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# Immunotherapy for breast cancer

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**Abstract**

Immunotherapy is revolutionizing the management of multiple solid tumors, and early data have revealed the clinical activity of PD-1/PD-L1 antagonists in small numbers of metastatic breast cancer patients. Clinical activity appears more likely if the tumor is triple negative, PD-L1+, and/or harbors higher levels of TILs. Responses to atezolizumab and pembrolizumab appear to be durable in metastatic triple negative breast cancer (TNBC), suggesting these agents may transform the lives of responding patients. Current clinical efforts are focused on developing immunotherapy combinations that convert non-responders to responders, deepen those responses that do occur, and surmount acquired resistance to immunotherapy. Identifying biomarkers that can predict the potential for response to single agent immunotherapy, identify the best immunotherapy combinations for a particular patient, and guide salvage immunotherapy in patients with progressive disease are high priorities for clinical development. Smart clinical trials testing rational immunotherapy combinations that include robust biomarker evaluations will accelerate clinical progress, moving us closer to effective immunotherapy for almost all breast cancer patients.

**Introduction**

Breast cancer remains a significant threat to the health and wellness of women in the United States, accounting for 30% of all new cancer diagnoses and almost 41,000 deaths annually(1). Although advances in early detection and therapy have resulted in a 38% decrease in the breast cancer death rate, almost all patients who develop metastatic disease will succumb to it. These sobering data illustrate a critical need for innovative approaches to breast cancer therapy that reduce relapse and death due to this disease. In recent years, accumulating data support a key role for the immune system in determining both response to standard therapy and long-term survival in breast cancer patients. Both these data and the striking clinical success of immune checkpoint antagonists across multiple solid tumors have re-ignited interest in immune-based strategies for breast cancer treatment and prevention.

The aim of the study about an over view that the Immune checkpoint blockade has shown promise for breast cancer treatment.

**Materials and Methods**

Department of Oncology, Sidney Kimmel Comprehensive Cancer Center and Bloomberg Kimmel Institute for Cancer Immunotherapy, Johns Hopkins University School of Medicine, Baltimore, MD 21231, USA supported by Breast Cancer Research Foundation, and the Bloomberg

Foundation, approved that the Immune checkpoint antagonists specific for CTLA-4, PD-1, and PD-L1 have revolutionized cancer therapy. Although several drugs are now FDA-approved for multiple cancers, none has yet been approved for breast cancer. Even so, the CTLA-4 antagonists tremelimumab and ipilimumab have been tested in small breast cancer trials, with evidence of immune modulation.

**Results**

CTLA-4 Blockade in Breast Cancer: CTLA-4 is up regulated shortly after T cell activation, binding CD80/CD86 to provide negative feedback to CD28 co-stimulation and limiting T cell activation during the priming phase of the immune response. This helps to prevent uncontrolled immunity. Two humanized monoclonal antibodies specific for CTLA-4 are in the clinic (5).

PD-1/PD-L1 Blockade in Breast Cancer: The programmed cell death-1 (PD-1) receptor is upregulated on activated T cells and binds two known ligands, PD-L1 and PD-L2. Through interactions with PD-L1 on the surface of tumor cells and immune cells, PD-1 signaling counters T cell activation during the effector phase of the immune response (3). Metastatic breast cancer responds to treatment with humanized monoclonal antibodies that target PD-L1 (avelumab and atezolizumab) and PD-1 (pembrolizumab) (3). Side effects associated with the use of these agents in breast cancer to date have been consistent with those expected for the drug class. These data are summarized in table 1.

Table 1

PD-1/PD-L1 Blockade in Metastatic Breast Cancer

| **Antibody** | **Target** | **Combination** | **Breast cancer subtype** | **Patients** | **ORR** | **DCR** |
|---|---|---|---|---|---|---|
| Avelumab | PD-L1 | Single agent | All | 168 | 4.8% | 28% |
| | | | PD-L1+ All | 12 | 33.3% | NR |
| | | | TNBC | 58 | 8.6% | 32% |
| | | | PD-L1+ TNBC | 9 | 44.4% | NR |
| | | | PD-L1− TNBC | 39 | 2.6% | NR |
| Pembrolizumab | PD-1 | Single agent | PD-L1+ TNBC | 27 | 18.5% | 26% |

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|---|---|---|---|---|---|---|
| | | Single agent | TNBC<br>PD-L1+ TNBC<br>PD-L1− TNBC | 170<br>105<br>64 | 4.7%<br>4.8%<br>4.7% | 7.6%<br>9.5%<br>4.7% |
| | | Single agent | PD-L1+ TNBC, 1st line | 52 | 23.1% | NR |
| | | | PD-L1+ ER+ HER-2- BC | 25 | 12% | 20% |
| Atezolizumab | PD-L1 | Single agent | TNBC | 112 | 10% | 23% |
| | | | PD-L1+ TNBC | 71 | 13% | 27% |
| | | | PD-L1− TNBC | 37 | 5% | 16% |
| Atezolizumab | PD-L1 | Nab-paclitaxel | TNBC | 32 | 38% | NR |
| Pembrolizumab | PD-1 | Eribulin | TNBC | 39 | 33.3% | 41% |

**Abbreviations:** PD-1=programmed death-1; PD-L1=programmed death ligand-1; ORR=overall response rate; DCR=disease control rate; NR=not reported; TNBC=triple negative breast cancer; ER=estrogen receptor; HER-2=human epidermal growth factor receptor-2.

## Discussion

The results, I mentioned in the table above which I have explained in the discussion. I want to inform you that these results were agreed by most research which have been done before. There are no differences between them.

CTLA-4 Blockade in Breast Cancer:

**Tremelimumab**: The anti-CTLA-4 agent tremelimumab remains investigational in every tumor type. Escalating doses of tremelimumab have been tested with concurrent exemestane in 26 patient s with ER+ HER-2- breast cancer. Five patients had dose limiting toxicity (DLT), which included diarrhea (4 counts) and elevated serum transaminase levels (1 count). The maximum tolerated dose (MTD) was 6 mg/kg every 90 days. The best response was stable disease (SD) for ≥12 weeks in 42% of patients, and a significant increase in the ratio of ICOS+/FoxP3+ CD4+ T cells was observed in most patients (4).

**Ipilimumab**: Ipilimumab is currently approved as a single agent for early and late stage melanoma, and is under investigation in multiple other tumor types both as a single agent, and in combination with PD-1/PD-L1 blockade (4). A study in breast cancer evaluated a single dose of neoadjuvant ipilimumab alone or given with cryoablation in 12 patients with early breast cancer prior to

mastectomy; 6 additional patients received pre-operative cryoablation alone. Combination immunotherapy induced circulating T helper type 1 cytokines, ICOS+Ki67+CD4+ and ICOS+Ki67+CD8+ T cells, and an increased CD8+ T cell/FoxP3+ T reg ratio within the tumor. Clonally expanded TILs (detected by deep sequencing of TCR DNA) correlated with the TIL score by H&E (1). Based on these promising results, a follow up study is evaluating cryoablation combined with CTLA-4 (ipilimumab 1 mg/kg) and PD-1 blockade (nivolumab 3 mg/kg) (4).

PD-1/PD-L1 Blockade in Breast Cancer:

**Avelumab**: was evaluated in multiple tumor types in the Phase Ia/1b JAVELIN study. The Phase 1b portion of this trial enrolled 168 patients in a breast cancer-specific expansion cohort regardless of either disease subtype or PD-L1 expression. The subtype distribution was 42.9% ER+/PR+/HER-2- disease, 34.5% TNBC, and 15.5% HER-2+ breast cancer; the disease subtype was unknown in 7.1% of patients. Over half of the patients had ≥3 prior lines of therapy for metastatic disease. The overall response rate (ORR) for the entire cohort was 4.8%, and included 1 complete response (CR), 7 partial responses (PRs), and 39 patients with stable disease (SD) for a disease control rate (DCR) of 28%. Responses were observed in all breast cancer subtypes, but appeared to be higher in TNBC. 58 patients showed an ORR of 8.6%, with 0 CRs, 5 PRs, and 13 patients with SD, and a DCR of 31%; PD-L1 expression was evaluable in 136 patients; 12 patients had ≥10% PD-L1+ immune cells in the TME, and 124 had <10%; the PR rates in these two groups were 33.3% and 2.4% respectively. In 48 TNBC patients evaluable for PD-L1 expression, 9 were PD-L1+ and 39 were PD-L1−, with ORRs of 44.4% and 2.6% respectively (4).

**Atezolizumab:** A Phase 1a study evaluated single agent atezolizumab in multiple tumor types, enrolling 115 patients with TNBC. PD-L1 expression was assessed using the SP142 antibody, where tumors were positive if they had ≥5% PD-L1+ tumor-infiltrating immune cells. Enrollment was initially restricted to PD-L1+ patients, and subsequently opened to patients with any level of PD-L1 expression. Ultimately, 63% of patients were PD-L1+, 33% of patients were PD-L1−, and 4% of patients had unknown PD-L1 status. Patients were generally heavily pretreated, with a median of 7 prior lines of therapy; 17% of enrolled patients received atezolizumab as their first line therapy for metastatic disease. The ORR in 112 evaluable patients was 10%, with an ORR of 13% in PD-L1+ patients and 5% in PD-L1− patients. Although numbers are small, the ORR in patients treated first line was 26%, whereas the ORR in patients treated second and third line was 4–8%. The DCR was 23% in all patients, 27% in PD-L1+ patients, and 16% in PD-L1− patients (4).

**Pembrolizumab:** has been evaluated in several clinical trials that demonstrated its safety and clinical activity in multiple tumor types. KEYNOTE-012 was a Phase Ib study that evaluated pembrolizumab monotherapy in advanced PD-L1+ TNBC. Tumor PD-L1 expression was evaluated by the 22C3 antibody, with staining in ≥1% of tumor cells or any PD-L1 expression by immune cells defined as positive. Of 111 patients pre-screened for PD-L1 expression, 58.6% (65 patients) were PD-L1+; 32 patients were enrolled and treated. Patients had a median of 2 prior lines of chemotherapy for metastatic disease, with 25% having ≥5 prior lines of therapy. In 27 patients evaluable for efficacy, the ORR was 18.5%, with 1 CR, 4 PRs, and 7 patients with SD; the DCR was 25.9%. The median OS was 10.2 months, and the OS rate at 1-year was 41.1%. The median duration of response (DOR) had not yet been reached. The KEYNOTE-086 Phase 2 trial evaluated pembrolizumab monotherapy both as salvage treatment for previously treated patients with metastatic TNBC expressing any level of PD-L1 (Cohort A), and as first-line therapy for patients with metastatic PD-L1+ TNBC (Cohort B). In Cohort A, 170 patients were enrolled and treated; about 62% (105 patients) had PD-L1+ TNBC, and over 40% of patients had been treated with ≥3 prior lines of therapy. Clinical activity was modest, with no apparent impact of PD-L1 expression level on clinical benefit (ORR of 4.7%-4.8%, PFS of 1.9–2.0 months, and OS of 8.3–10.0 months). Early analyses suggest longer OS at 9 months for patients with a CR or PR (100%) relative to patients with SD (89.6%) or PD (39%), similar to atezolizumab. Notably, the ORR for the 52 patients in Cohort B was higher than for patients overall, at 23.1%. This is also consistent with the atezolizumab data, where responses in metastatic TNBC appear to be highest when given first-line, and/or in PD-L1-selected patients. The KEYNOTE-119 Phase 3 trial, comparing pembroblizumab with chemotherapy of physician's choice, continues to accrue patients (4).

The evaluation of PD-1/PD-L1 agents in other breast cancer subtypes has been limited, but single agent pembrolizumab was evaluated in a small cohort of advanced ER+ HER-2- breast cancer as part of the KEYNOTE-028 study. Of 248 patients prescreened for PD-L1 expression, 19.4% (48 patients) had PD-L1+ tumors. Of these, 25 patients were enrolled and treated. All had received at least one prior line of therapy for metastatic disease, and 44% had received ≥5 lines of prior therapy. The ORR was 12%, with 0 CRs, 3 PRs and 4 patients with SD; the clinical benefit rate (CBR) was 20%. All responding patients had been on study for at least 26 weeks at the data cut-off (4).

**Conclusions**

Immune checkpoint blockade has shown promise for breast cancer treatment, illustrating the potential of harnessing the immune system for clinical benefit in this disease. Antagonists of the PD-1/PD-L1 pathway can induce durable clinical responses in some breast cancer patients with metastatic TNBC. Both validation of these early findings and efforts to extend immunotherapy to patients with HER-2+ and luminal breast cancer are underway. Personalized immunotherapy strategies that utilize vaccines that deliver tumor-specific neo-antigens and/or immune modulating agents chosen based on the immunologic milieu of a given tumor are under rapid development. Developing biomarkers that predict response and resistance to therapy, and identifying environmental modifiers of immunity (the microbiome, metabolic and hormonal parameters, and concurrent drug therapy) are areas of growing investigation. Both of these approaches currently are being explored as potential strategies for the treatment of breast cancer.

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