JOURNAL OF PHARMACEUTICAL SCIENCE AND BIOSCIENTIFIC RESEARCH (JPSBR)

(An International Peer Reviewed Pharmaceutical Journal that Encourages Innovation and Creativities)

A brief review on breast cancer and its treatment by novel drugs

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Article History:

Received 15 Jun 2022
Revised 12 Dec 2022
Accepted 10 March 2022
Available online 31 March 2022

Citation:
Jain D., Merai A., Paul A. Inego J.P. and A brief review on breast cancer and its treatment by novel drugs **J Pharm Sci Bioscientific Res**. 2022. 11(2): 64-72

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(www.jpsbr.org)

ABSTRACT:

Breast cancer is a type of cancer where uncontrolled growth of cells occurs in the breast. Breast carcinoma usually occurs in women and rarely in men. As per WHO, 14% of breast cancer occur in women in India. In India, the highest rate of breast cancer was observed in the Northeast and major cities like Mumbai, Delhi. Risk factor of breast cancer includes late at first pregnancy, delayed marriage, family history of breast cancer, alcohol consumption and obesity. Symptoms of breast carcinoma include a lump in the breast, bloody discharge from the nipple, and changes in the shape or texture of the nipple or breast. The treatment depends on the stage of cancer, which may consist of chemotherapy, radiation, hormone therapy, and surgery. Drugs like tamoxifen, doxorubicin, 5-fluorouracil, and cyclophosphamide are used in various stages of cancer. This article review on breast cancer and its novel drugs which were approved by the US FDA for the treatment at various stages of breast cancer.

KEY WORDS: Breast cancer, chemotherapy, treatment, surgery, Neratinib, Talazoparib

INTRODUCTION

One of the most common cancer in females is Breast cancer, which is nearly 23% of all cancers in women. (1) The occurrence of breast cancer is highest in USA and Europe as compared to Africa and Asia which is increasing in developing countries day by day. It can treatable if it is detected at an early stage. (2) However, it is important to provide education and awareness to rural and urban women of India. (3) In 2017, breast cancer was the third-highest incidence cancer with an estimated 1,960,681 incident cases. (2) In 2018, 2,088,849 new cases were found which leads to 626,679 deaths. In India, the highest rates of breast cancer were observed in the Northeast and major cities such as Mumbai and Delhi. The reason for this includes education, adiposity, age at first child and number of children, and lifestyle factors such as tobacco, alcohol use. (1)

ETIOLOGY:

The causes of breast cancer are associated with age, family or personal history of breast cancer, hormonal and reproductive factors like early menarche, short or no period of breastfeeding, later menopause, or late age at first pregnancy. (4) It also includes hormonal replacement therapy, obesity, consuming alcohol, exposure to ionizing radiation, and genetics. (5)

Reproductive factors and hormones

Age of menarche and menopause: Early age at menarche and late age at menopause is associated with an increased risk of breast cancer. (6) The ovary produces steroid hormone which affects the function and development of the breast. (4) In pre-and postmenopausal women, it is seen that exposure to high concentrations of estrogens for long term increases the risk of breast cancer due to its mechanism associated with estrogen receptors/progesterone receptor-positive tumor and etiology of ER/PR negative tumor is non-hormonal. (7)

Nulliparity and later age at first pregnancy: Delayed childbirth due to an increase of contraception and socio-economic development has been postulated to increase breast cancer. (8) At present, a childbearing pattern has been changed to fewer children and later age at births which can increase the risk of breast cancer. (9)

Exogenous hormones: Combined estrogen-progesterone contraceptives and estrogen-progesterone menopausal therapy are also causes of breast cancer. (10)

Family history of breast cancer and genetic susceptibility: In a study, it is seen that women with any relative, mother, or sister having a history of breast cancer have twice the chances of developing breast cancer. (11)

Breast density: Radio-dense fibro glandular tissue which is present in the breast is a predictor of breast cancer risk. In pre-diagnostic mammograms, it is seen that women with high breast density (≥75%) have a high risk of breast cancer. (12)

Ionization radiation: X-radiation and gamma radiation are the causative agents for breast cancer. In a study, it is seen that women who are exposure to x-radiation for the treatment of tuberculosis have 61% chance of breast cancer within 10 years after exposure. (13)

Alcohol consumption and tobacco smoking: Consumption of alcoholic beverages has been classified as a carcinogenic agent for female breast by IARC. A dose-response relationship has also been found between the risk of breast cancer and alcohol consumption. (14) Tobacco smoking is an agent with limited confirmation of causing breast cancer but it is suggested to avoid tobacco smoking as it is dangerous to health causing other cancer like mouth, lung cancer. (14)

Other causes of breast cancer:

Increased body weight: Increased BMI and obesity has also been associated with the risk of breast carcinoma as its relationship differs according to pre-postmenopausal status. (15)

Diet: The risk of breast cancer due to nutritional factors is heterogeneous, controversial, and inconclusive. (16) However, dairy products, meat, egg, and cereals have no evidence of risk of breast cancer. It is concluded that red meat is a possible cause of breast carcinoma. (17)

Physical activity: The dose-response relationship between physical activity and risk of breast cancer in which it was found that no physical activity has a high risk of breast carcinoma. (18)

TYPES OF BREAST CANCER

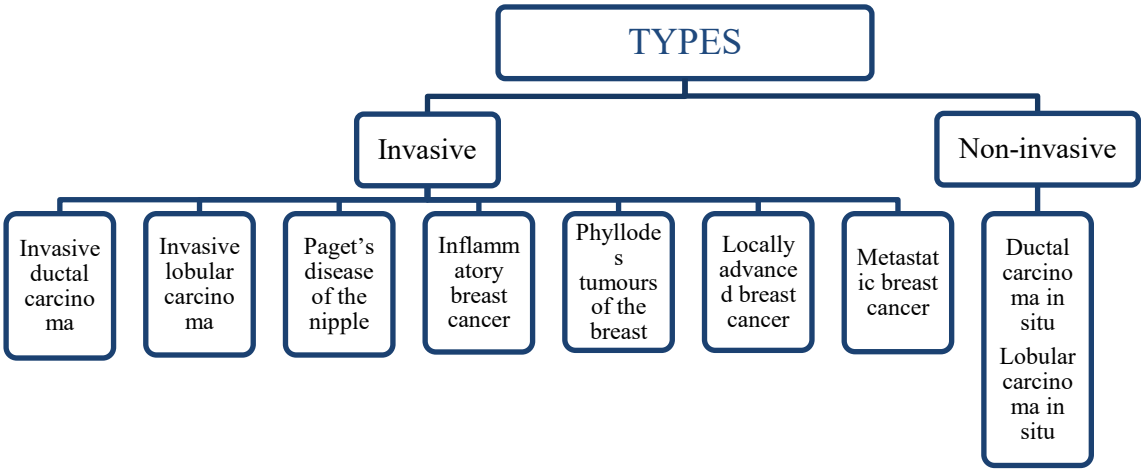

Figure 1 Types of Breast Cancer

Invasive breast cancer: Cancer which spreads outside the ducts of the breast into surrounding breast tissues is known as invasive breast cancer. (18)

Invasive ductal carcinoma: The most common type of breast cancer is invasive ductal carcinoma which began in the milk duct of breasts and spread surrounding the breast tissue. It can spread to lymph nodes and another part of the body if not treated on time. (19)

Invasive lobular carcinoma: This is the most common type of breast cancer after invasive ductal carcinoma in which the milk-producing lobule of the breast has broken through

the lining of the lobule and spread surrounding tissues in the breast. (20)

Paget's disease of the nipple: This is a rare form of breast cancer in which the cancer cells grow in the nipple or areola (the area around the nipple). The area becomes scaly, red, itch, and irritated. (21)

Inflammatory breast cancer: This type of breast cancer is a rare type of breast cancer that affects the blood vessels in the skin and/or lymphatic vessels of the breast. (22)

Phyllodes tumors of the breast: Most of the phyllodes tumors are benign (non-cancerous) and some are malignant (cancerous). They grow very quickly but rarely spread outside the breast. They develop in the breast's connective tissue or stroma. (23)

Locally advanced breast cancer: Locally advanced breast cancer is large or has spread beyond the breast area like chest wall, skin, or muscle. (24) Metastatic breast cancer: Metastatic breast cancer is also known as secondary or stage 4 cancer which starts from the breast and spread to another part of the body like the lungs, liver, or bones. (24)

Non-invasive breast cancer: Cancer that is contained within the milk ducts or lobules of the breast is known as non-invasive breast cancer. They do not grow or invade, the normal breast tissue. (25)

Ductal carcinoma in situ: Ductal carcinoma is the most common type of invasive cancer, which starts in the milk ducts and hasn't spread to the surrounding breast tissue. (26)

Lobular carcinoma in situ: This breast cancer grows in the lobules which are milk-producing glands at the end of breast ducts. (27)

Subtypes of breast cancer

Hormone receptor-positive breast cancer: Hormone receptor-positive cancer in which a patient needs female hormone (estrogen or progesterone) to grow and reproduce. About two-thirds of breast cancer is hormone receptor-positive cancer. (28)

HER-2 positive breast cancer: The (HER-2 known as human epidermal growth factor receptor-positive breast cancer has too much protein on the surface of the cancer cells. These proteins promote the growth of cancer cells. It can positive or negative receptor breast cancer. (29)

Triple-negative breast cancer: Around 15% of breast cancer is triple-negative. It is a type of cancer where none of the receptors of breast cancer cells are involved i.e. estrogen, progesterone,

or HER- 2. In this cancer, the main risk factor is a mutation of BRCA 1 or BRCA 2 genes which normally prevent the development of cancerous cells. (30)

TREATMENT OF BREAST CANCER

Local treatment: In local treatment, tumors are removed from the body by surgery without affecting other parts of the body. (31)

Surgery of breast cancer: There are different types of surgeries which can be done for a different reason according to a situation. Among them, mastectomy and breast-conserving surgery are two of the most used surgery. (31) In a mastectomy, the entire breast is removed with breast tissues during surgery. There are further different types of mastectomies like skin-sparing mastectomy, simple mastectomy, modified radical mastectomy, nipple-sparing mastectomy, double or radical mastectomy. (32)

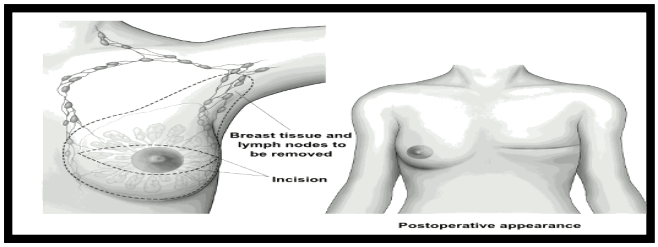

Figure 2 Modified radical mastectomy. (33)

Breast-conserving surgery which is also known as lumpectomy is a surgery that removes cancer without removing the entire breast. Along with breast-conserving surgery, radiation and chemotherapy are also necessary. (31)

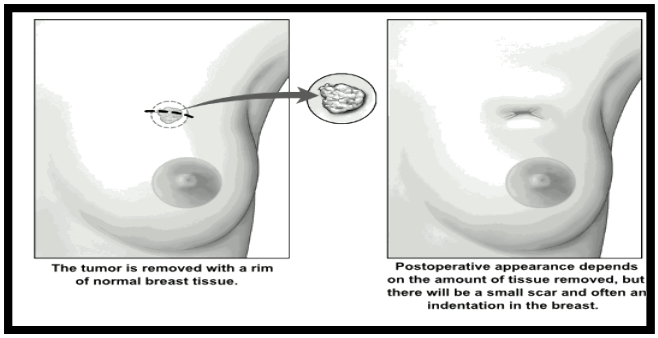

Figure 3 Lumpectomy or Partial Mastectomy. (34)

Radiation of breast cancer: In radiation therapy, cancer cells are destroyed by high-energy rays or particles. In some women along with the treatment radiation therapy is also necessary to treat breast cancer. It is done by external beam radiation. (35)

Systemic treatment of breast cancer

Chemotherapy: In chemotherapy, anticancer drugs are used which are given orally or intravenously. The drugs pass through the bloodstream to reach cancerous cells. Chemotherapy is used either after surgery (adjuvant) or before surgery (non-adjuvant). (36) Some of the drugs used in chemotherapy are;

- Anthracyclines like doxorubicin (Adriamycin) and epirubicin (Ellence)
- Taxanes like paclitaxel (Taxol) and Docetaxel (Taxotere)
- 5-fluorouracil (5-FU) or capecitabine
- Cyclophosphamide (Cytoxan)
- Carboplatin (Paraplatin)

Hormone therapy for breast cancer: Breast cancer that is affected by hormones like estrogen or progesterone can be treated by hormone therapy. It is used after surgery to reduce the risk of cancer coming back. (37) Class of drugs like estrogen receptor blockers, aromatase inhibitors, SERMs are used in hormone therapy. (37)

Targeted therapy for breast cancer: One of five women with breast cancer which have too much growth-promoting protein known as HER-2 which grows cancerous cells rapidly and aggressively. In this targeted therapy is used which directly targets in HER-2 protein. (38)

Different kinds of drugs like monoclonal antibodies, Herceptin, pertuzumab are used. (38)

Immunotherapy for breast cancer: Immunotherapy is medicine is used to stimulate a person's own immune system which can destroy cancerous cells. Drugs like PD-L1 inhibitors are used in this therapy. This therapy is also used to treat triple-negative breast cancer. (39)

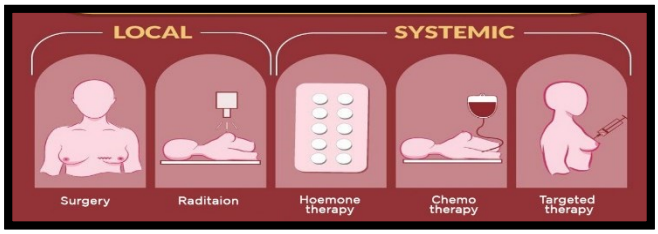

Figure 4 Treatment options for breast cancer. (40)

Novel drugs used in breast cancer

NERATINIB: Neratinib is an oral, irreversible pan-human epidermal growth factor receptor (HER) tyrosine kinase inhibitor of HER1, HER2, and HER4.(41) On July 17, 2017, Neratinib, a kinase inhibitor was approved by FDA for early HER 2 positive breast cancer. (42) Neratinib can be used as both monotherapy or in combination therapy in phase 3 development of HER 2 metastatic breast cancer. (43) It is also used in other cancer like non-small lung cancer. Colorectal cancer and glioblastoma. (41)

Mechanism of action: A kinase inhibitor, Neratinib irreversibly binds to HER-2, HER-4, and epidermal growth factor receptors (EGFRs). (41) The drug blocks several enzymes which promote cell growth. (43) The drug reduces autophosphorylation of HER-2 and EGFR which inhibits activation of downstream signal transduction pathways such as, MAPK and AKT involved in cell cycle regulation. (42) Neratinib can also be used in combination with Trastuzumab as both have different mechanisms one which binds with enzymes and the other binds to the extracellular domain of HER-2 respectively. (43)

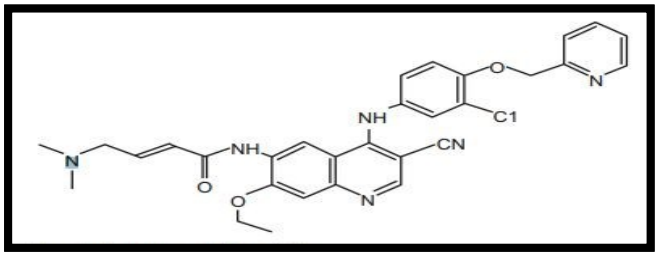

Figure 5 Chemical structure of Neratinib. (43)

Dosing and administration: The drug should be taken orally for 1 year at a dose of 240 mg i.e. 6 tablets daily (40mg/tablet). Loperamide which is an anti-diarrheal as prophylaxis is also recommended with Neratinib for the first 56 days of treatment. (43)

Pharmacokinetics: Neratinib is given orally and plasma concentration is 2-8 h. The drug should be taken with food. (41) Plasma protein binding was found to be >99% which bound mainly to albumin. It has a large apparent volume of distribution i.e. mean 6433 L. It metabolites via the CYP3A4 enzyme and excrete via faeces (97.1%) and minimal through urine (1.13%). (43)

Adverse reactions: The most common adverse reaction is Diarrhea (95%), abdominal pain (36%), nausea (43%), vomiting (23%), rashes (18%), stomatitis (14%), decreased appetite(12%), nail disorder ()8%, muscle spasm (11%), dry

skin (6%) and weight loss (5%).(42) Diarrhea is the most common adverse effect to overcome this Loperamide anti-diarrheal drug is given. (42)

Drug interactions: Neratinib should not give to breastfeeding women. It should not use with proton pump inhibitors. Neratinib should be avoided with rifampicin as it decreases the concentration of Neratinib. (42)

Therapeutic trials:

Table 1 Key clinical trials of Neratinib(43)

DRUGS	INDICATIONS	PHASE
Early-stage breast cancer		
Neratinib	HER-2	III
Neratinib + Transtuzumab	HER-2	II
Advanced stage breast cancer		
Neratinib + capecitabine	HER-2 + metastatic breast cancer	III
Neratinib + paclitaxel	Untreated HER-2 + advance breast cancer	II
Neratinib + paclitaxel	HER-2 + metastatic breast cancer	½

TALAZOPARIB: Talazoparib is an oral PRAP inhibitor, which was approved by the US FDA in October 2018 for the treatment of adults with deleterious or suspected deleterious germline BRCA-mutated, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced, or metastatic breast cancer. (44)Talazoparib, by inhibition of PARP catalytic activity and by PARP trapping exerts its cytotoxic effect. (45) Talazoparib becomes the second FDA-approved drug for the treatment of germline BRAC mutation and the fourth PARP inhibitor. (46)

Mechanism of action: Talazoparib is a potent PARP inhibitor which includes PARP-1 and PARP-2 enzymes. PARP enzymes play a role in DNA repair. (44)Talazoparib inhibits PARP enzymes. It will block PARP enzymatic activity by forming PARP-DNA complexes. (46) This results in DNA damage, decrease cell proliferation and apoptosis. (44) It exhibits antitumor activity by suppressing the growth of BRCA-1 mutated breast cancer. (46) It gives a synergistic or additive antitumor effect combine with temozolomide. (44)

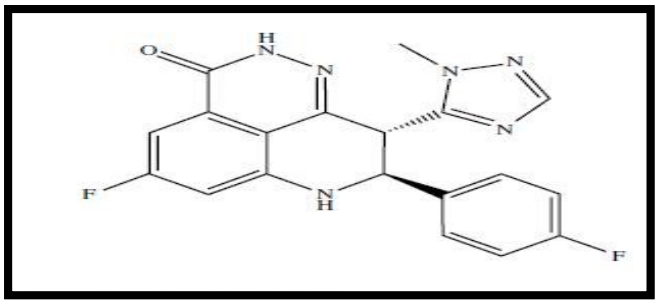

Figure 6 Chemical structure of Talazoparib. (44)

Adverse reactions: Talazoparib when used in monotherapy has a manageable tolerability profile in advanced and metastatic breast cancer. (44) The most common side effects which are graded are fatigue (62%), anemia (53%), nausea (49%), neutropenia (35%), headache (33%), thrombocytopenia (27%), vomiting (25%), alopecia (25%), diarrhea (25%), and decreased appetite (21%).(46)

Drug interaction: Talazoparib when co-administered with P-glycogen inhibitor, it increases exposure to talazoparib. To overcome this dose of talazoparib is reduced. (46)

Therapeutic trails

Table 2 Key clinical trials of talazoparib. (44)

DRUGS	INDICATION	PHASE
Talazoparib	Advanced solid	I/II
Talazoparib	Breast	II
Talazoparib v/s physician choice	Breast	III

ALPELISIB: Alpelisib a phosphatidylinositol 3-kinase (PI3K) inhibitor with specific activity against PI3K alpha (PI3Kα) for the treatment of breast cancer. (47) It was approved by FDA on May 24. 2019. It can be used in combination with Fulversant in HER-2 negative, hormone receptor, metastatic, and advanced breast cancer. (48)

Mechanism of action: Alpesilib inhibited the most common PIK3CA somatic mutations. (47)

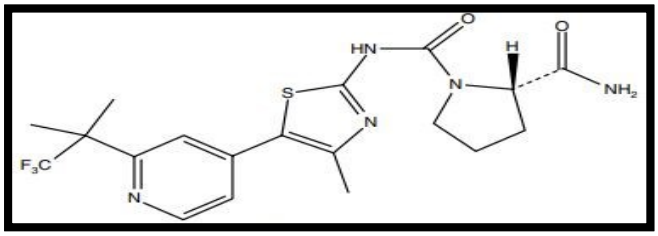

Figure 7 Chemical structure of Alpesilib. (47)

Dosing and administration: The dose recommended of alpesilib is 250 mg oral taken with food once daily. If adverse reactions occur dose can be reduced to 200 mg later. (49)

Pharmacokinetic: The drug is taken orally starting at a dose of 250 mg for 28 days cycles. Plasma concentration of drug was found to be 0-12 h. The volume of distribution is estimated at 10 L/h. it is excreted as unchanged form via faeces (79.8%) and urine (13.1%). (47)

Adverse reaction: The most frequent adverse effects are hyperglycemia, Diarrhea, rash, nausea, fatigue, and decrease appetite. Occasional adverse effects like severe pneumonitis, severe hypersensitive reactions may also occur. (49)

Therapeutic trails:

DRUGS	INDICATION	PHASE
Alpelisib, letrozole, ribociclib	Advance ER + breast cancer	I
Alpelisib, nab-paclitaxel	Locally recurrent or metastatic HER2− breast cancer	I/II
Alpelisib	Advanced breast cancer	II
Alpelisib, trastuzumab-MCC-DM1	HER-2 + metastatic breast cancer	I

FAM-TRASTUZUMAB DERUXTECAN-nxki: Trastuzumab deruxtecan(Enhertu®) is an antibody-drug conjugate composed of an anti-human epidermal growth factor receptor 2 (HER2) monoclonal antibody (trastuzumab) bound to a topoisomerase I inhibitor (deruxtecan). The drug was approved by FDA on December 23, 2019. (50)

Mechanism of action: The drug binds to HER-2 on tumor cells. In tumor cells, a tetrapeptide-based linker is present which cleaves lysosome enzymes between trastuzumab and deruxtecan leading to inhibition of topoisomerase I enzymes and DNA damage occurs which causes apoptosis of cells. (51)

Dosing and administration: The drug is given via intravenous route as 5.4 mg/kg once over 90 minutes every 3 weeks until unacceptable toxicity. (50)

Adverse effects: The most common side effects are nausea, fatigue, vomiting, alopecia, constipation, decreased appetite, anemia, neutropenia, diarrhea, leukopenia, thrombocytopenia, abdominal pain, headache, upper respiratory tract infection, stomatitis, dyspnea, epistaxis, dyspepsia, hypokalemia, dizziness, skin rash, and transaminitis. (50) The drug is mainly used in the treatment of metastatic breast cancer.

TUCATINIB: In April 2020 FDA approved the drug name Tucatinib (Tukysa™) for the treatment of advance, metastatic HER-2 positive breast cancer. The drug is used in combination therapy with trastuzumab and capecitabine. (52)

Mechanism of action: Tucatinib is a potent and selective tyrosine kinase inhibitor that reversibly binds to the ATP pocket of the internal domain of the HER-2 receptor, which prevents the activation of the ERBB-2 signal transduction pathway. Inhibition of HER-2 leads to apoptosis. (52)

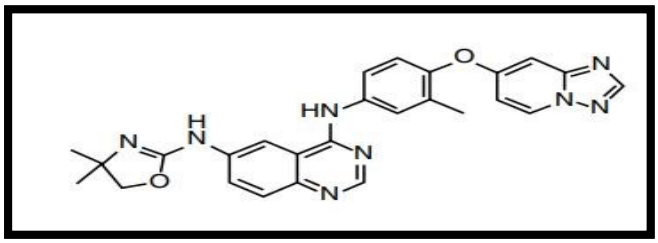

Figure 8 Chemical structure of Tucatinib. (52)

Dosing and administration: The dosage of tucatinib is 300 mg taken orally twice daily with or without food. (53)

Pharmacokinetics: Tucatinib is taken orally with plasma protein binding 97% and half-life 8.5 h. Tucatinib is primarily metabolized by CYP2C8, in addition to CYP3A to a lesser extent. The apparent volume of distribution is 1670 L. it is excreted through faeces and urine. (52)

Adverse reactions: The safety of tucatinib was evaluated in combination with trastuzumab. The most common adverse effects diarrhea (81%), palmar-plantar erythrodysesthesia syndrome (63%), and nausea (58%). (53)

Therapeutic trails:

Table 3 Key clinical trials of Tucatinib. (52)

DRUGS	INDICATION	PHASE
Tucatinib, trastuzumab emtansine	HER-2 + metastatic breast cancer	III
Tucatinib, chemotherapy	Breast	II

Tucatinib	HER-2 + solid malignancies	I
Tucatinib, capecitabine, trastuzumab	HER-2 + metastatic breast cancer	Ib

NOVEL DRUGS FOR TREATING CANCER

Table 4 Novel drugs

DRUGS	MODE OF ACTION	TARGETED POPULATION	LATEST STAGE OF CLINICAL DEVELOPMENT
Neratinib (Nerlynx®)	Irreversible binder of HER1, HER2, and HER4	Early-stage	Phase III
Talazoparib (TALZENNA™)	Oral PARP inhibitor	Metastatic breast cancer	Phase II
Alpelisib (Piqray™)	Oral small-molecule inhibitor of α-specific class I PI3	Advance stage Early-stage	Phase III Phase II
Trastuzumab deruxtecan(Enhertu®)	Combination of monoclonal antibody and topoisomerase I inhibitor	Metastatic breast cancer	Phase II
Tucatinib (Tukysa™)	Selective tyrosine kinase inhibitor	Advance, metastatic HER-2 breast cancer	Phase III

CONCLUSION

The most common cancer in females is breast cancer. The mortality rate of breast cancer is decreasing in the last decade with the advancement of chemotherapy and novel drugs. Drugs with the mechanism of HER-2 positive inhibitor, PARP inhibitors are used in metastatic and advanced breast cancer. In India, an awareness program should be conducted for the awareness for breast cancer examination which can diagnose breast cancer at an early stage and can treat it. Treatment should be tailored to individual patients accordingly.

ACKNOWLEDGEMENT: The authors are expressing sincere thanks to all the researchers involved and whose articles are used as sources of information to prepare this review work.

Conflict of Interest

The authors have no conflict of interest.

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