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Current Landscape of Immunotherapy in Breast Cancer:

A Review

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Abstract

IMPORTANCE—There is tremendous interest in using immunotherapy to treat breast cancer, as evidenced by the more than 290 clinical trials ongoing at the time of this narrative review. The objective of this review is to describe the current status of immunotherapy in breast cancer, highlighting its potential in both early-stage and metastatic disease.

OBSERVATIONS—After searching ClinicalTrials.gov on April 24, 2018, and PubMed up to June 30, 2018, to identify breast cancer immunotherapy trials, we found that immune checkpoint blockade (ICB) is the most investigated form of immunotherapy in breast cancer. Use of ICB as monotherapy has achieved objective responses in patients with breast cancer, with higher rates seen when administered in earlier lines of therapy. For responding patients, those responses are durable. More recent data suggest clinical efficacy when ICB is given in combination with chemotherapy. Ongoing studies are evaluating combination strategies pairing ICB with additional chemotherapeutic agents, targeted therapy, vaccines, and local ablative therapies to enhance response. To date, robust predictive biomarkers for response to ICB have not been established.

CONCLUSIONS AND RELEVANCE—It is anticipated that combination therapy strategies will be the way forward for immunotherapy in breast cancer, with an improved understanding of tumor, microenvironment, and host factors informing treatment combination decisions. Thoughtful study design incorporating appropriate end points and correlative studies will be critical in identifying optimal strategies for enhancing the immune response against breast tumors.

There is currently great enthusiasm for immunotherapeutic strategies to treat cancer. Several immunotherapeutic agents have received US Food and Drug Administration (FDA) approval, including adoptive cell therapies, vaccines, onco-lytic viruses, and most notably, immune checkpoint blockade (ICB). Agents of ICB such as inhibitors of cytotoxic T-lymphocyte–associated antigen (CTLA-4), programmed cell death receptor 1 (PD-1), and programmed cell death 1 ligand 1 (PD-L1) have been approved by the FDA for use in various solid tumors, refractory cancers with microsatellite instability, and classical Hodgkin lymphoma.[1] The first approval of an ICB agent for treatment of breast cancer came in March 2019 when the anti–PD-L1 antibody atezolizumab was approved for use in combination with nab-paclitaxel for patients with triple-negative breast cancer (TNBC) that is metastatic. This initial approval has increased enthusiasm for investigating immunotherapy agents to treat patients with breast cancer.

One perceived challenge for immunotherapy in breast cancer is that breast tumors have previously been considered immunologically quiescent compared with other tumor types such as melanoma and non–small cell lung cancer (NSCLC). Melanoma and NSCLC have

high somatic mutation rates, which can lead to neoantigen generation, which may stimulate antitumor immune responses.[2] In these tumor types, higher nonsynonymous mutational burden is associated with improved response, durable clinical benefit, and progression-free survival (PFS) with ICB.[3,4] The mutational burden in breast cancer is lower than in these other tumor types and varies by subtype, with ERBB2 (formerly HER2)-positive and basal-like tumors having higher burden than hormone receptor (HR)-positive tumors.[5,6] Consistent with this, tumor-infiltrating lymphocyte (TIL) rates are higher in ERBB2-positive and TNBCs when compared with HR-positive tumors.[7–11] Notably, higher TIL levels are associated with improved prognosis in ERBB2-positive breast cancer and TNBC, with each approximately 10% increase in TIL being associated with a 15% to 25% decrease in risk of relapse and death.[8,9,12,13] Inaddition, increased TIL predicts pathologic response to neoadjuvant therapy.[11,14] For example, 4% to 20% of breast tumors are lymphocyte predominant (defined by the presence of either ≥50% or ≥60% lymphocytic infiltration, depending on the study). Previous reports showed that lymphocyte-predominant breast cancers have significantly higher pathologic complete response (pCR) rates than breast tumors with fewer TILs (40% vs 5%).[7,14] Interestingly, in a recent report of ERBB2-positive patients treated with trastuzumab/pertuzumab-based chemotherapy in the TRYPHAENA trial,[15] TILs were associated with improved event-free survival but not pCR. These data underscore the immunogenicity of some breast tumors. Moreover, the findings highlight the opportunity to develop rational combinations of immune modulation with conventional or novel strategies for breast tumors that have minimal or no lymphocytic infiltrate.

Herein, we review the current status of immunotherapy in breast cancer, highlighting its potential in both early-stage and metastatic disease.

Immune Checkpoint Inhibition

Anti–PD-1/PD-L1 Monotherapy in Breast Cancer

Initial phase 1 ICB monotherapy studies enrolled patients with advanced TNBC that was PD-L1 positive (definedas ≥ 1% of tumor cells and/or tumor-infiltrating immune cells expressing PD-L1). Importantly, the PD-L1 assay used, and whether expression was evaluated in the tumor vs in the infiltrating immune cells, was determined by the trial sponsor. In a study evaluating 5 trial-validated PD-L1 antibodies for immunohistochemical analysis of lung cancer specimens, investigators found highly comparable PD-L1 staining in tumor cells, with 3 of the 5 antibodies demonstrating strong reliability among pathologists in PD-L1 scoring.[16] There was less reliability for PD-L1 scoring in infiltrating immune cells. This underscores the challenge of using PD-L1 expression as a biomarker.

The initial trials, which evaluated the anti–PD-1 antibody pembrolizumab (n = 27) and the anti–PD-L1 antibody atezolizumab (n = 21), reported objective response rates (ORRs) of 18.5%[17] and 19%,[18] respectively. Furthermore, some responses were durable, a hallmark of ICB-mediated immune modulation. An update of the phase 1 atezolizumab trial, reported after accrual of 112 patients, including patients with PD-L1–negative tumors, revealed a 10% ORR6.[19] Pembrolizumab was further evaluated in a multicohort, phase 2 study enrolling patients with metastatic TNBC. Cohort A (n = 170), which enrolled patients who had received prior chemotherapy, regardless of tumor PD-L1 status, reported a

4.7% ORR that did not differ by tumor PD-L1 status (4.8% for PD-L1–positive, 4.7% for PD-L1–negative tumors).[20] In cohort B (n = 84), which enrolled first-line patients with PD-L1–positive tumors, the ORR was 23%,[21] suggesting greater responsiveness with earlier treatment. Importantly, responses tended to be durable, with the median duration of response not reached at data cutoff (range, 1.2–21.5 months, unpublished data via written communication from Sylvia Adams, MD, September 1, 2018) in cohort A. Also, ICB has been evaluated in patients with metastatic HR-positive/ERBB2-negative and ERBB2-positive breast cancer. In a trial evaluating the anti–PD-L1 antibody avelumab, the ORR was 28% among HR-positive/ERBB2-negative patients (n = 72), while there were no responders in a cohort of 26 ERBB2-positive patients (n = 26).[22] The ORR for patients with TNBC (n = 58) in that study was 5.2%. The results of those studies are included in Table 1,[17,19–30] which summarizes available trial data for ICB in metastatic breast cancer.

Several randomized phase 3 ICB monotherapy trials are ongoing in the metastatic setting as well as a National Cancer Institute–sponsored trial in the adjuvant setting evaluating the efficacy of single-agent pembrolizumab in patients with residual TNBC after neoadjuvant chemotherapy (NCT02954874) (Table 2).

Strategies to Enhance Response to ICB

The median PFS or overall survival (OS) in the ICB monotherapy advanced TNBC trials was not longer than historical chemotherapy controls, suggesting that therapeutic benefit is limited to a minority of patients. To optimize use of immunotherapeutic agents in breast cancer, there is a need to better understand defects in the endogenous immune response to breast tumors. Considering the cancer immunity cycle, there are multiple steps required for an effective immune response.[31] Tumors must undergo immunogenic cell death with release of antigens, which must then be presented by antigen-presenting cells to prime and activate an immune response. Activated T cells must traffic to the tumor, infiltrate, recognize, and kill tumor cells. If tumor cells express PD-L1 in an effort to avoid immune destruction at this final step of the cycle, it is reasonable to assume that the proximal steps are intact. A lack of response to therapy targeting PD-1 or PD-L1 suggests defects in the initial steps.[32]

Although a comprehensive review is outside the scope of the present article, there is a growing body of literature detailing the effects of therapeutic strategies (including chemotherapy, targeted therapy, and radiation) on immunologic aspects of the tumor microenvironment, including effects on antigen release, antigen presentation, the presence of immunomodulatory cells and cytokines, and effects on the stroma that affect T-cell trafficking. This improved understanding of the impact of standard and experimental therapies has provided a rationale for evaluating combination approaches to enhance ICB response.

Combination of ICB With Chemotherapy—Several chemotherapeutic agents, including anthracyclines, cyclophosphamide, and microtubule-stabilizing agents, commonly used in breast cancer, promote immunogenic cell death resulting in release of antigens and danger signals that recruit antigen-presenting cells, promote engulfment of dying cells, and foster dendritic cell (DC) maturation, all of which are required for T-cell priming.[33,34] Thus,

there is great interest in combining chemotherapy with ICB. Table 1 outlines combination trials in metastatic TNBC. A phase 1 trial combining atezolizumab and nab-paclitaxel enrolled 33 women who had undergone 0 to 2 prior lines of chemotherapy.[24] No new or additive safety signals were identified. The confirmed ORR was 39.4% (95% CI, 22.9% −57.9%) with responses reported in both PD-L1-positive and PD-L1-negative patients. Responses were more frequent in first- vs later-line settings, 53.8% and 30%, respectively; and they were durable, with a median duration of response of 9.1 months (range, 2.0–20.9 months). The results of a phase 3 trial (IMpassion130, NCT02425891) (Table 2) evaluating nab-paclitaxel/atezolizumab in patients with previously untreated metastatic TNBC was recently reported.[35] This trial had co–primary end points of PFS in the overall and PD-L1–positive population, and OS in the overall population and, if significant, in the PD-L1–positive population. The trial randomized 902 patients to nab-paclitaxel/atezolizumab or nab-paclitaxel/placebo, and after a median follow-up of 12.9 months, the PFS in the overall population was 7.2 months vs 5.5 months, favoring the atezolizumabarm ($P = .002$). In the PD-L1–positive population, the PFS was 7.5 months for patients receiving atezolizumab vs 5.0 months for those receiving placebo ($P < .001$). The median OS in the overall population was 21.3 months in the atezolizumab arm vs 17.6 months in the placebo arm ($P = .08$). This OS difference did not reach statistical significance, precluding formal analysis in the PD-L1–positive population. However, it was notable that in that PD-L1–positive population, the median OS was 25.0 months in the atezolizumab arm vs 15.5 months in the placebo arm (hazardratio, 0.62; 95% CI, 0.45–0.86). Based on the results of this study, the combination of atezolizumab plus nab-paclitaxel was recently approved for use in patients with metastatic TNBC. A phase 1/2 trial evaluating pembrolizumab with eribulin mesylate reported a 26.4% ORR in patients who had undergone 0 to 2 prior therapies in the metastatic setting.[25] Again, responses were observed regardless of PD-L1 status and were greater in the earlier line of therapy.

Chemotherapy/ICB combinations are also being investigated for earlier disease stages in the neoadjuvant setting (Table 3).[36–39] In the I-SPY2 trial,[36] 69 ERBB2-negative breast cancer patients (40 HR-positive and 29HR-negative) received pembrolizumab with paclitaxel, while 180 patients (95HR-positive/ERBB2-negative and 85TNBC) were treated with paclitaxel alone, followed in all patients by doxorubicin and cyclophosphamide. In the TNBC cohort, estimated pCR rates were 60% and 20%, respectively, and in the HR-positive/ERBB2-cohort, estimated pCR rates were 34% and 13%, favoring those receiving pembrolizumab. An increased incidence of adrenal insufficiency was seen with pembrolizumab, often with delayed onset, after doxorubicin and cyclophosphamide treatment completion. While other trials combining standard neoadjuvant cytotoxic regimens with ICB have not reported increased toxic effects[37–39] (Table 3), it should be cautioned that if studies do not require long-term monitoring, underreporting of adverse events may result.

Interestingly, in the recently reported GeparNuevo trial[37] rates of pCR varied by therapy sequencing, with greater efficacy found when a short run-in of single-agent immunotherapy (durvalumab) was followed by combination chemo-immunotherapy. In the overall study population, the pCR rate for patients randomized to receive durvalumab was 53.4% (vs 44.2% for those receiving placebo), which failed to meet the prespecified rate of 66%. Interestingly, in a sub-population receiving the durvalumab run-in, the pCR rate was 61.0%.

It is possible that this finding was owing to chance, as the study was not powered to address this question, but it does highlight the need to better understand immunobiology to optimize combinations and sequencing. Several large randomized studies of chemotherapy with ICB are being explored in the curative setting (Table 2).

Combination of ICB With Local Ablative Therapies—Conventional local therapy strategies such as radiotherapy can induce antigen release and facilitate tumor-specific immune responses, and preclinical studies have shown synergy with systemic immune-modulating therapies.[40–43] Early-phase trials evaluating metastasis-directed radiotherapy combined with ICB enrolling only patients with solid tumors demonstrated safety and responses outside the irradiation field in approximately 10% of participants.[44–46] Several trials evaluating irradiation plus immune modulation in breast cancer are under way, including trials combining pembrolizumab plus irradiation in HR-positive breast cancer and TNBC[47] (NCT02303366, NCT02608385, NCT02730130, and NCT03051672), and a trial combining tremelimumab (anti–CTLA-4), with brain radiotherapy with or without trastuzumab in ERBB2-positive disease[48] (NCT02563925).[48] Given responses in the metastatic setting, trials of curative intent strategies combining preoperative radiotherapy with checkpoint blockade in early-stage TNBC are under way (NCT03872505). Questions remaining unanswered are optimal irradiation timing, dose, and schedule when partnered with ICB, although preclinical data suggest that multiple fractions are superior to single-fraction strategies.[49]

Another form of local ablative therapy evaluated in combination with ICB is cryoablation.[40] In a pilot study evaluating cryoablation with ipilimumab (anti–CTLA-4) in patients with early-stage breast cancer undergoing mastectomy, the combination was shown to be safe, and it induced immunologic effects systemically and in the tumor.[50]

Combination of ICB With Targeted Therapies—Several targeted agents routinely used in breast cancer, including trastuzumab and cyclin-dependent kinase (CDK) 4/6 inhibitors, have been shown to enhance antitumor immunity and thus are promising partners for ICB. Recently reported as well as ongoing phase 3 combination trials are summarized in Tables 1 and 2. As an example, trastuzumab functions in part via antibody-dependent cell-mediated cytotoxic effects to promote antigen cross-presentation and stimulation of anti-ERBB2 CD8-positive T cells.[51] Patients receiving trastuzumab have also been shown to have an increase in circulating anti-ERBB2 CD4-positive T cells as well as anti-ERBB2 antibody responses, providing support for combining trastuzumab with immunotherapy.[52,53] The PANACEA trial[29] investigated trastuzumab and pembrolizumab in trastuzumab-resistant ERBB2-positive advanced breast cancer and demonstrated a 15.2% ORR in the PD-L1–positive cohort with no responses in the PD-L1–negative cohort. With respect to CDK4/6 inhibitors, preclinical models have shown that these agents stimulate interferon-γ signaling leading to enhanced antigen presentation, increasing effector T-cell infiltration, increasing expression of antigen-processing and -presentation genes, and suppressing regulatory T-cell proliferation.[54,55] Preclinical data show synergy between CDK4/6 inhibition and PD-1 blockade.[55] Preliminary results of an ongoing phase 1b study

of pembrolizumab plus abemaciclib show an acceptable safety profile and suggested clinical benefit, with a 14.3% ORR and a 60% rate of stable disease at 16 weeks.[26]

PARP inhibitors are also of interest as combination partners for ICB. These agents are approved by the FDA for the treatment of advanced *BRCA*-mutant breast cancers that harbor a homologous re-combination repair defect leading to accumulation of DNA damage and mutations, possibly resulting in neoantigens. Preclinical models combining PARP inhibitors with ICB have shown augmented effector T -cell function.[56–58] Recently, clinical activity has been reported for the combination of olaparib with durvalumab in germline *BRCA*-mutated metastatic ERBB2-negative breast cancers[27] as well as niraparib with pembrolizumab in unselected metastatic TNBC.[28]

Vaccines and Adoptive Cellular Therapy (ACT)

Historically, breast cancer vaccines were tested as single agents in patients with metastatic disease. Early-phase trials showed that multiple different vaccine formulations could be administered safely and generate antigen-specific immune responses in peripheral blood; however, there was minimal evidence of clinical activity.[59–62] Vaccinating patients with metastatic disease is challenging owing to the extent of disease burden and the immunosuppressive tumor microenvironment. To address these limitations, several strategies are being investigated, including vaccinating in the adjuvant setting, where there is minimal disease burden,[63,64] and incorporating vaccines in combination strategies. As an example, a phase 2 trial evaluating a CD8 T-cell–eliciting vaccine demonstrated no recurrences after a median follow-up of 34 months in 48 patients with ERBB2-positive breast cancer vaccinated after completion of trastuzumab therapy.[63] While the trial's overall intention-to-treat analysis did not demonstrate benefit of vaccination as mono-therapy, this exploratory subgroup analysis was viewed as hypothesis generating, and ongoing trials are evaluating the combination of vaccine plus trastuzumab (NCT00971737, NCT01570036, and NCT02297698). There is also great interest in using vaccines to elicit a T-cell response that can be augmented by ICB (NCT03362060 and NCT02826434).

To date, most vaccines have targeted defined tumor antigens. With recent advances in genomic profiling and the ability to identify mutations within a tumor, there is interest in identifying neoantigens and developing vaccines to target them.[65] It has been reported that neoantigen recognition by T cells plays a role in response to ICB therapy,[66] suggesting that a combination therapy strategy with a neoantigen vaccine and ICB may be effective. A trial evaluating a neoantigen DNA vaccine alone or with durvalumab in stage II-III TNBC is currently recruiting (NCT03199040). Given the relatively low rate of mutations in breast tumors, it is possible that this strategy will be less effective in breast cancer than in other more mutagenic tumor types. However, a recent report showed clinical activity in a patient with metastatic breast cancer who was administered TIL-targeting mutated proteins identified in the tumor.[67] This report suggests that if the appropriate antigen is identified, an immunotherapeutic strategy targeting it may be effective. Administration of TIL is a type of ACT (reviewed by Rosenberg and Restifo[68]), a form of immunotherapy that also includes administration of lymphocytes genetically engineered to express T-cell receptors, or lymphocytes engineered to express chimeric antigen receptors (CARs). A

CAR involves an extracellular domain derived from an antibody with specificity for a tumor cell surface antigen linked to an intracellular signaling domain that stimulates T-cell activation. There is great enthusiasm regarding CAR T-cell therapy based on FDA approval of CAR T cells targeting the CD19 antigen in non-Hodgkin lymphoma and pediatric acute lymphoblastic leukemia. CAR T-cell therapy is currently being investigated in solid tumors, including breast cancer, with active trials evaluating CAR T cells targeting ERBB2 (NCT02713984), cMET (NCT01837602), mesothelin (NCT02792114) and mucin-1 (NCT02587689). However, caution is urged because an initial trial evaluating a ERBB2-targeted CAR resulted in the death of a patient due to cytokine storm, presumably occurring after the administered cells localized to the lungs where epithelial cells express low levels of ERBB2.[69]

Appropriate Clinical Trial End Points for Immunotherapy and FDA Regulatory Considerations

Common primary end points for oncology drug approval by the FDA include OS, PFS, disease-free survival/recurrence-free survival, and ORR. Concerns have been raised that conventional response criteria in the assessment of tumor measurement-based end points (eg, ORR) do not adequately capture clinical activity of immunotherapy agents. This is based on observations in a minority of patients who experienced initial disease progression, as defined by conventional criteria, followed by subsequent tumor burden reduction. To address this, a consensus guideline, iRECIST,[70] has been published that outlines a standardized approach to solid tumor measurements and definitions for objective change in tumor size for use in tumor-response assessments in immunotherapy studies. For studies planned to support marketing applications, the FDA has recommended continued use of conventional response criteria (RECIST 1.1) in the assessment of primary end points, with consideration of other measurement techniques as supportive information. With proper justification and patient protections, incorporation of immune-based response criteria (eg, iRECIST) into clinical trials for patient management decisions or exploratory end points may be acceptable from a regulatory standpoint. Use of immune-based criteria to guide patient management in clinical trials allows for carefully selected patients with initial disease progression who may be clinically benefitting to continue with this therapy—after consideration of the risks of continued use of a potentially ineffective drug and delay of alternative, potentially effective therapy. Ultimately, prospective inclusion of immune-based response criteria to assess tumor measurement-based end points is needed to determine whether such criteria more fully capture the clinical benefit of immunotherapeutic agents.

Patient Advocate Perspective

Clinical trials should be thoughtful and coordinated in their approach to investigating the safest and most effective ways to harness the immune system against breast cancer. Advocate groups caution that media hype surrounding success of immunotherapy in other disease sites has put patients with breast cancer at risk of having inflated views of potential benefits. As patients consider participating in clinical trials, a thorough explanation of potential risks and benefits is critical. Adequately informing patients about potential toxic

effects is especially important for early-stage disease, since data on the long-term impact of these therapies is lacking. Importantly, given the different toxic effects profiles of immune agents compared with more traditional agents, resources should be devoted to patient-reported outcomes and extending the follow-up time during which such measures are assessed. With respect to correlative studies, the advocate community emphasizes using minimally invasive measures and to scheduling tissue collection to coincide with other clinic visits. For approaches combining agents, care should be taken to systematically evaluate options for determining the most effective and least toxic (physically, financially, and emotionally) regimens. It is also important that exclusion criteria be minimized, maintaining only those that are critical to scientific interpretation and/or patient safety. For example, patients with manageable comorbidities, including stable brain metastases, should be included in trials. Additionally, substantial efforts should be made to ensure that underrepresented patient groups have access to trials.

Current Breast Cancer Immunotherapy Landscape

ClinicalTrials.gov was searched on April 24, 2018, to identify breast cancer immunotherapy trials. Figure 1 shows trial breakdown by category and phase of study. A total of 293 open studies were identified, with 65% (n = 191) of those studies actively recruiting. Most studies are phase1, phase2, or phase 1/2. Almost 80% are being conducted in the metastatic setting (n = 229), with 75% of these studies being specifically for breast cancer treatment (vs 25% for general solid tumors). Most trials are for patients with TNBC (n = 106; 46%) followed by ERBB2-positive breast cancer (n = 29; 12%) (Figure 2A). Some breast cancer–specific trials include more than 1 subtype. A breakdown of ICB trials is shown in Figure 2B. Combination trials were more common than single-agent studies, with the most commonly combined modalities being chemotherapy (23%) or targeted therapy (18%).

Limitations

Data included in this review, as well as the listing of open clinical trials, was up to date at the time of writing. However, the authors acknowledge that this is a rapidly progressing field, and readers should expect that additional preclinical and clinical trial data will become available, and new trials will be initiated, shortly after publication.

Conclusions

While immunotherapy has yet to realize its full potential in breast cancer, preclinical data and the results of recent clinical trials provide reason for optimism. Success will require an understanding of tumor, microenvironment, and host factors that determine response to immunotherapeutic strategies. Single-arm, mechanistically based trials are important for identifying promising agents and combinations, as well as predictive biomarkers. To date, robust predictive biomarkers for ICB have not been established in breast cancer. Expression of PD-L1 on infiltrating immune cells was required for response to the combination of atezolizumab plus nab-paclitaxel in the IMpassion130 trial.[35] Researchers studying other agents have used different strategies: studies evaluating pembrolizumab have looked at PD-L1 expression on the tumor cells.[20,21] These trials used different antibodies to assess PD-L1 expression and studies have demonstrated some of the challenges of using multiple

different antibodies for PD-L1 detection on tumor and infiltrating immune cells. TILs have shown some promise as predictive biomarkers in exploratory analyses, but larger data sets are needed for confirmation.[24,35,71,72] TIL assessment in ongoing and future studies should be performed according to the consensus guidelines established by the International Immuno-Oncology Biomarker Working Group on Breast Cancer.[73] And while microsatellite instability[74] and tumor mutational burden[3] have been identified as biomarkers of response in other tumor types, these alterations are infrequent in breast tumors, suggesting that they are unlikely to be helpful in identifying patients likely to benefit from ICB.

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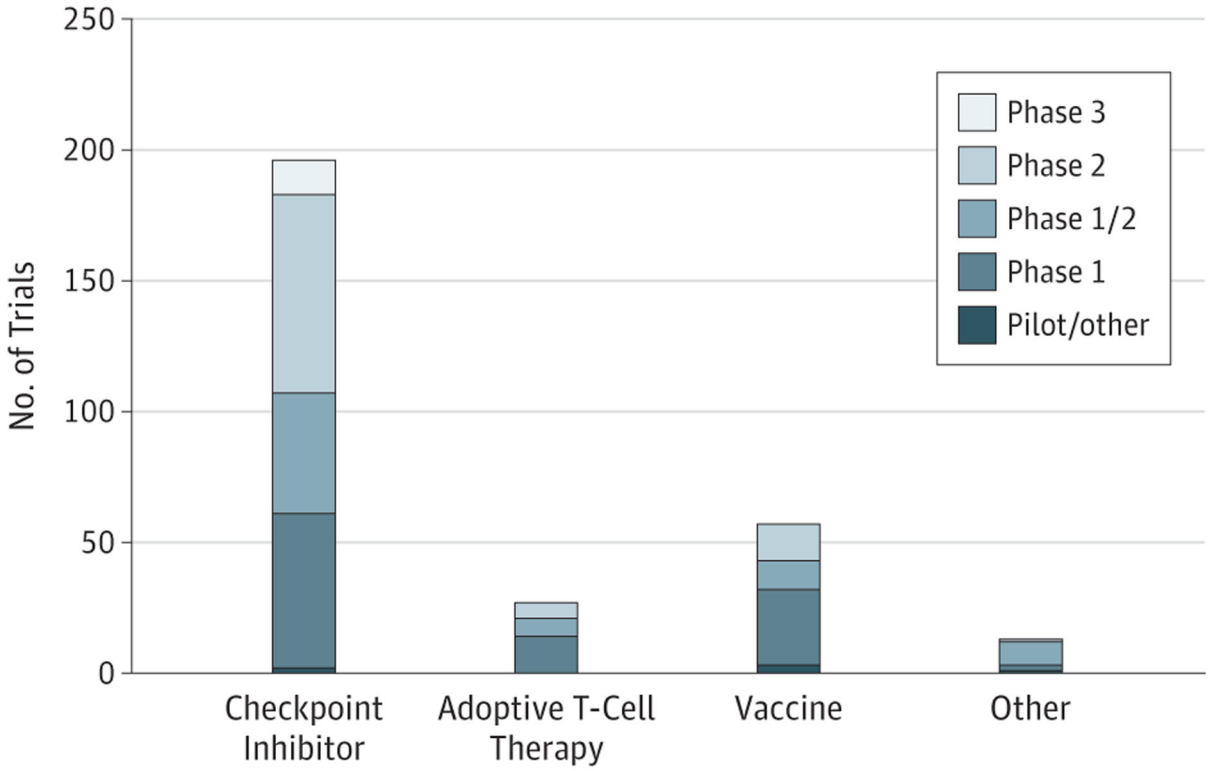

No. of trials	Checkpoint Inhibitor	Adoptive T-Cell Therapy	Vaccine	Other
Phase 3	13	0	0	0
Phase 2	76	6	14	1
Phase 1/2	46	7	11	9
Phase 1	59	14	29	2
Pilot/other	2	0	3	1

Figure 1. Breast Cancer Immunotherapy Trials by Type of Immunotherapeutic Agent or Strategy Being Investigated and by Study Phase

As of April 24, 2018, review of ClinicalTrials.gov identified 293 actively accruing trials evaluating immunotherapeutic agents in breast cancer. “Other” includes natural killer cell therapy, transarterial chemoembolization, and first-in-class agents.

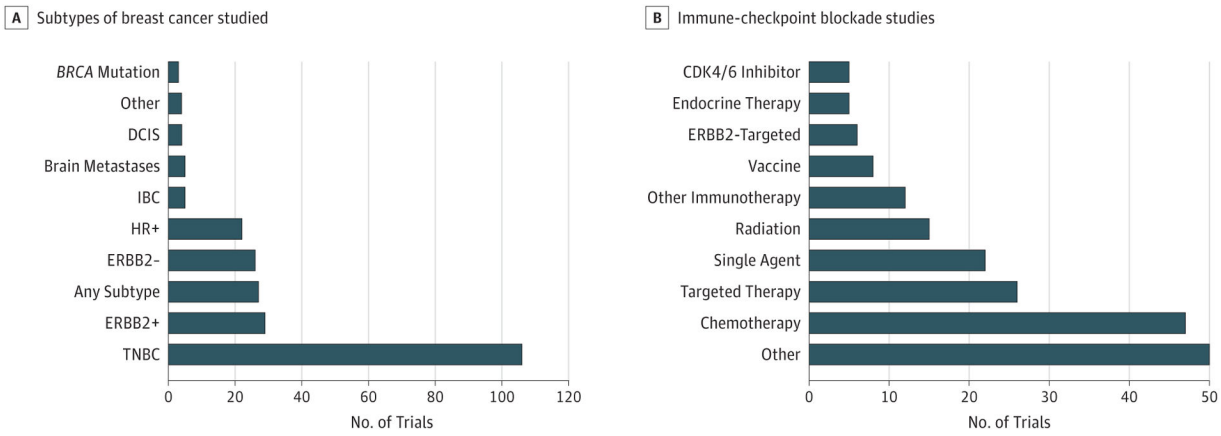

Figure 2. Breast Cancer Immunotherapy Trials

A, Trials by specific subtype of breast cancer being studied. B, Trials investigating immune checkpoint blockade agents alone or in various combinations. “Targeted therapy” includes ERBB2-targeting agents (trastuzumab, pertuzumab, T-DM1), CSFIR inhibitors, HDAC inhibitors, PARP inhibitors, pan-CDK inhibitors, P13K inhibitors, JAK2 inhibitors, adenosine A2 receptor inhibitors, AKT inhibitors, and tyrosine kinase inhibitors. “Other” includes novel monoclonal antibodies (eg, OX40, GITR), first-in-class molecules, as well as combinations with more than 2 active agents (eg, checkpoint inhibitors, vaccines, chemotherapy, irradiation, endocrine therapy, cytokines) in adaptive clinical trials. CDK indicates cyclin-dependent kinase; DCIS, ductal carcinoma in situ; HR, hormone receptor; IBC, inflammatory breast cancer; TNBC, triple-negative breast cancer.

Table 1.

Reported Trials of Anti–CTLA-4 or Anti–PD1/PD-L1 ICB in Metastatic Breast Cancer as of June 30, 2018

Source (Name)	Population and Line of Therapy	Evaluable Patients, No.	Safety Profile	ORR, %	Median Survival, mo	
					PFS	OS
Monotherapy						
Phase 1b; pembrolizumab; KEYNOTE-012[17]	mTNBC, PD-L1+, 15.6% 1st line	27	15.6% Gr 3–5 AEs; 5 Gr 3 AEs: anemia, aseptic meningitis, lymphopenia, headache, pyrexia; 1 death (DIC)	18.5	1.9	11.2
Phase 1a; atezolizumab[19]	mTNBC, PD-L1+, later expanded to include PD-L1−, 17% 1st line	115	11% Gr 3/4 treatment-related AEs, 2% Gr 5 treatment-related AEs (1 pulmonary hypertension, 1 not specified)	10 (12 for PD-L1+, 0 for PD-L1−	1.4	8.9
Phase 1b; avelumab; JAVELIN[22]	mBC, PD-L1+/− (58 TNBC, 72 HR+/ERBB2−, 26 ERBB2+), 1st to 4th line	168	14.3% Gr 3–5 AEs, immune-related events, autoimmune hepatitis (1.8%); 2 treatment-related deaths (acute liver failure, respiratory distress)	4.8 (33 for PD-L1+, 2.4 for PD-L1−); 5.2 for TNBC, 2.8 for HR+/ERBB2−, 0 for ERBB2+	5.9	8.1
Phase 1b; pembrolizumab; KEYNOTE-028[23]	HR+ mBC, PD-L1+, prior chemo/endocrine therapy allowed	25	16% Gr 3–4 AEs, immune-related AEs included hepatitis, pneumonitis, hyperthyroidism/hypothyroidism	12	1.8	8.6
Phase 2; pembrolizumab; KEYNOTE-086 Cohort A[20]	mTNBC, PD-L1+/−, 2nd line and beyond	170	12% with Gr 3–4 AEs; 19% with irAEs of any grade, of which 1.2% were Gr 3–4 (most common: hypothyroidism/hyperthyroidism, pneumonitis)	4.7 (4.8 PD-L1+, 4.7 PD-L1−)	2	8.9
Phase 2; pembrolizumab; KEYNOTE-086 Cohort B[21]	mTNBC, PD-L1+, 1st line	84	10% Gr 3–4 AEs; no discontinuations or deaths due of treatment-related AEs	23.1	2.1	NA
Combination Therapy						
Phase 1b; atezolizumab + nab-paclitaxel[24]	mTNBC, PD-L1 +/−, 1st to 3rd line	33	73% Gr 3–4 treatment-related AEs, most common: neutropenia, anemia, thrombocytopenia, diarrhea, pneumonia.	39	5.5	14.7
Phase 1b/2; pembrolizumab + eribulin mesylate; ENHANCE[25]	mTNBC, PD-L1 +/−, 1st to 3rd line	107	No DLTs, 66.7% Gr 3–4 AEs; most common, neutropenia and fatigue; most common immune-related AEs hypothyroidism/hyperthyroidism, rash, hyperglycemia, and pneumonitis	26.4	4.2	17.7
Phase 1b; pembrolizumab + abemaciclib; JPCE[26]	HR+, ERBB2− mBC, treatment line NA	28	28.6% serious AEs: Gr 5 AEs, 3.6%; no Gr 4 AEs; Gr 3 AEs: diarrhea (10.7%), neutropenia (28.6%), AST increase (14.3%), ALT (10.7%)	28.6	NA	NA
Phase 2; durvalumab + olaparib; MEDIOLA[27]	*BRCA1/2*-mutated, ERBB2− mBC, 1st and later lines	25	Gr 3–4 AEs were anemia (8%), neutropenia (8%), hemolysis (4%), dyspnea (4%), pancreatitis (4%), fatigue (4%), lymphopenia (4%), and leukopenia (4%)	52 (Includes unconfirmed responses)	NA	NA
Phase 2; niraparib + pembrolizumab; TOPACIO[28]	mTNBC, 1st to 3rd line	46	Gr 3–4 AEs were fatigue (7%), anemia (15%), and thrombopenia (13%)	28 (Includes unconfirmed responses)	NA	NA

Source (Name)	Population and Line of Therapy	Evaluable Patients, No.	Safety Profile	ORR, %	Median Survival, mo	
					PFS	OS
Phase 1/2; pembrolizumab + trastuzumab; PANACEA[29]	ERBB2+ mBC, 2nd line and later	58	No DLTs, 19% immune-related AEs (most common, thyroid and pneumonitis)	15.2 for PD-L1+; 0 for PD-L1−	2.7 for PD-L1+,; 2.5 for PD-L1−	17.1 for PD-L1+; 7 for PD-L1−
Phase 1 tremelimumab + exemestane[30]	HR+ mBC	26	5 DLTs	0	NA	NA

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; DIC, disseminated intravascular coagulation; DLT, dose-limiting toxic effect; Gr, grade; HR, hormone receptor; ICB, immune checkpoint blockade; irAE, immune-related AE; mBC, metastatic breast cancer; mTNBC, metastatic triple-negative breast cancer; NA, not applicable; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death 1; PD-L1, PD-1 ligand 1; PFS, progression-free survival.

Table 2.

Key Randomized Phase 3 Registration Studies of ICB in Breast Cancer as of July 7, 2018

Trial Information	Trial Description	Primary End Point(s)	Open (Estimated Completion) Date
A-Brave (NCT02926196)	Status: recruiting Setting: adjuvant TNBC in patients with high-risk disease (including residual cancer post-NAC) (N = 335) Treatment arms: (1) avelumab, once every 2 wk for 1 y; (2) observation	DFS DFS in PD-L1+	June 2016 (June 2023)
IMpassion030 (NCT03498716)	Status: active, not yet recruiting Setting: adjuvant TNBC (N = 2300) Treatment arms: (1) atezolizumab once every 2 wk × 10 with paclitaxel weekly × 12 followed by ddAC (or ddEC) × 4 followed by atezolizumab every 3 weeks maintenance to complete 1 y of treatment; (2) weekly paclitaxel × 12 + ddAC (or ddEC) × 4	iDFS	May 31, 2018 (December 29, 2024)
IMpassion031 (NCT03197935)	Status: recruiting Setting: neoadjuvant TNBC (N = 204) Treatment arms: (1) atezolizumab once every 2 wk + nab-paclitaxel once every 1 wk × 12→atezolizumab once every 2 wk + ddAC × 4→surgery →atezolizumab once every 3 wk to 1 y; (2) placebo once every 2 wk + nab-paclitaxel once every 1 wk→placebo once every 2 wk + ddAC × 4→surgery	pCR	July 25, 2017 (Sept26, 2021)
IMpassion130 (NCT02425891)	Status: active, not recruiting Setting: metastatic TNBC, front-line (N = 900) Treatment arms: (1) atezolizumab once every 2 wk + nab-paclitaxel on days 1, 8, and 15 of 28 d; (2) placebo once every 2 wk + nab-paclitaxel on days 1, 8, and 15 of 28 d	PFS PFS in PD-L1+ OS OS in PD-L1+ (See text for first analysis reported in October 2018)	June 23, 2015 (April 30, 2020)
IMpassion131 (NCT03125902)	Status: recruiting Setting: inoperable locally advanced or metastatic TNBC, front-line (N = 540) Treatment arms: (1) atezolizumab once every 2 wk + paclitaxel on days 1, 8, and 15 of 28 d; (2) placebo + Paclitaxel on days 1, 8, and 15 of 28 d	PFS	August 25, 2017 (June 30, 2021)
IMpassion132 (NCT03371017)	Status: recruiting Setting: inoperable, recurrent, or metastatic TNBC, front-line (N = 350) Treatment arms: (1) atezolizumab once every 3 wk + chemotherapy (gemcitabine or capecitabine or carboplatin); (2) placebo once every 3 wk + chemotherapy (gemcitabine or capecitabine or carboplatin)	OS	January 11, 2018 (January 31, 2021)
KEYNOTE-119 (NCT02555657)	Status: active, not recruiting Setting: metastatic TNBC, second- or third-line (N = 600) Treatment arms: (1) pembrolizumab once every 3 wk; (2) chemotherapy (capecitabine, eribulin, gemcitabine, vinorelbine)	OS	October 13, 2015 (May 30, 2019)
KEYNOTE-355 (NCT02819518)	Status: recruiting Setting: inoperable, locally recurrent or metastatic TNBC, front-line (N = 858) Treatment arms: Part 1: (1) pembrolizumab once every 3 wk + nab-paclitaxel on days 1, 8, and 15 of 28 d; (2) pembrolizumab once every 3 wk + paclitaxel on days 1, 8, and 15 of 28 d; (3) pembrolizumab once every 3 wk + gemcitabine/carboplatin on days 1 and 8 of 21 d Part 2: (1) pembrolizumab once every 3 wk + chemotherapy (nab-paclitaxel vs paclitaxel vs gemcitabine/carboplatin); (2) placebo + chemotherapy	Part 1: AE, drug discontinuation due to AE Part 2: PFS, PFS in PD-L1+, OS, and OS in PD-L1+	July 27, 2016 (December 30, 2019)
KEYNOTE-522 (NCT03036488)	Status: recruiting Setting: neoadjuvant TNBC (N = 1150) Treatment arms: (1) pembrolizumab once every 3 wk (plus weekly paclitaxel + carboplatin) × 4 cycles→pembrolizumab	pCR EFS	March 7, 2017 (March 14, 2025)

Trial Information	Trial Description	Primary End Point(s)	Open (Estimated Completion) Date
	once every 3 wk + AC once every 3 wk × 4→surgery→pembrolizumab once every 3 wk × 9 cycles; (2) placebo once every 3 wk (plus weekly paclitaxel + carboplatin) × 4 cycles→placebo once every 3 wk + AC (or EC) once every 3 wk × 4→surgery→placebo once every 3 wk × 9 cycles		
NeoTRIPaPDL1 (NCT02620280)	Status: recruiting Setting: neoadjuvant TNBC (N = 272) Treatment arms: (1) atezolizumab once every 3 wk + carboplatin on days 1 and 8 of 21 d + nab-paclitaxel on days 1 and 8 of 21 d→surgery→AC/EC/FEC once every 3 wk; (2) carboplatin on days 1 and 8 of 21 d + nab-paclitaxel on days 1 and 8 of 21 d→surgery→AC/EC/FEC once every 3 wk	EFS	April 2016 (October 2022)
NRG-BR004 (NCT03199885)	Status: active, not yet recruiting Setting: locally recurrent, unresectable, or metastatic ERBB2+, front-line (N = 480) Treatment arms: (1) pertuzumab once every 3 wk + trastuzumab once every 3 wk + paclitaxel on days 1 and 8 of 21 d; (2) pertuzumab once every 3 wk + trastuzumab once every 3 wk + paclitaxel on days 1 and 8 of 21 d + pembrolizumab once every 3 wk	PFS	July 11, 2018 (December 31, 2020)
NSABPB-59 (NCT03281954)	Status: active Setting: neoadjuvant TNBC (N = 1520) Treatment arms: (1) weekly paclitaxel × 12 + carboplatin once every 3 wk × 4 + placebo once every 3 wk × 4→AC (or EC) once every 2–3 wk × 4 →surgery→placebo once every 3 wk until 1 y; (2) weekly paclitaxel × 12 + carboplatin once every 3 wk × 4 + atezolizumab once every 3 wk × 4→AC (or EC) once every 2–3 wk × 4→surgery→atezolizumab once every 3 wk until 1 y	pCR EFS	December 19, 2017 (June 30, 2024)
SWOGS1418/ BR006 (NCT02954874)	Status: recruiting Setting: adjuvant TNBC with residual disease post-NAC (N = 1000) Treatment arms: (1) observation; (2) pembrolizumab once every 3 wk for 1 y	iDFS iDFSinPD-L1+	Nov 15, 2016 (May 31, 2026)

Abbreviations: AE, adverse event; arrow (→), followed by; dose dense; AC, doxorubicin/cyclophosphamide; EC, epirubicin/cyclophosphamide; EFS, event-free survival; FEC, fluorouracil/epirubicin/cyclophosphamide; ICB, immune checkpoint blockade; iDFS, invasive disease-free survival; NAC, neoadjuvant chemotherapy; OS, overall survival; pCR, pathologic complete response; PD-L1, programmed cell death 1 ligand 1; PFS, progression-free survival; TNBC, triple-negative breast cancer.

Table 3.

Trials of Neoadjuvant ICB and Chemotherapy in Early Breast Cancer As of June 30, 2018

Source (Name)	Population and No.	Safety	pCR Rate
Phase 2; pembrolizumab (with paclitaxel, followed by AC), I-SPY[36]	ERBB2−, 69 enrolled to investigational arm: TNBC (n = 29) and HR+/ERBB2− (n = 40); 180 controls	Adrenal insufficiency in 6 patients, at least 3 related to hypophysitis (5 late onset, after completion of AC; 1 during pembrolizumab)	yT0/Tis ypN0 46% vs 16% in ERBB2− (60% vs 20% in TNBC), 34% vs 13% in HR+/ERBB2−
Phase 2; durvalumab or placebo (with nab-paclitaxel, followed by EC), GeparNUEVO[37]	TNBC,cT1b-cT4a-d,174 enrolled	no significant differences in AEs between arms (except more hypothyroidism/hyperthyroidism with durvalumab)	ypT0N0 53.4% vs 44.2% (P = .29)
Phase 1b; pembrolizumab (with nab-paclitaxel +/− carboplatin, followed by AC), KEYNOTE-173[38]	TNBC; cohort A (n = 10), cohort B (n = 10)	No increased toxic effects	ypT0/Tis ypN0 60% in cohort A and 90% in cohort B
Phase 1/2; durvalumab (concomitant with nab-paclitaxel and AC)[39]	Stage I-III TNBC; phase 1, n = 7; phase 2, n = 50	1 Gr 2 AE, fatigue; 1 Gr 3 AE, dehydration and dyspnea; no Gr 4 or 5 AEs	71% in phase 1

Abbreviations: AC, doxorubicin/cyclophosphamide; AE, adverse event; EC, epirubicin/cyclophosphamide; Gr, grade; HR, hormone receptor; ICB, immune checkpoint blockade; SAE, serious adverse event; TNBC, triple-negative breast cancer.