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Immune Checkpoint Blockade for Breast Cancer

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Abstract

An effective antitumor immune response requires interaction between cells of the adaptive and innate immune system. Three key elements are required: generation of activated tumor-directed T cells, infiltration of activated T cells into the tumor microenvironment, and killing of tumor cells by activated T cells. Tumor immune evasion can occur as a result of the disruption of each of these three key T cell activities, resulting in three distinct cancer-immune phenotypes. The immune inflamed phenotype, characterized by the presence of a robust tumor immune infiltrate, suggests impaired activated T cell killing of tumor cells related to the presence of inhibitory factors. Programmed death receptor-1 (PD-1) is an inhibitory transmembrane protein expressed on T cells, B cells, and NK cells. The interaction between PD-1 and its ligands (PD-L1/L2) functions as an immune checkpoint against unrestrained cytotoxic T effector cell activity—it promotes peripheral T effector cell exhaustion and conversion of T effector cells to immunosuppressive T regulatory (Treg) cells. Immune checkpoint inhibitors, which block the PD-1/PD-L1 axis and reactivate cytotoxic T effector cell function, are actively being investigated for the treatment of breast cancer.

Keywords

Breast cancer; Immunotherapy; Immune checkpoint inhibitors

10.1 Introduction

The immune system is controlled by a delicate balance of factors that work to both initiate immune responses and inhibit excessive inflammation induced by immunity. Cells from both the innate and adaptive immune systems work to eradicate pathogens and other threats, including tumors. Early in tumorigenesis, an acute inflammatory response is triggered, leading to the recruitment of effectors of innate immunity, including macrophages, natural killer (NK) cells, and dendritic cells, resulting in the generation of interferon (IFN) gamma and interleukin-12. These factors stimulate tumor cell killing via macrophages and NK cells. Simultaneously, dendritic cells mature, process tumor-associated antigens, and present these antigens to naïve T cells. These T cells in turn become activated and travel to and infiltrate the tumor microenvironment, where they work to eradicate tumor cells. This adaptive immune response can result in either the complete eradication of a tumor or the selection of tumor cells which evade immune surveillance.

For an effective antitumor immune response, three key elements are required: generation of activated tumor-directed T cells, infiltration of activated T cells into the tumor microenvironment, and killing of tumor cells by activated T cells [1]. Tumor immune evasion can occur as a result of the disruption of each of these three key T cell activities, resulting in three distinct cancer-immune phenotypes [2]. The immune desert phenotype—characterized by the absence of tumor-infiltrating immune cells—is generally seen when there is impaired T cell generation, related to immunologic ignorance, tolerance, or failure of T cell priming and activation. The immune excluded phenotype is characterized by the inability of T cells to infiltrate the tumor microenvironment and is likely related to the expression of immune suppressive cytokines or to barriers of infiltration into the tumor bed. The immune inflamed phenotype, characterized by the presence of a robust tumor immune infiltrate, suggests an arrest in the antitumor immune response related to the presence of inhibitory factors. By characterizing the biology of these different phenotypes, underlying immune escape mechanisms can be identified and strategies to activate antitumor immune responses that will lead to effective and sustained tumor eradication can be developed.

Immune checkpoint inhibition has emerged as an effective treatment for a variety of malignancies, with FDA approvals for new indications occurring at a rapid pace. The study of immunotherapy in breast cancer has been relatively delayed compared to other malignancies, because until recently breast cancer was not thought to be an immunogenic disease. We now know that many breast cancers are immunogenic and are enriched in tumor-infiltrating lymphocytes (TILs) [3]. Reactivating the immune system to eradicate breast cancers has emerged as a promising treatment strategy, and immune checkpoint inhibition has demonstrated activity in both advanced and early stage breast cancer. This chapter provides an overview of breast cancer immunobiology and immune-based treatment strategies for breast cancer.

10.2 Rationale for Immunotherapy for Breast Cancer

Breast cancer has historically been viewed as immunologically silent. However, a number of observations over the last several years have suggested that at least a subset of breast cancers is capable of stimulating the immune system. It has long been observed that some breast tumors have a substantial lymphocytic infiltration [4]. These lymphocyte predominant breast cancers are characterized by a dense lymphocytic infiltration, with tumor-infiltrating immune (TILs) cells comprising 50% or more of the tumor bed. A number of studies have demonstrated that the higher the proportion of TILs, the more favorable the prognosis. In an analysis of almost 16,000 patients, the presence of TILs at diagnosis was prognostic of outcome in patients with TNBC and HER2-positive breast cancers [5]. In a study of 481 patients with TNBC, there was a 14% improvement in disease-free survival for each 10% increase in TILs [6]. In a series of 387 HER2-positive breast cancer patients, TILs were inversely correlated with recurrence, with each 1% increase in the proportion of TILs correlating with a 3% reduction in the risk of recurrence [7]. TIL density, however, does not appear to be prognostic of outcome in ER-positive disease [8]. In addition to being prognostic in some breast cancer subtypes, TILs appear to be predictive of response to therapy. Two studies demonstrated a correlation between TIL density and improved outcome with anthracycline-based therapy [9]. Outcomes of HER2-positive breast cancers treated

with trastuzumab-based therapies, however, show differing results. The FinHER study demonstrated an improved outcome with increased TIL density, while the opposite was observed in the NCCTG N9831 trial [10, 11].

Programmed death receptor-1 (PD-1) is an inhibitory transmembrane protein expressed on T cells, B cells, and NK cells. Its ligands are programmed death-ligand 1 (PD-L1), also known as B7-H1, and programmed death-ligand 2 (PD-L2), also known as B7-H2 [12]. PD-L1 is expressed on the surface of multiple types of cells, including tumor and hematopoietic cells, while PD-L2 is primarily expressed on hematopoietic cells. The interaction between PD-1 and its ligands directly inhibits apoptosis of tumor cells, promotes peripheral T effector cell exhaustion, and promotes conversion of T effector cells to immunosuppressive T regulatory (Treg) cells. PD-1 and PD-L1/L2 are upregulated in the context of pro-effector cytokines (such as IFN- γ) secreted by CD8⁺ TILs, highlighting their role as immune checkpoints—they function as a physiologic “brake” on unrestrained cytotoxic T effector function. PD-L1 is expressed by approximately 20% of breast cancers, with TNBC and HER2-positive breast cancers expressing higher levels of expression than ER-positive breast cancers (33, 56 and 11%, respectively). The prognostic value of PD-L1 expression has been evaluated, and while some studies suggest PD-L1 expression is associated with a more favorable prognosis, others suggest that expression is associated with a poor prognosis. While the prognostic significance of PD-L1 expression in breast cancer remains unclear, the greater likelihood of response to PD-1 and PD-L1 blockade in PD-L1 positive cancers led to the interest in investigating immune checkpoint inhibitors for breast cancer.

10.3 PD-1 Blockade

Pembrolizumab (MK-3475) is a highly selective, humanized immunoglobulin (Ig) G4- κ monoclonal antibody specific for PD-1, currently FDA-approved for use in advanced melanoma, non-small cell lung cancer, squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma, and classical Hodgkin lymphoma. In May 2017, it received accelerated approval for adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. This approval marks the first tumor tissue/site-agnostic indication granted by the FDA, with approval based on a common biomarker rather than the location of the body where the tumor originated. Pembrolizumab has been studied in breast cancer both as monotherapy and in combination with chemotherapy, for both advanced and early stage breast cancer.

KEYNOTE-012 was a phase Ib multicohort study of single agent pembrolizumab in patients with advanced PD-L1-positive (PD-L1+) solid tumors, including TNBC, gastric cancer, urothelial cancer, and head and neck cancer [13]. PD-L1 positivity was defined as PD-L1 expression in stroma or $\geq 1\%$ of tumor cells by immunohistochemistry (IHC) using the Merck 22C3 antibody. The TNBC cohort enrolled 32 women with recurrent or metastatic PD-L1+ TNBC; of the 111 patients screened for PD-L1 expression, 58.6% had PD-L1+ tumors. Median age was 50.5 years in this heavily pretreated population; patients had received a median of two prior lines of systemic therapy for metastatic disease, with 46.9%

of patients having received 3 lines of therapy. Among the 27 patients who were evaluable for antitumor activity, the primary endpoint of objective response rate [ORR; defined as complete responses (CR) plus partial responses (PR)] was 18.5% (1 CR, 4 PR), with a median time to response of 17.9 weeks (range 7.3–32.4 weeks). Durable responses were observed, with the median duration of response not yet reached (range 15.0 to 47.3 weeks), including three responders remaining on treatment for over 1 year. Treatment-related adverse events (TRAEs) were mild and similar to those observed in other tumor types; most common were arthralgias, fatigue, myalgias, and nausea. Five patients (15.6%) had grade 3 AEs, and there was one on treatment death due to disseminated intravascular coagulation (DIC).

The phase II KEYNOTE-086 study evaluated pembrolizumab monotherapy in two cohorts: previously treated metastatic TNBC (mTNBC) regardless of PD-L1 expression (Cohort A) and first-line PD-L1+ mTNBC (Cohort B) [14, 15]. Of the 170 patients enrolled in cohort A, (median age 53.5 years; range, 28–85 years), 43.5% had 3 prior lines of therapy and 61.8% had PD-L1+ tumors [14]. After a median follow-up of 10.9 months, 9 patients (5.3%) remained on pembrolizumab. Primary endpoint of overall ORR was 4.7% (95% CI, 2.3–9.2%); ORR was the same regardless PD-L1 expression (4.8% in PD-L1+ patients vs. 4.7% in PD-L1-negative patients). Disease control rate was 7.6% (DCR = CR + PR + stable disease [SD] 24 weeks; 95% CI, 4.4–12.7 weeks). Median duration of response (DOR) was 6.3 months (range 1.2+ to 10.3+ months); median progression-free survival (PFS) and overall survival (OS) were 2.0 months (95% CI 1.9–2.0) and 8.9 months (95% CI 7.2–11.2 months), respectively. TRAEs of any grade and grade 3 occurred in 60 and 12.4% of patients, respectively. There were no deaths due to AE and 4% of patients discontinued pembrolizumab due to TRAEs. Of the first 52 patients enrolled to cohort B of KEYNOTE-086 for first-line treatment of PD-L1+ mTNBC, median age was 53 years (range, 26–80 years), and 87% had received prior (neo)adjuvant therapy [16]. At median follow-up of 7.0 months (range 4.4–12.5 months), 15 (29%) patients remained on pembrolizumab. The primary endpoint was safety; TRAEs occurred in 37 (71%) patients and the most common were fatigue (31%), nausea (15%), and diarrhea (13%). Four (8%) patients experienced grade 3 TRAEs: back pain, fatigue, hyponatremia, hypotension, and migraine ($n = 1$ each). No patients died or discontinued pembrolizumab due to an AE. The ORR was 23.1% (95% CI 14–36%), with 2 CRs and 10 PRs. The median time to response was 8.7 weeks (range 8.1–17.7 weeks) and median DOR was 8.4 months (range, 2.1+ to 8.4 months), with 8 (67%) responses ongoing at data cutoff. The median PFS was 2.1 months (95% CI, 2.0–3.9 months), with estimated 6-month PFS rate 28%. A randomized phase III trial of pembrolizumab monotherapy versus chemotherapy in metastatic TNBC, KEYNOTE-119, is ongoing [17].

The phase Ib KEYNOTE-028 trial examined pembrolizumab in 25 patients with metastatic PD-L1+ ER+/HER2-negative breast cancer [18]. A total of 261 patients were screened, and 18.4% had PD-L1+ disease. The median age was 53 years (range, 36–79 years), and 80% of patients had received 3 prior lines of therapy for advanced disease. The overall response rate was 12% (95% CI, 2.5–31.2%), consisting of 3 PRs. Four patients (16%; 95% CI, 4.5–36.1%) had SD, and the clinical benefit rate (CBR; defined as ORR plus SD for 24 weeks) was 20%. The median time to response was 8 weeks, and all 3 responders remained on study

treatment at the time of initial presentation at the 2015 San Antonio Breast Cancer Symposium (SABCS). TRAEs included arthralgia, fatigue, myalgia, and nausea, and were mostly grade 1–2. Grade 3 TRAEs included autoimmune hepatitis, increased gamma-glutamyl transferase (GGT) levels, muscle weakness, nausea, and septic shock; there were no treatment-related deaths.

A phase Ib/II study evaluated pembrolizumab in combination with eribulin in patients with mTNBC unselected for PD-L1 expression [19]. An interim analysis of the first 39 enrolled patients ($n = 7$, phase Ib; $n = 32$, phase II) was presented at the 2016 SABCS. The median age of participants was 53 years (range, 32–80 years) and the study included patients previously treated with 0–2 lines of chemotherapy in the metastatic setting. Primary endpoints were determination of safety and tolerability (phase Ib) and evaluation of ORR (phase II); secondary endpoints included evaluation of PFS, OS, and DOR. No dose-limiting toxicities (DLTs) were observed in phase Ib. The most common TRAEs were fatigue, nausea, peripheral neuropathy, neutropenia, and alopecia, with the most frequent grade 3 AEs being neutropenia and fatigue, side effects frequently observed with eribulin monotherapy. The overall ORR was 33.3% (1 CR, 12 PR). In stratum 1, which consisted of patients that were previously untreated in the metastatic setting, the ORR was 41.2% (95% CI, 19.3–62.8%) versus 27.3% (95% CI, 11.3–46.4%) in stratum 2 (1–2 prior lines of treatment). PD-L1 status did not predict response to treatment: ORR was 29.4% (95% CI, 11.1–51.1%) in the PD-L1+ patients versus 33.3% (95% CI, 14.1–54.6%) in PD-L1– patients. Overall, the combination of pembrolizumab and eribulin demonstrated activity in mTNBC, and AEs observed with the combination were comparable to those observed historically with either treatment as monotherapy. A two-arm phase III clinical trial, KEYNOTE-355, to evaluate the safety and efficacy of pembrolizumab in combination with three different chemotherapies (paclitaxel, nab-paclitaxel, carboplatin/gemcitabine) in the first-line treatment of mTNBC is currently underway ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02819518) identifier: NCT02819518).

I-SPY2 (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging And molecular Analysis 2) is an ongoing phase II platform trial in patients with stage II–III breast cancer that is evaluating multiple novel therapies in combination with standard neoadjuvant chemotherapy (NACT) with paclitaxel followed by doxorubicin/cyclophosphamide [20]. The I-SPY2 trial utilizes a novel adaptive randomization algorithm, based on biomarker “signatures,” to assign patients to treatment arms that are performing well for patients who share their biomarker signature. The primary endpoint for I-SPY2 is pathologic complete response rate (pCR rate) defined as TNM stage ypT0/TisN0. In 69 patients, the addition of 4 cycles of pembrolizumab administered concurrently with paclitaxel significantly increased the estimated pCR rates. The estimated pCR rates in the TNBC population were 60% in the pembrolizumab group (95% Bayesian probability interval [PI], 43–78%) versus 20% (95% PI, 6–33%) in the control group of standard NACT alone. In patients with hormone receptor-positive (HR+)/HER2-negative breast cancer, the estimated pCR rate was 34% (95% PI, 19–48%) in the pembrolizumab arm versus 13% (95% PI, 3–24%) in the control arm. In the pembrolizumab arm, there were seven grade 3 immune-related adverse events (IRAEs): adrenal insufficiency ($n = 6$, includes primary and secondary adrenal insufficiency (AI) and colitis ($n = 1$). Five of those diagnosed with

adrenal insufficiency presented after completion of AC (10–12 weeks after last pembrolizumab dose), and one presented prior to AC (5 weeks after first pembrolizumab dose). Eight patients had grade 1–2 thyroid abnormalities. Due to the toxicities observed, serial screening AM cortisol levels have been incorporated into the trial, in addition to ongoing serial thyroid function testing. The most common grade 3 AEs in the pembrolizumab arm were diarrhea, febrile neutropenia, fatigue, anemia, and nausea. Based on Bayesian predictive probability of success in a confirmatory phase III trial, pembrolizumab “graduated” from the I-SPY2 trial for all signatures in which it was tested (TNBC, all HER2-negative, and HR+/HER2-negative). Of note, this is the first investigational agent in the trial to graduate in the HR+/HER2-negative signature.

The phase III KEYNOTE-522 study is an ongoing neoadjuvant trial evaluating the combination of carboplatin/paclitaxel with or without pembrolizumab followed by doxorubicin/cyclophosphamide with or without pembrolizumab in patients with TNBC ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03036488) identifier: NCT03036488). Primary endpoints are pCR (defined as ypT0/TisN0) and event-free survival (EFS). In the adjuvant setting, Southwest Oncology Group (SWOG) S1418 is an ongoing phase III clinical trial that seeks to define the role of pembrolizumab in patients with TNBC that have residual disease after NACT; patients are randomized to either adjuvant pembrolizumab or placebo for 1 year ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02954874) identifier: NCT02954874).

In HER2+ disease, both trastuzumab and ado-trastuzumab emtansine (T-DM1) have been shown to increase TILs, suggesting that untreated HER2 signaling could be a mechanism of immune suppression [21, 22]. Multiple studies are investigating the combination of anti-HER2 therapy with immune checkpoint inhibitors. PANACEA is a phase Ib/II trial evaluating the safety and efficacy of pembrolizumab and trastuzumab in trastuzumab-resistant, PD-L1+ HER2+ metastatic breast cancer [23]. PembroMab is a phase Ib/II trial evaluating the safety and efficacy of pembrolizumab and trastuzumab or ado-trastuzumab emtansine in patients with metastatic HER2+ breast cancer, regardless of PD-L1 status ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02318901) identifier: NCT02318901).

10.4 PD-L1 Blockade

Atezolizumab (MPDL3280A) is a high-affinity, engineered, fully human IgG₁ monoclonal antibody that inhibits the interaction of PD-L1 with PD-1 and B7.1 (CD80), both of which are negative regulators of T-lymphocyte activation [24]. Because PD-L1 is expressed on activated T cells, atezolizumab was engineered with a modification in the Fc domain that eliminates antibody-dependent cellular cytotoxicity (ADCC) at clinically relevant doses, thus preventing the depletion of T cells expressing PD-L1 [25]. It is currently FDA-approved for a number of advanced cancers, including urothelial carcinoma and non-small cell lung cancer.

A phase Ia study evaluated the safety and efficacy of atezolizumab monotherapy in multiple disease-specific cohorts, including a cohort of 115 mTNBC patients [26]. The TNBC cohort initially enrolled patients with PD-L1+ disease, but was later amended to include patients with PD-L1-negative disease. Among pre-screened patients, 63% had PD-L1+ tumors,

defined as containing ≥ 5% PD-L1+ tumor-infiltrating lymphocytes (TILs) using the SP142 antibody. Median age was 53 years (range, 29–82 years) and the population was heavily pretreated, with 58% of patients having received ≥ 3 systemic therapies in the metastatic setting. ORR in the 112 evaluable patients was 10% (95% CI, 5–17%), with median DOR 21.1 months (range, 2.8–26.5+ months) and median PFS 1.4 months (95% CI, 1.3–1.6 months). Three patients initially classified as having PD appear to have had pseudoprogression, with evidence of ongoing clinical benefit and durable regression of target lesions despite the appearance of new lesions [27]. There was a marked difference in ORR depending on the line of treatment; ORR in patients previously untreated for metastatic disease was 26% (95% CI, 9–51%), compared to 4% in the second-line setting (95% CI, 0–18%), and 8% in patients who had received three or more lines of therapy (95% CI, 3–17%). The median OS at a median follow-up of 15.2 months was 9.3 months (95% CI, 7.0–12.6 months). The OS rate was 41% at 1 year (95% CI, 31–51%) and 22% at both 2 and 3 years (95% CI 12–32%). Remarkably, OS for the 11 patients with an objective response (CR or PR) was 100% at 2 years. TRAEs were frequent (observed in 63% of patients); the most common were pyrexia, fatigue, and nausea, which were typically grade 1–2 and easily managed. Eleven percent of patients experienced grade ≥ 3 TRAEs, and there were two treatment-related deaths as assessed by the investigators (pulmonary hypertension and death not otherwise specified in a hospitalized patient). Exploratory biomarker analyses suggested that higher levels of TILs, and to a lesser extent PD-L1 positivity, are associated with a longer overall survival with atezolizumab monotherapy.

The combination of atezolizumab and nab-paclitaxel was evaluated for safety and clinical activity in a phase Ib study of patients with mTNBC unselected for PD-L1 expression [28]. Thirty-two patients were enrolled; median age was 55.5 years (range, 32–84 years), and patients could have received 0–3 prior lines of therapy. At time of data cutoff, confirmed ORR was 38% (95% CI, 21–56%) in the 32 patients evaluable for efficacy. Two additional patients had pseudoprogression; they developed new lesions and were scored as PD based on RECIST (Response Evaluation Criteria in Solid Tumors), but had partial responses in target lesions and remained on treatment with prolonged biologic response. In the PD-L1+ cohort, ORR was 36% (95% CI, 11–69%) compared to 30% (95% CI, 7–65%) in the PD-L1-negative cohort. Grade 3 or 4 hematologic AEs was observed in 56% of patients; however, these were manageable and did not require treatment discontinuation. No DLT or treatment-related deaths occurred. Based on these results, the combination of atezolizumab and nab-paclitaxel is currently being investigated in the IMpassion 130 trial, a phase III randomized, double-blind, placebo-controlled study for the first-line treatment of patients with mTNBC [29]. The phase III NeoTRIPaPDL1 study is evaluating the combination of nab-paclitaxel and carboplatin with or without atezolizumab for patients with locally advanced TNBC in the neoadjuvant setting; primary endpoint is EFS ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02620280) identifier: NCT02620280). A single arm, phase II clinical trial assessing the safety and efficacy of atezolizumab in combination with paclitaxel, trastuzumab, and pertuzumab in patients with locally advanced, unresectable, or metastatic HER2+ breast cancer has recently started enrolling patients ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03125928) identifier: NCT03125928).

Avelumab (MSB0010718C) is a fully human anti-PD-L1 IgG₁–κ monoclonal antibody that is currently FDA-approved for advanced urothelial carcinoma and Merkel cell carcinoma. In

the phase Ib JAVELIN solid tumor trial, avelumab was investigated in locally advanced or metastatic breast cancer refractory to standard of care therapy [30]. Patients were unselected for PD-L1 expression or breast cancer subtype. A total of 168 patients were enrolled, with median age 55 years (range, 31–81 years). The population was heavily pretreated, with 52.4% of patients having had ≥ 3 prior lines of therapy. Fifty-eight of 168 patients (34.5%) had TNBC; 43% had HR+/HER2-negative disease; 15.5% had HER2+ disease; and 7% had disease of unknown molecular subtype. The ORR for the entire cohort was 4.8% (95% CI, 2.1–9.2%), with 1 CR and 7 PR; 5 of the 8 responses were ongoing at the time of data cutoff. Stable disease was observed in 39 patients (23.2%) for an overall DCR of 28%. In the TNBC subgroup ($n = 58$), there were 5 PRs for an ORR of 8.6% (95% CI, 2.9–19.0%). In contrast, the response rates in the HR+/HER2-negative ($n = 72$) and HER2+ ($n = 26$) cohorts were 2.8% (95% CI, 0.3–9.7%) and 3.8% (95% CI, 0.1–19.6%), respectively. Among TNBC patients with ≥ 10% PD-L1 + immune cells within the tumor, so-called immune cell “hotspots,” 44.4% (4 of 9) had a response to therapy (PR). TRAEs were observed in 71.4% of patients; the most common were fatigue, nausea, and infusion-related reactions. Grade ≥ 3 TRAEs occurred in 14.3% of patients, and included fatigue, anemia, increased GGT, autoimmune hepatitis, and arthralgias. There were two treatment-related deaths (acute liver failure and respiratory distress).

10.5 Conclusions

A subset of breast cancer is clearly immunogenic. The observations that some tumors are characterized by dense lymphocytic infiltration and expression of PD-L1 led to the investigation of immune checkpoint inhibition in advanced breast cancer. Immune checkpoint inhibition has demonstrated modest single agent activity in advanced breast cancer. While overall response rates are relatively low, the responses observed are remarkably durable, and therapy is well tolerated with mild and easily manageable side effects. Response correlates with TIL density, and the highest response rates have been observed in TNBC, particularly in the frontline setting. PD-L1-positivity enriches for responders, but is not a consistent predictor of response. Initial studies of immune checkpoint inhibitors in combination with chemotherapy for early stage disease have demonstrated promising efficacy, but also an increased incidence of immune-related toxicity. While treatment with immune checkpoint inhibitors clearly benefits subsets of patients, more precise biomarkers of response are needed, as well as strategies to increase response rates. A number of randomized phase II and III clinical trials of PD-1/PD-L1 inhibitors in combination with chemotherapy, targeted therapies, radiotherapy, and other immune checkpoint inhibitors are underway, and based on the promising results observed to date, immune checkpoint inhibitors are likely to gain regulatory approval for breast cancer in the near future.

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