Breast Cancer Associated Conventional and Advanced Therapies

Kirti Amresh Gautam[1]*, Nimisha Singh[1], Priyanka Tyagi[1], Gunja Jha[1], Anushka Raman[1]

[1]Department of Basic & Applied Sciences, School of Engineering & Sciences, GD Goenka University, Gurugram, Haryana, India.

ABSTRACT

Globally, breast cancer (BC) is the second most lethal cancer that affects women and in rare cases, men as well. More than 90% of breast cancer-associated deaths are caused due to late identification that leads to metastasis. Biopsy report along with imaging work-up (MRI- and CT-scans) predicts the diagnosis that ultimately uses for the establishment of treatment options. Currently, breast cancer treatment has broad and diverse approaches, it comprises conventional treatments which include oncoplastic breast surgery, radiation therapy, and adjuvant chemotherapy while advanced treatments include systemic therapy approaches including targeted therapy, hormone therapy, and immunotherapy. Advanced treatments aim to attack cancer cells specifically, reduce side effects and improve treatment outcomes for patients. The therapies can be further diverged and depend on taking the grounds of molecular subtypes of BC, patient health, and personal preferences along with regular screening. In this review, we have highlighted different therapeutic approaches including targeted therapy, chemotherapy, and hormonal therapy employed based on molecular subtypes of BC.

Key Words: *Breast cancer, Target therapy, Chemotherapy, Hormonal therapy, Conventional therapy, Advanced therapy*

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INTRODUCTION

In 2020, 2.3 million females worldwide were diagnosed with BC, with 685 000 deaths. BC has been diagnosed in 7.8 million women in the previous five years as of the end of 2020, making it the most common type of cancer in the world. According to cancer data from the year 2020, Global breast cancer (GBC) accounts for 0.6 percent of all cancer cases and 0.9 percent of all cancer-related fatalities and it is the second most significant cause of cancer death after lung and bronchus cancer (13.9%) [1]. The accountability of BC occurrence and mortality varies by geological area. It is the most familiar identified cancer among females in a huge mainstream (140 out of 184) countries globally [2].

BC mortality interchanged little from the 1930s to the 1970s. Enhanced survival was initiated in the 1980s in countries with early observation programs incorporated with distinct modes of treatment to eliminate invasive disease. Age-standardized BC mortality dropped by 40% between the 1980s and 2020 in high-income countries. Nations that have accomplished the reduction of BC mortality were able to attain an annual BC mortality reduction of 2-4% per year. If an annual mortality reduction of 2.5% per year occurs globally, between 2020-2040 there were 2.5 million BC deaths that would be avoided [3].

BC is a multifactorial illness that can be triggered by a variety of variables, including genetic alterations, reproductive factors, biological carcinogens, chemical exposure, environmental factors, and obesity. BC emerges in the lining cell of lobules (15%), in glandular tissue (85%), and in the duct of the breast. BC patients with metastases have 4–10 % brain lesions, 30–60 % bone lesions, 21–32 % lung lesions, and 15–32 % liver lesions [4].

Corresponding author: Kirti Amresh Gautam
Address: Department of Basic & Applied Sciences, School of Engineering & Sciences, GD Goenka University, Gurugram, Haryana, India.
E-mail: ✉ emails2kirti@gmail.com
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BC is differentiated into five molecular subtypes depending on the histopathological differential genetic expressions **(Table 1)**. When these molecules and receptors overexpress, underperform, or cause mutations in one's body, it leads to the activation of several signaling pathways which may ultimately result in the formation of BC [5]. Since every newly recognized BC-affected person needs to be separated into a selected molecular subgroup to predict the diagnosis and the selection of the most appropriate treatment. Histological grade, which is derived by assessing the degree of tumor differentiation, nuclear pleomorphism/degree, and proliferation, is a crucial element of pathology reports [6]. Current ongoing research in the field of BC therapy is demanding focus on the development of a new treatment based on the sub-molecular type of BC to provide effective, individualized, and reduced side-effects treatment options to improve survival and quality of life. The aforesaid can be achieved by combining different treatment modalities or using less toxic drug regimens. In this review, we comprehensively discussed the conventional and advanced therapeutic approaches based on subtypes of BC.

Table 1. BC subtypes based on molecular classification

Subtypes	Characteristics
Luminal A	• Hormone receptor (HR) positive, HER2 negative • Identified by higher levels of ER, also the proliferation gene (Ki67) is in the lower range
Luminal B	• ER-positive, HER2 negative • Poor results against endocrine therapy
Basal Like/Triple Negative BC (TNBC)	• Lacks the ER, PgR, and HER2 protein • Characterized via low gene expression • Higher expression of cytokeratins (CK) • Common in women with BRCA1 mutations
HER Positive	• HER2 gene is responsible for encoding HER2 receptor, found on 17q21 chromosome • Consists of a ligand binding domain, a transmembrane domain, and an intracellular catalytic domain for tyrosine kinase
Normal Like (HR-positive and HER2 Negative)	• Rare type of breast carcinomas • Has fibroadenomas and normal breast samples • Lacks HR and HER2 • Also being negative for CK5 and Endothelial growth receptor (EGFR) • Not considered in basal-like cancer subtype • Lacks response toward neoadjuvant chemotherapy

Targeted therapy of BC

BC (BC) associated targeted therapies (TTs) considers drug or any other substance which identifies, attacks or blocks the specific cancer growth cell by interacting and interrupting with their special molecule and its function which is responsible for tumor growth, uncontrolled cell division, and its survival [7]. TTs majorly act upon cancer-associated or cancer-specific cells without harming normal cells and usually have fewer severe side effects as compared to conventional chemotherapy. TTs can be received orally and intravenously. Some major differences between TTs and conventional chemotherapy are listed in **Table 2**.

Table 2. Major differences between TTs and conventional chemotherapy

S/N	Targeted Therapy	Conventional Chemotherapy
1	Selectively interact with molecules and cells involved in cancer growth	Works on continuously dividing cancerous cells as well as normal cells
2	Not severe side-effects	severe side-effects
3	Cytostatic effects – block or inhibit the activity of tumor cells proliferation	Cytotoxic effects – destroy the cells

The practice of a combination of TTs or recognition of new TT molecules in BC may potentially explore the understanding of substitutive pathways. TT begins to discover the resistance mechanisms; however, subtypes of BC like Triple negative BC appear to utilize the different proliferative channels which are yet to be established on a priority basis [8].

Targeted drugs for BC seem to limit the efficacy of treatment because of its quick acquisition of resistance or due to some genetic mutation or oncogenic changes in molecular Pathways. It should be taken into account to consider several pathway blockades in order to get comprehensive treatment outcomes [9].

The conventional treatments available for BC comprise chemotherapy, immunotherapy, radiation therapy, and surgery [10]. In the current scenario, attributable to characteristics of BC including HER2 positive, HER2 negative, hormonal receptor-positive, and triple-negative BC (TNBC) tailored targeted therapy is a crucial aspect to consider for treatment. Individualized therapy for hormonal receptor-positive BC has been well accepted because it consists of selective estrogen receptor degraders

and modulators (SERDs and SERMs), endocrine therapy, and aromatase inhibitors (AI) [11].

Some examples of TT drugs are monoclonal antibodies, which act in more than one way to control or manage the cancer cells and it may also be examined under immunotherapy because they enhance the immune system. **Table 3** summarized the Target therapy-based available drugs that potentially affect specific pathways.

TT for HER2-positive BC

Statistically, about 1 in 5 Women with BC produce a high amount of growth-promoting protein known as Human epidermal growth factor receptor 2 (HER2). The HER2 is a transmembrane protein receptor that belongs to the EGFR/ERB family of tyrosine kinase receptors [12]. HER2 protein shows the most relevant biomarker for the treatment of BC because it is widely overexpressed in BC consequently, HER2 has both prognostic and diagnostic implications [13]. This proto-oncogene is highly expressed in 10%- 12% of over 2500 cases of human BC and has a relationship with malignant metastasis and a very poor survival rate overall, especially in BC with Lymph node metastasis [14].

The HER2 gene is located on chromosome 17 (17q12) and it is part of the EGFR family of Tyrosine kinase receptors [15]. The EGFR family consists of four receptors: EGFR/HER1, ErbB2/HER2, ErbB3/HER3, and ErbB4/HER4. These receptors have the same domain: a single transmembrane bridge area; a small juxta-membrane area; a kinase area and a cytoplasmic tail part with many tyrosine phosphorylation regions [16]. It is observed that HER2 is activated by estrogen which is present on the estrogen receptor, located on the outer surface of the nucleus [17].

HER2 is involved in the formation of kinase-active homo- and hetero-dimer with EGFR, HER3 and HER4 provide binding sites for ligands to the extracellular domain which activate kinase protein. The development of a heterodimer between HER2/HER3 is the most common event in these receptors. HER3 triggers activation of the AKT/ PI3K signaling pathway by six docking regions for the p85 adapter subunit of PI3K. In the survival of HER2-dependent cells, the role of HER3/ PI3K plays an important function, the loss of HER3, inhibits the survival of HER2 overexpressing BC cells [18] HER2- positive metastatic BC individuals can be treated by targeting the HER2 gene by combining targeted therapy with chemotherapy.

Monoclonal antibodies (MAs)

Monoclonal antibodies are laboratory-made proteins that act like antibodies. These proteins are attached to special target molecules to treat many diseases, including cancer. These antibodies can bind with specific cancer cells and kill or inhibit their key activity including proliferation and metastasis. In the case of BC, these antibodies bind with HER2 protein and help them to stop the growth of cancer cells [19]. These proteins may be used individually or to deliver toxins, drugs, or radioactive material straight to the cancer cells. Therefore, these antibodies can be utilized in combination with chemotherapy as adjuvant therapy. The finding of the anti-HER2 MA has rapidly changed the natural history of HER2-positive BC and has transformed the management of this subgroup of metastatic BC [20].

Antibody-drug conjugates (ADCs)

ADC is a monoclonal antibody linked to chemotherapy. In ADC, the anti-HER2 antibody works as a hormonal signal by connecting to the HER2 protein on cancer cells, administered locally at the site of cancer. The production of ADCs is depended on a creative perspective, which merges the capacity of MA to cell targeting with the high amount of cytotoxic effect of drugs [21]. According to the molecular point of view, ADC consists of a target-specific monoclonal antibody and a cytotoxic agent connected by a drug connector. This approach is effective in the treatment of HER2-positive BC, specifically through the maturing of TDM-1. Currently, several ADCs are in clinical and preclinical development, with optimistic results [22].

Trastuzumab is a recombinant monoclonal antibody that is used to target and block the effects of the growth factor protein HER2. Trastuzumab (Herceptin, Herzuma, Kanjinti, Ogivri, Ontruzant) is the first drug approved by the Food and Drug Administration (FDA) in 1998 for the curing of HER2-positive BC. The drug is combined with other therapy or drug (carboplatin, doxorubicin, docetaxel, paclitaxel cyclophosphamide) to treat HER2-positive BC. [23]. Early-stage BC and advanced BC both can be treated by Trastuzumab. It is delivered intravenously for 6 months before neoadjuvant or after adjuvant surgery. Trastuzumab has side effects including heart-related complications and should be monitored [24].

Pertuzumab is a monoclonal antibody (Perjeta) approved by the FDA on December 20, 2017. It can be combined with Trabtuzumab and with other chemotherapy drugs to treat first-line metastasized HER2-positive BC [25]. This drug can be delivered intravenously before or just after the surgery to cure early-stage BC or advanced BC or patients with locally advanced, and inflammatory conditions. It comprises minor side effects such as diarrhea and rashes. The combination of Trastuzumab, pertuzumab, and hyaluronidase (physio) drug is given as a shot dose subcutaneously for the treatment of HER2-positive BC [26]. The combination of these drugs has severe side-effects such as lowered red blood cells count, hair loss, nausea, and tiredness.

Margetuximab on December 16, 2020, FDA approved Margetuximab, a monoclonal antibody drug to treat advanced HER2-positive BC. The US brand name of this

drug is Metgena. This drug is given to a person who has already received at least two HER2-targeted therapies. It is delivered intravenously once every 3 weeks. Side-effects include heart problems so patients should go regularly for monitoring with an echocardiogram [27].

Fam Trastuzumab Deruxtecan is an antibody-drug conjugate (ADC) (Tukysa) combined with two different anti-cancer drugs. Trastuzumab part targets and attaches to the HER2 receptor of cancer cells and the Deruxtecan part of this drug is released into the cancer cells which destroy cancer cells. Applied to treat metastasized BC that cannot be removed by surgery and at least two anti-HER2 target drugs have already been given. This drug is used with a combination of another drug that is similar to Trastuzumab, it is called biosimilar [28]. It is delivered intravenously infusion every 3 weeks. It shows side-effects like interstitial lung disease (ILD), which causes injury to the lungs and can make it coughing and difficult to breathe.

Ado-trastuzumab emtansine (Kadcyla) is a monoclonal antibody that is coupled with an anticancer medication and delivered as salvage therapy. This antibody-drug combination binds HER2 antibody to the chemo agent emtansine, which is a paclitaxel-like medication used to treat HER2-positive BC including both early BC and for cancer that progressed to another part of the body or has recurred [29]. This drug is delivered into DM1 medication, a microtubule inhibitor, directly into the BC cells to stop the cancer cells' growth. This drug is delivered at 3.6mg/kg intravenously every three weeks until cancer progression or unacceptable toxicity. It is also approved for the treatment of metastatic BC in patients who have earlier got trastuzumab and paclitaxel or docetaxel-based chemotherapy.

Tyrosine kinase inhibitors (TKIs)

Tyrosine kinases are important mediators that convey information in a ligand-receptor manner in cells for various biological processes including growth, cell differentiation, migration and apoptosis, etc. Tyrosine kinase inhibitors (TKIs) are a group of pharmacologic agents that interrupt the activity of kinase proteins by different modes of inhibition and are used as life-extending cancer therapy. As adjuvant therapy, TKIs can be used with a combination of other anticancer drugs. TKIs' popularity used in recent years because of several advantages over monoclonal antibody therapies, including oral delivery, less cardiotoxicity, and the capacity to target many targets [30].

Lapatinib (Tykerb) is an anticancer drug that inhibits tyrosine kinase and prevents HER2 protein and other proteins from acting on tumor cells. Generally, lapatinib is given to treat advanced HER2-positive BC that has progressed after treatment with other cancer medications and this tablet is given orally and must be taken daily. It is typically combined with hormonal therapy like trastuzumab and capecitabine based on patients' characteristics. When a patient has already had chemotherapy along with trastuzumab, a combination of lapatinib or letrozole and the chemotherapy capecitabine has been approved to treat metastatic HER2-positive BC [31]. Lapatinib has the potential to enter the brain, making it a viable treatment choice for HER2-positive BC that has progressed to the brain. This medication has the potential to harm the liver and induce diarrhea [32].

Neratinib (Nerlynx) is a TKI that inhibits the HER2, HER4, and epidermal growth factor receptor (EGFR) proteins [31]. After one year of treatment with trastuzumab, it may be utilized to cure individuals with early-stage HER2-positive BC. Neratinib is also approved for the treatment of advanced or metastatic HER2-positive BC in patients who have received two or more anti-HER2-targeted treatments in combination with capecitabine chemotherapy. Administered orally once daily with food and almost at the same time daily. This medication can cause adverse reactions including diarrhea and hepatotoxicity [33].

Tucatinib (Tukysa**)** FDA approved, 2020 drug is used with a combination of trastuzumab and capecitabine to treat advanced HER2-positive BC by blocking its activity to increase the survival rate without cancer progression . This drug is effective for cancers that cannot be removed by surgery or has progressed to other parts of the body including the brain. Tucatinib tablets are given orally twice a day with or without meals and approximately at the same time daily. This drug shows side effects such as diarrhea and liver problems [34].

TT for metastatic HER2-negative BC and hormone receptor-positive BC

Hormones comprising estrogen and progesterone receptor-positive BC account for almost three out of every four cases and hormone therapy (HT) is usually beneficial for women with these hormone receptor-positive malignancies. Inhibitors of down-stream channels such as RAS/MEK/ERK and PI3K/AKT/mTOR, as well as agents targeting other tyrosine kinases such as SRC, insulin-like growth factor (IGF/IGF-receptor (IGFR)), poly-ADP ribose polymerase (PARP) inhibitors, and matrix metalloproteinases (MMPs) that are associated in cancer invasion and metastasis, are available for the BC treatment [35].

Cyclin-dependent kinase inhibitors

These inhibitor molecules inhibit the growth of the tumor by blocking cyclin-dependent kinases (CDKs) that are involved in various key physiological processes including cell cycle, gene transcription, metabolism, apoptosis, glycogen synthesis, insulin secretion, brain functioning, and communication [36]. Treatment of advanced hormone

receptors–positive HER2-negative BC with a combination of CDK4/6 inhibitors and hormone therapy may show successful results. The FDA has approved CDK inhibitors (CDKIs) for the treatment of metastatic hormone receptor (HR) positive BC, especially those with the disrupted enzymatic activity of CDK4 and CDK6 (CDK4/6) [37]. CDK4/6 inhibitors target the G1-to-S phase of the cell cycle via controlling checkpoint [38]. Currently, CDK4/6 inhibitors have been approved in combination with estrogen therapy, which has resulted in significantly improved survival rates [38]. The phosphorylation of retinoblastoma-associated protein (pRb) occurs when D-type cyclins activate CDK4 and CDK6. This delivers pRb's inhibition of the E2F transcription factor family, permitting the cell to complete its division and cycle [39]. The G1-to-S checkpoint is an ideal therapeutic target for the treatment of HR-positive BC since cyclin D overexpression is widespread and pRb loss is abnormal. CDK4/6 inhibitors prevent the cell cycle from progressing through this checkpoint, resulting in cell lysis and death [39]. Till now, 21 CDKs and 5 CDK-like genes have been identified depending on their homologous sequences in the human genome [40]. In higher eukaryotes, CDK1 seems to be a crucial factor in mitotic progression, whereas CDK2 is mainly connected with DNA replication.

Palbociclib This oral medication CDK4/6 inhibitor targets and blocks CDK4/6, enzymes responsible for cancer cell division and proliferation. Palbociclib was approved by the FDA in February 2015 to be used in combination with letrozole, anastrozole, an aromatase inhibitor (AI) used in hormone-based chemotherapy [41]. This drug is an option for first-line treatment for women who have gone through menopause and have ER-positive, HER2-negative metastatic BC. Palbociclib can also be combined with fulvestrant for patients whose cancer has progressed or recurred after being treated with an AI drug alone. Palbociclib has a low risk of adverse effects including a reduction of the level of WBC, [42].

Ribociclib It is a CDK inhibitor used in combination with letrozole to treat HR-positive and HER-2-negative BC that has recurred or metastasized to distant parts of the body [43]. It is administered orally in a 21-day therapy cycle. It can also be administered in postmenopausal women with HR-positive and HER2-negative BC and metastasized cancer in combination with fulvestrant [43].

Abemaciclib is approved by the FDA as a first-line treatment. This drug is used in combination with the AI medicine letrozole or anastrozole for menopause women with ER-positive and HER2-negative metastatic BC. It can also be combined with fulvestrant in patients who progressed or reverted cancer after taking only an AI drug. It has side-effect including diarrhea, which can be severe. An AI and CDK4/6 blocker should be used with a gonadotropin-releasing hormone analog or ovarian restriction in patients with male BC or women who have not gone through menopause.

Mammalian target of rapamycin (mTOR) inhibitors

mTOR may hamper cancer cell division and inhibit neo-angiogenesis. mTOR involves various signaling transduction pathways comprising cell proliferation, autophagy, and cell death. Recent research explains, the mTOR signaling pathway has also been connected to cancer, arthritis, insulin resistance, osteoporosis, and other disorders [44]. The mTOR signaling channels have a role in malignancies, control gene transcription and protein synthesis to control cell proliferation and immune cell differentiation, as well as tumor metabolism [45]. In most of mammalian cells, mTOR is expressed as a member of the phosphoinositide 3-kinase-related kinases (PIKKs) family protein. It acts as a cellular sensor for nutrients and causes an increase in cellular protein mass and growth while inhibiting autophagy [46].

Everolimus It (Afinitor) is an mTOR inhibitor approved in 2009 for the curing of advanced renal cell carcinoma and in 2010 for the prevention of kidney transplant rejection [47]. In 2012, US FDA approved this drug in combination with AI exemestane (Aromasin) while observing its role in advanced HR-positive, HER2-negative metastatic BC in postmenopausal women who already received medication [48]. It has been observed that Everolimus binds to the surface of the FK506-binding protein of 12 receptors, which interacts with mTOR to block further cell cycle progression, cell division, and growth [48]. Everolimus appears to improve the efficacy of hormone therapy drugs. Mouth sores, rash, diarrhea, nausea, fatigue or weary, low RBC counts, difficulty in breathing, and cough are the side-effects of everolimus. This drug can increase blood lipids (cholesterol and triglycerides) and blood sugar levels; therefore, patients must be kept under strict observation [49].

Poly(ADP-ribose) polymerases (PARP) inhibitors

PARP proteins have a significant role in DNA replication, DNA damage repair, and cellular growth. This advantage is being used by cancer cells to repair themselves and to survive [50]. This finding paved the door for the development of a new class of antineoplastic medications - PARP inhibitors, which can try to interfere with cancer cells' DNA damage repair processes. PARP inhibitors treatment is being investigated as a treatment for triple-negative BC (TNBC) and as adjuvant therapy in individuals with HER2-negative early BC with BRCA1 or BRCA2 gene abnormalities. There are eighteen members of this family, PARP-1 to -3 designated as DNA damage-dependent PARPs [51]. Only two PARP inhibitors are currently approved for BC: olaparib and talazoparib. Other PARP inhibitors have been approved for the treatment of

ovarian cancer [52]. Recently, adjuvant olaparib increased progression-free and remote disease-free survival among gBRCAm patients with HER2-negative high-risk early-stage BC [52].

Olaparib is a PARP inhibitor that is used to treat HER2-negative BC patients who have mutations in the BRCA1 or BRCA2 genes and tumor progression or spread to other regions of the body.

Talazoparib is a PARP inhibitor that is used to treat HER2-negative BC that has progressed to other regions of the body in individuals who have mutations in the BRCA1 or BRCA2 genes.

Veliparib is still being tested in clinical studies for its effectiveness in treating HER2-negative metastatic/locally progressed, gBRCA-mutated BC in combination with platinum-based chemotherapy. It attacks PARP1 and PARP2 and has a limited capacity to capture PARP [53].

Niraparib inhibits PARP1 and PARP2 action. Its effectiveness as neoadjuvant chemotherapy to decrease tumor volume in HER2-negative, gBRCA-mutated BC is now being studied in phase 1 clinical trials [53]. It is usually used as maintenance therapy to avoid recurrence conditions.

Rucaparib inhibits PARP1 and PARP2. It is majorly used for the treatment of ovarian, fallopian tube, and primary peritoneal cancer, although, it is now being tested as a mono-therapeutic treatment in patients with BRCA-mutated metastatic BC currently in a phase 2 clinical trial [54]. It's also being tested in a phase 1b/2 clinical trial in patients with TNBC or BRCA-mutated BC to see how safe and effective it is when combined with other anticancer agents
[53].

Pamiparib targets PARP1 and PARP2 and It is being tested as a monotherapy in patients with metastatic/locally advanced TNBC, or BRCA-mutated BC or only HER2-negative BRCA-mutated BC which is in a phase 2 trial [55].

Phosphoinositide 3-kinase (PI3K) inhibitors

These inhibitors generally inhibit the enzymes involved in signaling pathways including PI3K/AKT/mTOR. In BC patients, abnormal functioning of the phosphoinositide 3-kinase (PI3K) signaling pathway occurs which is associated with cell growth and survival [56]. BC initiation, development, and resistance development to hormone treatment and chemotherapy have all been linked to PI3K signaling pathway glucose uptake, cell growth, multiplication, and lifespan [57]. The most typically changed class of PI3Ks in BC is Class I, which is made up of a heterodimer containing a p85 regulatory component and a p110 catalytic subunit [58]. Multiple downstream signaling pathways are activated as a result of AKT activation, including the mTOR, which regulates activities including transcription and translation, and cell growth, among others [59]. Phosphate and tensin homology (PTEN) and inositol polyphosphate 4-phosphatase (INPP4B), which dephosphorylate PIP3 and reverse to PIP2, are negative controllers of the system. Many genetic abnormalities connected to genes encoding proteins in the PI3K signaling pathway have been identified [60]. Approximately, 40% of HR-positive/HER2 negative or HER2-positive metastatic BC and roughly 9% of TNBC tumors have alterations in the p110 subunit (PIK3CA) [61].

Alpelisib in 2019 FDA approved Alpelisib (Piqray and Vijoice). This targeted therapy blocks abnormally expressed PI3K protein in cancer cells and restrains cancer specifically HR-positive, HER2-negative advanced or metastatic BC with an abnormal PIK3CA in men and postmenopausal women [62]. A mutant PIK3CA gene is seen in 20 to 50 percent of breast tumors. It can be delivered in combination with fulvestrant and an aromatase inhibitor [63]. Before commencing therapy, a blood test for this mutation is recommended. Medication has side-effects including rashes, high blood sugar, symptoms of kidney, liver, or pancreatic problems, diarrhea, low RBC counts, blood coagulation issues, etc.

Angiogenesis Inhibitors (Vascular endothelial growth factor (VEGF)

BC growth and metastasis are dependent on neovascularization which is supported by the VEGF protein. Inhibiting angiogenesis, that is the formation of new blood vessels, can effectively prevent BC from progression. In the regulation of angiogenesis, VEGF binds to VEGF receptors (VEGFR), that is VEGFR-1 and VEGFR2. VEGFR2 receptor stimulates the proliferation and migration of endothelial cells through specific signaling transduction pathways, thereby supporting the formation of neovascularization [64]. VEGFR-1 controls blood vessel integrity in the late-developing stage of cancer. Targeted medicines against the VEGF have also been approved and the TT bevacizumab is effective in the treatment of advanced metastatic BC when combined with paclitaxel or docetaxel [65].

Bevacizumab (Avastin, Zirabev, Mvasi, and Alymsys). These drugs majorly inhibit the action of VEGF by binding to VEGF receptors thereby stopping the formation of new blood vessels, which are necessary for cancer cells to proliferate and for proper nutrients supplement for functioning [66].

Targeted therapy for mutations in the BRCA gene

BRCA susceptibility genes (BRCA1 and BRCA2) are tumor suppressor genes involved in the DNA repair mechanism. Alterations in BRCA genes due to mutations hamper this repair process and mutated genes can be

inherited by offspring from mother, father, or both parents [67]. A smaller percentage of BC patients are born with defective BRCA genes. If persons with metastatic hormone receptor-positive, HER2-negative BC who have a BRCA1 or BRCA2 gene mutation are no longer benefiting from hormonal therapy, the American Society of Clinical Oncology (ASCO) recommends administering PARP inhibitor as an alternative to chemotherapy. Furthermore, the ASCO suggested that people with metastatic TNBC who have previously received chemotherapy can be offered an oral PARP inhibitor as an alternative chemotherapy.

Olaparib (Lynparza) is a PARP inhibitor that may combine with other chemotherapy drugs. This drug prevents cancer progression by stopping them from DNA repairing mechanisms in patients with metastatic HER2-negative BC with BRCA1 or BRCA2 gene mutation [68]. Women with an early-stage HER2-negative BC with BRCA mutation have a high risk of cancer recurrence and who have been treated with chemotherapy before or after surgery can be administered olaparib [69]. Olaparib can also be given to women with HR-positive who have already had hormonal therapy. Some side effects include fatigue, nausea, vomiting headaches, diarrhea, decreased appetite, and low amount of certain blood cells.

Talazoparib (Talzenna) This targeted drug provides an alternative to chemotherapy for patients with metastatic HER2-negative BC and a BRCA1 or BRCA2 gene mutation. The common side-effects are fatigue, nausea, and vomiting, etc.

Target therapy for TNBC

Tumor cells in TNBC are hormone receptors- (estrogen- or progesterone-) as well as HER2-negative. TNBC reacts with PARP1 inhibitors and could be a possible target for HER1. A published study showed potential results [70] in a Phase II trial, the monoclonal antibody cetuximab combined with cisplatin treatment, suggesting that some subtypes of TNBC may be susceptible to EGFR inhibition. The study [70] also shows that the traditional approach for curing TNBC patients with taxol derivatives and anthracycline chemotherapy is still frequently used [71]. Recent research suggests that ixabepilone, a microtubule-stabilizing agent, is merging with capecitabine, may be useful in TNBC, which is resistant to anthracycline and taxane medications, and the PACS08 Phase III study is testing this therapy strategy [72].

Sacituzumab govitecan-hziy (trodelvy) This drug was approved by FDA in 2020 for the treatment of patients with TNBC with the metastatic condition or cancer that cannot be removed by surgery and who have already received at least two or more cancer therapies. It is an antibody-drug conjugate (ADC), which means that the antibody binds to a tumor cell and then releases the anticancer drug into the cell and begins to destroy the cancerous cell. The monoclonal antibody portion of ADC binds to the Trop-2 protein on BC cells and transfers a chemo agent similar to irinotecan directly to the cancer cells. Every 21-day cycle, trodelvy is delivered intravenously on days 1 and 8. Some common side effects of these drugs are nausea, vomiting, diarrhea, constipation, fatigue, rash, lack of appetite, hair loss, low RBC counts, and stomach pain are severe side-effects of this medication. Prior to curing with this drug, medications are usually administered to reduce the risk of an allergic reaction [73].

Table 3. List of available target therapy along with combined therapy based on BC sub-types

Targeted Therapy	Combined Therapy	Delivered to BC Type	Reference
Trastuzumab	Individually or in combination with drugs including carboplatin, doxorubicin, docetaxel, paclitaxel cyclophosphamide	HER2 positive BC, Early-stage and advanced BC both	[24]
Pertuzumab	Trastuzumab and with another chemotherapy drug	metastasized HER2-positive BC	[25]
Fam Trastuzumab Deruxtecan	Chemo drug deruxtecan which is the same as the drug – irinotecan	metastasized BC that cannot be removed by surgery, generally, after treatment with at least 2 anti-HER2 target drugs	[28]
Ado-trastuzumab emtansine	Emtansine (a paclitaxel-like medication)	HER2-positive BC that progressed to another part of the body or has recurred	[29]
Lapatinib	Trastuzumab and capecitabine	Metastatic HER2-positive BC (patient received trastuzumab and paclitaxel or docetaxel-based chemotherapy)	[31]

Neratinib	After treatment for one year with trastuzumab	advanced or metastatic HER2-positive BC in patients who have already had two or more HER2-targeted treatments in combination with capecitabine chemotherapy	[31]
Tucatinib	Trastuzumab and capecitabine	HER2 + BC which can be removed by surgery or has progressed to other areas of the body along with the brain	[31]
Palbociclib	Letrozole, anastrozole, an aromatase inhibitor	Postmenopausal females with ERstrogen Receptor-positive, HER2-negative metastatic BC	[38]
Ribociclib	Letrozole	Hormone receptor-positive, HER2 negative BC / recurred or metastatic	[43]
Abemaciclib	Letrozole or anastrozole	Postmenopausal females with ER-positive, HER2-negative metastatic BC.	[43]
Alpelisib	Fulvestrant	HR-positive and HER2-negative BC with a specific gene alteration in PIK3CA	[60]
Everolimus	Exemestane	HER2-negative metastatic BC in postmenopausal females	[49]
Veliparib	Platinum-based chemotherapy	HER2-negative metastatic, locally progressed	[53]
Niraparib	Neoadjuvant chemotherapy	HER2-negative	[53]
Olaparib	Chemotherapy drugs	Metastatic HER2-negative BC and a BRCA1 or BRCA2 gene mutation	[69]
Bevacizumab	Combination with taxanes or paclitaxel or docetaxel	Targets for HER2-negative BC drugs.	[66]

Chemotherapy

Chemotherapy for BC involves the use of a potential single or combination of chemicals to target and destroy fast-growing cancer cells. These medications can be delivered intravenously or orally. In recent years, adjuvant, as well as neoadjuvant chemotherapy, has been in practice for TNBC and HER-2 positive BC cases [74]. Through the years of clinical research, BC is known to produce a distinct prognosis and response to chemotherapy based on immunohistochemistry (IHC) sub-types. HER2 negative (ER/PgR positive) cancers have a good response and prognosis towards hormone therapy while HER2 positive and TNBC have a poor prognosis but a good response towards chemotherapy as well as targeted therapy [75]. Generally, BC patients receive chemotherapy after the surgery is known as an adjuvant, and in neoadjuvant the victims are treated before the surgery.

Chemotherapy for TNBC

Low-staged TNBC can be treated with surgery followed by adjuvant chemotherapy, whereas tumors with high stage do relapse frequently with occurrence within two years of resection [74]. Chemosensitivity in TNBC leads to pCR (pathological complete remission) by neoadjuvant chemotherapy. To achieve an increased probability of pCR, the inclusion of carboplatin can help up to 45% [74]. A meta-analysis [75], observed that including carboplatin in neoadjuvant chemotherapy gave rise to definite DFS (disease-free survival) and OS (overall survival). The analysis of Pathak et.al showed that the identification of biomarkers for treatment with platinum-containing agents is necessary and germline BRCA or PD-L1 expression never displayed any predictions of its impact [75, 76].

A study demonstrated the TP (docetaxel or paclitaxel combined with carboplatin) was no inferior for the efficacy exerted by EC-T (epirubicin and cyclophosphamide followed by docetaxel or paclitaxel) while finalizing the concept of a rarity in the activity of platinum-based adjuvant therapy in TNBC. The TP regimen also showed higher treatment adherence and reduced frequency of toxic reactions [77].

Carboplatin is a platinum complex and alkylating compound with cytotoxic DNA-damaging effects with DNA strands and consequently causing damage that leads to apoptosis. The drug is yet to be considered effective as there is very little evidence for its efficacy despite the number of clinical trials. This drug does not selectively kill cancer cells, although it also affects rapidly dividing growing normal cells. To deliver the treatment, the identification of predictive biomarkers is crucial for selecting patients for platinum-based regimens [78]. Treatment as side-effects including bleeding, low RBC and WBC, infection, liver and kidney problems.

Anthracyclines work efficiently by complexing with DNA and topoisomerase II which induces apoptosis inhibiting DNA and RNA synthesis and is employed in adjuvant and neoadjuvant chemotherapy. The toxicities of this drug include myelosuppression, cardiotoxicity, and secondary malignancies [79].

Taxanes effectively exert their actions by stabilizing microtubules which inhibit cell division and cell-associated functions and are employed in adjuvant and neoadjuvant chemotherapy. Toxicities may include myelosuppression, and neuropathy myalgia [79].

Chemotherapy for BRCA1 and BRCA2 mutations

In BRCA1/2 mutation cancer, the most commonly used therapeutic agent is platins. An alkylating compound attacks DNA gradually binding and induces multiple single-strand breaks resulting in cell death. The synergy of breaks caused by platinum and BRCA-associated mutation (BRCAmut) repairing double-strand breaks is clinically termed synthetic lethality [80]. PARP is a class of proteins that plays a significant role in the repair of DNA single-strand breaks. PARP is (inhibitors) hinder the repair of breaks in single-strand breaks which, therefore, justifies the synthetic lethality of PARP is in BRCAmut patients. PARP has more advantages over platins due to the inconveniences of intravenous employment and side effects such as nausea, neuropathy, hematologic toxicities, and ototoxicity, while PARPis are administered orally [80].

Olaparib is employed orally and falls under the category of PARPis and can be available in two kinds of formulation: tablets and capsules. The mechanism of this drug directly associates with DNA breakage. In the Olympia trial, Tutt *et al*. demonstrated that Olaparib has benefitted as adjuvant chemotherapy for victims with germline BRCA1/2 associated early BC who are likely to or had a high risk of developing HER2 negative primary BC. The trial provided proof that germline BRCA1/2 is a significant marker for the selection of systemic therapy in early BC type [69].

Chemotherapy for HER2-positive BC

For HER2 positive and TNBC, the diagnostic multigene assays are lacking, and the classical clinical method and pathological data such as tumor size, and nodal/distant metastases are employed in decision making. The HER2-positive tumors have an expression of differentiation in tumor genes along with numerous cell cycle and proliferation genes. To treat such types of BC, the patients are subjected to trastuzumab and pertuzumab-containing regimens [81].

- *Paclitaxel along with trastuzumab*

The analytical studies of Leon-Ferre *et al*. suggested that there were four neoadjuvant schemes including trastuzumab with docetaxel (taxane), Pertuzumab with docetaxel (TP), Both trastuzumab and pertuzumab with docetaxel (THP), Trastuzumab and pertuzumab without chemotherapy (HP). However, the anthracycline regimen showed a varied type of toxicity (especially cardiac and secondary leukemia) hence uplifting the oncologists to remove anthracyclines from the list. In the further conclusion, Leon-Ferre *et al*. discussed that chemotherapy is now administered before surgery replacing the sandwich therapy where the patients are treated with chemotherapeutic agents prior to surgery and the surplus was administered postoperatively [81].

One of the discussions also confirmed that combined treatment with weekly paclitaxel and dual anti-HER2 therapy with both trastuzumab and pertuzumab has favorable cardiac safety [82].

- *Sacituzumab Govitecan (SG)*

Usually, the trophoblast cell surface Ag-2 in epithelial tumors is a transmembrane glycoprotein Ca signal transducer that is overexpressed in developing tumors. The drug, Sacituzumab Govitecan is an anti-Trop-2 ADC. It mainly consists of SN-38 as cytotoxic payload (which is an active metabolite of irinotecan) and mAb. Its notable side-effects are nausea, diarrhea, fatigue, neutropenia, and anemia [83].

- *Trastuzumab Deruxtecan (T-Dxd)*

Trastuzumab is an anti-HER2 immunoglobulin G1 body and topoisomerase I inhibitor cargo and is conjugated by a cleavable tetrapeptide-based linker. Although the T-Dxd is approved by FDA it still risks ILD or pneumonitis among patients in which the signs and symptoms involve dyspnoea, cough, fever or other intensified respiratory factors [83].

- *Docetaxel*

Docetaxel falls under the category of taxanes which has antitumor activity, which targets the cell cycle to cease at the G2/M checkpoint. This gradually triggers cytotoxicity and results in apoptosis. Docetaxel is also known to lower the $CD8^+$ expression level in certain patients [84]. In the recent treatment regimen, docetaxel is used as one of the drugs in the first-line combination therapy of HER2 positive along with Pertuzumab.

Chemotherapy for HR-positive HER2-negative BC

Methotrexate (MTX)

Methotrexate, formerly known as amethopterin, is an anti-folate compound that acts as an antineoplastic agent and suppresses the immune system. The two carboxylic groups

in the MTX permit the other molecules in the linkage and produce prodrugs. MTX is used in combined therapy with multiple drugs. However, conjugated drug therapy depresses the MTX's ability to bind to albumins. MTX is not included in the first-line treatment for BC but still has clinical significance. Dastjerd *et al*., encapsulated the MTX in liposomal entities, hence forming MTX/Lip nanoparticles, and observed its action on the BT-474 BC cell line and found better efficacy of these modified nanoparticles [85].

- *Mitomycin C (MMC)*

MMC is an anti-tumor chemotherapeutic agent that ceases the action of DNA synthesis and cross-links DNA (at the N6 position of adenine). The most prominent activity of MMC is during the late G1 and early S phases of the cell cycle [86]. MMC and MTX have been proven effective on various types of BC subtypes.

- *Pixantrone*

Pixantrone is an aza-anthracene-dione which is a monotherapy and derivative of the anthracycline drug family. It is known to intercalate the major as well as minor grooves of DNA and forms the DNA adducts. Pixantrone alkylates DNA via amino entities on each side of the chain of the drug forming a covalent bond between pixantrone and DNA adducts. In comparison, it was found that the pixantrone has reduced toxicities unlike many anthracycline-based agents [87].

Hormonal therapy

Hormone therapy is also known as endocrine therapy. This therapy slows or stops the growth of hormone-sensitive tumors by blocking the ability of the body to produce hormones or interfere with the effects of hormones on BC cells [71]. The hormones, estrogen and progesterone are synthesized by the ovaries in premenopausal women and by some tissues like fat and skin in both premenopausal and postmenopausal women and men [71]. Estrogen and progesterone are involved in the growth of some types of BCs, which are known as hormone-sensitive (or hormone-dependent) BC. Hormone receptors bind with hormones then become activated and trigger the expression of specific genes and stimulate cell growth [88].

Hormone therapy for hormone-positive BC

Blocking ovarian function, the main source of estrogen in premenopausal women is overactive ovaries, estrogen levels in these women can be reduced by ovarian ablation. Permanent, ovarian ablation can be treated by radiation therapy or oophorectomy or by use of some medication. Ovarian function can be suppressed temporarily by treatment with drugs called gonadotropin-releasing hormone (GnRH) agonists also known as luteinizing hormone-releasing hormone (LHRH) agonists. Goserelin (Zoladex) and Leuprolide (Lupron) are the few drugs approved by the US FDA as ovarian suppression drugs.

Blocking estrogen aromatase inhibitors are the drugs used to block the activity of an enzyme called aromatase in postmenopausal women. Aromatase is an enzyme used to make estrogen in the ovaries and other tissues. These drugs can be used in premenopausal women given in combination with a drug that suppresses ovarian function. FDA-approved aromatase inhibitors are anastrozole (Arimidex) and letrozole (Femara), and exemestane (Aromasin).

Selective estrogen receptor modulators (SERMs) compounds bind to estrogen receptors which helps in preventing estrogen binding [89]. SERMs like tamoxifen (Nolvadex) and toremifene (Fareston) are approved by the FDA for the treatment of BC. These bind to the estrogen receptors, SERMs can potentially not only block estrogen activity but can also mimic the effects of estrogen, depending on the area where they are expressed in the body. For example, tamoxifen blocks the effects of estrogen in breast tissue but it acts like estrogen in the uterus and bone [89].

Other anti-estrogen drug fulvestrant (Faslodex), works in a different way to block estrogen's effects. Like SERMs, fulvestrant binds to the estrogen receptor and functions as an estrogen blocker but it does not mimic estrogen. When fulvestrant binds with the estrogen receptor, the receptor is targeted for destruction [89].

Hormone therapy for early-stage BC

This therapy destroys residue cancer cells left in the breast after surgery. It can also be given before surgery to aid in making the procedure easier. Adjuvant therapy also lowers the chance of recurrence of BC.

Tamoxifen is approved by FDA for adjuvant hormone treatment of premenopausal and postmenopausal women and men with ER-positive early-stage BC. The AIs anastrozole, letrozole, and exemestane are approved for treatment in postmenopausal women. According to the research, women who have received at least 5 years of adjuvant therapy with tamoxifen after having surgery for early-stage ER-positive BC have reduced risks of BC recurrence as well as increased survival rate [90]. Introducing newer hormone therapies like AIs, as compared with tamoxifen in clinical trials, additional approaches to hormone therapy have become common practice.

For example, (i) women can take an AI, in place of tamoxifen, every day for 5 years, (ii) women can receive additional treatment with a combination of an AI after 5 years of tamoxifen (iii) women can switch to an AI after 2 or 3 years of treatment with tamoxifen, for a total of 5 or more years of hormone therapy (iv) Research even shows that for postmenopausal women who have been treated for early-stage BC, adjuvant therapy combined with an AI reduces the risk of recurrence and improves overall survival rate as compared with adjuvant tamoxifen, (v) Premenopausal women with early-stage ER-positive BC can have ovarian suppression in combination with an AI, this was found to have a higher chance of freedom from recurrence than ovarian suppression with tamoxifen or tamoxifen alone [91] (iv) men with early-stage ER-positive BC who have gone through adjuvant therapy are usually first treated with tamoxifen. Those individuals who are treated with an AI usually also take a GnRH agonist.

Decision-making about the type and duration of adjuvant hormone therapy is very complicated and it should be made based on each individual by consulting with an oncologist.

Hormone therapy for advanced or metastatic BC

Different types of hormone therapy are approved for the treatment of metastatic or recurrent hormone-sensitive BC. The two selective estrogen receptor modulators (SERMs), tamoxifen and toremifene, are approved for the treatment of metastatic BC. Fulvestrant is approved for treating postmenopausal women with HR-positive, HER2-negative locally advanced, or metastatic BC who were not previously treated with hormone therapy [92] and it may be also used in premenopausal women who have had ovarian ablation.

The AIs anastrozole and letrozole are approved for postmenopausal women as initial therapy for metastatic or locally advanced hormone-sensitive BC. Both of these drugs when combined with the AIs exemestane are approved for treating postmenopausal women with advanced BC whose disease has been worsened after treatment with tamoxifen [92]. Men with advanced BC who received treatment with AIs also received a GnRH agonist. Details of the drugs used for the treatment of metastatic BC are listed in **Table 4**.

Table 4. Advanced BC treatment with a combination of hormone therapy and targeted therapies

Drug	Combining drug	Type of BC
Palbociclib (Ibrance)	Letrozole	HR-positive, HER2-negative advanced or metastatic BC in postmenopausal females
	Fulvestrant	postmenopausal females with HR-positive, HER2-negative advanced or metastatic BC whose cancer became worse after treatment with other hormone therapy
Abemaciclib (Verzenio)	Fulvestrant	HR-positive, HER2-negative advanced or metastatic BC in postmenopausal females whose disease has become worse after treatment with hormone therapy
	–	women and men with HR-positive, HER2-negative advanced or metastatic BC whose disease became worse after treatment with hormone therapy and previously given chemotherapy for metastatic disease
	aromatase inhibitor	first-line hormone therapy of postmenopausal females with HR-positive, HER2-negative advanced or metastatic BC.
Lapatinib (Tykerb)	Letrozole	Postmenopausal females with HR-positive, HER2-positive metastatic BC for whom hormone therapy is indicated.
Alpelisib (Piqray)	–	HR-positive and HER2-negative BC with a mutation in the *PIK3CA* gene
	Fulvestrant	postmenopausal women, and in men, whose BC is advanced or metastatic and has gotten worse during or after treatment with hormone therapy.

Some women with advanced BC with HER2 HR-positive may receive hormone therapy plus trastuzumab with or without pertuzumab [88].

Neoadjuvant treatment of BC

Neoadjuvant treatment is hormonal therapy to reduce the tumor size before the planned treatment. Clinical trials show that neoadjuvant hormone therapy individually or in combination with AIs can be effective in reducing the size of breast tumors in postmenopausal women, but it is still unknown how effective it is in premenopausal women [93]. Hormone therapy is also used for the neoadjuvant treatment of HR-positive BC in postmenopausal women who cannot go through chemotherapy or in cases where surgery needs to be delayed [94].

- *Related research*

Cancer therapy is the golden era to target cancer cells without affecting normal cells. The treatment for BC is regularly revised as current technology and biomedicine

progress. BC has been recognized as a systemic illness, and neoadjuvant chemotherapy has become an important element of the treatment of HER2-negative BC [95]. The death rate from BC has been reducing in the preceding decades as a consequence of advancements in various treatment strategies. The development of numerous innovative chemotherapeutic medications and techniques has arisen from an improved understanding of the genetic and pathophysiological pathways contributing to malignant transformation and carcinogenesis [96]. Targeting ERs has proven to be one of the most significant therapy options for HR-positive BC.

Furthermore, the success of TTs like anti-HER2 monoclonal antibodies [97] demonstrated the viability and importance of molecular therapeutics in BC therapy. HER2-negative BC treatment is a significant innovation, with more influential elements being added in the progress of new drugs [97]. Additionally, more research is pushing treatment that is "pinpoint accuracy". More research into the effectiveness, safety, and economics of combining TTs and chemotherapy drugs in the treatment of HER2-negative BC patients is needed, to maximize the effectiveness of TTs, which may become a better vision in the future for the treatment of BC patients [98]. Medications for the cure of HER2-negative BC work on several pathways such as PI3K/AKT/mTOR, PARP, CDK4/6, multiple kinases, or immune checkpoint inhibitors [99].

Angiogenesis inhibitors are currently only utilized in individuals with HER2-positive BC people, and their effectiveness in HER2-negative BC patients should be investigated further. CDK 4/6 inhibitors have given BC patients new hope by inhibiting cell proliferation. Many studies have shown and proven that combining this inhibitor with endocrine therapy can increase the survival rate of HR-positive and HER2-negative advanced BC patients [97]. Despite this, numerous recent research emphasizes the relevance of developing BC cell resistance to CDK 4/6 inhibitors. These inhibitors may be employed in the treatment of BC and prostate cancer [97].

As a response, many patents are concentrating on simple bioconjugate structures that are easy to synthesize and have a low cost, high yield, and high final production stability profile. This could give researchers around the world a practical direction for developing new management tools and medicines for BC, paving the way for economical, scalable, stable, efficient, and safe management techniques

CONCLUSION

BC has proved to be the most fatal cancer which makes it ideal for further development of new therapies. To this, several patents are meditating on simple bioconjugate structures that are less hideous to synthesize and have an inexpensive, high yield, and high final production stability profile. This could give developers around the world a pragmatic direction for manufacturing novel management tools and medicines for BC, paving the way for economical, scalable, stable, efficient, and safe management techniques. Multiple data have maintained the current portrait of BC therapies. Hence, the novel research has made the way in progressing the conventional as well as focusing on the current therapeutic methods.

Future randomized trials will explore novel medication r gimens with the response and residual disease-guided cure, and they will be included in routine clinical practices.

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