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MONOGRAPH

TRASTUZUMAB EMTANSINE

USAN

Tumor-Activated Prodrug (TAP) Immunoconjugate
Oncolytic

PRO-132365
R-3502
RG-3502
T-DM1
Trastuzumab-DM1
Trastuzumab-MCC-DM1
Trastuzumab-mertansine

Immunoglobulin G_1, anti-(human p185neu receptor) (human-mouse monoclonal rhuMab HER2 γ1-chain), disulfide with human-mouse monoclonal rhuMab HER2 light chain, dimer, tetraamide with *N2*'-[3-[[1-[(4-carboxycyclohexyl)methyl]-2,5-dioxo-3-pyrrolidinyl]thio]-1-oxopropyl]-*N2*'-deacetylmaytansine

Immunoglobulin G_1, anti-(human receptor tyrosine-protein kinase erbB-2 (EC 2.7.10.1, p185erbB2, MLN 19 or CD340)); humanized mouse monoclonal rhuMab HER2 γ1 heavy chain (223-214')-disulfide with humanized mouse monoclonal rhuMab HER2 rhuMab HER2 rhuMab HER2 κ light chain, dimer (229-229":232-232")-bisdisulfide in which the 6-amino groups of an average of 3.5 lysine residues are amidified by 4-[[3-[[3-[[(1*S*)-2-[[(1*S*,2*R*,3*S*,5*S*,6*S*,16*E*,18*E*,20*R*,21*S*)-11-chloro-21-hydroxy-12,20-dimethoxy-2,5,9,16-tetramethyl-8,23-dioxo-4,24-dioxa-9,22-diazatetracyclo[19.3.1.110,14.0^{3,5}]hexacosa-10,12,14(26),16,18-pentaen-6-yl]oxy]-1-methyl-2-oxoethyl]methylamino]-3-oxopropyl]sulfanyl]-2,5-dioxopyrrolidin-1-yl]methyl]cyclohexylcarbonyl groups

CAS: 1018448-65-1
EN: 310997

SUMMARY

Trastuzumab emtansine (T-DM1) is a novel antibody–drug conjugate. The conjugate is comprised of the antibody trastuzumab, which is directed against the receptor tyrosine-protein kinase erbB-2 (HER2), a derivative of the cytostatic agent maytansinoid DM1 (mertansine), and a linker that covalently binds these components together. Preclinically, trastuzumab emtansine has shown significant antitumor activity in HER2-positive breast cancer cell lines and xenografts, including those resistant to trastuzumab or lapatinib. The pharmacokinetic profile is predictable, with minimal systemic exposure to free DM1. Phase I and II studies have demonstrated manageable toxicity. Phase II studies of trastuzumab emtansine monotherapy have shown response rates of 25-35% in patients with metastatic breast cancer who had previously received trastuzumab. Several combination regimens are under investigation. Phase III studies will help to define the role of trastuzumab emtansine within current treatment strategies.

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BACKGROUND

Worldwide, breast cancer is the second most common type of cancer and the fifth most common cause of death due to cancer. Overexpression of receptor tyrosine-protein kinase erbB-2 (HER2) occurs in approximately 20% of all breast cancers (1) and is predictive of poor prognosis and reduced survival (2, 3). Treatment guidelines recommend the use of HER2-directed therapies in early and metastatic HER2-positive breast cancer. Despite the impact of currently approved HER2-directed therapies, i.e., trastuzumab and lapatinib, most patients with HER2-positive metastatic breast cancer (MBC) will ultimately experience disease progression. Furthermore, although HER2 overexpression identifies patients who are likely to respond to HER2-directed therapy, patients' individual sensitivity to current HER2-directed therapies varies enormously and spans from effectual responsiveness over acquired insensitivity to complete resistance.

HER2 belongs to a family of cell-surface tyrosine kinase receptors known as the epidermal growth factor receptor (EGFR) family, or HER family, comprised of four members: epidermal growth factor receptor (receptor tyrosine-protein kinase erbB-1, EGFR), HER2 (erbB2, Neu), receptor tyrosine-protein kinase erbB-3 (HER3) and receptor tyrosine-protein kinase erbB-4 (HER4). Apart from their importance in normal human physiology, these receptors are implicated in many human cancers. Ligand binding to EGFR, HER3 and

HER4 causes the formation of homo- or heterodimers, initiating intracellular signal transduction. No known natural ligand exists for HER2, but evidence suggests that HER2 is the preferred dimerization partner for activation of the other HER receptors (4). Major pathways involved in signal transduction include phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), mitogen-activated protein kinases (MAPKs) and signal transducer and activator of transcription (STAT). These activation signals lead to changes in cell growth, differentiation, migration, adhesion, apoptosis and angiogenesis (5). HER2 3+ expression by standardized immunohistochemistry (IHC) methods or gene amplification demonstrated by fluorescent in situ hybridization (FISH) is necessary for likely benefit from HER2-directed therapies (6, 7).

Since its approval by the FDA in 1998, trastuzumab (Herceptin®; Genentech/Roche), a humanized anti-HER2 monoclonal antibody directed against the extracellular domain of HER2, has been the standard of care for HER2-positive primary breast cancer and first-line MBC. In the adjuvant setting, trastuzumab has been approved in combination with chemotherapy or as a single agent after anthracycline-based therapy. In this setting, the addition of trastuzumab reduces the risk of recurrence by approximately 50% (8).

Trastuzumab has also been approved for MBC in combination with chemotherapy or as a single agent after prior chemotherapy. In the pivotal trial by Slamon et al. (9), women with HER2-positive MBC were randomized to first-line chemotherapy (doxorubicin + cyclophosphamide or paclitaxel) ± trastuzumab. Adding trastuzumab to the chemotherapeutic regimens significantly increased response rate (RR) from 32% to 50%, median duration of response from 6 months to 9 months and overall survival (OS) from 20 months to 25 months. The optimal combination of trastuzumab plus chemotherapy has been an area of intensive clinical investigation. In general, vinorelbine- and taxane-containing regimens appear to be the most active, with RR ranging from 45% to 86% and a median duration of time to progression of 7-17 months. The activity of single-agent trastuzumab has been moderate, with RR ranging from 15% to 26% and a median duration of 9 months (10).

Lapatinib (Tyverb®, GW-572016; GlaxoSmithKline) is a dual tyrosine-protein kinase inhibitor of both EGFR and HER2. The use of lapatinib in combination with capecitabine in the second-line treatment of patients with HER2-positive MBC previously treated with trastuzumab, anthracyclines and taxane therapy has been established (11, 12). Lapatinib was approved by the FDA in 2007 in this setting. The compound has also been approved for the treatment of postmenopausal women with hormone receptor-positive, HER2-positive breast cancer in combination with an aromatase inhibitor (13).

In preclinical studies, tumor cells selected for resistance to trastuzumab continued to overexpress HER2 (14). Furthermore, several retrospective analyses have shown that, in patients progressing on trastuzumab-containing therapy, continuing trastuzumab alone or in combination with other cytostatic drugs was feasible and safe (treatment beyond progression) (15-18). Moreover, some articles have reported encouraging results. Few randomized studies have been launched evaluating this treatment strategy. Thus, it has proved extremely difficult to recruit patients to such trials. A phase III study randomized patients with HER2-positive MBC who had progressed on chemotherapy in combination with trastuzumab to capecitabine monotherapy or capecitabine in combination with (continued) trastuzumab. Accrual to this study stopped prematurely because of slow accrual. However, after inclusion of 156 patients the median progression-free survival (PFS) was 8 months in the trastuzumab + capecitabine arm versus 6 months in the capecitabine arm (P = 0.034). RR was 48% versus 27% (P = 0.011), while median OS was not significantly different (26 months versus 20 months) (19). More recently, a phase III study comparing trastuzumab and lapatinib with lapatinib in 296 heavily pretreated MBC patients who had progressed on therapy with trastuzumab demonstrated synergy between the two compounds. Thus, PFS was 12 weeks in the combination arm compared to 8 weeks in the lapatinib arm and the clinical benefit rate was 25% and 12%, respectively (P = 0.01), whereas RR was not significantly different (20).

In conclusion, it has been firmly established that a single treatment with HER2-targeted therapy does not exhaust the potential benefit of subsequent therapies targeting this pathway. In accordance, treatment guidelines advocate continuing trastuzumab and chemotherapy in HER2-positive patients who have progressed on prior trastuzumab (21).

Trastuzumab emtansine (T-DM1; Genentech/Chugai, members of the Roche Group) is an antibody–drug conjugate comprised of a cytotoxic agent, an antibody and a linker that covalently binds the components together. It consists of trastuzumab covalently bound via a thioether linker to DM1, a highly potent derivative of the antimitotic drug maytansine. Trastuzumab emtansine has been described as a state-of-the-art immunoconjugate because of its high tumor specificity, the magnitude of expression of its target antigen in the tumor, the thorough clinical validation of the target and the high stability of the linker (22). These characteristics result in an agent capable of selectively delivering chemotherapy to the antigen-expressing tumor cells while potentially improving the therapeutic index, sparing the normal tissues and allowing the use of drugs which are otherwise too toxic for clinical application (23). A feature which also renders trastuzumab emtansine unique compared to other antibody–drug conjugates is the fact that the naked antibody (trastuzumab) not only has the function of localizing the target cells, but also in itself has antitumor activity.

A pivotal step in the development of the drug was the observation that a non-reducible thioether linker (*N*-maleimidomethyl cyclohexane-1-carboxylate, known as MCC after conjugation) connecting DM1 to trastuzumab was significantly more active in preclinical models than the traditional reducible disulfide linkers. Although it was initially hypothesized that the highly reducible linkers would allow for endosomal reduction of the disulfide and result in intracellular release of the cytotoxic agent, the clearance of this agent was rapid and it was concluded that it might not be available for prolonged antitumor activity (24).

PRECLINICAL PHARMACOLOGY

More recently, Junttila et al. (25) demonstrated that trastuzumab emtansine disrupted the HER2–HER3 complex and resulted in inhibition of PI3K signaling, prevented shedding of the extracellular domain of HER2 and therefore formation of p95-HER2, and activated antibody-dependent cell-mediated cytotoxicity (ADCC). Trastuzumab emtansine binds to the HER2 receptor with similar

affinity as trastuzumab. Thus, trastuzumab emtansine appears to maintain all the known mechanisms of action of trastuzumab. Lewis Phillips et al. (24) have shown in in vitro studies that lysine-MCC-DM1 was the predominant metabolite after degradation, acting as the tubulin binding agent, and the use of trastuzumab emtansine resulted in apoptotic cell death and cellular lysis. Since lysine-MCC-DM1 did not cross the cell membrane, the adjacent (normal) cells were not exposed to its toxic effect and remained unaffected. Studies of DM1 have shown the drug to be a tubulin toxin that causes apoptosis through inhibition of microtubule assembly, leading to cell cycle arrest in the G_2/M phase (26). The mechanisms of action are similar to the Vinca alkaloids, but DM1 is 20-100 times more potent than vincristine (27).

Preclinical in vitro studies have demonstrated superior antitumor potency for trastuzumab emtansine compared to trastuzumab in HER2-positive, trastuzumab-sensitive breast cancer cell lines. In cell lines not overexpressing HER2, the antiproliferative efficacy of trastuzumab emtansine was low, suggesting that it selectively targets HER2-positive cells. The antitumor activity of trastuzumab emtansine has also been shown in HER2-positive cells which are resistant to trastuzumab (24).

In vivo activity has been determined in mice bearing HER2-positive, trastuzumab-sensitive breast cancer KPL-4. In this model, treatment with trastuzumab emtansine led to complete tumor regression, whereas trastuzumab caused transient regression with regrowth after treatment cessation (24).

Other preclinical studies have shown trastuzumab emtansine to be effective even in breast cancer cell lines with moderate HER2 expression levels and cross-resistance to trastuzumab and lapatinib (28). In addition, Junttila et al. have shown that trastuzumab emtansine effectively inhibits the growth of breast cancer cell lines and tumor xenografs that are resistant to lapatinib (25).

In addition, trastuzumab emtansine may potentiate the antitumor effect of other agents. Thus, in vitro studies have demonstrated that trastuzumab emtansine potentiated the antiproliferative effect of the chemotherapeutic agents doxorubicin, paclitaxel and docetaxel (29). Furthermore, synergistic efficacy has been reported with trastuzumab emtansine in combination with the monoclonal antibody pertuzumab and the PI3K inhibitor GCD-0941 (30, 31). These results provide the rationale for clinical testing of trastuzumab emtansine in combination with various agents in HER2-positive breast cancer.

PHARMACOKINETICS AND METABOLISM

Determining the clinical factors affecting the pharmacokinetics of trastuzumab emtansine has been complicated by its constitution of both large and small molecules (29). Nonetheless, clinical studies have shown that the pharmacokinetics of trastuzumab emtansine are predictable (32, 33). Shen et al. (34) conducted a study with radiolabeled compound in Sprague–Dawley rats, which showed that radioactivity levels mainly were high in plasma and low in the perfused organs. By day 14, there was no persistence or accumulation of trastuzumab emtansine. About 80% was excreted in the feces, while < 10% was detected in the urine. In a phase I trial, Krop et al. showed that the maximum tolerated dose (MTD) of trastuzumab emtansine was 3.6 mg/kg and at this dose clearance was 12.9 ± 3.4 mL/kg/day, and thus higher than the clearance for total trastuzumab of 3.3 ± 2.7 mL/kg/day (33). In a phase II trial, C_{max} and AUC for trastuzumab emtansine were lower than for trastuzumab. Trastuzumab was also shown to have a longer half-life than trastuzumab emtansine. No accumulation of trastuzumab emtansine was found with a dosing schedule of every 3 weeks (32). The systemic exposure to DM1 was low; the highest reportable concentration was 17 ng/mL, but no formal pharmacokinetic analysis was possible, since DM1 was only measurable immediately after trastuzumab emtansine administration (33).

In conclusion, several studies have shown that the pharmacokinetics of trastuzumab emtansine are characterized by relatively slow clearance, a small volume of distribution (limited to plasma volume) and a half-life of approximately 4 days (35).

SAFETY

Generally, trastuzumab emtansine is well tolerated both as a single agent and in combination with chemotherapy. Several phase I trials of trastuzumab emtansine as a single agent or in combination with pertuzumab have demonstrated fatigue, nausea, transaminase elevation, anemia, thrombocytopenia, neutropenia and headache to be the most common adverse events (33, 36, 37). Another phase I study (TDM4652g, NCT00951665) is ongoing and evaluating the safety, tolerability and pharmacokinetics of trastuzumab emtansine, paclitaxel and pertuzumab in patients with HER2-positive, locally advanced or metastatic breast cancer. The phase II TDM3569g trial including 110 patients previously treated with lapatinib, trastuzumab and chemotherapy found the most common AEs to be fatigue (62%), nausea (37%) and thrombocytopenia (33%), mainly grade 1 and 2. Serious AEs included four cases of cellulitis, three cases of pneumonia and three cases of pyrexia (38). Another phase II trial including 112 patients previously treated with HER2-directed therapy found fatigue (65.2%), nausea (50.9%) and headache (40.2%) to be the most common AEs overall. The most frequent grade 3 or 4 AEs were hypokalemia (8.9%), thrombocytopenia (8.0%) and fatigue (4.5%). Four patients discontinued treatment (3.6%) (32). The only published randomized study compared trastuzumab emtansine to trastuzumab plus docetaxel. The most common AEs were alopecia (66.7%), neutropenia (63.6%), diarrhea (45.5%) and fatigue (45.5%) in patients treated with docetaxel and trastuzumab, and fatigue (49.3%), nausea (47.8%), increased AST (39.1%) and pyrexia (39.1%) in the trastuzumab emtansine group (39). The incidence of grade 3 or more AEs, however, was markedly different among the two groups: 46.4% in the trastuzumab emtansine group vs. 89.4% in the trastuzumab plus docetaxel group. Generally, AEs are mild (grade 1 or 2), thrombocytopenia is usually transient and manageable, and in contrast to trastuzumab, no cardiotoxicity has been noted among patients treated with trastuzumab emtansine (40). Two ongoing studies are assessing the cardiac safety of trastuzumab emtansine among patients with MBC (NCT00943670), as well as early breast cancer (NCT01196052).

CLINICAL TRIALS

The only published phase I trial is a first-in-human study to evaluate safety, pharmacokinetics and preliminary activity of trastuzu-

mab emtansine in HER2-positive patients with MBC (33). This dose-escalation study was conducted using two different administration schedules: in one part of the study trastuzumab emtansine was administered weekly, while in the other it was given every 3 weeks starting at 0.3 mg/kg and escalating to 4.8 mg/kg. The MTD was found to be 3.6 mg/kg every 3 weeks and the most common AEs were thrombocytopenia, elevated transaminases, fatigue, anemia and nausea. A total of 24 patients were enrolled, all of whom had progressed on prior trastuzumab, and the median number of previous chemotherapeutic agents was four. Fifteen patients received the MTD, and among these, 4 had a confirmed response, whereas the clinical benefit rate (objective response [OR] plus stable disease [SD] at 6 months) was 73%. On the basis of this trial, it was decided to further investigate trastuzumab emtansine at the dose of 3.6 mg/kg given every 3 weeks.

Several phase I trials are still ongoing. Among them are trials with trastuzumab emtansine given in combination with various other agents, including paclitaxel with or without pertuzumab (NCT00951665), docetaxel (NCT00934856) and the PI3K inhibitor GDC-0941 (NCT00928330) (Table I).

Two phase II trials have assessed the efficacy and safety of trastuzumab emtansine as a single agent in HER2-positive patients previously treated with trastuzumab and various chemotherapy regimens.

The first trial was an open-label, single-arm study including 112 patients (32). The median number of prior anticancer agents was 8

Table I. *Completed and ongoing trials of trastuzumab emtansine in patients with locally advanced or metastatic HER2-positive breast cancer.*

No./Name	Author	Phase	Treatment	Previous trastuzumab	No. of patients	Status
First-in-human TDM3569g	Krop et al. (33)	I	T-DM1	Yes	24	Completed
NCT00932373	Holden et al. (37)	I	T-DM1	Yes	55	Ongoing
GDC4627g; NCT00928330		I	T-DM1 and GDC-0941	Yes	Estimated enrollment 60	Recruiting
NCT00934856		I	T-DM1 and docetaxel		Estimated enrollment 50	Recruiting
TDM4652g; NCT00951665		Ib	T-DM1, paclitaxel and pertuzumab	Yes	Estimated enrollment 27	Recruiting
TDM4373g; NCT00875979	Diéras et al. (36)	Ib/II	T-DM1 and pertuzumab	Yes	67	Ongoing
TDM-4374g; NCT00679211	Krop et al. (41)	II	T-DM1	Yes + lapatinib and chemotherapy	110	Completed
NCT00509769		II	T-DM1	Yes	100	Completed
TDM4258g	Burris et al. (32)	II	T-DM1	Yes	112	Completed
NCT01120561		II	T-DM1	Yes and anthracycline + taxane + capecitabine or 5-FU	Not provided	Ongoing
NCT00679211		II	T-DM1	Yes plus prior chemotherapy	Estimated enrollment 100	Ongoing
TDM4450g/BO21976; NCT00679341	Perez et al. (40)	II	T-DM1 vs. trastuzumab and docetaxel	Yes but no previous chemotherapy for MBC	67/70	Ongoing
TDM4688g; NCT00943670		II	T-DM1 and pertuzumab	Yes	51	Ongoing
TDM1 (neo) adjuvant anthracycline-based therapy		II Early breast cancer	T-DM1 (neo) adjuvant anthracycline-based therapy	No enrollment 135	Estimated	Recruiting
EMILIA; NCT00829166		III	T-DM1 vs. capecitabine and lapatinib	Yes	980	Recruiting
MARIANNE; NCT01120184		III	T-DM1 and pertuzumab vs. trastuzumab and a taxane vs. T-DM1	Yes/no	Estimated enrollment 1,092	Recruiting

T-DM1, trastuzumab emtansine; MBC, metastatic breast cancer.

and the median prior exposure to trastuzumab was 17.6 months. In addition, 60% of the patients had also received lapatinib previously. An OR was found in 29 patients, corresponding to an overall RR of 25.9%. Median PFS for the efficacy-evaluable patients was 4.6 months. The most common AEs were fatigue, nausea and headache, and the most common grade 3 and 4 AEs were hypokalemia, thrombocytopenia and fatigue. Four patients discontinued treatment due to AEs (Table II).

The second phase II study was also an open-label, single-arm study and included 110 patients. All patients but one had previously been treated with trastuzumab, capecitabine, an anthracycline, a taxane and lapatinib, and the median number of prior therapies was 8.5. The most common AEs reported were fatigue, nausea, thrombocytopenia and elevated AST. An OR was observed in 34.5% of all patients, but no complete responses (CRs) were seen. The median duration of response was 7.2 months and the median PFS was 6.9 months (38) (Table II).

A randomized phase II trial compared trastuzumab emtansine versus trastuzumab plus docetaxel in HER2-positive patients with MBC and no prior chemotherapy for metastatic disease. A total of 137 patients were randomized 1:1 to either trastuzumab emtansine 3.6 mg/kg every 3 weeks or trastuzumab 8 mg/kg initially followed by 6 mg/kg every 3 weeks and docetaxel 75 or 100 mg/m^2 every 3 weeks. Primary efficacy data have been presented, with a median follow-up of approximately 10 months. Overall RR was 64.2% in the trastuzumab emtansine group versus 58% in the docetaxel plus trastuzumab (H+T) group. Seven CRs were observed in the trastuzumab emtansine group compared to three in the H+T group. PFS was statistically better in the trastuzumab emtansine group: 14.2 months compared to 9.2 months in the H+T group (P = 0.035). The AEs observed were similar to those seen in other studies with trastuzumab emtansine, but the incidence of serious AEs was lower in the trastuzumab emtansine group compared to the H+T group (18.8% vs. 25.8%) (39) (Table II).

A phase Ib/II trial investigated trastuzumab emtansine in combination with pertuzumab in 67 patients with HER2-positive, locally advanced breast cancer or MBC. Treatment was given every 3 weeks. A total of 45 patients had relapsed on previous treatment and 22 patients received trastuzumab emtansine and pertuzumab as first-line treatment. Preliminary results showed 15 confirmed responses in the relapsed population, with a median follow-up of 8 treatment cycles. In the first-line population, two confirmed responses were seen with a median follow-up of three cycles. The most common AEs were thrombocytopenia, fatigue, increased ALT and increased AST. The combination of trastuzumab emtansine and pertuzumab appears to be tolerable and effective, although final analysis of the study is still anticipated (36) (Table II).

A study investigating the potential benefit of trastuzumab emtansine in the adjuvant or neoadjuvant setting combined with anthracycline-based therapy is ongoing and plans to enroll 135 patients with early breast cancer (NCT01196052).

Two large phase III studies are currently ongoing. The first is an open-label study of trastuzumab emtansine versus capecitabine and lapatinib in patients with HER2-positive, locally advanced breast cancer or MBC who have previously received trastuzumab therapy (EMILIA; NCT00829166). In total, 980 patients are expected to participate (Table II). The other study (MARIANNE; NCT01120184) is a randomized study of trastuzumab emtansine with or without pertuzumab compared with trastuzumab plus taxane for the first-line treatment of HER2-positive, progressive or

Table II. *Efficacy data from clinical trials with T-DM1 in patients with HER2-positive metastatic breast cancer.*

Trial	Author	Design	Treatment	No. of patients	ORR %	PFS (months)
TDM3569g	Krop et al. (33)	Phase I	T-DM1 0.3 mg/kg to 4.8 mg/kg every 3 weeks	24	25*	NR
TDM4652g		Phase Ib	T-DM1 every 3 weeks and paclitaxel every week (part 1 of study)	14	14.2	NR
TDM4373g	Diéras et al. (36)	Phase Ib/II	T-DM1 3.6 mg/kg and pertuzumab 840 mg; 420 mg every 3 weeks	67 (45 relapsed, 22 first-line)	Relapsed 42%***; first-line 41%***	NR
TDM4258g	Burris et al. (32)	Phase II	T-DM1 3.6 mg/kg every 3 weeks	112	25.9	4.6
TDM14374g	Krop et al. (41)	Phase II	T-DM1 3.6 mg/kg every 3 weeks	110	34.5	6.9
TDM4450g	Hurvitz et al. (39)	Phase II, randomized	T-DM1 3.6 mg/kg vs. trastuzumab 8 mg/kg; 6 mg/kg and docetaxel 75 or 100 mg/m^2 every 3 weeks	137	64.2 vs. 58.0**	NR

T-DM1, trastuzumab emtansine; NR, not reported; OOR, overall response rate; PFS, progression-free survival. *5/6 confirmed; **preliminary results only investigators' assessment; ***unconfirmed data.

recurrent locally advanced breast cancer or MBC. The study started enrollment in July 2010 and is still recruiting patients, with a total of 1,092 patients expected to participate.

Based on the results from the TDM4374g study (41), a Biologics License Application (BLA) was submitted to the FDA in July 2010 requesting approval for trastuzumab emtansine. Data from TDM4258g were included in the application as well. However, the FDA rejected this application in August 2010 and requested phase III data. A new submission is expected in 2012 based on the EMILIA trial.

CONCLUSIONS

Several new anti-HER2 drugs are in development. These include pertuzumab (2C4, Omnitarg®; Genentech), a monoclonal antibody that sterically blocks dimerization of HER2 with HER1 and HER3. The drug inhibits signaling from HER2/HER1 and HER2/HER3 heterodimers (42). Results from a phase II trial evaluating the combination of trastuzumab and pertuzumab in 66 patients with MBC who had progressed during treatment with trastuzumab demonstrated an RR of 24% and a clinical benefit rate of 50% (≤ 3 lines of prior chemotherapy) (43). A phase III study comparing docetaxel/trastuzumab/placebo with docetaxel/trastuzumab/pertuzumab as first-line therapy in HER2-positive MBC patients is under way (CLEOPATRA; NCT00567190).

In addition, a range of tyrosine kinase inhibitors targeting multiple HER family members are also in development. Neratinib (HKI-272; Pfizer) is an irreversible pan-HER inhibitor blocking HER1, HER2 and HER4. In a phase II study in 136 patients with MBC, among whom 70 had received trastuzumab and 66 were trastuzumab-naive, 24% and 56%, respectively, of the patients obtained response after treatment with neratinib (12% were chemotherapy-naive, 48 had received 1-2 regimens and 40% had received ≥ 3 prior chemotherapy regimens) (44). The compound is currently being evaluated in phase III trials (NCT00777101: Study Evaluating Neratinib Versus Lapatinib Plus Capecitabine for ErbB2-Positive Advanced Breast Cancer; NCT00915018: Study Evaluating Neratinib Plus Paclitaxel VS Trastuzumab Plus Paclitaxel In ErbB-2 Positive Advanced Breast Cancer). Afatinib (BIBW-2992; Boehringer Ingelheim) is an irreversible inhibitor of HER1, mutated HER1 and HER2 (45). Preliminary phase II data of afatinib monotherapy are emerging. One study has shown promising activity, with 4 partial responses and 8 stable diseases (4 months) in 41 patients (34 evaluable) with HER2-positive MBC after failure of trastuzumab (median 3 lines of prior therapy) (46).

The new anti-HER2 drugs have the potential to change the clinical practice of targeting HER2 in the future. In addition to those drugs directly targeting HER2, several drugs inhibiting downstream signaling mediators are also in development. Thus, a variety of phase I/II trials are under way in HER2-positive breast cancer, including inhibitors of mammalian target of rapamycin (serine/threonine-protein kinase mTOR), PI3K inhibitors and dual PI3K-mTOR inhibitors (47).

Furthermore, other therapeutic strategies are under way. A promising novel approach in HER2-positive breast cancer is the inhibition of heat shock protein HSP 90 (48). This chaperone protein exerts its function to maintain conformation, activity, turnover and localization of many proteins that are involved in proliferation and survival, including HER2 and Akt. A phase II study of the HSP 90 inhibitor tanespimycin (17-AAG, KOS-953; Bristol-Myers Squibb) in combination with trastuzumab in 31 patients with HER2-positive breast cancer who all had received prior trastuzumab and a median of 1 prior chemotherapy regimen has shown a 22% overall RR and a 59% clinical benefit rate, with a median PFS of 6 months and a median survival of 17 months (49).

The potential role of trastuzumab emtansine in the field of other active drugs and regimens has yet to be determined. Thus, as a single agent the RR for trastuzumab emtansine of 64% and 26-36% in the first line and fourth to eighth line of therapy, respectively, is comparable to that obtained for capecitabine plus lapatinib (48%; second line) pertuzumab plus trastuzumab (24%; ≤ three lines of prior chemotherapy) and neratinib (24%; 60% ≤ two prior chemotherapy regimens). In addition, all these treatment strategies have shown robust overall clinical benefit rates. Whether trastuzumab emtansine is significantly superior to these treatment strategies should therefore be addressed (47). A retrospective study of 20 patients with HER2-positive MBC who all had received prior trastuzumab-based therapy before enrollment in clinical trials of trastuzumab emtansine monotherapy has shown a partial response rate of 33% to first- or second-subsequent HER2-directed regimen(s) after discontinuation of trastuzumab emtansine (50). Thus, exposure to trastuzumab emtansine did not exhaust the potential benefit of subsequent HER2-directed therapy.

In conclusion, trastuzumab emtansine is a novel HER2-directed agent that combines the biological activity of an antibody with the cytotoxicity of a chemotherapeutic drug via a stable linker. Preclinical models have shown activity for this drug in HER2-positive breast cancer cell lines and xenografts, including those which are resistant to trastuzumab or lapatinib. The pharmacokinetic profile is predictable, with minimal systemic exposure to free DM1. Phase II studies have shown a response rate of 25-35% in heavily pretreated patients with MBC. The toxicity has been manageable. Several combination regimens are under investigation. Phase III studies should help to define the role of trastuzumab emtansine within current treatment strategies.

SOURCES

Genentech, Inc. and Chugai Pharmaceutical Co., Ltd., both members of the Roche Group.

DISCLOSURES

The authors state no conflicts of interest.

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