Proceedings of the 6th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/2026.33673

Checkpoint Inhibition Therapy and Triple Negative Breast Cancer

Man Sin Xiang

ShaTin College, Hong Kong, China
xiangms2009@gmail.com

Abstract. According to the Cambridge Dictionary, immunotherapy, or biotherapy, is defined as 'treatment that improves the ability of the immune system to fight diseases'. The method of immunotherapy relies heavily on the ability of our immune cells to recognize cancer cells. In recent times, immunotherapy research has advanced significantly for 'hot' tumors, but progress has been limited for 'cold' tumors. An example of cold tumors is breast cancer, the most common cancer that typically targets women. In 2022 alone, around 2.3 million girls were diagnosed, and over 670,000 deaths occurred due to breast cancer. The specific subtype of breast cancer on which this paper focuses is triple-negative breast cancer, a highly aggressive form that shows the most promise for immunotherapy. This paper has compiled the basic knowledge to understand why immunotherapy works, its application to cold tumors, specifically triple-negative breast cancer, and the future directions for improving biotherapy for cold tumors.

Keywords: Checkpoint inhibitors, Neoadjuvant treatments, Cancer adaptivity, Triple Negative Breast Cancer.

1. Introduction

Cancer is a genetic disease caused by mutations that cause uncontrolled cell growth in the human body. Naturally, with time, cells will undergo many different mutations, and one can only be aware that by chance one of these mutations can lead to cancer. This is also why senior citizens have a higher chance of cancer. In the late stages of any cancer, malignant tumors penetrate the circulatory system and grow in distant parts of the body, blocking essential bodily functions and causing organ failure. Immunotherapy is a type of treatment that aids the immune system in better targeting cancerous cells and more effectively eliminating the disease [1-3].

The earliest documented use of immunotherapy stems from Dr. William Bradley Coley, who found that his cancer patients who suffered a bacterial infection experienced tumor regression [4]. He then injected the bacteria, coined Coley's toxins, into other patients and found that the infection triggered an immune response which stimulated their immune cells to attack the tumors. Fast forward to the early 21st century, and pharmaceutical companies have developed three important types of immunotherapy: CAR-T cell therapy, checkpoint inhibitors, and, most importantly, cancer vaccines. There is a wide range of checkpoint inhibitors. Early examples include ipilimumab and nivolumab, but the most relevant to this discussion is pembrolizumab.

© 2026 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/2026.33673

Triple negative breast cancer (TNBC) is an aggressive, fast-growing subtype of breast cancer that accounts for roughly 15% of breast cancer patients. It is characterized by its negativity for progesterone receptors (PR), estrogen receptors (ER), and human epidermal growth factor receptors 2 (HER2) and has a large amount of biological heterogeneity [5]. Even with recent advancements, TNBC is recognized to have high recurrence, and standard treatment often is a mix of chemotherapy, radiation, and immunotherapy.

Despite the advancements in immunotherapies, cancers that don't present as many neoantigens, such as TNBC, continue to face challenges with this treatment, but it is possible, as shown in research papers such as Guo et al.: Tumor Microenvironment and Immunotherapy for Triple Negative Breast Cancer [5]. As of 2025, researchers are able to use high-throughput and artificial intelligence to design specific cancer vaccines that target an individual's unique cancer. In other words, research such as "Engineering Neoantigens to Form Immunogenic Biopolymer Particles to Target Metastatic Breast Cancer" demonstrates this approach.

2. The tumor microenvironment

Cancer has always been at the forefront of complex diseases to treat due to its being highly adaptable to its surroundings, giving it an advantage for avoiding detection by the immune system. The adaptations for its survival, which are mentioned in this paper, include uncontrolled cell proliferation, loss of apoptosis, angiogenesis, and metastasis.

2.1. Cell proliferation

Cell proliferation is the increase in cell number through the process of mitosis. At first, tumor cells experience hyperplasia, an increase in the number of cells in the tissue. The descendant cells appear normal and continue to grow until one of them undergoes a mutation that increases the speed of mitosis and causes the tissue to appear abnormal—in other words, dysplasia.

2.2. Loss of apoptosis

Apoptosis is programmed cell death. The loss of it is essentially how cancers become 'immortal'. Normal cells go through apoptosis after proteins trigger the cell's response to internally break down. A primary example of this is p53, which is normally suppressed by MDM2 (mouse double minute 2) protein. Under stress, p53 halts the cell cycle, allowing for DNA repair. If the damage is irreparable, p53 triggers apoptosis. If a cell doesn't have the gene to produce p53, it will continue to undergo mitosis even after its counterparts deteriorate. Eventually, however, a large number of these cells will experience a crisis, though a small fraction may escape and become 'immortal' [6]. Under normal circumstances, apoptosis is able to regulate and prevent the reproduction of damaged cells, leading to the prevention of cancer.

2.3. Angiogenesis

Angiogenesis is described as the growth of blood vessels from the existing vasculature. It is vital for growth and repair. Angiogenesis is essentially what allows tumors to have accelerated growth by providing the tumor with additional nutrients and oxygen. The primary chemical signal used by tumors to send signals is VEGF (vascular endothelial growth factor). As its name suggests, it is able to send signals to nearby endothelial cells, triggering a cascade of responses triggering vascular proliferation. In the diagram below, angiogenesis first starts with growth factors being sent out by

DOI: 10.54254/2753-8818/2026.33673

the tumor cell. Furthermore, the tumor cell also secretes MMPs (matrix metalloproteinases), which function to break down the basement membrane of the vessel, thereby exposing the lumen. Next, endothelial cells migrate along the angiogenic factor gradient and go through tube formation. VEGF further stimulates DLL4, preventing endothelial cells from proliferating.

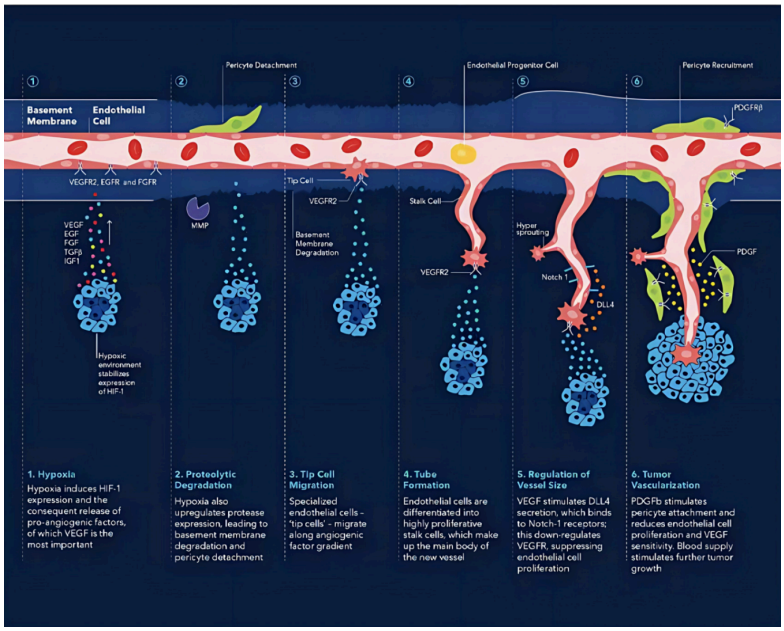


Figure 1. Step-by-step process showing examples of growth factors sent out by tumor cells, leading to a cascade of different signals, eventually leading to the formation of blood vessels [7]

2.4. Metastasis

Metastasis is the spread of cancer cells from the primary starting site to distant parts of the body through the circulatory system. This happens when tumor cells break off from the main tumor and are able to spread as the tumor actively breaks down the surrounding tissue in order to reach the main vessel. Metastatic cancer increases its chance of survival by gaining more resources throughout the body and increasing the rate of multiplication. It occurs in stages 3 and stage four of cancer. By migrating to different areas, the cancer is nearly impossible to remove using a surgical procedure. After metastasis, the cancer will become fatal by potentially blocking vital processes in different organs. After metastasization, tumors typically will like to infiltrate the lymph nodes as the lymph nodes act as a filtration and drainage system for the body. Most cancer-related deaths are due to vital organ failure following metastasis.

3. Cancer immunotherapies

Immune checkpoint inhibitors are the cornerstone of immunotherapy, primarily targeting the receptors PD-1 (programmed death-1) on T cells, PD-L1 (programmed death-ligand 1), and CTLA-4 (cytotoxic T-lymphocyte-associated protein 4). It is important to note that despite all of these proteins being a part of cancer immunotherapy, they may act in different stages, with PD-1 and PD-L1 being related to the elimination of cancer after activation, and CTLA-4 having to do with the activation of naive T-cells.

Dendritic cells are a subgroup of APCs (antigen presenting cell). They process antigens through the means of phagocytosis (the process of engulfing and digesting large pathogens),

DOI: 10.54254/2753-8818/2026.33673

macropinocytosis (constant sampling of their environment), and several other methods.These processes allow dendritic cells to produce antigen fragments that are later presented to naive T-cells to initiate T-cell activation.

4. Pembrolizumab

Pembrolizumab is a monoclonal antibody used to treat many forms of cancer, from melanoma to TNBC. It blocks the PD-1 pathway and allows the immune system to effectively kill tumor cells. PD-1 is used as an 'off switch' by normal cells, to prevent autoimmune attacks by making the T-cells excrete less cytokine production and reduce T-cell activation. Alongside the PD-1 and PD-L1, TCR (T-cell receptors) and MHC (major histocompatibility complex) on tumor cells have to bind to meet the requirements of this mechanism. Tumor cells may overexpress PD-L1, thereby increasing the chances of this interaction and enabling them to avoid immune detection.

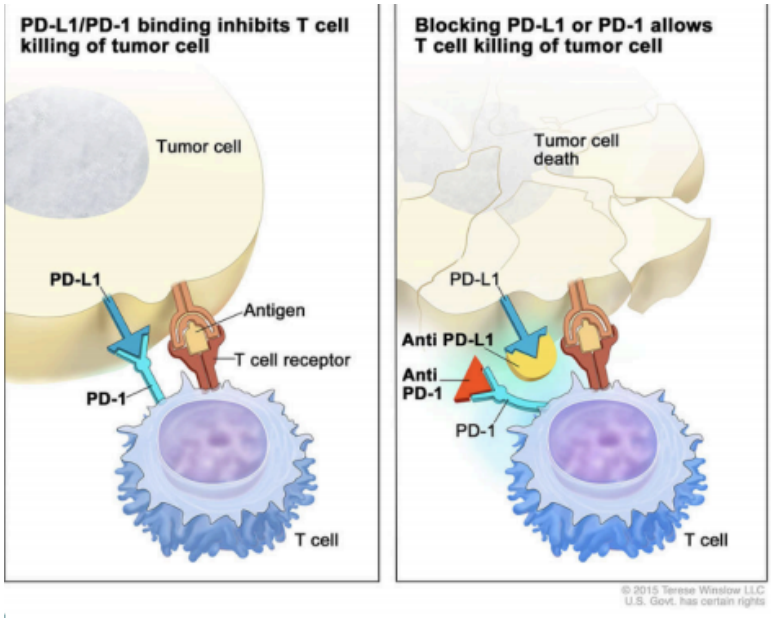


Figure 2. The PD-1 pathway is shown in blue. The MHC is presented as an antigen in the diagram. The bonding of PD-1 and PD-L1 triggers T-cell deactivation [8]

Whether or not PD-1 inhibitors work may rely on whether or not tumors express PD-L1. This is usually tested using samples of the tumor through histochemical methods, using dyes to identify the presence of PD-L1 on the surface of tumor cells.

5. Triple negative breast cancer

As mentioned previously, triple-negative breast cancer is distinguished by its absence of ER, PR, and HER2. Survival rates in TNBC depend on the stage of tumor development, and tumor recurrence is high. There's a strong link between the BRCA1 gene and the development of TNBC; Those with breast cancer who have this gene typically have TNBC. TNBC is diagnosed through imaging tests and biopsies.

Before treatments such as immunotherapy, TNBC was commonly treated with chemotherapy. Immunotherapy is becoming more common; patients with positive PD-L1 expression are able to use immune checkpoint inhibitors. However, even now, late-stage immunotherapy isn't plausible to late

DOI: 10.54254/2753-8818/2026.33673

stage metastatic TNBC. Despite this, immunotherapy can be applied alongside chemotherapy to more effectively target the cancer.

Studies show that the use of neoadjuvant therapy and PARP inhibitors (an enzyme involved in many cellular functions, including DNA repair) achieves higher rates of pathologic complete response.

6. Clinical study

Schmid et al.: Pembrolizumab for Early Triple Negative Breast Cancer provides evidence of the effectiveness of this treatment. The phase 3, double blind study randomly sorted patients into pembrolizumab-chemotherapy and placebo-chemotherapy groups. The pembrolizumab group had a significantly higher pathological complete response rate, demonstrating the study's efficacy.

The study was conducted from March 2017 through September 2018, where 1174 patients were assigned to a random group. Baseline demographics and disease characteristics were noted. PD-L1 status was tested at a central lab and was characterized according to the combined positive score or the number of PD-L1-positive TNBC cells. 83.7 percent of patients tested positive for PD-L1 on their tumor cells. In addition to testing PD-L1 positivity, the functionality of the patients was measured using the ECOG system. The range of the scale is from 0-5, where 0 is fully functional, 4 is completely disabled, and 5 is dead. Most participants (86.5%) scored 0, and the remaining scored 1.Throughout the study, adverse events were documented in 99 percent of pembrolizumab treatment patients and 100 percent in the placebo group. Adverse events ranged from anemia to rashes [9,10]. Similar numbers were documented between the groups, with the treatment group being arguably higher in some prospects.

The results showed that patients in the pembrolizumab group showed significantly higher pathological complete responses compared to the placebo group. This result was consistent throughout further subgroups, with PD-L1 expression being among them.

7. Conclusion

The findings of this study differ from the findings of previous studies, such as the IMpassion30 trial, which found efficacy in only patients who had PD-L1-positive expression.

Researchers in this paper concluded that it could be due to other variables, such as the different drugs administered or participant variablesSchmid et al. also discussed their findings in comparison with other studies, such as the phase 1b KEYNOTE-173 study and the I-SPY2 trial, which showed similar improvements in pathologic complete response rate with pembrolizumab.

Whilst the study was limited to a specific time, which was too limited to conclude definitive event-free survival, a large analysis was conducted that determined that pathological complete response was associated with long-term benefits. The limitations were confined to the duration of the experiment, as an optimum duration of the therapy wasn't determined.

These results may serve as one of the earlier stepping stones toward a better understanding of how to effectively treat later stages of this cancer. Further research can be extended to determine whether this efficacy continues in late-stage TNBC, particularly with the introduction of new technologies, such as cancer vaccines.

This conference paper aimed at investigating and explaining the key concepts involved in using the checkpoint inhibitor pembrolizumab in treating TNBC using scientific evidence from a study. The study reveal effectiveness of pembrolizumab in the early stages of TNBC, which may be used later on in the development of new and more advantageous neoadjuvant drugs for treating TNBC.

DOI: 10.54254/2753-8818/2026.33673

Overall, this conference paper provides an easily comprehensible introduction to the intricate fields of cancer immunology and TNBC more broadly, highlighting the importance of developing drugs that can treat this extremely common cancer and, hopefully, serve as a means to foster interest among younger students in further studying this complex subject.

References

[1] Cancer. (2026). https: //dictionary.cambridge.org/dictionary/english/cancer.
[2] World Health Organization: WHO & World Health Organization: WHO. (2025b, August 14). Breast cancer. https: //www.who.int/news-room/fact-sheets/detail/breast-cancer
[3] Cancer Research UK. (n.d.-b). Age and cancer | Cancer Research UK. https: //www.cancerresearchuk.org/about-cancer/causes-of-cancer/age-and-cancer
[4] Dobosz, P., & Dzieciątkowski, T. (2019). The Intriguing History of Cancer Immunotherapy. Frontiers in immunology, 10, 2965. https: //doi.org/10.3389/fimmu.2019.02965
[5] Guo, Z., Zhu, Z., Lin, X., Wang, S., Wen, Y., Wang, L., Zhi, L., & Zhou, J. (2024). Tumor microenvironment and immunotherapy for triple-negative breast cancer. Biomarker research, 12(1), 166. https: //doi.org/10.1186/s40364-024-00714-6
[6] Weinberg R. A. (1996). How cancer arises. Scientific American, 275(3), 62–70. https: //doi.org/10.1038/scientificamerican0996-62
[7] Angiogenesis in Cancer Guide (1st ed., 2024)..
[8] Immune checkpoint inhibitors. (2022, April 7). Cancer.gov. https: //www.cancer.gov/about-cancer/treatment/types/immunotherapy/checkpoint-in hibitors
[9] Zanna, M. Y., Yasmin, A. R., Omar, A. R., Arshad, S. S., Mariatulqabtiah, A. R., Nur-Fazila, S. H., & Mahiza, M. I. N. (2021). Review of dendritic cells, their role in clinical immunology, and distribution in various animal species. International Journal of Molecular Sciences, 22(15), 8044. https: //doi.org/10.3390/ijms22158044
[10] Schmid, P., Cortes, J., Pusztai, L., McArthur, H., Kümmel, S., Bergh, J., Denkert, C., Park, Y. H., Hui, R., Harbeck, N., Takahashi, M., Foukakis, T., Fasching, P. A., Cardoso, F., Untch, M., Jia, L., Karantza, V., Zhao, J., Aktan, G.... O'Shaughnessy, J. (2020b). Pembrolizumab for early Triple-Negative breast cancer. New England Journal of Medicine, 382(9), 810–821. https: //doi.org/10.1056/nejmoa1910549