HHS Public Access

Author manuscript

Clin Cancer Res. Author manuscript; available in PMC 2022 August 08.

Published in final edited form as:

Clin Cancer Res. 2016 May 01; 22(9): 2105–2110. doi:10.1158/1078-0432.CCR-15-1315.

New Strategies in Breast Cancer: Immunotherapy

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Abstract

More than 70% of breast cancers contain lymphocytic infiltration in the stroma and preclinical studies suggest that immune-editing and partial control of cancer progression by the local immune microenvironment operates in most breast cancers. Consistent with this hypothesis, a large number of studies demonstrated a favorable prognostic and chemotherapy response predictive role for immune infiltration in breast cancer. The evidence is particularly strong for triple negative and HER2 positive cancers. The development of clinically effective immune checkpoint inhibitors now provides an opportunity to test the therapeutic potential of augmenting the local anti-tumor immune response. Several Phase I clinical trials using single agent anti-PD1 and anti-PDL1 antibodies demonstrated objective tumor response rates, with remarkably durable responses, in heavily pretreated, metastatic, triple negative cancers and somewhat lower responses in estrogen-receptor positive cancers. Currently, close to 50 ongoing, or soon to open, clinical trials evaluate the role of this new treatment modality in breast cancer.

Background

The prognostic and predictive roles of the immune microenvironment in breast cancer

The presence of immune cells in the breast cancer microenvironment has long been recognized as a good prognostic indicator (1). More recently, it also became clear that the prevalence of lymphocytic infiltration and its prognostic role varies by molecular subtype. Immune infiltration is most prevalent in triple negative breast cancers (TNBC) followed by HER2 positive and highly proliferative estrogen receptor (ER) positive cancers. Immune infiltration is least prominent in low grade, luminal A type, ER positive cancers.

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Disclosure of Potential Conflicts of Interest

L. Pusztai reports receiving research support from AstraZeneca, Genentech, and Merck and speakers bureau honoraria from Merck. G. Bianchini reports receiving speakers bureau honoraria from Roche. No potential conflicts of interest were disclosed by the other authors.

In TNBC, high levels of immune infiltration, measured either as tumor infiltrating lymphocyte (TIL) count or captured by various immune gene signatures, predicts for good survival even in patients not receiving systemic adjuvant therapy, indicating a pure prognostic function (2,3). Additionally, several neoadjuvant (preoperative) chemotherapy studies demonstrated significantly higher pathologic complete response (pCR) rates among immune-rich compared to immune-poor TNBC, indicating a chemotherapy response predictive role (4–7). Not surprisingly, among TNBC patients who received adjuvant chemotherapy, TIL counts are strongly predictive of cancer-free survival; each 10% increase in TIL count is associated with an 18% reduction of risk of distant recurrence (8,9).
At diagnosis, approximately 5–15% of TNBCs are classified as lymphocyte predominant (LPBC), variably defined as either ≥ 50% or ≥ 60% lymphocytes in the stroma, another 15–20% has no lymphocytic infiltration, while the majority (65–80%) harbor low to moderate level of immune cells (9,10). Both stromal lymphocytes (residing in the stroma without direct contact with neoplastic cells) and intratumoral lymphocytes (intermingled with and in direct contact with cancer cells) provide prognostic and predictive information but stromal TILs are more abundant and therefore, can be quantified more reliably (11). Lymphocyte predominance in residual cancer (≥ 60% of stromal cells) after neoadjuvant chemotherapy is seen in about 10% of TNBC treated with neoadjuvant chemotherapy, and is also associated with excellent survival even in patients who have high risk pathologic features such as positive nodes or > 2 cm residual tumor size (12).

In HER2 positive breast cancer, TIL and immune signatures are also associated with better prognosis with or without systemic adjuvant therapy (13). Similar to TNBC, each 10% increase in TILs is associated with a significantly decreasing risk of distant recurrence in patients receiving adjuvant chemotherapy concomitant with trastuzumab (14). This association with outcome was confirmed in the NeoALTTO, but not in the N9831 trial (15). The expression of CD40 (a co-stimulatory protein on antigen presenting cells) related genes was associated with higher probability of achieving pCR to neoadjuvant trastuzumab containing chemotherapy in HER2 positive cancers (16), however, TILs did not show a linear association with pCR in the NeoALTTO and NeoSphere trials, while it was shown that patients with intermediate TIL infiltration significantly benefited from HER2-targeted therapies (15,17). NeoSphere also demonstrated a more complex interplay between the immune system and clinical response in the presence of monoclonal antibodies. This trial included a combined treatment arm of trastuzumab and pertuzumab without chemotherapy. Higher expression of several immune genes and metagenes were associated with a higher pCR rate, while PDL1 mRNA expression and MHC1 metagenes were associated with resistance. (17).

The prognostic and predictive value of immune cells in estrogen receptor (ER) positive cancers is less extensively studied. However, the available literature suggests that in low risk ER positive patients no such prognostic role is apparent while in highly proliferative ER-positive cancers immune cells do predict for better prognosis (18).

Overall, a highly consistent body of literature indicates an association between survival and immune cells in the breast cancer microenvironment. These associations are particularly strong in TNBC and HER2 positive cancers, but can also be seen in high risk ER positive

cancers and raise the possibility that immune cells mediate the observed favorable clinical outcome.

The local immune system in breast cancer

Several outstanding reviews have been published recently on the tumor promoting and suppressing roles role of immune and inflammatory cells (19–21). Cancer tissues are host to multiple different types of immune cells mediating innate and adoptive immunity. However, there are large cancer to cancer differences in the extent and composition of immune cells. In the majority of the literature, T-lymphocytes represent the largest proportion of immune cells in breast cancer (70–80%), followed by B-cells (10–20%), macrophages (5–10%), natural killer (NK) cells (<5%) and antigen presenting dendritic cells (4,10, 22). Each of these main cell types can be subdivided into further functional subtypes (e.g. CD8+ effector T cells, CD4+ T helper cells and CD4+ regulatory T cells [Th1, Th2, Treg]) and cells can be found in different activity states (e.g. naïve, activated and memory). The cells form a complex system with dynamic transitions between immune activating and suppressing functions. The obligatory, simultaneous presence of multiple different immune cell types in the microenvironment accounts for the highly correlated nature of immune gene expression patterns (5,17). The strong co-expression of various immune genes explains several seemingly paradoxical associations. For example, high PD1 (programmed death 1) and PD-L1 (programmed death ligand 1) expression, both negative regulators of the local immune response, are associated with better overall survival and higher pCR rate in TNBC (23, 24). Also, high expression of CTLA4 (cytotoxic T lymphocyte associated protein 4), a complimentary immune checkpoint mechanism to PD1/PD-L1, was associated with benefit from anti-PD-L1 antibody therapy to the same extent as PD-L1 expression in lung cancer (25). The strong correlation between immune marker expression and lymphocyte counts could also limit the independent predictive and prognostic value that immune marker expression adds to TIL counts (5,7). It is also important to recognize that there are several methodological concerns regarding detection of PD-L1 (and other immune marker) expression; these include lack of standardized detection methods by immunohistochemistry (IHC), variable cutoffs to determine positivity, and often substantial discordance between mRNA and IHC based measurements (7,24). Furthermore, multiple different cell types (neoplastic as well as stromal) can express these markers and expression levels can be up- or down-regulated in response to an ongoing antitumor immune response, hypoxia, and oncogenic pathway activation (26). These sources of variation contribute to the conflicting results reported in the literature. A central question also remains unanswered; what biological mechanism underlies the variable levels of immune infiltration and different levels of immune control in different breast cancers.

Results from pre-clinical experiments and correlative observations in patients suggest that most breast cancers trigger some immune response (22). According the immune-editing hypothesis, the local immune response plays a dual role in cancer progression. On one hand, it suppresses tumor growth through immune-mediated cell death, which may result in complete elimination of some cancers (before they become detectable) and slow growth or stagnation in others. On the other hand, it also promotes tumor progression by establishing inflammatory conditions that facilitate tumor growth and selecting for tumor cells that

survive immunosurveillance (27). An important corollary of this hypothesis is that even during the escape phase, when cancers are clinically apparent, some degree of immune-mediated control is retained, which may account for the better prognosis observed in the immune-rich cancers (Figure 1).

Another important concept emerging from preclinical models is that tumor response to chemotherapy and trastuzumab is influenced by the host immune system (28). Chemotherapy-induced cellular injury, particularly caused by doxorubicin and cyclophosphamide, can elicit a cytotoxic immune response that partially mediates the clinical response. It has also been suggested that chemotherapy may induce somatic mutations, leading to new antigens which, in turn, elicit immune responses. Chemotherapy, in a drug and dose dependent manner, can also stimulate anticancer immune effectors indirectly by inhibiting immunosuppressive regulatory cells (e.g. myeloid-derived suppressor cells and FOXP3+ regulatory T cells) (29, 30). Consistent with these pre-clinical observations, analysis of TILs in pre- and post-neoadjuvant chemotherapy specimens showed that development of lymphocytic infiltration during treatment correlates with clinical response (31). The development of clinically effective immune checkpoint inhibitors now provides an opportunity to test the therapeutic potential of augmenting the local anti-tumor immune response.

On the Horizon

Immune biomarkers

In most analyses, the prognostic and predictive values of TILs and immune gene signatures are independent of histologic grade, tumor size or nodal status and therefore, immune markers hold a potential for increasing the predictive accuracy of existing prognostic models (2–6). Furthermore, the reproducibility of stromal TIL counts among pathologists is high; for LPBC category, inter-pathologist agreement ranged from good to moderate (Cohen's kappa, $\kappa = 0.60$ to 0.90) and consistency for semi-quantitative TIL scoring was excellent (correlation coefficient, 0.97) (4). These results are similar to other broadly accepted measures such histologic grading or hormone receptor scoring and better than inter-observer agreement for Ki-67. An international guideline was recently published to standardize TIL assessment and reporting which sets the stage for introducing this prognostic variable into routine pathology reporting (11). However, no studies have been performed to date that included immune signatures, or TIL counts, in existing multivariate prognostic models such as Adjuvant Online, Nottingham Prognostic Index, 21-gene Recurrence Score, Risk of Recurrence (ROR) score, or others to demonstrate improved prognostic accuracy and therefore lymphocyte markers are not yet recommended for routine clinical use.

Immune parameters are also attractive candidates to be predictors of response to immunotherapy. In the simplest form, one could hypothesize that immunotherapy will be most useful for cancers with intermediate TIL counts because LPBCs already have an excellent prognosis and cancers with no lymphocytes have no local immune surveillance to boost. The validity of this hypothesis is being tested in ongoing immunotherapy trials in breast cancer. The therapeutic anti-PD1/PDL1 antibodies represent one of the most exciting novel class of therapies due to the remarkably durable responses in melanoma, lung, head

and neck and bladder cancers (32). PD1 is broadly expressed on several different cells types including CD4 and CD8 positive T-cells, B lymphocytes, NK cells and T regulatory cells, and therefore it is considered of limited biomarker value. Most studies focused on PD-L1 expression as a potential response marker for PD1/PD-L1 targeted therapies. In breast cancer, PD-L1 protein expression (i.e. ≥ 1% of IHC+ cells) is detected in 20–30% of cases, primarily seen in TNBC (7, 33–35) while PD-L1 mRNA expression is identified in substantially larger subsets of breast tumors (16, 23, 24, 34, 35). The correlation between PD-L1 protein and mRNA levels is modest (Spearman Rank Correlation Coefficient 0.15–0.17) (35). In other cancer types, there is a statistically significant association between PD-L1 expression and the amount of clinical benefit from immune checkpoint therapy; but in each of these studies response and clinical benefit is also consistently seen in PD-L1 negative cancers (25). Pembrolizumab, an anti-PD1 antibody, is currently approved by the US Food and Drug Administration (FDA) for the treatment of metastatic non-small cell lung cancer (NSCLC) that expresses PD-L1 protein detected by a companion diagnostic IHC assay (IHC 22C3 pharmDx test made by Dako North America). Interestingly, another anti-PD1 antibody, nivolumab, is also approved by the FDA for the treatment of metastatic squamous cell lung cancer, but without the requirement of a companion diagnostic test. However, a recent FDA indication extension of nivolumab to patients with NSCLC (including non-squamous cell) endorses the use of a complementary diagnostic assay (IHC 28-8 pharmDx, also made by Dako North America but distinct from IHC 22C3 and applying a different threshold to define positivity) to help guide patient selection for treatment. The test is considered “complementary,” not “companion,” diagnostic because its use is not mandated prior to administering nivolumab. It is important to note that most PD-L1 expression is detected on stromal cells and not on cancer cells, hence the often cited explanation that PD-L1 expression by tumor cells is a main mechanism of immune escape appears simplistic.

Currently, no published data exists on the predictive value of PD-L1 expression for immune checkpoint inhibitor therapy in breast cancer. However, all Phase I trials in breast cancer that reported clinical outcome required PD-L1 expression for eligibility.

Immunotherapy of breast cancer

Preliminary results from 5 Phase I clinical trials testing the activity of immune checkpoint inhibitors in metastatic breast cancer are currently available in abstract form. There is also one published phase I trial (n=26) that reported results for tremelimumab (anti-CTLA4 antibody) in combination with exemestane in ER positive metastatic breast cancer and demonstrated stable disease for ≥12 weeks in 11 patients (42%) as the best overall response (36). The KEYNOTE-012 trial assessed the safety and efficacy of single pembrolizumab (10 mg/kg every 2 weeks) in metastatic TNBC that showed ≥ 1% PD-L1 positivity by IHC. One hundred and eleven patients were screened for PD-L1 expression using the 22C3 antibody and 59% were positive. In the 27 patients who were evaluable for efficacy assessment, the overall response rate was 18.5% and the median duration of response was not reached at the time of the presentation at the 2014 San Antonio Breast Cancer Symposium (37). The KEYNOTE-028 trial assessed the same drug in metastatic ER-positive breast cancer and also required ≥ 1% PD-L1 positivity by IHC; PD-L1 positivity rate was 19%. In the

25 patients who were evaluable for efficacy, the overall response rate was 12% and all 3 responders remained on study treatment for ≥26 weeks at the time of presentation at the 2015 San Antonio Breast Cancer Symposium (38). Adverse events were mostly grade 1–2 and included arthralgia, fatigue, myalgia, and nausea in both studies. Another Phase I trial tested the efficacy and safety of the anti-PD-L1 antibody atezolizumab (15 mg/kg, 20 mg/kg, and 1200 mg fixed dose) in metastatic TNBC and also required ≥5% PD-L1 positivity by IHC using the SP142 antibody (39). Sixty-nine percent of patients tested positive for PD-L1 expression, 21 were evaluable for efficacy, and 19% objective response rate was observed, the 24-week progression-free survival rate was 27%. Adverse events were mostly ≤ grade 2 but 11% of pastients had treatment-related ≥ grade 3 adverse events. The JAVELIN study tested the anti-PD-L1 antibody avelumab (10 mg/kg every 2 weeks) and included all breast cancer subtypes regardless PDL1 status (40). In the TNBC cohort (n=58), the response rate was 8.6%. In the ER-positive/HER2-negative (n=72) and HER2-positive (n=26) cohorts the response rate was 2.8% and 3.8%, respectively. The preliminary results suggested higher response rate in tumors with PD-L1 positive immune cells (33.3% [4/12] vs 2.4% [3/124]). Preliminary results were also reported from a study that combined atezolizumab (anti-PDL1 antibody) with Nab-Paclitaxel in metastatic TNBC (n=24) (41). The combination was well tolerated and 42% of patients had objective response. Due to these promising early results, there are currently around 50 clinical trials that evaluate this class of drugs in breast cancer in the metastatic, neoadjuvant and adjuvant treatment settings (Table 1).

Summary

Immune checkpoint inhibitors emerged as a new and effective treatment modality for melanoma, NSCLC and RCC where these drugs are now approved by the US FDA. Clinical trials also show activity in a broad range of solid tumors including TNBC and to a lesser extent ER-positive breast cancer. A large number of clinical trials in the neoadjuvant and metastatic setting are now underway to determine the clinical role of immunotherapies and their combinations in breast cancer.

Acknowledgments

Grant Support

This work was supported in part by grants from the Breast Cancer Research Foundation and Yale Cancer Center Core Grant NIH/NCI P30CA16359 (to L. Pusztai), the H.W. & J. Hector-Stiftung, Mannheim (M67; to T. Karn), and the Associazione Italiana per la Ricerca sul Cancro (AIRC) (MFGA 13428; to G. Bianchini).

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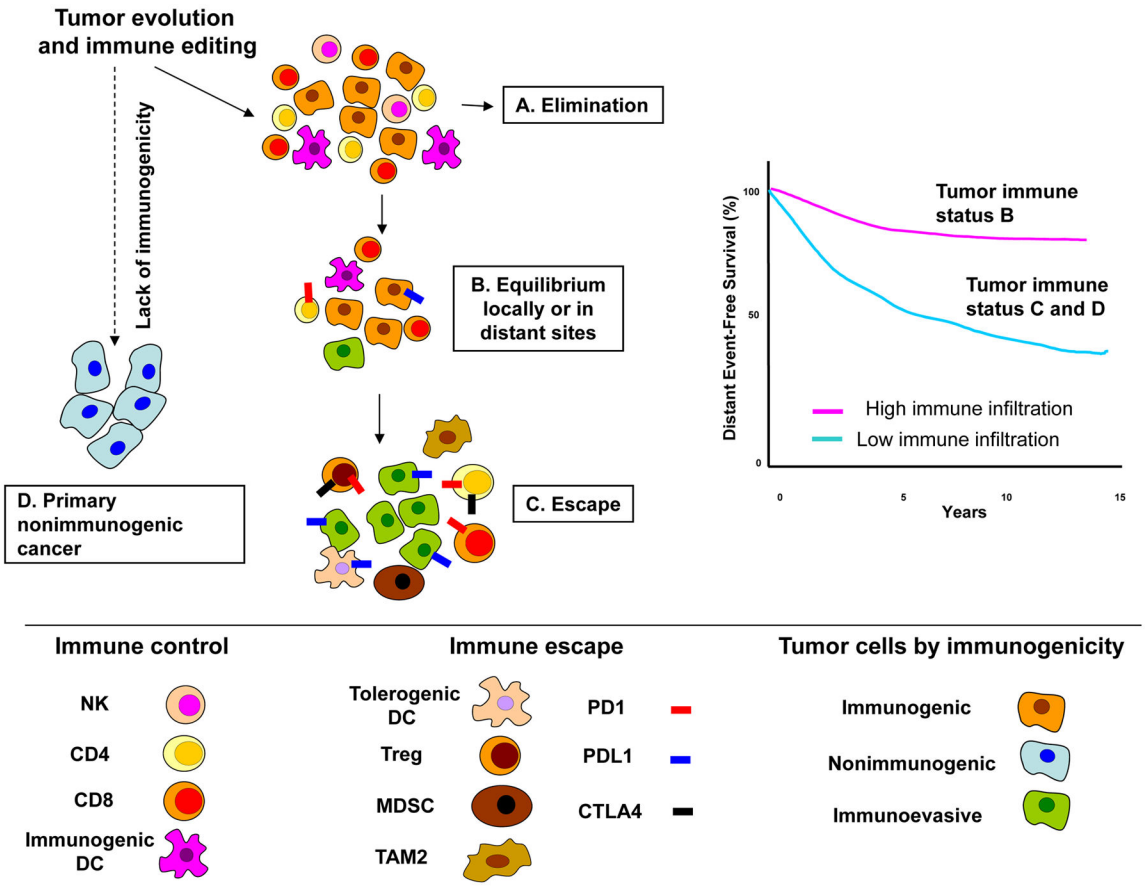

Figure 1.

Immunoediting during tumor evolution. All clinically apparent early breast cancers are already partially edited or not immunogenic enough since the elimination phase (A) has failed. Tumors in the equilibrium phase (B) are likely represented in the high immune infiltration group. Recurrences in this group are at least in part due to subsequent immune escape. Tumors with low immune infiltration may include cancers with intrinsicly low immunogenicity and cancers that have effectively escaped from immune surveillance (C, D). Abbreviations: DC, dendritic cells; MDSC, myeloid-derived suppressor cells; TAM1, tumor-associated macrophages M1 or classically activated; TAM2, tumor-associated macrophages M2 or alternatively activated.

Table 1

Ongoing clinical trials with immunotherapies that accrue breast cancer patients. Data extracted from https://clinicaltrials.gov/ and accessed on January 24, 2016.

Phase	Clinical Trial Gov	Disease setting	Type of disease	Breast cancer subtype	Immunotherapies	Combined treatments
I	NCT02303366	Metastatic	Only BC	All	Pembrolizumab	Stereotactic Ablative Body Radiosurgery
I	NCT02605915	Metastatic and neoadjuvant	Only BC	HER2-pos	Atezolizumab	Trastuzumab/pertuzumab or T-DM1 or Trastuzumab/Pertuzumab/Carbopla tin/Docetaxel
I	NCT02649686	Metastatic	Only BC	HER2-pos	Durvalumab	Trstuzumab
I/II	NCT02129556	Metastatic	Only BC	HER2-pos	Pembrolizumab	Trastuzumab
I/II	NCT02513472	Metastatic	Only BC	TNBC	Pembrolizumab	Eribulin mesylate
I/II	NCT02628132	Metastatic	Only BC	TNBC	Durvalumab	Paclitaxel
II	NCT02411656	Metastatic*	Only BC	TNBC or ER+/HER2−	Pembrolizumab	
II	NCT02447003	Metastatic	Only BC	TNBC	Pembrolizumab	
II	NCT02499367	Metastatic	Only BC	TNBC	Nivolumab	Doxorubicin low dose, Cyclophosphamide metronomic, Radiation therapy, Cisplatin
II	NCT02411656	Metastatic	Only BC	HER2-neg	Pembrolizumab	
II	NCT02447003	Metastatic	Only BC	TNBC	Pembrolizumab	
II	NCT02395627	Metastatic	Only BC	HR+ (endocrine resistant BC)	Pembrolizumab	Vorinostat and Tamoxifen
II	NCT02536794	Metastatic	Only BC	TNBC ER+/HER2-neg	Durvalumab Tremelimumab	
II	NCT02563925	Metastatic (brain)	Only BC	All	Tremelimumab	Brain radiotherapy or Stereotactic
II	NCT00083278	Metastatic	Only BC	All	Ipilimumab	
II	NCT02648477	Metastatic	Only BC	TNBC and ER+/HER2−	Pembrolizumab	Doxorubicin or Letrozole or Anastrozole or Exemestane
III	NCT02555657	Metastatic	Only BC	TNBC	Pembrolizumab‡	
III	NCT02425891	Metastatic	Only BC	TNBC	Atezolizumab¶	Nab-paclitaxel
I	NCT02622074	Neoadjuvant	Only BC	TNBC (LABC)	Pembrolizumab	Nab-paclitaxel → AC or Nab-paclitaxel/ Carboplatin → AC
I/II	NCT02489448	Neoadjuvant	Only BC	TNBC	Durvalumab	Nab-paclitaxel → ddAC
II	NCT01042379	Neoadjuvant	Only BC	All	Pembrolizumab	Paclitaxel
II	NCT02530489	Neoadjuvant	Only BC	TNBC	Atezolizumab	Nab-paclitaxel
III	NCT02620280	Neoadjuvant	Only BC	TNBC	Atezolizumab§	Nab-paclitaxel/Carboplatin

Phase	Clinical Trial Gov	Disease setting	Type of disease	Breast cancer subtype	Immunotherapies	Combined treatments
II	NCT01502592	Pre-surgical	Only BC	All	Ipilimumab	Cryoablation
I	NCT02453620	Metastatic or LABC	Multiple	TNBC ER+/HER2-neg	Nivolumab +/− Ipilimumab	Etinostat
I	NCT01375842	Metastatic	Multiple	TNBC	Atezolizumab	
I	NCT02309177	Metastatic	Multiple	TNBC ER+/HER2-neg	Nivolumab	Nab-paclitaxel
I	NCT00836888	Metastatic	Multiple	All	Nivolumab	
I	NCT02655822	Metastatic	Multiple	TNBC	Atezolizumab CPI-444	
I	NCT01848834	Metastatic	Multiple	TNBC	Pembrolizumab	
I	NCT02054806	Metastatic	Multiple	All	Pembrolizumab	
I	NCT01772004	Metastatic	Multiple	All	Avelumab	
I	NCT01975831	Metastatic	Multiple	ER+/HER2− and HER2-pos	Durvalumab Tremelimumab	
I	NCT02658214	Metastatic	Multiple	TNBC	Durvalumab Tremelimumab	Gemcitabine/carboplatin or nab-paclitaxel/ carboplatin
I/II	NCT02318901	Metastatic	Multiple	HER2-pos	Pembrolizumab	Trastuzumab or TDM1
I/II	NCT02543645	Metastatic	Multiple	TNBC	Atezolizumab Varlilumab	
I/II	NCT02657889	Metastatic	Multiple	TNBC	Pembrolizumab	Niriparib
I/II	NCT02178722	Metastatic	Multiple	TNBC	Pembrolizumab INCB024360 (IDO inhibitor)	
I/II	NCT02331251	Metastatic	Multiple	TNBC and ER+/HER2−	Pembrolizumab	Vinorelbine (ER+/HER2−) Gemcitabine (TNBC)
I/II	NCT01928394	Metastatic	Multiple	TNBC	Nivolumab +/− Ipilimumab	
I/II	NCT02452424	Metastatic	Multiple	TNBC	Pembrolizumab PLX3397 (anti-CSF1R)	
I/II	NCT02331251	Metastatic	Multiple	All	Pembrolizumab	Various CT
I/II	NCT02318901	Metastatic	Multiple	HER2-pos	Pembrolizumab	Trastuzumab or TDM1
I/II	NCT02543645	Metastatic	Multiple	TNBC	Atezolizumab Varlilumab (CD27 agonist)	
I/II	NCT02403271	Metastatic	Multiple	TNBC and HER2-pos	Durvalumab	Ibrutinib
I/II	NCT02404441	Metastatic	Multiple	TNBC	PDR001	
I/II	NCT02643303	Metastatic	Multiple	All	Durvalumab and Poly-ICLC +/− Tremelimumab	

Phase	Clinical Trial Gov	Disease setting	Type of disease	Breast cancer subtype	Immunotherapies	Combined treatments
II	NCT02661100	Metastatic	Multiple	TNBC	Pembrolizumab CDX-1401 and Poly-ICLC	
II	NCT02644369	Metastatic	Multiple	TNBC	Pembrolizumab	
II	NCT02527434	Metastatic	Multiple	TNBC	Tremelimumab Durvalumab	
II	NCT02478099	Metastatic	Multiple	TNBC	Atezolizumab	

Note: Ipilimumab, Tremelimumab (anti-CTLA4); Nivolumab, Pembrolizumab, PDR001 (anti-PD1); Durvalumab, Atezolizumab, Avelumab (anti-PDL1)

Abbreviations: BC, Breast Cancer; TNBC, triple negative breast cancer; ddAC, dose dense doxorubicin and cyclophosphamide; IBC, inflammatory breast cancer;

*Including only metastatic inflammatory breast cancer, with clinical response after receiving chemotherapy

†Usage of investigational imaging (89Zr-MPDL3280A-PET and 18F-FB-IL2-PET) as complementary tools for selection of patients to be treated with Atezolizumab

‡Randomized trial versus chemotherapy single agent (capecitabine, eribulin, gemcitabine, or vinorelbine)

¶Randomized versus nab-paclitaxel (first line metastatic disease)

§Randomized versus nab-paclitaxel/carboplatin in locally advanced TNBC

Clin Cancer Res. Author manuscript; available in PMC 2022 August 08.