IJMPR 2025, 9(3), 39-42

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article
SJIF Impact Factor: 6.669

A REVIEW ON PEMBROLIZUMAB IN TNBC

R. Harsha Sree[1*], K. Sravani[1], G. Imran[1], S. Aisha[1] and Dr. K. Thirumala Naik[2]

[1]*Pharm D. Interns, Krishna Teja Pharmacy college, Tirupati, Andhra Pradesh.
[2]Associate Professor & Clinical Preceptor, Krishna Teja Pharmacy College, Tirupati, Andhra Pradesh.

Article Received on: 27/12/2024
Article Revised on: 17/01/2025
Article Accepted on: 07/02/2025

***Corresponding Author**
R. Harsha Sree1
Pharm D. Interns, Krishna Teja Pharmacy college, Tirupati, Andhra Pradesh.

ABSTRACT

Triple-negative breast cancer (TNBC) is a highly aggressive subtype of breast cancer characterized by the absence of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2) as determined by immunohistochemistry (IHC). TNBC accounts for 15–25% of all breast cancer cases and is associated with unique molecular profiles, limited treatment options, and poor prognosis. Epidemiological studies highlight various risk factors, including prolonged oral contraceptive use, younger age at first childbirth, higher parity, and modifiable lifestyle factors such as body mass index and smoking. Pembrolizumab, a humanized monoclonal antibody targeting the programmed cell death protein 1 (PD-1) pathway, has emerged as a promising therapeutic option for TNBC. By blocking the PD-1/PD-L1 interaction, pembrolizumab reactivates T-cells to effectively target and eliminate tumor cells. Its efficacy has been demonstrated in multiple cancers, leading to FDA approval for advanced melanoma, non-small cell lung cancer (NSCLC), and other solid tumors, including TNBC. Administered intravenously at fixed doses, pembrolizumab offers convenience and cost-effectiveness compared to weight-based dosing. Adverse effects associated with pembrolizumab include immune-mediated reactions such as colitis, pneumonitis, endocrinopathies, and infusion-related hypersensitivity. Despite these risks, pembrolizumab represents a breakthrough in TNBC management by addressing its immune-evasive nature. Ongoing clinical trials continue to expand its therapeutic applications, providing hope for improved outcomes in this challenging cancer subtype.

KEYWORDS: Triple-negative breast cancer (TNBC), pembrolizumab, PD-1, PD-L1, immunotherapy, breast cancer, monoclonal antibody, immune checkpoint inhibitor.

TNBC

Triple-negative breast cancer (TNBC) is a subtype of breast cancer characterized by the absence of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2) as determined by immunohistochemistry (IHC). This cancer type is known for its aggressive nature, unique molecular profile, distinct patterns of metastasis, and lack of targeted therapies.[1,2]

EPIDEMOLOGY

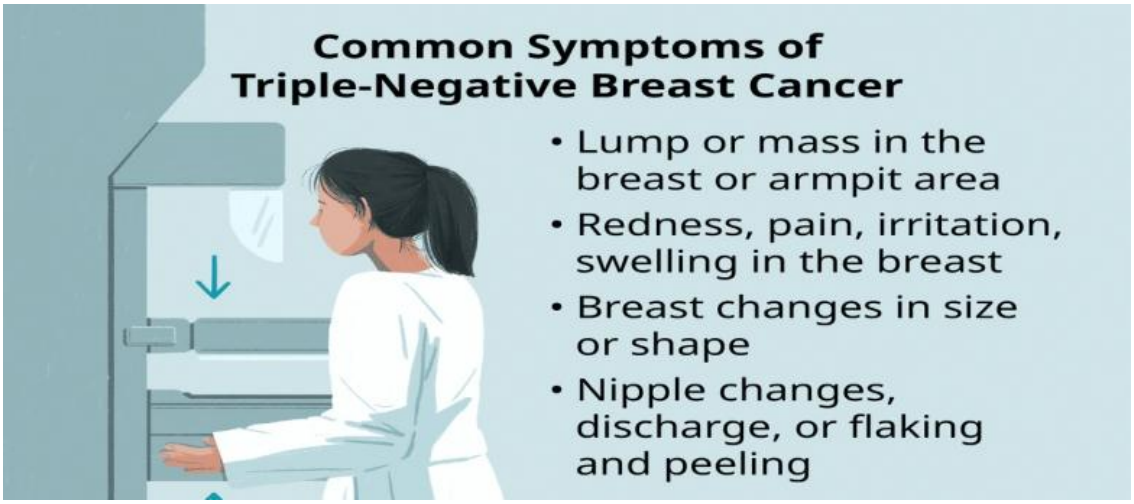
Triple-negative breast cancer (TNBC) accounts for 15–25% of all breast cancer cases. Epidemiological studies have shown that women who use oral contraceptives for more than one year have a 2.5% increased risk of developing TNBC, with the risk rising to 4.2% among women under the age of 40. The risk is further amplified with longer durations of oral contraceptive use. Additionally, higher parity (having more children) and a younger age at first childbirth may be associated with an increased risk of developing TNBC.[3,4]

RISK FACTORS OF TNBC

NON-MODIFIABLE RF	MODIFIABLE RF
• Age	• Body mass index
• Sex	• Physical activity
• Genetic mutations	• Alcohol intake
• Race/ Ethnicity	• Insufficient Vitamin Supplements
• Genetic history	• Exposure to chemicals & drugs
• Breast tissue density	• Smoking

• History of radiation therapy • History of breast diseases	• Intake of processed food[5]

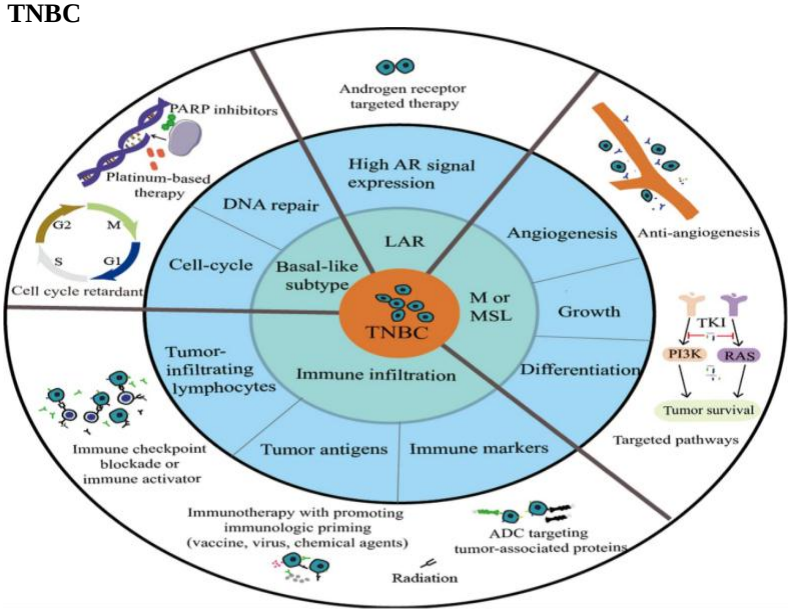
SIGNS AND SYMPTOMS OF TNBC



DIAGNOSIS

Triple-negative breast cancer (TNBC) is usually diagnosed with a lab test called immunohistochemistry (IHC). In practice, doctors often use a two-step process that includes imaging tests, like ultrasound or mammography, followed by IHC. These imaging tests can show the edges of the tumor but may not clearly show internal features like dead tissue (necrosis) or scarring (fibrosis), which are common in TNBC.[6]

MANAGEMENT OF TNBC



PEMBROLIZUMAB

Pembrolizumab is a highly selective, humanized monoclonal IgG4-kappa isotype antibody targeting PD-1. PD-1, expressed on antigen-stimulated T-cells, triggers downstream signaling that suppresses T-cell proliferation, cytokine release, and cytotoxic activity. Many tumors evade immune responses by expressing PD-1 ligands on their surface, thereby suppressing cytotoxic T-cell activity. Anti-PD-1 and anti-PD-L1 antibodies counteract this suppression, restoring T-cell function and inducing anti-tumor responses in patients with advanced solid tumors.[7]

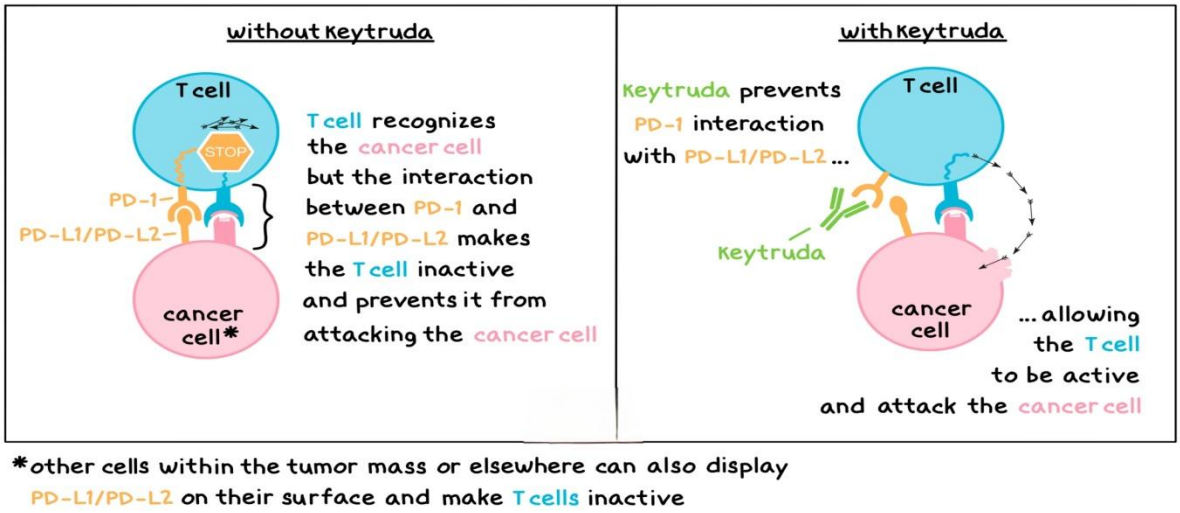
Mechanism of Action

Pembrolizumab is a humanized monoclonal antibody that targets PD-1, a receptor found on the surface of lymphocytes (a type of white blood cell). PD-1 acts as an "immune checkpoint," helping to prevent the immune system from attacking normal, healthy cells.

Some tumors take advantage of this checkpoint by producing high levels of PD-L1, a molecule that binds to PD-1. When PD-L1 connects with PD-1, it shuts down the T-cells, which are crucial for attacking and killing

harmful cells. This allows the tumor to escape immune detection and grow unchecked.

Pembrolizumab works by blocking the interaction between PD-1 and PD-L1. By preventing this connection, pembrolizumab reactivates T-cells, allowing them to recognize and attack tumor cells more effectively. This helps the immune system fight against cancer.[8,9]



Administration

Pembrolizumab is FDA-approved for intravenous administration and is available in two forms: a 50 mg lyophilized powder for reconstitution or a 25 mg/mL solution. The standard dosing schedule involves a 200 mg infusion administered over 30 minutes every three weeks. While most monoclonal antibodies are typically dosed based on body size, studies have demonstrated that fixed dosing of pembrolizumab provides sufficient therapeutic coverage. Fixed dosing also offers several advantages, including reduced risk of dosing errors, increased convenience, and minimized drug waste, which is particularly beneficial given the high cost of this therapy.[10]

Adverse Effects

Clinically significant adverse reactions associated with pembrolizumab include

- **Immune-mediated skin reactions:** Exfoliative dermatitis, bullous pemphigoid, Stevens-Johnson syndrome, and toxic epidermal necrolysis.
- **Immune-mediated endocrinopathies:** Thyroid disorders, type 1 diabetes, and hypophysitis.
- **Immune-mediated colitis.**
- **Immune-mediated pneumonitis.**
- **Immune-mediated hepatotoxicity/hepatitis.**
- **Immune-mediated renal dysfunction:** Including nephritis.
- **Infusion-related reactions:** Anaphylaxis and hypersensitivity.
- **Other immune-mediated reactions:** Guillain-Barré syndrome, uveitis, myasthenia gravis, pancreatitis, sarcoidosis, vasculitis, hemolytic anemia, arthritis, myositis, and encephalitis.[11,12]

Indications (FDA Approved)

Pembrolizumab, an FDA-approved monoclonal antibody targeting programmed cell death protein 1 (PD-1), is marketed in the United States. It initially gained FDA accelerated approval in September 2014 for the treatment of refractory, advanced melanoma. Since then, it has been approved for a variety of other oncologic conditions, with numerous additional indications currently under clinical investigation.

- Melanoma
- Non-Small Cell Lung Cancer (NSCLC)
- Head and Neck Squamous Cell Carcinoma (HNSCC)
- Renal Cell Carcinoma (RCC)
- Breast cancer
- Urothelial Carcinoma
- Others: Classical Hodgkin Lymphoma (cHL), Gastric Cancer, Cervical Cancer, Hepatocellular Carcinoma (HCC).
- Non FDA Approved indications: Nasopharyngeal cancer, Mesothelioma, Liver cancer, Esophageal cancer, Cutaneous squamous cell carcinoma, Colorectal cancer, Prostate cancer, Ovarian cancer [13].

DISCUSSION

Triple-negative breast cancer (TNBC) represents a challenging subtype of breast cancer characterized by the lack of estrogen, progesterone, and HER2 receptor expression, resulting in aggressive behavior, unique molecular profiles, and limited targeted treatment options. TNBC accounts for 15–25% of all breast cancer cases and is associated with specific epidemiological and reproductive risk factors, such as prolonged oral contraceptive use, higher parity, and younger age at first

childbirth. Diagnosis relies on immunohistochemistry (IHC) following imaging studies to confirm receptor absence, while conventional imaging techniques help assess tumor boundaries.

Despite advances in breast cancer management, TNBC treatment options remain limited, with chemotherapy being the mainstay. However, immunotherapies like pembrolizumab, a PD-1 inhibitor, have emerged as promising alternatives, particularly for advanced and metastatic cases. Pembrolizumab works by blocking the interaction between PD-1 on T-cells and PD-L1 on tumor cells, reactivating T-cells to recognize and attack the tumor. Administered intravenously, pembrolizumab is available in fixed doses, offering convenience and minimizing drug waste.

While pembrolizumab has demonstrated efficacy in treating TNBC and other cancers, its use is associated with immune-mediated adverse effects, including skin reactions, endocrinopathies, colitis, and pneumonitis, necessitating close monitoring. Since its initial FDA approval for advanced melanoma in 2014, pembrolizumab has expanded to treat various cancers, including breast cancer, with ongoing clinical trials exploring additional indications. The emergence of pembrolizumab in TNBC therapy underscores the potential of immunotherapy to improve outcomes in aggressive cancers lacking traditional targeted treatments.

CONCLUSION

triple-negative breast cancer (TNBC) remains a challenging and aggressive subtype with limited targeted therapies due to the absence of estrogen, progesterone, and HER2 receptors. Despite this, the development of immunotherapy, particularly pembrolizumab, offers promising new treatment options. Pembrolizumab's ability to reactivate T-cells by blocking the PD-1/PD-L1 interaction has shown efficacy in TNBC and other cancers, making it a valuable therapeutic tool. However, its immune-related side effects require close monitoring and management. As research continues, immunotherapies like pembrolizumab may significantly improve outcomes for patients with TNBC.

REFERENCES

1. Kartik Aysola Et al, Triple Negative Breast Cancer – An Overview, 2013.
2. Li Yin et al, Triple-negative breast cancer molecular subtyping and treatment progress, 2020; 22: 61.
3. Howard, F. M., and Olopade, O. I. (2021). Epidemiology of Triple-Negative Breast Cancer. Cancer J., 27: 8–16. doi:10.1097/ppo.0000000000000500.
4. Shona Nag Et al, Risk factors for the development of triple-negative breast cancer versus non-triple-negative breast cancer: a case–control study, 2023; 13: 13551.
5. Nahlah Makki Almansour Et al, triple negative breast cancer: a brief review about epidemiology, risk factors, signaling pathways, treatment and role of artificial intelligence, 25 january, 2022.
6. F. Penault-Llorca Et al, Pathological and molecular diagnosis of triple negative breast cancer: a clinical perspective, 2012; 19.
7. Caroline Robert Et al, Antiprogrammed- Death-Receptor-1 treatment with pembrolizumab in Ipilimumab- refractory advanced melanoma: A randomized dose comparison cohort of a Phase 1 trail, July 15, 2014.
8. Drew M. Pardoll Et al, The blockade of immune checkpoints in cancer immunotherapy, Nat Rev Cancer, 12(4): 252–264. doi:10.1038/nrc3239.
9. Loise M. Francisco Et al, The PD-1 Pathway in Tolerance and Autoimmunity, Immunol Rev, 2010 July; 236: 219–242. doi:10.1111/j.1600-065X.2010.00923.x.
10. Tomoko Freshwater Et al, Evaluation of dosing strategy for pembrolizumab for oncology indications, Freshwater et al. Journal for ImmunoTherapy of Cancer, 2017; 5: 43.
11. DANIEL L. SUZMAN Et al, FDA Approval Summary: Atezolizumab or Pembrolizumab for the Treatment of Patients with Advanced Urothelial Carcinoma Ineligible for Cisplatin-Containing Chemotherapy, 2019; 24: 563–569 www.TheOncologist.com
12. Sarah Tomassetti Et al, The role of pembrolizumab in relapsed/ refractory primary mediastinal large B-cell lymphoma, 25 October 2018.
13. James P. Flynn Et al, Pembrolizumab, June 26, 2023.