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ORIGINAL ARTICLE

Trastuzumab emtansine plus pertuzumab in Japanese patients with HER2-positive metastatic breast cancer: a phase Ib study

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Abstract

Purpose To investigate the safety, pharmacokinetics, and efficacy of trastuzumab emtansine (T-DM1) in combination with pertuzumab in Japanese patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer.

Patients and methods Patients with HER2-positive advanced or recurrent breast cancer who had received trastuzumab and chemotherapy-containing therapies were eligible. Patients received T-DM1 (3.6 mg/kg) with full-dose pertuzumab (a loading dose of 840 mg and then 420 mg) intravenously every 3 weeks. This study was registered at the Japan Pharmaceutical Information Center-Clinical Trials Information (JapicCTI-101234).

Results Six patients enrolled in this study. The median duration of treatment was 11 (range 1–32) cycles. The most common treatment-emergent adverse event (TEAE) for any grade was diarrhea. Grade 3 or greater TEAEs included aspartate aminotransferase increased, left ventricular ejection fraction (LVEF) decreased, and neutrophil count decreased. The dose-limiting toxicity of grade 3 LVEF decreased was observed in one patient during cycle 1; however, it resolved within 30 days. The pharmacokinetic parameters of T-DM1 and pertuzumab were not affected by co-administration of the drugs. The best overall response included a partial response (PR) in 3 patients (50%) and stable disease (SD) in 2 patients (33%).

Conclusions The combination of T-DM1 and pertuzumab was tolerated and showed exploratory efficacy in Japanese patients with HER2-positive metastatic breast cancer.

Keywords T-DM1 · Trastuzumab emtansine · Pertuzumab · HER2-positive · Metastatic breast cancer

Introduction

Trastuzumab emtansine (T-DM1; RO5304020) is a novel human epidermal growth factor receptor 2 (HER2)-directed antibody-drug conjugate. T-DM1 comprises the monoclonal antibody trastuzumab bound to potent anti-microtubule agent DM1, a maytansine derivative, via a stable linker. T-DM1 demonstrated robust clinical efficacy with less toxicity in the EMILIA trial [1, 2], a phase III study of T-DM1 versus lapatinib plus capecitabine in patients with previously treated HER2-positive advanced breast cancer. T-DM1 significantly improved both median progression-free survival [PFS; hazard ratio (HR), 0.65; 95% confidence interval (CI), 0.55–0.77; $p < 0.001$; 9.6 versus 6.4 months] and overall survival (OS; HR, 0.68; 95% CI, 0.55–0.85; $p < 0.001$; 30.9 versus 25.1 months) [1]. Results from the TH3RESA trial, another phase III study of T-DM1 versus a treatment of the physician's choice in patients with heavily treated HER2-positive advanced breast cancer, confirmed those of the

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EMILIA trial, with significant prolongation of both median PFS (HR, 0.53; 95% CI, 0.42–0.66; $p < 0.0001$; 6.2 versus 3.3 months) [3] and OS (HR, 0.68; 95% CI, 0.54–0.85; $p = 0.0007$; 22.7 versus 15.8 months) [4].

Pertuzumab (RO4368451) is a novel recombinant, humanized immunoglobulin (Ig) G1κ monoclonal antibody against HER2. The combination of pertuzumab, trastuzumab, and docetaxel tremendously prolonged both median PFS (HR, 0.62, 95% CI, 0.51–0.75; $p < 0.001$; 18.5 versus 12.4 months) and OS (HR, 0.68, 95% CI, 0.56–0.84; $p < 0.001$; 56.5 versus 40.8 months) in patients with previously untreated HER2-positive metastatic breast cancer in the phase III CLEOPATRA trial [5–7].

The combination of T-DM1 and pertuzumab has been tested in a preclinical study [8] and a phase Ib/IIa study [9], suggesting synergistic antitumor activity. These results provided the rationale for conducting a global phase III MARIANNE trial [10, 11]. In the MARIANNE trial, T-DM1 or T-DM1 plus pertuzumab was compared with trastuzumab plus a taxane in patients with previously untreated HER2-positive advanced breast cancer. T-DM1 alone or in combination with pertuzumab did not significantly differ in efficacy to that of trastuzumab plus a taxane. The median PFS was 15.2 months with T-DM1 plus pertuzumab (HR, 0.87; 95% CI, 0.69–1.08; $p = 0.14$) and 14.1 months with T-DM1 (HR, 0.91; 95% CI, 0.73–1.13, $p = 0.31$), whereas the median PFS was 13.7 months with trastuzumab plus a taxane. The median OS rates were 51.8, 53.7, and 50.9 months for T-DM1 plus pertuzumab, T-DM1, and trastuzumab plus a taxane, respectively.

This phase Ib study was conducted to assess the safety, pharmacokinetics (PKs), and preliminary efficacy, and to confirm the recommended dose of T-DM1 in combination with pertuzumab in Japanese patients with HER2-positive metastatic breast cancer before participating in the MARIANNE trial from Japan.

Patients and methods

Study design

This was a multicenter, non-randomized, open-label, phase Ib study of the combination of T-DM1 plus pertuzumab in Japanese patients with HER2-positive metastatic breast cancer. The primary objective was to assess the safety and PKs of T-DM1 in combination with pertuzumab in Japanese patients with HER2-positive metastatic breast cancer. The secondary objective was to assess antitumor activity.

The study protocol was approved by the Institutional Review Board at each site, and all patients provided written informed consent for study participation. The study was conducted in accordance with the Declaration of Helsinki, the Pharmaceutical Affairs Laws, and the International Conference on Harmonisation Good Clinical Practice (ICH-GCP). This study was registered at the Japan Pharmaceutical Information Center-Clinical Trials Information (JapicCTI-101234).

Patients

Women ≥ 20 years old with histologically or cytologically diagnosed inoperable advanced or recurrent HER2-positive breast cancer [immunohistochemistry (IHC) 3+ or fluorescence in situ hybridization (FISH) positive by central testing] were eligible. Disease progression was required during or after treatment with trastuzumab (including adjuvant therapy) and prior systemic chemotherapy for the advanced or recurrent breast cancer, with no other preferred treatment. Other inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and adequate organ and bone marrow function, defined as an absolute neutrophil count of $\geq 1500/mm^3$, platelet count $\geq 100{,}000/mm^3$, hemoglobin ≥ 9.0 g/dL, total bilirubin (T-Bil) ≤ 1.5 mg/dL, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × the upper limit of normal (ULN), serum albumin ≥ 2.5 g/dL, serum creatinine ≤ 1.5 mg/dL or creatinine clearance ≥ 50 mL/min, and left ventricular ejection fraction (LVEF) ≥ 50% as measured by echocardiography or a multiple-gated acquisition (MUGA) scan.

Key exclusion criteria included clinically significant cardiac disease, defined as New York Heart Association (NYHA) II–IV heart failure; National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade ≥ 3 cardiac disorders, and a history of unstable angina, congestive heart failure, myocardial infarction, and ventricular arrhythmia requiring medical treatment within 6 months; administration of a cumulative doxorubicin dose of $> 500\ mg/m^2$ or equivalent (e.g., in the case of epirubicin, $> 720\ mg/m^2$); a history of grade ≥ 3 hypersensitivity to trastuzumab; and symptomatic brain metastasis. Patients who previously received T-DM1 or pertuzumab were excluded.

Study treatment

T-DM1 was administered at a dose of 3.6 mg/kg with full-dose pertuzumab (a loading dose of 840 mg and then 420 mg) intravenously every 3 weeks. T-DM1 was given after completion of the pertuzumab infusion over 90 min in Cycle 1, and if well-tolerated, over 30 min in subsequent cycles. Pertuzumab was given over 60 min in Cycles 1 and 2, and if well-tolerated, over 30 min in subsequent cycles. Treatment was continued until objective disease progression or unacceptable toxicity was observed.

Assessments

Criteria for dose-limiting toxicity

Dose-limiting toxicities (DLTs) were defined as any of the following treatment-related adverse events (AEs) occurring during Cycle 1: thrombocytopenia (grade ≥ 4) lasting for > 24 h; anemia (grade ≥ 4); neutropenia (grade ≥ 4) lasting for > 4 days or accompanied by a fever of ≥ 38 °C; increased T-Bil, AST, ALT, or blood alkaline phosphatase (ALP) (grade ≥ 3) lasting for > 72 h; non-hematologic toxicity (grade ≥ 3) with the exception of controllable diarrhea, nausea, vomiting, and/or infusion-related reactions; AEs that required delaying the initiation of Cycle 2 by 21 days; or AEs judged to be intolerable by the investigator. Severity of the AEs was assessed in accordance with NCI-CTCAE version 4.0. To establish tolerability assessment criteria, we determined that the combination of T-DM1 and pertuzumab would be declared tolerable if ≤ 2 of the 6 patients developed DLTs.

Safety

Safety assessments included AE reporting, physical examination, vital signs (blood pressure, pulse rate, and body temperature), laboratory testing (hematology, blood chemistry, coagulation profiles, and urinalysis), 12-lead electrocardiogram, and echocardiogram or MUGA scan. The echocardiogram or MUGA scan was measured every 2 cycles for the first 24 weeks, then every four cycles.

PK sampling

PK samples for T-DM1 and total trastuzumab in serum, as well as DM1 in plasma were collected pre-dose, 30 min, 3, 24, 48, and 96 h after the end of the infusion, as well as on days 8 and 15 of cycle 1; pre-dose, 30 min, 3 h, and on day 8 of cycle 3; pre-dose and at 30 min of cycles 2, 4, 5, and 6; and at study completion. PK samples for pertuzumab were collected pre-dose, 30 min after the end of the pertuzumab infusion, and 30 min after the end of the T-DM1 infusion on days 2, 5, 8, and 15 of cycle 1; pre-dose and 30 min after T-DM1 on day 8 of cycle 3; pre-dose and 30 min after T-DM1 for cycles 2, 4, 5, and 6; and at study completion.

Serum concentrations of T-DM1, total trastuzumab and pertuzumab, anti-T-DM1 antibodies, and anti-pertuzumab antibodies were analyzed using a validated enzyme-linked immunosorbent assay from Pharmaceutical Product Development Inc. (Richmond, VA, USA). Concentrations of free DM1 in plasma were determined using a validated liquid chromatography and tandem mass spectrometry method from QPS Netherlands B.V. (Groningen, The Netherlands). The PK parameters of each patient, including maximum serum concentration (C_{max}), area under the time–concentration curve (AUC), terminal half-life ($t_{1/2}$), clearance, and the apparent volume of distribution at steady state (V_{ss}) were determined by noncompartmental analysis of concentration data for serum T-DM1, serum total trastuzumab, and serum pertuzumab from cycle 1, including data from immediately before cycle 2 dosing; similar analyses of plasma free DM1 concentrations were performed. Summary statistics were calculated for concentrations of serum T-DM1, serum total trastuzumab, plasma free DM1, serum pertuzumab, and for PK parameters of T-DM1, total trastuzumab, free DM1, and pertuzumab.

Samples for anti-T-DM1 antibodies and anti-pertuzumab antibodies were collected before pertuzumab infusion on day 1 from cycles 1 to 6 and at the follow-up visit. Assays for anti-T-DM1 antibodies and anti-pertuzumab antibodies, as well as drug concentration were performed centrally.

SAS software (version 9.2, SAS Institute, Inc., NC, USA) was used for statistical analyses.

Antitumor activity

Tumor assessments using computed tomography (CT) or magnetic resonance imaging (MRI) scans of the chest, abdomen, and pelvis were performed every 6 weeks for the first four assessments, then every 12 weeks. Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.

Analysis populations and statistical analyses

The intent-to-treat (ITT) and safety evaluable population included all patients who received one or more doses of the study treatment. The DLTs evaluable population was defined as patients from the ITT population who did not meet the unevaluable criteria for DLTs, including patients who discontinued study treatment for reasons other than treatment-related AEs during cycle 1; patients with insufficient safety assessment during cycle 1; or patients with insufficient study drug administration during cycle 1 for reasons other than AEs. The PK evaluable population included patients who received one or more doses of T-DM1 and whose PK parameters were measured.

The sample size was set to 6 patients to confirm tolerability, based on the Japanese Guidelines for Clinical Evaluation Methods of Anti-cancer Drugs and Guidelines for Exploratory Clinical Trials of Combination Anti-cancer Chemotherapy. Statistical analyses were descriptive.

Results

Six patients were enrolled from 4 institutes in Japan between August 2010 and October 2010. All patients received study treatment, thus the ITT and safety evaluable population included all 6 patients. One patient was not evaluable for DLTs because administration of study treatment of cycle 2 was initiated before meeting the administration continuation criteria. All 6 patients were evaluable for antitumor efficacy according to the RECIST criteria.

Baseline characteristics for the six patients are shown in Table 1. Median patient age was 57.5 (range 46–68) years, most patients (83%) had an ECOG performance status of 0. All patients had HER2 IHC 3+/FISH-positive breast cancer. Four patients (67%) had estrogen receptor (ER)-negative and progesterone receptor (PgR)-negative breast cancer, and 2 patients (33%) had ER-positive/PgR-negative breast cancer.

Safety

The median duration of treatment was 11 (range 1–32) cycles. All patients experienced ≥ 1 treatment-emergent AEs (TEAEs) of any grade. The incidence of TEAEs is listed in Table 2. The most common TEAEs observed in three or more patients were diarrhea ($n=4$), AST increased, nausea, chills, pyrexia, rash, headache, dysgeusia, muscle spasms, and rhinorrhea ($n=3$). Grade 3 or greater TEAEs were observed in three patients, including grade 3 AST increased, grade 3 LVEF decreased and grade 3 neutrophil counts decreased ($n=1$). A DLT was observed in one patient (grade 3 LVEF decreased); the patient had a moderate amount of pericardial effusion before initiating study treatment, and LVEF decreased from 51% at baseline to 26% on day 15 of cycle 1. The patient discontinued study treatment, and LVEF recovered to 60% on day 45. Since DLT was observed in only one out of the 5 DLT-evaluable patients, the data monitoring committee determined the combination of T-DM1 and pertuzumab to be tolerable in Japanese patients.

Serious AEs (SAEs) were observed in two patients, including a grade 2 hemorrhagic gastric ulcer and grade 2 epistaxis. No AEs leading to death were observed. AEs leading to treatment discontinuation were observed in 4 patients and included epistaxis, serum bilirubin increased, LVEF decreased and AST increased ($n=1$). AEs leading to dose reduction or treatment interruption were not observed, whereas AEs leading to treatment delay occurred in 4 patients and included AST increased, and platelet count decreased ($n=2$), as well as ALT increased, blood ALP increased, epistaxis, hemoglobin decreased, serum bilirubin increased, hemorrhagic gastric ulcer, neutrophil count decreased and anemia ($n=1$).

Table 1 Baseline characteristics

	$N=6$
Median age, years (range)	57.5 (46–68)
ECOG PS, *n*	
0	5
1	1
HER2 status (IHC/FISH), *n*	
3+/+	6
2+/+	0
Hormone receptor (ER/PgR), *n*	
−/−	4
+/−	2
HER2-targeted therapy as a component of neoadjuvant or adjuvant therapy	
Yes	6
No	0
HER2-targeted therapy for MBC	
Yes	6
No	0
Regimens for MBC, *n* (%)	
Trastuzumab	6 (100.0)
Taxane	5 (83.3)
Vinorelbine	3 (50.0)
Lapatinib	1 (16.7)
Median number of prior regimens for MBC (range)	2.5 (1–5)
Median number of prior trastuzumab-containing therapies for MBC (range)	2.5 (1–4)

Table 2 Treatment-emergent adverse events (TEAEs)

Adverse event	Any	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	4	4	0	0	0
AST increased	3	1	1	1	0
Nausea	3	2	1	0	0
Chills	3	3	0	0	0
Pyrexia	3	3	0	0	0
Rash	3	3	0	0	0
Headache	3	3	0	0	0
Dysgeusia	3	3	0	0	0
Muscle spasms	3	3	0	0	0
Rhinorrhea	3	3	0	0	0
Thrombocytopenia	2	0	2	0	0
Blood bilirubin increased	2	0	2	0	0
Epistaxis	2	1	1	0	0
Malaise	2	2	0	0	0
Fatigue	2	2	0	0	0
Myalgia	2	2	0	0	0
Nasopharyngitis	2	2	0	0	0
Decreased appetite	2	2	0	0	0
Ejection fraction decreased	1	0	0	1[a]	0
Neutrophil count decreased	1	0	0	1	0
ALT increased	1	0	1	0	0
Hemoglobin decreased	1	0	1	0	0
Blood ALP increased	1	0	1	0	0
Anal fistula	1	0	1	0	0
Hemorrhagic gastric ulcer	1	0	1	0	0
Vomiting	1	0	1	0	0
Cystitis	1	0	1	0	0
Anemia	1	0	1	0	0

Grade 1 TEAEs that occurred in one case are excluded

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase

[a]Dose-limiting toxicity

Pharmacokinetics

PK samples were obtained from all 6 enrolled patients. PK parameters for serum T-DM1, serum total trastuzumab, plasma free DM1, and serum pertuzumab are summarized in Table 3. Serum concentrations of T-DM1, total trastuzumab, and pertuzumab quickly reached steady state when administered repeatedly at 3-week intervals; accumulation was insignificant.

The PKs for serum T-DM1, serum total trastuzumab, and plasma free DM1 when T-DM1 was administered in combination with pertuzumab were compared with the results from the Japanese phase I study (JO22591) [12], in

Table 3 Pharmacokinetic parameters of T-DM1, total trastuzumab, free DM1, and pertuzumab

Analyte	C_{max} (μg/mL)		AUC_{last} (μg day/mL)		AUC_{inf} (μg day/mL)		$t_{1/2}$ (days)		V_{ss} (mL/kg)		CL (mL/day/kg)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
T-DM1	65.0	8.78	275	84.7	282	85.0	3.73	0.990	71.8	11.4	14.1	5.19
TTmab	72.0	17.4	434	197	479	233	6.06	2.12	70.7	17.8	9.72	5.83
Analyte	C_{max} (ng/mL)		AUC_{last} (ng day/mL)		AUC_{inf} (ng day/mL)		$t_{1/2}$ (days)		V_{ss} (mL/kg)		CL (mL/day/kg)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Free DM1	3.75	0.794	6.37	3.05	10.9	4.95	2.97	1.51	–		–	
Analyte	C_{max} (μg/mL)		AUC_{last} (μg day/mL)		AUC_{inf} (μg day/mL)		$t_{1/2}$ (days)		V_{ss} (L)		CL (L/day)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Pertuzumab	301	28.9	2760	524	3970	1270	14.1	5.45	4.09	0.733	0.235	0.0929

T-DM1 trastuzumab-DM1, *TTmab* total trastuzumab, C_{max} maximum serum concentration, AUC_{last} area under the serum concentration–time curve from time zero to the last measurable concentration, AUC_{inf} area under the serum concentration–time curve from time zero extrapolated to infinity, $t_{1/2}$ terminal half-life, V_{ss} volume of distribution at steady state, *CL* total clearance, *SD* standard deviation

which T-DM1 was investigated as a single-agent (Figs. 1, 2). PK parameters for serum T-DM1, serum total trastuzumab, and plasma free DM1 were in a similar range for both studies. The PKs for serum pertuzumab when administered in combination with T-DM1 were also compared with the results from the Japanese phase I study (JO17076) [13], in which pertuzumab as a single-agent was investigated, and the CLEOPATRA trial, in which pertuzumab, as well as trastuzumab plus a taxane were investigated (Fig. 3). PK parameters for serum pertuzumab were similar regardless of whether pertuzumab was administered alone or in combination with T-DM1 or with trastuzumab plus a taxane.

All patients were tested for the presence of anti-T-DM1 and anti-pertuzumab antibodies. Two patients developed anti-T-DM1 antibodies and one patient developed anti-pertuzumab antibodies. One patient who was positive for both antibodies had earlier clearance of serum T-DM1, trastuzumab, and pertuzumab than that of the other patients; however, there were no obvious differences in plasma concentration of free DM1.

Efficacy

All 6 patients were evaluable for tumor response according to RECIST version 1.0. The best overall responses included

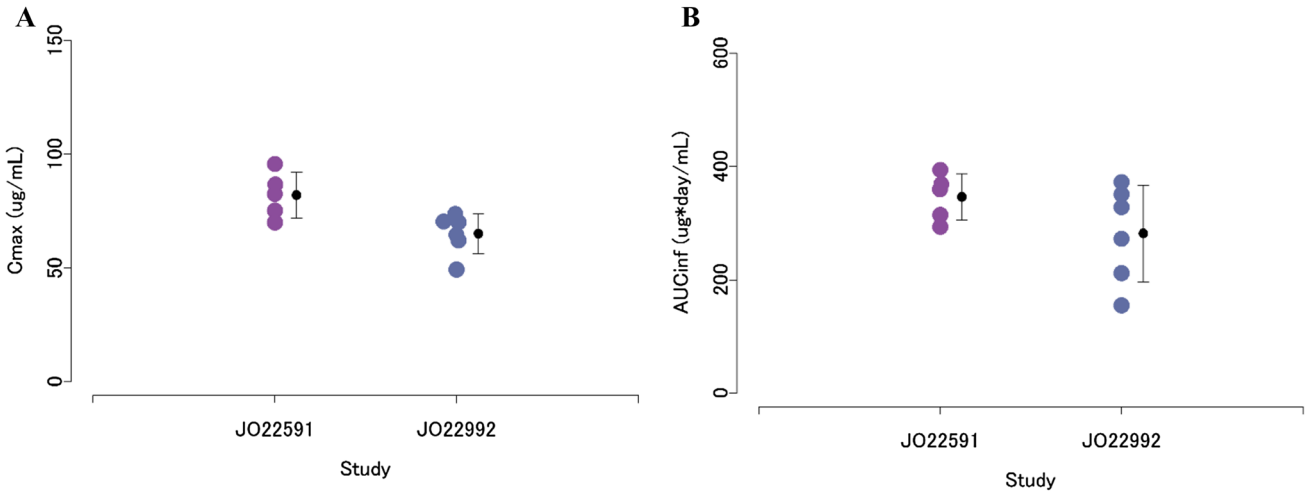

Fig. 1 Comparison of PK parameters for serum T-DM1 in Japanese patients between JO22591 [12] (T-DM1 3.6 mg/kg, $N=5$) and JO22992 (T-DM1 3.6 mg/kg and pertuzumab, $N=6$): **a** comparison of maximum serum concentration (C_{max}), **b** comparison of area under the serum concentration–time curve from time zero extrapolated to infinity (AUC_{inf}). Error bars indicate standard deviation of the mean

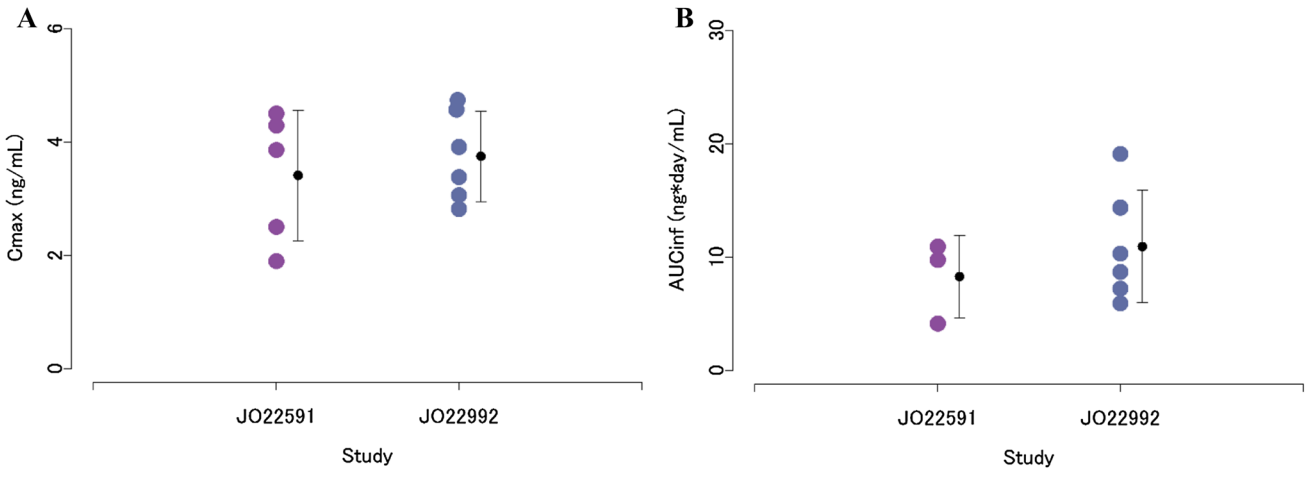

Fig. 2 Comparison of PK parameters for free T-DM1 in Japanese patients between JO22591 [12] (T-DM1 3.6 mg/kg, $N=5$) and JO22992 (T-DM1 3.6 mg/kg and pertuzumab, $N=6$): **a** comparison of maximum serum concentration (C_{max}), **b** comparison of area under the serum concentration–time curve from time zero extrapolated to infinity (AUC_{inf}). Error bars indicate standard deviation of the mean

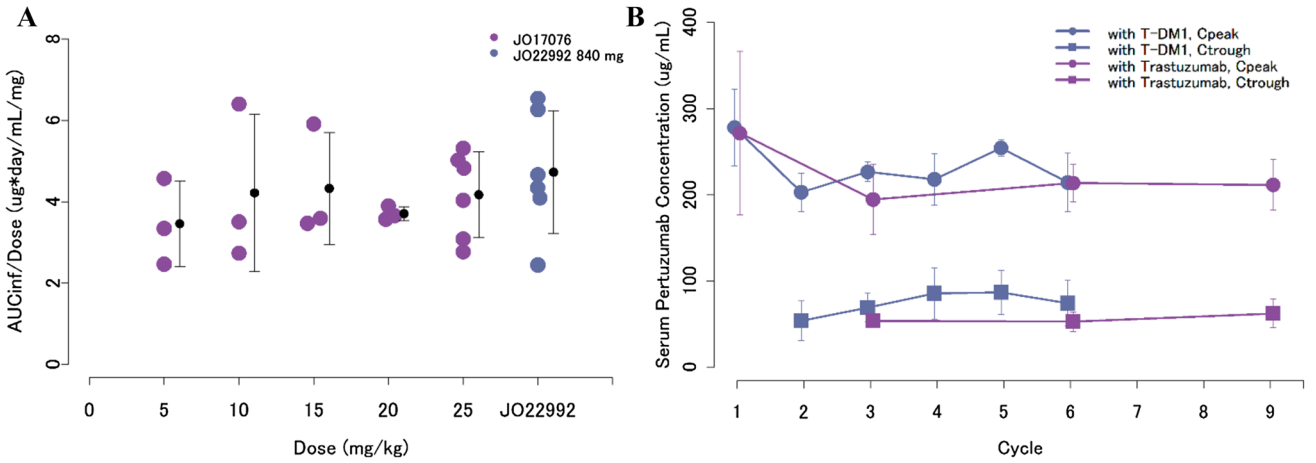

Fig. 3 Comparison of PK parameters for serum pertuzumab in Japanese patients: **a** comparison of area under the serum concentration–time curve from time zero extrapolated to infinity (AUC_{inf}) for serum pertuzumab between JO17076 [13] (pertuzumab, $N=18$) and JO22992 (T-DM1 3.6 mg/kg and pertuzumab, $N=6$), **b** comparison of serum pertuzumab concentration between CLEOPATRA [5–7] (pertuzumab, trastuzumab and docetaxel, $N=4$) and JO22992 (T-DM1 3.6 mg/kg and pertuzumab, $N=6$). Error bars indicate standard deviation of the mean

a partial response (PR) in 3 patients (50%) and stable disease (SD) in 2 patients (33%); the response in 1 patient was not evaluable (NE). For the 3 patients who experienced a PR, the median duration of response was 259 (range 38–554) days.

The best overall responses of the patients who developed anti-T-DM1 antibodies, or anti-T-DM1 and anti-pertuzumab antibodies were SD and PR, respectively.

Discussion

This was the first clinical trial examining T-DM1 and pertuzumab as a combination therapy in Japanese patients with HER2-positive metastatic breast cancer who previously received trastuzumab and a chemotherapy-containing treatment. T-DM1 administered in combination with pertuzumab was generally well tolerated. A DLT was found in one patient (grade 3 LVEF decreased); however, it resolved within 30 days. The results of this study satisfied the tolerability assessment criteria, and the combination of T-DM1 plus pertuzumab was concluded to be tolerable in Japanese patients. The PK parameters of T-DM1 and pertuzumab were not affected by co-administration of the drugs. The effects of anti-drug antibodies on the efficacy and safety of T-DM1 and pertuzumab were unclear. Most patients had a durable response, with 3 PRs, despite having been previously treated with trastuzumab and chemotherapy-containing therapies for their metastatic disease, none of which showed progressive disease (PD).

The combination therapy of T-DM1 plus pertuzumab did not appear to substantially increase toxicity in our study, as reported in previous studies [9–11]. Nevertheless, results of the MARIANNE trial showed no additional benefit from adding pertuzumab to T-DM1 treatment; therefore, the combination of T-DM1 with pertuzumab is not standard of care for patients with HER2-positive advanced breast cancer.

The combination of T-DM1 with pertuzumab was also investigated in patients with HER2-positive early breast cancer. The phase III KRISTINE trial (NCT02131064) compared neoadjuvant T-DM1 plus pertuzumab with docetaxel plus carboplatin plus trastuzumab plus pertuzumab (TCH + P). The primary endpoint of KRISTINE trial was pathologic complete response (pCR). TCH + P yielded a significantly higher pCR rate (55.7%) than that of T-DM1 plus pertuzumab (44.4%) [14]. However, T-DM1 plus pertuzumab was associated with a better safety profile, a longer maintenance of patient-reported health-related quality of life, and physical functioning. Another phase III study (KAITLIN; NCT01966471) comparing adjuvant anthracyclines followed by T-DM1 plus pertuzumab with anthracyclines followed by trastuzumab plus pertuzumab plus a taxane is ongoing.

Considering the favorable safety profile of the combination of T-DM1 with pertuzumab, there is the possibility that the combination may be a preferable option for elderly patients or patients with poor performance status who cannot tolerate toxicity attributable to cytotoxic agents. A confirmatory clinical trial targeting “unfit” patients will be needed. Furthermore, translational research for biomarkers may help to identify patients who can benefit most from the combination therapy of T-DM1 and pertuzumab.

In conclusion, the combination therapy of T-DM1 plus pertuzumab was tolerable for Japanese patients with HER2-positive metastatic breast cancer, suggesting the combination

of T-DM1 with pertuzumab is useful; these results support participation in the MARIANNE study from Japan.

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Compliance with ethical standards

Conflict of interest KT and JH declare no conflicts of interest. EN has received honoraria from Chugai and Novartis. MH has received honoraria from Chugai, AstraZeneca, Eli Lilly, Pfizer, Eisai, Daiichi-Sankyo, and Novartis. NS has received remuneration from Chugai, AstraZeneca, Eisai, Pfizer, and Taiho. KK and KM are employees of Chugai. HI has received grants from Chugai, AstraZeneca, Bayer, Eli Lilly, GSK, Kyowa Hakko Kirin, MSD, Novartis, and Pfizer; honoraria from Chugai, AstraZeneca, Eisai, and Pfizer. YF has received grants from Chugai and Takeda; honoraria from Chugai, Astra Zeneca, Daiichi-Sankyo, Eisai, Eli Lilly, Novartis, and Taiho.

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