Overview of Triple Negative Breast Cancer And FDA Approved Therapies

Breast cancer is cancer that occurs in breast cells. Breast cancer is one of the most common cancers diagnosed in women in the United States, second only to skin cancer. Both men and women can develop breast cancer, but the incidence is much higher in women than in men. **This article provides an overview of triple negative breast cancer and a summary of FDA-approved therapies.** Survival rates for breast cancer have now improved, and deaths associated with the disease have steadily declined, largely due to factors such as early detection, new personalized treatments, and a better understanding of the disease.

A Brief Introduction of Triple Negative Breast Cancer

Breast cancer is divided into **three categories** according to whether estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER-2) are positive: **hormone receptor-positive breast cancer, HER2-positive breast cancer cancer and triple negative breast cancer (TNBC)**.

Triple-negative breast cancer (TNBC) accounts for 10-15% of breast cancers, with 60,000-80,000 new cases of TNBC in 2020. It is a severely invasive and highly proliferative subtype, accounting for a higher proportion in young women. The prognosis is poor, with most patients relapsing after three years and dying five years before diagnosis. **Chemotherapy remains the primary treatment for patients with early and advanced TNBC,** an area of highly unmet medical need that urgently requires improved treatment regimenand optimized precision medicine.

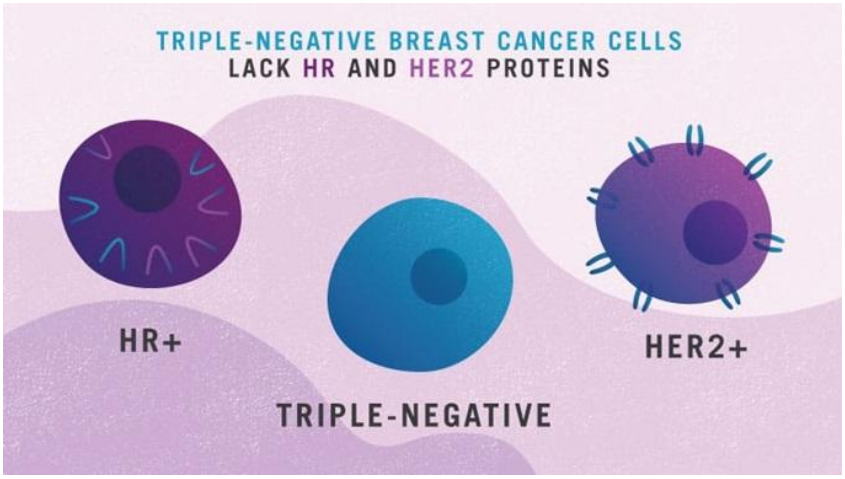


Image source: https://www.gene.com

Characteristics of Triple Negative Breast Cancer

Because TNBC lacks estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor-2 (HER-2) receptors, **TNBC cannot be treated with conventional HER2-targeted therapies**. Breast cancer is also considered a "cold" tumor from an immunological point of view, however, due to the higher number of tumor-infiltrating lymphocytes (higher PD-L1 expression, higher tumor mutational load), TNBC has been shown to be the preferred subtype for immunotherapy strategies.

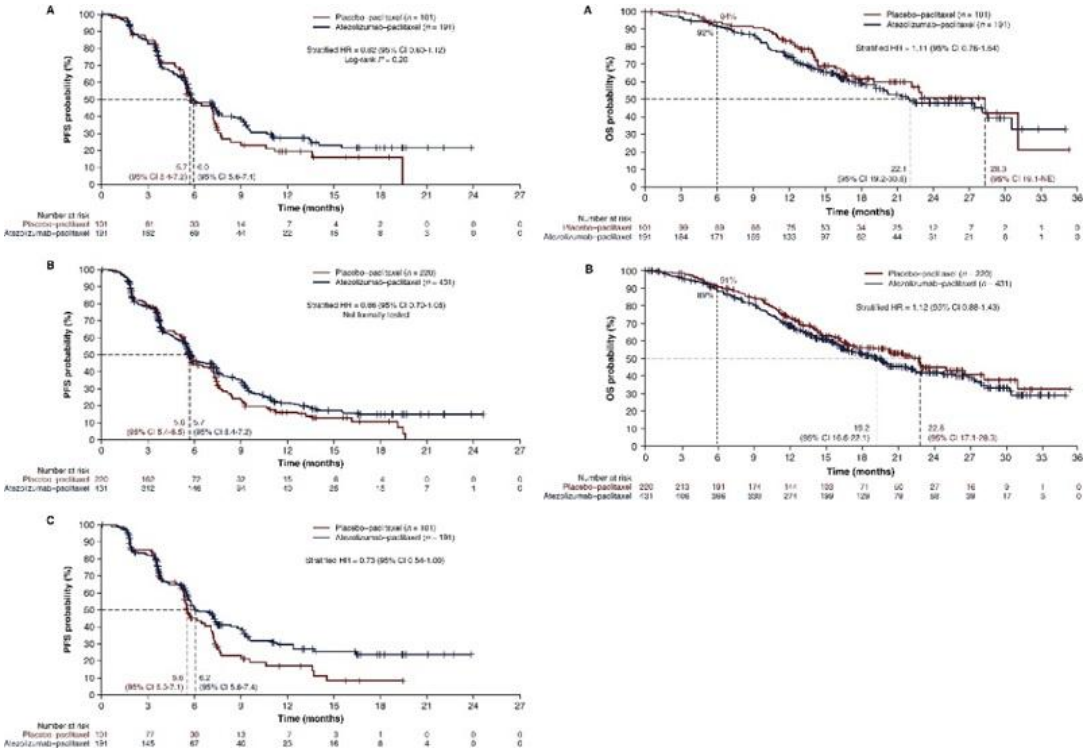
Currently Approved Therapies For Triple Negative Breast Cancer

① Atezolizumab(TECENTRIQ, Genentech Inc.) combined with Albumin-bound paclitaxel

On March 8, 2019, the U.S. Food and Drug Administration (FDA) accelerated approval of atezolizumab (TECENTRIQ, Genentech Inc.) in combination with Albumin-bound paclitaxel for PD-L1-positive unresectable locally advanced or metastatic triple-negative breast cancer.

The approval is based on **IMpassion130 (NCT02425891)**, a multicenter, international, double-blind, placebo-controlled, randomized trial including 902 patients with unresectable locally advanced or metastatic TNBC who had not received chemotherapy. Among patients whose tumors expressed PD-L1, atezolizumab and **albumin-bound paclitaxel** had a median progression-free survival (PFS) of 7.4 months (95%CI:6.6, 9.2). Median progression-free survival (PFS) was 4.8 months (95%CI:3.8, 5.5) for patients receiving placebo and albumin-bound paclitaxel. But overall survival data are not mature, with 43% of intent-to-treat (ITT) people dying.

However, in the IMpassion131 (NCT 03125902) clinical trial(a post-marketing validation clinical trial of atezolizumab combined with Albumin-bound paclitaxel), atezolizumab combined with paclitaxel and placebo combined with paclitaxel were used in patients with mTNBC. In this clinical trial, atezolizumab plus paclitaxel did not significantly reduce the risk of cancer progression and death compared with placebo plus paclitaxel in the PD-L1-positive population. Furthermore, in the PD-L1-positive population and the overall population, the interim overall survival outcome turned out to favor paclitaxel + placebo over paclitaxel + atezolizumab.



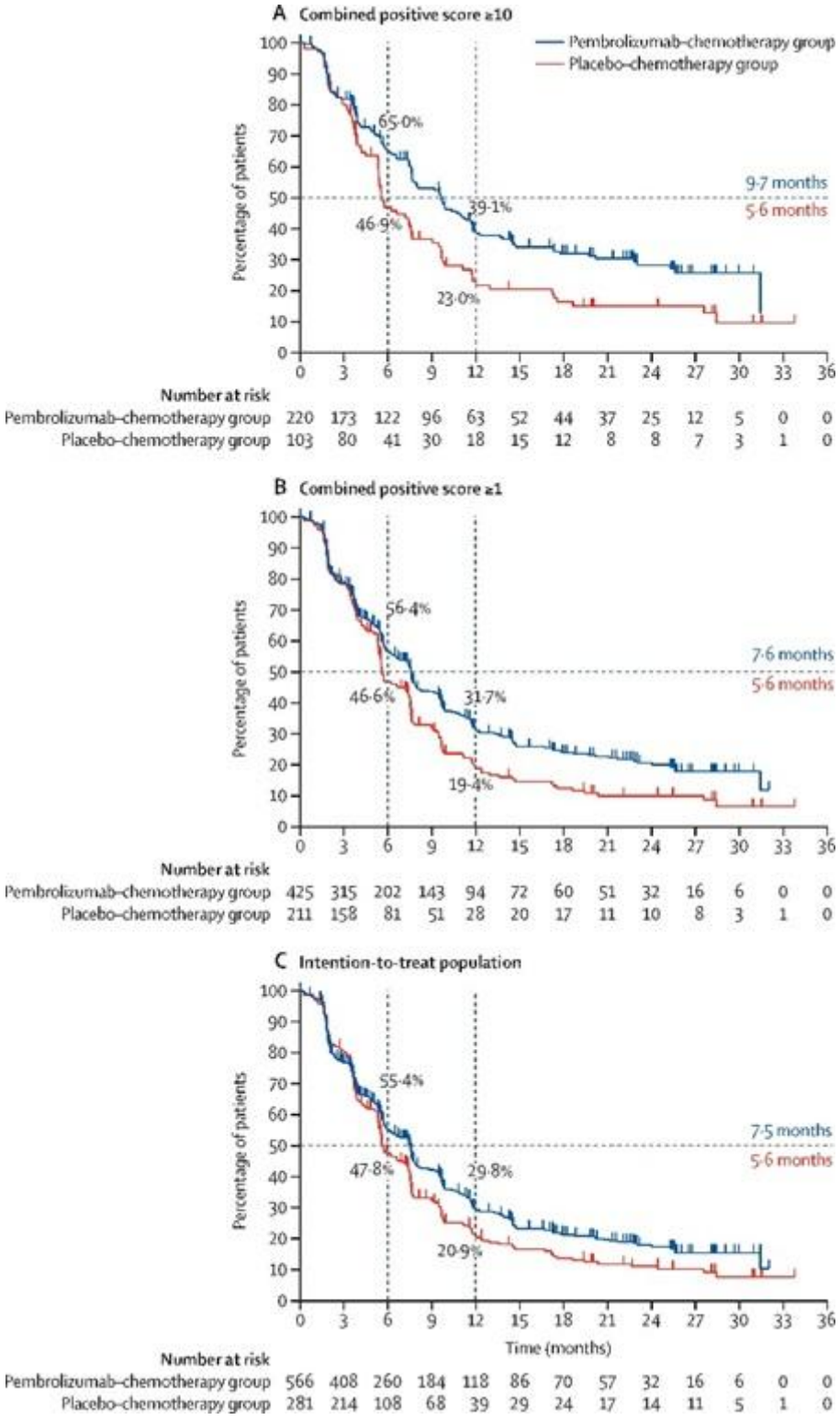
Combination of atezolizumab with paclitaxel did not improve PFS or OS compared with paclitaxel alone

Therefore, on September 8, 2020, FDA issued a warning that health care professionals should not use paclitaxel in place of albumin-bound paclitaxel in clinical practice. This also indirectly led to Roche's decision to voluntarily withdraw the therapy for the mTNBC indication in the United States, but the decision only affects the mTNBC indication in the United States, and does not affect atezolizumab in the United States and other approved indications outside the United States (including mTNBC). Roche also stated that it will continue to explore atezolizumab in the field of mTNBC.

② Pembrolizumab in combination with chemotherapy for locally recurrent unresectable or metastatic TNBC

In November 2020, the FDA approved **pembrolizumab** (Keytruda, Merck) in combination with chemotherapy for patients with locally recurrent unresectable or metastatic TNBC (tumors expressing PD-L1 (combination positive score [CPS] ≥10)).

The approval was based on KEYNOTE-355 (NCT02819518), a randomized, double-blind, phase III clinical trial. Among patients with locally recurrent unresectable or metastatic TNBC whose tumors expressed PD-L1 (combined positive score [CPS] ≥10), median PFS was 9.7 months in the pembrolizumab + chemotherapy group and 5.6 months in the control group. This difference was more pronounced with an increase in PD-L1 CPS.



KEYNOTE-355 Phase 3 Clinical Trial: Analysis of Progression-Free Survival in Different Cohorts

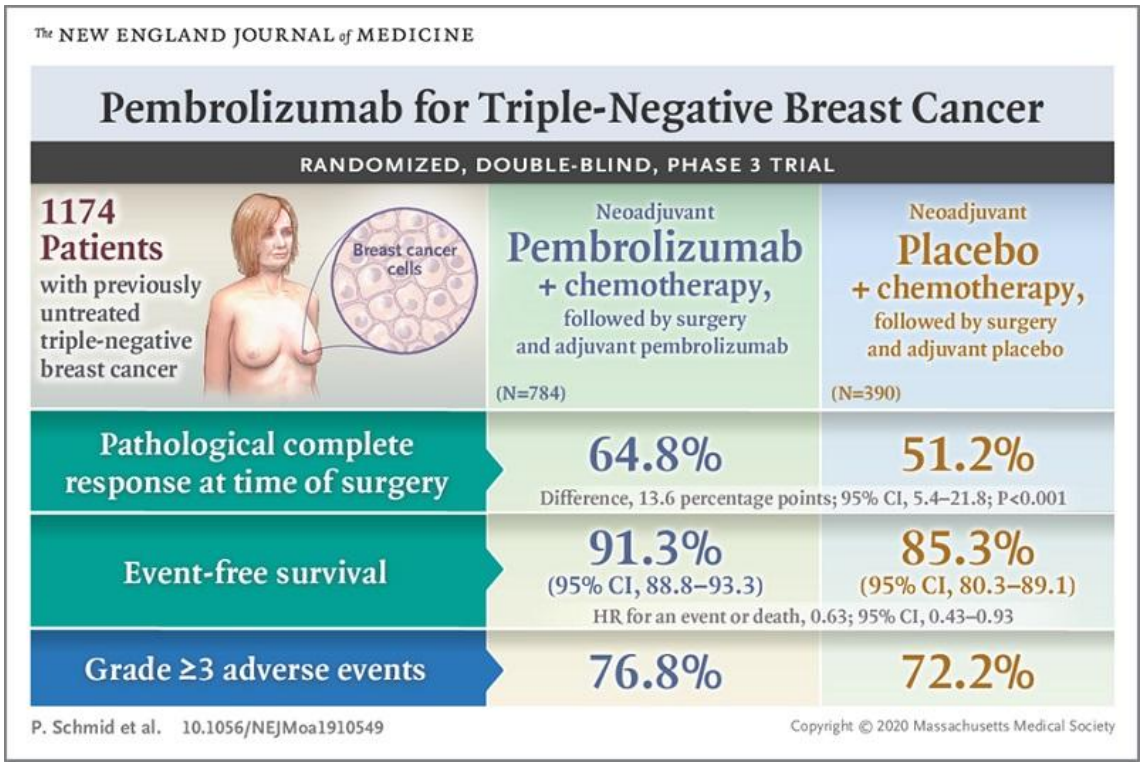
③ Pembrolizumab combined with chemotherapy in high-risk, early-stage TNBC

In July 2021, the FDA approved pembrolizumab in combination with chemotherapy as neoadjuvant therapy for high-risk, early-stage, triple-negative breast cancer (TNBC), followed by continuation of monotherapy as adjuvant therapy after surgery.

The approval is based on KEYNOTE-522 (NCT03036488), a randomized, multicenter, double-blind, placebo-controlled trial of 1174 patients with newly diagnosed, previously untreated, high-risk early-stage TNBC (tumor size >1 cm but diameter ≤2 cm, lymph node involvement or tumor size > 2 cm regardless of lymph node involvement). Patients were randomly assigned (2:1) to receive pembrolizumab plus chemotherapy or placebo plus chemotherapy.

In the trial results, the pathological complete response rate was 64.8% (95% CI: 59.9, 69.5) in patients receiving pembrolizumab plus chemotherapy, compared with 51.2% (95% CI: 44.1, 58.3) in patients receiving chemotherapy alone. Median follow-up at the fourth interim analysis (data as of March 23, 2021) was 39.1 months. The event-free survival rate at 36 months was 84.5% (95% CI, 81.7-86.9) in the pembrolizumab-chemotherapy group and 76.8% (95% CI, 72.2-80.7) in the placebo group.

FDA recommended dosage: The recommended dose of pembrolizumab is 200 mg every 3 weeks or 400 mg every 6 weeks by IV infusion over 30 minutes. Pembrolizumab was given in combination with chemotherapy for 24 weeks and then as a single agent in adjuvant therapy for up to 27 weeks.



KEYNOTE-522 (NCT03036488) Details

④ ADC drug - Sacituzumab Govitecan (Trodelvy, Immunomedics Inc.)

In April 2021, sacituzumab govitecan was approved by the FDA for adult patients with unresectable locally advanced or metastatic TNBC who have received at least 2 prior therapies, at least one of which is for metastatic disease.

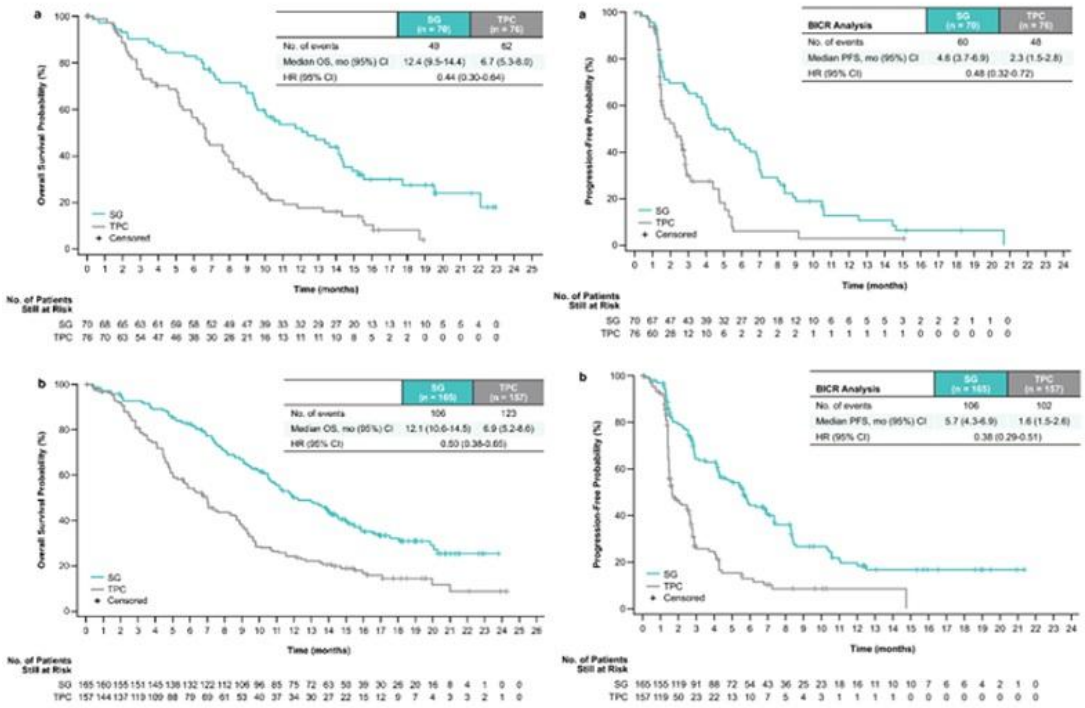
Sacituzumab govitecan was originally developed by Immunomedics. On June 7, 2022, Sacituzumab Govitecan was approved for marketing in China for the second-line treatment of metastatic triple-negative breast cancer. This is Everest Medicines's first innovative drug approved for marketing in China, and sales in China are expected to start in the fourth quarter of this year.

Sacituzumab govitecan is formed by coupling a humanized IgG1 antibody targeting TROp-2 (human trophoblastocyte surface antigen 2) with SN-38, a metabolically active product of the chemotherapeutic drug Irinotekan, a topoisomerase I inhibitor. Trop2 is expressed in 85% of TNBC cells.

The approval was based on the Phase III ASCENT clinical trial (NCT02574455). Among patients with advanced TNBC who had received at least two treatments, PFS was 5.7(4.3 to 6.9) months in the Sacituzumab govitecan group compared with 1.7 (1.5 to 2.6) months in monotherapy. OS was 12.1 months (10.6-14.5) in the treatment group and 6.9 months (5.2-8.6) in the chemotherapy group. ORR was 34.0 months (28.0-40.5) in the treatment group and 6.4 months (3.6-10.4) in the chemotherapy group. Sacituzumab govitecan is the first treatment to improve **progression-free survival (PFS)** and overall survival (OS) in patients with mTNBC.

FDA recommended dosage: The recommended dose of Sacituzumab govitecan is 10 mg/kg once a week or administered on days 1 and 8 of the

21-day treatment cycle until disease progression or unacceptable toxicity.



Comparative analysis of PFS and OS between Sacituzumab Govitecan group and chemotherapy group

Conclusion

In recent years, immunotherapy, especially antibodies and antibody-drug conjugates, have achieved staged breakthroughs in the field of triple-negative breast cancer, which has brought hope to this tumor type with high heterogeneity, high recurrence and high mortality. At present, all kinds of immunotherapy are distributed in the field of triple negative breast cancer. These include anti-angiogenic inhibitors (containing antibodies and small molecule proteins), bisspecific antibodies, CAR T/NK, etc., all of which are worthy of attention. In particular, **combination therapy is particularly important in the field of triple negative breast cancer**.

As a professional manufacturer of PEG derivatives, pharmaceutical intermediates and research chemicals, Huateng Pharma provides anti-cancer intermediate products for some drugs, such as Palbociclib and Ribociclib which used for the treatment of certain kinds of breast cancer.
Both Palbociclib and Ribociclib are inhibitors of CDK4 and CDK6.
Sacituzumab govitecan (IMMU-132) is **an ADC drug** approved in 2020 which used to treat adults triple-negative breast cancer. Huateng Pharma is dedicated to being your most reliable partner to provide high-quality PEG linkers to promote the progress of your ADC R&D.

References:

[1]https://www.fda.gov/drugs

[2]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

[3] Analysis of patients without and with an initial triple-negative breast cancer diagnosis in the phase 3 randomized ASCENT study of sacituzumab govitecan in metastatic triple-negative breast cancer.

[4] Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer.