PD-1 and PD-L1 Immune Checkpoint Blockade to Treat Breast Cancer

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The PD-1-blocking antibodies pembrolizumab and nivolumab obtained Food and Drug Administration (FDA) approval for the treatment of advanced melanoma in 2014, and of non-small-cell lung cancer (NSCLC) in 2015 [3–7].

As breast cancer is also capable of stimulating immune responses, targeting the immune system is an encouraging strategy for its treatment. Triple-negative breast cancer (TNBC) in particular seems highly immunogenic because tumor-infiltrating lymphocytes (TILs), which have been demonstrated to positively correlate with response to cytotoxic therapy and prognosis, are predominantly present within hormone receptor (HR)-negative subtypes [8–11]. Encouraging results from phase I trials using checkpoint inhibitors directed against PD-1/PD-L1 have been reported, and phase II and III trials are currently ongoing. In this review, we aim to summarize recent data on PD-1/PD-L1 antibodies to treat breast cancer. While our focus lies on clinical experience and challenges, we also cover the underlying preclinical rationale of these highly promising agents.

Introduction

The immune system plays an integral role in cancer development and therefore potentially offers novel targeted therapies. Complex interactions of tumor cells, immune effector cells, stromal cells, and soluble factors are crucial for disease progression and/or eradication of tumor cells [1]. Hence, the modulation of immunogenic regulators (checkpoints) is a promising approach to treat malignant disease [2]. The programmed death receptor-1 (PD-1) and its ligand, PD-L1, are increasingly recognized as powerful targets to enhance tumor-directed cytotoxic T-cell function.

Biology and Preclinical Rationale of Targeting PD-1 and PD-L1

Although the immune system protects its host against malignant tumor cells, it can also promote cancer development by selecting for tumor cell clones that escape immune surveillance [12, 13]. Interaction between cancer progression and immune response occurs in 3 phases. In the initial elimination phase, an acute inflammatory response activates immune effector cells (macrophages, dendritic cells, natural killer cells) that migrate into the tumor microenvironment. However, some tumor cell clones may still survive (immunosurveillance), shifting inflammation to a chronic equilibrium phase that may last for a period of many years. Finally, the tumor escapes from immune detection (escape phase), result-
PD-1 is an immune checkpoint receptor that is expressed by activated lymphocytes (T and B cells, natural killer cells, monocytes, dendritic cells, myeloid cells, thymocytes). Interaction with its ligands PD-L1 or PD-L2 induces a negative control signal that limits T cell activity. PD-L1 suppresses autoimmunity and is constitutively expressed by T and B cells, dendritic cells, macrophages, mesenchymal stem cells, and mast cells [14]. It is also upregulated in multiple solid malignancies including breast cancer [15–18]. Figure 1 illustrates a condensed snapshot of the complex interaction between PD1 and PD-1/PD-L1 that occurs at multiple steps of an antitumor immune response and enables tumor cells to evade the immune defense [19].

Preclinical in vivo models have shown that blocking the PD-1/PD-L1 axis promotes T cell-mediated antitumor immune activity and that PD-1-deficient mice develop various spontaneous autoimmune diseases [20–22]. A number of antibodies directed against PD-1 (nivolumab, pembrolizumab, pidilizumab, PDR001) or its ligand PD-L1 (atezolizumab, durvalumab, avelumab, BMS-936559) are currently under clinical investigation. Table 1 summarizes ongoing clinical trials, identified at ClinicalTrials.gov.

There are several reasons why most current trial protocols focus on TNBC:
- PD-L1 expression is highest in TNBC (approximately 20–30% of all TNBCs express PD-L1) [15, 23].
- A significant infiltration of TILs that facilitate immune response has been reported in TNBC [8–11, 24–26].
- Loss of PTEN correlates with HR-negative breast cancer and leads to upregulation of PD-L1 [27, 28].
- TNBC is associated with a higher mutational burden that can produce immunogenic neoantigens [27, 29].
- Apart from chemotherapy, treatment alternatives for TNBC are limited, which is in contrast to HR-positive or human epidermal growth factor receptor 2 (HER2)-positive breast cancer.

Clinical Experiences in Targeting PD-1 and PD-L1 for Breast Cancer Treatment

The humanized monoclonal antibody pembrolizumab is highly selective for PD-1. KEYNOTE is a series of clinical trials to determine whether pembrolizumab is effective in the treatment of various cancers. In the phase I trial KEYNOTE-12, Nanda et al. [30] recently found clinical activity and an acceptable safety profile of pembrolizumab given intravenously at 10 mg/kg every 2 weeks to women with PD-L1-positive TNBC. The expression rate for PD-L1 was 59% and 32 patients were enrolled. Only 5 patients (16%) had toxicities grade ≥ 3. Although most patients were heavily pretreated, the overall response rate was 19%, with durations of response of up to 47 weeks (median duration not yet reached). Currently, there are ongoing phase II (KEYNOTE-86, NCT02447003) and phase III clinical trials (KEYNOTE-119, NCT02555657) that will evaluate pembrolizumab as a monotherapy for TNBC, while other phase I–III studies investigate the combination of pembrolizumab with chemotherapy (table 1).

Atezolizumab (MPDL3280A) is a humanized monoclonal antibody that binds to PD-L1. Emens et al. [31] presented results of a phase I trial in patients with metastatic TNBC. Atezolizumab administered at 15 mg/kg, 20 mg/kg, or a 1200-mg flat dose every 2 weeks was well tolerated, and only 11% of a heavily pretreated population experienced adverse events of grade ≥ 3 (adenal insufficiency, neutropenia, nausea, vomiting, and 1 pulmonary hypertension event in a patient with an atrial septal defect). Among 21 patients whose data were ready for efficacy evaluation at the time of data presentation, 3 patients had partial remission and 2 patients had complete remission. Additionally, 3 patients appeared to have progressive disease but later showed evidence of durable nonclassical responses (‘pseudoprogression’). Overall, the 24-week progression-free survival rate was 33%.

Adams et al. [32] investigated the combination of nanoparticle albumin-bound paclitaxel (nab-paclitaxel; 125 mg/m², days 1, 8, 15, q4w) with atezolizumab (800 mg, q2w) in 32 patients with metastatic TNBC. The most common treatment-related toxicity was neutropenia (53% all grades; 41% grade 3–4). No dose-limiting toxicity or drug-related deaths occurred. Among the 24 patients who were evaluable at the time of data analysis, 1 had complete remission and 16 had partial response. In addition, 3 patients developed new lesions and were therefore scored as having progressive disease, but remained on treatment with prolonged biologic response. Treatment efficacy was observed in both PD-L1-positive and PD-L1-negative patients. An ongoing phase III trial (IMpassion) is currently evaluating the combination of atezolizumab and nab-paclitaxel in previously untreated patients with metastatic TNBC (NCT02425891).
Avelumab (MSB0010718C) is a human anti-PD-L1 antibody. In a phase 1 trial, presented by Dirix et al. [33], 168 patients with metastatic or advanced breast cancer of any subtype received 10 mg/kg avelumab every 2 weeks. Adverse events of any grade occurred in 71% of the patients, with fatigue (20%), nausea (14%), and infusion-related reactions (12%) being the most common. 14% of the patients experienced toxicities of grade $\geq 3$ (fatigue, anemia, increased γ-glutamyl transferase (GGT)/autoimmune hepatitis, and...
Clinicians should be aware of the toxicity profile of PD-1 checkpoint inhibitors to avoid delay in diagnosis and treatment [34]. irAEs can affect any organ system, but typically include the skin, the gastrointestinal (GI) tract, and the hepatic, endocrine and respiratory systems [35]. Other rare events such as uveitis, pancreatitis, hematological events, neurologic adverse events, and nephritis have also been reported [36–40]. In general, irAEs are manageable by the use of immunosuppressive therapy (e.g., glucocorticoids) without impeding the antitumor response. Whether checkpoint blockade can trigger an underlying autoimmune disorder is unclear as these patients have been excluded from clinical trials.

The spectrum of immune-related adverse events (irAEs) differs from the toxicity known from other anticancer drugs. Although the huge majority of events are mild (grade 1–2) and reversible, clinicians should be aware of the toxicity profile of PD-1 checkpoint inhibitors to avoid delay in diagnosis and treatment [34]. irAEs can affect any organ system, but typically include the skin, the gastrointestinal (GI) tract, and the hepatic, endocrine and respiratory systems [35]. Other rare events such as uveitis, pancreatitis, hematological events, neurologic adverse events, and nephritis have also been reported [36–40]. In general, irAEs are manageable by the use of immunosuppressive therapy (e.g., glucocorticoids) without impeding the antitumor response. Whether checkpoint blockade can trigger an underlying autoimmune disorder is unclear as these patients have been excluded from clinical trials.

The patterns of response to immune checkpoint blockade may differ from classical response criteria, such as the Response Evaluation Criteria in Solid Tumors (RECIST) [2]. The time to achieve clinical response to treatment may be prolonged and can manifest after an initial increase in tumor burden or the onset of new tumor lesions [48]. In contrast to chemotherapy, where stable disease is often regarded as transient, achievement of stable disease by the use of immunotherapeutic agents may be viewed as an indicator of a meaningful therapeutic effect [49]. Therefore, Wolchok et al. [49] and Nishino et al. [50] proposed guidelines for the evaluation of immune therapy activity in solid tumors. These immune-related response criteria continue to be refined, and further prospective evaluation is warranted.

In the era of precision oncology, predictive factors that forecast the efficacy of immune checkpoint therapy are essential to identify patients who are most likely to benefit from PD-1/PD-L1-directed therapy. Additionally, biomarkers that monitor tumor-specific immune responses as well as irAEs are warranted. A recent meta-analysis of patients with malignant melanoma or NSCLC demonstrated a significant association of PD-L1 expression and response to PD-1/PD-L1-directed treatment [51]. Nevertheless, PD-L1-negative patients may still respond to PD-1 blockade. Therefore, assessment of PD-L1 expression to identify patients for PD-1/PD-L1-directed therapy should be considered with caution and is not yet ready for clinical routine [2]. Biological and technical challenges have to be considered and standardization is required as different irAEs can affect any organ system, but typically include the skin, the gastrointestinal (GI) tract, and the hepatic, endocrine and respiratory systems [35]. Other rare events such as uveitis, pancreatitis, hematological events, neurologic adverse events, and nephritis have also been reported [36–40]. In general, irAEs are manageable by the use of immunosuppressive therapy (e.g., glucocorticoids) without impeding the antitumor response. Whether checkpoint blockade can trigger an underlying autoimmune disorder is unclear as these patients have been excluded from clinical trials.

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antibodies and cut-off values have been used for immunohistochemistry (IHC) staining in recent trials [14]. Furthermore, PD-L1 expression is a dynamic marker which can change in response to disease progression and treatment [52, 53]. Examples of other biomarkers that are currently under investigation are mutational load, neoantigens, the presence of TILs, inflammatory gene signatures, and blood-based immune biomarkers [16, 54–57].

Combination approaches, such as adding other immunotherapeutic, cytotoxic, or targeted agents to PD-1/PD-L1 antibodies may enhance checkpoint inhibition. However, it is still unclear if any specific combination is superior to single-agent treatment [2]. The optimal dose and schedule of immune checkpoint blockade need to be determined in future clinical trials.

Conclusions

Early clinical trials of using antibodies directed against PD-1 and PD-L1 to treat breast cancer patients demonstrated exciting clinical activity. However, given the complexity of breast cancer biology and immune responses to breast cancer, many questions remain to be answered. Examples are optimal dosing, scheduling, combination approaches, response criteria, and biomarkers for immunotherapy. Clinical experience with respect to the management of irAEs is warranted. As immunotherapies may establish durable long-term disease control, this approach holds great promise to significantly improve the outcome of breast cancer patients.

Disclosure Statement

All authors declare that they have no conflicts of interest.

References


