



Molecular perspective on targeted therapy in breast cancer: a review of current status

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Abstract

Breast cancer is categorized at the molecular level according to the status of certain hormone and growth factor receptors, and this classification forms the basis of current diagnosis and treatment. The development of resistance to treatment and recurrence of the disease have led researchers to develop new therapies. In recent years, most of the research in the field of oncology has focused on the development of targeted therapies, which are treatment methods developed directly against molecular abnormalities. Promising advances have been made in clinical trials investigating the effect of these new treatment modalities and their combinations with existing therapeutic treatments in the treatment of breast cancer. Monoclonal antibodies, tyrosine kinase inhibitors, antibody–drug conjugates, PI3K/Akt/mTOR pathway inhibitors, cyclin-dependent kinase 4/6 inhibitors, anti-angiogenic drugs, PARP inhibitors are among the targeted therapies used in breast cancer treatment. In this review, we aim to present a molecular view of recently approved target agents used in breast cancer.

Keywords Breast cancer · Targeted therapy · PI3K/Akt/mTOR pathway inhibitors · CDK4/6 inhibitors · PARP inhibitors

Introduction

Breast cancer is a type of cancer that occurs mostly in the lobules (milk glands) or in the milk canals connecting the lobules to the nipple, in which cells change and divide uncontrolled that cause the formation of a mass. Cancer that occurs in the lobules is called lobular carcinoma, while cancer that occurs in the milk ducts is called ductal carcinoma. Ductal carcinoma accounts for 80% of all breast cancer cases (80% of all breast cancer cases are ductal carcinomas) [1, 2].

Breast cancer is the second most frequently diagnosed cancer type worldwide [3] and has the highest incidence of all cancer types seen in women [4]. It was recorded that there were approximately 316,700 new cases of breast cancer in American women in 2019, and the incidence of

breast cancer increased each year (272,400 cases in 2015 and 367,900 cases in 2018). Considering population growth rates, it is thought that there will be approximately 3.2 million new breast cancer cases per year worldwide by 2050 [5]. Breast cancer is common in underdeveloped and industrialized countries and is the second leading cause of death after lung cancer in Europe and the United States [2]. In addition, it is observed that the rate of being affected by the disease in young people has increased [5]. In recent years, it has been reported that breast cancer incidence and mortality rates have decreased due to increased awareness, advanced screening methods used for early diagnosis, advances in evidence-based treatment methods, and a decrease in hormone replacement therapy [4]. The majority of research in the field of oncology in recent years has focused on the development of targeted therapy. Targeted therapies are new therapies developed directly against molecular abnormalities or tumor cells that cause cancer development. The use of compounds such as Tyrosine Kinase Inhibitors (TKI), mammalian target of rapamycin (mTOR) inhibitors, PI3K (phosphoinositide 3-kinases) inhibitors that are named according to the target and that selectively target different signaling pathways associated with cell growth, proliferation or apoptosis, alone or together, have led to more successful results in cancer

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treatment [6]. In this review, we present a molecular view of the recently approved targeted agents used in breast cancer.

Anti-HER2 target therapies

Monoclonal antibodies

Monoclonal antibodies such as Trastuzumab and Pertuzumab bind to the extracellular domain of human epidermal growth factor receptor (HER) 2 and inhibit HER2 signal and show a direct antitumor effect [7]. In this way, inhibits the signaling of the receptor and downstream signaling pathways such as PI3K-Akt and mitogen-activated protein kinase (MAPK) independent of the ligand [8].

Trastuzumab

The first anti-HER2 agent used in the clinic was trastuzumab [8]. Trastuzumab was approved by the Food and Drug Administration (FDA) in 1998 for the treatment of HER2 positive (HER2+) breast cancer patients [9]. In addition to its direct antitumor effect, trastuzumab has been found to have immune system-mediated antitumor activity [10] by stimulating innate cellular immunity by means of natural killer cells and macrophages [8]. It has been determined that the main side effect of trastuzumab is left ventricular dysfunction, this effect is dose-independent and may cause congestive heart failure (CHF). However, it has been reported that this effect is often reversible, and it may be safe to restart the drug while using standard treatment for CHF after the complications have resolved [11].

Pertuzumab

Pertuzumab, another monoclonal antibody, was approved by the FDA in 2017 for use in combination with trastuzumab and chemotherapy as adjuvant therapy in patients with HER2+ early breast cancer at high risk of recurrence [12]. In addition to triggering antibody-dependent cellular cytotoxicity like trastuzumab, pertuzumab also prevents ligand-initiated heterodimerization of HER2 and other HER family members, especially HER3, unlike trastuzumab [11]. Evaluation of the early toxicity of co-administration of radiotherapy, pertuzumab, and trastuzumab in HER2+ breast cancer patients determined that the combination was well tolerated and toxicities such as an asymptomatic decrease in left ventricular ejection fraction, asymptomatic radiation pneumonia, acute skin toxicity, esophagitis, and radio dermatitis were noted, while no cardiac symptoms were observed [13, 14].

Margetuximab

Margetuximab, a second-generation HER2 monoclonal antibody, was approved by the FDA in 2020 for use in combination with chemotherapy for the treatment of adult patients with HER2+ metastatic breast cancer who have received two or more prior anti-HER2 treatments [15, 16]. It is suggested that margetuximab enhances the activation of innate and adaptive anti-HER2 immune responses relative to trastuzumab. Margetuximab plus chemotherapy has been shown to have acceptable safety and a statistically significant improvement in progression-free survival (PFS) compared to trastuzumab plus chemotherapy in HER2+ advanced breast cancer after progression on 2 or more previous anti-HER2 treatments [17]. It has been determined that the adverse effects of margetuximab therapy combined with chemotherapy are fatigue, pyrexia, nausea, diarrhea, vomiting, constipation, abdominal pain, alopecia, palmar-plantar erythro-dysesthesia, headache, peripheral neuropathy, cough, dyspnea, decreased appetite, arthralgia/myalgia, extremity pain, and infusion-related reactions [18].

Tyrosine kinase inhibitors (TKIs)

HER family proteins, which are type I transmembrane receptor tyrosine kinase (RTKs), have four members: HER1 (epidermal growth factor receptor (EGFR), ErbB1), HER2 (ErbB2), HER3 (ErbB3), and HER4 (ErbB4). There are several ligands such as epidermal growth factor (EGF) and Transforming growth factor α (TGF α) that bind to HER1, HER3, and HER4. By binding ligands to these receptors, intracellular signal pathways such as PI3K / Akt / mTOR, Ras / Raf / MEK (MAP kinase kinase) / ERK (MAP kinase) / MAPK, Src and Signal Transducer of Activators of Transcription (STAT), which regulate cell proliferation, migration, differentiation, cell motility, and apoptosis, are activated. Since HER2 does not have a known natural ligand, activation of intracellular signaling pathways occurs indirectly through dimerization with other ligand-coupled receptors [19, 20]. TKIs such as lapatinib, neratinib, tucatinib, and pyrotinib bind to the intracellular tyrosine kinase domains HER family members including HER2 [7]. HER signaling pathway and its inhibitors are shown in Fig. 1.

Lapatinib

Lapatinib ditosylate monohydrated, which is an oral 4-anilinoquinazoline derivative, reversibly binds to the cytoplasmic adenosine triphosphate (ATP) binding site of the tyrosine kinase of HER1, HER2 / ErbB2, and EGFR, subsequently prevents the receptor phosphorylation and activation, and in this way inhibit downstream signaling pathways such as ERK-1/2 and PI3K/Akt [21, 22]. Lapatinib

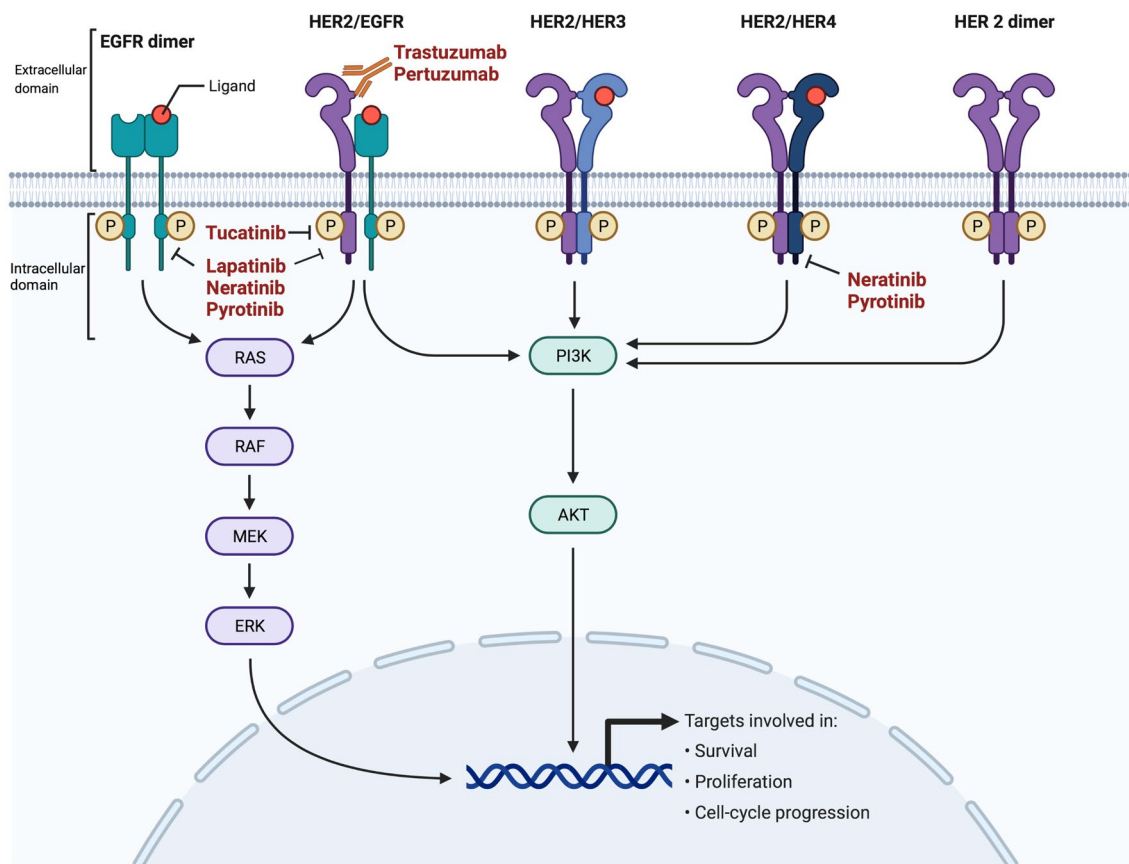


Fig. 1 Trastuzumab and pertuzumab inhibit HER2 signaling by binding to the extracellular domain of HER2. Lapatinib, neratinib, tucatinib, and pyrotinib inhibit HER signaling by binding to the intracellular tyrosine kinase domain of the Her family members. *EGFR* epidermal growth factor receptor, *HER* human epidermal growth fac-

tor receptor, *MEK* MAP kinase kinase, *ERK* MAP kinase, *PI3K* phosphoinositide 3-kinases (adapted from “HER2 Signaling Pathway”, by BioRender.com (2022). Retrieved from <https://app.biorender.com/biorender-templates>)

dystocylate monohydrate was approved by the FDA in 2007 for the treatment of metastatic HER2 + patients who have received prior therapy such as an anthracycline, a taxane, and trastuzumab [23] and is often used with chemotherapeutics, other agents targeting HER2 such as trastuzumab or with endocrine therapy [20]. The most common side effects associated with the use of lapatinib, which is generally well tolerated like other small molecule tyrosine kinase inhibitors, are diarrhea, rash, nausea, fatigue, abdominal cramping, gastroesophageal reflux disease [24].

Neratinib

Neratinib, oral TKIs, irreversibly binds to the tyrosine kinase domain of HER1, HER2, and HER4 and prevent its interaction with ATP and thereby inhibit receptor phosphorylation [25, 26]. Neratinib was approved by the FDA in 2017 for the adjuvant treatment of stage I-III HER2 + patients who have received one year adjuvant trastuzumab therapy [27].

Its most common adverse effects are diarrhea, fatigue, nausea, and vomiting [27, 28].

Pyrotinib

Pyrotinib is an orally administered irreversible TKI targeting HER family including HER1 (EGFR), HER2, and HER4 [29, 30]. Pyrotinib was conditionally approved in China for use in combination with capecitabine for the treatment of HER2 +, advanced or metastatic breast cancer in patients who have received prior anthracycline or taxane chemotherapy [31]. Pyrotinib is more effective than trastuzumab and lapatinib in drug resistance induced by EGFR or HER2 mutations due to covalent binding of tyrosine kinase receptors to cysteine residues and it has also been approved as a new method to increase the sensitivity of cancer cells to radiation by targeting the HER family and enhancing the therapeutic efficacy of radiation therapy [32]. The most common side effects associated with the use of pyrotinib are diarrhea, hand and foot syndrome, nausea, and vomiting [33].

Tucatinib

Tucatinib is an oral TKI. It minimally inhibits EGFR while being highly selective to HER2. By inhibiting the phosphorylation of HER2, preventing downstream signal transduction through the MAPK and PI3K pathways [34, 35]. Tucatinib was approved in April 2020 by the FDA in combination with trastuzumab and capecitabine for adult patients with advanced, unresectable, or metastatic HER2 + breast cancer, including those with brain metastasis who received at least one previous anti-HER2 treatment in metastatic setting and have failed [36]. The most common side effects associated with tucatinib are diarrhea, palmar-plantar erythrodysesthesia syndrome, nausea, fatigue, and vomiting [34, 36].

Antibody–drug conjugates (ADCs)

Antibody–drug conjugates are a new and promising group of anticancer drugs that combine the cancer specificity of antibodies with the cytotoxic properties of chemotherapeutics [37].

Trastuzumab emtansine (T-DM1)

Trastuzumab Emtansine, which consists of 1) trastuzumab 2) a non-cleavable thioether linker, N-maleimidomethyl cyclohexane-1-carboxylate (MCC); and 3) a potent microtubule-depolymerizing maytansinoid derivative, DM1, was approved by the FDA in 2013 for the treatment HER2 + metastatic breast cancer (MBC) [37, 38]. The mechanism of action of T-DM1 is believed to be mediated by trastuzumab-mediated inhibition of HER2 signaling and metabolites of DM1, which is a cytotoxic antimicrotubule agent and ultimately causes cell apoptosis [37, 39]. The most common adverse reactions associated with T-DM1 treatment are anemia, thrombocytopenia, and fatigue [40].

Trastuzumab deruxtecan (DS-8201a)

Trastuzumab-Deruxtecan, which consists of 1) trastuzumab; 2) an enzymatically cleavable maleimide glycine-glycine-phenylalanine-glycine (GGFG peptide linker that can be cleaved by lysosomal proteases while maintaining stable in serum; and 3) a topoisomerase I inhibitor Dxd, which is a novel water-soluble derivative of exatecan, a hexacyclic camptothecin analogue, was approved by the FDA in 2019 for the treatment HER2 + MBC [37, 41]. The mechanism of action of DS-8201a is mediated by trastuzumab-mediated inhibition of HER2 signaling and the Dxd component, which binds to the topoisomerase I-DNA complex, inducing double-stranded deoxyribonucleic acid (DNA) damage and cell apoptosis [37]. Unlike trastuzumab emtansine, trastuzumab

deruxtecan has a released charge that readily crosses the cell membrane and enables it to exert a potentially potent cytotoxic effect on neighboring tumor cells regardless of target expression [42]. The most common adverse reactions associated with DS-8201a treatment are decrease neutrophil count, anemia, and nausea (in 7.6%) [42].

Anti-angiogenics

Angiogenesis is a process involving the formation of new blood vessels from existing blood vessels. Angiogenesis is a critical factor that directly affects tumor growth and metastasis, since tumor growth is not possible in the absence of vascularization, and on the contrary, metastatic spread is possible [43, 44]. Although tumor angiogenesis is controlled by various cytokines and genetic factors [45], the main molecular trigger is vascular endothelial growth factor A (VEGF-A) [44].

Bevacizumab

Bevacizumab, a human recombinant antibody, prevents the binding of all VEGF-A isoforms to VEGF receptors and thereby inhibits angiogenesis [46, 47]. With pre-clinical study results showing that bevacizumab improves drug delivery and stabilizes the tumor microenvironment by inducing vascular remodeling and subsequent tissue oxygenation [47], it has created a positive prospect for its clinical use for the treatment of solid tumors, including breast cancer [46]. In a randomized phase III clinical study in patients with advanced and / or metastatic breast cancer, the addition of bevacizumab to paclitaxel treatment showed significant improvements in PFS, but did not result in prolongation of overall survival (OS), compared to cases where paclitaxel was used alone [47]. In conclusion, bevacizumab was approved by the FDA in 2008 for the treatment of HER2 negative (HER2-) breast cancer in combination with paclitaxel in metastatic conditions, but FDA approval was withdrawn in 2011 due to studies reporting that bevacizumab provided only minor improvements in PFS. In addition, in the preoperative setting, there are findings in various clinical studies showing that bevacizumab in combination with chemotherapy shows an improved pathological complete response in HER2- breast cancer and improved OS [48]. Bevacizumab is a treatment option for HER2- MBC, in combination with paclitaxel or capecitabine approved by the European Medicines Agency (EMA) [49]. The most common side effects associated with bevacizumab are hypertension, asymptomatic proteinuria, thromboembolism, impaired wound healing, bleeding, gastrointestinal perforation, reversible leukoencephalopathy syndrome, skin rash,

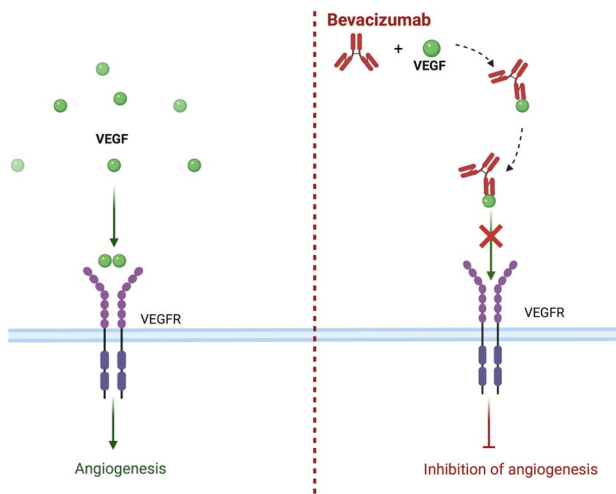


Fig. 2 Bevacizumab, a human recombinant antibody, inhibits angiogenesis. *VEGF* vascular endothelial growth factor (adapted from “Bevacizumab: Potential Repurposed Drug Candidate for Covid-19”, by BioRender.com (2022). Retrieved from <https://app.biorender.com/biorender-templates>)

and infusion-related hypersensitivity reactions [50, 51]. The inhibition of angiogenesis by bevacizumab is shown in Fig. 2.

CDK 4/6 inhibitors

Cyclin-dependent kinases (CDKs) are critical enzymes that direct cell division by regulating cell cycle transitions [52]. Retinoblastoma (Rb) protein, a tumor suppressor protein, stops G1 / S transition by binding E2F transcription factors, thereby controlling early cellular division. In the G1 phase, CDK4 and 6, which are members of Cyclin-dependent kinases, form complexes with cyclin D1, D2, D3 through various growth signals. By phosphorylating the CDK4/6-cyclin D complex Rb, it causes the release of E2F, which is bound to Rb, and thus ensures the progression of the cell cycle. Small molecule CDK4/6 inhibitors inhibit cell cycle progression by inhibiting Rb phosphorylation [52, 53]. Since cyclin D1 is a transcriptional target of the estrogen receptor (ER) and is overexpressed in about half of breast cancers, CDK4/6 inhibitors are important for the treatment of ER positive (ER+) breast cancer. CDK4/6 inhibitors have been reported to show activity in ER+ breast cancer in both pre-clinical and clinical trials [54]. CDK4/6 inhibitors, palbociclib, ribociclib, and abemaciclib, are approved by the FDA in combination with endocrine therapy for the treatment of hormone receptor positive (HR+) / HER2- breast cancer and have had a significant effect for the treatment [52, 55]. These drugs can be administered orally and are well tolerated, and

have shown an increase in OS [55]. Inhibition of the cell cycle progression by CDK4/6 inhibitors is shown in Fig. 3.

Palbociclib

Palbociclib, which was first approved by the FDA in 2015 to be used in combination with letrozole in breast cancer patients with continued disease progression following endocrine therapy, palbociclib received granted regular approval in 2016 for use in combination with fulvestrant for the treatment of continued disease progression following endocrine treatment of women with HR+, HER2- MBC. Approved for use in pre-treated settings on the specified dates, palbociclib was approved by the FDA in 2017 as a first-line treatment for postmenopausal women for use in combination with any aromatase inhibitor. Palbociclib, with a well-defined toxicity profile, has been shown to cause neutropenia, which is noticeable but not associated with serious infections [56, 57].

Ribociclib

Ribociclib, one of the orally administered, selective, small molecule inhibitors of CDK4/6 [58, 59] was approved by the FDA in 2017 for use as first-line treatment in combination with an aromatase inhibitor such as letrozole in postmenopausal women with HR+ /HER2- advanced or MBC, as well as in combination with letrozole in postmenopausal women with HR+ /HER2- resectable (early) stage breast

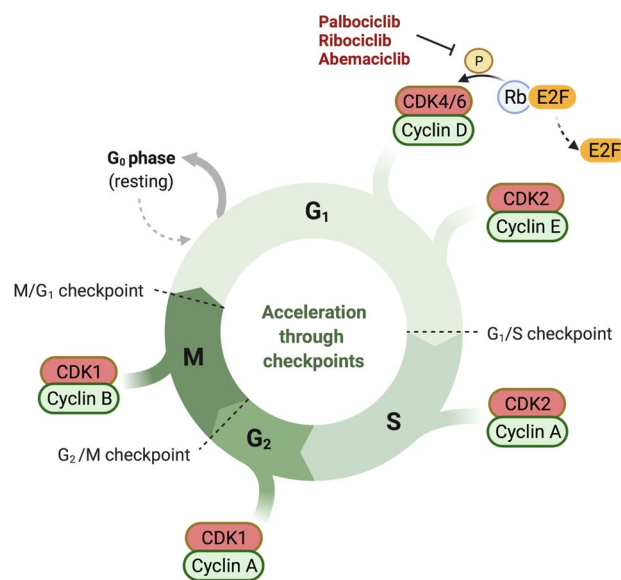


Fig. 3 Small molecule CDK4/6 inhibitors inhibit cell cycle progression by inhibiting Rb phosphorylation. *CDK* cyclin-dependent kinases, *Rb* retinoblastoma (adapted from “Cell Cycle Deregulation in Cancer”, by BioRender.com (2022). Retrieved from <https://app.biorender.com/biorender-templates>)

cancer [60]. The most common adverse reactions associated with ribociclib, which has an acceptable safety profile, are neutropenia, leukopenia, nausea, infection, fatigue, and diarrhea [60, 61].

Abemaciclib

Another orally administered, selective, small molecule CDK4/6 inhibitor, abemaciclib was approved by FDA in 2017 for the treatment of postmenopausal women with HR+, HER2- advanced breast cancer [62]. Abemaciclib, which has been approved for use in combination with endocrine therapy [63], can also be used as monotherapy in adult patients with disease progression following endocrine therapy and previous chemotherapy in a metastatic setting [64]. Hematological toxicities are common with palbociclib and ribociclib, while abemaciclib has a lower incidence of neutropenia but a higher incidence of diarrhea [63].

PI3K/ Akt/ mTOR pathway

PI3K/ Akt/ mTOR pathway is involved in physiologic functions linking several factors like as growth factors, nutrients, energy availability [65], and plays a significant role in the modulation of cell proliferation, survival, motility, apoptosis, and development of tumor cells [66, 67]. PI3K signaling pathway is one of the most frequently altered pathway in the numerous cancer [68]; this pathway is aberrantly activated in human cancers, including breast cancer [69]. PI3K family is classified into three groups [69]. Class I PI3Ks have heterodimeric structure and consists of catalytic and regulatory subunits [70]. The catalytic subunits of Class IA PI3Ks are p110 α , p110 β , p110 γ , and p110 δ encoded by the genes PIK3CA, PIK3CB, PIK3CG, and PIK3CD, respectively while the regulatory subunits are p85 α (p85 α , p55 α , p50 α), p85 β , and p55 γ encoded by the genes PIK3R1, PIK3R2, and PIK3R3, respectively. Each catalytic subunit has the ability to link each regulatory subunit [69]. Class IA PI3Ks play a role in tumor formation [66]. Class 2 PI3Ks have a monomeric structure and Class 3 PI3K consists of a single member, Vps34 [70]. For activation of PI3K, there are need to be the growth factors bind to RTKs like as insulin receptor (IR), insulin like growth factor 1 receptor (IGF-1R), and HER. In addition, PI3K can also be activated through G protein coupled receptor and by oncogenes such as Ras. When activated, PI3K phosphorylate the phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-triphosphate (PIP3) [66, 71]. The tumor suppressor phosphatase and tensin homolog deleted on chromosome 10 (PTEN) acts as a negative regulator on this process [71]. PIP3 is dephosphorylated to PIP2 by PTEN. Thus, PTEN prevents PI3K signaling [72]. PIP3 binds to Akt and PDK1

proteins, then leads to recruitment them to the inner membrane. In here, Akt is activated through the phosphorylation its serine/threonine residues [71, 73]. Activated Akt leads to phosphorylation of mTOR and thus controls protein synthesis and cell growth [74]. mTOR is in the two different protein complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) [75]. mTORC1 is the main downstream effector of Akt and its downstream targets are related to the control of protein synthesis while mTORC2 takes part in the activation of Akt [71]. mTORC1 is inhibited by the tumor suppressor proteins tuberous sclerosis complex 1/ tuberous sclerosis complex 2 (TSC1/TSC2). Akt activates mTORC1 by phosphorylating and inhibiting TSC1/2: Inhibition of TSC1/TSC2 contributes GTP binding protein Rheb (Ras homology enriched in brain) to stay its active form. Activated Rheb leads to mTORC1 and mTORC2 activation. mTORC1 is downregulated under stress conditions like as hypoxic and and lower energy conditions. Activation of mTORC1 leads to phosphorylation of p70S6K (70 kDa ribosomal protein S6 kinase) and 4E-BP1 (eIF4E-binding protein) and thus causes increase in translation, protein synthesis, and cell growth. p70S6K can interrupt PI3K signaling pathway through phosphorylation and inhibition insulin receptor substrate-1 (IRS-1). The fact that mTORC1 can prevent PI3K signaling pathway by the activation of p70S6K is proof that it has negative feedback activity on PI3K signaling pathway. mTORC2, another mTOR complex, phosphorylate and activate Akt and thus increase downstream signaling of PI3K signaling pathway [69, 76]. Based on this information it is clearly seen that mTORC1 and mTORC2 have different effects on PI3K signaling pathway. The PI3K/ Akt/mTOR pathway and its inhibitors are shown in Fig. 4.

Alpelisib

Alpelisib, the first oral PI3K inhibitor selectively to inhibit the class I p110a isoform, was approved by the FDA in 2019 for use in combination with fulvestrant, an estrogen receptor antagonist, in postmenopausal women and men with HR+/HER-, PIK3CA-mutated, advanced or MBC following progress in during or after endocrine-based therapy [77]. The most common adverse event in patients treated with alpelisib is hyperglycemia, which is explained by the drug's inhibition of PI3K α . Diarrhea and rash have been noted in these patients to a lesser extent than hyperglycemia [78]. It has been noted that these toxicities were observed despite the exclusion of patients with diagnosed type 1 diabetes or uncontrolled type 2 diabetes [77].

Everolimus

Everolimus, a sirolimus derivative (also known as rapamycin) with significant immunosuppressive and

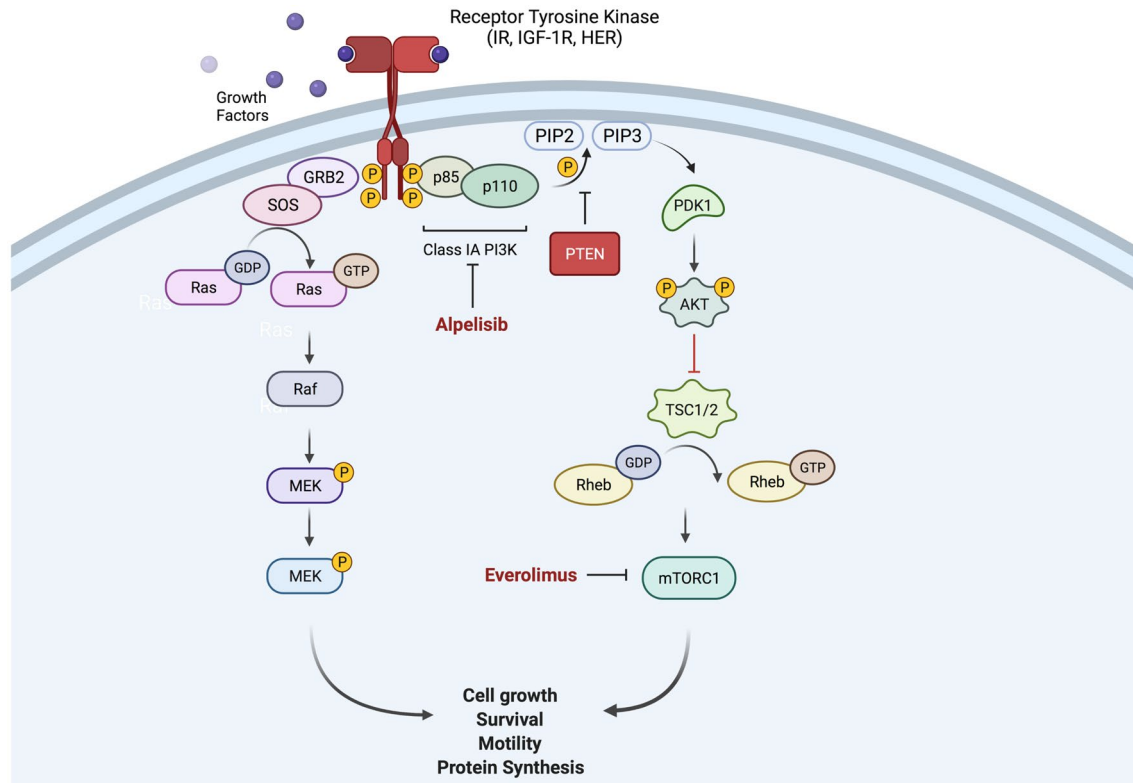


Fig. 4 Alpelisib inhibits the class I p110a isoform and Everolimus inhibits the mTORC1 complex, thereby preventing downstream signaling of PI3K/Akt/mTOR signaling pathway. *IR* insulin receptor, *IGF-1R* insulin like growth factor 1 receptor, *HER* human epidermal growth factor receptor, *GRB2* growth factor receptor-bound protein 2, *MEK* MAP kinase kinase, *PIP2* phosphatidylinositol 4,5-bisphosphate, *PIP3* phosphatidylinositol 3,4,5-triphosphate, *PTEN* tumor

suppressor phosphatase and tensin homolog deleted on chromosome 10, *PDK1* 3-Phosphoinositide-dependent protein kinase-1, *TSC* tuberous sclerosis complex, *mTORC1* mTOR complex 1 (adapted from “PI3K/Akt, RAS/MAPK, JAK/STAT Signaling”, by BioRender.com (2022). Retrieved from <https://app.biorender.com/biorender-templates>)

antiproliferative properties, binds with high affinity to the intracellular FK506 binding protein 12 (FKBP-12) and forms a complex with it. The everolimus-FKBP12 complex inhibits the mTORC1 complex, thereby preventing downstream signaling required for cell cycle progression, cell growth, and proliferation. Everolimus is also known to decrease the elongation factor 4E-binding protein (4E-BP1) involved in protein synthesis, inhibit the expression of hypoxia-inducible factor 1 (HIF-1) and decrease the expression of VEGF [79, 80]. Everolimus was approved by the FDA in 2012 for use in combination with exemestane, a steroidal aromatase inhibitor, in postmenopausal women with advanced HR +/HER2- breast cancer who have relapsed or progressed following treatment with a non-steroidal aromatase inhibitor [79]. The everolimus/exemestane combination was added to the National Comprehensive Cancer Network guidelines as part of its treatment advice for the treatment of HR + MBC in 2012 [80]. Everolimus has also been evaluated for overcoming drug resistance by adding it to other systemic treatments in different breast cancer phenotypes. However, the role of everolimus in these settings has

not been fully defined, as results were found to be inconsistent between trials [81]. Side effects related to Everolimus such as stomatitis, rash, fatigue, myelosuppression, noninfectious pneumonia have been recorded. It is also known that everolimus causes hyperglycemia and hyperlipidemia by affecting insulin and lipid metabolisms [79].

PARP inhibitors

DNA replication errors and deficiencies in DNA repair pathways are common in cancer and are critical features of cancer pathology [82, 83]. Healthy cells maintain genomic integrity by defending themselves against DNA damage through five major DNA damage response (DDR) mechanisms. Repair of single strand breaks (SSBs) is achieved by base excision repair (BER), damage that disrupts the helix is achieved by nucleotide excision repair, and repair of replication errors is achieved by mismatch repair. Double-strand breaks are repaired by either the homologous recombination repair (HRR) pathway or non-homologous

end-joining [82]. Poly (ADP-ribose) polymerase (PARP) enzymes, a family of enzymes involved in diverse activities in response to DNA damage, are an integral part of the BER pathway [82, 83]. Activation of PARP1, which plays a critical role in repairing SSBs, is among the earliest responses to DNA damage in human cells [83, 84]. PARP1 binds to the damaged DNA region with SSBs, and the ADP-ribose polymer synthesized here mediates the activation of DNA repair enzymes in the damaged region [83, 85]. BRCA1 and BRCA2 proteins are critically important proteins in HRR pathway [83]. At the DNA repair site, BRCA1 acts by forming a multiprotein scaffold that organizes repair proteins, and BRCA2 recruits the recombinase RAD51 [82]. Deficiency of either of these two proteins results in inefficient activation of homologous recombination [83]. Suppression of PARP catalytic activity with PARP inhibitors blocks the formation of ADP-ribose polymers in the SSB region, resulting in the inability of PARP-dependent DNA damage repair complexes to assemble effectively and ultimately the repair of SSBs [83]. Unrepaired SSB causes replication forks to crash and double strand breaks (DSBs). Failure to repair SSB causes replication forks to collapse and form DSBs. In normal cells, the efficiency of the homologous recombination pathway is sufficient so that these DSBs are immediately repaired, compensating for the loss of function in the BER pathway. However, this compensatory mechanism fails in tumors with homologous recombination deficiency, as in tumors with BRCA1 and BRCA2 mutations. Unrepaired DNA damage eventually accumulates and causes cell death, a concept called synthetic lethality [85]. In contrast, healthy cells are protected against this lethal mechanism, thus providing patients with benefits that cannot be achieved with conventional chemotherapy [82]. Inhibition of PARP catalytic activity with PARP inhibitors is shown in Fig. 5.

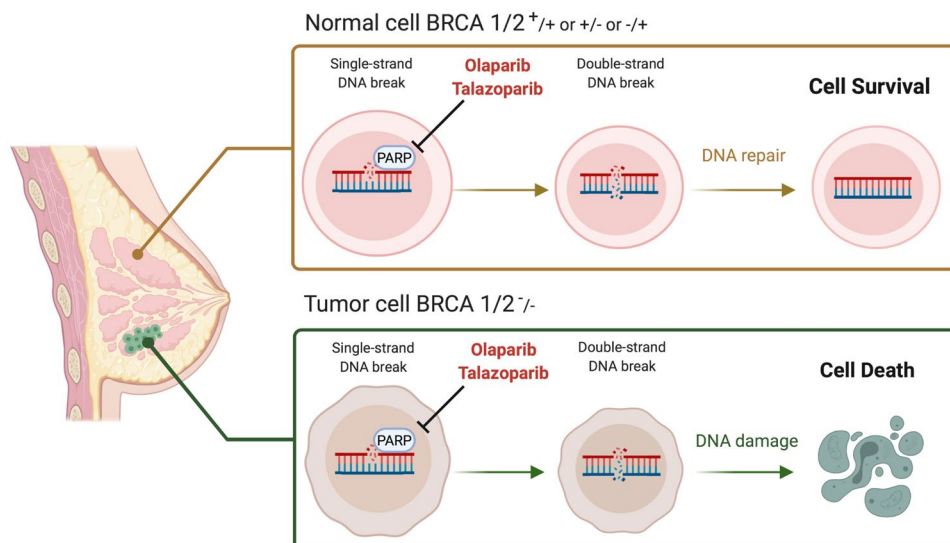
Olaparib

Olaparib was approved by the FDA in 2018 for the treatment of patients with HER2 – MBC with germline BRCA mutations, who were treated with chemotherapy in a neo-adjuvant, adjuvant, or metastatic setting [86]. Specifically, olaparib has been approved by the FDA for metastatic breast cancer and has been approved by the EMA for the treatment of locally advanced/metastatic breast cancer [82]. The most commonly reported adverse reactions in patients receiving Olaparib during clinical studies were anemia, nausea, fatigue (including asthenia), vomiting, neutropenia, leukopenia, nasopharyngitis/upper respiratory tract infection/influenza, respiratory tract infection, diarrhea, arthralgia/myalgia, dysgeusia, headache, dyspepsia, decreased appetite, constipation, and stomatitis [87].

Talazoparib

Talazoparib was approved by the FDA in 2018 for the treatment of adults patients with HER2 – , locally advanced or MBC with deleterious or suspected deleterious germline *BRCA*-mutations. Talazoparib has been noted to exhibit selective antitumor activity with 20 to 200 times greater potency in vitro than the other parp inhibitors, olaparib, rucaparib, and veliparib, by targeting tumor cells that were either BRCA1-, BRCA2-, or PTEN-deficient [88]. Prescribing information of talazoparib includes warnings and precautions for myelodysplastic syndrome/acute myeloid leukemia, myelosuppression, and embryo-fetal toxicity, and the most common adverse reactions are fatigue, anemia, nausea, neutropenia, headache, thrombocytopenia, vomiting, alopecia, diarrhea, decreased appetite [89].

Fig. 5 Olaparib and talazoparib suppress PARP catalytic activity and cause cell death in tumors with BRCA1 and BRCA2 mutations. *PARP* Poly (ADP-ribose) polymerase (adapted from “PARP Inhibitors: Treatment for BRCA Mutant Breast Cancer” by BioRender.com (2022). Retrieved from <https://app.biorender.com/biorender-templates>)



Conclusions and future perspectives

Breast cancer is a heterogeneous disease that can be subdivided into different subgroups based on origin, progression, and molecular characteristics. Histologically the same tumors may have different prognosis, and this difference is thought to be due to differences at the molecular level. Therefore, understanding the subtypes of breast cancer is important to provide effective treatment [90–92]. Breast cancer is categorized at the molecular level according to the status of certain hormone or growth receptors. Tumors with estrogen receptor (ER) or progesterone receptor (PR) are named hormone receptor positive (HR +), while tumors with epidermal growth factor 2 (HER2 or ERBB2) amplification or overexpression are named HER2 +. Tumors in which all three ER, PR, and HER2 are not expressed are named triple-negative tumors [91, 93]. The development of resistance to treatment and recurrence of the disease have led researchers to develop targeted therapies. Monoclonal antibodies, tyrosine kinase inhibitors, PI3K/Akt/mTOR pathway inhibitors, cyclin-dependent kinase 4/6 inhibitors, anti-angiogenic drugs, PARP inhibitors are among the targeted therapies used in breast cancer treatment. Promising progress has been made as a result of clinical studies investigating the effectiveness of these new treatment modalities and their combinations with existing therapeutic treatments, and some have been approved by relevant authorities for use in combination with existing therapies. In HER2 + patients, monoclonal antibodies such as trastuzumab, pertuzumab, and margetuximab are administered together with chemotherapy, while the tyrosine kinase inhibitor drugs lapatinib, neratinib, pyrotinib, and tucatinib are administered together with chemotherapy, radiation therapy, endocrine therapy, or trastuzumab. Antibody–drug conjugates are frequently used as second-line therapy in HER2 + patients [93]. Several clinical trials are underway to evaluate the use of T-DM1 and DS-8201a for other types of HER2-driven cancer types or the use of T-DM1 in combination with other agents such as immune checkpoint inhibitors, CDK4/6 inhibitors, and TKIs [37]. In HER2- patients, CDK4/6 inhibitor drugs palbociclib, ribociclib, abemaciclib, and PI3K/Akt/mTOR inhibitor drugs alpelisib and everolimus are administered together with endocrine therapy, while the antiangiogenic drug bevacizumab is administered together with paclitaxel or capecitabine. In HER2- patients with BRCA gene mutation, PARP inhibitor drugs olaparib and talazoparib are used.

In conclusion, while there are various targeted treatment options in advanced or metastatic HER2 ± breast cancer patients, such treatment options may be needed in early stage breast cancer patients with a high risk of recurrence.

In the meantime, treatment options are limited as targeted therapy cannot be applied in triple-negative breast cancer patients. It is predicted that it may be beneficial to focus on biomarkers in order to apply targeted therapies in these patients.

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