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Advanced Therapy Modalities That Have Potential In Overcoming Medication Resistance In HER2-Positive Breast Cancer: In Clinical Scenario

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KEYWORDS

Breast Cancer, HER2 gene, signalling pathway, Antibody drug conjugate (ADCs), tyrosine kinase inhibitions, therapies.

ABSTRACT

Breast cancer, the most common cancer in women worldwide and the leading to cause of death. Approximately 20% of breast cancers due to her2 overexpression and is associated with shorter overall survival and poor prognosis. Tratuzumab, Monoclonal Antibody is the standard care of treatment directed to against the her2 receptor. However, a 3rd of the her2 Positive Breast cancer patients does not respond to therapies. Given the higher rate of resistance, other type of her2-targeted strategies has developed, including monoclonal antibodies such as-Pertuzumab, Margetuximab. Among others, Trastuzumab-based antibody Drug conjugates such as, trastuzumab-emtansine (T-DM1), trastuzumab-deruxtecan (T-DXd), tyrosine kinase inhibitors such as- lapatinib, tucatinib. Moreover, T-DXd has proven to be use of, in the her2-low subclass, which suggests that, in this recently defined new breast cancer subclassification, other her2-targeted therapies could be successful. There are several her2-targeted therapies available, when patients progress to multiple strategies. However, treatment options are limited, and in this era, the potential combination with other drugs, that is still in development, exosomes, immune checkpoint inhibitors, vaccines are an interesting and appealing field. In this review, we will be discussing the pitfalls, highlights of the various her2-targeted therapies, potential combinations to overcome her-2 breast cancer metastatic disease and resistance to therapies.

1.Introduction:

Breast cancer is the, 2nd most common Cancer-related to death globally induce among females. and is a prevalent form of cancer at United States (1). According to data from GLOBOCAN 2020, there were around -2.3 million newly identified Cases. which positioned it, as the 5th leading to cause of cancer related death worldwide (2). Breast cancer disease is a diverse condition, its categorized in Luminal -A and Luminal-B, triple- negative breast cancer (TNBC), her2-Positive(3). Based on cell surface receptors, Approximately 20 to 30% of breast cancer patient exhibit or overexpression the Human epidermal growth factor receptor (4) and a part of these receptors known as EGFR/her-1, her-2, her-3,her-4. HER2 has been found to stimulate the growth of cancer cells. her2, it's a transmembrane Tyrosine Kinase Receptor which can form EGFR/her-1 active dimer and another receptor family member of her2. when tyrosine residues on the receptor are phosphorylated, intracellular signalling pathways are activated, promoting cell growth, proliferation through PI3K/Akt-Ras/Raf/MEK/MAPK pathway (5). There are two types of Her2 breast cancer, 1st is her2 low breast cancer, these types of breast cancers also display higher levels of ERBB2, present significant biological diversity and are commonly found in HR-positive tumours, 2nd is her enriched breast cancer. her2-enriched tumours demonstrate the most notable activation to EGFR or HER-2 pathway and increased genes level. Around 20% of patients display

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amplification her2 gene at the mRNA level in early stage of Breast Cancer (6). It's associated to short overall survival with poor prognosis, z. That being so her2 became, an optimal target of her2 positive Breast Cancers, its therapeutic intervention and development therapeutics targeted. The HER2-positive (HER2+) subtype of breast cancer is characterized using immunohistochemistry (with a score of 3+ or 2+ and positive in situ hybridization), and the prevailing therapeutic approach involves trastuzumab, monoclonal antibody which specifically to target her-2 receptor [7]. This treatment is to, guided by the level of HER2 expression. Presently, a novel classification known as HER2-low subtype is emerging, identified by immunohistochemistry scores of 1+ or 2+. Notwithstanding the demonstrated enhancements in overall survival, progression-free survival for her-2 positive cases through trastuzumab therapy (7). the efficacy of this approach is hampered by occurrences of treatment resistance. Approximately 27–42% of patients experience disease progression despite receiving adjuvant or neoadjuvant trastuzumab. Given these clinical challenges, substantial endeavors have been dedicated to the development of supplementary therapies targeting HER2. These include antibody-drug conjugates monoclonal antibodies, bispecific antibodies, tyrosine kinase inhibitors, as well as vaccine, exosome-based interventions directed to distinct her-2 epitope. Trastuzumab evolution remains, remarkable achievement to treatment and induced therapeutic modalities for her2 Positive Breast Cancer (8) Anti-HER2 ADCs, which approved as an adjuvant therapy, beneficial to the treatment of HER-2 positive breast cancer. Some ADC based therapies have demonstrated and we discussed about these therapies in this review, such as chemotherapy, hormonal therapy, immunotherapy and combination therapies to the treatment of HER2-Positive Breast Cancer. Currently various, in progress scientific research appraise, efficacy of Antibody Drug Conjugates, to the Breast cancer treatment. In this study we provided example of that demonstrated. In this comprehensive analysis, our intension will be directed towards the stablished regimen utilized individuals afflicted her2 positive breast carcinoma. We shall delve into the ongoing investigation in managing involving her2 targeted interventions with in the clinical milieu, as well as those interventions that have exhibited auspicious outcomes with in principle paradigms. Moreover, we shall explore the prospect of synergistic amalgamations with alternative therapeutic modalities, including immunomodulatory interventions, in order to attain a state of neoplasm regression with in both the her2 positive and her2 low subclasses of breast malignancy, additionally deliberations shall encompass alternative therapeutic avenues such as exosomal therapeutic approaches and oncolytic vaccinations strategies.

2. HER2 Gene:

HER-2 is a receptor tyrosine kinase family of (EGFR), which consists of her1, her2, her3, her4. These EGFR receptors have a crucial function in the normal growth and differentiation of cells(9). However, the excessive activation or overexpression of these receptors has been associated with the occurrence of different types of cancers in humans, for example- Ovarian, Breast, Gastric cancers (10) (11). HER2 is a transmembrane protein-1255 amino acids in length, with molecular weight 185Kda. It is located on the chromosomal locus 17q21.1 (12). While in normal tissues her2 present at low level, its amplification is associated with uncontrolled cellular growth and the formation of tumours (13), (14), (15). Approximately 20-30% of primary breast tumours show HER2 gene amplification/HER2 protein overexpression. Its overexpression leads to increased signalling pathway activation which promote cell proliferation, inhibit apoptosis. These findings have been consistently reported in several studies. More aggressive forms of carcinoma associated with the amplification or overexpression of the HER2 gene. Its characterized through higher resistance rates resistance to treatments and lower rates of survival(13).

3. Genetic basis of HER2 gene mapping, its amplification/Overexpression and downstream signalling pathways

3.1Her2 gene position

The HER-2 gene is situated on chromosome 17 at q21.2, it produces transmembrane receptor tyrosine kinase called p185HER2 RTK. This receptor consists of 1255 building blocks it's called amino acids, has weight of 185 kilodaltons (kD) (12). Despite their molecular differences, all members of the HER family have three structural parts: a short segment that spans the cell membrane and connects the external domain responsible for binding to ligands and the internal domain that acts as a catalyst for kinase activity. The prevailing belief that ligand binding is the main trigger for activating downstream signals has been challenged. It is now understood that the arrangement or configuration of the receptors is the crucial factor for initiating phosphorylation reactions (16). The response of cells depends on the intricate processing of signals resulting from HER-2 gene hetero and homodimers formation, besides interactions with other type of receptors that can impact the survival, growth, and resistance of breast cancer.

3.2. Her2 overexpression/Amplification and its implication in breast cancer

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HER2 variation and overexpression both are early events, to the development of breast cancer, occurring around 50% in situ carcinomas 20% other cases(9). Numerous studies have shown that HER2 gene amplification is linked to a higher risk of cancer recurrence and lower amount of disease-free and overall survival (15). It has observed, in breast cancers HER-2 amplification are more sensitive for specific chemotherapy drugs like doxorubicin but less responsive to hormonal agents such as tamoxifen (9),(17). Studies suggested that the importance of HER2 as a prognostic indicator (13). Various techniques has developed to determine HER-2 and currently using immunohistochemistry, fluorescence in situ hybridization authorized by College of American Pathologists, the (ASCO)American Society of Clinical Oncology, the College of American Pathologists to evaluating HER-2 expression (17),(11). Evaluating HER-2 expression has mandatory for diagnosed HER-2 breast cancer individual. Research has shown that only samples IHC 3+ positive, F-ISH+ results typically respond to anti-HER-2 drug therapies. immunohistochemistry 2+ result is considered inconclusive and is often confirmed with a fluorescence in situ hybridization test. The scientific literature extensively documents the oncogenic potential of HER2 overexpression signalling pathways which is inversely correlated with patient outcomes (17),(11). However, the use of HER2 inhibitors has been shown to significantly improve patient survival rates.

3.3. Signalling pathways of overexpressed HER2 Gene:

With reference to Figure 1, the HER2 protein consists of multiple structural domains, including transmembrane element, extracellular domain (ECD), intracellular tyrosine kinase domain and C-terminal tail. Crystallographic data has revealed ECD of HER-2 which adopts stable configuration similar to an activated state induced by a ligand (17),(11). This conformation allows the ECD to readily engage in dimerization, even the absence of ligand strap. Breast cancer cell lines, tumours with HER2-positive status can have varying copies of the HER2 gene per cell, ranging from 8 to 66 (17). The dimerization of HER2 can occur without the need for ligand binding, although ligand binding enhances the association of other receptor tyrosine kinases (RTKs) with HER-2. It has preference for dimerization with family members, particularly HER-3 (11). The precise molecular mechanism underlying the promiscuous, hetero-dimerization between HER-2 and RTKs is not fully understood. Both HER2 homodimers and heterodimers contain kinase domains with C-terminal tails, which can express auto-phosphorylation with trans-phosphorylation. The resulting its serve as docking sites and phosphorylated tyrosine residues serve for different signalling proteins and leads various signalling pathway activation. These pathways include RAS-RA-ERK pathway, SRC-PTEN-PI3K-AKT , JAK- STAT3 pathways (17), (11), (5).

Oncogenic activity of HER2 is augmented by its interaction with non-receptor tyrosine kinase cell surface proteins such as mucin 1 (MUC1), cannabinoid receptor type 2 (CB2R), and mucin 4. The CB2R molecule is classified as G protein coupled receptor, while MUC1, MUC4 categorised into mucin membrane. The stabilisation of HER-2 into HER2-positive breast cancer cell is facilitated by CB2R and MUC4, as demonstrated by (17),(11),(15), while the activation of HER2 is attributed to MUC1. The overexpression of HER2 leads to activation of transcription factor that govern HER-2 gene expression that are implicated to various cellular processes such as - cell proliferation, survival, angiogenesis, differentiation invasion, as reported in previous studies (17),(11). In addition, it has been observed that the dimerization process of her-2 receptor results in the misplacement and cell-cycle inhibitor p27Kip1 deterioration, thereby facilitating to the progression of the cell-cycle (17).

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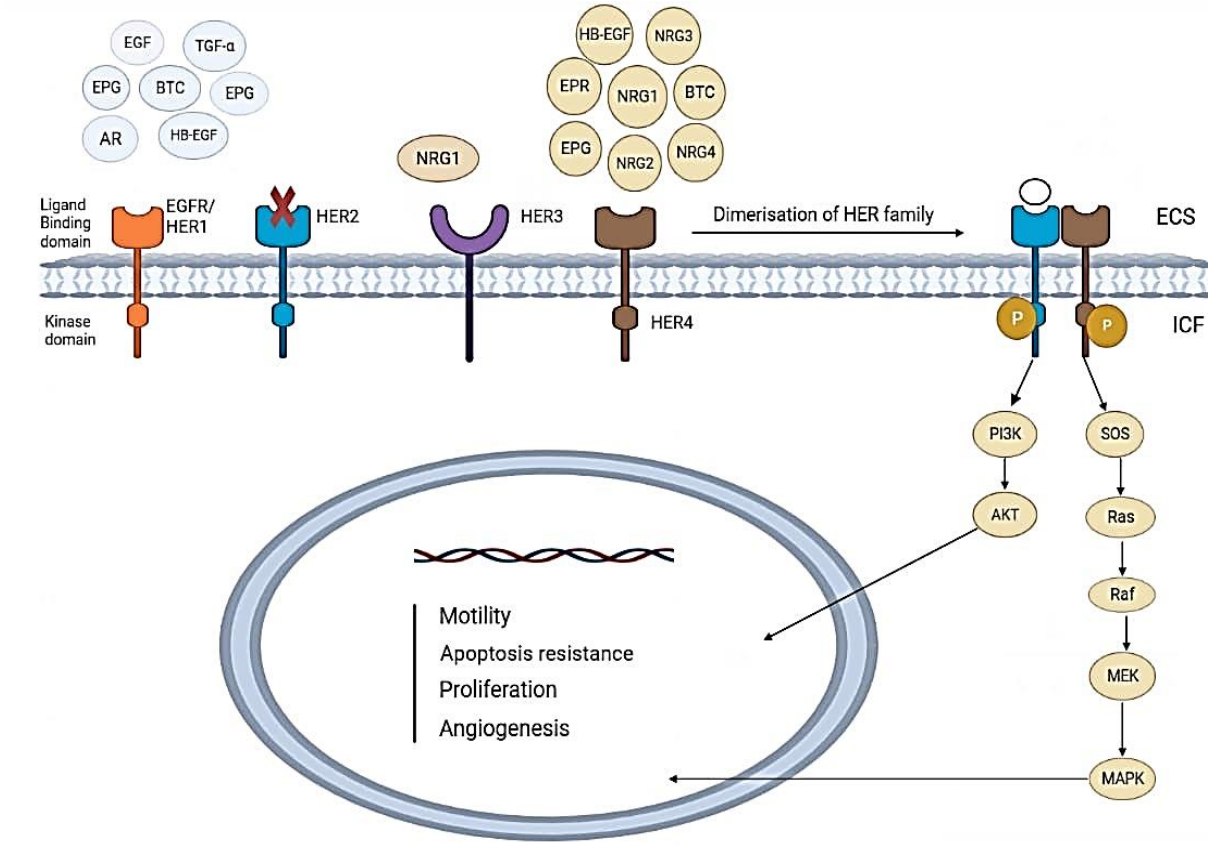

Figure 1. Heterodimer formation of member of HER family and downstream signalling pathways.

4. Current and emerging therapeutic targets and clinical trials to overcome her-2 Positive Breast Cancer:

In recent epochs, diligent investigations have been undertaken to address diminished levels of HER2 expression in breast cancer (BC) through the utilization of anti-HER2 therapeutic modalities. Presently documented data concerning anti-HER2 treatments in cases of HER2-low BC are delineated as follows:

4.1 Antibody Drug conjugates:

Conjugates of Antibody and Drug: This remedial methodology capitalizes on the precise targeting capability of monoclonal antibodies, synergizing them with potent cytotoxic agents to achieve precision drug conveyance (18). The comprehensive framework of Antibody-Drug Conjugates (ADCs) manifests a cooperative impact surpassing the cumulative effects of its individual components. This synergy predominantly arises from the bystander killing phenomenon, wherein the therapeutic payload not only affects the intended target cells but also extends its influence to the surrounding tumour microenvironment (TME)(19). Moreover, ADCs have validated their efficacy even in instances where the target protein is sparsely expressed.

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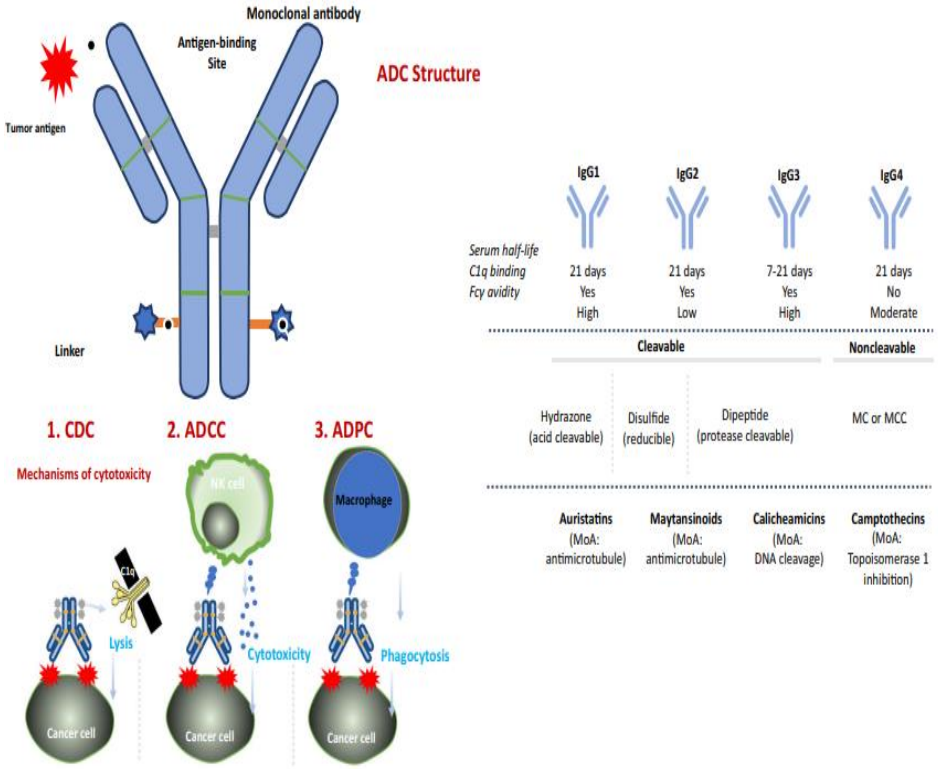

Figure.2: Structure and components of Antibody Drug Conjugates (20)

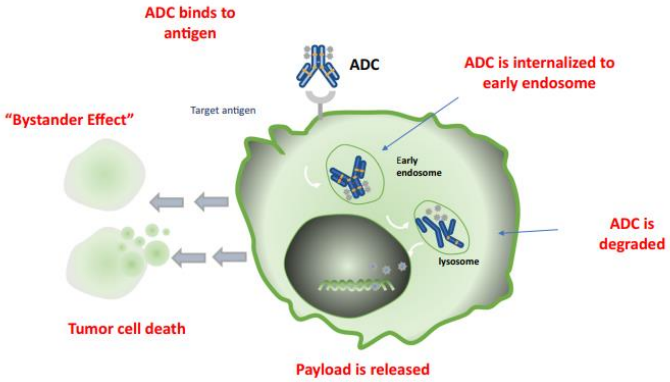

Figure-3: Mechanism of action

The operational mechanism of ADCs is intricate, encompassing antibody binding to the specific target antigen, ensuing internalization, linker disintegration, and liberation of intracellular payload. In the ADC construct, the monoclonal antibody selectively attaches to the tumour cell's distinctively expressed target antigen. Subsequently, the ADC is internalized by the tumour cells and ultimately fuses with lysosomes. This fusion facilitates the discharge of the cytotoxic agent, culminating in cellular demise or apoptosis through the targeted disruption of DNA or microtubules.

In the realm of HER2-positive breast cancer, the advent of T-DM1 marked a revolutionary milestone (21) and further advancements in ADCs are underway to enhance therapeutic options. The current armamentarium encompasses 14 ADCs approved by the FDA for diverse cancer types, with variations in addresses molecules, linkers employed, drug conjugates, to adverse reactions linked to antibody drug conjugate, account for 10 to 15% cases (22),(23). In our article segment, we will be succinctly outline, primary Trastuzumab linked Antibody drug conjugates implemented to remedial contexts, as well as those demonstrating promising

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outcomes in preclinical investigations for HER2-positive breast cancer.

4.2 Fam-Trastuzumab Deruxtecan (T-Dxd)

Fam-trastuzumab deruxtecan-nxk, also known as DS-8201a and T-DXd, Enhertu® has received FDA approval as the second anti-HER2 ADC. In 2022, United States has approved this drug to treating HER-2-positive Breast cancer patients those were previously received HER2-targeted therapy(24). Subsequently, T-DXd was approved to managing individuals with HER-2 low Breast cancer which could not be surgically removed. It has spread to other body parts and its undergone prior chemotherapy or experienced recurrence (25). The validated therapeutic applications of drug are grounded to evidence derived by the clinical trials of Phase-Ist and 2nd DESTINY-BREAST-01, Phase-3rd DESTINY-BREAST-03, and Phase-3rd DESTINY-BREAST-04 (26). The T-DXd structure consists of the monoclonal antibody trastuzumab. The anti-tumour derivative of exatecan is potent topoisomerase1st obstacle, conjugated to trastuzumab through a cleavable Maleimide tetrapeptide linker, as reported in reference (27). The cleavable linkers are subject to the catalytic activity of lysosomal enzymes, namely cathepsins, which are widely present in numerous cancerous cells (28). Upon cleavage, exatecan derivatives with cytotoxic properties can permeate the membrane and induce bystander effects, leading to enhanced efficacy in heterogeneous tumours as reported in references (29).

The drug T-DXd has been granted accelerated approval for managing unresectable Breast cancer which is HER-2 positive and has undergone two or excess anti-HER-2 based regimen in the previous. It has indicated that received approval subsequent, to outcomes of the initial phase- I clinical research involving human subjects, phase- II DESTINY-BREAST01 research, as reported in references (30). The objective of the Phase-1st clinical research has evaluate to protection, tolerability and efficacy of this drug to treating the individual with HER-2 positive Breast cancer, who had undergone previous therapies (31). The United State has recently granted approval T-DXd, for her-2 Positive Breast Cancer patient cases, undergone previous treatment(5). The extension of the indication was granted based on favourable outcomes observed in the phase III clinical trial, DESTINYBREAST03 (32),(33). This investigation objective is to, examine T-DXd impact compared with T-DM1 on individuals diagnosed with her-2 Positive Breast Cancer previously, undergone treatment with trastuzumab, taxane based. The sample size for the study was 524 (34). The trial yielded findings indicating that T-DXd led to, remarkable healing in progression free survival, as compared to T-DM1, PFS rate 75.8% versus 34.1% respectively. Additionally, the T-DXd treated cohort exhibited 79.7% an objective response rate. Notably, in the T-DM1 cohort investigation observed that its higher 34.2% than the ORR (35).

T-DXd uses for incurable HER-2 low breast cancer adult individual has been approved by the FDA. According to the source (36), this is relevant after the administration of preceding chemotherapy and adjuvant chemotherapy. Endorsement of T-DXd is grounded to the findings of the- DESTINY-Breast-04 Phase III clinical practice, where in T-DX-d demonstrated 50% decrease, likelihood of mortality compression to the chemotherapies selection, in 557 metastatic Breast cancer cases of cohort study characterised by low level of HER-2 and either HR + or HR- cases (37). At present, clinical trials are underway, namely Phase-Ib/II (NCT04538742), phaseIb (NCT04556773) to investigate T-DX-d effectiveness as anti-cancer, for metastatic HER2-low progressed breast cancer in combination with other treatments.

4.3. Ado-Trastuzumab Emtansine's(TDM1):

FDA has granted approval to (TDM1; Kadcyla®), the 1st ADC targeted HER-2, sustain such authorization (13). In 2019, FDA has approved TDM1 usage in 2019, include early-stage her-2 positive Breast Cancer patients who diagnosed with higher risk and have residual invasive illness following, neoadjuvant taxane - trastuzumab-based therapy, as mentioned reference (14). TDM1 is based on EMILIA investigation results, its phase-3rd research practice comparing to, the effectiveness of T-DM-1. Capecitabine, lapatinib is a 2nd -line therapies for HER-2 Positive metastatic breast cancer patient, those had prior received healing with trastuzumab and taxane. The investigation has enrolled 991 participants (13).

The ongoing ATOP Phase- 2nd clinical research (NCT03587740) is currently explore to feasibility using T-DM1 as the primary treatment option instead of trastuzumab combination with chemotherapies for who diagnosed early her-2 positive Breast cancer (38). Phase- II basket trial demonstrated the effectiveness of T-DM1 opposed to tumours with HER2 variation, regardless of their amplification status (18). This trial provided initial pragmatic findings for specific molecular subsection, emphasizing the need for further studies and trials involving T-DM1 (18). In 2016, Phase-Ib/IIa study conducted a scientific practice and evaluate to synergistic possessions of T-DM1, docetaxel, possibly with pertuzumab, in advanced her-2 positive Breast cancer patients. Previous trial has showed that combination of T-DM-1 with docetaxel ± pertuzumab was effective. Approximately 50% patients experienced adverse events stand in need of dose reductions (39). These studies aim to establish a basis for future research endeavors that seek to precisely determine the efficacy of this particular combination.

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4.4. Trastuzumab-duocarmycine/SYD985:
This represents the foremost advanced Antibody-Drug Conjugate (ADC) subsequent to T-DXd, featuring the fusion of trastuzumab with duocarmycine, an irreversible DNA alkylating agent recognized for its actions on both proliferating and quiescent cells, displaying potent bystander cytotoxicity (40). This culminates in the initiation of TULIP phase-3rd practice NCT03262935. With in the context of the I-SPY clinical study (NCT01042379), SYD985isundergoing evaluation in conjunction with various agents, alongside chemotherapies in neoadjuvant scenario, involving Paclitaxel NCT04602117 or NCT04235101, PARP inhibitor (NCT04235101), with in the context of her2+ or her-low Breast Cancer. In respect to latter, robust bystander manifest by syd985 renders it markedly efficacious in her-2 low breast cancer context (41),(42).

Table1- Antibody Drug Conjugates:

ADC	Payload	Clinical Trial	Combination with	Population
TDXd	Deruxtecan (topoisomerase I inhibitor)	NCT04784715 NCT04538742 NCT04539938 NCT04556773	Pertuzumab Durvalumab Anti-PDL1, Tucatinib Durvalumab, Paclitaxel, Capivasertib, Anastrozole, Fulvestrant, or Capecitabin	Her-2+ metastatic Breast Cancer HER-2+ metastatic breast cancer her-2+ breast cancer or her2+ metastatic Breast Cancer her2-low advanced or metastatic Breast Cancer
Trastuzumab Duocarmycine (syd985)	Duocarmycine DNA Alkylating Agent	NCT03262935 NCT01042379 (I-SPY NCT04602117 (ISPY-P1.01) NCT04235101	Chemotherapy Paclitaxel Niraparib PARP Inhibitor	Her-2+ locally advanced or metastatic Breast cancer Breast cancer Metastatic cancer Solid tumours
Disitamab vedotin (rc48)	Monomethyl Auristatin E Microtubule Inhibitor	NCT02881190 NCT05331326 NCT05134519 NCT04400695 NCT05331326	Penpulimab (ak105)	advanced or metastatic her-2+ tumours her2-expression metastatic Breast Cancer with -abnormal Activation of PAM-pathway her-2+ Breast Cancer Locally Advanced or Metastatic her-2-low Breast Cancer

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		NCT03052634 NCT05726175 NCT03500380		her2-expression metastatic Breast Cancer with - abnormal activation of PAM - pathway Advanced Breast Cancer her-2-low Breast Cancer 2 positives metastatic Breast Cancer with or without Liver Metastases
Zanidatamab Zovodotin (zw49)	Auristatin based microtubule inhibitor	NCT03821233		metastatic her2 positive tumours
BDC- 1001	TLR7/8 agonist	NCT04278144	Nivolumab	advanced her2 expressing solid tumours
PF- 06804103	Auristatin Derivative	NCT03284723		Her-2 positive Breast Cancer

4.5. Disitamab- vedotin.

Distamab- vedotin groundbreaking ADC, denoted as rc48, composed hertuzumab linked to- vedotin, consisting linker, four entities of cytotoxic compound monomethyl auristatin E. Vedotin have heretofore undergone FDA scrutiny and approval in 2011 for lymphoma treatment (43),(44) obtaining approval within China, addressing gastric with metastatic Breast Cancer (45). Phase 1 clinical examination encompassing patients afflicted by advanced or metastatic HER2+ tumours has unveiled encouraging outcomes and tolerability of RC48 monotherapy (NCT02881190), particularly her-2 Breast Cancer. These findings have subsequently contributed to the provisional authorization of- rc48 administration to Gastric Cancer cases. An assemblage, 48 practice is currently engaged to investigating RC48 across diverse cancer manifestations; of particular relevance within breast cancer, six ongoing investigations probe de-escalation, synergistic therapeutic approaches, liver metastasis effects, her-2 low expressing Breast Cancers NCT-05134519, NCT-04400695, NCT-05331326 NCT-03052634, NCT-05726175, NCT-03500380 (46).

4.6. MRG002

Comprising a humanized anti-HER2 entity, MRG002 is equipped with a linker carrying approximately 3.8 MMAE (47). This construct has manifested anti-tumour impact a discernible, tolerable toxicity in her-2 positive Breast Cancer. MRG002 influence metastatic tumour scenarios NCT04924699, NCT04742153, in advanced NCT05263869 is under three research trials exploration, cantered on her-2 positive, her-2 low Breast Cancer cases.

4.7. Zanidatamab -Zovodotin -ZW49.

Zanidatamab -Zovodotin -ADC based upon previously mentioned zw25, is bispecific- Antibody featuring-Pertuzumab binding epitope, trastuzumab united with Auristatin, boasting heightened incarnate compared to monospecific-Trastuzumab ADCs (48). At present, zw49 is undergoing assessment within, phase-1st research investigation among patient beset by metastatic her-2 positive Breast Cancer NCT03821233.

4.8. BDC-1001.

BDC-1001 Antibody Drug conjugate showcases, TLR7/8 agonist combination with Trastuzumab bio-similar harmonized, designed to invigorate antigen presenting cells. Preclinical models have substantiated the elicitation of a robust antitumor immune response by BDC-1001, thereby prompting the launch of the pioneer clinical investigation examining this compound within advanced HER2+ tumour settings, in conjunction to NCT04278144 Nivolumab. Preparatory evaluation of this investigation has unveiled admissible safety with tolerability(49).

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Its Comprising to Trastuzumab-derived Antibody in union with potent Auristatin -derivative this ADC have demonstrated anti-tumours activity across her-2 positive, her-2 low Breast, gastric, lung cancers (50),(51). Phase-1st research study conducted among massively pre-treated individual cases harbouring her-2 positive tumours (NCT03284723) has corroborated promising anti-tumours response alongside manageable toxicity (51).

4.9. Alta ADC.

Its genetically well-developed ADCs, fashioned upon the foundation of pertuzumab, has solely been scrutinized in-vivo, in-vitro settings. Alta- Antibody Drug Conjugate is characterized by diminished affinity to her-2 under low pH condition (52). Its attribute proves advantageous as internalization- antibody drug conjugates disengage by her-2 within endosomes, allowing payload to be liberated within lysosomes while the antibody persists available for binding to unoccupied targets. Capitalizing on this property, Alta-ADC demonstrates efficacy at reduced dosages, holding potential to mitigate instances of toxicity. Notably, ALTA-ADC has showcased significant antitumor potency within preclinical models.

5. Monoclonal antibodies:

Trastuzumab has significantly enhanced the therapeutic landscape for individuals afflicted with HER2-positive breast carcinoma over the past quarter-century. Its implementation has established it as the standard modality of care due to its favorable clinical outcomes. Trastuzumab functions as a monoclonal antibody that selectively binds to the intravenous (IV) domain of the HER2 receptor, resulting in the attenuation of downstream signaling cascades. This engagement also elicits immune-mediated cytotoxic effects, specifically antibody-dependent cell-mediated cytotoxicity (ADCC) (53) and antibody-dependent cell-phagocytosis (ADCP) (54). Within the neoadjuvant context, and post the KRISTINE. protocol, when tumors surpass 2 cm in size, trastuzumab is co-administered with pertuzumab, another monoclonal antibody that targets the II domain of the HER2 molecule, thereby impairing its dimerization (55). Notably, pertuzumab, akin to trastuzumab, is capable of modulating natural killer (NK) cell Fc receptors to stimulate ADCC (56).

Owing to the substantial resistance encountered during the initial-line treatment of HER2-positive breast malignancies, novel monoclonal antibodies with HER2-targeting attributes are continually under development. For instance, the FDA-sanctioned usage of margetuximab alongside chemotherapy has emerged as a notable advancement (57). Margetuximab, binding the identical epitope on the HER2 molecule as trastuzumab and evincing akin affinity, manifests amplified CD16A binding capacity and diminished CD32B binding, thereby heightening ADCC potential (58). In a phase 3 clinical trial, the amalgamation of margetuximab with chemotherapy has showcased enhanced progression-free survival (PFS) in contrast to trastuzumab plus chemotherapy within HER2-positive advanced breast cancer (59). Nevertheless, the ultimate evaluation indicates no superior benefit with regard to overall survival (OS) in comparison to trastuzumab administration (60).

The utility of margetuximab in patients harbouring allelic variations in CD16A remains a subject of investigation. The ongoing MARGOT clinical trial (NCT04425018) is actively enrolling subjects with HER2-positive breast carcinoma and low affinity CD16A alleles. The augmentation of antibody-dependent cellular cytotoxicity (ADCC) alongside HER2-targeted interventions is an additional avenue for the evolution of novel combined therapeutic strategies within breast cancer management. MM-302, comprising a HER2-targeted liposomal entity encompassing 45 anti-HER2 antibodies and 20,000 doxorubicin molecules [has evinced synergistic effects in combination with trastuzumab within breast cancer xenograft models (60).

5.1 Bispecific Antibodies:

Bispecific antibodies (BsAb) are immunoglobulins that bind concurrently to two disparate antigens present on either the same or distinct molecules. The biologic activities of BsAbs are executed through their Fab and Fc regions, encompassing complement-dependent cytotoxicity (CDC), antibody-dependent cell-phagocytosis (ADCP), antibody-dependent cellular cytotoxicity (ADCC), the hindrance of signal transduction via interaction with membrane-bound receptors, and the instigation of apoptosis. Bispecific antibodies (BsAb) are immunoglobulins that bind concurrently to two disparate antigens present on either the same or distinct molecules. The biologic activities of BsAbs are executed through their Fab and Fc regions, encompassing complement-dependent cytotoxicity (CDC), antibody-dependent cell-phagocytosis (ADCP), antibody-dependent cellular cytotoxicity (ADCC), the hindrance of signal transduction via interaction with membrane-bound receptors, and the instigation of apoptosis his section pertains to certain exemplars of BsAbs (61).

5.2. Zanidatamab (ZW25):

Zanidatamab constitutes a bispecific antibody grounded upon the molecular frameworks of pertuzumab and trastuzumab. The unique architecture of ZW25 engenders dual binding to the designated domains within the HER2 molecule (62). ZW25 surpasses trastuzumab in terms of robust engagement with neoplastic cells,

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thereby curbing cellular proliferation, instigating receptor internalization, and orchestrating the downregulation of HER2 expression within various HER2-expressing tumor contexts, including HER2-positive and HER2-low breast malignancies (63). The clinical inquiry into ZW25 (NCT02892123) has meticulously assessed the maximal tolerated dose and optimal dosing regimen in patients afflicted with solid tumors exhibiting HER2 overexpression (64). Presently, numerous trials are underway, exploring ZW25 within diverse clinical scenarios, encompassing early-stage breast cancer (NCT05035836) and advanced breast carcinoma in conjunction with palbociclib and fulvestrant (NCT04224272). Additionally, evaluations involving ZW25 combined with anti-CD47 interventions in HER2-positive solid tumors, encompassing both HER2-overexpressing and HER2-low breast cancers, are actively ongoing (NCT05027139).

5.3. MBS301:

The architecture of MBS301 is derivative of the fusion of trastuzumab and pertuzumab. Experimental in vivo assessments have unveiled the heightened antineoplastic effects of MBS301, with the suppression of fucosylation further accentuating ADCC in comparison to the discrete monoclonal antibodies (65). A phase 1 clinical trial is presently in progress, enrolling individuals with malignant HER2-expressing solid tumors (NCT03842085).

5.4. Zenocutuzumab (MCLA-128):

Zenocutuzumab assumes a distinctive role, not only intercepting HER2/HER3 signalling pathways (66) but also galvanizing tumor obliteration through ADCC (42), inclusive of instances characterized by An ongoing phase 1 investigation is presently focused on dose escalation, tolerability, safety, and the antineoplastic activity of zenocutuzumab in NRG1 fusion-positive malignancies (NCT02912949). Additionally, a phase 2 trial is scrutinizing the potential of HER2-low cellular lines (67) or cellular lines harboring limited CD16 affinity (68). Zenocutuzumab in synergy with chemotherapy, trastuzumab, and endocrine therapy for HER2-low and estrogen receptor-positive breast carcinomas, respectively (NCT03321981). Noteworthy outcomes from this study have demonstrated efficacy within patients suffering from metastatic HER2-positive breast carcinoma (48).

Table-2 Bispecific Antibodies:

Drug	Clinical-Trial Identifier	Combination with	Population
Zanidatamab (ZW25)	NCT05035836 NCT02892123 NCT04224272 NCT05027139	 Chemotherapy Palbociclib and fulvestrant Anti-CD47	Early HER2+ breast cancer HER2-expressing solid tumours Advanced HER2+ breast cancer Solid HER2+ tumours including the HER2-low breast cancer
MBS301	NCT03842085		Malignant HER2-expressing solid tumours
Zenocutuzumab (MCLA-128)	NCT03321981	Trastuzumab and chemotherapy or trastuzumab and vinorelbine	HER2-low breast cancer and metastatic HER2+ breast cancer that progressed to T-DM1 treatment
MM-111	NCT01097460 NCT00911898	Trastuzumab	Advanced HER2 amplified and heregulin-positive breast cancer Advanced, refractory HER2 A\amplified and hereguli positive cancers

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5.5.MM-111:

MM-111 is a representative of bispecific antibodies targeting both HER2 and HER3, effectively suppressing the activation of HER3 and PI3-K signalling cascades (69). Preclinical models have attested to the antineoplastic consequences of its combination with trastuzumab or lapatinib (47). In a phase 1 clinical trial, a clinical benefit rate of 55% was observed across HER2-positive solid tumours (70). Although subsequent investigations have been completed, outcomes remain pending (NCT01097460 and NCT00911898).

The realm of bispecific antibodies is rapidly advancing, as evidenced by the multitude of antibodies being harnessed and evaluated across clinical and preclinical paradigms. The imminent culmination of ongoing clinical trials possesses the potential to reshape the therapeutic management of individuals grappling with HER2-positive breast carcinoma.

6.Tyrosine kinase inhibitors:

Tyrosine kinase inhibitors (TKIs) represent a class of diminutive bioactive compounds aimed at obstructing the activity of protein tyrosine kinases, pivotal mediators of signal transduction orchestrating the governance of various cellular, physiological, and biochemical cascades. By competitively binding to the adenosine triphosphate (ATP) binding site within the tyrosine kinase receptors. TKIs impede the downstream propagation of signaling events (71). In this context, TKIs manifest the capacity to impede cellular proliferation, migration, and invasiveness, while instigating apoptosis. Owing to their molecular dimensions, TKIs possess an enhanced ability to traverse the blood-brain barrier when juxtaposed with alternative therapeutic agents targeted against human epidermal growth factor receptor 2 (HER2), such as monoclonal antibodies or antibody-drug conjugates (72). Within the purview of this discourse, our deliberation encompasses extant TKIs utilized within clinical practice alongside emerging inhibitory agents that have demonstrated efficacy within preclinical and clinical trial settings, thus affording novel therapeutic avenues.

6.1. Lapatinib:

Lapatinib, the vanguard TKI sanctioned for the management of breast malignancies typified by elevated or diminished HER2 expression, embodies a reversible diminutive molecule inhibitor designed to counteract the activity of epidermal growth factor receptor (EGFR/HER1) and HER2. By impeding receptor phosphorylation, Lapatinib curtails the activation of mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3-K) pathways, culminating in the attenuation of cellular proliferation (58). The NeoALTTO clinical trial substantiated that the concurrent application of trastuzumab and lapatinib during the neoadjuvant phase conferred heightened pathological complete response (pCR) rates among HER2+ breast cancer patients; however, discernible discrepancies were not observed concerning overall survival and disease-free survival (73),(74). Notably, Lapatinib has demonstrated the ability to traverse the blood-brain barrier, resulting in a diminution of cerebral metastatic occurrences, as affirmed by the EGF105084, LANDSCAP, and CEREBEL (75),(76) clinical investigations. Presently, Lapatinib is not accorded approval for employment in the neoadjuvant setting.

Table-3 Tyrosine kinase inhibitors:

Drug	Combination with	Description	Clinical Trial Identifier	Population
Neratinib		Targeting EGFR/ERBB2 With Neratinib in Hormone Receptor (HR)-Positive/HER2-negative HER2-enriched Advanced/ Metastatic Breast Cancer (NEREA)	NCT04460430	Advanced/ Metastatic
Epertinib (S-222611)		Reversible pan-HER inhibitor	2013-003894-87	HER2+ tumors
Tucatinib	T-DM1	Selective and reversible HER2 inhibitor with minimal inhibition of EGFR/HER1	NCT04457596, NCT03975647, NCT01983501, NCT05323955	HER2+ breast cancer
DZD1516	Trastuzumab and	Selective HER2 inhibitor	NCT04509596	Metastatic HER2+ breast cancer

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	capecitabine or T-DM1			

6.2. Epertinib (S-222611):
Epertinib, a reversible pan-HER inhibitor, manifests heightened pharmacological potency relative to lapatinib in both in vitro and in vivo contexts (77). Noteworthy accomplishments encompass the favorable outcomes elicited within an HER2+ brain metastasis model [96]. Epertinib's pharmacokinetic and pharmacodynamic attributes have undergone scrutiny in a phase 1 clinical study involving patients harboring solid tumors including those characterized by HER2+ phenotypes. This inquiry substantiated Epertinib's commendable tolerability, safety profile, and the induction of efficacious antineoplastic effects.

6.3. Neratinib is a whispered administered pan-HER Tyrosine Kinase Inhibitor, that exhibits irreversible binding affinity towards HER1, HER2, and HER4. The agent exhibits the ability to surmount innate or acquired trastuzumab resistance in models of HER2 breast cancer, as evidenced by previous research (78). In 2020, FDA granted approval- for the use of neratinib combination with capecitabine for metastatic patients, who have undergone prior treatment with HER2-targeted medications (79). Neratinib exhibits favourable central nervous system (CNS) permeability and exhibits encouraging therapeutic efficacy. According to a study, the use of neratinib as a monotherapy may offer certain therapeutic advantages. Nonetheless, its effectiveness is more apparent when used in conjunction with capecitabine (80). Ongoing clinical trials are also assessing its usefulness when combined with other treatments, such as fulvestrant (NCT03289039 and NCT01670877, exclusively, patients with HER2 mutations).

6.4. Tucatinib- is an orally administered and amendable inhibitor which exhibits over thousands-fold specificity for HER-2 as compared to EGFR, thereby demonstrating a decreased incidence of EGFR-related toxicity. The preclinical investigations exhibited robust antineoplastic efficacy in HER2- overexpressing malignancies when employed as a solitary agent and in conjunction with trastuzumab (81). When combined with CDK4/6 inhibitors or hormone treatment, it caused tumour regression in xenograft models of HER2 cancer (82). The triple combination of Tucatinib, Capecitabine, Trastuzumab and were granted acquiescence by FDA, in April 2020 for advanced disease patients who had experienced progression following prior anti-HER2 treatments. This information is supported by reference (83). Several clinical trials are currently underway to evaluate the efficacy of tucatinib in different drug combinations, including chemotherapy, T-DM1 (clinical trial identifiers: NCT04457596, NCT03975647, NCT01983501, and NCT05323955) and T-DXd (clinical trial identifiers: NCT04539938 and NCT04538742), along with letrozole (an aromatase inhibitor), palbociclib (a CDK4/6 inhibitor), and Pembrolizumab (an immunotherapy agent), are under investigation in a variety of phases. These clinical trials span different developmental stages.

6.5. DZD1516.
DZD1516, is characterized as a reversible and selective HER2 inhibitor, exhibited regression of tumours in preclinical models of breast cancer, including brain metastases. A phase 1 clinical trial (NCT04509596) is currently underway to assess the impact of DZD1516 in combination with trastuzumab and capecitabine or with T-DM1. Initial findings suggest that DZD1516 has the ability to effectively traverse the blood-brain barrier and boasts a favourable safety profile (84).

7. HER2-Targeted Interventions:
Immunomodulatory Strategies: A plethora of interventions directed towards HER2, orchestrated with precision, hinge upon monoclonal antibodies as vehicles for therapeutic application. Efficacy of these interventions is contingent upon the orchestration of Antibody-Dependent Cellular Cytotoxicity (ADCC) and Antibody-Dependent Cellular Phagocytosis (ADCP). Within the realm of HER2-positive breast cancer therapeutic paradigms, ADCC is prompted through the coupling of CD16 or FcγRIII on Natural Killer (NK) cells with the Fc region of trastuzumab—a moiety that has previously recognized the HER2 entity on malignant cells. This interaction serves as the harbinger, instigating the liberation of granules replete with granzymes and perforins from NK cells to the immunologic synapse. The net result of this intricate sequence is the termination of the cancer cell. An innovative avenue involves the interception of the suppressive cues generated by the interplay between HLA-E and NKG2A. Monalizumab, an IgG4 monoclonal antibody targeting NKG2A, represents a novel tactic under scrutiny in clinical trials (85). A paradigmatic instance is the MIMOSA trial—a phase 2 exploration aiming to enroll 38 subjects afflicted with metastatic or locally incurable HER2-positive breast cancer. These individuals shall receive combined treatment encompassing monalizumab and trastuzumab. The landscape of oncological therapeutics has been irrevocably transformed by the advent of strategies employing antibodies to reinvigorate the immune response against malignancies. Noteworthy among these are antibodies directed against PD-1, expressed in T cells, and its ligand, PD-L1, present in neoplastic cells.

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This class of antibodies interdicts the molecular signals that precipitate T cell exhaustion.
PD-L1, a cogent participant in this interplay, is also expressed in Antigen-Presenting Cells (APCs), and it can dimerize with the costimulatory molecule CD80 on the same cellular milieu, consequently modulating the PD-1/PD-L1 liaison (86).

7.1. Pembrolizumab,
an exemplar of clinical efficacy, bears the imprimatur of FDA endorsement for the treatment of metastatic and high-risk early-stage Triple-Negative Breast Cancer (TNBC). The ensuing discussion encapsulates the salient outcomes of these trials. Pembrolizumab, a humanized IgG4k monoclonal antibody, intricately immobilizes the PD-1 receptor, thus inhibiting the PD-1 interaction with its cognate ligands, PD-L1 and PD-L2 (87). Pioneering clinical investigations have been embarked upon to elucidate the potential synergism between trastuzumab and pembrolizumab against refractory HER2-positive advanced breast cancer, typified by the PANACEA trial. Additionally, the NCT03032107 trial orchestrated the amalgamation of pembrolizumab with T-DM1. The study cohort, consisting of 20 metastatic breast cancer subjects, showcased previous trastuzumab and pertuzumab exposure but remained untouched by T-DM1. Notably, the objective response rate amounted to 20%, with no discernible correlation between PD-L1 expression and therapeutic retort (88).

7.2. Durvalumab
Durvalumab,a wholly human IgG1κ monoclonal antibody, exerts its influence by targeting PD-L1. Its synergy with trastuzumab was scrutinized within the phase 1 CCTG IND.229 clinical trial, encompassing a cohort of 14 HER2-positive metastatic patients marked by PD-L1 negativity in their neoplastic cells. Albeit the alliance demonstrated safety, discernible objective responses remained elusive.

Table-4 HER-2 targeted interventions:

Type of Study	ID	Status	Population	No. Patients	Treatment
Pembrolizumab Antibody					
Phase 1b	NCT03032107	Active, not recruiting	MetastaticHER2+ breast cancer	27	Pembrolizumab + T-DM1
Phase 2 open-label, randomized	NCT03747120	Recruiting	Naive patients with invasive human HER2+ breast cancer whose primary tumors are > 2 cm and/or clinically lymph node-positive	174	Neoadjuvant trastuzumab, pertuzumab, and paclitaxel Arm A: trastuzumab+ pertuzumab+ paclitaxel, Arm B: trastuzumab+ pertuzumab+ paclitaxel+ pembrolizumab or ArmC: trastuzumab+ pembrolizumab+ paclitaxel
Phase 1/2	NCT03272334 Breast-47	Recruiting	Metastatic HER2+ breast cancer	33	Pembrolizumab administered in combination with HER2 and CD3 bispecific antibody armed activated T cell (BATs) infusions
Durvalumab					
Phase 1b/2, open labal	NCT04538742 DB-07	Recruiting	Metastatic HER2+ breast cancer	450	Trastuzumab Deruxtecan(T-DXd) in

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					Combination with Other Anti-cancer Agents
Phase 1, open label	NCT02649686 CCTG IND.229	Completed	Metastatic HER2+ breast cancer receiving trastuzumab	15	Durvalumab+ trastuzumab
Atezolizumab					
Phase 3, doble blind	NCT04740918 KATE3	Recruiting	Locally advanced or metastatic HER2+ and PD-L1+ breast cancer who have received prior trastuzumab- (+/− pertuzumab) and taxane-based therapies	320	Atezolizumab and T-DM1 Arm A: T-DM1 + placebo, Arm B: T-DM1 + atezolizumab
Phase 2, double blind	NCT02924883 KATE2	Completed	Locally advanced or metastatic HER2+ breast cancer	133	Atezolizumab and trastuzumab-emtansine (T-DM1) Arm 1: T-DM1+ atezolizumab, Arm 2: T-DM1+ placebo
Phase 1, open label	NCT02605915	Completed	HER2+ and HER2− breast cancer	98	Atezolizumab + T-DM1 or with trastuzumab and pertuzumab (with and without docetaxel) in patients with HER2+breast cancer and atezolizumab+ doxorubicin and cyclophosphamide in HER2− breast cancer
Phase 2, open label	NCT04759248 ATREZZO	Recruiting	Advanced/metastatic HER2+ breast cancer	110	Atezolizumab+ trastuzumab+ vinorelbine
IMM2902 (HER2/SIRPα Bispecific mAb-Trap Antibody-receptor Fusion Protein)					
Phase 1, open label	NCT05076591	Recruiting	Advanced solid tumors HER2+	135	IMM2902, dose escalation
Avelumab (anti PD-L1 antibody)					
Phase 1, open label	NCT01772004 JAVELIN solid tumour	Completed	Metastatic or locally advaced solid tumours	1756	Avelumab monotherapy to 26 HER2+ breast cancer [21
Phase 2, open label	NCT03414658 AVIATOR	Recruiting	Advanced HER2+ breast cancer	100	Trastuzumab+ vinorelbine with avelumab or avelumab+ utomilumab (anti CD137)

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7.3. Atezolizumab,

Atezolizumab, an engineered humanized IgG1κ immunoglobulin monoclonal antibody, precipitates PD-L1 entrapment, thereby disrupting its interactions with PD-1 and CD80. An intricate matrix of trials, including KATE and IMpassion050, were instrumental in gauging the potential of atezolizumab. KATE, an engineered humanized IgG1κ immunoglobulin monoclonal antibody, precipitates PD-L1 entrapment, thereby disrupting its interactions with PD-1 and CD80 (89). An intricate matrix of trials, including KATE and IMpassion050, were instrumental in gauging the potential of atezolizumab. KATE, a phase 2 randomized, double-blind, placebo-controlled endeavour, encompassed 133 patients subjected to atezolizumab plus T-DM1 and 69 counterparts receiving T-DM1 supplemented by a placebo. Stratification based on PD-L1 positivity, deemed viable at 1% or more of infiltrating immune cells expressing PD-L1, was instrumental in elucidating improved outcomes. IMpassion050, a phase 3 trial, probed the impact of atezolizumab, in conjunction with dose-dense chemotherapy and trastuzumab trastuzumab plus pertuzumab, on high- risk early breast cancer.(90)

Intricately woven into the fabric of scientific exploration are initiatives aimed at the tandem attenuation of HER2 signalling and the rekindling of T cell functionality within the Tumour Microenvironment (TME). Notably, a phase 1 clinical trial (NCT05145179) is poised to be initiated in 2021. A notable stride involves the creation of Bispecific Antibodies (BsAb), epitomized by anti-HER2×PD1. This hybrid entity, forged by merging anti-PD-1 antibody (SSGJ-609A) and trastuzumab, demonstrates promising in vitro and in vivo antineoplastic efficacy. This innovation not only reactivates T cells and foments ADCC for the eradication of HER2-expressing tumour cells, but also cements a linkage between tumour cells and T cells, thus precipitating an immunological synapse capable of engendering tumour elimination bereft of antigen presentation (90).

8. HER2-Targeted Immunogens:

The emergence of HER2-targeted immunogens has engendered novel contemplations regarding vaccination as an innovative therapeutic modality within HER2-positive breast carcinoma (91)

Immunogens offer distinct advantages relative to conventional cancer treatments, such as anti-HER2 immunotherapy utilizing monoclonal antibodies, encompassing heightened tolerability, diminished toxicity, and the establishment of enduring immune responses with a specific focus on tumors (92). Immunogens necessitate infrequent administration intervals (93). A novel immunogen was devised exploiting an alpha viral vector encoding a segment of HER2 (VRP-HER2), and it underwent assessment within a phase 1 clinical trial, wherein its favorable tolerance profile was affirmed without the manifestation of dosage-constraining toxicity. Analysis conducted prior to and following immunization of peripheral blood mononuclear cells unveiled the proliferation of a memory CD8+ T cell subpopulation expressing HER2 within a subset of patients and a rise in the prevalence of HER2-specific polyfunctional antibodies. The expanded presence of HER2-specific memory T cells correlated with heightened, progression-free survival in this study. These findings substantiate subsequent endeavors combining this immunogen with immune checkpoint inhibitors (ICIs), such as anti-PD1, for the enhanced engagement of expanded T cell populations (94). A phase 2 investigation is currently underway, wherein participants receive VRP-HER2 immunizations concomitant with pembrolizumab (NCT03632941).

Alternate viewpoints suggest that the limited success of cancer immunogens stems from clinical trials targeting advanced stages of the disease, characterized by maximal tumor burden and marginal efficacy of standard therapies (95). Consequently, an immunogen was trialed during this disease stage. The regimen entailed the activation of dendritic cells (DCs) through cytokines and clinical-grade bacterial LPS to stimulate a distinctive array of chemokines and cytokines, such as IL-12, capable of priming T cells for superior antitumor immune responses and sustained memory (NCT02063724) (96). The administration of these DCs to patients exhibiting ductal carcinoma in situ (DCIS) transpired within the neoadjuvant context, directed at combating the early disease stage. The immunogen accomplished substantial success in provoking robust, persistent immune responses, ultimately culminating in the reduction or elimination of HER2/neu expression in the majority of vaccinated patients (97).

Another avenue presently under phase 1 clinical evaluation involves a plasmid DNA immunogen encoding the intracellular domain of HER2 in advanced HER2-positive breast cancer patients. Immunogens designed to bolster HER2-specific T-helper cell counts hold potential to elicit HER2 immunity within a majority of patients, eliciting a clinical response (98). The potential failure of HER2-targeted immunogens may be attributed to their design, particularly those tailored to induce CD8+ T cell activation through short epitopes, which may curtail responsiveness to a limited subset of HLA types and confer transient immunity (99). Disis et al. have demonstrated that immunization with a 100-µg dose of the HER2 intracellular domain plasmid-based immunogen yielded the generation of HER2-specific Th1 cells across a substantial portion of patients with HER2-expressing breast cancer; this immunogen is presently undergoing assessment within a randomized phase 2 trial (100). Lastly, an investigation within

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patients harbouring HER2-low tumours merits attention, notwithstanding outcomes contrary to initial projections, as it offers pertinent insights. Passive immunotherapy or monoclonal antibodies have demonstrated inefficacy in HER2-low tumours, suggesting the potential utility of active immunotherapy or HER2-targeted immunogens for this subgroup. Capitalizing on this premise, a HER2-derived peptide.

immunogen encompassing nelipepimut-S (NPS) was devised and synergistically combined with granulocyte-macrophage colony-stimulating factor (GM-CSF) as an immunoadjuvant. Preclinical data indicate synergism between HER2-targeted peptide immunogens and trastuzumab (101). This inquiry marks the inaugural randomized trial scrutinizing the amalgamation of trastuzumab with immunization within the adjuvant context, underscoring the need for continued exploration to ascertain optimal dosing, immunization schedules, administration routes, and immune augmentation methods to achieve maximal immunogen efficacy.

9. Extracellular Vesicles (Exosomes):

Exosomes have garnered recognition as pivotal mediators facilitating intercellular exchange of materials and information (102). Additionally, exosomes have exhibited the capacity to surmount drug resistance across heterogeneous cancer cell populations, thereby influencing the efficacy of therapeutic interventions for diverse cancer types (103). Consequently, harnessing exosome-based strategies emerges as a promising avenue for managing HER2-positive breast cancer. Wang et al. have pioneered HER2-specific exosome-T cell immunogens (HER2-Texo), employing active polyclonal CD4+ T cells capable of internalizing HER2-specific dendritic cell-released exosomes. Notably, HER2-specific exosome-T cell-stimulated cytotoxic T lymphocytes (CTLs) have demonstrated potent therapeutic efficacy against T47D, a HER2-positive breast cancer cell line. A distinctive facet of this novel exosome-T cell immunogen is its capacity to reverse the exhausted CTL phenotype. The ultimate aspiration involves fabricating a human therapeutic HER2/Neu-specific exosome-T cell immunogen employing autologous polyclonal T cells adept at internalizing HER2/Neu-specific autologous dendritic cell (DCHER2/Neu)- released exosomes, thereby constituting a personalized breast cancer vaccine (104).

Another intriguing avenue emerges from Han et al.'s investigation, which scrutinized a vital autophagy-regulating microRNA (miR-567) that impedes autophagy-mediated enhancement of cell susceptibility to trastuzumab within HER2-positive breast cancer cells. Autophagy is closely linked to the preservation of tumour cell viability under adverse conditions encompassing nutrient scarcity, chemotherapy, and radiation therapy(105). The investigation revealed diminished levels of miR-567 in trastuzumab-resistant patients relative to responders, with in vitro assays corroborating miR-567 downregulation within trastuzumab-resistant cells. Exosomal miR-567 holds promise as both a therapeutic target and a prognostic indicator within HER2-positive breast cancer patients due to its pivotal role in reversing trastuzumab resistance through autophagy modulation (106). Furthermore, the unique attributes of exosomes, marked by their non-toxic, non-immunogenic, biodegradable, and orientable nature, render them an attractive vehicle for gene targeting (107). By engineering exosome-producing cells, ligands can be expressed and fused with exosomal surface proteins, thus enabling precise targeting of cancer cell receptors HER2-positive breast cancer cells were successfully targeted using modified exosome-producing HEK293T cells transduced with a lentiviral vector bearing the LAMP2b-DARPin G3 chimeric gene. Stable HEK293T cells facilitated the production of DARPin G3 on exosomal surfaces, imparting specific binding to HER2 and facilitating the delivery of short interfering RNA molecules against TPD52 into the SK-BR-3 cell line, culminating in gene expression downregulation (108). This study introduces a novel avenue for streamlining gene therapy and drug delivery to tumour cells, thereby broadening the spectrum of options available for gene.

10. Conclusion:

The objective of, our review is to facilitate - fundamental biology and a comprehensive overview of the her-2, its downstream signalling pathways including PI3K/AKT/mTOR, CDK4/6 Inhibitors, Anti-her-2 treatment options, including their modes of action. We also want to discuss the most recent data about the clinical and safety profiles of ADCs used to treat HER2-positive breast cancer. The therapy options accessible to those with breast cancer that is HER2-positive have demonstrated a consistent increase in recent years. With a plethora of innovative strategies currently undergoing pre-research investigation or research validation. It’s anticipated that in upcoming days, the conventional Anti-her-2 Antibodies, tyrosine kinase inhibitors become superseded through more efficacious, pioneering therapeutic interventions such as antibody-drug conjugates and immunotherapy, vaccines, exosomes. resistance events impair the clinical benefit, indicating that the development of novel HER2-targeted therapies is not only desirable but also required. In this sense, there are more than 2000 clinical trials registered to date to evaluate new HER2-targeted therapies. Anticipated outcomes include the potential emergence of novel mechanisms of resistance in response to these pioneering agents. The therapeutic landscape for HER2+ cases can avail itself of a multitude of monoclonal

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antibodies targeting HER2, as well as HER2-targeted antibody-drug conjugates (ADCs), which have demonstrated considerable promise within the clinical milieu. Notably, T-DXd has ascended to the status of second-line therapy for patients with HER2+ breast carcinoma. Anticipated outcomes include the potential emergence of novel mechanisms of resistance in response to these pioneering agents. The therapeutic landscape for HER2+ cases can avail itself of a multitude of monoclonal antibodies targeting HER2, as well as HER2-targeted antibody-drug conjugates (ADCs), which have demonstrated considerable promise within the clinical milieu. Notably, T-DXd has ascended to the status of second-line therapy for patients with HER2+ breast carcinoma. Diverse novel tyrosine kinase inhibitors (TKIs) have been formulated and assessed, exhibiting enhanced adeptness in the management of patients afflicted by HER2+ breast cancer, thereby engendering paradigm shifts in clinical praxis.

An overarching complication within the realm of cancer pertains to the establishment of metastatic foci. Within this context, certain therapeutic modalities expounded upon in this manuscript have evinced efficacy within the metastatic milieu. These aforementioned endeavors collectively beckon the scientific community to partake in collaborative endeavors aimed at devising innovative HER2-targeted therapeutic strategies, alongside the orchestration of clinical trials exploring varied therapeutic amalgamations These initiatives bear the potential to surmount tumor progression and potentially hinder metastatic dissemination. Underscoring the significance of identifying novel biomarkers, prognostic of therapeutic responsiveness, becomes paramount in this context. Such endeavors will impart the capability to discern patient cohorts poised to derive optimal benefit from specific therapeutic regimens or combinatorial interventions, thereby proffering an optimal treatment course.

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