

# Immune checkpoint inhibitor therapy for breast cancer

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## Abstract:

Breast cancer is a common malignancy among women, with a reported incidence rate of 7-10% among all types of malignant tumors. Heredity frequently contributes to its incidence, and the prevalence typically increases with age, peaking in women between the ages of 40 and 60. Immune checkpoint inhibitors are a type of molecule that can activate the immune cells to enhance the host immune system to fight cancer. With these inhibitors, immune checkpoint inhibitor therapy (ICIT) aims to block the inhibitory signal of immune cell activation by antibodies or chemicals to promote an anti-tumor immune response, which lets immune cells recognize and kill cancer cells more effectively. This article offers crucial insights into immune checkpoint inhibitor therapy, outlining its principles and diverse applications.

Moreover, it delves into the findings derived from previous clinical trials of immune checkpoint inhibitors, analyzing the collected data. Specifically, the article will extensively examine the role of immune checkpoint inhibitor therapy in the context of breast cancer treatment.

By summarizing existing examples of immune checkpoint inhibitor therapy and their outcomes, the article aims to evaluate the feasibility of employing this therapeutic approach in breast cancer treatment.

**Keywords:** Immune checkpoint inhibitors; Immune checkpoint inhibitor therapy; Breast cancer; PD-1/PD-L1 blocker.

## 1. Introduction

Breast cancer is the most prevalent form of cancer in females, while it is less frequently observed in men. Thanks to technological developments, breast cancer has become one of the most effectively curable types of solid tumors [1]. Many carcinogenic causes cause the uncontrolled growth of mammary epithelial cells. Annually, there are 2.3 million newly diagnosed instances of breast cancer worldwide, resulting in 420,000 deaths. This is a 2% increase each year. Among women in industrialized countries like Western Europe and North America, breast cancer has the highest occurrence rate. With the highest incidence rate, the United States has the greatest number of cases of breast cancer, making it the most common cancer among women and the second most significant contributor to cancer-related fatalities. The lifetime incidence rate of breast cancer in women is 1 in 7, meaning that 1 out of every seven women will acquire breast cancer.

Furthermore, the likelihood of experiencing risk grows as one gets older. China, previously characterized by slow economic expansion, has had a consistent yearly growth rate of 4.6 percent over the past two decades [2]. Urban areas in China, particularly coastal cities, have a higher prevalence of this condition compared to rural and inland

regions. In major cities like Beijing and Shanghai, it is the most common type of tumor among females, whereas in rural areas, it ranks as the fifth most prevalent. According to statistics, breast cancer causes the deaths of more than 40,000 women every year in China. This highlights the importance and severity of the disease for women [3]. The initial phase of the disease commonly presents breast masses, nipple discharge, enlargement of axillary lymph nodes, and other symptoms.

In contrast, the advanced stage can result from the spread of cancer cells to distant sites and the development of lesions in many organs, posing a direct threat to the lives of patients. Immune surveillance is a vital process in which the human immune system identifies and removes cancer cells [4]. Nevertheless, cancer cells can adopt diverse ways to avoid immune identification and elimination, resulting in the formation and advancement of tumors [4]. Of them, the activation and recruitment of immune cells are crucial in inhibiting tumor growth [5]. T cells play an important role in the immune system's reaction to cancer and are important in inhibiting the growth of tumors [6]. To elicit an immunological response against tumors. Three essential elements in the process are the initiation of tumor-directed T cell production, the activation of T cells

inside the tumor microenvironment, and the stimulation of T cells to eliminate tumor cells. In the absence of any of the three categories, three distinct cancer-immune phenotypes may arise: the immunological desert phenotypes, the immune excluded phenotypes, and the immune inflamed phenotypes. There are three distinct phenotypes. They will reveal their issues, such as immunological desert phenotypes and poor T cell production, which are connected to immunologic ignorance or the inability to properly initiate and activate T cells. T lymphocytes can infiltrate tumor microenvironments due to immune-excluded characteristics. Probably associated with the production of immunosuppressive cytokines and the infiltration of barriers into the tumor site.

Tumor immune-inflamed phenotypes are characterized by the infiltration of the immune system into the tumor. Several factors are likely to be connected, as indicated by a reference [7]. Through the process of identifying these characteristics, we are able to recognize and stimulate the immune response that fights against tumors. Furthermore, it is possible to establish a method that is both efficient and long-lasting in eliminating tumors [7]. Immune checkpoint inhibitor therapy is a cancer treatment that harnesses the body's immune system to fight against cancer [8]. Its mechanism of action involves the inhibition of immunological checkpoints, which are proteins that typically hinder the immune system from targeting healthy cells. Immune checkpoint inhibitors enhance the immune system's ability to identify and kill cancer cells by obstructing these checkpoints [9]. Immunotherapy using immune checkpoint inhibitors has greatly revolutionized the field of cancer treatment and has been authorized for various types of cancer, including melanoma, breast cancer, and others. It has demonstrated exceptional effectiveness in certain patients, resulting in long-lasting responses and enhanced rates of survival. This article primarily focuses on the present state of immune checkpoint inhibitor therapy for breast cancer.

## **2. Immune checkpoint inhibitor therapy (ICIs)**

Immune checkpoints are inherent components of the immune system [10]. Their role is to inhibit the immune response from reaching a level of intensity that would destroy healthy cells in the body. Immunological checkpoints are activated when T cells recognize and bind to partner proteins in other cells, including specific tumor cells. The proteins in question are referred to as immunological checkpoint proteins [10]. When the checkpoint and chaperone proteins form a complex, they inhibit the signaling pathway in T cells. This hampers the immune

system's capacity to eliminate cancer cells. Immune checkpoint inhibitors work by inhibiting the interaction between checkpoint proteins and their respective partner proteins. This interrupts the signaling process, so enabling the T cells to eliminate the cancer cells. Immune checkpoint inhibitor therapy is a form of cancer treatment that enhances the immune system's ability to identify and combat cancer cells with greater efficiency [11]. Immune checkpoint inhibitor therapy provides several notable benefits in the treatment of cancer, including long-lasting responses, enhanced survival rates, a broader range of effectiveness, and efficacy against several forms of cancer [11]. Although ICIs have been highly successful, patients who have received this treatment may experience concomitant symptoms. Based on a reexamination conducted between 2010 and 2019 [12], it was found that patients diagnosed with melanoma who received at least one immune checkpoint inhibitor (ICI) treatment and subsequently experienced a recovery from grade 3 to 4 ICI-induced hepatitis. A total of 102 individuals diagnosed with melanoma experienced high-grade ICI hepatitis, whereas 32 patients received ICI retreatment. Out of the total number of persons, 48% (15 individuals) experienced immune-related adverse events (irAE). However, only six patients had to stop taking ICI medication because of the severity of these adverse events. Recurrent hepatitis was observed in 4 out of the 6 cases. Patients who were not required to stop immune checkpoint inhibitor (ICI) treatment were far less likely to be prescribed ipilimumab compared to anti-PD-1 or anti-PD-L1 monotherapy.

Additionally, the likelihood of reconsidering the need for their initial ICI treatment was dramatically decreased. No noticeable differentiation was detected between patients who had rechallenge and those who did not undergo rechallenge in terms of their ideal overall response or time to death. Therefore, patients who have recovered from grade 3 to 4 ICI hepatitis and have melanoma can resume ICI therapy without significant danger, but there is a slight level of risk. The impact of ICI retreatment on clinical outcomes remains uncertain. Between December 2011 and September 2019, Massachusetts General Hospital documented that 4683 individuals underwent ICI therapy [13]. A total of 317 patients experienced oral problems, with 68.5% reporting xerostomia, 33.4% reporting abnormalities, and 24% reporting dysgeusia. Oral side effects seem to be more prevalent than what is reported in news articles. Additional investigation is required to have a comprehensive understanding of the nature and biological processes underlying oral immune-related adverse events (irAEs).

### **3. ICIs for breast cancer**

Traditional treatment methods, such as surgery, radiation therapy, and chemotherapy, have limitations in efficiently treating metastatic breast cancer. Immunotherapy, a therapeutic approach that harnesses the body's immune system to fight against cancer, has emerged as a promising technique for the treatment of breast cancer. Some breast cancers are thought to stimulate the immune system. According to research, lymphatic infiltration has been found in some breast cancer tumor cells, and their features are numerous and dense. Immunotherapy, whether administered independently or in combination with chemotherapy, has shown positive therapeutic results. It can effectively treat various types of cancer, such as lung cancer, resulting in enhanced progression-free survival (PFS) and overall survival (OS). Triple-negative breast cancer (TNBC) is a specific kind of breast cancer characterized by the absence of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2) expression [14]. This means that hormone therapy and HER2-targeted therapies, which are effective treatment options for other breast cancer subtypes, are not effective for TNBC. Recently, the use of ICIs for the treatment of breast cancer has become an active area of research since it can more effectively activate the immune cells, especially the T cells. It has emerged as a promising therapeutic approach in breast cancer treatment, particularly in certain subtypes, such as TNBC, where the immune response plays a significant role. One of the famous strategies for ICIs is the blockade of the PD-1/PD-L1 signal pathway.

#### **3.1 PD-1 blocker**

In recent years, immuno-oncology therapy has become one of the most important ways to treat cancer. Immunology oncology therapy does not attack tumor cells directly but activates the human body's immune system to attack tumor cells. We guarantee its safety and tolerability. Since 2014, the world's first PD1 inhibitor has been born, marking a breakthrough in tumor immunotherapy. PD-1's full name is Programmed Death 1. It is a member of the CD28 family and is mainly expressed in activated T, B cells, and monocytes [15]. It was discovered in 1992 by Professor Tasuku Honjo of Kyoto University in Japan. It can be found on the cell membrane of immune cells, specifically T cells and B cells [16].

Nevertheless, in the absence of activation, T cells do not display PD-1. PD-1 expression on the surface of T cells only occurs following their activation [16]. At present, a PD-1 inhibitor has been authorized for the therapy of tiny melanoma with early, incomplete tumor manifestations. Pembrolizumab is a humanized monoclonal anti-PD-1 an-

tibody. A study was conducted to examine the therapeutic impact of pembrolizumab on patients diagnosed with non-small cell lung cancer. The study involved a group of 495 individuals who had different forms of cancer. The overall remission rate among all patients was roughly 19%. The observed median response time was 12.5 months, but the median progression-free survival (PFS) was 3.7 months.

When specifically considering patients with non-small cell lung cancer, the rate of objective remission was 23.5%, which was significantly higher than the rate observed in other forms of cancer (18.7%). Another study conducted a clinical trial to evaluate the effectiveness and safety of pembrolizumab in combination with radiation therapy among patients diagnosed with metastatic TNBC [17]. This present study comprises a cohort of 17 patients whose ages range from 37 to 73 years. Pembrolizumab was given intravenously at a dosage of 200 mg over 3 days. The treatment has been repeated three times every three weeks since the progression of the disease happened. The observation period was 13 weeks. The overall remission rate for the entire group was 17.6% (3 out of 17 patients), consisting of 3 complete responses, one patient with stable disease, and 13 patients with progressing disease. Eight patients died within 13 weeks. Among the nine women who were assessed using RECIST at week 13, three patients obtained a complete mitigation index, showing a 100% reduction in tumor volume outside of the irradiated portal. A total of eight patients expired within 13 weeks. The predominant grade 1 to 2 toxicity seen was dermatitis, with a prevalence of 29%. Pembrolizumab was responsible for four grade 3 adverse events, namely weariness, lymphocytopenia, and infection. There were no severe adverse events or deaths connected to the treatment recorded. The study's findings indicate that the administration of pembrolizumab in combination was determined to be safe.

#### **3.2 PD-L1 blocker**

PD-L1 (programmed cell death ligand), often referred to as CD274 or B7-H1, serves as the binding partner or ligand for PD-1. It is present in several cell types, including cancer cells, as well as certain normal cells, including endothelium cells and immune cells [18]. PD-L1 inhibitors hinder the binding between PD-L1 molecules in cancer cells and PD-1 molecules in T cells, hence impeding the inhibitory signals that dampen T cell activity. Atezolizumab, a kind of PD-L1 inhibitor, is a humanized monoclonal antibody developed by Roche as a PD-L1 blocker that was approved by the U.S. Food and Drug Administration (FDA) in 2016. Atezolizumab can connect with PD-L1 on tumor cells, blocking its interaction with T cells and antigen-presenting cell PD-1, thereby relieving PD-1-me-

diated immunosuppression and promoting T cells to attack tumor cells [19]. Research assessing the efficacy and cost-effectiveness of atezolizumab has been concluded, with a total of about 1244 patients participating in the trial. A partitioned survival model was employed to assess the cost-effectiveness. When comparing the results of utilizing nivolumab, a monoclonal antibody that attaches to the PD-1 protein, with atezolizumab, the hazard ratio for overall survival increased by 1.13 years and by 0.69 quality-adjusted life years (QALYs) with atezolizumab, surpassing the results of nivolumab. In addition, there is a cost increase of \$78,280 per patient. Ultimately, atezolizumab can be deemed cost-effective when used as the initial treatment for advanced or unresectable hepatocellular carcinoma in comparison to nivolumab. Atezolizumab has undergone clinical trials to assess its efficacy as a therapeutic option for breast cancer, predominantly when used in conjunction with chemotherapy or other targeted therapies. The majority of research has been on TNBC, as this particular subtype is recognized for its heightened immunogenicity and potential advantages from immune checkpoint blockade. In March 2019, the U.S. FDA swiftly approved atezolizumab for the treatment of inoperable locally progressed or spreading PD-L1-positive TNBC. The permission was granted based on the findings of the IMpassion130 research, and atezolizumab is recommended for usage in conjunction with nab-paclitaxel. Ongoing research is being conducted on the utilization of atezolizumab in breast cancer. Additional clinical studies are investigating its effectiveness and safety in different scenarios, such as early-stage TNBC and other subtypes of breast cancer.

#### 4. Summary

Immunotherapy with checkpoint inhibitors has shown promise as a treatment method for breast cancer, particularly for subtypes with limited treatment options or resistance to standard therapies. While the efficacy of immune checkpoint inhibitors has been more modest in breast cancer compared to other malignancies, ongoing research efforts are focused on optimizing their application and identifying patients most likely to benefit. TNBC, known for its immunogenic nature and high tumor mutational burden, has been the primary focus of immune checkpoint inhibitor trials. Monoclonal antibodies that specifically target the PD-1/PD-L1 pathway, such as pembrolizumab and atezolizumab, have demonstrated encouraging outcomes in treating TNBC. These antibodies can be used alone or in conjunction with chemotherapy. The FDA has given accelerated approval for atezolizumab, when used together with nab-paclitaxel, for treating TNBC that is unresect-

able, locally progressed, or metastatic, and is positive for PD-L1. However, the efficacy of immune checkpoint inhibitors in hormone receptor-positive and HER2-positive breast cancer subtypes has been limited, highlighting the need for further research to understand the mechanisms underlying their limited responses. Identifying reliable predictive biomarkers, optimizing combination strategies, and managing potential immune-related adverse events remain crucial challenges. Although the outcomes in treating breast cancer with immune checkpoint inhibitor medication have been limited thus far, there is potential for this treatment to effectively utilize the body's immune system, leading to long-lasting responses and increased survival rates in certain individuals. Ongoing clinical trials and continued research into tumor immunology, combination approaches, and patient selection strategies will be essential to fully realize the potential of immunotherapy in the treatment of breast cancer across all subtypes.

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