Journal on Oncology

www.journalononcology.org

Review Article

Open Access, Volume 3

Immunotherapy in Triple Negative Breast Cancer: Approved and in Development Anti PD-(L) 1

Briseño Nathael[1]; Ramírez Ramsés[1]; Vázquez Miguel A[2]; Alcaraz-Contreras Yolanda[1]*

[1]Department of Pharmacy, Division of Natural and Exact Sciences, University of Guanajuato, Mexico.

[2]Department of Chemistry, Division of Natural and Exact Sciences, University of Guanajuato, Mexico.

Abstract

Breast cancer is the most diagnosed cancer in women, it can be classified based on the expression of certain types of receptors. Triple Negative Breast Cancer (TNBC) is the least common subtype but with the worst diagnosis for patients because it is an aggressive cancer without expression of Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal Growth Factor Receptor 2 (HER2), for this reason its treatment is complicated. Nevertheless, immunotherapy represents a promising option for the treatment of TNBC due to its high rate of expression of Programmed Death Ligand 1 (PD-L1) and the increase in tumor infiltrating T cells. The use of antibodies that inhibit specific immune checkpoints represents a therapeutic option that contributes to the treatment of patients.

In this review we develop and highlight the importance of immunotherapy directed at PD1/PD-L, as well as a review of the clinical studies of two antibodies designed in recent years, atezolizumab and pembrolizumab which inactivate this signaling pathway and represent a substantial progress for the treatment of TNBC.

Keywords: Breast cancer; Triple negative breast cancer; PD-1/PD-L1 inhibitors; Atezolizumab; Pembrolizumab.

Abbreviations: TNBC: Triple Negative Breast Cancer; ER: Estrogen Receptor; PR: Progesterone Receptor; HER2: Human Epidermal Growth Factor Receptor 2; PD-1: Programmed Cell Death Protein 1; PD-L1: Programmed Death Ligand 1; BC: Breast Cancer; M: Mesenchymal; MSL: Mesenchymal Steam-Like; IM: Immunomodulatory; LAR: Luminal Androgen Receptor; OS: Improved Overall Survival; PFS: Progression-Free Survival; DFS: Disease Free Survival; iDFS: Invasive Disease-Free Survival; pCR: Pathological Complete Response.

Introduction

Breast Cancer (BC) has been growing in its incidence in the past years. "In 2020, there were 2.3 million women diagnosed with BC and 685,000 deaths globally" [1]. BC affects women in a major proportion. There are three types of BC: the first type expresses hormone receptors estrogen receptor (ER+) or Progesterone Receptor (PR+). The second type expresses Human Epidermal Receptor 2 (HER 2+) and the last one is the Triple Negative Breast Cancer (TNBC) (ER-, PR-, HER2-) [2]. TNBC has six subtypes, two Basal Like (BL1 and BL2), a Mesenchymal (M), Mesenchymal Steam-Like (MSL), Immunomodulatory (IM) and Luminal Androgen Receptor (LAR) [3] (Figure 1).

Manuscript Information: *Received: Jul 17, 2023; Accepted: Aug 11, 2023; Published: Aug 18, 2023*

Correspondance: *Yolanda Alcaraz-Contreras, Department of Pharmacy, Division of Natural and Exact Sciences, University of Guanajuato, Mexico. Email: yolaalca@ugto.mx*

Citation: *Nathael B, Ramírez R, Miguel VA, Yolanda AC. Immunotherapy in Triple Negative Breast Cancer: Approved and in Development Anti PD-(L) 1. J Oncology. 2023; 3(2): 1102.*

The factors that influence BC activation are not clearly described, however the most common subtype is hormone receptor positive with 60% of the documented cases, while HER2 positive has an incidence of 20% and TNBC as only 10-20%, which has the worst prognosis for the patient [2].

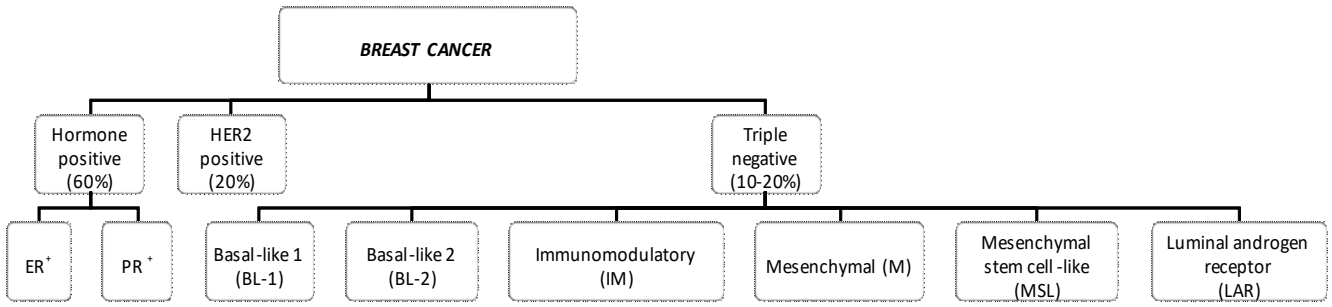

Figure 1: Breast cancer subtypes category.

Patients with BC have a big number of treatments, depending on the type of BC that they present. The pharmacotherapeutic approach can be based on the BC molecular characteristics with the objective of improving the specificity and prognosis of the patient [2].

Many treatments are approved by the US Food and Drug Administration (FDA), but for TNBC there are a few that are accepted, and others are in different investigation stages, one of the reasons is the unspecificity of chemotherapy. Scientists have researched different ways to attack TNBC, and one way to treat this condition is immunotherapy, in conjunction with chemotherapy [3].

TNBC treatment

Previously, the only treatment option for TNBC was surgery, radiotherapy, and chemotherapy. Nevertheless, these therapeutic approaches did not recognize the difference between cancer cells and normal cells, so they performed their effects on both and caused unnecessary adverse effects in the patient associated with their low specificity [4].

Traditional adjuvant or neoadjuvant chemotherapy for the treatment of TNBC is based on the administration of anthracyclines with cyclophosphamide, and some regimens include taxanes [5]. These schemes achieve a favorable response in approximately 40% of cases, while the use of platinum reaches 50% but has high toxicity.

In recent years, much research has been carried out with the objective of increasing the selectivity and effectiveness of treatment, as well as reducing damage to the patient. Based on research and reports, immunotherapy was developed [6].

Immune response

Our body has a natural way to protect ourselves from tumor cells, the responsible of this labor are T cells. They require two signals to attack damaged cells, the first is to recognize an antigen, then this is followed by CD28 costimulation.

Recent investigations suggest that some types of BC are immunogenically active and that some breast tumors have a substantial lymphocytic infiltrate [7]. The first attempt to modify the immune response in the research of a new treatment was blocking Cytotoxic T Lymphocyte-associated Antigen 4 (CTLA-4), this is a checkpoint in the cytotoxic T-lymphocyte response. Other T-cell checkpoints that modulate inhibitory signaling are programmed cell Death Protein 1 (PD-1), mucin-domain containing 3 (TIM-3) and Lymphocyte-Activation Gene-3 (LAG-3).

In recent years, many scientists have focused their investigations on the PD1/ Programmed Death Ligand 1 (PD-L1) pathway [8].

PD-1 and PD-L1 in cancer immunotherapy

Immune evasion is an adaptive mechanism developed by tumor cells that allows them to escape the immune system and consequently promote their survival and metastatic spreading [9], which results in a poor prognosis for the patient.

Recent studies have showed that tumor cells can express high levels of immune inhibitory signaling proteins as PD-L1, a transmembrane glycoprotein encoded by the Cd274 gen located on chromosome 9 in humans [10].

PD-L1 interacts with PD-1 and generates a negative costimulation of T cell activation and reduce the cytokine expression such as INF-Ɣ, TNF-α and IL-2, which plays a key role in activation of cellular immunity and subsequently, stimulation of antitumor immune-response [11].

In the tumor microenvironment, the binding of PD-1/PD-L1 causes the activation of an evasion mechanism of the immune system because it induces phosphorylation of tyrosine residues in the cytoplasm, decreasing the induction of apoptosis of tumor cells, inhibits secretion of granular enzymes, perforins and IFN-γ, IL-2 and TNF-α [3].

Discovery of this negative regulation pathway of T cell activation provides a new opportunity for clinical application in diverse advanced cancers, especially in patients with TNBC, with agonists and antagonists of PD-1. The use of antibody-based PD-1 and PD-L1 inhibitors in clinical studies have shown durable tumor remissions in patients with TNBC [12].

Monotherapy or combination therapy as adjuvants or neoadjuvants represents a promising clinical alternative for the treatment of TNBC due to the remarkable clinical response in these

patients. Nevertheless, these new strategies also are limited by the social and economic accessibility of the patients, as well as immune-related toxicity, innate and acquired drug resistance [12].

Immunotherapy is an ideal option for the treatment of TNBC, because it allows selective inhibition of specific immune checkpoints, such as the documented expression of PD-L1 in tumor or immune cells that allows it to evade the immune system [13].

Atezolizumab

Atezolizumab is a monoclonal antibody that blocks PD-L1 on tumor cells or tumor infiltrating immune cells. Atezolizumab, Tecentriq, Genentech Inc., on March 8, 2019, the Food & Drug Administration (FDA) granted accelerated approval in combination with paclitaxel protein-bound for adult patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 > 1%. This approval was based on a phase 3 study, IMpassion130 (NCT02425891), multicenter, double-blind, placebo-controlled study, with 902 participants randomized 1:1 in two-arm, for evaluated the efficacy, safety, and pharmacokinetics. The status of the study is completed on August 31, 2021. Clinical benefit was observed in patients who were treated with atezolizumab and nab-paclitaxel demonstrated improved Overall Survival (OS) and Progression-Free Survival (PFS) in both the Intention-To Treat (ITT) population and the subgroup of PD-L1 positive population [14]. The data of the second prespecified interim OS analysis showed that are consistent with the first interim OS analysis where although median OS in the ITT population was longer with Atezolizumab plus nab-paclitaxel than with placebo plus nab-paclitaxel, the significance boundary was not crossed. However, the magnitude of OS benefit with atezolizumab in PD-L1 positive patients remained clinically meaningful, with an increase of 7 months in median OS with atezolizumab plus nab-paclitaxel treatment. The updated PFS results in PD-L1 positive population showed an improvement of 2.2 months with atezolizumab plus nab-paclitaxel compared with placebo group [15].

IMpassion031 (NCT03197935), is a global phase 3, double blind, placebo-controlled study, with 333 participants randomized 1:1 in two arms, for evaluated the efficacy and safety of atezolizumab or placebo in combination with neoadjuvant chemotherapy with nab-paclitaxel followed by doxorubicin plus cyclophosphamide for the treatment of early-stage TNBC. Atezolizumab with chemotherapy demonstrated improved pathological complete response (pCR) in the ITT population in patients with early TNBC including patients with PD-L1 negative [16].

IMpassion131 (NCT03125902), multicenter, phase 3, double blind, placebo-controlled study, with 651 participants randomized 2:1 to receive atezolizumab or placebo plus paclitaxel in patients with previously untreated inoperable locally advanced or metastatic TNBC. This study was designed to evaluate the efficacy and safety of atezolizumab in combination with paclitaxel compared with placebo plus paclitaxel. The data of the primary PFS analysis showed that adding atezolizumab to paclitaxel did not show statistically significant improvement in investigator-assessed PFS in the PD-L1 positive population. Final OS results was 22.1 months in the atezolizumab plus paclitaxel group versus 28.3 months in the placebo plus paclitaxel group [17]. Do to treatment with atezolizumab combined with paclitaxel did not significantly reduce the risk of cancer progression and death, on September 8, 2020, the FDA alerted to health care professionals should not replace paclitaxel protein-bound with paclitaxel in clinical practice when use in combination with atezolizumab [18].

Pembrolizumab

Pembrolizumab, Keytruda manufactured by Merck Sharp & Dome Corp., is a monoclonal antibody that binds to the PD-1 receptor found on T cells and blocks its interaction with PD-L1 and PD-L2. On November 13, 2020, the FDA granted accelerated approval to pembrolizumab in patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 combined positive score (CPS) $\geq$10 [19]. This approval was based on KEYNOTE-355 (NCT02819518) a phase 3, double-blind, multicenter, placebo-controlled study, with 847 participants, in part 2, randomized 2:1 in two-arm, for evaluated the efficacy and safety of pembrolizumab or placebo plus chemotherapy (nab-paclitaxel; paclitaxel; or gemcitabine plus carboplatin). The data showed that pembrolizumab plus chemotherapy clinically meaningful improvement in OS and PFS, in participants with CPS $\geq$ 10 [20].

On July 26, 2021, FDA approved pembrolizumab for high-risk, early-stage TNBC in combination with chemotherapy (carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide) as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery [21]. This approval was based on KEYNOTE-522 (NCT03036488) a phase 3, double-blind, multicenter, placebo-controlled study, with 1174 participants randomized 2:1 in two arms. In the first interim analysis, in first 602 participants randomly, neo-adjuvant pembrolizumab in combination with chemotherapy followed by adjuvant pembrolizumab improved in pCR (64.8% versus 51.2%) compared with the neoadjuvant placebo in combination with chemotherapy followed by placebo after surgery [22].

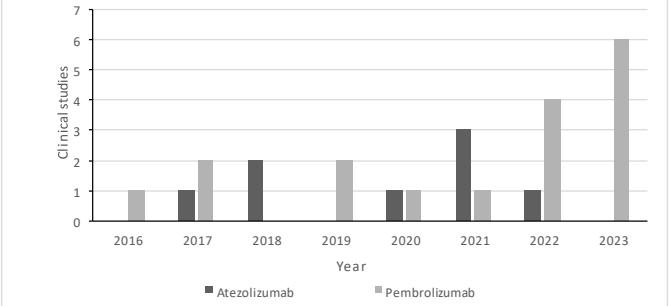

Figure 2: Clinical trials with atezolizumab or pembrolizumab intervention for patients with BC, and it start year since 2016 due July 2023 [23,24].

Ongoing clinical trials

Because patients with TNBC have high relapse rate and upon relapse the median overall survival is less than a year, treatment for the TNBC is the most challenging in comparison with breast cancer expressing hormone receptor or human epidermal receptor 2 [23]. Based on the available clinical evidence and the recent approvals for atezolizumab and pembrolizumab in TNBC, in Figure 2 we can observe the clinical trials that are proving atezolizumab or pembrolizumab as a treatment in conjunction with other interventions, in the last eight years. On the other hand,

there are many clinical trials evaluating PD-1/PD-L1 inhibitors to continue the investigation of other Immune Checkpoint Inhibitor (ICI) in combination with chemotherapy, vaccines, or even other immunomodulatory drugs. Here, we summarize the ongoing and recruiting clinical trials based on PD-1/PD-L1 inhibitors combined with chemotherapy or with other therapeutic agents that are registered in ClinicalTrials.gov [24]. We excluded clinical trials with not yet recruiting, completed, terminated, withdrawn, and unknown recruitment status. Table 1 includes some characteristics of the clinical trials for anti-PD-1 and anti-PD-L1 antibodies.

Avelumab, toripalimab, nivolumab, sintilimab, spartalizumab, tislelizumab, cemiplimab and durvalumab are antibody PD-1/PD-L1 inhibitors that we found with registered clinical trials. Each of these antibodies is being evaluated in combination with chemotherapy-based regimen but also with other drugs that have different therapeutic targets. We found studies in different clinical phases of development, most of them are in phase I and phase II. The studies for avelumab, toripalimab and durvalumab in advanced clinical phases are described below.

The clinical trial phase III for avelumab as adjuvant or post-neoadjuvant treatment for high-risk TNBC (NCT02926196), is an open label study with 474 patients who have completed treatment with curative intent including surgery followed by adjuvant chemotherapy (stratum A) or including neoadjuvant chemotherapy followed by surgery further adjuvant chemotherapy (stratum B). Treatment with avelumab will be given for 1 year. The primary outcome measure is Disease Free Survival (DFS) and the secondary outcome measure is overall survival up to 5 years after randomization. The study started on June 2016 and the estimated date to complete the study is June 2023.

The clinical trial phase III (NCT04085276), multicenter, double-blind study with 531 participants for evaluate toripalimab or placebo with nab-paclitaxel for first/second line treatment of metastatic or recurrent TNBC. The primary outcome measure is PFS up to approximately 61 months from first patient in. The study started on December 21, 2018, and the estimated date to complete the study is on December 31, 2024.

The clinical trial phase III (NCT05629585), is a multicenter, open label, 3-arm study with 1075 participants for evaluate the efficacy and safety of datopotamab deruxtecan with or without durvalumab versus investigator´s choice of therapy (capecitabine, pembrolizumab) in participants with stage I to III TNBC. The primary outcome measure is invasive Disease-Free Survival (iDFS); it will be determined based on disease recurrence per investigator assessment based on all available clinical assessments. The study started on November 28, 2022, and the estimated date to complete the study is on March 27, 2030.

Undoubtedly, the findings and results of these studies will provide further insight into the benefit that PD-1/PD-L1 inhibitors can have when combined with different drugs. On the other hand, it is important to highlight that in the most ongoing clinical trials in patients with TNBC, the therapies such as platinum, capecitabine, gemcitabine, anthracycline, and taxane-based regimens combined with PD-1/PD-L1 inhibitors the activity in patients with TNBC has been demonstrated.

Table 1: Clinical trials for PD-1/PD-L1 inhibitors in TNBC that are active or in recruiting status.

		Avelumab			
Identifier	**Phase**	**Treatment**	**Condition**	**Status**	**Estimated study completion date**
NCT05069935	I	Avelumab and FT538 is an allogeneic natural killer cell immunotherapy	TNBC	Active, not recruiting	August 5, 2025
NCT04551885	I	Avelumab and FT516	TNBC	Active, not recruiting	January 25, 2037
NCT04360941	Ib	Palbociclib Avelumab	Metastatic androgen receptor (AR)+TNBC	Recruiting	July 1, 2024
NCT02630368	I/**II**	Avelumab and JX-594 and cyclophospamide	TNBC	Recruiting	November 2024
NCT03475953	I/**II**	Avelumab and regorafenib	TNBC	Recruiting	December 31, 2025
NCT05329532	I/II	Modi-1/Modi-1v vaccines Avelumab	TNBC	Recruiting	June 30, 2026
NCT03971409	II	Avelumab combined with binimetinib or anti-OX40 antibody PF-04518600 or utomilumab or doxorubicin or sacituzumab govitecan	Metastatic TNBC	Recruiting	June 30, 2024
NCT02926196	III	Avelumab adyuvant or post-neoadjuvant	High-risk TNBC	Active	June 2023
		Toripalimab			
Identifier	**Phase**	**Treatment**	**Condition**	**Status**	**Estimated study completion date**
NCT05103917	I/II	Toripalimab with X4P-001	Locally advanced or metastatic TNBC	Enrolling by invitation	May 21, 2023
NCT04418154	II	Epirubicin and cyclophosphamide followed by albumin bound paclitaxel and toripalimab	TNBC	Active, not recruiting	December 31, 2023

NCT04085276	III	Toripalimab with nab-paclitaxel	Metastatic or recurrent TNBC	Active, not recruiting	December 31, 2024
		Sintilimab			
Identifier	**Phase**	**Treatment**	**Condition**	**Status**	**Estimated study completion date**
NCT05402722	II	Sintilimab with eribulin	Metastatic TNBC	Recruiting	June 30, 2023
NCT05386524	II	Sintilimab combined with bevacizumab biosimilar and pegylated liposomal doxorubicin	Metastatic TNBC	Recruiting	March 15, 2025
		Spartalizumab			
Identifier	**Phase**	**Treatment**	**Condition**	**Status**	**Estimated study completion date**
NCT02936102	I	PDR001 (spartalizumab) with FAZ053 (Anti-PD-L1)	TNBC	Active, not recruiting	June 14, 2024
NCT04802876	II	Spartalizumab or tislelizumab	Tumors with PD1-high mRNA expressing (TNBC)	Recruiting	March 31, 2027
		Cemiplimab			
Identifier	**Phase**	**Treatment**	**Condition**	**Status**	**Estimated study completion date**
NCT04243616	II	Cemiplimab with chemotherapy (paclitaxel, carboplatin, doxorubicin, cyclophosphamide)	TNBC	Recruiting	January 1, 2025
NCT04916002	II	Cemiplimab with vidutolimod	TNBC	Recruiting	March 7, 2027
		Nivolumab			
Identifier	**Phase**	**Treatment**	**Condition**	**Status**	**Estimated study completion date**
NCT02637531	I	Eganelisib with nivolumab	TNBC	Active, not recruiting	December 2020
NCT03667716	I	In column for treatment the correct is: Nivolumab with COM701 (an inhibitor of poliovirus receptor related immunoglobulin domain containing (PVRIG))	TNBC	Active, not recruiting	December 2023
NCT04925284	I	Nivolumab with XB002	TNBC	recruiting	October 7, 2024
NCT02393794	I/II	Nivolumab combined with cisplatin and romidepsin (histone deacetylase inhibitor)	Active, not recruiting	Active, not recruiting	July 2025
NCT04331067	Ib/II	Nivolumab and chemotherapy	Early stage TNBC	Active, not recruiting	May 31, 2026
NCT05329532	I/II	Nivolumab or Pembrolizumab with Modi-1 vaccine (with potent anti-tumour activity)	Advanced TNBC	Recruiting	June 30, 2026
NCT04895709	I/II	Nivolumab combined with BMS-986340	TNBC	Recruiting	September 15, 2026
NCT05888831	I/II	Nivolumab with BMS986449	Advanced, unresectable /metastatic TNBC	Recruiting	July 1, 2027
NCT03487666	II	Nivolumab with capecitabine	High risk TNBC and residual disease after effective neoadjuvant chemothera py	Active, not recruiting	December 2022
NCT03818685	II	Nivolumab with Ipilimumab combined with radiotherapy	TNBC with residual disease after neoadjuvant chemothera py	Active, not recruiting	March 1, 2024

NCT03414684	II	Nivolumab with carboplatin	Metastatic TNBC	Active, not recruiting	June 30, 2025
NCT02499367	II	Induction treatment (radiotherapy, doxorubicin, cyclophosphamide, cisplatin) combined with nivolumab	TNBC	Active, not recruiting	August 2025
NCT03546686	II	Ipilimumab with nivolumab pre-operative cryoablation. Post surgery only nivolumab	Early stage / resectable TNBC	Recruiting	June 2026
NCT04159818	II	Induction treatment with cisplatin or doxorubicin combined with nivolumab	TNBC	Recruiting	December 15, 2026
		Durvalumab			
Identifier	**Phase**	**Treatment**	**Condition**	**Status**	**Estimated study completion date**
NCT03199040	I	Durvalumab plus Neoantigen DNA vaccine	TNBC	Active, not recruiting	August 23, 2023
NCT03983954	I	Durvalumab with naptumomab estafenatox	TNBC	Active, not recruiting	August 30, 2023
NCT02826434	I	Durvalumab with PVX410 (vaccine)	TNBC with human leukocyte antigen (HLA)-A2+	Active, not recruiting	September 2023
NCT04504669	I	Durvalumab with AZD8701 (FOXP3 antisense oligonucleotide)	TNBC	Active, not recruiting	December 15, 2023
NCT03739931	I	Durvalumab with mRNA-2752 (a Lipid Nanoparticle Encapsulating mRNAs Encoding Human OX40L, IL-23, and IL-36γ)	TNBC	Recruiting	April 1, 2025
NCT03356860	I/II	Durvalumab with chemotherapy (paclitaxel, followed with epirubicin and cyclophosphamide)	TNBC	Active, not recruiting	January 2023
NCT03742102	I/II	Durvalumab and paclitaxel combined with capivasertib or oleclumab. Durvalumab combined with trastuzumab deruxtecan, or datopotamab deruxtecan	Metastatic TNBC	Recruiting	August 15, 2024
NCT03616886	I/II	Durvalumab combined with carboplatin and paclitaxel with or without oleclumab (antiCD73)	Advanced TNBC	Active, not recruiting	April 2025
NCT04176848	II	Durvalumab with CFI-400945 (blocking a specific protein called Polo-like Kinase 4 (PLK4) that is involved in cancer cell growth)	Metastatic TNBC	Active, not recruiting	December 31, 2022
NCT03606967	II	Durvalumab with nab-paclitaxel, tremelimumab, and neoantigen vaccine	Metastatic TNBC	Recruiting	December 31, 2024
NCT05582538	II	Durvalumab combined with ceralasertib and nab-paclitaxel	Advanced TNBC	Recruiting	November 2025
NCT03740893	II	Durvalumab	TNBC	Recruiting	December 2025
NCT05215106	II	Durvalumab	Early small TNBC	Recruiting	June 2026
NCT03801369	II	Durvalumab with olaparib	Metastatic TNBC	Recruiting	December 31, 2027
NCT01042379	II	Durvalumab combined with olaparib or datopotamab deruxtecan	TNBC	Recruiting	December 2031
NCT05629585	III	Durvalumab with datopotamab deruxtecan	TNBC	Recruiting	March 27, 2030

Conclusion

TNBC is a disease that represents a therapeutic challenge due to its highly invasive nature, the non-expression of receptors that leads to a low response to conventional therapy, and the expression of PD-L1 that contributes to evading the immune system.

Immunotherapy based on the use of immune point control antibodies such as atezolizumab and pembrolizumab, allows to regulate T cell regulatory mechanisms, blocking PD-1/PD-L1 has represented an unprecedented advance in the treatment of TNBC as shown in clinical studies that enhance the antitumor immune response, increase Overall Survival (OS) and Progression-Free Survival (PFS) in patients.

In addition, there are still many clinical trials in the research phase, with the objective of discovering new combinations of treatments, reducing adverse effects, and increasing specificity, resulting in a more economical and safer intervention for the patient.

Conflict of interest: Authors declare no conflict of interest.

References

1. World Health Organization. https://www.who.int/news-room/factsheets/detail/breast-cancer. Breast Cancer. 2023.
2. Barzaman K, Karami J, Zarei Z, Hosseinzadeh A, Kazemi MH, et al. Breast cancer: Biology, biomarkers, and treatments. International Immunopharmacology. Elsevier B.V. 2020; 84.
3. Popovic LS, Matovina-Brko G, Popovic M, Punie K, Cvetanovic A, et al. Targeting triple-negative breast cancer: A clinical perspective. Oncol Res. 2023; 31: 221-38.
4. Jiang Y, Chen M, Nie H, Yuan Y. PD-1 and PD-L1 in cancer immunotherapy: clinical implications and future considerations. Vol. 15, Human Vaccines and Immunotherapeutics. Taylor and Francis Inc. 2019; 1111-22.
5. Di Cosimo S. Advancing immunotherapy for early-stage triple-negative breast cancer. The Lancet. Lancet Publishing Group. 2020; 396: 1046-8.
6. Tarantino P, Corti C, Schmid P, Cortes J, Mittendorf EA, et al. Immunotherapy for early triple negative breast cancer: research agenda for the next decade. Breast Cancer. Nature Research. 2022; 8.
7. Nanda R, Liu MC, Yau C, Shatsky R, Pusztai L, et al. Effect of Pembrolizumab Plus Neoadjuvant Chemotherapy on Pathologic Complete Response in Women with Early-Stage Breast Cancer: An Analysis of the Ongoing Phase 2 Adaptively Randomized I-SPY2 Trial. JAMA Oncol. 2020; 6: 676-84.
8. Jiang Y, Chen M, Nie H, Yuan Y. PD-1 and PD-L1 in cancer immunotherapy: Clinical implications and future considerations. Human Vaccines and Immunotherapeutics. Taylor and Francis Inc. 2019; 15: 1111-22.
9. Kythreotou A, Siddique A, Mauri FA, Bower M, Pinato DJ. PD-L1. J Clin Pathol. 2018; 71: 189-94.
10. Vargas-Rojas M, Jiménez-Álvarez L, Ramírez G, Torres-García D, Barquera R, et al. PD-1 y sus ligandos como reguladores de la respuesta inmune. Revista Instituto Nacional de Enfermedades Respiratorias. 2008; 21: 272-9.
11. Jorgovanovic D, Song M, Wang L, Zhang Y. Roles of IFN-γ in tumor progression and regression: A review. Biomark Res. 2020; 8: 49.
12. Sun C, Mezzadra R, Schumacher TN. Regulation and Function of the PD-L1 Checkpoint. Immunity. 2018; 48: 434-52.
13. Wu M, Huang Q, Xie Y, Wu X, Ma H, et al. Improvement of the anticancer efficacy of PD-1/PD-L1 blockade via combination therapy and PD-L1 regulation. Vol. 15, Journal of Hematology and Oncology. 2022.
14. US Food & Drug Administration. U. S. Food & Drug Administration. FDA approves atezolizumab for PD-L1 positive unresectable locally advanced or metastatic triple-negative breast cancer. 2023.
15. Schmid P, Rugo HS, Adams S, Schneeweiss A, Barrios CH, et al. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2020; 21: 44-59.
16. Mittendorf EA, Zhang H, Barrios CH, Saji S, Jung KH, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracyclinebased chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): A randomised, double-blind, phase 3 tri. Lancet. 2020; 396: 1090-100.
17. Miles D, Gligorov J, André F, Cameron D, Schneeweiss A, et al. Primary results from IMpassion131, a double-blind, placebo-controlled, randomised phase III trial of first-line paclitaxel with or without atezolizumab for unresectable locally advanced/metastatic triple-negative breast cancer. Ann Oncol. 2021; 32: 994-1004.
18. US Food & Drug Administration. U. S. Food & Drug Administration. FDA issues alert about efficacy and potential safety concerns with atezolizumab in combination with paclitaxel for treatment of breast cancer. 2023.
19. US. Food & Drug Administration. U. S. Food & Drug Administration. FDA grants accelerated approval to pembrolizumab for locally recurrent unresectable or metastatic triple negative breast cancer. 2023.
20. Cortes J, Cescon DW, Rugo HS, Nowecki Z, Im SA, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): A randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet. 2020; 396: 1817-28.
21. US Food & Drug Administration. U.S. Food & Drug Administration. FDA approves pembrolizumab for high-risk early-stage triple-negative breast cancer. 2023.
22. Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, et al. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med. 2020; 382: 810-21.
23. Barzaman K, Karami J, Zarei Z, Hosseinzadeh A, Kazemi MH, et al. Breast cancer: Biology, biomarkers, and treatments. Int Immunopharmacol. 2020; 84: 106535.
24. NIH. National Library of Medicine. ClinicalTrials.gov. 2023.