appear to augment those responses and may be particularly effective when administered earlier in the course of disease. For example, the combination of atezolizumab and nab-paclitaxel as first-line therapy for metastatic triple negative breast cancer demonstrated significant improvements in progression-free survival when compared with chemotherapy alone. Herein, we review the data for immune therapy in breast cancer and highlight promising future directions.

Introduction

Breast cancer is the most common and deadly female cancer worldwide [1, 2]. This is in spite of all the advances in breast cancer detection programs, improvements in locoregional treatments, and development of novel systemic therapies. Therefore, breast cancer researchers in the field must seek answers to biological questions related to breast cancer development, clinical tumor progression, and treatment resistance.

Treatment paradigms for patients with early stage and metastatic breast cancer are defined by the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status of the tumor [3]. For metastatic breast cancer, the goals are to control disease, increase survival, and improve quality of life [4]. But for the most aggressive forms of breast cancer, such as triple negative breast cancer (TNBC), the median survival is still modest with the current available treatment strategies [5].

Evasion of immune destruction is now commonly accepted as a hallmark of cancer development. Understanding the status and interaction between cancer and the immune system in the tumor microenvironment is vital for cancer immunotherapy strategies [6]. Leveraging immune strategies to augment the immune system and overcome the immunosuppressive tumor immune microenvironment are necessary to create durable anti-tumor responses and anti-tumor immune memory. The seminal discoveries of the CTLA-4 and PD-1 axes, collectively referred to as immune checkpoints, have allowed for development of novel therapeutic approaches that have created durable responses against tumor growth [7, 8]. Monoclonal antibodies targeted against the immune checkpoints have created the most dramatic durable responses against tumor growth [9].

In metastatic breast cancer, initial clinical trials with immune checkpoint inhibitors have shown modest but interesting responses [10, 11•, 12•, 13•]. Treatment combinations with checkpoint blockade and chemotherapy in the neoadjuvant setting have resulted in increased pCR rates compared with chemotherapy alone [14, 15]. Randomized clinical trials are under way to investigate strategies that may overcome treatment resistance in the early and metastatic breast cancer setting. In this article, we aim to briefly review the current treatment options available to breast cancer patients and have a more in-depth discussion of how immunotherapeutic strategies are changing the breast cancer treatment landscape.

Current Immunotherapeutic Strategies in Metastatic Breast Cancer

Immune checkpoint inhibitors have proven significant benefit in improving the outcomes of several cancer subtypes including melanoma, lung, bladder, kidney, head and neck, Merkel cell carcinoma, and Hodgkin's disease [16]. Breast cancer is not as inherently sensitive as other tumors to immune therapy alone as evidenced by several monotherapy studies; however, several combination strategies appear to enhance responsiveness to checkpoint blockade and, therefore, represent promising future directions (Table 1).

Hormone Positive, HER2 Negative Breast Cancer

The KEYNOTE 028 trial investigated the PD-1 inhibitor, pembrolizumab, as monotherapy in heavily pre-treated, PD-L1 positive, hormone receptor-positive, HER2 negative metastatic breast cancer patients and demonstrated an overall response rate (ORR) of 12% [13•]. However, the median duration of response of 12 months was longer than one might expect in a chemotherapy-resistant population. In the phase 1b JAVELIN study, the ORR was 3% for the 72 patients with heavily pre-treated, metastatic hormone receptor-positive, HER2-

Table 1. Trials using immune checkpoint inhibitors in metastatic breast cancer

Reference	Intervention	Phase	Inclusion criteria	Number of patients	Efficacy endpoints
Keynote-028 (Rugo H, et al., 2018)	Pembrolizumab	Ib	Prior therapy MBC, ER+, HER2 - PD-L1 positive	25	ORR 12% DoR 12 months PFS 1.8 months OS 8.6 months
Keynote-014 (Loi S, et al., 2017)	Pembrolizumab plus Trastuzumab	Ib/II	Prior therapy MBC, HER2+	58 (46 PD-L1 positive)	PD-L1 positive ORR 15% PFS 2.7 months 12 months OS 65%
Keynote-012 (Nanda R, et al., 2016)	Pembrolizumab	Ib	Prior therapy MBC, TN PD-L1 positive	32 (27 evaluable)	ORR 18.5% DoR 15 - >47.3 (weeks) PFS 1.9 months OS 11.2 months
Keynote-086 (Adams S, et al., 2017, 2018)	Pembrolizumab	II	Cohort A Prior therapy MBC, TN Cohort B No prior therapy MBC, TN PD-L1 positive	170 (60% PD-L1 positive) 52	ORR 5% (PD-L1+ and PD-L1-) DoR 6.3 months PFS 2.0 months OS 8.9 months ORR 23% DoR 8.4 months PFS 2.1 months OS 16.1 months
Javelin (Dirix LY, et al., 2018)	Avelumab	Ib	Prior therapy MBC, TN (34.5%), ER+ (42.9%, HER2+ (15.5%)	168 (85 PD-L1 positive)	ORR (ITT) 3.0% ORR TN 5.2% ORR ER+ 2.8% HER2+ 1 patient responded
Emens LA, et al., 2018	Atezolizumab	Ia	0–3 lines prior therapy MBC, TN	115 (71 PD-L1 ≥ 5%)	ORR (ITT) 10% ORR (1^{st}L) 24% DoR 21 months PFS 1.4 months OS 8.9 months
Adams S, et al., 2018	Atezolizumab plus Nab-paclitaxel	Ib	0–2 lines prior therapy MBC, TN	33	ORR 39.4% DoR 9.1 months PFS 5.5 months OS 14.7 months
Schmid P, et el, 2018	Atezolizumab plus Nab-paclitaxel	III	No prior therapy MBC, TN	902	ITT population: PFS 7.2 vs 5.5 months ($p = 0.002$)

Table 1. (Continued)

Reference	Intervention	Phase	Inclusion criteria	Number of patients	Efficacy endpoints
	vs placebo plus Nab-paclitaxel				OS: 21.3 vs 17.6 months ($p = 0.08$) ORR 56 vs 45.9% DoR 7.4 vs 5.6 months PD-L1+ population: PFS 7.5 vs 5.0 months ($p < 0.001$) OS 25.0 vs 15.5 months** ORR 58.9 vs 42.6% DoR 8.5 vs 5.5 months
Tolaney SM, et al., 2017	Pembrolizumab plus Eribulin	Ib/II	0–2 lines prior therapy MBC, TN	107	ORR 26.4% DoR 9.1 months PFS 8.3 months OS 17.7 months
McArthur HL, et al., 2018	Pembrolizumab plus radiotherapy	II	Prior therapy MBC, TN	9	ORR (outside radiation field) 33% DoR 49 weeks
TONIC Trial (Kok M, et al., 2018)	Nivolumab vs Induction therapy (RT, cyclophosphamide, cisplatin or doxorubicin) then Nivolumab	II (Simon's 2-stage, non-comparative)	0–3 lines prior therapy MBC, TN	66	ORR - ITT 20% - Control 17% - RT 8% - Cyclophosphamide 8% - Cisplatin 23% - Doxorrubicin 35%

MBC, metastatic breast cancer; *TN*, triple negative; *DoR*, duration of response; *ORR*, overall response rate; *PFS*, progression-free survival; *OS*, overall survival; *PD-L*, programed death ligand; *ITT*, intention to treat; *ER*, estrogen receptor; *HER2*, human epidermal receptor 2

negative breast cancer treated with the PD-L1 directed antibody, avelumab [10]. However, when chemotherapy with or without pembrolizumab was administered in the pre-operative curative-intent setting on the I-SPY-2 study, the estimated pCR rate increased from 13% to 34%, indicating that combination strategies administered early in the course of disease may be effective for this subtype [14].

HER2 Positive Breast Cancer

Trastuzumab is a HER2-directed IgG1 monoclonal antibody that can stimulate antibody-dependent cell-mediated cytotoxicity (ADCC) [17, 18] and has demonstrated synergy when administered in combination with checkpoint blockade in preclinical models [19]. The PANACEA (KEYNOTE-014) phase Ib/II trial was developed to investigate the activity of pembrolizumab with trastuzumab in HER2-positive, trastuzumab-resistant metastatic breast cancer [20]. The ORR for the 40 patients with PD-L1 positive disease was 15% while the ORR for the 12 patients with PD-L1 negative disease was 0%. In patients with ≥ 5% stromal tumor infiltrating lymphocytes (TILs) in a metastatic lesion, the ORR was 39% and the disease control rate (DCR) was 47% (vs 5% ORR and 5% DCR for the patients with TILs < 5%). In the JAVELIN study, 26 HER2-positive metastatic breast cancer patients were treated with avelumab alone, with only one response observed. Given that the synergy between trastuzumab and checkpoint blockade may be optimized earlier in the course of disease, prior to the development of trastuzumab resistance, studies are planned in the curative-intent setting.

Triple Negative Breast Cancer

The overwhelming majority of checkpoint inhibitor trials have been conducted in TNBC because it may be an exquisitely immunogenic phenotype [5, 21]. The KEYNOTE-012 phase Ib trial investigated the use of pembrolizumab in patients with PD-L1 positive chemotherapy-resistant metastatic TNBC [12•]. Although safety was the primary endpoint of this study, there were 27 patients evaluable for efficacy with an ORR of 18.5%. The KEYNOTE-086 randomized phase II study investigated the use of pembrolizumab monotherapy in newly diagnosed and previously treated metastatic TNBC [22, 23]. In Arm A (previously treated patients), an ORR of 4.7% and a DCR of 8% were reported with response observed regardless of PD-L1 status. In Arm B (previously untreated patients), an ORR of 23% and a DCR of 24% were reported, regardless of PD-L1 status, with approximately 60% of patients deemed PD-L1 positive (≥ 1% expression). In 58 women with metastatic TNBC unselected for PD-L1 expression, avelumab conferred a modest ORR of 8.6% [10]. Atezolizumab was also studied in metastatic TNBC patients following 0–3 lines of chemotherapy as part of a phase Ia study [11•]. The response rate was 10% overall, but improved to 24% in the first-line setting with 24-week PFS of 33% and median duration of response of 21 months.

BRCA-Mutated Breast Cancer

Patients with germline BRCA mutations have increased mutations per megabase compared with sporadic cancers developed by age alone [24]. This suggests that breast cancer patients harboring a germline BRCA mutation may

have an altered tumor immune microenvironment. The tumor immune microenvironment in germline BRCA-mutated non-breast cancers has been studied and demonstrated to have more immune cells present [25]. Unique immune phenotypes have been demonstrated in germline BRCA-mutated breast cancers compared with BRCA-wildtype breast cancers [26]. A preclinical study using a genetically modified BRCA1-mutated murine model of breast cancer investigated whether the immunogenic microenvironment seen in BRCA1-mutated TNBC could be leveraged with checkpoint blockade [27]. Cisplatin combined with dual checkpoint blockade was found to inhibit BRCA1-mutated TNBC growth more than cisplatin alone, cisplatin combined with single-agent immune checkpoint blockade, or dual checkpoint blockade [27]. The MEDIOLA trial investigated the use of olaparib combined with durvalumab in metastatic HER2 negative breast cancer patients harboring a germline BRCA mutation [28]. This combination demonstrated an ORR of 67% in both first- and second-line treated patients and a disease control rate of 80%.

Enhancing Immunotherapy Responses in Breast Cancers

It is clear that checkpoint inhibitors have reasonable responses in breast cancers when used as monotherapy, but rarely work against tumors that are relatively devoid of CD8+ T cells, which are also referred to as "cold" tumors [16]. It is paramount to determine strategies that increase CD8+ T cell populations within breast cancers, which, in theory, would make the tumor "hot." Some promising combination strategies include, but are not limited to, dual checkpoint blockade [27], induction chemotherapy [29], PARP inhibitors [30], CDK 4/6 inhibition [31], cryoablation [32], radiation therapy [33, 34], STING agonists [35], and oncolytic virotherapy [36, 37]. We will discuss some of these approaches.

A few promising trials combining chemotherapy with checkpoint blockade have reported encouraging results. Results from the ENHANCE 1 (KEYNOTE-150) trial investigating the combination of eribulin mesylate with pembrolizumab in metastatic TNBC patients demonstrated an ORR of 26% across the entire TNBC population regardless of PD-L1 status and an ORR of 29% in the patients who received the combination in the first-line setting [38]. A phase Ib study investigating the safety of atezolizumab combined with nab-paclitaxel embarked to identify the safety of this regimen [39••]. The combination was revealed to be safe and a signal of a survival advantage was detected in metastatic TNBC patients receiving atezolizumab and nab-paclitaxel. Therein, the randomized placebo-controlled phase III IMpassion130 trial set forth to determine if nab-paclitaxel combined with atezolizumab would improve the outcomes of metastatic TNBC patients [40••]. PFS was significantly longer in patients receiving the combination compared with nab-paclitaxel alone (7.2 vs 5.5 months, $p = 0.002$). There was a non-significant increase in OS of 21.3 vs 17.6 months in the combination and nab-paclitaxel cohorts, respectively. Since OS was not significant in the intent to treat population, OS analyses in the PD-L1 positive group was not analyzed; however, the median OS in the PD-L1 positive subgroup was 25 months with the combination and 15 months with nab-paclitaxel alone. Nab-paclitaxel combined with atezolizumab may become a new standard of care for metastatic TNBC patients.

Agents that physically perturbate the tumor in hopes of creating a "hot" tumor immune microenvironment include cryoablation, radiation therapy, and direct injections of oncolytic virotherapy. The concept of combining cryoablation with checkpoint blockade to treat breast cancer patients was investigated in a pilot study where women with early stage breast cancer of any subtype received cryoablation alone (group A), single-dose ipilimumab alone at 10 mg/kg (group B), or both cryoablation and single-dose ipilimumab (group C) [32]. The study demonstrated that cryoablation and ipilimumab were safe and well tolerated with all patients undergoing standard-of-care mastectomy without complication or delay. Furthermore, no treatment associated grade 3–4 AEs was noted. The T cell receptor (TCR) was sequenced in the tumor and blood of patients in this study. The combination approach diversified the TCR clonality repertoire and increased the number of T cell clones in the peripheral blood and within the tumor [41]. Based on these results, a randomized phase II study of peri-operative combination ipilimumab with nivolumab and cryoablation vs standard peri-operative care in early stage TNBC patients is being investigated (NCT03546686).

Several preclinical studies have demonstrated that utilizing radiation therapy with checkpoint blockade may increase the abscopal effect in metastatic breast cancer patients [33]. In a phase II study evaluating the combination of pembrolizumab and radiation therapy in a heavily pre-treated metastatic TNBC patient population, three out of nine evaluable patients (33%) had a response outside of the irradiated field, with durable responses of up to 49 weeks [42]. Several phase I and phase II clinical trials are underway investigating the combination of radiation therapy with novel immunotherapeutic approaches [43].

Recent preclinical evidence has demonstrated that the oncolytic poliovirus (PVSRIPO) stimulates a robust type I IFN and inflammatory response that subsequently transitions to an innate and adaptive immune response in breast cancers [37]. According to further investigations in preclinical models, this adaptive immune response can be leveraged with checkpoint blockade. It was shown that one injection of PVSRIPO is equivalent to multiple administrations of anti-PD1 or anti-PD-L1 therapy and the combination of PVSRIPO with either checkpoint inhibitor halts tumor growth more than monotherapy [36]. PVSRIPO has been tested in a phase I study in subjects with recurrent glioblastoma, which is universally a fatal disease within 6–12 months. With one injection of PVSRIPO, 21% of recurrent GBM patients were alive at 24 months [44]. Currently, a pilot study is open investigating the use of PVSRIPO in TNBC patients who have recurrent disease after neoadjuvant chemotherapy or have chest wall recurrence that is amenable to surgery (NCT03564782).

Immunotherapy Biomarkers

Checkpoint inhibitors when used as monotherapy or in combination have reasonable response rates, but they are not without their side effects [45]. It is abundantly clear that robust biomarkers are needed to determine which breast cancer patients may or may not respond to checkpoint blockade. This is especially relevant for those breast cancer patients with curable disease in the early stage setting. Response to checkpoint blockade has been associated with

several biomarkers, including PD-L1 expression on tumor cells and/or associated immune cells, tumor-infiltrating lymphocytes (TILs), tumor mutational burden (TMB), and microsatellite instability (MSI).

The role of PD-L1 as a predictive biomarker for anti-PD-1 or anti-PD-L1 therapy has not been definitive. There is a discrepancy between the antibodies used to detect PD-L1 expression, the cutoff points to determine PD-L1 positivity, and the varying sources of tissue that have been provided from different checkpoint inhibitor trials in breast cancers [10, 11•, 12•, 13•, 40••, 46]. Moreover, it appears that anti-PD-1/anti-PD-L1 therapy can be effective in patients with PD-L1 negative tumors, as demonstrated in the initial breast cancer trials with avelumab and atezolizumab [10, 40••]. However, PD-L1 expression does appear to have at least a mild predictive role of response in that the higher the expression the higher the likelihood of response to anti-PD-1/anti-PD-L1 therapies [11•, 40••].

TILs may have utility as a biomarker of response. TILs are measured as a continuous variable. It has been demonstrated that for every 10% increase in TILs, there is a 17% reduction in the risk of relapse and 27% reduction in the risk of death with the use of chemotherapy [47, 48]. Until recently, the predictive and prognostic features to TILs in breast cancer have been relatively unknown. The KEYNOTE-086 trial evaluated TILs as a marker of response and observed that patients with increased TILs were more likely to experience responses to pembrolizumab. Additionally, the PANACEA trial showed similar findings in HER2 positive metastatic breast cancers [20]. This study reported increased response rates to the combination of trastuzumab and pembrolizumab in HER2+ breast cancers with ≥ 5% TILs.

TMB is another promising biomarker of response to chemotherapy or checkpoint blockade [49, 50]. TMB is defined as the total number of mutations per coding area of a tumor genome. In order for a tumor to be considered as TMB-high, it is currently thought the mutations per megabase (mut/Mb) need to exceed 10 [50]. This is an arbitrary cutoff and we do not know if ≥ 10 mut/Mb is appropriate for breast cancers. MSI-high is associated with increased TMB and is already an FDA-approved biomarker of response to checkpoint inhibitors [51]. However, there is a paucity of breast cancers with MSI. Investigations into the TMB of breast cancers have demonstrated that the highest TMB is a consequence of APOBEC mutagenesis patterns [52]. Patients with germline BRCA mutations also have increased TMB and may have increased TILs [24]. Additionally, TMB combined with RNA gene expression profiling may be a potential biomarker, but needs to be validated in a cohort of breast cancer patients treated with immunotherapy [53, 54]. Further investigation biomarkers are underway and it may be that a combination of markers or novel interrogation of checkpoint expression levels, like that seen in the IMPRES data set [55], are needed to appropriately select breast cancer patients that may or may not respond to immunotherapy.

Future Directions

The field of immunotherapy continues to look promising for breast cancer patients. We have learned from our metastatic breast cancer checkpoint

blockade monotherapy trials that combination strategies are needed. Given the significant results from the IMpassion 130 trial, first-line nab-paclitaxel combined with atezolizumab may become a new standard of care for metastatic TNBC patients [40••]. We will better understand if paclitaxel with or without atezolizumab may provide similar results from the IMpassion 131 trial in metastatic TNBC (NCT03125902). Several combination approaches with chemotherapy and checkpoint blockade are under way. The Triple-B randomized phase II study will investigate a combination of carboplatin with cyclophosphamide or paclitaxel monotherapy both with or without atezolizumab in metastatic TNBC (NCT01898117). The ACE trial is combining the MEK inhibitor, cobimetinib, with eribulin and atezolizumab in recurrent and metastatic inflammatory breast cancer (NCT03202316). The DORA phase II trial is planned to assess the combination of olaparib and durvalumab in patients with platinum-treated TNBC (NCT03167619). The TONIC study investigated 5 strategies of induction therapy in metastatic TNBC including radiation therapy, doxorubicin, cyclophosphamide, cisplatin, and no induction treatment followed by nivolumab therapy (NCT02499367) [29]. Interestingly, from stage I of the trial, the ORR was highest in the doxorubicin group with and ORR of 35%, which was followed by an ORR of 23% in the cisplatin arm and 8% in both the radiation and cyclophosphamide arms. The ALICE trial is investigating a semi-metronomic approach with the use of immunogenic chemotherapies, such as liposomal doxorubicin, in combination with atezolizumab in a phase II study (NCT03164993). Additionally, a study is being planned to investigate olaparib with atezolizumab in germline BRCA-mutated HER2 negative metastatic breast cancers.

Metastatic breast cancer patients who receive checkpoint inhibitors earlier appear to have improved responses (NCT02849496). With this in mind, checkpoint blockade has been and is being studied in the neoadjuvant setting (Table 2). The I-SPY-2 adaptive Bayesian designed trial investigating a chemotherapy backbone with pembrolizumab reported a tripling of pCR in the TNBC group and doubling of pCR in the hormone positive, HER2 negative cohort. The control arm demonstrated a pCR rate of 20% in TNBC patients, which arguably is low. Preliminary results from the KEYNOTE-173 trial evaluating pembrolizumab in combination with chemotherapy as neoadjuvant treatment for TNBC were previously presented (NCT02622074) [56]. The pCR with an anthracycline and taxane (cohort A) and anthracycline, taxane, and carboplatin (cohort B) was 60% and 80%, respectively. In the GeparNuevo trial, patients were randomized between neoadjuvant chemotherapy plus durvalumab or placebo, with the opportunity to start durvalumab 2 weeks before chemotherapy was initiated [15]. There was a non-significant increase in pCR in the durvalumab group at 53.4% vs 44.2% in the placebo group. In a predefined subgroup analysis, patients that received durvalumab 2-weeks before chemotherapy had significantly higher pCR rates of 61% compared with 41.4% in the placebo arm. While these findings are encouraging, they need to be validated. The KEYNOTE-522 phase III trial is investigating the efficacy of chemotherapy (carboplatin, paclitaxel, anthracycline, and cyclophosphamide) with or without pembrolizumab (NCT03036488). The NSABP Foundation is investigating the use of chemotherapy (carboplatin, paclitaxel, anthracycline, and cyclophosphamide) with or without atezolizumab (NCT03281954). We will better understand if less neoadjuvant chemotherapy can be provided to stage II-III TNBC

Table 2. Trials using neoadjuvant immune checkpoint inhibitors in early stage breast cancer

Reference	Intervention	Phase	Inclusion criteria	Number of patients	Efficacy endpoints
Keynote-173 (Schmid P, et al., 2017)	Cohort A: Pembrolizumab + nab-paclitaxel -> pembrolizumab + doxorubicin + cyclophosphamide Cohort B: Pembrolizumab + nab-paclitaxel + carboplatin -> pembrolizumab + doxorubicin + cyclophosphamide	Ib	No prior therapy LABC, TN	20 (10 each cohort)	Cohort A: - ypT0 ypN0 50% - ORR 70% Cohort B: - ypT0 ypN0 80% - ORR 90%
I-SPY-2 (Nanda R, et al., 2017)	Pembrolizumab + paclitaxel -> doxorubicin + cyclophosphamide vs control (paclitaxel -> doxorubicin + cyclophosphamide)	II (Bayesian model to predict pCR probability)	No prior therapy LABC HER2 negative (includes TN and ER+)	69 (Pembrolizumab arm) 180 (control arm)	Estimated pCR (Pembro vs control): - TN 60% vs 20% - ER+ 34% vs 13%
GeparNuevo (Loibl S, et al., 2018)	2-week induction with durvalumab vs placebo Durvalumab + nab-paclitaxel -> durvalumab + epirubicin + cyclophosphamide vs placebo + nab-paclitaxel -> placebo + epirubicin + cyclophosphamide	II	No prior therapy LABC, TN	174	pCR ypT0 ypN0 (durva vs placebo): - ITT 53.4% vs 44.2% - Induction 61% vs 41.4% - Age < 40: 69.2% vs 42.9%

LABC, locally advanced breast cancer; *TN*, triple negative; *pCR*, pathologic complete response; *ITT*, intention to treat; *ER*, estrogen receptor; *HER2*, human epidermal receptor 2

patients from a phase II trial investigating the combination of carboplatin and paclitaxel with or without atezolizumab (NCT02883062). All patients in this trial will undergo surgery and have the option of receiving adjuvant anthracycline and cyclophosphamide.

Checkpoint blockade is being investigated in early stage breast cancer patients with HER2-positive or ER-positive disease. The APTneo study will identify if neoadjuvant paclitaxel, carboplatin, trastuzumab, and pertuzumab combined with atezolizumab will increase pCR rates of HER2 positive early stage high-risk or locally advanced breast cancers (NCT03595592). Recently, it was shown that CDK 4/6 inhibition combined with anti-PD1 therapy increases T cell infiltration, depletes regulatory T cells and decreases tumor growth in a genetically engineered murine model of breast cancer [31]. The neoMONARCH trial showed that providing neoadjuvant abemaciclib-enhanced TILs in the tumor tissue [57]. Several studies are currently investigating the use of CDK 4/6 inhibition in combination with endocrine therapy and checkpoint blockade in hormone receptor-positive metastatic breast cancer patients. A trial that may leverage the potential advantage of some hormone positive hypermutated breast cancers is the MUTATION2 trial, which is investigating pembrolizumab in hormone positive hypermutated metastatic breast cancers as determined by whole exome sequencing (NCT03492918).

Despite the encouraging results seen in IMpassion 130 study and I-SPY-2 trial, there is much room for improvement. Given that checkpoint blockade has known life-threating toxicities [45], not explicitly discussed in this manuscript, above that of chemotherapy it is vitally important that robust biomarkers are developed to assist physicians in determining which breast cancer would or would not respond to immunotherapy. Arguably, this would be most important in patients receiving neoadjuvant therapy since they are technically curable. Unfortunately, biomarkers of response are lacking.

Conclusions

Early results from clinical trials investigating novel immunotherapy approaches against breast cancers demonstrate encouraging results. These results have paved the way for rational combination studies in both metastatic and early stage breast cancers. Informative clinical trials using novel immunotherapy combination approaches are ongoing in various metastatic breast cancer subtypes. Phase III trials investigating neoadjuvant checkpoint blockade need to demonstrate a significant benefit before they can be routinely recommended given the potential for increased long-term toxicity above that of standard chemotherapy. Biomarkers are actively being studied to more accurately identify the breast cancers that will or will not respond to checkpoint inhibition. The potential to provide durable responses in metastatic breast cancer patients and increase the cure rate of early stage breast cancers is on the horizon. Novel combination immunotherapy strategies have the potential to de-escalate conventional chemotherapy and also provide long-term immunity, which could translate into increased cure rates.

Compliance with Ethical Standards

Conflict of Interest

Jeremy Force has received compensation from Pfizer and Myriad Genetics for service as a consultant and from NanoString Technologies and Genomic Health as a paid speaker.

Jorge Henrique Santos Leal has received compensation from Pfizer, Roche/Genentech, Novartis, and AstraZeneca for service as a consultant and participation on advisory boards. He also received travel accommodations from Pfizer, Roche/Genentech, Novartis, and AstraZeneca in both 2016 and 2017.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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metastatic TNBC. Response rates were 18.5% in the evaluable TNBC patients.

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