FABAD J. Pharm. Sci., 49, 2, 435-448, 2024
Doi: 10.55262/fabadeczacilik.1444169
REVIEW ARTICLE

Molecularly Targeted Therapies in Breast Cancer: A Traditional Review

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SUMMARY

Globally, breast cancer stands as the most frequently diagnosed cancer among women, with its incidence continually on the rise. Conventional treatment methods for breast cancer have inherent limitations. Consequently, the development of innovative treatment approaches is imperative. Among these, targeted therapy strategies have emerged as a critical point in contemporary clinical research, significantly diversifying the treatment landscape for breast cancer in recent years. The goals of these new treatment strategies are evolving toward a future that can overcome the limitations of traditional treatment methods, protect patients from side effects, and improve patients' survival rates and life quality. Nowadays, therapeutic agents that bind to preferred targets are used based specifically on various subtypes of breast cancer. The FDA-approved targeted therapeutic agents—such as monoclonal antibodies, gene therapies, immunotherapeutic cancer vaccines, and small molecule inhibitors, are reviewed in this article.

Key Words: *Molecular targeted therapies, breast cancer, small molecule drugs, monoclonal antibodies, immunotherapeutic cancer vaccines, gene therapy.*

Meme Kanserinde Moleküler Hedefe Yönelik Tedaviler: Geleneksel Bir Derleme

ÖZ

Küresel olarak, meme kanseri, kadınlar arasında insidansı sürekli artan ve en sık teşhis edilen kanserlerden biridir. Meme kanserinin konvansiyonel tedavi yöntemlerinin doğal sınırlamaları vardır. Sonuç olarak, yenilikçi tedavi yaklaşımlarının geliştirilmesi zorunludur. Bunlar arasında, hedefe yönelik tedavi stratejileri, çağdaş klinik araştırmalarda kilit bir nokta olarak ortaya çıkmış ve son yıllarda meme kanseri için tedavi ortamını büyük ölçüde çeşitlendirmiştir. Bu yeni tedavi stratejilerinin hedefleri, geleneksel tedavi yöntemlerinin sınırlamalarının üstesinden gelebilen, hastaları yan etkilerden koruyabilen ve hastaların hayatta kalma oranlarını ve yaşam kalitesini iyileştirebilen bir geleceğe doğru evrilmektedir. Günümüzde, özellikle meme kanserinin çeşitli alt tiplerine göre tercih edilen hedeflere bağlanan terapötik ajanlar kullanılmaktadır. Bu makalede monoklonal antikorlar, gen tedavileri, immünoterapötik kanser aşıları ve küçük molekül inhibitörleri gibi FDA onaylı hedefe yönelik terapötik ajanlar gözden geçirilmiştir.

Anahtar Kelimeler: *Moleküler hedefe yönelik tedaviler, meme kanseri, küçük moleküllü ilaçlar, monoklonal antikorlar, immünoterapötik kanser aşıları, gen tedavisi.*

Received: 29.02.2024
Revised: 13.06.2024
Accepted: 03.07.2024

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INTRODUCTION

Lowering the likelihood of disease and preventing fatalities is the primary goal of all cancer research and innovations (Akram, Iqbal, Daniyal, & Khan, 2017; Engin, 2005). Following a cancer diagnosis, the primary treatment modalities often involve surgery, immunotherapy, radiation, endocrine therapy, traditional cytotoxic chemotherapy, or a combination of them (Kimiz-Gebologlu, Gulce-Iz, & Biray-Avci, 2018; Waarts, Stonestrom, Park, & Levine, 2022). These traditional treatments are subject to challenges such as multi-drug resistance, a lack of tumor cell selectivity in comparison to normal cells, insufficient drug concentrations in tumors, and systemic toxicity (Seledtsov, Goncharov, & Seledtsova, 2015; Xu & Mcleod, 2001). These challenges make the design of innovative and potent treatments for cancer necessary.

Over the past two decades, significant initiatives such as the Cancer Genome Atlas (NCI/NIH) have combined next-generation sequencing with cutting-edge computational data analysis methods to develop molecularly targeted pharmacological therapeutics (Bedard, Hyman, Davids, & Siu, 2020; M. F. Berger & Mardis, 2018; Jacobs, Martinez Castaneda-Cruz, Rose, & Connelly, 2022). These therapeutics can complement or even eventually replace broad-spectrum cytotoxic drugs (Inal et al., 2013). For instance, the term "magic bullet" was first used for these therapeutics by Paul Rich in 1906 to emphasize their capacity to target microorganisms selectively and promote the targeted release of therapeutics at the site of the disease, while minimizing off-target side effects in healthy tissues (Adams & Weiner, 2005).

The U.S. Food and Drug Administration (FDA) has authorized various molecularly targeted medicines that have demonstrated great clinical effectiveness in treating a variety of malignancies including breast, colorectal, lung, ovarian cancers and leukemia as well as other non-cancer illnesses (Akçay, 2002; Brodsky, 1988; Gerber, 2008; Gray et al., 2020; Lee, Tan, & Oon, 2018). Numerous studies have demonstrated that hybrid treatment of cancer using a variety of medications (conventional + targeted) produces better synergistic anti-tumor benefits than single-drug therapy (Fisusi & Akala, 2019; Kay et al., 2021).

The characteristics and effects of molecularly targeted therapeutic medicines used to treat cancer may vary. Depending on the tumor type, cell surface antigens, telomeres, or telomerase as well as substances in the tumor microenvironment can be targeted to activate the immune system. These medicines can control the cell cycle progression, apoptosis, metastasis, and angiogenesis. They also act on growth factors, receptors, or signal transmission pathways. More specifically, they can limit metastasis, assist cell cycle control, promote apoptosis or autophagy, and disrupt signals that aid in the proliferation of cancer cells. As such, they can deliver toxic substances to cancer cells' particular molecules in a targeted manner to destroy them (Amer, 2014; Gerber, 2008; Lee et al., 2018; Padma, 2015; Saijo, 2010).

Breast cancer

Breast cancer, the most common type of cancer in women, is a heterogeneous neoplasm with many hereditary and clinical subtypes (Cadirci & Sengül, 2023). The classification of clinical subtypes has evolved. Classifications include treatment decisions and prognosis, tumor size, lymph node involvement, histological grading, age of the patient, ki67 (a marker of proliferation index) proliferation index, estrogen receptors (ER) expression, and progesterone receptors (PR) expression. Traditional classification systems for biological and immunohistochemical (IHC) markers such as human epidermal growth factor-2 (Her-2 or c-erbB2) expression are carried out (Gao & Swain, 2018; Gholikhani et al., 2022; Yersal & Barutca, 2014). Immunohistochemical classification of breast cancer is the most commonly used classification system. This classification system includes the expression of hormone receptors (HR) ER and PR and Her-2 (Erasmo

Orrantia-Borunda, Patricia Anchondo-Nuñez, Lucero Evelia Acuña-Aguilar, Francisco Octavio Gómez-Valles, & Claudia Adriana Ramírez-Valdespino, 2022). Positive HR indicates the presence of estrogen or progesterone receptors, which can stimulate the development of tumor cells. ER-positive tumors express ER and PR, ER-responsive genes, and other genes that encode ER and PR, which are typical proteins of lumen epithelial cells, so they are called lumen groups. It is defined in two subtypes Lumen-a and Lumen-b (Yersal & Barutca, 2014). This classification is divided into four subgroups according to NCI SEER data: HR+/Her-2-, HR-/Her-2-, HR+/Her-2+, and HR-/Her-2+ (Kaplan et al., 2015; National Cancer Institute, 2020). Table 1 lists the molecular subtypes of breast cancer.

Table 1. Molecular subtypes of breast cancer.

Molecular Subtype	**Hormone Receptor Status**	**Characteristic**
Luminal A	ER and, or PR Positive Her-2 Positive	30-45% of the patients Low proliferation (Ki67<14) Better prognosis Longer survival rates
Luminal B	ER and, or PR Positive Her-2 Positive or Negative	10-20% of the patients High proliferation rate (Ki67>14) Grade II, III, or IV Poorer prognosis
Her-2-enriched	HR and, or PR Negative Her-2 Positive	15-20% of the patients High proliferation (Ki67>14) Poorer prognosis
Basal-like/Triple Negative	ER, PR, and Her-2 Negative	15-20% of the patients High proliferation rate (Ki67>14) Poorer prognosis

Hormone Receptors

Approximately 75% of breast cancers are positive for ER and, or PR. HR is divided into two subtypes: lumen-a and lumen-b. Lumen-a is the most common subtype and represents 50-60% of all breast cancers. These tumors often have low histological grade, low nuclear pleomorphism, low mitotic activity, and a good prognosis. Lumen-α is characterized by higher levels of ER and lower levels of proliferation-related genes. Lumen-a serotype is defined by immunohistochemistry as ER-positive and, or PR-positive tumors with low Her-2 and low Ki67 (proliferative cell nuclear antigen) index. Lumen-b tumors constitute 15-20% of breast cancers and have a more aggressive phenotype, higher histological grade, proliferative index, and worse prognosis. Lumen-b subtype is defined as ER-positive, Her-2 negative, and Ki67 high or ER and Her-2 positive tumors or ER-negative PR-negative, Her-2 negative (Yersal & Barutca, 2014).

Endocrine therapy is the first step in HR-positive breast cancers (Corti et al., 2023). Tamoxifen, an anti-estrogen treatment for ER-positive breast cancers, was approved by the FDA in 1970 and is considered the first targeted therapy in the history of cancer (Debien, de Azambuja, & Piccart-Gebhart, 2023). There are approaches such as suppression of ovarian function, inhibition of aromatase enzyme, and inhibition of selective estrogen receptors in the treatment of ER-positive breast cancers (Debien et al., 2023). At the same time, small molecule inhibitors such as CDK4/CDK6 and PI3k/AKT/mTOR pathway inhibitors approved by the FDA are listed in Table 2.

Her-2

An over-expression of Her-2 is observed in 20% of all breast tumors. Her-2 is an oncogene that regulates angiogenesis, invasion, proliferation, survival, differentiation, and metastasis, and is the main target in targeted therapeutic methods (Gutierrez & Rachel Schiff, 2011; Kunte, Abraham, & Montero, 2020; Moasser, 2007; Tarantino, Morganti, & Curigliano, 2021). Tyrosine kinase receptors, or type I transmembrane growth factors, comprise the Her family of proteins. When these receptors receive signals from outside the cell, intracellular signaling pathways are activated. The extracellular ligand-binding layer, the transmembrane layer, and the intracellular tyrosine kinase layer are the three levels of the complex biological network that comprise Her-2-Neu receptors.

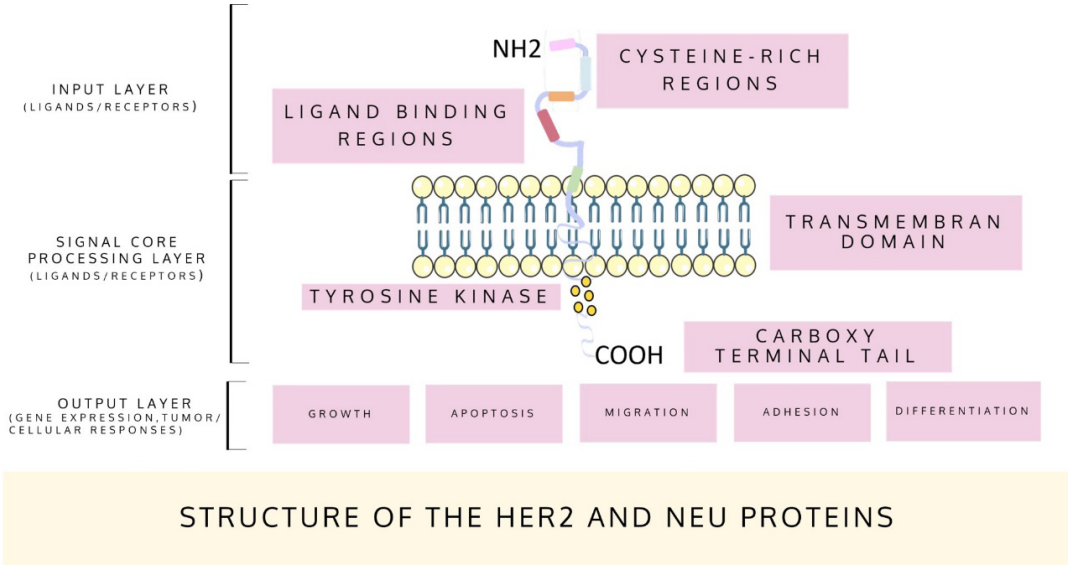

Figure 1. Structure of the Her-2 and Neu proteins.

As more specifically shown in (Figure 1.), the first layer of the Her-2 protein receptors is the extracellular ligand binding layer in contrast the second layer is the core processing layer of the kinases that transmit the signals to the nucleus. The third layer is the intracellular outlet layer, which is the tyrosine kinase field of transcription factors that control genes that affect various cellular functions (Gutierrez & Rachel Schiff, 2011; Moasser, 2007; Swain, Shastry, & Hamilton, 2023). Homodimerization or heterodimerization of receptors which is a result of ligand binding to Her proteins activates the signaling pathways that prevent apoptosis, cell growth, and division (Swain et al., 2023). The invention of medications against Her-2, also known as ERBB2, is an essential advancement for targeted therapy in breast cancer treatment. For instance, as shown in (Figure 2.), four alternative therapies have been established since the formulation of the drug Trastuzumab: 1) Her-2 antibody-drug conjugates, 2) anti-Her-2 monoclonal antibodies, 3) tyrosine kinase inhibitors for Her2+ subtypes, and 4) immunotherapy and therapeutic cancer vaccines (Loibl & Gianni, 2017). When we checked most monoclonal antibodies and other immunotherapies, most approvals for breast cancer were for Her-2 positive subtypes. The response for monoclonal antibody treatment is higher in Her-2 positive types is higher than in other types.

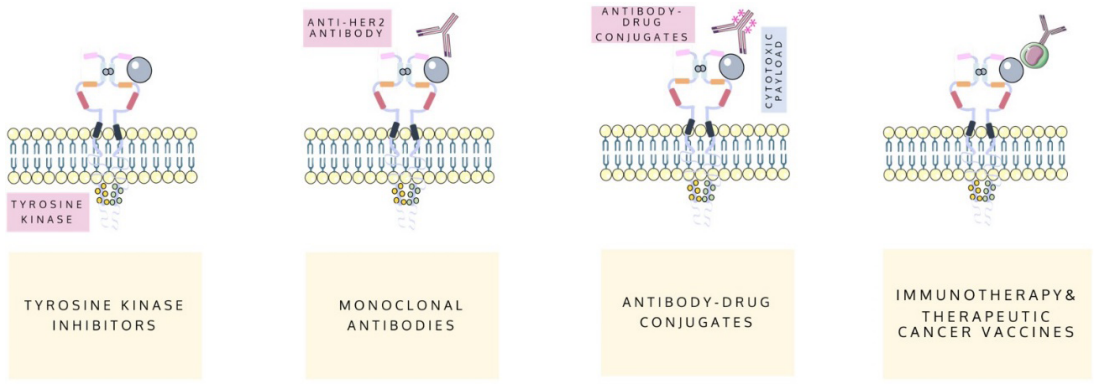

Figure 2. Basic mechanisms of dimerization of Her-2 receptor family in breast cancer

Types of Molecularly Targeted Therapy

Molecularly targeted therapeutic agents used in cancer treatment may exhibit different functions and properties. Depending on the targets, it acts on cell surface antigens, apoptosis, telomeres or telomerase, growth factors, receptors, or signal transduction pathways that regulate cell cycle progression, cell death, metastasis, and angiogenesis (Saijo, 2010). Agents used in molecular targeted therapy are classified as small molecules, monoclonal antibodies, immune therapeutic cancer vaccines, and gene therapy (National Cancer Institute, 2017; Padma, 2015). Drugs used in molecular targeted therapy can target cancer cells and components of the tumor microenvironment to activate the immune system, as well as block signals that promote cancer cell growth, interfere with cell cycle regulation, and, or induce cell death to kill cancer cells. (Amer, 2014; Padma, 2015). These are further explored in the subsequent subsections.

Small molecule inhibitors

Small molecule inhibitors are substances with a relatively low molecular weight (900 <Da) which enables them to enter the cells and target a particular protein (Joo, Visintin, & Mor, 2013). The majority of monoclonal antibodies are designed to attack targets outside of cells or on the cell surface because they cannot cross the plasma membrane of cells (Joo et al., 2013). Owing to their smaller size relative to monoclonal antibodies, small molecule inhibitors can bind to a broader array of extracellular and intracellular targets. Moreover, specific small-molecule inhibitors can diminish tumor-related brain lesions by penetrating the blood-brain barrier (Berger & Mardis, 2018; Gharwan & Groninger, 2016; Martínez-Reyes & Chandel, 2021; Shi et al., 2022). Table 2 lists the FDA-approved small molecule inhibitors that are utilized in the treatment of breast cancer. Tyrosine kinase inhibitor is one of the small chemical inhibitors that targets the intracellular catalytic kinase domain of Her-2 and inhibits phosphorylation while also triggering the downstream signaling cascades (Swain et al., 2023). Small molecule inhibitors work by targeting and neutralizing key enzymes like cyclin-dependent kinases (CDKs) and poly ADP-ribose polymerase (PARP) inhibitors. These agents disrupt signaling pathways involved in carcinogenesis, activate cell cycle checkpoints, induce apoptosis, and inhibit the activity of target proteins by binding to specific "pockets" on cell membranes (Berger & Mardis, 2018; Gharwan & Groninger, 2016; Joo et al., 2013; Lee et al., 2018; Martínez-Reyes & Chandel, 2021; Shi et al., 2022). For example, Lapatinib and Neratinib are dual-targeted inhibitors that block the actions of both EGFR and Her-2 (Paul, Trovato, & Thompson, 2008).

Table 2. List of FDA-approved therapeutic small molecule drugs used in clinic.

SMALL MOLECULE DRUGS	TARGET	CANCER TYPE	YEAR APPROVED	REFERENCES
Abemaciclib (Ly2835219) Verzenio	CDK4, CDK6	Combination Therapy With An Aromatase İnhibitor Or With Fulvestrant Or As A Monotherapy For Breast Cancers	2017	(Fassl, Geng, & Sicinski, 2022; Pandey et al., 2019; Roskoski, 2021, 2023; Royce et al., 2022)
Palbociclib (Pd-0332991) Ibrance	CDK4, CDK6	Estrogen Receptor- And Her-2 Positive Breast Cancers	2019	(Fassl et al., 2022; Gharwan & Groninger, 2016; Pandey et al., 2019; Rocca et al., 2017; Roskoski, 2021, 2023; Wedam, Fashoyin-aje, et al., 2020)
Ribociclib (Lee011) Kisqali	CDK4, CDK6	Combination Therapy With An Aromatase İnhibitor For Breast Cancers	2017	(Fassl et al., 2022; Pandey et al., 2019; Rascon et al., 2018; Roskoski, 2021, 2023)
Lapatinib (Gw572016) Tykerb	EGFR, ERBB2, Her-2	Her-2 Positive Breast Cancer	2007	(Gharwan & Groninger, 2016; Mcarthur, 2009; Paul et al., 2008; Roskoski, 2021, 2023)
Tucatinib (Ont-380) Tukysa	ERB2, Her-2	Combination Second-Line Treatment For Her-2 Positive Breast Cancers	2020	(Roskoski, 2021, 2023; Sirhan, Thyagarajan, & Sahu, 2022)
Neratinib (Hkı-272) Nerlynx	ERB2, Her-2	Her-2 Positive Breast Cancer	2017	(Roskoski, 2021, 2023)
Everolimus (Rad001) Afinitör	FKBP12, mTOR	Her-2 Negative Breast Cancer	2009	(Finn, Linnartz, Chen, & Slamon, 2015; Houghton, 2010; Roskoski, 2021, 2023)
Alpelisib	PI3K-α		2019	(Narayan, Prowell, et al., 2021)
Olaparib	PARP's		2014	(Le & Gelmon, 2018)

Therapeutic monoclonal antibodies

The body's protection is provided by the immune system which makes antibodies against foreign substances (Canpolat, Avcı, & Çadırcı, 2023)specific proteins known as antigens. Monoclonal antibodies are specialized antibodies that target a particular antigen and are widely used in clinical settings in cancer immunotherapy. They exhibit many modes of action stemming from their natural features, their binding of cytotoxic T cells, and their delivery of cytotoxic loads. (Canpolat et al., 2023; Goydel & Rader, 2021). In addition to their direct biological effect, antibodies can deliver chemicals such as radioactive isotopes, poisons, and anti-cancer medicines to specific cells. Five monoclonal antibodies are used in clinical settings: rituximab, trastuzumab, gemtuzumab ozogamicin, alemtuzumab, and ibritumomab tiuxetan (Cersosimo, 2003). For instance, the antibody-drug conjugate trastuzumab emtansin combines trastuzumab's Her-2 targeted antitumor properties with the cytotoxic activity of the microtubule-inhibiting drug imptansin (a derivative of maytansin), enabling intracellular drug delivery to cells that overexpress Her-2 while minimizing exposure to the healthy tissue (Loibl & Gianni, 2017).

FDA-approved therapeutic monoclonal antibodies used and monoclonal antibody-drug conjugates used in the treatment of breast cancer are listed in (Table 3).

Table 3. List of FDA-approved therapeutic monoclonal antibodies and antibody-drug conjugates used in the clinic.

THERAPEUTIC MONOCLONAL ANTIBODY	TARGET	CANCER TYPE	YEAR APPROVED	REFERENCES
Adotrastuzumab Emtansine (Kadcylavr)	Her-2	Her-2 Positive Breast Cancer	2013	(Wedam, Fashoyin-Aje, et al., 2020)
Fam-Trastuzumab Deruxtecan (Daiichi Sankyo)	Her-2	Her-2 Positive Breast Cancer	2019	(Narayan, Osgood, et al., 2021)
Sacituzumab Govitecan (Immunomedics)	Trop-2	Trıble Negative Breast Cancer	2020	(Spring et al., 2021)
Margetuximab	Her-2	Her-2 Positive Breast Cancer	2020	(Markham, 2021)
Pertuzumab	Her-2	Her-2 Positive Breast Cancer	2017	(Amiri-Kordestani et al., 2014)
Trastuzumab Emtansin (T-Dm1)		Her-2 Positive Breast Cancer	2019	(Abelman, Medford, Spring, & Bardia, 2022; Bahçeci et al., 2021)
Trastuzumab Deruxtecan (Ds-8201)		Her-2 Positive Breast Cancer	2022	(Abelman et al., 2022)

Therapeutic cancer vaccines

Vaccines used in cancer treatment are different from vaccines developed against infections. Vaccines against infections prevent the disease from occurring. Unlike these vaccines, cancer vaccines create an immune defense against the existing disease. cancer vaccines, comprising cancer cells, cell fragments, or specific antigens, are often enhanced with adjuvants to amplify immune system response. These vaccines are crafted to provoke tumor-specific immune reactivity within the body. The most prominent type among therapeutic cancer vaccines is the peptide-based variety, typically containing immunogenic epitopes from either tumor-specific or tumor-associated antigens. Broadly, cancer vaccines are categorized into five types: whole cell-based vaccines, multi-peptide vaccines, DNA/RNA-based vaccines, dendritic cell-based vaccines, and in situ vaccination methods (Corti, Giachetti, Eggermont, Delaloge, & Curigliano, 2022; Zhang, Zhou, Sha, Xie, & Liu, 2022).

Among the treatment strategies, peptide-based, whole protein-based, cell-based, allogeneic cell-based, viral vector-based, and gene-based vaccine studies are carried out, generally targeting Her-2. In addition, peptide-based and gene-based vaccine studies targeting HR are being carried out (Corti et al., 2022). Although different types of breast cancer vaccines have been evaluated in clinical studies, none of them have provided significant benefits and among the vaccines in phase studies, there is not yet a therapeutic cancer vaccine that has received FDA approval (Corti et al., 2022; Zhu & Yu, 2022).

Active vaccination therapy for breast cancer has several theoretical advantages over conventional chemotherapy and anti-HER2 immunotherapy via monoclonal antibodies: better tolerance, lower toxicity, and prolonged immune response with tumor specificity. Additionally, some vaccines may provide immunity against tumors lacking HER2 expression if the vaccine target is derived from non-HER2-related antigens (Zhu & Yu, 2022).

A significant drawback of cancer vaccines is that patients might not respond as expected due to immune suppression caused by chemotherapy. Consequently, cancer patients with advanced tumors often may not be suitable candidates for immunotherapy (Jain, 2021).

Gene therapy

Gene therapy is the insertion, repair, or alteration of faulty genes with functional counterparts to therapeutically address the absence or lowered levels of gene expression activity. It was first used to cure hereditary illnesses. Some examples of gene therapy techniques that are employed in the treatment of cancer are gene editing, suicide gene therapy, gene suppression/silence, the use of entrapment oligodeoxynucleotides to target transcription factors, miRNA targeting, and vaccination with DNA. To prevent the side effects of traditional treatments, gene therapy targets solely the tumor cells and the gene seeks to convey the genetic material to target cells via a vector and cure the gene flaw (Lundstrom, 2015; Zhou et al., 2017). This makes developing a safe, reliable, and controlled gene delivery device a crucial stage in the gene therapy process. Through a vector, genetic material is transferred from the source cell to the target cell. Today, both viral and non-viral vectors are used to transfer genes (Lundstrom, 2015; Sun et al., 2019). Viral vectors are frequently utilized since they can infiltrate into the cells. The retrovirus, lentivirus, alphavirus, adenovirus, adeno-associated virus, pox virus, and baculovirus are the most often employed viral vectors (Lundstrom, 2015; Zaimy et al., 2017). In addition to their nature, viral vectors are thought to be harmful due to their toxicity and immunogenicity. Non-viral vectors based on polymers and liposomes have been created as a result of this drawback. These vectors could be safer, convey more genetic information, and elicit a milder immune response (Sun et al., 2019). For the efficient transmission of genetic material to cells, non-viral vectors need chemical, physical, or biological delivery methods. The biological delivery system's primary function is to transfer genetic material to cancer cells and the blood circulation starts this process. The gene therapy agent travels through the blood to the tumor and builds up there. The substance that has gathered around the tumor cells enters the tumor tissue and is taken up by the tumor cells. It then starts working by releasing the genetic material into the cytosol and cell nucleus. The oscillation in the cell nucleus allows DNA replication and the oscillation in the cytosol affects the RNA (Zhou et al., 2017). An example of an FDA-approved gene therapy agent used in breast cancer is doxorubicin, which was approved in 1993 (Barenholz, 2012).

Targeted Therapies for Triple-Negative Breast Cancer

Triple-negative breast cancer (TNBC) is a type of breast cancer that is particularly aggressive and has high recurrence rates, typically with a worse prognosis compared to other types of breast cancer, accounting for 20% of all breast cancer cases (Berger et al., 2021; Camorani et al., 2020; Newman, Reis-Filho, Morrow, Carey, & King, 2015; Won & Spruck, 2020)and in the metastatic setting, the 5-year overall survival is 12%. Due to the lack of receptor expression, there has been a paucity of targeted therapeutics available, with chemotherapy being the primary option for systemic treatment in both the neoadjuvant and metastatic setting. More recently, immunotherapy has revolutionized the landscape of cancer treatment, particularly immune checkpoint inhibitor (ICI). TNBC describes a group of mammary tumors that lack ER and PR receptors and express a heterogeneous group of tumors with low expression of Her-2 receptors (Camorani et al., 2020; James, Quinn, Mullan, Johnston, & Harkin, 2007; Newman et al., 2015; Won & Spruck, 2020)progesterone receptor, and HER2. These tumors account for 12–17 % of all breast cancers, preferentially affect young women, are more frequent in women of African and Hispanic descent, and are enriched in the population of patients diagnosed with "interval cancers." TNBCs account for the majority of breast cancers arising

in BRCA1 germline mutation carriers (approximately 80 %. ER limits targeted therapeutic options due to the lack of PR and Her-2 expression, and TNBC does not respond to hormonal or anti-Her-2 therapies for which no treatment is yet approved by the FDA (Erasmo Orrantia-Borunda et al., 2022; Newman et al., 2015; Seiffert, Schmalfeldt, & Müller, 2017; Van Swearingen et al., 2017; Won & Spruck, 2020)lacking expression of hormone and human epidermal growth factor receptor 2 receptors, is an aggressive subtype that frequently metastasizes to the brain and has no FDAapproved systemic therapies. Previous literature demonstrates mitogen-Activated protein kinase (MEK). TNBC is sensitive to chemotherapy, so the current standard of treatment includes chemotherapy and surgery. Commonly used chemotherapy agents include anthracycline, alkylating agents, and the anti-metabolite fluorouracil. Responses to treatment are usually short-lived and recur rapidly. There is no standard chemotherapy regimen for patients with relapsing TNBC (Caswell-Jin et al., 2018; O'Shaughnessy et al., 2014; Plevritis et al., 2018). Therefore, there is a dire need to identify novel agents for specific TNBC targeting and treatment (Camorani et al., 2020)the lack of any known targetable proteins has not allowed a specific anti-tumor treatment. Therefore, the identification of novel agents for specific TNBC targeting and treatment is desperately needed. Here, by integrating cell-SELEX (Systematic Evolution of Ligands by EXponential enrichment).

CONCLUSION

Molecular targeted therapy can be used alone or in conjunction with conventional chemotherapy drugs to treat cancer. Biomarkers for every form of cancer can now be found and predicted, thanks to the advancements in molecular medicine. The efficacy of treatment may be increased by combining molecularly targeted therapy with cytotoxic chemotherapy medications or other molecularly targeted therapy agents that co-inhibit two or more targets in a single or complementary pathway. Numerous studies have demonstrated that hybrid treatment of cancer using a variety of medications produces better synergistic anti-tumor benefits than single-drug therapy. However, the main obstacle to developing effective cancer therapies and biomarkers is tumor heterogeneity. Tumor heterogeneity can lead to the formation of diverse cell populations with various genomes. Inconclusive biopsy results due to the existence of tumor subclonal populations may have negative clinical effects. Additionally, a high degree of cancer clonal heterogeneity, intratumor genetic heterogeneity, epigenetic editing, and cell signaling complexity may contribute to drug resistance associated with molecularly targeted therapy for cancer treatment. These factors can cause the cancer cells to adapt to the selective impact of therapeutic regimens. Therefore, to design medications that can effectively stop the spreading of cancer cells that are already resistant to conventional therapies, it is necessary to identify the prognostic marker for intratumor heterogeneity and identify novel therapeutic targets. The therapeutic outcomes rely on discovering tumor-specific protein expression patterns and interaction signaling networks that function stand-alone or in concert to prevent drug resistance before the treatment. In addition, the success of molecularly targeted therapeutics is limited by the one-size-fits-all pharmacological strategy because different patients do not react the same to the same medications. Therefore, the transition from the existing strategy to the precision medicine paradigm holds considerable potential for the treatment of cancer. As such, precision medicine is developed using molecularly focused therapy and takes into account the unique genetic profile of each patient.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTIONS STATEMENT

B.I.S. and H.H. organisation of paper and collection of data. E.C. Supervision

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