Treatment of Breast Cancer by Monoclonal Antibodies

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Abstract
Breast cancer continues to be a significant global health concern, prompting ongoing research to create innovative treatment options. Monoclonal antibodies (mAb) are emerging as a promising and targeted method for treating breast cancer, offering greater specificity and fewer side effects than traditional treatments. This overview highlights the current landscape of monoclonal antibody therapy for breast cancer. These antibodies are engineered proteins designed to specifically identify and attach to antigens found on cancer cell surfaces. A key benefit of monoclonal antibody therapy is its ability to inhibit the growth and survival of cancer cells while protecting normal cells. This targeted method minimizes side effects and enhances the treatment's safety profile. Combination therapies, which may include monoclonal antibodies alongside standard chemotherapy or other targeted treatments, are being explored for their potential to create synergistic effects and improve patient outcomes. Despite the promise of this approach, challenges persist, such as the emergence of resistance mechanisms and the necessity for tailored treatment strategies. Ongoing clinical trials are examining combination therapies and investigating new targets to tackle these challenges. Additionally, managing side effects and addressing economic factors associated with monoclonal antibody treatments are active areas of research. While mAb therapies can lead to side effects like fever, chills, fatigue, headaches, muscle pain, nausea, vomiting, breathing difficulties, skin rashes, and bleeding, this study reviews the current and future prospects of monoclonal antibodies in diagnosing and treating breast cancer, taking into account the advantages and disadvantages of this technique.
Key words: monoclonal antibody; breast cancer; HER2-positive breast cancer

1. Introduction

Breast cancer is a growth of abnormal cells in the ducts or lobules and can be classified into invasive and non-invasive cancers that affect both male and female [1]. The use of monoclonal antibodies in breast cancer can restore or improve immune system function. A monoclonal antibody (mAb) is defined as a laboratory-created molecule designed to bind to antigens on the surface of cancer cells in order to attack cancer cells by restoring, strengthening, or mimicking the immune system [2]. monoclonal antibody was fully licensed in 1986, the development of monoclonal antibodies is a new way to target specific mutations and defects in protein structure and expression in many diseases and conditions [3]. Today, humanized monoclonal antibodies are the fastest growing class of biotechnology-derived molecules in clinical trials, as the translation of genetic sequencing and basic medical research into clinical practice has progressed rapidly. The global value of the antibody market is approximately $20 billion annually. The FDA currently has 30 monoclonal antibodies approved for use in humans for a variety of diseases and conditions, including cancer, chronic inflammatory diseases, organ transplants, infectious diseases, and hearts diseases [4]. Monoclonal antibodies are drugs that inhibit specific targets on the surface of cancer cells. The target may also be present in nearby areas of the cancer cells/tissues. Monoclonal antibodies possess the ability to generate toxicity towards cancer cells. Chemotherapy and radiation therapy can successfully and efficiently target cancer cells, as example (5). Monoclonal antibodies possess three key distinguishing features that set them apart from other treatment methods. Firstly, they exhibit tumor selectivity, meaning they specifically target tumors. Secondly, monoclonal antibodies can be modified, such as by attaching stable linkers that are cleaved upon entering a cell. Lastly, humanized monoclonal antibodies are not immunogenic and cause low systemic toxicity [6]. This review covers the types, mechanisms of action and targeted delivery to breast cancer cells of monoclonal antibodies used to treat breast cancer. Three major molecular markers categorize breast cancer patients into subtypes: estrogen receptor (ER), progesterone receptor (PR), and Human epidermal growth factor receptor-2 (2). Targeted antibodies act on tumor cells through several mechanisms. Tumor signaling can be inhibited by antibodies that interfere with growth signaling pathways through modulation of the active state of receptors located on the cell membrane or by inhibiting cytokines that play a crucial role in tumor growth and development. Various agents, including drugs, radioactive materials, and toxins, have the ability to effectively eradicate tumor cells. However, their toxicity towards healthy tissues restricts their therapeutic application. Conjugating anticancer drugs to antibodies can minimize adverse effects. Optimal antibodies are those that specifically bind to antigens exclusively present on malignant cells [5].

2. Main Body

The traditional monoclonal antibody (mAb) production process typically begins with the generation of mAb-producing cells (i.e., hybridomas) by fusing myeloma cells with spleen cells (e.g., B cells) that produce the desired antibody. Typically, these B cells are derived from animals, particularly mice. Following cell fusion, a large number of clones undergoes screening and selection according to their antigen specificity and immunoglobulin class. After identifying prospective hybridoma cell lines, each one was subsequently confirmed, validated, and characterized by a series of upstream functional assays. Once the clones have matured, they are expanded with further downstream bioprocesses occurring [7]. A typical monoclonal antibody production process:

1. Mice are subjected to immunization with an antigen, followed by the isolation of splenocytes. Subsequently, the blood of the mice is examined to determine the generation of antibodies. The spleen cells that produce antibodies are subsequently separated for the purpose of generating hybridomas in a laboratory setting.

2. Myeloma cells are prepared as they are immortal cells that, when combined with spleen cells, can generate a hybridoma with the ability to grow indefinitely. The myeloma cells are prepared for fusion.
3. Fusion - The process involves combining myeloma cells with separated spleen cells to create hybridomas. This fusion is achieved by using polyethylene glycol (PEG), which facilitates the merging of cell membranes.
4. The process of screening and selecting clones involves evaluating their antigen specificity and immunoglobulin class.
5. Conduct functional characterization by confirming, validating, and characterizing each possible high-producing colony using techniques such as ELISA.
6. Cultivate and Gradually Separate - Cultivate genetically identical copies that generate the desired antibodies and gradually separate the chosen individuals from the rest.
7. Expansion - increase the number of desired clones that produce antibodies, for example, by using bioreactors or big flasks (7).

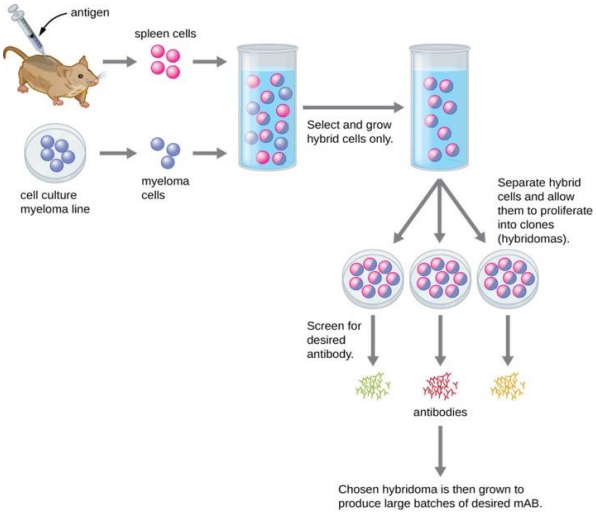


Figure 1: typical monoclonal antibody production process

2.1. Half-life of antibodies

The half-life of a monoclonal antibody (mAb) can vary widely depending on the specific antibody, its structural characteristics, its interaction with the target antigen, and also its interaction with the immune system [5]. Monoclonal antibodies are molecules created in the laboratory that can mimic the immune system and its ability to fight harmful pathogens such as viruses and cancer cells. Several monoclonal antibodies have been developed and studied for therapeutic effects in the setting of breast cancer. It is important to note that the availability and approval of specific monoclonal antibodies varies by region and may vary over time [8]. Some monoclonal antibodies kill cancer cells by binding directly to them. These monoclonal antibodies are called targeted therapies because they target specific receptors on cells. An example is trastuzumab (Herceptin), which is used to treat HER2-positive breast cancer. HER2-positive breast cancer is a type of breast cancer that is characterized by the presence of a protein known as human epidermal growth factor receptor 2 (HER2). This protein stimulates the proliferation of cancer cells. In 20% of breast cancer cases, the tumor cells exhibit gene amplification, resulting in an additional copy of the HER2 protein gene. HER2-positive breast cancer exhibits a higher level of aggressiveness compared to other forms of breast cancer [9]. Trastuzumab binds to the HER2 receptor on cancer cells and prevents them from growing, stopping the growth and slowing the progression of the cancer. Additional monoclonal antibodies enhance the immune system's ability to combat cancer cells. These substances are referred to as immunotherapies. Nivolumab is an instance of a drug that specifically targets the PD-1 receptor. It is employed for the treatment of various types of cancers such as lung cancer, kidney cancer, melanoma, lymphoma, and some head and neck cancers [10].

2.2. Examples of Monoclonal antibodies.

Here are some examples of monoclonal antibodies. used or under investigation for breast cancer:

2.2.1. Trastuzumab (Herceptin):

- Mechanism of Action: Trastuzumab functions by attaching to the HER2 receptors located on the outside of cancer cells, thereby impeding the signaling pathways that stimulate cell proliferation and viability. Trastuzumab obstructs these pathways, so inhibiting the growth of HER2-positive cancer cells and improving the body's immunological response against them.
- Clinical Use: Trastuzumab is a cornerstone in the treatment of HER2-positive breast cancer and is used in various settings. It is employed as adjuvant therapy following surgery to reduce the risk of cancer recurrence, in the neoadjuvant setting to shrink tumors before surgery, and in the metastatic setting to control the spread of the disease.
- Adjuvant Therapy: Administered in combination with chemotherapy, trastuzumab has significantly improved disease-free survival and overall survival rates.
- Safety profile: While generally well-tolerated, trastuzumab can be associated with side effects, with cardiac toxicity being a notable concern
- Metastatic Setting: Used as a single agent or in combination with chemotherapy for advanced or metastatic HER2-positive breast cancer.
- Half-life: Approximately 3 to 7 days.

The addition of trastuzumab into chemotherapy resulted in several positive outcomes, including a delayed disease progression, an increased rate of objective response, a prolonged response duration, a decreased mortality rate, extended survival, and a reduced risk of death [11].

Figure 2: Monoclonal antibodies like Herceptin, block HER2 receptors, preventing growth factors binding to the cell. This stops the accelerated growth and division.

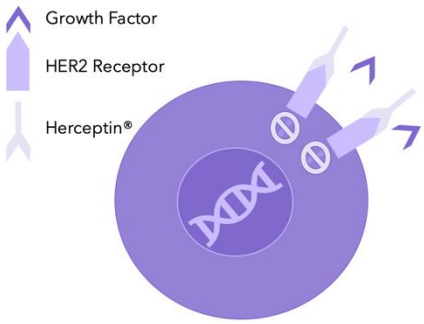


Figure 2: Monoclonal antibodies like Herceptin, block HER2 receptors, preventing growth factors binding to the cell. This stops the accelerated growth and division.

2.2.2. Pertuzumab (Perjeta):

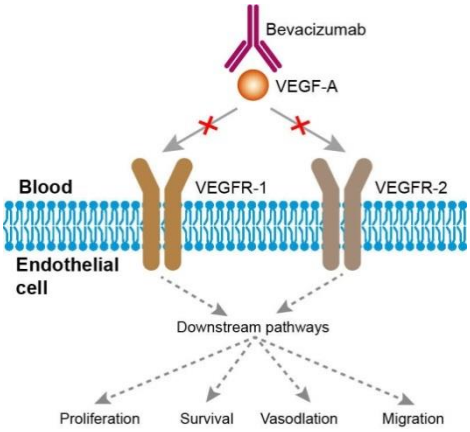
- Mechanism of Action: Pertuzumab is another monoclonal antibody targeting HER2, Pertuzumab acts by inhibiting HER2 dimerization, a process critical for the activation of HER2 signaling pathways that promote cell growth and survival. By preventing HER2 from forming dimers with other HER family receptors, such as HER3, pertuzumab disrupts downstream signaling, thereby impeding the proliferation of HER2-positive cancer cells.
- Clinical Use: Pertuzumab is primarily utilized in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of early-stage HER2-positive breast cancer.
- Neoadjuvant Setting: Pertuzumab is commonly administered in the neoadjuvant setting, allowing for the treatment of breast cancer before surgery. This approach aims to shrink tumors, facilitate surgical removal, and assess the response to treatment.
- Safety Profile:Pertuzumab's safety profile is generally well-tolerated, with adverse effects commonly including diarrhea, nausea, and fatigue. Notably, pertuzumab has been associated with a low incidence of cardiac toxicity, a concern often associated with HER2-targeted therapies [12].

2.2.3. Ado-trastuzumab Emtansine (T-DM1, Kadcyla):

- Mechanism of Action: T-DM1 is an antibody-drug conjugate that combines trastuzumab with a chemotherapy agent (emtansine). It delivers chemotherapy directly to HER2-positive cancer cells.
- Clinical Use: Indicated for the treatment of HER2-positive metastatic breast cancer that has progressed following HER2-targeted treatments.
- Adjuvant and Neoadjuvant Settings: T-DM1 is also being investigated in both adjuvant and neoadjuvant settings. In the neoadjuvant setting, it is used before surgery to shrink tumors, while in the adjuvant setting, it is administered post-surgery to reduce the risk of cancer recurrence. Ongoing clinical trials are exploring the potential benefits of T-DM1 in these settings.
- Safety Profile: While generally well-tolerated, T-DM1 can be associated with side effects such as nausea, fatigue, and thrombocytopenia [13].

2.2.4. Bevacizumab (Avastin):

- Mechanism of Action: Bevacizumab acts by attaching to VEGF and excluding its interaction with its receptors on the surface of endothelial cells, which are responsible for blood vessel formation. By inhibiting this interaction, Avastin disrupts the process of angiogenesis, impeding the growth of new blood vessels that supply nutrients and oxygen to tumors.
- Clinical Use: Avastin has been used in combination with chemotherapy for the treatment of metastatic breast cancer, particularly in HER2-negative cases. Its application aims to enhance the effectiveness of chemotherapy by cutting off the blood supply to tumors, thereby inhibiting their growth.
- Safety profile: Avastin is associated with specific side effects, including an increased risk of hypertension, bleeding, and gastrointestinal perforations. The potential for severe adverse events underscores the importance of careful patient selection and monitoring during treatment.
- Half-life: Approximately 20 days [14].



2.2.5. Denosumab (Xgeva, Prolia):

While not a traditional monoclonal antibody, denosumab is a targeted therapy that inhibits the activity of a protein involved in bone destruction. It is used to prevent bone complications in certain cases of advanced breast cancer [15].

2.2.6. Hormone Receptor-Positive Breast Cancer:

Palbociclib, Ribociclib, and Abemaciclib: While not traditional monoclonal antibodies, these drugs are cyclin-dependent kinase 4/6 (CDK4/6) inhibitors and are often used in combination with hormone therapy. They work to inhibit the activity of CDK4 and CDK6, which are proteins involved in cell cycle regulation.it is approved for the treatment of HR+, HER2- advanced breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy or in combination with fulvestrant in patients who have received prior endocrine therapy [16].

promising target for monoclonal antibody is the programmed cell death protein 1 (PD-1) and its ligand PD-L1, which are key components of the immune system and play a crucial role in regulating immune responses. PD-1 is a cell surface receptor expressed on activated T cells, which are a type of immune system cells. The primary function of PD-1 is to regulate the immune response and prevent excessive activation, which could lead to autoimmune reactions. When PD-1 binds to its ligands, PD-L1 or PD-L2, it inhibits the activity of T cells, dampening the immune response. which play a crucial role in immune checkpoint regulation. Antibodies that block the PD-1/PD-L1 interaction have been developed as cancer immunotherapies. These antibodies, such as pembrolizumab and nivolumab (targeting PD-1) Atezolizumab, which targets PD-L1, is part of a group of drugs called immune checkpoint inhibitors. checkpoint inhibitors work by releasing the "brakes" on the immune system, allowing T cells to recognize and attack cancer cells more effectively. These therapies have shown significant success in the treatment of various cancers, including melanoma, lung cancer, and certain types of breast cancer, especially triple-negative breast cancer (TNBC). targeting the PD-1/PD-L1 pathway with monoclonal antibodies has become a groundbreaking approach in cancer immunotherapy, providing a way to enhance the body's natural immune response against cancer cells. These antibodies unleash the immune system to recognize and attack cancer cells, providing a novel immunotherapeutic approach [17].

Monoclonal antibodies can be used with other treatment methods such as chemotherapy, radiation therapy, and surgery, depending on the stage and characteristics of the breast cancer.

2.3. Indications for Use and Administration

Indications for mAbs in oncology include both solid tumor and hematologic malignancies. mAbs may be administered intravenously as well as subcutaneously [9].

2.4. Benefits of Monoclonal Antibody Therapy for Breast Cancer:

Monoclonal antibody therapy has brought about significant benefits in the treatment of breast cancer, particularly in the context of targeted therapies. Here are some key advantages:

1. Targeted Approach: Monoclonal antibodies are designed to specifically target and bind to specific molecules, such as receptors on the surface of cancer cells. This targeted approach minimizes damage to healthy cells, reducing side effects compared to traditional chemotherapy [18].
2. Precision Medicine: Monoclonal antibody therapy allows for a more personalized and precise treatment strategy. By targeting specific molecular markers or pathways, these therapies are tailored to the individual characteristics of the patient's cancer [19].
3. Improved Efficacy: Monoclonal antibodies have demonstrated improved efficacy in certain breast cancer subtypes. For example, in HER2-positive breast cancer, antibodies like trastuzumab have significantly improved response rates, progression-free survival, and overall survival [20].
4. Combination Therapies: Monoclonal antibodies can be effectively combined with other treatment modalities, such as chemotherapy, radiation therapy, or other targeted agents. This combination approach aims to enhance the overall treatment response and may provide synergistic effects [20].
5. Reduction of Metastasis: In some cases, monoclonal antibodies have been shown to reduce the risk of metastasis. For example, in the treatment of HER2-positive breast cancer, the addition of antibodies like trastuzumab has been associated with a decreased risk of distant metastases [21].

6. Neoadjuvant and Adjuvant Settings: Monoclonal antibodies are utilized in both neoadjuvant (pre-surgery) and adjuvant (post-surgery) settings. In neoadjuvant therapy, they can shrink tumors before surgery, making the surgical intervention more effective. In the adjuvant setting, they help prevent cancer recurrence [5].
7. Enhanced Survival Rates: The incorporation of monoclonal antibodies into treatment regimens has contributed to improved survival rates for certain breast cancer subtypes. This is particularly evident in HER2-positive breast cancer, where targeted therapies have significantly extended survival outcomes [12].
8. Reduced Recurrence Risk: Monoclonal antibodies, especially when combined with standard treatments, have been associated with a reduction in the risk of cancer recurrence. This is crucial for long-term outcomes and the prevention of disease progression [10].
9. Minimized Systemic Toxicity: Compared to traditional systemic treatments like chemotherapy, monoclonal antibody therapy often results in reduced systemic toxicity. This is because they specifically target cancer cells, minimizing harm to healthy tissues and reducing the severity of side effects [6].
10. Biosimilar Options for Improved Access: The development of biosimilar versions of monoclonal antibodies increases accessibility by offering more cost-effective alternatives while maintaining comparable efficacy and safety profiles [22]. monoclonal antibody therapy has revolutionized breast cancer treatment by providing a targeted, personalized, and effective approach. These therapies have significantly contributed to improved outcomes, reduced side effects, and better quality of life for patients with breast cancer.

2.5. Considerations and Challenges:

1. Mechanisms of resistance: One major challenge in monoclonal antibody (mAb) therapy for breast cancer is the development of mechanisms of resistance. Cancer cells can adapt and evolve, making them less effective over time. Understanding and overcoming these resistance pathways is critical to the long-term success of mAb therapies [23].
2. Personalized treatment approach: Breast cancer is a heterogeneous disease with subtypes, each requiring a unique treatment approach. The development of personalized strategies based on individual patient information, including genetic and molecular characteristics, presents difficult but important challenges for optimizing the therapeutic benefit of monoclonal antibodies [24].
3. Combination therapy: Some monoclonal antibodies have shown significant efficacy, but combining them with other treatments, such as chemotherapy or targeted therapies, is still an area of research. Determining the most effective combination, order of administration, and combination can be a challenge that requires careful consideration [10].
4. Immunogenicity: The development of an immune response to a monoclonal antibody, known as immunogenicity, affects the efficacy and safety of the antibody. To maintain benefit in breast cancer patients, strategies to reduce morbidity and optimize the durability of treatment effects must be implemented [24].
5. Economic considerations: Monoclonal antibody treatments are expensive and difficult to obtain widely. Balancing costs and clinical benefits and finding ways to structure and distribute costs are important considerations for incorporating these treatments into breast cancer treatment regimens [25].
6. Managing side effects: Monoclonal antibodies generally have reduced side effects compared to conventional treatments, but may still be associated with some side effects. Recognizing and managing these adverse events, such as infusion reactions and immune-related toxicities, is essential to ensure patient safety and regulatory compliance [26].
7. Clinical trial design: It is important to design robust clinical trials to assess the efficacy and safety of monoclonal antibodies in diverse patient populations. Challenges include enrolling patients, identifying appropriate parameters, and ensuring that tests reflect the true complexity of breast cancer [25].
8. Long-term follow-up: Efficacy and durability of response to monoclonal antibody therapy for breast cancer require ongoing follow-up. Longitudinal studies are important to assess the severity of late toxicity, the emergence of resistance, and the impact on overall survival [27].

2.6. Future perspectives of monoclonal antibodies for breast cancer:

The future prospects for monoclonal antibodies against breast cancer are bright. This is because research and development are focused on improving the effectiveness of treatment, reducing side effects and expanding the range of treatments that are prescribed. Some key areas for future exploration include:

- Advances in immunotherapy: Research continues to explore and optimize the use of immunotherapy for breast cancer, including the development of new monoclonal antibodies targeting immune checkpoints and novel antigens. Immunotherapy strategies are aimed at using the body's immune system to more effectively identify and eliminate cancerous cells [28].
- Bispecific antibodies: Bispecific antibodies that can simultaneously target two different antigens are being studied in breast cancer therapy. These antibodies can increase specificity and target multiple pathways involved in cancer progression [28].
- Combined treatment: Future directions include exploring innovative combinations of monoclonal antibodies with other targeted therapies, chemotherapy, radiotherapy or immunotherapies. Combination approaches aim to address multiple aspects of cancer biology and improve treatment responses. Personalized medicine and biomarkers [29].
- Personalized medicine and biomarkers: Advances in molecular profiling and the identification of predictive biomarkers are expected to enhance patient stratification. Tailoring monoclonal antibody therapy based on individual tumor characteristics and patient profiles will improve precision medicine approaches [30].
- Overcoming resistance mechanisms: Understanding and overcoming the mechanisms of resistance to monoclonal antibody therapy is a critical area of research. The research aims to identify strategies to prevent or overcome resistance, which may include the development of new combination therapies [31].
- Access and affordability: Issues related to the cost and availability of monoclonal antibody therapy continue to be addressed. This includes the development of biosimilars and strategies to increase the availability of these innovative therapies [32].

- Novel Targets and Antigens: The identification of new molecular targets and antigens specific to breast cancer subtypes is a key area of research. Monoclonal antibodies targeting novel antigens may offer additional therapeutic options, especially for subtypes that currently have limited targeted therapy options [33].
- Extended Use and Sequencing: Research into the optimal duration of monoclonal antibody therapy and sequencing strategies is an ongoing focus. The purpose of the study is to identify the benefits of extended treatment and the most effective periods to maximize treatment results [34].

Conclusion

Monoclonal antibodies have emerged as a transformative force in breast cancer treatment, changing the landscape of treatment options and significantly improving patient outcomes. Engineered to selectively bind to particular chemicals present on the outer membrane of cancer cells, these laboratory-developed antibodies represent a paradigm shift in precision medicine, providing individualized and targeted approaches to breast cancer patients. This conclusion discusses major achievements, challenges, and ongoing developments in monoclonal antibody therapy for breast cancer. One of the most important success stories in monoclonal antibody therapy is the victory over HER2-positive breast cancer. Trastuzumab, a pioneering monoclonal antibody, has become the cornerstone of therapy for HER2-positive breast cancer. Trastuzumab, which specifically targets the HER2 receptor overexpressed in cancer cells, has led to unprecedented improvements in survival and disease. The addition of pertuzumab and ado-trastuzumab emtansine (T-DM1) to the treatment arsenal continues to demonstrate the success of combination strategies, providing more comprehensive and effective approaches to the treatment of HER2-positive breast cancer. Equally important is the study of monoclonal antibodies in the complex landscape of triple negative breast cancer (TNBC). The emergence of immune checkpoint inhibitors, such as pembrolizumab and atezolizumab, has opened new avenues for the treatment of TNBC, which lacks targeted receptors commonly found in other breast cancer subtypes. Designed to unleash the power of the immune system against cancer cells, these immunotherapies offer hope to a patient population that has historically had limited options for targeted therapies. The promise of monoclonal antibodies extends beyond their efficacy; it includes a vision of personalized medicine. These antibodies are adapted to recognize specific molecular signatures of tumors, enabling treatment strategies tailored to the unique characteristics of each patient and cancer. This customization not only increases therapeutic effectiveness, but also mitigates potential side effects, marking an important step forward in the pursuit of more patient care. However, the journey of monoclonal antibody therapy in breast cancer is not without its challenges. Mechanisms of resistance, variable patient responses, and the need for improved biomarkers are areas that require continued investigation and clarification. The dynamic and heterogeneous nature of breast cancer requires a nuanced understanding of the complex interactions between the immune system and cancer cells. Unraveling the complexity of the tumor microenvironment and identifying strong prognostic biomarkers are critical steps in optimizing the use of monoclonal antibodies in breast cancer therapy. Development of monoclonal antibody therapy for breast cancer has not stopped at all; it is a continuum characterized by relentless research and innovation. Clinical trials investigating new antibodies, targets and combinations are at the forefront of this development and aim to further improve outcomes and expand the applicability of these therapies. The emphasis on combination strategies that include monoclonal antibodies in combination with chemotherapy, targeted agents, and immunotherapies emphasizes a holistic approach to overcoming the challenges of breast cancer. In conclusion, monoclonal antibodies have steadily shaped the history of breast cancer treatment, offering hope, efficacy and personalization. The success stories of HER2-positive breast cancer and promising advances in TNBC are examples of the transformative power of precision medicine. As the field advances, the integration of biosimilars, ongoing research projects and dedication to unraveling the complexities of breast cancer biology point to a future where monoclonal antibody therapy is a sign of progress in the fight against breast cancer.

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