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A Review On The Advancements In Targeted Therapies For Hormone Receptor-Positive (Hr+), Her2-Positive (Her2+) And Triple-Negative Breast Cancer (Tnbc)

Kalyani Kahandal^{*1}, Mayuri Choundkar², Saloni Pandere³, Mansi Landge⁴

¹Assistant Professor RJSPM College of Pharmacy, Pune.

^{2,3,4}Students RJSPM College of Pharmacy, Pune.

Pune. Maharashtra, India 412105

ABSTRACT

Breast cancer is the second most common and deadly disease among women and is a serious global health concern. Despite advances in medical technology, breast cancer rates are still rising. It is expected that by 2040, there will be more than three million new cases every year. Targeted medicines have greatly changed the way breast cancer is treated, allowing for personalized approaches that reduce side effects and improve patient outcomes. This review provides a detailed look at the latest developments in targeted breast cancer treatments. It examines different types of breast cancer, such as hormone receptor-positive (HR+), HER2-positive (HER2+), and triple-negative breast cancer (TNBC), and recognizes the variety of the disease. It offers treatment plans tailored to each type's specific characteristics. The review also explores how genetic mutations like BRCA1/2 and PIK3CA and molecular profiling help in choosing the right therapy. It discusses targeted medicines like monoclonal antibodies and small molecule inhibitors, explaining how they work and supporting their effectiveness with clinical trial data. The study also looks at potential new drugs and addresses ongoing challenges, such as resistance to treatment, opportunities for combining therapies, and new methods for classifying patients. This study aims to provide healthcare professionals, researchers, and patients with a comprehensive overview of the latest advancements in targeted breast cancer therapy. The goal is to develop customized, effective treatments to strengthen the fight against this challenging disease.

KEYWORDS: Therapy, Hormone Receptor-Positive (Hr+), Her2-Positive (Her2+), Triple-Negative Breast Cancer

INTRODUCTION

Breast cancer remains a serious and widespread disease among women, ranking as the second most common. Over the past 40 years, the number of breast cancer cases has increased significantly. In 2020, there were about 685,000 new cases worldwide, with differences seen in various countries and regions. Breast cancer death rates are especially high in wealthy countries. By 2040, it's predicted that over one million people will die from breast cancer, and more than three million will be diagnosed. Despite early detection and treatment advancements, cancer continues to be the leading cause of death among women and a major global health threat. Breast cancer still has a significant impact on public health.

In recent years, our understanding of the complex molecular and genetic causes of breast cancer has improved, leading to changes in treatment. Targeted medicines have become a powerful tool in fighting breast cancer, offering precision treatment and better outcomes for patients. This study aims to summarize the latest knowledge in this important area and provide a complete overview of the newest advancements in targeted breast cancer treatments.

In the past, non-specific chemotherapy, radiation, and surgery were the main treatments for breast cancer. While these methods greatly improved patient survival, they often had serious side effects and unpredictable results. The development of targeted medicines marked a new era in breast cancer treatment, focusing on personalized care by matching treatments to the specific molecular features of each patient's tumor. This shift has made treatments more effective while reducing side effects.

REVIEW

In this review article, the researchers carried out a detailed investigation and comparison of various studies related to breast cancer. They also examined the latest diagnostic methods, medical discoveries in breast cancer treatments, and advancements in therapy for breast carcinoma. To do this, the researchers conducted a thorough search of literature using keywords like "breast carcinoma," "targeted therapies," "HER2-positive," "hormone receptor," and "triple-negative BC" across various academic journals and search engines such as Google Scholar, PubMed, and Scopus.

The selection criteria for this study were as follows: (1) targeted therapy; (2) breast cancer; (3) HER2-positive; (4) hormone receptor; (5) metastatic; and (6) English language. The following were excluded: (1) irrelevant topics; (2) technical issues; (3) articles that required payment; and (4) non-English language articles. This review also explored advances in Breast cancer therapy procedures, such as surgery, radiation, chemotherapy, and immunotherapy.

Breast Cancer: A Major Global Health Concern

Breast cancer is challenging for clinicians and researchers since it is categorized based on membrane receptor tumor profile and clinical presentations. Over the years, significant research efforts have been directed at creating customized medicines that can enhance patient outcomes, decrease side effects, and enhance their quality of life.

Breast cancer subtypes

Breast cancer mainly affects women and is a type of tumor with several subtypes. Currently, there are three main categories based on the tumor profile: (1) hormone receptor-positive (HR+), (2) HER2-positive breast cancer, and (3) triple-negative breast cancer. The estrogen receptor (ER) helps accurately diagnose between 70% and 75% of cases. In more than 50% of cases with ER-positive breast cancer, the progesterone receptor (PR) is also present. Since ER controls PR functions, having normal PR is important for ER to work properly. The biomarkers ER and PR are highly expressed in breast cancer cells and are used in both diagnosis and prognosis [1, 2, 3, 4].

ADVANCED TARGETED THERAPIES:

Hormone receptor-positive (HR+)

1. Progesterone Receptor-Positive (PR+)

The presence of PR on the cell surface can help identify PR+ breast cancer. Progesterone, a hormone that usually influences breast tissue growth and development, activates these receptors. Since PR+ breast cancer often responds to similar hormone-targeted therapies as estrogen receptor-positive (ER+) breast cancer, they are often considered together [4].

Progesterone Receptor Function

In PR+ breast cancer, progesterone receptors are found on cancer cells, making them responsive to hormonal treatments. Medicines like Tamoxifen and aromatase inhibitors, which target hormones, play a key role in treating PR+ cancer and significantly impact patient outcomes. Progesterone receptors, which are nuclear hormone receptors, control cell division and growth in healthy breast tissue. When breast cancer cells have PRs, progesterone can affect them, potentially leading to increased growth. To determine PR status, which is reported as positive (PR+) or negative (PR-), tumor tissue is analyzed using immunohistochemistry. About 60-70% of breast cancer cases are both ER+ and PR+. These tumors often have a better prognosis than ER- and PR- cancers because hormone-targeted therapy can slow cancer growth. It's important for patients to discuss their specific diagnosis and treatment options with their healthcare team to make informed decisions [5].

2. Prognosis and Therapy Response

Knowing a patient's PR status is important for predicting how they will respond to hormone therapy and how they will do overall. Hormone-targeted treatments usually work well on PR+ tumors, leading to better outcomes. Tumors that are positive for both ER and PR often respond better to hormonal therapy. The choice of hormone therapy is influenced by factors such as the patient's menopausal status, overall health, other medical conditions, and personal preferences.

HER2+

In about 25-30% of breast cancer cases, there is an overexpression of the HER2 receptor, which means there is an excess of proteins, gene amplification, or both. Regardless of the stage of the disease, this

overexpression is linked to worse outcomes in terms of disease-free survival and overall survival. Without targeted HER2-directed therapies, HER2+ breast cancer tends to be more aggressive [6].

3. Specialized Treatments

One of the first targeted treatments for HER2+ breast cancer was trastuzumab (Herceptin), a monoclonal antibody that targets HER2-positive cells and has improved patient outcomes. Trastuzumab-based combination therapies have become the standard treatment. For HER2-positive breast cancer, trastuzumab is often combined with chemotherapy and another monoclonal antibody called pertuzumab (Perjeta), which targets a different part of the HER2 receptor and has shown effectiveness in clinical studies. Another treatment is ado-trastuzumab emtansine (T-DM1, Kadcyla), a combination of trastuzumab and a chemotherapy drug, which has been effective in treating HER2+ cancer cells [7,8].

4. More Recent Targeted Therapies

For advanced HER2+ breast cancer, the small molecule tyrosine kinase inhibitor tucatinib (Tukysa) has been approved for use with trastuzumab and capecitabine, particularly benefiting patients with brain metastases. For those with early-stage HER2+, another tyrosine kinase inhibitor, neratinib (Nerlynx), is given as extended adjuvant therapy after trastuzumab-based treatment. New treatments for HER2-positive breast cancer are being studied in ongoing clinical trials, including recent developments like antibody-drug conjugates, bispecific antibodies, and HER2 immunotherapies [9, 10].

5. Immunotherapy

Clinical studies are exploring the use of immune checkpoint inhibitors like pembrolizumab and atezolizumab with HER2-targeted treatments. These combinations help the immune system better target HER2-positive tumor cells. Some patients may still have residual disease after neoadjuvant therapy, so research is ongoing into other treatments like surgery, radiation, and additional systemic therapies to improve outcomes for these individuals.

Pertuzumab, a monoclonal antibody that targets HER2, has recently been approved for use as an adjuvant therapy. It works alongside trastuzumab to enhance treatment effectiveness. Pertuzumab prevents HER2 from forming pairs with other HER2 receptors, while trastuzumab blocks HER2 from interacting with other cells [11, 12, 13].

A successful approach for adjuvant treatment is using both trastuzumab and pertuzumab together. However, some patients may still experience a relapse of the disease despite the benefits of adding trastuzumab to early breast cancer treatment. This area needs further research and development in the future. For ER+ breast cancer, targeting estrogen receptors is a key part of treatment. Recent advancements have focused on improving outcomes and reducing side effects [14].

6. Hormone Treatment

Hormone therapy is crucial for managing ER+ breast cancer because it targets estrogen receptors on cancer cells. There are two main types of hormonal therapy:

Tamoxifen: This is a widely used selective estrogen receptor modulator (SERM) and has been the standard treatment for ER+ breast cancer. Tamoxifen works by blocking estrogen from attaching to the receptors on cancer cells, which helps prevent cell division. Clinical studies have shown that tamoxifen is effective in reducing the chance of recurrence and improving survival [15].

Aromatase inhibitors (AIs): Postmenopausal women commonly use aromatase inhibitors (AIs) like anastrozole, letrozole, and exemestane. These drugs work by blocking the aromatase enzyme, which converts androgens into estrogen. By lowering estrogen levels, AIs effectively reduce the growth signals for ER+ cancer cells. Clinical trials have shown that AI treatment improves outcomes and reduces recurrence rates [16].

7. Applied Therapies

i) CDK4/6 inhibitors: The development and approval of CDK4/6 inhibitors like palbociclib, ribociclib, and abemaciclib represent a major advance in treating ER+ breast cancer. These drugs target CDK4 and CDK6, which are important for controlling the cell cycle. They have shown significant progress in preventing the spread of metastatic ER+ breast cancer and are now also used in adjuvant therapy [17].

ii) Inhibitors of Immune Checkpoints

Immune checkpoint drugs like pembrolizumab have changed the treatment of some cancers, but research is still ongoing to see how they affect ER+ breast cancer. Early studies suggest that immunotherapy might help some patients with ER+ breast cancer who have high levels of tumor mutations. Clinical trials are still exploring the potential of these treatments.

iii) The Use of Genomic Profiling

Genomic profiling tests like Oncotype DX and MammaPrint are important tools for assessing the risk of relapse and the potential benefit of adjuvant chemotherapy for patients with early-stage ER+ HER2-negative breast cancer. These tests analyze the expression of various cancer-related genes in tumor tissue to predict the likelihood of recurrence and the benefits of treatment. Oncotype DX and MammaPrint have shown strong performance in predicting outcomes and are commonly used in clinical practice [18].

iv) Neoadjuvant and Adjuvant Treatment

Adjuvant therapy is important for treating ER+ breast cancer. The choice between hormone therapy and chemotherapy depends on factors like the size of the tumor, whether lymph nodes are involved, and the patient's preferences. Adjuvant therapy aims to reduce the risk of both local and distant recurrence.

Neoadjuvant therapy, on the other hand, is used before surgery to shrink the tumor, increase the chances of achieving clean surgical margins, provide evidence of how well the tumor responds to treatment, and improve long-term surgical and medical outcomes, making surgery more effective [19].

Reducing Side Effects

New hormone treatments with improved safety profiles are being developed to reduce side effects. Treatment strategies now also include supportive care, such as managing menopausal symptoms, addressing mental health, and controlling pain. Ongoing research and clinical trials aim to further improve outcomes while minimizing side effects and enhancing quality of life. This shows how care for ER+ breast cancer is evolving. For people with ER+ breast cancer, personalized treatment plans developed with medical oncologists remain crucial [20].

PROGRESS AND CHALLENGES OF PRECISION-MEDICINE THERAPY OF BREAST CANCER

1. Oral HER2-Targeting Tyrosine Kinase Inhibitors

HER2 is a good target for inhibitory drugs like tyrosine kinase inhibitors (TKIs), which are used for various tumors. In 2020, lapatinib was the only FDA-approved HER2-specific TKI. Since then, other TKIs such as neratinib, pyrotinib, tucatinib, and afatinib have also been approved.

Neratinib is an irreversible TKI that blocks HER1, HER2, and HER4. It has shown strong activity against HER2-positive breast cancer, but it can cause significant diarrhea, which may be managed with preventive antidiarrheal treatment. Neratinib has recently been tested in phase III trials for patients with early-stage HER2-positive breast cancer who completed standard trastuzumab-based therapy.

Pyrotinib is a small, irreversible inhibitor of HER1, HER2, and HER4. It has shown good results in preclinical studies, inhibiting HER2-related signaling and tumor growth. A phase III study compared capecitabine with either lapatinib or pyrotinib in HER2-positive or metastatic breast cancer patients who had already received trastuzumab, taxanes, or anthracyclines. In this study, 267 patients were randomly assigned to receive either pyrotinib or lapatinib with capecitabine. Pyrotinib plus capecitabine was associated with better progression-free survival compared to lapatinib plus capecitabine. Diarrhea rates were 30.6% for pyrotinib and 8.3% for lapatinib [19, 20].

2. HER2 Monoclonal Antibodies

HER2, a member of the HER family, is overexpressed in about 20% of breast cancer cases. Before HER2-targeted monoclonal antibodies were available, HER2-positive breast cancer had a very poor prognosis. Several new HER2-targeting monoclonal antibodies have been developed, which either bind more specifically to the HER2 receptor than trastuzumab or bind to additional parts of the receptor to enhance activity or boost the immune response [21].

Trastuzumab was the first monoclonal antibody used for both metastatic and early-stage breast cancer and has improved survival rates in clinical trials.

Margetuximab is a modified version of trastuzumab designed to enhance immune system activity. It has shown a modest improvement in progression-free survival for patients with HER2-positive metastatic breast cancer in the SOPHIA trial. This trial compared margetuximab plus chemotherapy to trastuzumab plus chemotherapy in patients who had already received two lines of anti-HER2 therapy [22, 23].

ZW25 is a bispecific antibody that targets two HER2 epitopes (ECD2 and ECD4). It has been effective in treating breast cancer models with low HER2 expression and has improved overall survival rates. It is currently being tested in phase I and II trials for advanced HER2-expressing cancers [24].

PRS-343 is another bispecific antibody that targets HER2 and CD137, a costimulatory receptor. PRS-343 helps activate T cells by linking them to HER2-positive cancer cells, increasing the immune response. It is being tested in phase I trials both as a standalone treatment and in combination with atezolizumab for advanced solid tumors [21].

3. Antibody-Drug Conjugates

Antibody-drug conjugates (ADCs) are treatments that combine a monoclonal antibody with a cytotoxic drug through a linker. They are designed to deliver the drug directly to the target site, reducing side effects [25]. ADCs are transforming the treatment of HER2-positive breast cancer by delivering cytotoxic agents more precisely. Some examples include:

Trastuzumab deruxtecan: This ADC combines trastuzumab with a drug linker and a topoisomerase I inhibitor (exatecan derivative). It has been approved by the FDA for HER2-positive, unresectable breast cancer patients who have already received at least two previous anti-HER2 treatments [26].

ZW49: This ADC combines ZW25 with monomethyl auristatin E. Studies have shown that ZW49 is quickly taken up by HER2-expressing cells and has demonstrated antitumor activity in models with both high and low HER2 levels.

On August 5, 2022, the ADC fam-trastuzumab deruxtecan-nxki (Enhertu) was approved by the FDA for patients with unresectable or metastatic HER2-low breast cancer who had previous chemotherapy or disease recurrence within six months of completing adjuvant therapy.

On February 3, 2023, the FDA approved sacituzumab govitecan-hziy (Trodelyv) for treating patients with unresectable locally advanced or metastatic hormone-receptor-positive (HR+) and HER2-negative metastatic breast cancer who have received endocrine-based therapy and at least two other systemic treatments.

Overall, ADCs show promise for treating HER2-positive metastatic breast cancer patients.

4. Challenges in Precision Medicine

Since the FDA approved trastuzumab in 1998, treatment options for HER2-positive breast cancer have greatly improved. Many new drugs have been approved, and more are being developed with promising results for HER2-positive breast cancer. As treatment options continue to expand, future research will help determine the best way to use these therapies for maximum benefit.

HER2-positive breast tumors have a lot of HER2 on their surface, which provides two main treatment strategies:

Inhibiting signaling functions: This approach is more challenging, with lapatinib being the primary drug available for this purpose.

Delivering tumor-killing agents: This method is more transformative, with trastuzumab and pertuzumab being key treatments for early-stage HER2-positive breast cancer.

Developing predictive biomarkers and understanding immune markers has been difficult, and these areas are still under investigation.

The therapy approaches for various stages of HER2-positive breast cancer are summarized in Table

Table: Therapy approaches for various stages of HER2-positive breast cancer

Breast Cancer	Treatment Protocol
Early Stage Breast Cancer	Chemotherapy, Trastuzumab, Pertuzumab
First-line therapy	Taxane, Trastuzumab, Pertuzumab
Second-line therapy	Trastuzumab emtansine
Third-line therapy	Capecitabine, Lapatinib
	Aromatase inhibitor, Trastuzumab/Lapatinib
	Chemotherapy, Trastuzumab
	Vinorelbine, Trastuzumab

Current Landscape of Precision-Medicine Therapy for TNBC

In 2020, there were an estimated 2.3 million new cases of breast cancer in women, making up 11.7% of all new cancer cases [27]. Triple-negative breast cancer (TNBC) was the second most common type, affecting 10 to 20% of patients worldwide [28]. TNBC does not have hormone receptors (for estrogen or progesterone) or HER2, which are targets for other treatments [29, 30, 31]. As a result, TNBC does not respond to hormonal or HER2-targeted therapies. The main treatments for TNBC are surgery and chemotherapy [32, 33].

According to the National Cancer Institute, for women diagnosed with triple-negative breast cancer (TNBC) in the U.S. between 2012 and 2018, the overall 5-year survival rate was 77.1%.[86] However, this rate varies depending on the cancer stage at diagnosis. It can be as high as 91.3% for tumors only in the breast, but drop to 12% for tumors that have spread to distant organs like the lungs or bones [34, 35].

Relapses are a significant issue for TNBC patients. About 25% of women with localized TNBC will have a relapse with metastasis, and the highest risk for this relapse occurs within the first 2–3 years after treatment. Factors that can affect the risk of relapse and overall survival include the size and stage of the cancer at diagnosis and the type of chemotherapy used [36].

Surgery is a common treatment for triple-negative breast cancer (TNBC). The choice of surgery depends on factors such as the cancer's size and location, the stage of the disease, and the patient's overall health. The two main types of surgery are:

Lumpectomy: This involves removing the cancerous tissue along with some surrounding healthy tissue, aiming to conserve the breast.

Mastectomy: This involves removing the entire breast, including the tumor and surrounding healthy tissue. Patients may also receive additional treatments like radiotherapy or chemotherapy, either before (neoadjuvant) or after (adjuvant) surgery, based on the tumor's stage [31, 33].

Recent reviews have highlighted the benefits of using radiotherapy as an adjuvant treatment for advanced triple-negative breast cancer (TNBC), especially for patients at high risk of recurrence.

In addition to surgery, chemotherapy is a key treatment for TNBC, whether used before (neoadjuvant), after (adjuvant), or during metastatic disease [29, 33, 35]. Common chemotherapy regimens include:

Anthracyclines (e.g., doxorubicin, epirubicin)

Taxane-based agents (e.g., paclitaxel, docetaxel)

Alkylating agents (e.g., cyclophosphamide)

Antimetabolites (e.g., capecitabine)

Platinum-based agents (e.g., carboplatin, cisplatin) [31, 33].

Although surgery and cytotoxic chemotherapy remain the standard treatments for triple-negative breast cancer (TNBC), targeted therapies have shown promise and some have received FDA approval. These include:

PARP inhibitors

Immune checkpoint inhibitors

Antibody–drug conjugates

The choice of treatment depends on the specific characteristics of each patient's cancer and their overall health [14]. Among these targeted therapies, PARP inhibitors were the first to receive FDA approval for TNBC [37].

PARP (poly ADP ribose polymerase) is an enzyme involved in repairing damaged DNA in cells. In about 25% of TNBC patients, a germline BRCA mutation impairs DNA repair. PARP inhibitors block this enzyme, preventing cancer cells from fixing DNA damage, which leads to their death [39, 40, 41].

Olaparib (Lynparza®) was the first PARP inhibitor approved by the FDA in January 2018 for treating germline BRCA-mutated, HER2-negative metastatic breast cancer [38]. The approval followed the results of the OlympiAD clinical trial, which showed that olaparib was significantly more effective than standard chemotherapy (capecitabine, eribulin, or vinorelbine) in terms of progression-free survival (PFS) and had a lower rate of grade three adverse events and treatment discontinuation.[42]

Olaparib was later approved for adjuvant treatment of BRCA-mutated, HER2-negative high-risk early breast cancer based on the Olympi A trial[43]. This phase III trial demonstrated olaparib's superiority in both invasive disease-free survival and distant disease-free survival compared to placebo [44].

Talazoparib (Talzenna®) is another PARP inhibitor that received FDA approval in 2018. This approval was based on the EMBRACA trial, which evaluated the drug for germline BRCA-mutated, HER2-negative metastatic breast cancer. Like olaparib, talazoparib works by inhibiting the PARP enzyme, which impairs the cancer cells' ability to repair DNA damage, ultimately leading to their death.

In the EMBRACA trial, talazoparib demonstrated significant benefits compared to standard therapies, particularly in progression-free survival (PFS), showing its effectiveness for patients with BRCA mutations. This makes it a valuable addition to the treatment options available for TNBC patients with specific genetic profiles [39,40,41].

The first PARP inhibitor to receive FDA approval was olaparib (Lynparza®), in January 2018. This approval was granted for use in germline BRCA-mutated, HER2-negative metastatic breast cancer, following neoadjuvant, adjuvant, or metastatic chemotherapy. The approval was based on the results of the Olympi AD trial (NCT02000622), a randomized, open-label, phase III clinical trial that included 302 patients. The study demonstrated that olaparib significantly improved progression-free survival (PFS) compared to standard chemotherapy (7.0 months vs. 4.2 months). Additionally, olaparib was associated with fewer grade three adverse events and a lower rate of treatment discontinuation compared to standard therapy (4.9% vs. 7.7%).

More recently, olaparib received FDA approval for adjuvant treatment of BRCA-mutated, HER2-negative high-risk early breast cancer, based on the OlympiA trial (NCT02032823). This phase III, double-blinded trial involved 1,836 patients who were randomized to receive either olaparib or placebo. The results showed that olaparib had statistical superiority in both invasive disease-free survival and distant disease-free survival [42,43,44].

Other PARP inhibitors like rucaparib, veliparib, and niraparib have been evaluated in clinical trials for triple-negative breast cancer (TNBC), but they have not yet received FDA approval.

Recent reviews indicate that:

Monotherapy with PARP inhibitors can be effective for patients with BRCA-deficient tumors. Combination therapy with PARP inhibitors and other cytotoxic drugs or immunotherapy may be necessary for BRCA-proficient tumors to enhance efficacy and overcome resistance.

The evolving landscape of PARP inhibitors and their integration into treatment regimens for TNBC continues to be an area of active research and clinical investigation [41, 45, 46].

Another target therapy that may benefit TNBC patients is immunotherapy that works by stimulating the immune system to recognize and combat cancer cells. The importance of the immune system in cancer disease course has long been described, with many studies pointing to favorable outcomes in tumors with tumor-infiltrating lymphocytes in the tissue [47, 48, 49]. Approximately 20% of TNBCs express the programmed death-ligand 1 (PD-L1) molecule [50, 51].

In early 2019, the FDA granted accelerated approval to atezolizumab (Tecentriq®) in combination with albumin-bound paclitaxel (nab-paclitaxel) for the treatment of triple-negative breast cancer (TNBC). This marked a significant advance in the immunotherapy approach to TNBC [52]

Atezolizumab is a humanized monoclonal antibody targeting PD-L1, a protein that helps tumors evade immune detection.

The approval was based on results from the IMpassion130 clinical trial (NCT02425891), which focused on: Unresectable locally advanced or metastatic TNBC with PD-L1 expression.

The trial demonstrated a prolonged progression-free survival in patients treated with the atezolizumab + nab-paclitaxel combination compared to those receiving placebo + nab-paclitaxel. This benefit was observed in both the intention-to-treat population and specifically in the PD-L1-positive subgroup [53, 54]. Despite the initial approval of atezolizumab (Tecentriq®) combined with nab-paclitaxel for TNBC, the final overall survival analysis did not confirm a significant benefit in the intention-to-treat population. This result led to the decision by the FDA and the pharmaceutical company to withdraw the accelerated approval [55]. In the exploratory subgroup analysis of PD-L1-positive patients, there was an observed increase in overall survival in the atezolizumab group (25.4 months) compared to the control group (17.9 months). However, this finding was not sufficient to sustain the accelerated approval [56].

Pembrolizumab (Keytruda®) was granted FDA accelerated approval for use with chemotherapy in treating locally recurrent unresectable or metastatic TNBC with PD-L1 expression. Unlike atezolizumab, pembrolizumab showed some benefits in combination therapy, despite not significantly enhancing overall survival or progression-free survival (PFS) when used alone [57].

The Keynote-355 trial investigated pembrolizumab combined with chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine plus carboplatin). This study included 847 patients randomized into two groups: pembrolizumab–chemotherapy or placebo–chemotherapy.

Key findings from the trial:

In patients with a combined positive score (CPS) of 10 or higher, pembrolizumab–chemotherapy significantly improved median PFS compared to the placebo–chemotherapy (9.7 months vs. 5.6 months). However, this benefit was not observed in the CPS <10 subgroup or in the overall intention-to-treat population. The combination therapy with pembrolizumab showed a lower incidence of grade 3–4 adverse events (14%) compared to chemotherapy alone (36%), highlighting its relative safety profile [58].

The final overall survival analysis from the Keynote-355 trial revealed that:

For patients with a combined positive score (CPS) of 10 or higher, pembrolizumab–chemotherapy significantly improved median overall survival compared to placebo–chemotherapy (23.0 months vs. 16.1 months).

No significant overall survival difference was observed in the CPS <10 subgroup or in the intention-to-treat population.

These results underscore the potential benefit of pembrolizumab when combined with chemotherapy for patients with higher CPS scores, while indicating that its impact might be limited in broader or lower CPS populations [59].

In 2021, pembrolizumab received FDA routine approval for several uses in triple-negative breast cancer (TNBC):

Neoadjuvant Therapy: Pembrolizumab was approved for high-risk, early-stage non-metastatic TNBC in combination with chemotherapy. In this regimen, patients received:

Pembrolizumab or placebo with four cycles of paclitaxel + carboplatin, followed by four cycles of doxorubicin (or epirubicin) + cyclophosphamide [60].

Adjuvant Therapy: Pembrolizumab was approved as a monotherapy for high-risk, early-stage TNBC, administered for nine cycles or until unacceptable toxicity.

This approval marked the first use of immunotherapy for early-stage TNBC, representing a significant advancement in the treatment of this aggressive subtype [61]. In the Keynote-522 trial, pembrolizumab demonstrated notable improvements in both primary endpoints for high-risk, early-stage non-metastatic TNBC:

Pathological Complete Response Rate: Pembrolizumab showed a significant increase compared to placebo (64.8% vs. 51.2%).

Event-Free Survival: Pembrolizumab also led to a significant improvement in event-free survival (84.3% vs. 76.8%).

These results underscore the efficacy of pembrolizumab in enhancing treatment outcomes for early-stage TNBC when combined with chemotherapy [62].

Sacituzumab govitecan (Trodelvy®) is the latest class of antibody-drug conjugates (ADCs) to receive US-FDA approval for TNBC.

Initial Approval: In 2020, sacituzumab govitecan was granted accelerated approval for patients with metastatic TNBC who had undergone at least two prior therapies, based on the IMMU-132-01 (NCT01631552) trial [63]

Regular Approval: In 2021, sacituzumab govitecan received full approval for patients with unresectable locally advanced or metastatic TNBC who had previously received two or more systemic therapies, including at least one for metastatic disease. This approval was based on the ASCENT trial (NCT02574455). This ADC combines a monoclonal antibody with a potent cytotoxic agent, enhancing its effectiveness while minimizing off-target effects [64]. Sacituzumab govitecan consists of two key components:

Sacituzumab: A humanized monoclonal antibody targeting Trophoblast Cell-Surface Antigen 2 (Trop-2). Trop-2 is a transmembrane protein overexpressed in various tumors, including TNBC. It plays a role in tumor growth, invasion, and metastasis.

Govitecan: A topoisomerase I inhibitor, which is a potent cytotoxic agent. It interferes with DNA replication and repair, leading to cancer cell death.

The combination of these components allows sacituzumab govitecan to specifically target and kill cancer cells expressing Trop-2 while minimizing damage to normal cells [65, 66, 67]. The IMMU-132-01 trial, a phase I/II study, demonstrated that sacituzumab govitecan provided durable objective responses in patients with refractory metastatic TNBC, with myelotoxicity being a notable adverse effect. The subsequent phase III ASCENT trial confirmed its efficacy, showing significant improvements in both median progression-free survival (5.6 months vs. 1.7 months) and median overall survival (12.1 months vs. 6.7 months) compared to single-agent chemotherapy. This substantial benefit led to its approval for use in patients who have received multiple prior therapies.

Other ADCs like ladiratuzumab vedotin and U3-1402 are still under investigation for TNBC and have not yet received clinical approval. These drugs represent ongoing efforts to develop new, effective treatments for this challenging breast cancer subtype [68, 69].

Indeed, while PD-L1 expression has been used to guide the use of anti-PD-L1/anti-PD-1 therapies, its utility as a biomarker has limitations. Some reviews highlight the following issues:

Variability in PD-L1 Testing: Different assays and testing methods can yield inconsistent results, complicating the interpretation of PD-L1 expression levels and their correlation with clinical outcomes.

Incomplete Correlation: High PD-L1 expression does not always predict a strong response to immunotherapy. Some patients with low or negative PD-L1 expression may still benefit from these therapies, while others with high expression may not respond.

Tumor Heterogeneity: PD-L1 expression can vary within different areas of the same tumor or between primary and metastatic sites, which can impact the accuracy of using PD-L1 as a sole biomarker.

Immune Environment Factors: The broader tumor immune microenvironment and other immune checkpoints might also influence treatment response, suggesting that a more comprehensive biomarker approach may be necessary.

Emerging Biomarkers: Research is ongoing to identify additional biomarkers and combination approaches to better predict patient responses to immunotherapy, such as tumor mutational burden (TMB), microsatellite instability (MSI), and other immune-related markers.

Overall, while PD-L1 remains a valuable tool in selecting candidates for immunotherapy, its limitations underscore the need for further research and development of more reliable and comprehensive biomarkers. [70, 71, 72]. There is a broad range of emerging biomarkers and novel immunotherapy approaches being explored to improve the management of cancers like TNBC. Here's a brief overview of the ongoing research areas:

Emerging Biomarkers

Tumor Mutational Burden (TMB): TMB measures the number of mutations in a tumor's DNA and can indicate how likely a tumor is to respond to immunotherapy.

Tumor-Infiltrating Lymphocytes (TILs): These are immune cells present within the tumor microenvironment, and their presence and density can provide insights into the immune response against the tumor.

Microsatellite Instability (MSI): MSI reflects defects in DNA repair mechanisms and is associated with a higher likelihood of response to certain immunotherapies.

Lactate Dehydrogenase (LDH) Levels: Elevated LDH levels can be indicative of tumor burden and disease progression.

Visceral Disease: The presence of visceral metastases may influence treatment choices and responses.

Major Histocompatibility Complex (MHC): The role of MHC in presenting tumor antigens to the immune system is critical for immunotherapy efficacy.

Circulating Tumor DNA (ctDNA): ctDNA can provide real-time information on tumor dynamics and treatment response.

CD274 Amplifications: CD274 (PD-L1) amplifications can affect the expression and effectiveness of PD-L1 inhibitors.

Immune Gene Expression Profiles: Analysis of gene expression related to immune responses can offer insights into how tumors interact with the immune system.

Novel Immunotherapy Approaches

Vaccines: Cancer vaccines aim to stimulate the immune system to target specific tumor-associated antigens.

Adoptive Cell Therapies: These include CAR-T cell therapy and TIL therapy, where patients' own immune cells are engineered or expanded to better target their cancer.

Autologous Tumor-Infiltrating Lymphocytes: These are immune cells extracted from a patient's tumor and then expanded or modified ex vivo before being reinfused.

Oncolytic Virus Therapies: These use genetically modified viruses that selectively infect and kill cancer cells while stimulating an immune response.

Cytokine Agents: These include agents like interleukins and interferons that can boost the immune system's ability to fight cancer.

The combination of advanced biomarkers and novel therapies holds great promise for improving treatment outcomes and personalizing care for patients with difficult-to-treat cancers like TNBC [32, 72, 73, 74].

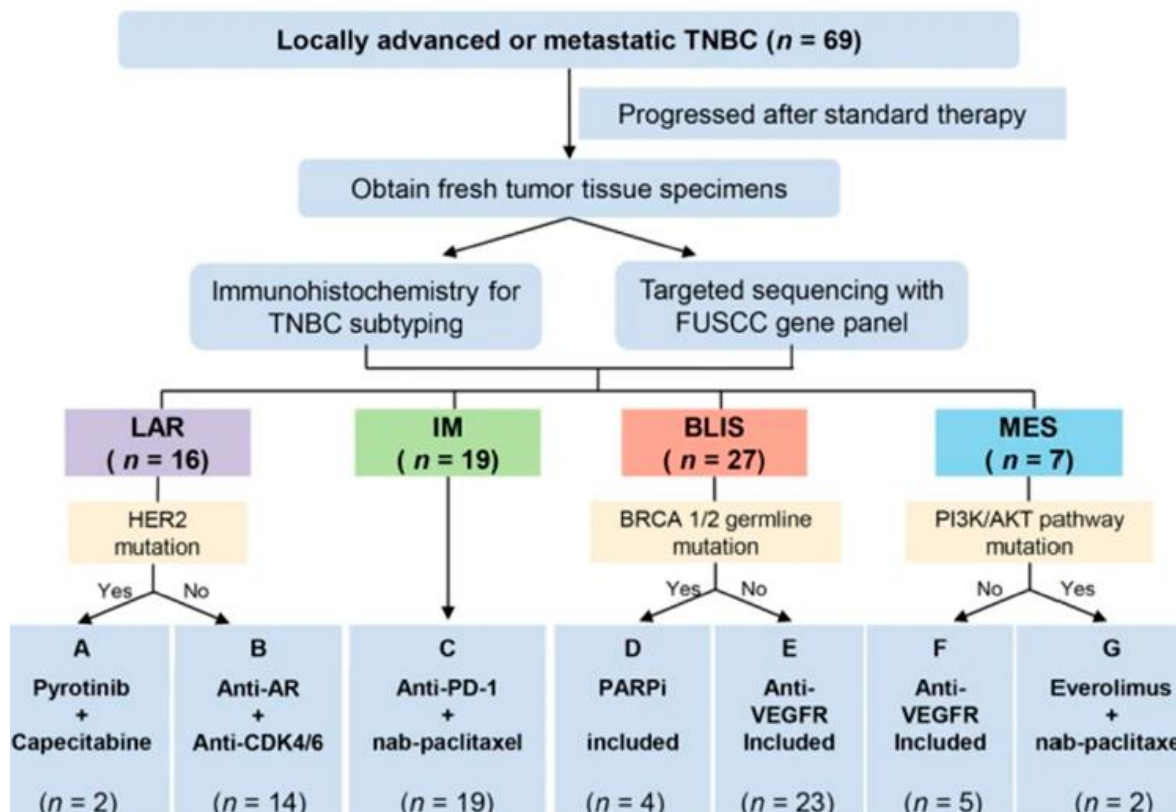


Figure: The FUTURE trial schema: integrating TNBC subtyping and genomic targeting. n, number of the patients; TNBC, triple-negative breast cancer; FUSCC, Fudan University Shanghai Cancer Center; LAR, luminal androgen receptor; IM, immunomodulatory; BLIS, basal-like immune-suppressed; MES, mesenchymal-like; AR, androgen receptor; PD-1, programmed cell death-1; PARPi, poly ADP-ribose polymerase inhibitor; VEGFR, vascular endothelial growth factor receptor (adapted from [75]).

CONCLUSION

Precision medicine is a prospective approach to lower the off-target toxicities of chemotherapeutic agents and enhance the benefits to patients in the clinic. This is a crucial approach for the effective treatment of breast cancer. Precision medicine requires the selection of suitable biomarkers to predict the efficiency of targeted therapy in specific groups of patients. In breast cancer therapy, several possible druggable mutations have been identified in breast tumors that may be utilized for therapy design. Developments in omics technologies have focused on the more precise strategies of precision therapy. The development of next-generation sequencing technologies has raised hopes for precision-medicine treatment strategies in breast cancer and triple-negative breast cancer. Targeted therapy approaches such as ICIs, EGFRi, PARPi, ADCs, CD44i, OV6s and GLUT1i are prospective treatment options for BC and TNBC. Further, targeting signalling pathways may also represent a promising approach for breast cancer therapy. Combination therapy strategies in combination with appropriate single modalities may significantly improve the precision-medicine treatment of metastatic breast cancer and TNBC patients. However, the development of predictive biomarkers and immunologic markers has been challenging and necessitates further investigation. The development and utilization of next-generation sequencing technologies, and further clinical trials on precision-medicine-based therapeutics, will enhance breast cancer therapy and improve the survival of patients. Precision-medicine approaches have the potential to revolutionize the therapy of metastatic breast cancer and TNBC. It is crucial for researchers, healthcare providers, and regulatory bodies to work in an organized way to advance the field of precision medicine for deadly breast cancer therapy.

FUTURE PERSPECTIVE

To advance precision medicine in breast cancer therapy, collaboration among researchers, healthcare providers, and regulatory bodies is essential. Efforts should focus on:

Expanding Biomarker Research: Identifying new biomarkers and validating their clinical utility.

Improving Technology: Leveraging advancements in sequencing and other omics technologies for better patient stratification and treatment personalization.

Conducting Comprehensive Clinical Trials: Ensuring trials are designed to evaluate the effectiveness of combination therapies and new treatment modalities.

Precision medicine holds the potential to significantly enhance the treatment of metastatic breast cancer and TNBC, offering hope for improved survival and quality of life for patients.

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