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New Drugs for Breast Cancer Treatment

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Abstract

Breast cancer is the most common type of cancer in women, affecting approximately 12% of women over the course of their lifetime. It was estimated that there would be 81,550 new cases of invasive breast cancer in women in the United States (US), along with 49,290 new cases of non-invasive breast cancer. A search was conducted to find out the number of new breast cancer drugs that have been approved by US Food and Drug Administration (FDA) in the last 2 years (2020-2021), and the number of breast cancer drugs that are currently under Phase 3 clinical trials. Between 2020 and 2021, 4 new drugs have been approved by FDA for the treatment of breast cancer: Tukysa (Seagen), Margenza (MacroGenics), Phesgo (Genentech), and Trodelvy (Gilead Sciences). Research continues to find out new drugs that can help treat breast cancer. Currently, there are several breast cancer treatment drugs in Phase 3 clinical trials including two major new breast cancer drugs Palbociclib (Pfizer) and Ribociclib (Novartis). Pharmaceutical and biotech companies are making incredible contributions by developing many innovative and effective treatments for breast cancers. We are hopeful that many new breast cancer drugs will be approved in the coming years.

Keywords: *Breast cancer, Food and Drug Administration(FDA), New Drugs, Clinical Trials.*

Introduction

Breast cancer is the most common type of cancer in women, affecting approximately 12% of women over the course of their lifetime [1]. In 2021, it was estimated that there would be 81,550 new cases of invasive breast cancer in women in the U.S., along with 49,290 new cases of non-invasive (in situ) breast cancer [2]. Breast cancer occurs when normal cells in the breast undergo changes in their molecular characteristics, allowing them to grow and multiply uncontrollably. Breast cancers are of the following types [3 and 4]:

Estrogen Receptor-positive (ER) Breast Cancer

In estrogen receptor (ER) positive breast cancer, cancerous cells receive their growth signals from estrogen hormone. Estrogen receptors are the most common type of hormone receptor on breast cells; hence, ER-positive breast cancers are the most common and the most treatable form of breast cancer. According to the American Cancer Society, about 2 out of every 3 cases of breast cancers are hormone receptor-positive. While most people treated for early stage HER2-positive breast cancer do not relapse after their treatment, breast cancer can return in some cases. Recurrent ER-positive breast cancers are less likely to respond to the same therapy that was used to treat primary breast cancer.

Human Epidermal Growth Factor Receptor 2 (HER2) - Positive Breast Cancer

Human epidermal growth factor receptor 2 (HER2) positive breast cancer is when breast cancer cells have a protein receptor called HER2. Normally, this protein helps breast cells grow, divide, and repair themselves. But

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sometimes, something goes wrong in the gene that controls the HER2 protein and our body makes too many of these receptors. This causes the breast cells to grow and divide uncontrollably. About 1 of 5 breast cancers are HER2-positive.

Triple Negative Breast Cancer (TNBC)

Triple negative breast cancers lack estrogen, progesterone, and HER2 receptors. Triple negative breast cancers are considered to be more aggressive and have poor prognosis compared to other breast cancers. Growth of TNBC cancer is not fueled by the hormone's estrogen and progesterone, or by the HER2 protein. TNBC accounts for about 15% of breast cancer cases in the US and is known for high relapse rates and poor overall survival (OS) [5].

Breast cancer is treated in different ways. Breast cancer patients often get more than one treatment at a time.

1. Surgery involves cutting out/removal of the cancer tissue.
2. Chemotherapy involves use of drugs that shrink or kill the cancer cells.
3. Hormonal therapy blocks the cancer cells from getting the hormones they need to grow.
4. Radiation therapy involves use of high-energy rays to kill the cancer cells.

Breast cancer deaths have declined significantly in recent years. Treatment advances play a major role in the reduction of breast cancer related deaths. Researchers around the world are working to find better ways to prevent, detect, and treat breast cancer, and to improve the quality of life of patients and survivors [6]. This review presents available literature on the recently approved (2020-2021) breast cancer drugs and breast cancer drugs currently under Phase 3 clinical trials.

Methods

A search was conducted on *fda.gov* and *clinicaltrials.gov* sites to find out the following:

1. How many new breast cancer drugs or treatments have been approved by the US Food and Drug Administration (US FDA) in last 2 years (2020-2021)?
2. How many breast cancer treatment drugs are currently under Phase 3 clinical trials (2017-2021)? (***Search criteria***: breast cancer≠females≠interventional clinical trials≠Phase 3≠Active≠2017 to 2021).

Results

The following sections present search results for the following:

1. Drugs approved by FDA for the treatment of breast cancer between January 2020 to July 2021.
2. Breast cancer treatment drugs currently under Phase 3 clinical trials (2017-2021).

Breast Cancer Drugs Approved Between 2020-2021

Four new drugs have been approved by FDA between 2020 and 2021 for the treatment of breast cancer. These drugs are presented Table 1 and are described in detail below.

Table 1. Breast Cancer Drugs Approved by FDA in 2020-2021

Year	Drug Name	Approval Date	Indication	Manufacturer
2020	Tukysa (tucatinib)	17 April 2020	HER2-positive metastatic breast cancer that cannot be surgically removed	Seagen
	Margenza (margetuximab-cmkb)	16 December 2020	Metastatic HER2-positive breast cancer	MacroGenics
	Phesgo (fixed-dose combination of pertuzumab, trastuzumab, and hyaluronidase–zzxf)	29 June 2020	Triple-negative breast cancer	Genentech
2021	Trodelvy (sacituzumab)	07 April 2021	Triple-negative breast cancer who received at least two prior therapies for metastatic disease	Gilead Sciences
FDA=Food and Drug Administration; HER2=human epidermal growth factor receptor 2				

Breast Cancer Drugs Approved in 2020-2021

Trodelvy (Gilead Sciences) [7 and 8]

Generic name: sacituzumab govitecan-hziy.

Clinical indication: For adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease.

Mechanism of action: Trodelvy is a first-in-class antibody and topoisomerase inhibitor conjugate directed to the Trop-2 receptor, a protein frequently expressed in multiple types of epithelial tumors.

Results of clinical study that led to drug approval: The regulatory body (FDA) granted accelerated approval to Trodelvy in April 2020 based on a Phase 1/2, single-group, multicenter trial involving patients with advanced epithelial cancers who received sacituzumab govitecan-hziy intravenously on days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxic effects. Trodelvy demonstrated a statistically significant and clinically meaningful 57% reduction in the risk of disease worsening or death. Trodelvy also extended median OS to 11.8 months versus 6.9 months, representing a 49% reduction in the risk of death. Four deaths occurred during treatment; 3 patients (2.8%) discontinued treatment because of adverse events. Grade 3 or 4 adverse events (in ≥10% of the patients) included anemia and neutropenia; 10 patients (9.3%) had febrile neutropenia.

Serious side effects: Trodelvy also caused serious side effects, including neutropenia, severe diarrhea, serious infusion-related reactions, and allergic reactions that can be life-threatening, and nausea and vomiting in the phase 3 trial. Serious adverse reactions occurred in 27% of patients receiving Trodelvy [9]

Margenza (Macrogenics) [7 and 10]

Generic name: margetuximab-cmkb.

Clinical indication: Treatment of adult patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.

Mechanism of action: Margenza is an HER2-targeting antibody. Margenza produces its anti-cancer effects by binding to and disabling a growth stimulatory pathway on cancer cells referred to as the human epidermal growth factor receptor 2 (HER2) pathway.

Results of clinical study that led to drug approval: FDA approval was based on a randomized, multicenter, open-label trial of 536 patients. Median progression-free survival in the margetuximab arm was 5.8 months (95% CI: 5.5, 7.0) compared with 4.9 months (95% CI: 4.2, 5.6) in the control arm (HR 0.76; 95% CI: 0.59, 0.98; p=0.033).

Possible side effects: Margenza may cause serious side effects, including weakening of the heart, harm to unborn baby and infusion reactions.

Tuksya (Seagen) [7 and 11]

Generic name: tucatinib.

Clinical indication: A triple-combination therapy for people with previously treated advanced or metastatic HER2-positive breast cancer.

Mechanism of action: Tiksya is a tyrosine kinase inhibitor of HER2 and blocks the activity of HER2, a protein receptor that is known to promote the growth of certain types of breast cancer.

Results of clinical study that led to drug approval: FDA approval of Tuksya was based on results from a pivotal Phase 2 trial in 612 people with HER2-positive breast cancer that was inoperable or metastatic. Compared with a placebo, Tukysa significantly extended patients' progression-free survival (median 5.6 vs. 7.8 months), representing a 46% reduced risk of disease progression or death with the therapy.

Possible side effects: Tukysa may cause serious side effects including severe diarrhea, liver damage, and harm to an unborn baby.

Phesgo (Genentech) [7 and 12]

Generic name pertuzumab, trastuzumab, and hyaluronidase-zzxf.

Clinical indication: As neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer as part of a complete treatment regimen for early breast cancer and as adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence.

Mechanism of action: Phesgo is a combination of two HER2/neu receptor antagonists and the endoglycosidase hyaluronidase.

Results of clinical study that led to drug approval: Phesgo is a subcutaneous formulation of pertuzumab and trastuzumab with recombinant human hyaluronidase in one ready-to-use, fixed-dose combination vial (pertuzumab, trastuzumab, and hyaluronidase-zzxf) and was approved by the FDA on June 29, 2020 based on the results of a non-inferiority study in patients with HER2-positive early breast cancer, which demonstrated Phesgo had comparable efficacy and safety as IV pertuzumab and IV trastuzumab, except for administration-related reactions, which were higher with Phesgo due to the subcutaneous route of administration.

Possible side effects: Phesgo may cause serious heart and lung problems [13]. Please see Phesgo prescribing information/label for more details.

Breast Cancer Drugs Currently Under Phase 3 Clinical Trials

Currently, there are several ongoing Phase 3 clinical trials of breast cancer drugs; of these, those clinical trials that are active since 2017 but not recruiting patients are presented in Table and are described below [14].

Table 2. Breast Cancer Drugs Currently Under Phase 3 Clinical Trials (Active but not Recruiting [2017-2021])

Study	Clinical Trials.gov Identifier	Intervention	Sponsor/Collaborator
Neoadjuvant Hormonal Therapy Plus Palbociclib in Operable, Hormone Sensitive and HER2-Negative Primary Breast Cancer	NCT03969121	Palbociclib	Kyoto Breast Cancer Research Network/Pfizer
PAlbociclib Plus Tamoxifen for the Treatment of Hormone Receptor-positive, HER2-negative Advanced Breast Cancer Women - Asian studY (PATHWAY)	NCT03423199	Palbociclib, Tamoxifen, and Goserelin	National Cancer Center, Japan/Pfizer
Study of the Molecular Features of Postmenopausal Women With HR+ HER2-negative aBC on First-line Treatment with Ribociclib and Letrozole and, in Patients with a PIK3CA Mutation, on Second-line Treatment with Alpelisib Plus Fulvestrant (BioItaLEE)	NCT03439046 Novartis Pharmaceuticals	Ribociclib, Letrozole, Alpelisib, and Fulvestrant	Novartis Pharmaceuticals
A Study of evaluating the Effects of Pyrotinib After Adjuvant Trastuzumab in Women with Early Stage Breast Cancer	NCT03980054	Pyrotinib	Jiangsu HengRui Medicine Co., Ltd.
The Neoadjuvant Combined Hormone Therapy in Premenopausal Women with Locally Advanced ER+/HER2- Breast Cancer	NCT04753177	Doxorubicin, cyclophosphamide, paclitaxel	Saint Petersburg State Budgetary Healthcare Institution, City Clinical Oncology Dispensary
ER=estrogen receptor; HER2=human epidermal growth factor receptor 2			

Study 1

Neoadjuvant Hormonal Therapy Plus Palbociclib in Operable, Hormone Sensitive and HER2-Negative Primary Breast Cancer.

Clinical Trials.gov Identifier: NCT03969121.

Recruitment Status: Active, not recruiting.

First Posted on ClinicalTrials.gov: May 31, 2019.

Last Update Posted on ClinicalTrials.gov: June 22, 2021.

Sponsor: Kyoto Breast Cancer Research Network.

Collaborator: Pfizer.

Intervention/Treatment: Palbociclib.

Study Description: The study is a randomized, double blind, placebo controlled, Phase 3 clinical trial with the primary objective of demonstrating the efficacy of palbociclib in

combination with Endocrine therapy over Endocrine therapy alone measured by PEPI and EndoPredict™ EPclin Score in women with operable HR+, HER2 negative breast cancer. The Clinical Response Rate, drop in Ki67 index ≤ 2.7% and Breast conserving rate will be compared between two arms.

Study 2

PAlbociclib Plus Tamoxifen for the Treatment of Hormone Receptor-positive, HER2-negative Advanced Breast Cancer Women - Asian studY (PATHWAY).

Clinical Trials.gov Identifier: NCT03423199.

Recruitment Status: Active, not recruiting.

First Posted on ClinicalTrials.gov: February 6, 2018.

Last Update Posted on ClinicalTrials.gov: November 19, 2020.

Sponsor: National Cancer Center, Japan.

Collaborator: Pfizer and Korean Cancer Study Group.

Intervention/Treatment: Palbociclib, Tamoxifen, and Goserelin.

Study Description: This study is conducted to evaluate the benefit of adding palbociclib in hormone receptor (HR)-positive, HER2-negative advanced or metastatic breast cancer patients, regardless of menopausal status, treated with tamoxifen (with or without goserelin) versus tamoxifen alone (with or without goserelin).

Study 3

Study of the Molecular Features of Postmenopausal Women With HR+ HER2-negative aBC on First-line Treatment with Ribociclib and Letrozole and, in Patients with a PIK3CA Mutation, on Second-line Treatment with Alpelisib Plus Fulvestrant (BioItaLEE).

Clinical Trials.gov Identifier: NCT03439046.

Recruitment Status: Active, not recruiting.

First Posted on ClinicalTrials.gov: February 20, 2018.

Last Update Posted on ClinicalTrials.gov: May 27, 2021.

Sponsor: Novartis Pharmaceuticals.

Intervention/Treatment: Ribociclib, Letrozole, Alpelisib, and Fulvestrant.

Study Description: The purpose of this clinical trial is to study of the molecular features of postmenopausal women with hormone receptor-positive (HR+) HER2-negative advanced breast cancer on first-line treatment with ribociclib and letrozole and, in patients with a PIK3CA mutation, on second-line treatment with alpelisib plus fulvestrant.

Study 4

A Study of evaluating the Effects of Pyrotinib After Adjuvant Trastuzumab In Women With Early-Stage Breast Cancer.

Clinical Trials.gov Identifier: NCT03980054.

Recruitment Status: Active, not recruiting.

First Posted on ClinicalTrials.gov: June 10, 2019.

Last Update Posted on ClinicalTrials.gov: May 24, 2021.

Sponsor: Jiangsu HengRui Medicine Co., Ltd.

Intervention/Treatment: Pyrotinib.

Study Description: This is a randomised, double-blind multicenter Phase III study for evaluating the efficacy and safety of pyrotinib in women with early-stage high-risk breast cancer after adjuvant trastuzumab. The main purpose of this study is to investigate whether pyrotinib can further reduce the risk of recurrence from previously diagnosed HER-2 positive breast cancer after adjuvant treatment with trastuzumab.

Study 5

The Neoadjuvant Combined Hormone Therapy in Premenopausal Women with Locally Advanced ER+/HER2- Breast Cancer.

Clinical Trials.gov Identifier: NCT04753177.

Recruitment Status: Active, not recruiting.

First Posted on ClinicalTrials.gov: February 15, 2021.

Last Update Posted on ClinicalTrials.gov: February 15, 2021.

Sponsor: Saint Petersburg State Budgetary Healthcare Institution, City Clinical Oncology Dispensary.

Intervention/Treatment: Doxorubicin, cyclophosphamide, paclitaxel.

Study Description: The proposed research is an innovative investigation. The study will consist of two modes of treatment, combined hormone therapy with CDK4/6-ingibitors and chemotherapy (the control), each replicated four times in a randomized, complete block design. This research aims to improve the results of treatment, namely, to increase the percentage of successfully treated patients and reduce toxicity from treatment. Primary study endpoints will include the frequency of objective response and complete pathomorphological response (according to the Miller-Payne classification). Secondary endpoints will include a decrease of the Ki67 level in postoperative material compared to primary biopsy, the frequency of organ-preserving operation after neoadjuvant treatment and quality of life. Study hypothesis: neoadjuvant combined hormone therapy with CDK4/6-ingibitors in premenopausal women with luminal breast cancer leads to at least the same results as neoadjuvant chemotherapy, but with less toxicity.

Discussion

Breast cancer is a cancer that develops from breast tissue. Breast cancer is the most common type of cancer in women. Outcomes for breast cancer vary depending on the cancer type, the extent of disease and the person's age [15]. Worldwide, breast cancer is the leading type of cancer in women, accounting for 25% of all cases [16]. In 2018, it resulted in 2 million new cases and 627,000 deaths [17]. It is more common in developed countries and is more than 100 times more common in women than in men [16].

Over recent decades, there have been significant advances in the variety of therapies available for the treatment of breast cancer. These developments have produced many improvements in patient response and survival. In primary breast cancer, chemotherapy has been shown to provide significant long-term benefits in the prevention of recurrence and prolongation of patient survival [18, 19, 20].

Pharmaceutical and biotech companies are making incredible contributions by developing many innovative and effective treatments for breast cancers. Despite increasing cases, survival rates of breast cancer are improving significantly. In this article, we presented the breast cancer drugs that have recently been approved by US FDA. Between January 2020 and July 2021, FDA approved 4 new drugs for the treatment of breast cancers, Tukysa, Margenza, Phesgo, and Trodelvy. Research continues to find out new drugs that can help treat breast cancer. Currently, there are several breast cancer drugs undergoing Phase 3 clinical trials including two major new breast cancer drugs Palbociclib (Pfizer) and Ribociclib (Novartis).

Conclusion

Pharmaceutical and biotech companies are making incredible contributions by developing many innovative and effective treatments for breast cancers. Despite increasing cases, survival rates of breast cancer are improving significantly. We are hopeful that many new breast cancer drugs will be approved in the coming years.

Conflict of Interest

There is no conflict of interest.

Acknowledgement

None.

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