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REVIEW

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Anti-ErbB2 immunotherapeutics: struggling to make better antibodies for cancer therapy

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ABSTRACT

Over the past 3 decades, monoclonal antibodies and their related derivatives, including recently approved antibody-drug conjugates, conquered a central role in cancer therapy because of their contribution to improve survival, time to progression and quality of life of patients compared to chemotherapy protocols. This review summarizes information on approved original and biosimilar products, as well as investigational antibody-based therapeutics, targeting ErbB2. This target has been selected as a paradigmatic example because of its relevant role in sustaining the malignancy of major cancer diseases including, breast, gastric and other chemotherapy-resistant solid tumors. This work analyzes the drivers affecting research and development of next-generation anti-ErbB2 immunotherapeutics, taking into account unmet medical needs and pharmacoeconomic issues related to sustainability. The analysis may help with the design of future research and development strategies.

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Background

In the past three decades, monoclonal antibodies (mAbs) have changed the treatment landscape of inflammatory/autoimmune diseases and cancer. MAbs and their related derivatives, including antibody-drug conjugates (ADCs), have achieved remarkable success, becoming the fastest growing class of biopharmaceuticals with more than 80 products on the market. In 2018, George P. Smith and Gregory P. Winter were awarded the Nobel Prize in Chemistry for discovering the phage display technology, which provided a breakthrough in antibody selection.[1] The same year, James P. Allison and Tasuku Honjo were awarded the Nobel Prize in Physiology or Medicine for the development of the revolutionary cancer therapy unleashing the immune system toward the tumor, based on the use of antibodies against immune checkpoint inhibitors (ICPI).[2]

Currently, antibody therapeutics are entering clinical trials and are being approved, in record numbers. The investigational pipeline is robust, with more than 570 antibody therapeutics at various clinical phases, including 62 in late-stage clinical development. Interestingly, approximately half (18 of 33) of the late-stage pipeline therapeutics for cancer are immune checkpoint modulators or ADCs.[3]

Commercial exploitation of antibody therapeutics for cancer therapy is so appealing that several antibodies are competing for the same target, thus raising the need for head-to-head clinical studies to drive selection of the most suitable drug for each clinical indication.[4] Moreover, upon patent expiration of the oldest antibodies, and because of the pressure from health care systems dealing with sustainability issues deriving from the high costs of antibody treatments, several players invested in the development of biosimilars, which are now a reality.[5] On the other hand, innovative antibody treatments for cancer, particularly those under the umbrella of "ImmunoOncology products" including ICPI antibodies and ADCs, are gaining acceptance for their efficacy while adding to the problem of sustainability. In fact, the cost of these treatments can be more than $US100,000 per patient. Cost of treatments, coupled with high disease prevalence and the ever-expanding number of indications, means the overall costs are not affordable for most healthcare systems,[6] and particularly for poorer countries.[7] Therefore, cost-effectiveness analyses, which are built on Quality Adjusted Life Year (QALY) values (figures taking into account the quality of each added year of life) and on incremental cost-effectiveness ratio (ICER) (statistical value obtained from the difference in cost between two possible interventions divided by the difference in their effect), are increasingly becoming key drivers to research and development of next-generation immunotherapeutics.[8] This means that future products are expected to be more effective and less toxic than current ones to be reimbursed, and ultimately gain a meaningful place in the market. It is worth noting that the affordability concept is going to be very much affected by several economical/political elements that might be highly diverse in different countries, thus leading to different willingness-to-pay thresholds, which represent an estimate of what individual health care systems might be prepared to pay for the health benefit, given other competing demands on that health system resources.

This review deals with the effects of the need for innovation and sustainability on the development pathways of anti-ErbB2 immunotherapeutic products. This single tumor target has been selected as an example because ErbB2 is widely pursued, with a variety of approved and investigational products, making it a good model for analyzing sustainability-dependent development issues of antibody therapeutics. First, the review describes the development history of approved anti-ErbB2 immunotherapeutic

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products, and discusses sustainability issues affecting the adoption of such expensive treatments in different countries. The subsequent section explains how combined clinical and commercial success and costs of the original anti-ErbB2 products drove investments in the development of their biosimilars. In the last section, new investigational anti-ErbB2 drug candidates that have resulted from investments in the development of products with higher potency/reduced toxicity or those able to by-pass tumor resistance, in some cases exploiting new mechanisms of action, are discussed.

Anti-ErbB2 approved products

To date, four innovative anti-ErbB2 antibody-based therapeutics (Herceptin®, Perjeta® and Kadcyla® from Roche, and Enhertu® from Daiichi Sankyo) and 5 biosimilar products (Tables 1 and 2, respectively) have been granted marketing approvals. The first anti-ErbB2 antibody approved, trastuzumab, is a humanized immunoglobulin that targets the extracellular domain of the human epidermal growth factor receptor 2 (ErbB2, also known as HER2). Developed by Genentech and marketed by Roche as Herceptin®, trastuzumab is indicated for the treatment of ErbB2-overexpressing tumors, and it gained increasingly wide approval, with or without concurrent chemotherapy, starting with metastatic breast cancer and then moving to early breast and advanced gastric cancer. Each step in the trastuzumab product evolution has been driven by medical needs continuously weighed against cost-benefit assessments. Trastuzumab's first approval in 1998 was based on two Phase 3 studies. Study HO649g evaluated trastuzumab as second-line single agent treatment in 222 women who had relapsed after one or two cytotoxic chemotherapy regimens. In 16% of this poor prognostic patient population, trastuzumab induced a clinical response (partial or complete) with an average survival time of 16.4 and 8.8 months for ErbB2 3+ and ErbB2 2 + patients, respectively.[9] The clinical significance of the objective tumor responses was supported by quality-of-life data. In fact, responders had clinically meaningful improvements in physical, role, social functions and global quality of life during trastuzumab treatment, compared to non-responders.

Study HO648g assessed first line treatment in combination with chemo/paclitaxel in 469 women showing that the addition of trastuzumab to chemotherapy prolonged progression-free survival by three months (time to progression; 7.4 vs 4.6 months), increased tumor response rate (50% vs 32%), increased duration of response (9.1 vs 6.1 months).[9] Efficacy data, as well as safety issues, of trastuzumab were confirmed and extended in additional studies involving several thousands of patients and more than 8-year follow up.[9]

In 2013, the European Commission approved a trastuzumab subcutaneous formulation, and in February 2019, US Food and Drug Administration (FDA) also approved Herceptin Hylecta (trastuzumab and hyaluronidase-oysk), a new subcutaneous formulation for the treatment of patients with ErbB2-positive earl breast cancer (node-positive, or node-negative and estrogen receptor/progesterone receptor-negative or with one high-risk feature) in combination with chemotherapy and ErbB2-positive metastatic breast cancer in combination with paclitaxel or alone in people who have received one or more chemotherapy regimens for metastatic disease. Approval of the trastuzumab subcutaneous formulation was supported by clinical data showing advantages for both patients and caregivers compared to the intravenous one, including substantial reduction of the time spent on drug administration for both patients and health care professionals, ultimately leading to meaningful savings on the overall costs of treatment.[10]

As Herceptin achieved product maturity, Roche started activities to reinforce trastuzumab anti-tumor efficacy and/or compliance (i.e., subcutaneous formulation) while putting in place strategies to mitigate the prospective competition from Herceptin biosimilars. In this context development of the second anti-ErbB2 antibody pertuzumab (Perjeta®) was initiated. Perjeta was approved based on one pivotal study involving 808 patients with previously untreated ErbB2-positive metastatic breast cancer. The effects of Perjeta, given together with trastuzumab and docetaxel, was compared with placebo. Patients were treated until their disease got worse or the side effects of treatment became unmanageable. Patients treated with Perjeta lived an average of 18.5 months without advancement of their disease, compared with 12.4 months for patients given placebo. Perjeta has also been studied in two pivotal studies involving a total of 642 patients with earlier stages of breast cancer who were to undergo surgery. In these studies, Perjeta was given with trastuzumab or chemotherapy or both. The studies evaluated how many patients responded to treatment (i.e., patients who had no cancer cells in the surgical tissue). In the first study, 46% of the patients treated with Perjeta plus trastuzumab and docetaxel responded to treatment, compared with 29% of patients who received trastuzumab and docetaxel alone.

Table 1. Anti-ErbB2 approved immunotherapeutics.

Brand Company	INN/ Drug code	Type of product	Approved indications	Year of first approval US	Year of first approval EU
Herceptin Genentech/ Roche	Trastuzumab	Humanized IgG1/k	Metastatic breast Early breast Metastatic gastric	1998	2000
Perjeta Genentech/Roche	Pertuzumab/ 2C4, R1273	Humanized IgG1/k	Metastatic and early breast add-on to trastuzumab and chemo	2012	2013
Kadcyla Genentech/ Roche	Trastuzumab-emtansine/ T-DM1	ADC	Metastatic breast relapsing after previous trastuzumab-including treatments. Adjuvant therapy in early breast with a residual disease after neoadjuvant chemo plus trastuzumab	2013	2013
Enhertu Daiichi Sankyo AstraZeneca	Fam-trastuzumab-deruxtecan-nxki DS8201	ADC	Metastatic breast relapsing after previous trastuzumab-including treatments	2019	

Source: EMA and FDA web sites.

Response to treatment in the second study ranged from 57% to 66% where Perjeta was given with trastuzumab and chemotherapy.[11]

Clinical efficacy of trastuzumab translated into its commercial success with sales of Herceptin that topped, for more than 14 years, about 7 billion/year, representing one of the most valued biotechnology-derived products.[12]

Pharmacoeconomic analyses have constantly monitored the cost-effectiveness of Herceptin for its specific indications to orient prescription policies of healthcare systems. Particularly, the cost-effectiveness of trastuzumab as adjuvant therapy for early breast cancer was evaluated in a systematic review of 13 studies selected from among more than 239 published papers dealing with QALY values about the trastuzumab use in developed countries. This analysis indicated that trastuzumab 1-year treatment of early breast cancer may be cost-effective.[13]

It is worth noting that differential pricing of innovative/expensive drugs is recommended by the World Health Organization to secure affordable medicines for countries with different purchasing power. Nevertheless, in developing countries innovative drugs often have similar or even higher prices than in high-income countries. Evaluation of trastuzumab global pricing in terms of coverage and accessibility for patients with breast cancer was evaluated in Latin America. From this analysis, the price of trastuzumab would need to decrease by up to about 95% for the drug to become cost-effective.[14] Similarly, a cost-effectiveness analysis performed in Iran of 1-year trastuzumab adjuvant chemotherapy for early breast cancer, estimating outcomes, coverage and costs over a 20-year period, concluded that the treatment would not be cost-effective in this country.[15] The same conclusion was reached in a pharmacoeconomic study evaluating the addition of trastuzumab to standard chemotherapy in patients with advanced gastric cancer in China.[16]

On the other hand, 1-year trastuzumab adjuvant chemotherapy for early breast cancer has been found cost-effective in Taiwan where, since 2010, the national health system (NHS) started to reimburse the treatment, having fixed a willingness-to-pay threshold at 3-times the per capita gross domestic product.[17] In this same country, a study estimated that the addition of pertuzumab to trastuzumab, as first-line treatment for metastatic breast cancer, would be cost-effective only under favorable drug cost assumptions.[18]

Coping with willingness to pay also affected the fate of the third anti-ErbB2 product of Roche, ado-trastuzumab emtansine (T-DM1; Kadcyla®). This product was also generated with the aim of improving anti-tumor efficacy of previous anti-ErbB2 products while also aiming at a softer landing upon patent expirations. Although clinical trials demonstrated that T-DM1 significantly increased median progression-free and overall survival compared to chemotherapy in patients with advanced breast cancer relapsing after trastuzumab and a taxane, an analysis taking into account the costs of the therapies, major adverse events, laboratory tests, and disease progression, as well as indirect costs (productivity loss due to morbidity and mortality), and health utilities, obtained from published sources, estimated that the ICERs from the payer's perspective were about $200,000/QALY. From this analysis it was concluded that, for both payers and country, T-DM1 was not cost-effective in the US at a willingness-to-pay threshold of $150,000/QALY.[19]

Upon this kind of analyses, performed in Europe by the UK National Institute for Health and Care Excellence (NICE), Roche was invited to submit evidence of T-DM1 cost-effectiveness. As an independent Evidence Review Group (ERG), the School of Health and Related Research technology appraisal group at the University of Sheffield produced a critical evaluation of the company's submission to NICE. Following analysis, Roche reported a ICER for T-DM1 compared with lapatinib in combination with capecitabine of £ 167,236, the latter of which was estimated to have an ICER of £ 49,798 compared with capecitabine monotherapy. The ERG produced similar values of £ 166,429 and £ 50,620 respectively. The NICE Appraisal Committee concluded that, while the clinical effectiveness of T-DM1 had been proven, it was not likely to represent a cost-effective use of NHS resources and therefore its use could not be recommended.[20] Upon negotiation, in 2017 Roche established an agreement with NICE on a reduced price that brought T-DM1 within the range considered to be cost effective,[21] thus starting its routine use upon NHS funding.[22]

As a consequence of cost-effectiveness evaluations toward the willingness-to-pay of NHSs, which resulted in price reduction, Kadcyla never quite performed up to business expectations. When first approved in 2013, analysts projected peak sales up to $5 billion. In 2018, the product's sales were about $927 million, and it is not clear whether Kadcyla's use will be affected by recently reported data on T-DM1-induced resistance[23,24] and off-target toxicity.[25] Therefore, despite innovation brought by Perjeta and Kadcyla, Herceptin still remains the best-selling product for the treatment of ErbB2+ cancer, and, for this reason, several players continue to pursue development of trastuzumab biosimilar/biobetter products.

On December 20, 2019, trastuzumab deruxtecan (Enhertu®, DS8201), an ADC composed of trastuzumab conjugated to a topoisomerase I inhibitor (camptothecin analogue), was granted FDA accelerated approval. Enhertu was showed to be well tolerated and able to overcome T-DM1 resistance in pre-clinical models.[26,27] Clinical data indicated a manageable safety profile and preliminary efficacy in heavily pre-treated patients (including those relapsing after T-DM1 protocols) with breast and gastric cancer.[28–30] Enhertu's approval was based on the results of a clinical trial enrolling 184 patients with ErbB2-positive, unresectable and/or metastatic breast and gastric cancer. These patients were heavily pretreated, having received between two and 17 treatments prior to receiving Enhertu. The overall response rate to Enhertu was 60.3%, with a median duration of response of 14.8 months.[31]

Trastuzumab biosimilars

Biosimilars are biologic products that have been shown to be substantially similar in terms of quality, efficacy, safety and immunogenicity to an already approved reference biological product. Biosimilars have a good value proposition, as their adoption allows reduction of healthcare drug budgets, and potentially relocation of funds to new therapies. Price discounts can be as high as 60–90% of the originator price, depending on the product and country. As already discussed, trastuzumab is currently not accessible in poorer countries

Table 2. Trastuzumab biosimilars.

Brand/ code	Company	First approval	Update January 2020
Ontruzant SB3	Samsung Bioepis	2017	Approved USA, EU, Australia and Korea (as Samfenet) for breast and gastric indications. Marketing agreement with MSD in USA and with C-Bridge in China. On 2019 settled patent infringement case with Genentech.
Herzuma CT-P6	Celltrion	2018	Approved USA, EU, Korea, Japan and Brazil for breast and gastric indications. Marketing agreement with Teva in USA.
Ogivri MYL-1401O	Mylan/ Biocon	2018	Approved USA, Canada, EU, emerging markets and Australia for breast and gastric indications.
Kanjinti ABP980	Amgen	2018	Approved USA and EU for breast and gastric indications. Marketing agreement with Allergan.
Trazimera PF-05280014	Pfizer	2018	Approved USA, Canada and EU for breast and gastric indications. Licensing agreement with Genentech.

Source: Company's web sites and www.centerforbiosimilars.com.

because of its high cost. Therefore, the entry of more-affordable versions of trastuzumab could increase treatment access. Upon sustainability pressure, five trastuzumab biosimilars have been recently approved and ignited a fierce competition toward the originator (Table 2). The companies that engaged in the development of trastuzumab biosimilars adopted different development strategies aimed at winning the race to marketing authorization and/or to obtain higher acceptance from payers. Therefore, biosimilar comparability exercises were performed in different patient populations (i.e., metastatic or early breast cancer patients), adopting different trial end points (i.e., overall response rate or pathological complete response).[32] Two analyses of the treatment costs of biosimilars compared to originator antibodies in Italy and Japan pointed to a potential economic advantage of trastuzumab biosimilars of about 30–40%.[33,34] In another study, the impact on economic burden for treating cancer from a payer's perspective upon the introduction of the Herceptin biosimilar CT-P6 (Herzuma) in 28 European countries was analyzed. This analysis indicated budget savings in the billion range over the next 5 years. These savings could be used to extend access to expensive biologics across the European Union.[35]

As a major counteracting measure of biosimilar competition, at least in the major markets, Genentech/Roche developed Herceptin that could be administered by subcutaneous, rather than intravenous, injection. This shift should provide for preference-based selection of Herceptin over biosimilar products, as supported by data from prefHER study (ClinicalTrials.gov Identifier: NCT01401166), in which 86% of patients preferred subcutaneous Herceptin over intravenous administration.[36–38]

Anti-ErbB2 investigational products

Approved anti-ErbB2 products are multibillion-dollar drugs that, with the approval of trastuzumab biosimilars, will occupy increasingly wide positions in the therapeutic protocols of breast and gastric cancer worldwide. Nevertheless, because of the need to further improve efficacy and tolerability and respond to substantial pressure to reduce the costs of therapies, several players have put novel anti-ErbB2 investigational products in their research and development pipelines. Consequently, further changes will probably occur during the next decade in the management of metastatic ErbB2-positive cancer, as several new candidates hold promise and will challenge the drugs currently used.[39]

Most recent research and development efforts are directed toward the discovery of products that might eventually be able to complement and/or replace trastuzumab, including drug candidates with new mechanisms of action, higher potency, ability to by-pass tumor resistance and potentially lower costs of treatment. Information for publicly disclosed anti-ErbB2 investigational products are reported in the following tables. Candidates have been classified in three categories: a) alternative/improved trastuzumab (Table 3); b) alternative/improved T-DM1 (Table 4); c) new products/new mechanisms of action (Table 5).

Alternative/improved trastuzumab

As detailed in Table 3, margetuximab is an improved version of trastuzumab obtained by engineering the glycosylation of the immunoglobulin Fc in order to increase the antibody binding affinity to the Fc-receptor CD16A, thus leading to improved

Table 3. Anti-ErbB2 immunotherapeutics as alternative/improved trastuzumab.

Product	Company	Type of product	Effector moiety	Development stage	Intended improvement	Clinicaltrials.gov Jan 2020
Margetuximab	MacroGenics/ MSD	Trastuzumab biobetter	Fc glycoeng	Phase 2/3	Increased ADCC	7 studies 2 recruiting
TrasGex Timigutuzumab	Glycotope	Trastuzumab biobetter	Fc glycoeng	Phase 1	Increased ADCC	1 study completed
3E10	Laboratory of Antibody Medicine and Targeted Therapy, Shanghai, China	Human IgG	VH new epitope	Preclinical	Synergy with trastuzumab and pertuzumab	NA
H2-18	Second Military Medical University, Shanghai, China	Human IgG	VH new epitope	Preclinical	Overcoming trastuzumab resistance	NA
HuA21	Anhui Medical University, Hefei, China	Humanized IgG	VH new epitope	Preclinical	Overcoming trastuzumab resistance	NA

Source: Company's web sites, clinicaltrials.gov and PubMed.

Table 4. Clinical stage anti-ErbB2 ADCs as alternative/improved T-DM1.

Product	Company	Antibody/Effector moiety	Development stage	clinicaltrials.gov Jan 2020
SYD985	Synthon	Trastuzumab-duocarmazine	Phase 3	3 studies 1 completed
BAT8001	Bio-Thera	Trastuzumab-maytansine	Phase 3	3 studies
RC48	RemeGen	New antibody-MMAE	Phase 2	8 studies 1 completed
A166	Kluspharma	Undisclosed Mab and toxin	Phase 1/2	1 study
MEDI4276	MedImmune	Bispecific biparatopic-tubulysin variant	Phase 1/2	1 study completed
DHES0815A	Genentech	Engineered trastuzumab- pyrrolobenzodiazepine	Phase 1	1 study
ALT-P7	Alteogen	Trastuzumab biobetter-MMAE	Phase 1	1 study
ARX-788	Ambrx	New antibody-MMAF	Phase 1	2 studies
B003	Shanghai Pharm.	New antibody-DM1	Phase 1	1 study
LCB14-0110	LegoChem	Trastuzumab-MMAF	Phase 1	1 study
SHR-A1201	Jiangsu HengRui Medicine	Trastuzumab-undisclosed toxin	Phase 1	1 study
DP303c	CSPC Pharm.	New antibody-cytotoxic agent	Phase 1	1 study
ZW49	Zymeworks	Bispecific biparatopic antibody-auristatin	Phase 1	1 study
MT-5111	Molecular Templates	Recombinant immunotoxin Shiga-like toxin	Phase 1	1 study

Source: Company's web sites and clinicaltrials.gov.

antibody-dependent cell-mediated cytotoxicity against tumor cells. The FDA granted margetuximab Fast Track designation for the treatment of patients with metastatic or locally advanced breast cancer who have previously been treated with anti-ErbB2 -targeted therapy. Preliminary results of a Phase 3 trial show that margetuximab outperformed trastuzumab in a head-to-head protocol.[40] To date, margetuximab is the most advanced antibody-based potential competitor/companion trastuzumab, and Biological License Application submission for margetuximab was announced December 19, 2019.

TrasGEX (timigutuzumab) is another antibody that has been glyco-optimized to enhance antibody-dependent cell-mediated cytotoxicity. In a Phase 1 dose-escalation study (NCT01409343), clinical benefit, without dose limiting toxicity, was observed in 15 of 30 patients.[41] Developed by Glycotope, the company is seeking a partnering to further clinical development of the drug.

Other new anti-ErbB2 antibodies directed toward new receptor epitopes are springing from academic research activities (Table 3). The human anti-ErbB2 antibody coded 3E10 has been shown to inhibit receptor heterodimerization, possibly by inducing major conformational changes and providing synergistic inhibition of ErbB2 when combined with trastuzumab and pertuzumab.[42] In the same fashion, the human antibody coded H2-18 recognizing an as yet untargeted epitope of the ErbB2 receptor was found to be able to circumvent trastuzumab resistance and to be more effective at inhibiting tumor growth than the combination of trastuzumab and pertuzumab in both in vitro and in vivo pre-clinical models.[43] HuA21 is a chimeric antibody targeted to subdomain I of the ErbB2 extracellular domain and it has been shown to markedly suppress the growth of trastuzumab-resistant cells.[44]

Alternative/improved T-DM1

Clinical-stage examples of investigational ADCs positioned as Kadcyla competitors are listed in Table 4. With the aims of overcoming T-DM1 resistance and reducing toxicity, SYD985 and BAT8001 are trastuzumab-based candidates that are the most advanced in clinical development. SYD985 is an ADC made of trastuzumab conjugated to a duocarmycin payload that causes irreversible alkylation of tumor cell DNA. This product has been shown to be effective also in low ErbB2-expressing tumor cells. In clinical trials, it induced partial response in 33% of patients whose tumors were resistant to T-DM1.[45] Based on these promising results, SYD985 obtained Fast Track designation from FDA.

BAT8001, comprising trastuzumab conjugated to maytansine, is proposed as an improved version of T-DM1 being constructed with a highly stable non-cleavable linker. A Phase 3 trial planning to start recruitment of approximately 410 patients in China (NCT04185649) was announced at the American Association for Cancer Research Annual Meeting last March 2019, after encouraging tolerability and efficacy results in more than 130 patients treated in Phase 1/2 studies.[46]

Several other ADCs are being investigated in Phase 1/2 clinical trials aiming at by-passing tumor resistance to the existing drugs and/or improving efficacy/toxicity ratios. RC48 is made of an antibody exhibiting higher ErbB2 affinity than trastuzumab, conjugated to monomethyl auristatin E, which, like the maytansinoids, is a tubulin disrupting agent. This drug was shown to be able to reduce or stabilize urothelial cancer in more than 90% of heavily pre-treated patients.[47] ADC A166, with a composition that has not been disclosed, is currently being investigated in patients with low and high ErbB2-expressing tumors who relapsed after previous treatments (NCT03602079). MEDI4276 is a bispecific antibody comprising the single-chain variable fragment (scFv) of trastuzumab, fused to the heavy chains of the second anti-ErbB2 antibody 39S (which binds to an independent ErbB2 domain), and conjugated to tubulysin.[48] A Phase 1/2 study (NCT02576548) of MEDI4276 in patients with select ErbB2-expressing advanced solid tumors has been completed.

In the ADC DHES0815A, a highly toxic pyrrolobenzodiazepine molecule was conjugated to trastuzumab. To improve stability of the conjugate, the toxin was linked to rationally designed cysteines introduced in the antibody by mutagenesis.[49] A Phase 1 study (NCT03451162) of DHES0815A in patients with ErbB2-positive breast cancer has a primary completion date of April 2020. At least two additional pre-clinical stage ADCs based on pyrrolobenzodiazepines are under development by Spirogen/MedImmune.

Table 5. Innovative anti-ErbB2 products/new mechanisms of action.

Product name/code	Company	Type of product	Development stage	Description	clinicaltrials.gov Jan 2020
KN026	Jiangsu Alphamab	Bispecific/biparatopic trastuzumab/ pertuzumab	Phase 2	Obtained by using Charge Repulsion Induced Bispecific (CRIB) technology	5 studies
ZW25	Zymeworks BeiGene	Bispecific/biparatopic trastuzumab/ pertuzumab	Phase 2 FTD	Obtained by using Azymetric technology	3 studies
Zenocutuzumab MCLA-128	Merus	Bispecific ErbB2/ErbB3	Phase 2	Full-length IgG bispecific antibody humanized and defucosylated using GlymaxX technology	3 studies
GBR-1302	Harbor BioMed Ichnos Sciences	Bispecific ErbB2/CD3	Phase 2	Obtained by using Glenmark's Bi-specific Engagement by Antibodies based on the T cell receptor (BEAT) technology	1 study
MBS301	Beijing Mabworks Biotech	Bispecific/biparatopic trastuzumab/ pertuzumab	Phase 1	Glyco-engineered bispecific consisting of two half antibodies	1 study
BCD-147	Biocad	Bispecific/biparatopic trastuzumab/ pertuzumab	Phase 1	Undisclosed technology	1 study
BTRC4017A RG6194	Genentech	Bispecific ErbB2/CD3	Phase 1	T cell-dependent bispecific	1 study
M802	Wuhan YZY Biopharma	Bispecific ErbB2/CD3	Phase 1	Obtained by using YBODY technology	1 study
NJH395	Novartis	Immunoconjugate	Phase 1	Immune stimulator antibody conjugate (ISAC), consisting of an anti-ErbB2 conjugated to TLR7 agonist	1 study
DF1001	Dragonfly Therapeutics	Trispecific ErbB2/2NK receptors	Phase 1	TriNKETs are trispecific antibodies directing NK cells toward tumor cells	1 study
ADC-PEG-AuNP	Sydney University	Targeted nanoparticles	Preclinical	Trastuzumab-MMAE + HIV-TAT Gold nanoparticle	NA
Anti-ErbB2-DOX-NPs	Thonburi University Bangkok	Targeted nanoparticles	Preclinical	Anti-ErbB2-doxorubicin chitosan nanoparticle	NA
FHR4-based immunoconjugate	Luxembourg Institute of Health	Recombinant protein	Preclinical	Engineered immunoconjugate anti-ErbB2 antibody-FHR4 with increased CDC and phagocytosis	NA
Multiple constructs	Naples University	Bispecific-aptamers	Preclinical	Anti-EGFR/ErbB2/PDL1 constructs with increased cytotoxicity	NA
Multiple candidates	Alfasigma	Targeted delivery	Preclinical	AvidinOX-targeted biotinylated trastuzumab and/or pertuzumab exhibiting increased potency	NA
ST8176AA1	Alfasigma	ADC	Preclinical	Immunoconjugate trastuzumab-HDACi targeting epigenetic modulation	NA

Source: Company's web sites, clinicaltrials.gov and PubMed.

Other ADCs exploiting either an improved version (biobetter) of trastuzumab, new anti-ErbB2 antibodies, bispecific/biparatopic antibodies or new toxins are also listed in Table 4. These drug candidates are also being investigated in Phase 1 studies for treating patients resistant to T-DM1.

As an alternative to chemically conjugated ADCs, MT-5111 is a recombinant immunotoxin made of an anti-ErbB2 antibody genetically fused to the enzymatically active de-immunized Shiga-like toxin. This candidate is cytotoxic for both T-DM1 sensitive and T-DM1 resistant cell lines, and, because it recognizes a different epitope than trastuzumab, could be used in combination protocols. Moreover, because the MT-5111 cytotoxic payload is a large molecule, it is not expected to be subject to efflux mechanisms, potentially allowing this drug to be less affected by resistance phenomena (NCT04029922).

A recent review of the failures of some investigational ADCs, as well as the suspension of a few programs, points to technical hurdles encountered during the development of this type of product, and provides a view on the issues that might affect the design and development of next-generation ADCs for the treatment of ErbB2-expressing tumors.[50]

New products/new mechanisms of action

Widely diverse anti-ErbB2 drug candidates in early clinical or preclinical development stages are designed to bypass resistance, reduce toxicity or costs of approved anti-ErbB2 immunotherapeutics. Details regarding the drugs are provided in Table 5.

The clinical success of the combined use of trastuzumab and pertuzumab prompted several groups to initiate research and development activities aiming at the generation of drug candidates targeting two independent ErbB2 epitopes at the same time. Currently, two bispecific/biparatopic antibodies, incorporating the paratopes of trastuzumab and pertuzumab, are in Phase 2 clinical studies and two in Phase 1 clinical studies. KN026 was obtained by heterodimeric Fc engineering,[51] and showed encouraging clinical results particularly in patients with advanced gastric/gastroesophageal junction cancer. ZW25 biparatopic antibody, also generated by using a proprietary technology, showed excellent tolerability and considerable efficacy in breast and gastroesophageal cancer patients that had progressed after therapies that included trastuzumab, pertuzumab, and T-DM1.[52] Based on promising Phase 1 data, FDA granted ZW25 Fast Track designation for the treatment of patients with ErbB2-overexpressing gastroesophageal adenocarcinoma to be used in combination with standard-of-care chemotherapy.[53] ZW25 is currently being investigated in a multicenter, open-label Phase 2 clinical trial (NCT03929666) of patients with this disease.

MBS301[54] and BCD-147 (Phase 1 study NCT03912441) are also bispecific antibodies that include binding sites derived from trastuzumab and pertuzumab. MBS301 was genetically modified to knock out fucosylation, thus improving its binding to low affinity FcγR.[54] MBS301 is being evaluated in a Phase 1 study (NCT03842085) of patients with ErbB2-positive recurrent or metastatic malignant solid tumor, while the Phase 1 study of BCD-147 (NCT03912441) includes healthy volunteers.

Zenocutuzumab (MCLA-128) is an ErbB2/ErbB3 bispecific antibody able to inhibit the heregulin (HRG)/ErbB3 pathway via ErbB2-guided ligand blockade.[55] This antibody is being evaluated in a Phase 2 study (NCT03321981) of patients with metastatic breast cancer.

Moreover, there are several other bispecific/trispecific antibodies in clinical trials designed to activate T or natural killer (NK) cells against ErbB2-expressing tumors. GBR-1302 (ISB 1302) is bispecific ErbB2/CD3 antibody in a Phase 2 clinical trial in patients with metastatic breast cancer resistant to all known therapies (NCT03983395). The bispecific ErbB2/CD3 antibodies BTRC4017A (Phase 1 NCT03448042) and M802[56] are in clinical trials in heavily pre-treated patients. NJH395 and DF1001, which are both in Phase 1 studies (NCT03696771 and NCT04143711, respectively), aim at activating the immune system toward the tumor by delivering a Toll Like Receptor 7 agonist and directing NK cells, respectively.

ErbB2-targeted nanoparticles and immunoconjugates are pre-clinical-stage examples resulting from scientific and technological efforts to improve efficacy against cancer and exploit immune-related anti-tumor mechanisms. ADCs delivering gold nanoparticles are described as novel drug candidates with higher therapeutic index because of enhanced nanoparticle-dependent tumor permeability and retention.[57] A similar approach is reported with doxorubicin loaded nanoparticles.[58] An immunoconjugate incorporating factor H-related protein 4, a multivalent-positive regulator of the alternative complement pathway, has been shown to be active also in most complement- and phagocytosis-resistant tumor cell lines.[59] Novel human bispecific (anti-epidermal growth factor receptor (EGFR)/anti-ErbB2) aptamer (DNA oligonucleotide)-antibody conjugates have been recently described as innovative drug candidates being able to dramatically enhance tumor cell cytotoxicity.[60] ADCs that include anti-ErbB2 antibodies derived from synthetic antibody libraries are proposed as new powerful vectors for targeting toxic molecules to tumors.[61] Improved cytotoxicity toward tumor cells expressing low ErbB2 levels of an ADC made by using a pertuzumab engineered variant exhibiting increased lysosomal localization was recently reported. In pre-clinical tumor models, this ADC showed higher therapeutic efficacy than T-DM1.[62]

Attempts to uniquely improve trastuzumab efficacy are also coming from our group at Alfasigma SpA. From our long experience in tumor pre-targeting based on the exploitation of the avidin-biotin interaction,[63–69] we recently found that by anchoring biotinylated trastuzumab or pertuzumab to AvidinOX (modified avidin chemically reacting with tissue proteins)-treated tumor cells, antibody reactivity is increased by several orders of magnitude.[70] This peculiar phenomenon, which is related to the inhibition of the targeted receptor trafficking, could allow significant reduction of antibody doses with consequent reduction of toxicity and costs. Pre-clinical proof of concept of this principle has been previously obtained in models of head and neck[71] and aerosol therapy of lung cancer[72] with the anti-EGFR antibody cetuximab. Our

group also recently produced an ADC using trastuzumab to target epigenetic modulation to tumor cells. This ADC was obtained by conjugating a histone deacetylase inhibitor molecule to the antibody, and it was found able to induce upregulation of ErbB2 and estrogen receptors in triple-negative breast cancer (TNBC) cells thus representing an interesting therapeutic opportunity to make TNBC sensitive to standard therapies.[73]

Conclusions

Breast cancer is the most prevalent type of malignancy in women and the main cause of cancer-related death in females worldwide. Despite early detection programs and advances made in the therapeutic management, there is still a big portion of patients who will relapse and die from metastatic disease. ErbB2 is confirmed to be a key molecule in sustaining malignancy of breast, gastric as well as other solid tumors, particularly those becoming resistant to standard therapies. Therefore, anti-ErbB2 therapeutics are widely pursued due to both the medical need and the prospect of appealing business opportunities. Fierce competition and pharmacoeconomic issues are molding next-generation anti-ErbB2 products that consequently are expected to exhibit improved tolerability and efficacy and to be able to cope with NHS's sustainability.

Abbreviations

ADC	Antibody-drug conjugate
EGFR	Epidermal growth factor receptor
ERG	Evidence Review Group
FDA	Food and Drug Administration
mAb	Monoclonal antibody
ICPI	Immune Check Point Inhibitors
ICER	Incremental Cost-Effectiveness Ratio
NHS	National health system
NICE	National Institute for Health and Care Excellence
QALY	Quality Adjusted Life Year
TNBC	Triple-negative breast cancer

Disclosure of potential conflicts of interest

Publication of this review has been approved by Alfasigma SpA. The author has been leading research and development in the field of antibody and antibody-based therapeutics for more than 3 decades. Tumor pre-targeting is a major topic. Currently, author's group is dealing with trastuzumab-related projects that fit the investigational pipeline of anti-ErbB2 drugs discussed in this review.

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