Introduction

The role of immune system in treating cancer is being increasingly seen as important [1]. Cancer cells have oncogenic mutations and express neo-antigens that make them distinct from normal cells thus prone to immune recognition. However, cells of innate and adaptive immune system which recognize and destroy these cells are held in check by various molecular pathways called “immune checkpoints” [2]. Attempts have been made to block these immune checkpoints to develop anticancer immunotherapies. Blockage of Cytotoxic T Lymphocyte Antigen 4 (CTLA4) and Programmed Death 1 (PD1), the first 2 checkpoint receptors to be discovered, has been studied widely in various cancers. Bristol Myers Squibb (BMS)’s ipilimumab, a monoclonal antibody against CTLA4, was efficacious and produced a durable response against melanoma. It was approved as the standard treatment for melanoma [3-5]. BMS's nivolumab, Merck's pembrolizumab, and Roche's atezolizumab are monoclonal antibodies against PD1 (nivolumab, pembrolizumab) or PD Ligand 1 (PD-L1) (atezolizumab). They are efficacious in various malignancies including melanoma, kidney cancer, non-small cell lung cancer; urothelial cancer; and colon cancer [6-17].

PD-L1 expression has been suggested as a predictive biomarker for these antibodies but due to lack of a single standardized assay for measuring the expression of these surface proteins and lack of consistency in trial design across different antibodies, data supporting the predictive value of PD-L1 expression are not uniform [18].

PD1/PD-L1 in Breast Cancer

Ghebeh et al. published data on PD-L1 expression in breast cancer in [19]. They evaluated the presence of PD-L1 in either tumor cells or tumor infiltrating lymphocytes in primary breast cancers by immunohistochemistry (IHC) [19]. A large scale pooled analysis of almost 4000 primary breast cancer samples from 3 different studies also showed PD-L1 expression of >1% of immune cells in 6% of tumors [20]. However, only 1.7% tumors expressed PD-L1 in >1% of tumor cells. Subset analysis in the study showed that the breast cancers with core basal phenotype have higher PD-L1 expression. In tumor cells, 8% of the samples had more than 1% of PD-L1 expression. In immune cells, it was seen in 18.5% of the samples [20]. As core basal phenotype has a strong association with triple negative breast cancer (TNBC), this data suggested potential role of immune checkpoint inhibitors in TNBC [21]. Analysis of The Cancer Genome Atlas data demonstrated higher PD-L1 mRNA expression in breast tissue specimens from patients with TNBC (n=120) compared to patients with non-TNBC (n=716) [22]. In the study, immuno-histochemical stain for PD-L1 expression was performed on a tissue microarray. It comprised of 105 tumors from early stage triple negative breast cancer patients that had not received neo-adjuvant chemotherapy. PD-L1 expression, defined as > 5% membranous staining, was identified in 20 (19%) of the tumors in the study [22]. Additionally, TNBCs have the highest frequency of tumor infiltrating lymphocytes (TILs) [23]. The higher incidence of PD-L1 expressing cells (both immune and tumor cells) and the higher incidence of TILs in TNBC, has led to studies assessing efficacy of immune checkpoint inhibition in this type of breast cancer.

Checkpoint Inhibition in Metastatic Triple Negative Breast Cancer

KEYNOTE-012, a multicenter, nonrandomized phase Ib trial of single-agent pembrolizumab was done among patients with...
advanced PD-L1-positive (expression in stroma of ≥1% of tumor cells by immunohistochemistry) TNBC, gastric cancer, urothelial cancer, and head and neck cancer [24]. Among 27 women with TNBC, the overall response rate was 18.5%. Disease control rate, defined as complete response (CR), partial response (PR) or stable disease (SD) for at least 24 weeks, was seen in a 25% of patients. The 6-month progression free survival (PFS) was observed in 25% of patients. The median duration of response was not reached by the time of data analysis. The duration of response ranged from 15 to >47.3 weeks. Based on historical data, the median duration of disease control in metastatic TNBC with first line, second and third line standard cytotoxic chemotherapy was 12 weeks, 9 weeks and 4 weeks respectively [25]. This study showed a promising disease control rate with pembrolizumab with acceptable safety and tolerability profile in a heavily pretreated TNBC patient population [24].

Keynote 086 (cohort A), a phase II trial assessed the safety and the efficacy of pembrolizumab in previously treated metastatic TNBC regardless of PD-L1 expression. Primary outcome was overall response rate for up to 24 months. Sixty percent of the patients had PD-L1 positive tumors. After a median follow-up of 11.9 months among 170 patients, the overall response rate was 5% and the disease control rate was 8%. The response rate was similar between PD-L1 positive and negative tumors. The median PFS and the overall survival (OS) were 2.0 months (95% CI 1.9-2.0) and 8.9 months (95% CI 7.2-11.2). Six months of PFS and OS were seen in 12% and 69% patients respectively [26]. Cohort B of KEYNOTE 086 assessed the safety and antitumor activity of pembrolizumab as first-line therapy for patients with PD-L1 positive metastatic TNBC.

After a median follow-up of 7 months in 52 enrolled patients, the overall response rate was 23%, the median PFS was 2.1 months (95% CI, 2.0-3.9); the estimated 6-month PFS rate was 29% and the median duration of response was 8.4 months [27]. Though full manuscripts are awaited for Keynote 086 studies, these presented data show promising antitumor activity and disease control in previously untreated metastatic PD-L1 positive TNBCs.

Schmid et al. evaluated atezolizumab in a cohort of 115 metastatic TNBC patients in a Phase Ia study (NCT01375842) for long-term clinical outcomes (CR, PR and SD for > =12 weeks) and biomarkers [28]. Baseline PD-L1 expression on tumor infiltrating immune cells (IC) was centrally scored as IC0/1/2/3 based on VENTANA SP142 assay. Enrollment was initially limited to TNBC patients with PD-L1 expression in ≥ 5% of tumor-infiltrating immune cells (IC2/3), and then opened to all TNBC patients regardless of PD-L1 status. Atezolizumab was well tolerated. The overall response rate in 1st line and subsequent line therapies was 26% and 11% respectively. The overall response rate (ORR) for PD-L1 IC2/3 patients was 17% vs 8% in IC0/1. The median duration of response was 21.1 months. The overall survival rates in all patients at 1, 2, and 3 years were 41%, 22%, and 22%, respectively. This study showed that atezolizumab has acceptable safety profile and promising antitumor activity with durable responses in both 1st line and subsequent lines of therapy. Also, ORR was higher among tumors with high PD-L1 expressing immune cells. But this study and earlier mentioned Keynote 086 are early phase single arm studies. Phase III randomized studies are underway to establish the clinical benefit of these agents in metastatic TNBCs (Table 1).

**Table 1:** List of ongoing phase III clinical trials assessing checkpoint inhibitors in TNBC in metastatic and perioperative settings.

<table>
<thead>
<tr>
<th>Trial Number</th>
<th>Study Overview</th>
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<tbody>
<tr>
<td>NCT02555657</td>
<td>A randomized open-label phase III study of single agent pembrolizumab versus single agent chemotherapy per physician’s choice for metastatic triple negative breast cancer</td>
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<tr>
<td>NCT02819518</td>
<td>A randomized, double-blind, phase III study of pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple negative breast cancer</td>
</tr>
<tr>
<td>NCT03036488</td>
<td>A phase III, randomized, double-blind study to evaluate pembrolizumab plus chemotherapy versus placebo plus chemotherapy as neo-adjuvant therapy and pembrolizumab versus placebo as adjuvant therapy for triple negative breast cancer</td>
</tr>
<tr>
<td>NCT02954874</td>
<td>A randomized, phase III trial to evaluate the efficacy and safety of pembrolizumab as adjuvant therapy for triple negative breast cancer with ≥1 cm residual invasive cancer or positive lymph nodes (ypn+) after neo-adjuvant chemotherapy</td>
</tr>
<tr>
<td>NCT03125902</td>
<td>A phase III, multicenter, randomized, double-blind, placebo-controlled study of atezolizumab in combination with paclitaxel compared with placebo with paclitaxel for patients with previously untreated inoperable locally advanced or metastatic triple negative breast cancer</td>
</tr>
<tr>
<td>NCT02425891</td>
<td>A phase III, multicenter, randomized, placebo-controlled study of atezolizumab in combination with nab-paclitaxel compared with placebo with nab-paclitaxel for patients with previously untreated metastatic triple negative breast cancer</td>
</tr>
<tr>
<td>NCT03197935</td>
<td>A phase III randomized study to investigate the efficacy and safety of atezolizumab in combination with neo-adjuvant anthracycline/nab-paclitaxel-based chemotherapy compared with placebo and chemotherapy in patients with primary invasive triple negative breast cancer</td>
</tr>
<tr>
<td>NCT02620280</td>
<td>A phase III neo-adjuvant study of atezolizumab in triple negative locally advanced breast cancer undergoing treatment with nab-paclitaxel and carboplatin</td>
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Novel Approaches in Cancer Study

Checkpoint Inhibition in Adjuvant/Neo-adjuvant Setting for Triple Negative Breast Cancer

I-SPY 2 is a multi-center, phase 2, platform trial that evaluates novel neo-adjuvant therapies; the primary endpoint being the pathological complete response (pCR). The result from I-SPY 2 studying pembrolizumab plus standard neo-adjuvant therapy for high-risk breast cancer was presented at ASCO annual meeting 2017 [29]. Enrolled patients in the study had clinically or radiologically measurable disease in the breast after diagnostic biopsy, defined as ≥ 2.5 cm by exam or ≥ 2 cm by imaging; eligible patients also had to meet one of the following criteria: stage II/III, or T4/anyN/M0 (including clinical or pathologic inflammatory cancer or regional stage IV disease, where supraclavicular lymph nodes are the only sites of metastasis). The patients were randomized to either weekly paclitaxel x 12 or with pembrolizumab prior to surgery followed by doxorubicin/cyclophosphamide x 4 cycles in the adjuvant setting. The study showed that the patients with locally advanced TNBC or hormone receptor (HR)-positive/HER2-negative breast cancer had an increase in the estimated pCR rate in pembrolizumab arm. In TNBC, there was nearly threefold increase in patients who achieved pCR (60% vs 20%). Similar benefit was seen in patients with HR-positive/HER2-negative breast cancer (34% vs 13%) and in all HER2-negative patients (46% vs 16%). The safety profile of pembrolizumab was consistent with that observed in previously reported studies across tumors. The results of this study show potential promise for the anti PD1 therapy in combination with cytotoxic chemotherapy in a neo-adjuvant setting in high-risk locally advanced breast cancers especially in TNBC. Further studies are currently underway assessing the benefit of checkpoint inhibitors in TNBC in adjuvant/neo-adjuvant settings (Table 1).

Conclusion

Anti PD1 and anti PD-L1 therapies have shown to have antitumor activity and durable responses in metastatic breast cancer. The best efficacy has been seen in patients with TNBCs. Similarly, in neo-adjuvant setting, results are encouraging with the highest responses seen in TNBC. Pembrolizumab has shown to produce a 3 fold increase in the pathological CR when used in combination with weekly paclitaxel in high risk locally advanced TNBCs. It is unclear if PD1 expression or other biomarkers will be predictive for response to this class of agents; this is an area of intensive research. Pembrolizumab, nivolumab, atezolizumab, durvalumab, ipilimumab and tremelimumab are being tested in phase I/II studies as single agents or in combinations in patients with high risk or metastatic breast cancer. We will await the results of these studies to determine how this class of drugs can be best used to maximize the efficacy in breast cancer patients.

Conflict of Interest

Ajay Dhakal MMBS and Nibash Budhathoki MBBS: None
Mateusz Opyrchal MD, PhD: Has received research fund from Pfizer.

References


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