

Trastuzumab emtansine in the treatment of HER2-positive metastatic breast cancer in Japanese patients

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Abstract: Anti-HER2 agents, such as trastuzumab, lapatinib, trastuzumab emtansine (T-DM1), and pertuzumab, are standard agents in the treatment of breast cancer overexpressing the human epidermal growth factor receptor 2 (HER2). Trastuzumab is the first approved HER2-targeted agent. Subsequent developments include agents with different mechanisms. In this paper, we review the results of clinical trials of T-DM1, a new anti-HER2 agent, with a focus on Japanese patients with breast cancer. On the basis of results from a Phase I study (JO22591), the maximum tolerated dose was determined to be 3.6 mg/kg every 3 weeks for both Japanese and western patients. In a Phase II study (JO22997), the overall response rate was 38.4% (90% confidence interval 28.8–48.6). T-DM1 was well tolerated in Japanese patients; however, the incidence of grade 3 or 4 thrombocytopenia was higher than that observed in earlier western studies, but was not associated with clinically important symptoms. Pharmacokinetic parameters for T-DM1 and its metabolites were consistent with those reported previously from a Phase I or II study in non-Japanese patients, and the data obtained showed no suggestion of ethnic differences. Several Phase III studies of T-DM1 are ongoing throughout the world, including in Japanese patients with breast cancer.

Keywords: breast cancer, *HER2/neu*, trastuzumab emtansine, anti-HER2 therapy

Introduction

The human epidermal growth factor receptor 2 (HER2) protein is a unique and useful target for antibody therapy against breast cancers overexpressing the *HER2/neu* gene. HER2 is overexpressed in 15%–25% of human breast cancers^{1–3} and is correlated with a poor prognosis in women with both node-positive and node-negative disease.^{4–6} Overexpression of HER2 has also been associated with potentially more aggressive tumors. Trastuzumab, a humanized monoclonal antibody, was the first agent approved for anti-HER2-targeted treatment. Subsequent developments have included agents with different mechanisms, such as lapatinib, trastuzumab emtansine (T-DM1), and pertuzumab.

T-DM1 is an antibody-drug conjugate incorporating the HER2-targeted antitumor properties of trastuzumab with the cytotoxic activity of the microtubule-inhibitory agent, DM1 (a derivative of maytansine); the antibody and cytotoxic agent are conjugated via a stable linker. In the pivotal T-DM1 study (A Randomized, Multicenter, Phase III Open-label Study of the Efficacy and Safety of Trastuzumab Emtansine vs. Capecitabine + Lapatinib in Patients With HER2-positive Locally Advanced or Metastatic Breast Cancer Who Have Received Prior Trastuzumab-based Therapy [EMILIA]),⁷ T-DM1 significantly prolonged progression-free survival and overall survival, with less toxicity than lapatinib plus capecitabine in HER2-positive patients with

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advanced breast cancer previously treated by trastuzumab and a taxane. On the basis of that trial, the US Food and Drug Administration approved marketing of T-DM1 in February 2013. T-DM1 has not yet been approved (as of January 2014) in Japan, but approval is expected in 2014. This review describes the results obtained with T-DM1, with particular reference to Japanese patients with breast cancer.

Phase I study in Japanese patients

A Phase I, multicenter, single-arm, dose-escalation study (JO22591) was performed in Japanese patients with HER2-positive metastatic breast cancer who had received prior anti-cancer therapy.⁸ Ten patients were recruited, divided into three groups, and started at the following T-DM1 doses: 1.8 mg/kg (n=1); 2.4 mg/kg (n=4); and 3.6 mg/kg (n=5). Each dose was given at 3-weekly intervals. Maximum tolerated dose was defined as the dose at which the estimated probability of dose-limiting toxicity is closest to 25%, which is the target probability of dose-limiting toxicity using the continual reassessment method. One patient in the 2.4 mg/kg group experienced a dose-limiting toxicity (a grade 3 increase in aspartate aminotransferase and alanine aminotransferase). No other adverse events indicating a dose-limiting toxicity were observed in any of the other patients. The most frequently reported adverse events were nausea, fatigue, arthralgia, and pyrexia. The main changes in laboratory test values recorded were a decrease in platelet count and increases in aspartate aminotransferase and alanine aminotransferase levels. Most of the adverse events were mild and manageable, although two serious adverse events were observed, ie, cholelithiasis (grade 3) in the 2.4 mg/kg group and gastric ulcer hemorrhage (grade 2) in the 3.6 mg/kg group. In total, one patient treated with T-DM1 2.4 mg/kg developed a dose-limiting toxicity. No other dose-limiting toxicities were observed for the three doses tested. Thus, as a result of this Phase I study in Japanese patients with breast cancer, the maximum tolerated dose was determined to be 3.6 mg/kg every 3 weeks.

T-DM1 showed linear pharmacokinetics, with no significant accumulation across the dose levels tested. There

were no marked differences between this study and the two western studies (TDM3569g⁹ and TDM4258g¹⁰) in any of the pharmacokinetic parameters for T-DM1, DM1; a derivative of maytansine, or total trastuzumab following administration of T-DM1. Moreover, there was no suggestion in the data of any ethnic differences between Japanese and western patients.

Phase II study in Japanese patients

After completing the Phase I study,⁸ which determined a maximum tolerated dose for T-DM1 of 3.6 mg/kg every 3 weeks, a multicenter, single-arm, Phase II study was started in Japanese patients with HER2-positive metastatic breast cancer who had received prior trastuzumab and at least one line of chemotherapy (JO22997).¹¹ T-DM1 was infused as a single agent at a dose of 3.6 mg/kg every 3 weeks to patients with HER2-positive metastatic breast cancer. The primary endpoint was the objective response rate based on assessment by the independent review committee. Seventy-six patients were enrolled, of whom 73 received at least one dose of T-DM1 and a median of three (range 1–8) prior chemotherapy regimens for metastatic breast cancer, including lapatinib in 43 (58.9%) patients. The median duration of treatment with T-DM1 was 23.1 (0.1–63.3) weeks. The objective response rate was 38.4% (90% confidence interval [CI] 28.8–48.6). The clinical benefit rate was 45.2% (95% CI 33.5–57.3) and median progression-free survival was 5.6 months (95% CI 4.6–8.2). The most frequently observed grade ≥ 3 adverse event was thrombocytopenia (22%). Seventy patients (96%) experienced an adverse event of any grade, 15 patients (21%) experienced a serious adverse event and 41 patients (56%) experienced a grade ≥ 3 adverse event. The incidence of grade 3 or 4 thrombocytopenia was higher than that previously reported in other studies,^{7,10,12} although no patient required a platelet transfusion. Thrombocytopenia is the most common adverse event and key dose-limiting toxicity associated with T-DM1,^{9,13,14} and is thought to be due to antimetabolic effects on megakaryocyte precursors. However, the rapid onset and recovery of T-DM1-associated thrombocytopenia, even after repeated dosing, suggests that other tubulin-dependent

Table I Pharmacokinetic parameters of T-DM1 at 3.6 mg/kg

Trial name	Mean (SD)			
	AUC _{inf} (day μ g/mL)	t _{1/2} (day)	V _{ss} (mL/kg)	Clearance (mL/day/kg)
JO22591 ⁸ (n=5)	346 (41.1)	3.74 (1.15)	59.1 (6.62)	10.6 (1.26)
JO22997 ⁴ (n=31)	365 (68)	3.62 (0.78)	54.9 (13.9)	10.3 (2.30)
TDM4258g ^{10,15} (n=101)	457 (129)	3.52 (0.71)	28.4 (12.9)	8.51 (2.69)
TDM4374g ¹⁵ (n=105)	486 (141)	3.96 (0.96)	31.2 (10.9)	8.04 (2.97)

Abbreviations: AUC_{inf}, area under the concentration-time curve from time 0 extrapolated to infinity; t_{1/2}, half-life; V_{ss}, volume of distribution at steady state; SD, standard deviation; T-DM1, trastuzumab emtansine.

Table 2 Efficacy of T-DMI as monotherapy

Trial name	Phase	n	Treatment setting	ORR (%)	PFS (months)	Reference
JO22997	II	73	Second-line	38.4 (90% CI 28.8–48.6)	5.6 (95% CI 4.6–8.2)	Masuda et al ¹¹
TDM4258g	II	112	Second-line	25.9 (95% CI 18.4–34.4)	4.6 (95% CI 3.9–8.6)	Burris et al ¹⁰
TDM4374g	II	110	Second-line	34.5 (95% CI 26.1–43.9)	6.9 (95% CI 4.2–8.4)	Krop et al ¹²
TDM4450g	II (randomized)	67	First-line	64.2 (95% CI 51.8–74.8)	14.2	Hurvitz et al ²³
EMILIA	III	495	Second-line	43.6 (95% CI 38.6–48.6)	9.4	Verma et al ⁷

Abbreviations: CI, confidence interval; PFS, progression-free survival; ORR, objective response rate; T-DMI, trastuzumab emtansine; EMILIA, A Randomized, Multicenter, Phase III Open-label Study of the Efficacy and Safety of Trastuzumab Emtansine vs. Capecitabine + Lapatinib in Patients With HER2-positive Locally Advanced or Metastatic Breast Cancer Who Have Received Prior Trastuzumab-based Therapy.

mechanisms, such as release of proplatelets from mature megakaryocytes, may be important.⁹

The pharmacokinetic parameters of T-DMI identified in the Phase I and II studies from Japan are summarized in Table 1. There were no marked differences in any of the pharmacokinetic parameters for T-DMI, DM1, or total trastuzumab following administration of T-DMI between the four studies, ie, the Japanese Phase I study (JO22591; n=5),⁸ the Japanese Phase II study (JO22997; n=31),¹¹ TDM4258g (n=101),¹⁵ and TDM4374g (n=105).¹⁵

In summarizing the Phase II study, the objective response rate (the primary endpoint established by the independent review committee) was 38.4%, and T-DMI was well tolerated. Table 2 gives a comparison of the efficacy of T-DMI in Japanese patients versus western patients. A good response was seen in both patient populations. These results support the use of T-DMI in the treatment of Japanese patients with advanced HER2-positive breast cancer previously treated with chemotherapy and trastuzumab.

Phase Ib study in Japanese patients

A multicenter, single-arm, Phase Ib study (JO22992) using a combination of T-DMI and pertuzumab was performed in

Japanese patients with HER2-positive metastatic breast cancer who had received prior treatment with trastuzumab and chemotherapy.¹⁶ Six patients received T-DMI 3.6 mg/kg with pertuzumab (a 840 mg loading dose, then a 420 mg maintenance dose) given every 3 weeks. The median duration of treatment was eleven (range 1–32) cycles. Grade ≥ 3 adverse events included one case each of increased aspartate aminotransferase, decreased left ventricular ejection fraction, and neutropenia. A grade 3 decrease in left ventricular ejection fraction during cycle 1 led to discontinuation, but resolved within 30 days. Two serious adverse events (hemorrhagic gastric ulcer and epistaxis) occurred in one patient. The pharmacokinetic parameters of both drugs were similar to those seen in the single-agent trials. The objective response rate was 50%. In conclusion, the combination of T-DMI and pertuzumab showed encouraging results regarding tolerability in Japanese patients with HER2-positive metastatic breast cancer.

Phase III study

The Phase III studies of T-DMI are summarized in Table 3. EMILIA, the global Phase III study of T-DMI, showed novel efficacy and less toxicity than lapatinib and capecitabine as

Table 3 Phase III studies of T-DMI

Trial name	Standard arm	Experimental arm	Treatment setting	Target number (total)
MARIANNE ^{18,*} (NCT01120184)	Trastuzumab + taxane (docetaxel or paclitaxel)	T-DMI + pertuzumab T-DMI + pertuzumab placebo	MBC; first-line	1,095
TH3RESA ²⁰ (NCT01419197)	Treatment of physician's choice	T-DMI	MBC; third-line	604
KAITLIN ^{21,*} (NCT01966471)	Trastuzumab + pertuzumab + taxane	T-DMI + pertuzumab	Adjuvant therapy; following anthracyclines	2,500
KATHERINE ²³ (NCT01772472)	Trastuzumab	T-DMI	Adjuvant therapy; following preoperative therapy	1,484

Note: *Japanese breast cancer patients participating.

Abbreviations: MBC, metastatic breast cancer; T-DMI, trastuzumab emtansine; MARIANNE, A Study of Trastuzumab-DMI Plus Pertuzumab Versus Trastuzumab [Herceptin] Plus a Taxane in Patients With Metastatic Breast Cancer; TH3RESA, A Study of Trastuzumab Emtansine in Comparison With Treatment of Physician's Choice in Patients With HER2-Positive Breast Cancer Who Have Received at Least Two Prior Regimens of HER2-Directed Therapy; KAITLIN, A Study of Kadcyla (Trastuzumab Emtansine) Plus Perjeta (Pertuzumab) Following Anthracyclines in Comparison With Herceptin (Trastuzumab) Plus Perjeta and a Taxane Following Anthracyclines as Adjuvant Therapy in Patients With Operable HER2-positive Primary Breast Cancer; KATHERINE, A Study of Trastuzumab Emtansine Versus Trastuzumab as Adjuvant Therapy in Patients With HER2-Positive Breast Cancer Who Have Residual Tumor in the Breast or Axillary Lymph Nodes Following Preoperative Therapy.

a second-line treatment for HER2-positive metastatic breast cancer.⁷ In the first-line and third-line treatment settings for HER2-positive metastatic breast cancer, the efficacy of T-DM1 when compared with other standard therapies has not been clarified. At present, combination therapy of taxane, trastuzumab and pertuzumab used as standard first-line anti-HER2 therapy.¹⁷ The Study of Trastuzumab-DM1 Plus Pertuzumab Versus Trastuzumab [Herceptin] Plus a Taxane in Patients With Metastatic Breast Cancer (MARIANNE) trial¹⁸ will show whether or not T-DM1 with or without pertuzumab is superior to a taxane with trastuzumab as first-line therapy, although the Phase III, Randomized, Double-blind, Placebo-controlled Clinical Trial to Evaluate the Efficacy and Safety of Pertuzumab + Trastuzumab + Docetaxel vs. Placebo + Trastuzumab + Docetaxel in Previously Untreated HER2-positive Metastatic Breast Cancer (CLEOPATRA) trial¹⁹ indicates notable efficacy of pertuzumab plus trastuzumab plus docetaxel in this setting.¹⁷ This trial included Japanese breast cancer patients.

The Study of Trastuzumab Emtansine in Comparison With Treatment of Physician's Choice in Patients With HER2-Positive Breast Cancer Who Have Received at Least Two Prior Regimens of HER2-Directed Therapy (TH3RESA) trial²⁰ is comparing T-DM1 with physician's choice of treatment as a third line for HER2-positive metastatic breast cancer, although Japanese breast cancer patients are not included. This trial has completed accrual and results are awaited.

In the Study of Kadcyla (Trastuzumab Emtansine) Plus Perjeta (Pertuzumab) Following Anthracyclines in Comparison With Herceptin (Trastuzumab) Plus Perjeta and a Taxane Following Anthracyclines as Adjuvant Therapy in Patients With Operable HER2-positive Primary Breast Cancer (KAITLIN) trial,²¹ T-DM1 plus pertuzumab is being compared with trastuzumab plus taxane plus pertuzumab followed by anthracycline as adjuvant therapy for HER2-positive breast cancer. Japanese breast cancer patients will participate in KAITLIN. In this trial, trastuzumab with taxane plus pertuzumab is the standard treatment arm, but whether or not addition of pertuzumab is superior to trastuzumab plus a taxane has not yet been clarified, and this is expected to be answered by the Randomized Multicenter, Double-blind, Placebo-controlled Comparison of Chemotherapy Plus Trastuzumab Plus Placebo Versus Chemotherapy Plus Trastuzumab Plus Pertuzumab as Adjuvant Therapy in Patients With Operable HER2-positive Primary Breast Cancer (APHINITY) trial.²²

Disclosure

The author reports no conflicts of interest in this work.

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