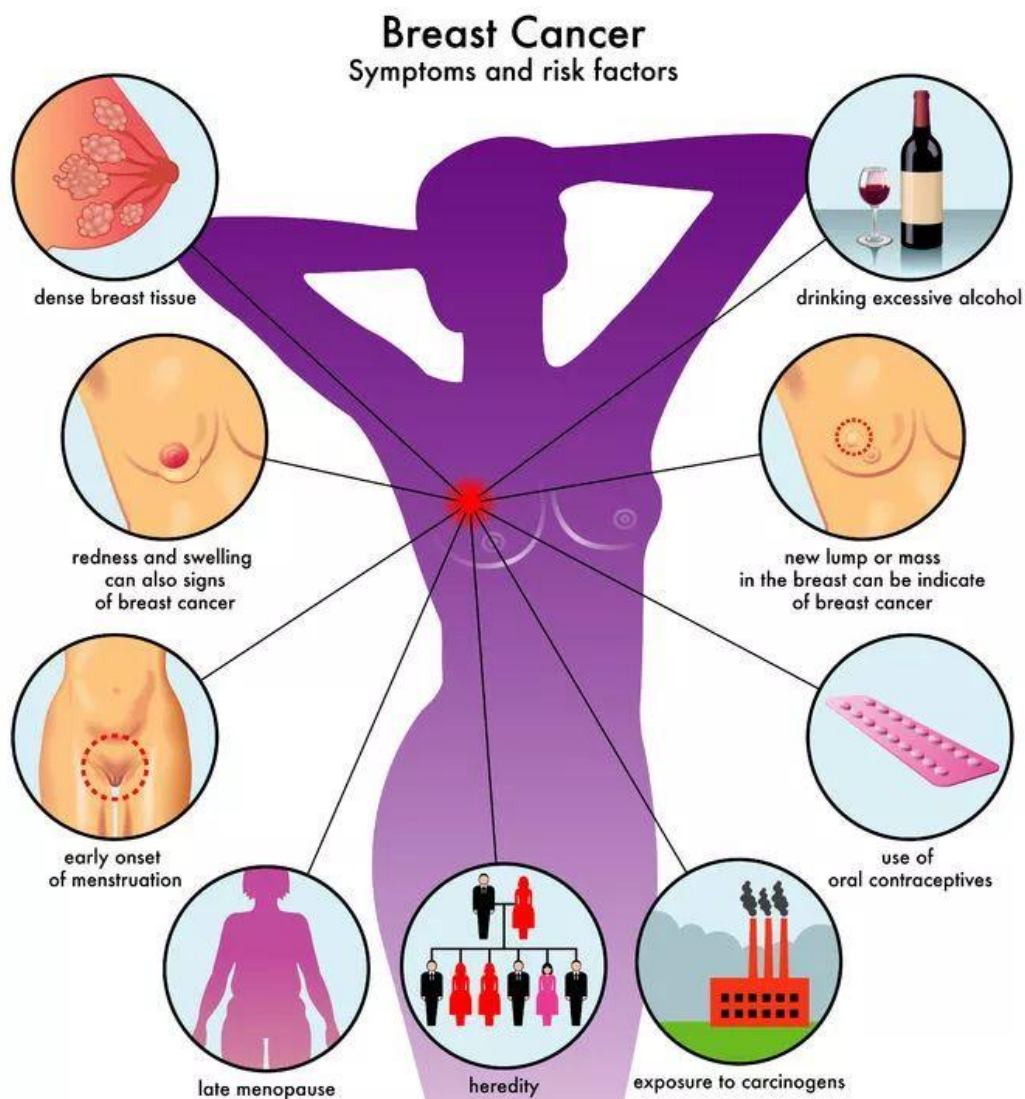


# Targeted Drug Therapy And Immunotherapy For Breast Cancer

According to the World Health Organization, breast cancer is the most common cancer worldwide, surpassing even lung cancer. According to the latest statistics in 2020, there were approximately 2.3 million new breast cancer patients worldwide that year, resulting in 685,000 deaths. And breast cancer is not limited to women, in rare cases, men can get breast cancer too.

With the development of tissue type and molecular pathological detection methods for breast cancer, the treatment of breast cancer has gradually stepped into the stage of individualized precision medicine. According to the official information of the American Cancer Society, **we reviewed the [targeted drug therapy](#) and [immunotherapy](#) currently available for the clinical treatment of breast cancer.**



## What Targeted Therapies Are Commonly Used In Breast Cancer Treatment?

Targeted drugs work on breast cancer cells by inhibiting cancer-causing targets that help them grow, spread and survive, either by destroying cancer cells or slowing their growth. Targeted drugs commonly used in the treatment of breast cancer can be divided into four categories according to their different targets.

### 1. What are the targeted drugs for HER2?

About 15% to 20% of breast cancer cases are [HER2-positive breast cancer](#), a protein that promotes cancer growth and spread, so patients with HER2-positive breast cancer tend to progress faster and metastasize more easily than those with HER2-negative breast cancer. So far, researchers have successfully developed a variety of drugs that target the HER2 protein.

#### Monoclonal Antibody Drugs

**Monoclonal antibody drugs** that are clinically used to treat breast cancer include trastuzumab, pertuzumab, and margetuximab, all of which target HER2.

Trastuzumab can be used as monotherapy or in combination with chemotherapy drugs to treat early and advanced breast cancer. The U.S. FDA has approved the combination of trastuzumab and capecitabine in 2020 for the treatment of patients with unresectable locally advanced or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2 regimens. The drug has been approved for marketing by the National Medical Products Administration (NMPA) for the treatment of a variety of solid tumors, including HER2-positive breast cancer.

Pertuzumab (Perjeta) has been widely used in the clinical treatment of breast cancer. In 2012, the US FDA approved pertuzumab for the treatment of breast cancer-related indications, such as HER2-positive metastatic breast cancer, HER2-positive locally advanced, inflammatory or early breast cancer neoadjuvant therapy (before surgery), and in combination with trastuzumab and chemotherapy as adjunctive therapy for HER2-positive early breast cancer at high risk of recurrence (postoperative). The drug has also been approved by the National Medical Products Administration (NMPA) for the treatment of HER2-positive breast cancer.

Compared with the above two drugs, margetuximab (trade name: Margenza) was launched later, and its marketing application in China is still under review.

The US FDA approved it in 2020 for the treatment of patients with metastatic HER2-positive breast cancer who have received 2 anti-HER2 treatment regimens (at least one of which is a treatment regimen for metastatic disease).

## Antibody Drug Conjugates

An antibody drug conjugate (ADC) is a monoclonal antibody linked to a chemotherapy drug. Taking anti-HER2 ADC drugs as an example, antibodies targeting HER2 act as "homing signals" by attaching to the HER2 protein of cancer cells, delivering chemotherapy drugs directly to tumor cells. [ADC drugs](#) currently used for the treatment of breast cancer include **ado-trastuzumab emtansine (Kadcyla)** and **fam-trastuzumab deruxtecan (trade name: Enhertu)**.

The drug molecule design of Trastuzumab emtansine links an antibody targeting HER2 with the chemotherapy drug emtansine to fight HER2-positive cancers together. Emtansine, a paclitaxel-like drug, can be used by itself in patients with early-stage breast cancer after surgery, or in patients with advanced breast cancer who have already been treated with trastuzumab and chemotherapy. In 2013, the U.S. FDA approved Trastuzumab emtansine and paclitaxel alone or in combination for the treatment of patients with HER2-positive metastatic breast cancer, and further expanded its indications in 2019: for the adjuvant (post-operative) treatment of HER2-positive early-stage breast cancer. At present, Trastuzumab emtansine has been approved for marketing by the NMPA for the indication of HER2-positive breast cancer.

The molecular structure of Fam-trastuzumab deruxtecan is also a combination of antibody and chemotherapy drugs. The drug linked to FAM-Trastuzumab deruxtecan is a similar drug of irinotecan. It was approved by the US FDA in 2019 for the treatment of patients with unresectable or metastatic HER2-positive breast cancer who have received more than two previous anti-HER2 therapies, and further expanded for indications in 2022: For the treatment of unresectable or metastatic breast cancer with low HER2 expression and recurrence 6 months after previous chemotherapy or completion of adjuvant therapy. Fam-trastuzumab deruxtecan's application for marketing in China is still under review.

## Kinase Inhibitors

HER2 is a protein with kinase activity. Kinases are protein molecules involved in signal transmission (such as cell growth signals) in cells. For cancer cells, blocking the activity of kinases may inhibit their growth. HER2 kinase inhibitors commonly used in the treatment of breast cancer mainly include Lapatinib

(Tykerb), Neratinib (Nerlynx), and tucatinib (Tukysa). At present, both Lapatinib and Neratinib have been approved for marketing in China, and the marketing application of tucatinib is still under review.

## **2. What are the targeted drugs for hormone receptor positive breast cancer patients?**

About three-quarters of breast cancer cases are hormone (estrogen or progesterone) receptor-positive breast cancer, for which hormone therapy is usually effective, and some targeted therapy drugs can make hormone therapy even more effective. According to the different targets, the targeted drugs commonly used in the treatment of hormone receptor positive breast cancer can be divided into three categories -- CDK4/6 inhibitors, mTOR inhibitors and PI3K inhibitors.

### **CDK4/6 Inhibitors**

[CDK4/6 inhibitors](#) commonly used in the clinical treatment of breast cancer include Palbociclib(Ibrance), Ribociclib(Kisqali) and Abemaciclib(Verzenio), which block cyclin-dependent kinases (CDKs) in cancer cells, specifically targeting CDK4 and CDK6. Blocking these CDK proteins in hormone-receptor-positive breast cancer cells helps prevent cell division, which in turn slows tumor growth.

The above three drugs have all been approved by the US FDA. Palbociclib and Abemaciclib can be used in combination with Letrozole, Fulvestrant, or aromatase inhibitors for the treatment of patients with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer. Ribociclib is primarily used with aromatase inhibitors as initial endocrine therapy for premenopausal, postmenopausal, or postmenopausal patients with advanced or metastatic breast cancer. The molecular typing of these patients was hormone receptor positive and HER2 negative. In addition, Ribociclib can be used in combination with Fulvestrant as a first/second line endocrine therapy for postmenopausal breast cancer patients.

Palbociclib and Abemaciclib have been approved in China for the treatment of hormone-receptor-positive, HER2-negative breast cancer patients, and the marketing application for Ribociclib is still pending.

### **mTOR Inhibitor Drugs**

mTOR inhibitors can specifically block mTOR signal transduction, a protein that helps cells grow and divide. Blocking the activity of this protein can inhibit tumor progression. One mTOR inhibitor commonly used in breast cancer is

Everolimus (Afinitor), which slows tumor growth by blocking the production of new blood vessels. In the clinical treatment of breast cancer, Everolimus can help hormone drugs work better. The FDA approved Everolimus and exemestane in 2012 for the treatment of postmenopausal women with hormone-receptor-positive, HER2-negative advanced breast cancer who were treated with letrozole or anastrozole. The NMPA also approved the marketing application of Everolimus in February 2022 for the treatment of hormone receptor positive, HER2-negative breast cancer.

### **PI3K Inhibitor Drugs**

The PI3K protein drives the growth of cancer cells, and blocking its activity can halt tumor progression. The PI3K inhibitor drug commonly used in breast cancer treatment is Alpelisib (Piqray), which is used with fulvestrant to treat hormone receptor-positive, HER2-negative advanced breast cancer in postmenopausal women who develop PIK3CA gene mutations during or after treatment with aromatase inhibitors. Alpelisib received FDA marketing approval in 2019 in combination with Fulvestrant for the treatment of women and men with hormone receptor-positive, HER2-negative, advanced postmenopausal or metastatic breast cancer with a PIK3CA gene mutation. Alpelisib's application to list in China is still under review.

### **3.Targeted Therapies For BRCA Gene Mutations**

Common targeted drugs used clinically for breast cancer patients with BRCA mutations include Olaparib (Lynparza) and Talazoparib (Talzenna), both of which are PARP inhibitors. The PARP protein helps repair damaged DNA in cells, as do the BRCA genes (BRCA1 and BRCA2), but mutations in either of these genes can disable DNA repair. PARP inhibitors work by blocking the PARP protein, which often leads to the accumulation of DNA damage and cell death because the DNA repair function of tumor cells with BRCA mutations has been impaired.

Olaparib received FDA approval in 2018 for the treatment of metastatic breast cancer with BRCA germ line mutations, and a new indication was approved in 2022 for the treatment of HER2-negative early breast cancer patients with or suspected BRCA germ line mutations who had previously received chemotherapy before/after surgery. At present, Olaparib for breast cancer indication has been submitted to the NMPA for marketing application. Talazoparib was approved by the U.S. FDA in 2018 for the treatment of locally advanced or metastatic breast cancer with germline BRCA gene mutations and HER2-negative disease. The indications for breast cancer have not yet been filed with Chinese regulators.

#### 4.Targeted Therapies for Triple Negative Breast Cancer

In [triple-negative breast cancer \(TNBC\)](#), the cancer cells do not have estrogen or progesterone receptors and have very low or no levels of the HER2 protein, so this group of patients is not sensitive to endocrine therapy or to drugs targeting the hormone receptor, HER2. Currently, Sacituzumab Govitecan (Trodelvy) is the main target drug that can be used for TNBC treatment in clinic. It is an antibody-drug conjugate consisting of a chemotherapy drug and a monoclonal antibody bound to it. When the drug enters the body, its monoclonal antibody component can attach to a protein called Trop-2 on breast cancer cells and bring chemotherapy drugs to the cancer cells to exert their effects. Because cancer cells have much higher levels of the Trop-2 protein than normal cells, this approach can partly reduce the damage chemotherapy drugs do to healthy cells.

In 2020, the U.S. FDA approved Sacituzumab Govitecan (Trodelvy) as monotherapy for the treatment of patients with [advanced or metastatic TNBC](#) who have previously received at least two or more systemic therapies. In June this year, Sacituzumab Govitecan (Trodelvy) was approved by the NMPA for the treatment of triple-negative breast cancer.

#### What AreThe Immunotherapies For Breast Cancer?

Immunotherapy works by using drugs to boost the immunity of the body's own immune system to more effectively identify and destroy cancer cells. Immunotherapy usually works on specific proteins involved in the function of the immune system. The main immunotherapy currently used in the clinical treatment of breast cancer is the drug **Pembrolizumab (Keytruda)**, an inhibitor of the immune checkpoint PD-1, which has side effects different from those of chemotherapy.

Pembrolizumab (Keytruda) is a drug that targets PD-1, an important component of immune cells -- a protein on T cells that helps T cells not attack healthy tissue in the body. By blocking PD-1, these drugs boost the immune system's immune response against breast cancer cells, causing tumors to shrink.

The US FDA approved Pembrolizumab in 2020 to be used in combination with chemotherapy for the treatment of non-resectable locally recurrent or metastatic triple-negative breast cancer. In 2021, Pembrolizumab was approved for a new indication: the US FDA approved combination chemotherapy as a neoadjuvant therapy for high-risk early-stage triple-negative breast cancer patients, and continued as a monotherapy



adjuvant therapy after surgery. Pembrolizumab has been submitted to Chinese regulators for an indication for breast cancer.

## Conclusion

With the increasing application of innovative treatment models represented by targeted therapy, immunotherapy and combination therapy in breast cancer patients, we have made some progress in curbing tumor growth and improving the survival rate of breast cancer. More research is needed on how to use precise and individualized treatment to improve the efficacy, and how to find better biomarkers to make individualized treatment more feasible in clinical practice, which will be the development direction of breast cancer in the future. Only some breast cancer treatments are introduced, not all of them are listed. We will also pay close attention to the progress of cancer research and introduce the latest treatment methods to readers.

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### References:

- [1]. Targeted Drug Therapy for Breast Cancer, Retrieved Oct 24th, 2022, from <https://www.cancer.org/cancer/breast-cancer/treatment/targeted-therapy-for-breast-cancer.html>
- [2]. Immunotherapy for Breast Cancer, Retrieved Oct 24th, 2022, from <https://www.cancer.org/cancer/breast-cancer/treatment/immunotherapy.html>
- [3]. Arnold, Melina et al. "[Current and future burden of breast cancer: Global statistics for 2020 and 2040.](#)" *Breast (Edinburgh, Scotland)*, vol. 66 15-23. 2 Sep. 2022, doi:10.1016/j.breast.2022.08.010

### Related articles:

- [1]. [Overview of Triple Negative Breast Cancer And FDA Approved Therapies](#)
- [2]. [Immunotherapy + mRNA Technology To Treat Triple Negative Breast Cancer](#)
- [3]. [CDK4/6 Inhibitors for Treatment of Advanced Breast Cancer](#)