The Role of Monoclonal Antibodies in Breast Cancer

Jingran Luo [1, *, a], Xinxin Chang[2, a], Suri Yuqing Wang[3, a], Hongchuan Yu[4, a]

[1] RDFZ Xishan School, Beijing, China

[2] RDFZ International Curriculum Center, Beijing, China

[3] St. Stephen's and St. Agnes School, Virginia, USA

[4] Bullis School, Maryland, USA

* Corresponding Author Email: li3882@purdue.edu

[a] Those authors contributed equally.

Abstract. Monoclonal antibody-based therapy is a promising strategy to treat breast cancer because, as a targeted cancer drug, it locates and binds to a specific cancer cell. The importance of monoclonal antibodies to give an additional and efficient channel remains a serious issue because several kinds of breast cancer, particularly Triple-negative breast cancer (TNBC), have limited methods and a low response to conventional drug therapy. Although patients associated with metastatic diseases used to experience short survival and poor prognosis, developments have been achieved recently. The development of targeted cancer drugs is thought to improve clinical therapies for breast cancers and the overall survival length of patients. Expectations are that targeted cancer drugs will be pair used with chemotherapy, and data has already shown that patients lived nearly two times longer compared to before. This review provides an overview of three types of monoclonal antibodies, trastuzumab, pertuzumab, and trodelvy (sacituzumab govitecan) respectively, which all act as targeted cancer drugs in breast cancer treatments. Three main parts are included in this review, involving the historical development of the drugs, the mechanism of the drugs, and the issues of the drugs while being utilized to treat breast cancer, which is separated into two parts: the side effects and drug resistance.

Keywords: Breast Cancer, Monoclonal Antibody, Trastuzumab, Pertuzumab, Trodelvy.

1. Introduction

Cancer immunotherapy is a biotherapy that utilizes the immune system to fight cancer as it recognizes and attacks cancer cells. Monoclonal antibodies, checkpoint inhibitors, vaccinations, cytokines, and CAR-T cell therapy are a few examples of immunotherapies. Since Monoclonal antibody technology was first announced and licensed, it has been a considerable option for new therapy development. It has expanded drastically and the global annual value in 2014 was approximately 20 billion US dollars. Monoclonal antibodies (MAbs) in particular, trigger the immune system and helps it to fight cancers. MAb treatments are synthetic versions of natural antibodies. There are numerous MAbs that can be used to treat cancer. They function in many ways, some of which function more than once. MAbs are essential tools for study, diagnosis, and therapy since they are highly specific to their target.

Breast tissue becomes infected with breast cancer (BC), and BC has overtaken all other types of cancer as the most common in the world in 2021 from the data of WHO. Each year, it accounts for 12% of all new occurrences of cancer, and most of them without a family history of BC. As opposed to hereditary mutations, these are the result of genetic changes brought on by age and life in general. The lining of milk ducts is where ductal carcinoma, the most prevalent type of BC, originates. Lobular carcinoma is also commonly reported, which occur in the lobules. The origin of BC cells affects how they behave. Mammary development is defined by cell mobility and changes in cell contact. Embryonic mammary cells have the ability to move and invade. Invasive BC is that has spread past the primary breast ducts or lobules. BCs are divided into three primary subgroups based on estrogen or progesterone receptor expression and ERBB2 gene amplification. Risk profiles and treatment

options for the three subtypes are unique. Each patient's optimal treatment is determined by tumor subtype, anatomic cancer stage, and personal preferences. The type of BC and the degree of its metastases will determine this. People with BC may get many types of therapy. It is possible for patients to first have surgery, at which time doctors remove cancerous tissue. Additionally, chemotherapy uses specific drugs to reduce or kill cancer cells. The drugs can sometimes be given intravenously and sometimes orally. Third Hormone Treatment Prevents cancer cells from obtaining the elements they require for growth. Fourth Biological therapy makes use of the immune system to lessen the side effects of other cancer treatments or to help the body fight off cancer cells. Ultimately, radiation treatment utilizes comparable to X-rays high-energy radiation to destroy cancer cells. One-fourth of BCs have a latent and sly nature, growing slowly but metastasizing early, despite the fact that the majority are benign and surgically treatable. Monoclonal antibodies are crucial in preventing recurrence and metastasis as well as lowering mortality. Trastuzumab may be used to treat BC at both the early and late stages. While chemotherapy is a common time to take this medicine, it can also be used on its own (especially if chemo alone has already been tried).

This paper introduces three types of drugs--Trastuzumab, Pertuzumab, and Trodelvy respectively--that are invented to treat BC. These drugs work by inhibiting the activity of tumor cells. The paper mainly discusses the discovery process, mechanism, current challenges, and future perspectives of the drugs. As modifications to previous drugs are made gradually, the results get better and better, some are even target-specific, making surrounding tissues and cells free from contamination, thus increasing overall survival. Experts have high hopes for the pharmaceuticals since they have been shown in clinical trials to be successful and because they outperform previously identified medications in a clear number of ways.

2. Discovery process of the drugs

2.1. Discovery of trastuzumab

In 1982, an oncogene has been isolated in ethyl nitrosourea-induced rat neuro glioblastomas known as neuroblastoma. Robert Weinberg named it the neu gene based on the type of cancer that owns it in 1984. A neu gene is a heterogeneous group, and most oncogenes, such as ras and myc, are sequestered inside the cell. But the neu gene encoded proteins in the cell membrane with a large part remaining outside the cell, which any drug can easily contact. In the same year, Axel Ullrich identified the human homologs of the neu gene [1], which is known as HER2.

In 1987, HER2 is provided as a DNA probe by Ullrich and thus can bridge the gap between oncogenes and human cancer. Slamon found a high amplification of HER2 in BC samples, but not all BCs are so. Based on the pattern of BC staining, BC can be divided into HER2-amplified specimens and HER2 amplification-free specimens, namely, HER2-positive and HER2-negative specimens. After studying whether the behavioral performance of the two types of tumors varied, the researchers explored an abnormal pattern in which those breast tumors with gene amplification tend to be more aggressive, more metastatic, and more lethal. The results prompted researchers to further investigate what would happen if HER2 activity was somehow turned off by using anti-HER2 drugs and whether it could organize the growth of cancer cells. While Ullrich looks for a specific antibody protein as a drug, Slamon implants cancer cells into mice, and bursts of cancer cells form metastatic tumors that recapitulate invasive human cancers. In 1988, Ullrich and his team successfully produced a murine antibody that binds and inactivates HER2 (figure 1). Slamon treated BC cells with HER2 overexpression in the dish with this antibody, resulting in cells stopping growth, fading, and dying. Impressively, the tumor disappeared when he injected the HER2 antibody to live mice with tumors.

In 1989, Michael Shepard improved the HER2 antibody production and purification, but purified murine antibodies can trigger an immune response in the human body. So, the fully humanized HER2 antibody occurred which was created by Paul Carter in 1990 as a potential drug called Herceptin.

Three-phase clinical trials were started in 1995 to test the effect of trastuzumab. Trastuzumab reduced tumors in half of the women, while only one in three were in the control group. The breast

tumor cell development was delayed by 4 to 7.5 months, and survival also increased. Finally, the FDA approved trastuzumab for marketing in 1998.

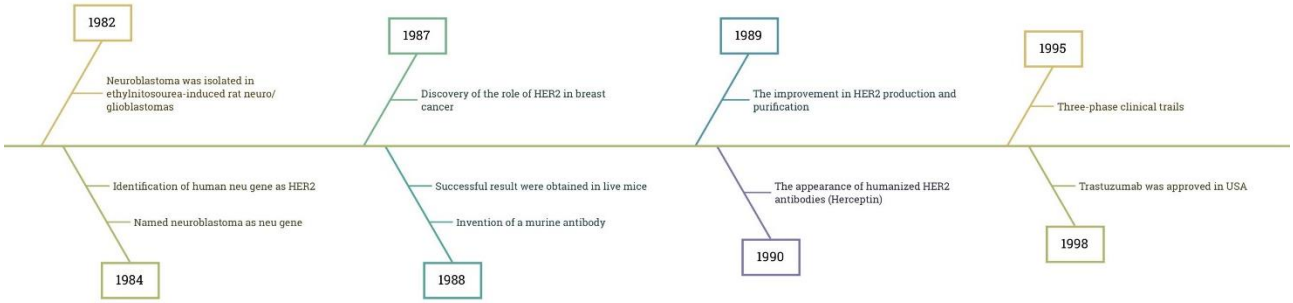

Figure 1. Timeline of trastuzumab discovery.

2.2. Discovery of pertuzumab

For the 15 years since 1998 (figure 2), trastuzumab was the only available HER2 antibody. It has improved survival in many trials. However, HER3 overexpression became one of the most widespread drug resistance mechanisms. Particularly for the strongest HER2-HER3 dimer, trastuzumab is ineffective at preventing heterodimerization. Since HER2-HER3 dimerization is thought to be an appealing target, a novel class of HER2-targeted treatments has been created. Pertuzumab is complementary to trastuzumab in its mechanism of action to improve efficacy by extra blocking the HER2 protein and inhibiting signaling between HER2 and other HER family receptors (including HER3). According to the data on pertuzumab from preclinical to phase I trials, pertuzumab is well tolerated [2]. In 2005, it was used as a single agent. Later on in 2012, it is shown to have synergistic anti-tumor activity when combined with trastuzumab.

In 2013, 41% of patients in the study evaluating the effectiveness and safety of pertuzumab for stage II ovarian cancer experienced long-term stable clinical and biological responses, and no unexpected side effects were reported [3]. In 2017, the FDA granted the use of pertuzumab (Perjeta) as an assistant therapy for trastuzumab and chemotherapy. It was used in patients who suffer from early BC that was HER2-positive and patients who experience a high recurrence risk.

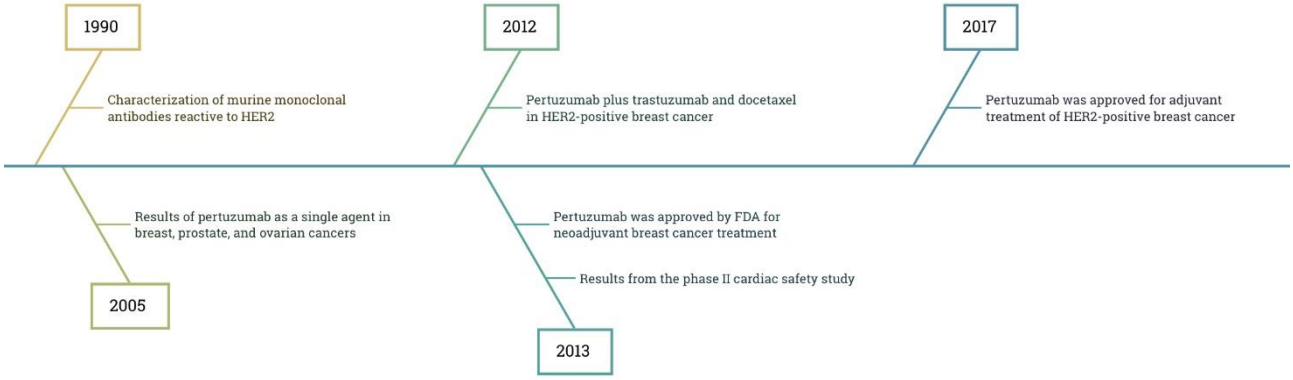

Figure 2. Timeline of pertuzumab discovery.

2.3. Discovery of trodelvy

The use of sacituzumab govitecan (trodelvy) is recommended for adults with mTNBC and having received two or more prior systemic therapies. Sacituzumab govitecan was licensed based on a single-arm, multicenter clinical trial that included 108 patients. The percentage of patients who experienced a specific level of tumor decrease, or the ORR, was used to value the effectiveness of sacituzumab govitecan. The ORR was 33.3%. In addition, out of the 33.3% of survey participants that responded, 2.8% provided comprehensive replies. The results show that the median response time of the patients

was 7.7 months (95% confidence interval), the median overall survival time was 13.1 months, and the median progression-free survival time was 5.5 months. Moreover, 55.6% of the participants who received sacituzumab govitecan and experienced an objective response kept that response for at least six months, while 16.7% kept it for at least a year [4]. In mTNBC patients, received a lot of prior treatment, sacituzumab govitecan was found to be associated with long-lasting objective responses. A most common drawback was shown in patients who experienced myelotoxicity. Sacituzumab govitecan also received priority review as others, as well as a breakthrough therapy, fast-track status, and accelerated approval. Awards have been received from FDA by Immunomedics, Inc. clearance for the discovery of trodelvy.

According to Immunomedics' 2013 report, the FDA has given the drug fast-track status as a possible treatment for mTNBC and SCLC have received the label of an orphan disease. In the February of 2016 (figure 3), sacituzumab govitecan get the therapy designation for treating patients who had failed at least two other treatments when treating mTNBC [5].

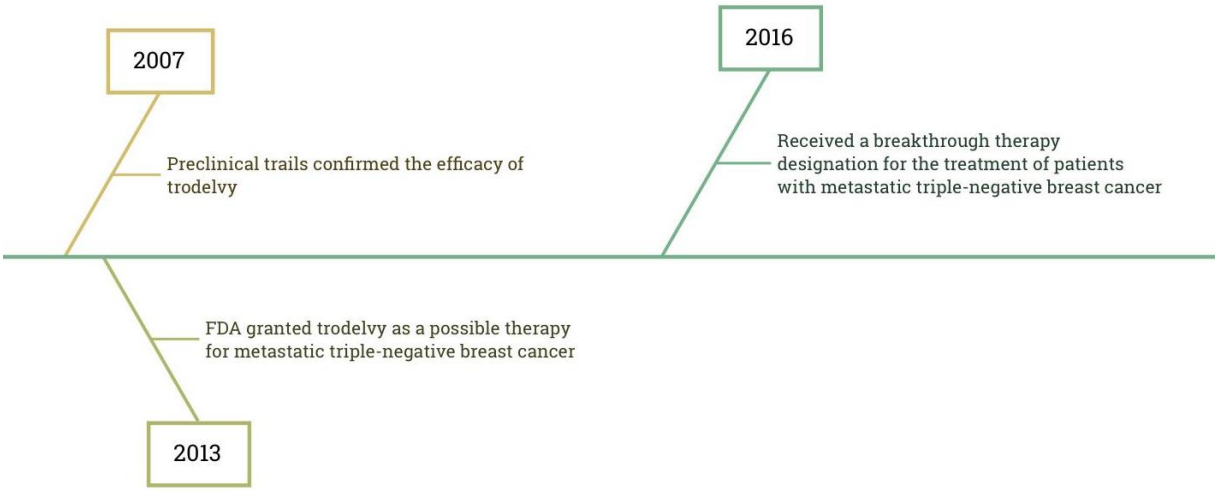

Figure 3. Timeline of trodelvy discovery.

3. Mechanism of the drugs

3.1. Working mechanism of trastuzumab

3.1.1 Introduction of HER2

BC, ovarian cancer and stomach cancer are just a few examples of prevalent malignancies whose aberrant expression is intimately correlated with HER-2. But the extracellular domain of HER2 may adopt a stationary conformation that is similar to the state of ligand activation, enabling it to size in the absence of the ligand. Tyrosine kinase, an enzyme that regulates intracellular signaling pathways, is driven by homodimerization and heterodimerization, which are often brought on by ligand interaction. In fact, the extracellular area of HER2 can adopt a stationary pattern that is similar to the state of ligand activation, allowing it to size in the absence of the ligand. Following dimer formation, HER2 successfully promotes cell proliferation by two complex intracellular pathways that occur concurrently and indirectly produce a pro-angiogenic VEGF [6]. The extracellular domain of HER2 is released upon overexpression, and a shortened, membrane-bound segment (P95) is produced instead. This is demonstrated in Figure C. Trastuzumab, however, prevented HER2 cleavage [7].

3.1.2 Specific working mechanism

Trastuzumab has two distinct binding sites that attach to the HER2 receptor's proximal extracellular area and stop it from activating the intracellular tyrosine kinase. Trastuzumab also may recruit effector cells in the immune system or cause cytotoxicity (figure 4), leading to tumor cell death.

In addition, other mechanisms include endocytosis leading to receptor downregulation as in figure F [8].

Focusing on the relationship between HER2 overexpression and increased angiogenesis in BC cells, some researchers treated mice carrying HER2 overexpressing BC in three ways: 1. Trastuzumab alone, 2. Paclitaxel alone, and 3. Combination of both drugs. This result showed that the treatment effect was best when the drugs were used in combination. This study may reflect the ability of trastuzumab to induce tumor vascular normalization, after which other drugs can be delivered more efficiently [9]. Based on the literature, the researchers found that cells treated with trastuzumab were shut down of the cell cycle and inhibitd proliferation, which revealed the action mechanism of trastuzumab that has an impact on the regulators of the cellular cycle. [10].

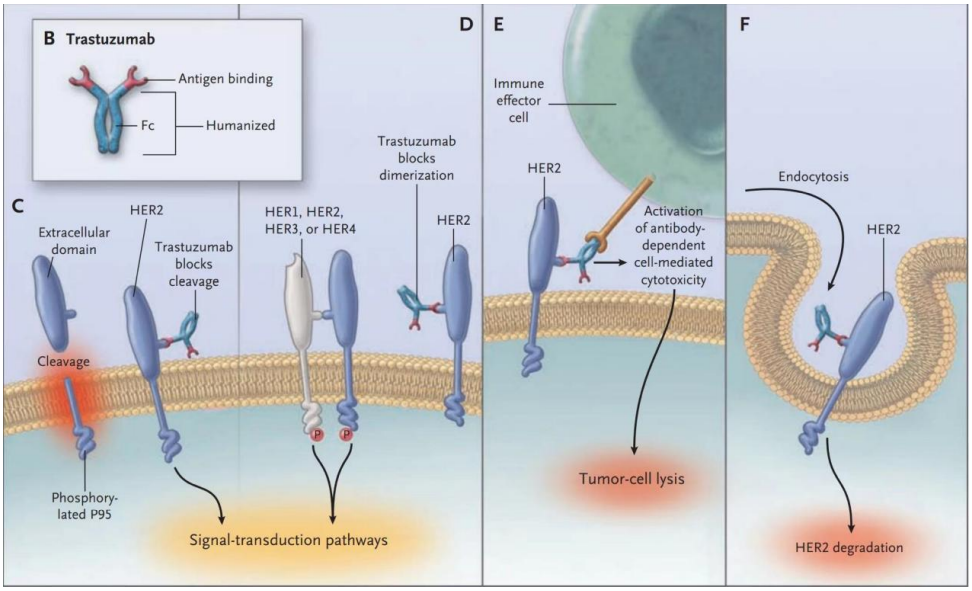

Figure 4. Mechanism [7].

3.2. Working mechanism of pertuzumab

The HER2 receptor is likewise targeted by the humanized monoclonal antibody pertuzumab, and results indicate that pertuzumab, like the previously stated trastuzumab, suppresses HER2 heterodimerize. Pertuzumab has been shown in numerous clinical studies to be more efficient when being pair treated with trastuzumab. When worked as monoclonal antibodies, they bind to definite epitopes on the HER2 receptor without interfering with one another, there will be unique mechanisms that interfere with HER2 signaling. These mechanisms complement and strengthen the therapeutic effect if pertuzumab and trastuzumab are combined [10].

3.2.1 Difference between trastuzumab and pertuzumab

Pertuzumab binds to HER2 domain II, which is necessary for dimerization, whereas trastuzumab binds to domain IV. Different loci mean that they don't conflict, and they can complement each other functionally, for example, pertuzumab inhibits heterodimerization of HER2 with HER3, HER4, and others, whereas trastuzumab preferentially activates tumors that are caused by HER2 homodimers. Specifically, pertuzumab prevented ligand-induced HER2 and HER3 dimerization, thereby inhibiting the activation of downstream cellular signaling pathways, which effectively inhibited tumor growth. Furthermore, pertuzumab did not prevent the formation of a truncated form of p95, but trastuzumab did.

3.3. Working mechanism of trodelvy

Sacituzumab govitecan is a drug-antibody conjugate (ADC) that uniquely contains three parts, the antibody, the anti-cancer drug, and a chemical linker. In ADCs, antibodies are used to find antigens that are overexpressed, antigen-cancer drugs are used to kill cancer cells, and chemical linkers are

used to connect the two. In particular, the sacituzumab govitecan is commonly found to treat TNBC as an anti-Trop2 therapy. It works by inhibiting the activity of Trop-2 since it is often overexpressed (fig 5). Sacituzumab govitecan as ADC humanized the monoclonal antibody RS7 IgG1κ Trop-2 conjugated with SN-38 using a patented hydrolyzable linker called CL2A linker [11, 12]. The SN-38 is an energetic metabolite of irinotecan that triggers its potent anti-tumor activity, which has made camptothecins, an inhibitor of topoisomerase I for anticancer treatment, highly applicable [11]. It first binds to the Trop-2 protein as it is identified by monoclonal antibodies as shown in Figure 5. Trop-2 in BC is often overexpressed and controls several intracellular signaling pathways in cells, including self-renewal, proliferation, invasion, and survival.

The attachment then allows internalization of the sacituzumab govitecan in the cancer cells, which leads to direct and intra-cellular penetration and administration of SN-38 to TNBC tumor cells. Inside the cell, lysosomes cleave the CL2A linker, allowing the release of SN-38.

Finally, the cancer cells are destroyed from within. This is done by the cytotoxic. The anti-tumor activity of the cytotoxic is high because of the high concentration of SN-38, which is resulted in many ways. First, a significant attribute of the ADCs is their high drug-to-antibody ratio (DAR), which means that the average number of drugs conjugated to the antibodies is relatively high, with 7 to 8 molecules for each antibody in this case [12]. Furthermore, the hydrolysis of the CL2A linker allows the release of SN-38 to kill tumor cells. Moreover, CL2A linkers have intermediate stability which allows the binding of SN-38 to Sacituzumab and the tumor microenvironment. Unlike traditional chemotherapy, ADCs selectively transfer cytotoxic SN-38 to tumor cells, which limits its exposure to nearby tissues and cells. The SN-38, as a topoisomerase inhibitor, also affects the efficacy by inducing DNA breaks, which leads to apoptosis and blockage of DNA replication in tumor cells. This helps patients to live almost twice as long, holding an increase of 34% compared to ones who received traditional chemotherapy.

In a sample of patients, who have advanced mTNBC and received numerous prior treatments, trodelvy has exhibited a clear therapeutic benefit. Due to its excellent clinical performance, it has now become the first ADC, providing drugs for refractory mTNBCs or relapses who have not responded to two previous chemotherapies.

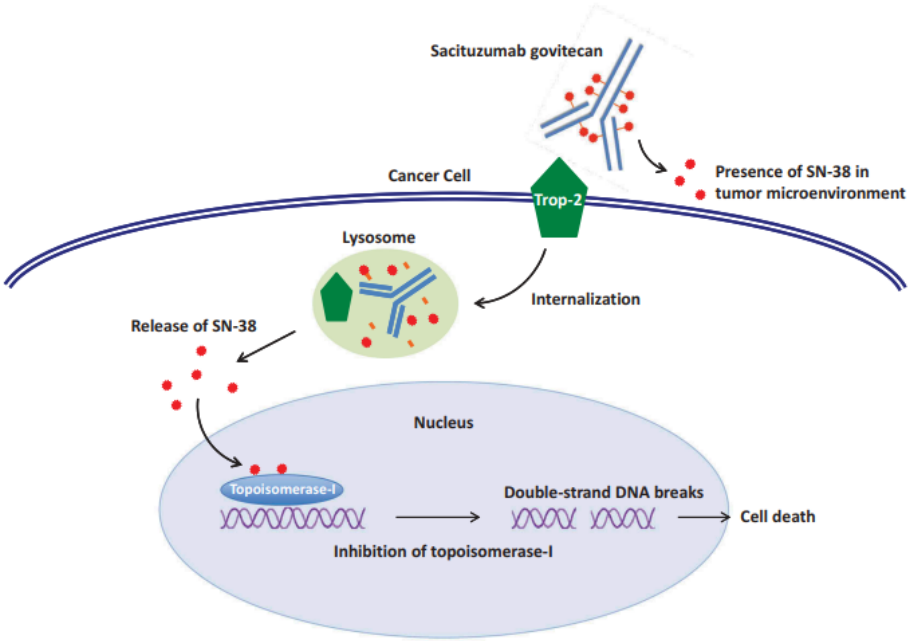

Figure 5. Mechanism of sacituzumab govitecan [12].

4. Issues of the drugs

4.1. Issues of trastuzumab

4.1.1 Side effects

The side effects of trastuzumab are mainly cardiotoxicity, but the mechanism of trastuzumab-induced cardiotoxicity is not clear, and it can be associated with inhibiting the HER2 signaling pathway. According to the investigators, HER2 was expressed on myocardial and endocardial cells in embryonic wild-type mice. The expression of HER2 in cardiomyocytes is mainly restricted to the T-tube network, so the arrangement of HER2 is regular and they are likely to be involved in the regulation of cardiac physiological activity [13]. The researchers studied the role of HER2 in mammalian development in mice that did not carry the HER2 allele. The results of this experiment could prove that HER2 exerts a crucial part in cardiac development [14]. As a means of cancer treatment, trastuzumab can inhibit the expression of HER2, leading to a series of side effects such as cardiotoxicity and many serious problems.

Trastuzumab also prevents the activation of Src and focal adhesion kinase (FAK) which is mediated by neuregulin 1(NRG1), potentially exacerbating left ventricular dysfunction.

4.1.2 Drug resistance

A link has been established between resistance to trastuzumab and increased expression of membrane-associated MUC4 glycoprotein. MUC4 can spatially bind and block the HER2 bond to trastuzumab. MUC4 interacts directly with HER2 because MUC4 structurally owns an epidermal growth factor type domain (EGF). Thus, the expression of MUC4 blocks the HER2 trastuzumab linkage epitope, resulting in the spatial detachment of the antibody to its therapeutic target. Finally, pharmacoresistance develops [15].

HER2 activates the PI3K signaling pathway. Earlier studies have demonstrated that PI3K/Akt can inhibit stopping the cell cycle and apoptosis induced by trastuzumab [16]. Investigators have shown that patients, who have PTEN-deficient HER2-overexpressing BC, are insensitive to trastuzumab and have a poor response. Furthermore, they showed that PI3K inhibitors have great power to salvage drug resistance in PTEN-deficient cells. This suggests that loss of PTEN may contribute to trastuzumab resistance.

4.2. Issues of pertuzumab

4.2.1 Side effects

Pertuzumab isn’t a suitable medication for everyone during BC treatment. Some people who are treated with pertuzumab experience side effects such as muscle or joint pain, rash, and chills that should pay attention to them immediately.

Nearly 70% of patients who get pertuzumab-based therapy experience diarrhea and abdominal pain as side effects. When taken in conjunction with chemotherapy, pertuzumab increases the risk of gastrointestinal problems. Chemotherapy-induced diarrhea frequently results from mucosal injury. However, because of EGFR/HER2 signaling block and diarrhea has several potential mechanisms, including regulation of changing the intestinal motility and microbiome, including small intestinal bacteria overgrowth, may also change nutritional metabolism [17]. All-grade diarrheas occurred in 43–72.4% of patients with early-stage, HER2-positive BC who were receiving pertuzumab in combination [18]. 66.8% of patients who received pertuzumab occurred diarrhea in in the phase III study.

Trastuzumab cardiotoxicity is well known, however, there is a lack of data on pertuzumab-based therapies used in routine clinical practice. Since pertuzumab's binding site differs from trastuzumab's, taking these two medications at the same time can have a beneficial effect. Generally, cardiac toxicity will reduce cardiac blood capacity and cause insufficient blood supply. With decreased blood ability to recover, patients have a risk of lower limb or pulmonary edema. About 5% of moderate to severe patients use pertuzumab alone, and this proportion is not optimistic. Pertuzumab brought up and

placed patients at risk of experiencing clinical heart failure (HF) [19]. Shortness of breath is a common symptom of HF because blood frequently backs up and fluid can accumulate in the lungs. Left ventricular dysfunction (LVD) incidence increased in the pertuzumab group in the NeoSphere study. Considering the observations above, using pertuzumab requires a high cardiac function of patients and makes a comprehensive cardiac function evaluation before medication.

4.2.2 Drug resistance

Because acquired resistance renders HER2-targeting antibodies like pertuzumab ineffective over time, patients urgently require alternate therapy. An irreversible selective HER2 kinase inhibitor is TAS0728. To evaluate the impact of TAS0728 in HER2 antibody-resistant populations, in vivo cancer resistance models for a trastuzumab and pertuzumab combination have been established in the current study. Trastuzumab and pertuzumab treatment-related tumor regrowth suggested a decline in medication efficacy. HER2-HER3 phosphorylation was kept in malignancies with acquired resistance to trastuzumab and pertuzumab. TAS0728 in combination with HER2-HER3 signal inhibition, however, can have a strong anti-tumor impact. As a result, cancers rely on HER2-HER3 signaling and resistant to trastuzumab and pertuzumab are susceptible to HER2 signal suppression by TAS0728.

4.3. Issues of trodelvy

4.3.1 Side effects

The percentage of patients that showed signs of side effects associated with sacituzumab govitecan is a significant number. A study shows that 98% of patients were associated with side effects, which is notably higher than the ones of chemotherapy, regardless of overall survival, which is 86% [20]. Common and severe side effects with relatively high association include neutropenia (64%), diarrhea (63%), and anemia (8%). Other relatively uncommon side effects are pleural effusion, antibody development, and pneumonia, which all have a low association of around 2% [21].

Neutropenia is one sort of side effect that can cause bacterial and fungal infections, as well as fatalities. It is characterized by a low white blood cell count. It is diagnosed when the ANC is more than two standard deviations, severe ones are less than $0.5 \times 109\ L{-}1$. Mild Neutropenia is treated by lowering the dose and antibiotic medicines are used for febrile neutropenia, while G-CSF is often considered for secondary prophylaxis and severe neutropenia [20]. The symptoms of neutropenia include a fever, sore throat, abdominal pain, and so on.

Additionally, an increase in bowel movements and increased stool fluidity are defining features of another side effect -- Diarrhea. Disrupted enteral water and electrolyte balance is the pathophysiological cause of diarrhea, so patients are offered fluids and electrolytes when treated [22]. As the time and severity increase, medicines such as administer atropine, and loperamide are used respectively. When diarrhea becomes severe, trodelvy will be withheld.

4.3.2 Drug resistance

A study has found a link between the lack of TROP2 expression and the absence of response to sacituzumab govitecan, which supports the claim made on primary resistance. Furthermore, some resistance was not present in the primary tumors. It is noticed that they have acquired resistance later. In a clinical study, different resistant mechanisms of molecules were found in different metastatic lesions of the patient. It is shown that TNBC cells exposed to sacituzumab govitecan may develop parallel resistance due to changes in the gene of both the antibody's target and the SN-38's target [23].

5. Future improvements

Reducing immunogenicity, and the increase of all antigen-binding affinity, effector functions, and pharmacokinetics are targets for enhancing antibody efficacy. To assess immunogenicity, reducing non-human genetic sequences were required. Without an Fc domain, antibody fragments are typically less immunogenic [24]. However, occasionally, antibodies of a low affinity for the antigen are necessary for greater tumor penetration. Once within the body, the unique pharmacokinetic properties

of antibodies are a particularly intriguing component of their effectiveness. Additionally, developing antibodies with a higher affinity for FcRn (for example, through phage display) is another way to lengthen the plasma half-life of IgG. Additionally, it has been discovered that polyethylene glycol (PEGylation)-treated antibody fragments had longer plasma half-lives. There is also a possibility to alter the monoclonal antibodies to produce various effects. Typically, ligands are used to chemically link effector molecules to monoclonal antibodies. Monoclonal antibody coupling sites usually contain thiol groups, and amine groups, such as -NH2 groups on lysine residues, or carbohydrates. Anywhere in a monoclonal anti.

6. Conclusion

The monoclonal antibody makes a substantial contribution to the treatment of BC in several different ways. Trastuzumab, pertuzumab, and trodelvy can successfully limit the activity of specific tumor cells thanks to the extensive study that was conducted for the main drug trials that were included in this article. Targeted treatment for cancer, Herceptin, Herzuma, and Ontruzant are some of the brand names used for trastuzumab. Individuals with different stage of BC may take advantage of this therapy. The FDA authorized trastuzumab in 1998 after it was proven to reduce the number of BC cells in treatment group participants by more than 50%. Pertuzumab, trastuzumab, and docetaxel make up the medication cocktail used to deal with metastatic BC that is HER2-positive. The same combination is also utilized in early HER2-positive BC as a neoadjuvant. The monoclonal antibody pertuzumab is sold under the brand name Perjeta. With its clearance by the FDA in 2017, this research article demonstrates that this medication may reduce the relative frequency of occurrence of BC in patients by over 41%. In 2013, the FDA gave its approval to a therapeutic combination called trodelvy, which is made up of a Trop-2-directed antibody and a topoisomerase inhibitor. This combination is used to treat mTNBC. Trodelvy was approved based on its ability to inhibit BC. However, the efficiency of the monoclonal antibody may still be increased if the plasma half-life of IgG is extended.

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