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ORIGINAL ARTICLE

Ethnic sensitivity assessment of the antibody–drug conjugate trastuzumab emtansine (T-DM1) in patients with HER2-positive locally advanced or metastatic breast cancer

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Abstract
Purpose Trastuzumab emtansine (T-DM1) is indicated for previously treated HER2-positive metastatic breast cancer. Ethnic sensitivity assessment of T-DM1 was conducted using data from eight clinical studies to ensure that the clinically recommended dose is appropriate across ethnicities.
Methods Four approaches were used: (1) non-compartmental analysis (NCA) comparing pharmacokinetic parameters of T-DM1 and relevant analytes across ethnic groups, (2) population pharmacokinetic (popPK) analysis assessing the impact of ethnicity on pharmacokinetics, (3) comparison of T-DM1 pharmacokinetics in Japanese patients versus the global population, and (4) exposure–response analyses assessing the impact of ethnicity on safety and efficacy.
Results NCA pharmacokinetic parameters (T-DM1, total trastuzumab, DM1) were comparable across ethnic groups; mean cycle 1 T-DM1 AUC_{inf} was 475, 442, and 518 day μg/mL for white ($n = 461$), Asian ($n = 68$), and others ($n = 57$), respectively. PopPK analysis showed that ethnicity (white, Asian, and others) was not a significant covariate for T-DM1 pharmacokinetics ($n = 671$). Additionally, visual predictive check plots indicated that observed pharmacokinetic profiles in Japanese patients ($n = 42$) were within the prediction interval generated from the final PopPK model. Exposure–response analyses showed that ethnicity was not a significant covariate impacting efficacy or hepatotoxicity risk, but there was a trend of greater thrombocytopenia risk among Asians versus non-Asians, which could not be explained by similar exposure between the ethnic groups. Most Asians with thrombocytopenia were able to continue T-DM1 using dose-adjustment rules recommended for the global population.
Conclusions These results suggest that T-DM1 pharmacokinetics are comparable across ethnic groups and that use of the current dosing regimen is appropriate across ethnicities.

Keywords T-DM1 · Trastuzumab emtansine · Antibody–drug conjugate · Metastatic breast cancer · Pharmacokinetics · Ethnic sensitivity

Introduction

Trastuzumab emtansine (T-DM1) is an antibody–drug conjugate that contains the humanized anti-human epidermal growth factor receptor 2 (HER2) IgG1 antibody trastuzumab conjugated through a stable thioether linker to the maytansine derivative DM1. T-DM1 delivers DM1 specifically to HER2-overexpressing cells. Once internalized, T-DM1 undergoes lysosomal degradation leading to the release of DM1, which induces apoptosis by inhibiting microtubule polymerization [1]. In addition, like trastuzumab, T-DM1 inhibits HER2 signaling and shedding and induces antibody-dependent cellular cytotoxicity [2]. In two randomized, phase III studies of patients with previously treated HER2-positive locally advanced breast cancer (LABC) or metastatic breast cancer (MBC), single-agent T-DM1 3.6 mg/kg administered every 3 weeks (q3w) conferred statistically significant benefits in progression-free

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survival (PFS) [3, 4] and overall survival (OS) [3] relative to control treatment regimens. In these studies, T-DM1 was also associated with a numerically lower incidence of grade ≥3 adverse events (AEs) and AEs leading to treatment discontinuation [3, 4]. T-DM1 is approved for the treatment of HER2-positive MBC previously treated with trastuzumab and a taxane (separately or in combination) in many countries, including the USA, European Union countries, Canada, Switzerland, and Japan.

The pharmacokinetics of T-DM1 and relevant analytes (total trastuzumab and DM1) after T-DM1 dosing were characterized in phase I–III studies by non-compartmental analysis (NCA) [5, 6]. Phase I data suggested that T-DM1 conjugate, the major analyte of interest, exhibits faster clearance (CL) at doses ≤1.2 mg/kg and dose-independent pharmacokinetics at doses ≥2.4 mg/kg q3w [7]. In phase II and phase III studies with T-DM1 3.6 mg/kg q3w, linear pharmacokinetic characteristics with no apparent target-mediated elimination were confirmed, and no significant accumulation was observed upon repeated q3w dosing, consistent with T-DM1's terminal half-life of approximately 4 days [5]. A population PK (popPK) model was developed to further characterize the pharmacokinetics of T-DM1 conjugate based on single-agent T-DM1 pharmacokinetic data across phase I–III studies [8]. T-DM1 conjugate pharmacokinetics at the clinical dose range were adequately described by a linear two-compartment model with first-order elimination from the central compartment. The estimated total body clearance, central volume of distribution, and elimination half-life of T-DM1 were 0.676 L/day, 3.127 L, and 3.94 days, respectively.

Ethnicity and race have generally been considered important demographic variables that may contribute to the observed interindividual variability in small molecule pharmacokinetics and pharmacodynamics, potentially resulting in variability in response to drug therapy. Ethnic differences have been identified in the frequencies of functional variants of several polymorphic drug metabolizing enzymes (e.g., CYP2C19, CYP2C9, and CYP2D6) and transporters (e.g., P-gp) [9–11]. These differences could contribute to variable enzyme-mediated metabolism of a drug, potentially affecting the drug's pharmacokinetics and therapeutic effects [9, 11]. Extrinsic factors, such as diet and environmental factors, may also contribute to differences in the pharmacokinetics of small molecule drugs among ethnic groups. Ethnic differences in pharmacokinetics and/or pharmacodynamics have been demonstrated for several approved small molecule drugs, such as tacrolimus, warfarin, and rosuvastatin [9–11]. In pharmacokinetic studies, rosuvastatin exposure was approximately twofold higher in Asian subjects compared with white subjects, which resulted in a lower recommended starting dose of rosuvastatin for Asian patients in the USA prescribing information [12]. Ethnic differences in the allelic frequencies of breast cancer-resistant protein (BCRP) were shown to partly contribute to the observed ethnic differences in pharmacokinetics of rosuvastatin [13]. In contrast, monoclonal antibodies undergo both non-specific and specific catabolic elimination pathways via intracellular catabolism followed by fluid-phase or receptor-mediated endocytosis. Ethnic differences in these antibody clearance mechanisms have not been demonstrated. Accumulating evidence shows that ethnicity may not play a significant role in the disposition of monoclonal antibodies [14, 15]. Given that T-DM1 is an antibody–drug conjugate with both small and large molecule components, the clinical development of T-DM1 included assessments of pharmacokinetics, efficacy, and safety in different ethnic groups to ensure that the clinically recommended dose regimen (3.6 mg/kg q3w) is appropriate for patient populations of different ethnicities, particularly Asian patients.

Materials and methods

Patients

This ethnic sensitivity assessment used data from the eight phase I–III clinical trials of single-agent T-DM1 available at the time of the present analysis: TDM3569g [7, 16], TDM4258g [17], TDM4374g [18], TDM4450g [19], TDM4688g [20], TDM4370g/EMILIA [3], JO22591 [21], and JO22997 [22]. Detailed inclusion and exclusion criteria are described in each of the respective reports. Briefly, all patients had HER2-positive (immunohistochemistry 3+ and/or in situ hybridization-positive) LABC or MBC. Most of these studies recruited patients who had received prior treatment in the metastatic setting, but all patients in the TDM4450g study were previously untreated in the metastatic setting [19], and EMILIA study participants could have been either treatment naïve or treatment experienced in the metastatic setting. The majority of patients participating in these eight clinical trials were administered single-agent T-DM1 3.6 mg/kg q3w. However, both TDM3569g and JO22591 were phase I dose-finding studies; the former sought to identify the maximum tolerated dose (MTD) of weekly T-DM1, with doses ranging from 1.2 to 2.9 mg/kg [16], and of q3w T-DM1, with doses ranging from 0.3 to 4.8 mg/kg [7]. The JO22591 study sought to identify the MTD of q3w T-DM1 in Japanese patients. JO22591 study participants received T-DM1 1.8, 2.4, or 3.6 mg/kg q3w [21]. An overview of these clinical studies, as well as their respective pharmacokinetic sampling schedules, is provided in Table 1. Similar pharmacokinetic sampling schedules were adopted for most of these studies.

All patients from each clinical trial provided written informed consent. Each trial was approved by the

Table 1 Overview of the clinical studies informing the ethnic sensitivity assessment of T-DM1 3.6 mg/kg q3w

Study	Study design	Patients enrolled, *n*	Patients with available T-DM1 PK samples	T-DM1 regimen	PK sampling schedule
TDM3569g [7, 16]	Phase I, dose-escalating	54	52	0.3, 0.6, 1.2, 2.4, 3.6, 4.8 mg/kg q3w 1.2, 1.6, 2.0. 2.4, 2.9 mg/kg qw	Intensive sampling in cycle 1; peak/trough sampling in subsequent cycles
TDM4258g [17]	Phase II, single-arm	112	109	3.6 mg/kg q3w	Frequent sampling[a] in cycles 1 and 4; peak/trough sampling in subsequent cycles
TDM4374g [18]	Phase II, single-arm	110	106	3.6 mg/kg q3w	Frequent sampling[a] in cycles 1 and 4; peak/trough sampling in subsequent cycles
TDM4688g [20]	Phase II, single-arm	51	51	3.6 mg/kg q3w	Frequent sampling[a] in cycles 1 and 3; peak/trough sampling in cycle 2
TDM4450g [19]	Phase II, two-arm, randomized	139 (T-DM1, $n = 69$; trastuzumab + docetaxel, $n = 70$)	65	3.6 mg/kg q3w	Frequent sampling[a] in cycles 1 and 5; peak/trough sampling in every other cycle
EMILIA [3]	Phase III, two-arm, randomized	991 (T-DM1, $n = 495$; lapatinib + capecitabine, $n = 496$)	307	3.6 mg/kg q3w	Frequent sampling[a] in cycles 1 and 4; peak/trough sampling in cycles 2, 4, 6, 8, 12, 16
JO22591 [21]	Phase I, dose-escalating	10	10	1.8, 2.4, 3.6 mg/kg q3w	Intensive sampling in cycle 1; peak/trough sampling in subsequent cycles
JO22997 [22]	Phase II, single-arm	76	32	3.6 mg/kg q3w	Frequent sampling in cycle 1, 2, and 4; peak/trough sampling in subsequent cycles

PK pharmacokinetic, *q3w* every 3 weeks, *qw* every week, *T-DM1* trastuzumab emtansine

[a] Blood samples were collected prior to dosing and at the end of infusion (30 min post-infusion); additional blood samples were collected on days 8 and 15

relevant institutional review board at each site according to local clinical guidelines. These studies were conducted in accordance with ethical guidelines such as the Good Clinical Practice Guidelines laid down by the Declaration of Helsinki and other relevant local guidelines.

Assessments

Ethnic sensitivity was assessed via four approaches using pharmacokinetic data derived from the eight aforementioned phase I–III studies.

Ethnic assessment using non-compartmental analysis (NCA)

The impact of ethnicity on the pharmacokinetics of T-DM1, total trastuzumab (sum of T-DM1 conjugate and unconjugated trastuzumab), and DM1 was assessed by categorizing patients into one of three groups based on ethnicity: white, Asian, or others. To ensure adequate numbers of patients in each ethnic group, patients from ethnic groups other than white or Asian (i.e., black, Native Hawaiian or Pacific Islander, American Indian or Alaska Native, Hispanic, or patients with more than one self-selected race category) were grouped together as "Others."

The pharmacokinetic parameters of T-DM1, total trastuzumab, and DM1 at cycle 1 were calculated using a standard NCA method (WinNonlin 5.2.1) across six of the eight aforementioned clinical studies; data from JO22591 and JO22997 were not included in the NCA, as the pharmacokinetics of T-DM1 in Japanese patients was assessed separately. All patients from studies TDM3569g, TDM4258g, TDM4374g, TDM4450g, TDM4688g, and EMILIA with at least one available pharmacokinetic parameter [e.g., maximum concentration (C_{max})] were included in the analysis. Cycle 1 was selected as the time point to calculate pharmacokinetic exposures because T-DM1 3.6 mg/kg q3w has been shown not to accumulate, with an elimination half-life ($t_{1/2}$) of 3–4 days [5].

Ethnic assessment using population pharmacokinetic modeling approaches

A previously established population pharmacokinetic model based on the available T-DM1 conjugate concentration data from studies TDM3569g, TDM4258g, TDM4374g, TDM4450g, and EMILIA was used for this analysis [8]. Covariate analysis was performed to assess whether ethnicity is a statistically significant covariate for pharmacokinetic parameters [8]. Bayesian post hoc pharmacokinetic parameter estimates of T-DM1, including clearance (CL), central volume of distribution (V_c), and $t_{1/2}$, were summarized by ethnicity (white, Asian and others). T-DM1 exposures at steady state [i.e., area under the plasma concentration time curve (AUC), C_{max}, and trough concentration (C_{trough})] were simulated using Bayesian post hoc pharmacokinetic parameters after repeated administration of T-DM1 at the approved dose of 3.6 mg/kg q3w. Visual predictive check (VPC) plots were constructed to evaluate whether the observed pharmacokinetic profiles for patients from the three ethnic groups were within the 90 % prediction interval generated from the model simulation using parameters estimated from the global population.

Ethnic assessment using pharmacokinetic data from Japanese patients

T-DM1 pharmacokinetic data from Japanese patients with MBC were available from the phase I JO22591 and phase II JO22997 studies. Bayesian post hoc pharmacokinetic parameters (CL, V_c, AUC, and C_{max}) in Japanese patients were estimated using the final population pharmacokinetic model and compared with non-Japanese patients. VPC plots were constructed for Japanese patients using the final population pharmacokinetic model and study-specific data from JO22591 and JO22997.

Ethnic assessment using exposure–response analysis

The exposure–efficacy analysis was performed using data from the phase III EMILIA study, which recruited patients with HER2-positive LABC or MBC previously treated with trastuzumab and a taxane in any setting [3]. The efficacy endpoints were objective response rate (ORR), PFS (assessed by an independent review committee), and OS. The relationship between T-DM1 exposure and safety was assessed using data pooled from the TDM4258g, TDM4374g, TDM4450g, TDM4688g, and EMILIA studies. The safety endpoints were grade $\geq$3 AEs related to thrombocytopenia and hepatotoxicity. These safety endpoints were selected for assessment because thrombocytopenia and elevated ALT and AST were the most commonly reported grade $\geq$3 AEs with T-DM1 at the time of the analysis [3, 23]. The exposure endpoints selected for assessment included observed and model-predicted serum T-DM1 AUC, C_{max}, and C_{trough}; observed serum total trastuzumab AUC; and observed plasma DM1 C_{max} at cycle 1. Time-to-event endpoints (e.g., PFS and OS) were analyzed via the Cox proportional hazard model, with baseline covariates and exposure metrics added for regression analysis. Multivariate logistic regression was used for binary endpoints (e.g., ORR and safety endpoints). Ethnicity (Asian and non-Asian) was tested as a potential covariate. Covariates were tested at the two-sided, 0.05 level of significance using log-likelihood criteria. A two-step forward-selection and backward-elimination method ($P < 0.05$ for

forward and backward steps) was used for covariate selection [6, 24].

Results

Ethnic assessment using NCA

Across the six clinical studies used for the NCA, 626 patients who received T-DM1 3.6 mg/kg had adequate data for the determination of at least one NCA pharmacokinetic parameter at cycle 1. Of these 626 patients, 489 (78.7 %) were white, 70 (11.3 %) were Asian, and 67 (10.7 %) were classified as others. The mean estimated values for key pharmacokinetic parameters at cycle 1 for serum T-DM1 and plasma DM1 were comparable across the three ethnic groups (Table 2). Mean cycle 1 AUC_{inf} of T-DM1 conjugate was 475, 442, and 518 day μg/mL for white ($n = 461$), Asian ($n = 68$), and others ($n = 57$), respectively. Mean cycle 1 DM1 C_{max} values for white ($n = 488$), Asian ($n = 70$), and others ($n = 67$) were 5.02, 4.30, and 5.36 ng/mL, respectively. Compared with Asians, whites appeared to have an approximately 31 % higher mean AUC_{inf} value for serum total trastuzumab (702 vs. 1020 day μg/mL); however, the 90 % confidence intervals for mean serum total trastuzumab exposures overlapped for the two ethnic groups. The observed numerical difference in exposure between the two ethnic groups may be partly attributable to the higher mean level of serum total trastuzumab present at baseline in whites (12.24 μg/mL; range 0–57.83) versus Asians (6.21 μg/mL; range 0–28.21). Box plots of the distributions of AUC_{0-inf}, C_{max}, CL, and V_{ss} at cycle 1 for serum T-DM1, serum total trastuzumab, and plasma DM1 for Asian and other patients were within the range of values estimated for whites (Fig. 1), further illustrating the comparability of T-DM1 pharmacokinetics across different ethnic populations.

Ethnic assessment using population pharmacokinetic modeling

A total of 671 patients across five studies were included in the population pharmacokinetic model. Of these 671 patients, 541 (80.6 %) were categorized as white, 73 (10.9 %) were categorized as Asian, and 57 (8.5 %) were categorized as others. The final population pharmacokinetic model showed that ethnicity was not a statistically significant covariate for the CL or V_c of T-DM1 [8]. As shown in Table 3, Bayesian post hoc estimated pharmacokinetic parameters (CL, V_c, and $t_{1/2}$) and population pharmacokinetic-simulated exposure parameters (AUC at steady state, C_{max}, and C_{trough}) of T-DM1 conjugate were similar across the three ethnic groups. The percent differences of mean estimated pharmacokinetic and exposure parameters (CL, V_c, and $t_{1/2}$, AUC at steady state, C_{max}, and C_{trough}) between the Asian and white ethnic groups were less than 20 %. Additionally, VPC plots showed that the observed concentration–time profiles for patients who received T-DM1 3.6 mg/kg q3w across the three ethnic groups (all, $n = 634$; white, $n = 506$; Asian, $n = 73$; and others, $n = 55$) were

Table 2 Mean pharmacokinetic parameter estimates at cycle 1 for serum T-DM1, serum total trastuzumab, and plasma DM1 after treatment with T-DM1 3.6 mg/kg q3w by ethnicity

Ethnic group	Patients, *n* (%)[a]	Mean (90 % CI)			
		C_{max} (μg/mL)	AUC_{0-inf} (day μg/mL)	CL (mL/day/kg)	V_{ss} (mL/kg)
Serum T-DM1					
White	489 (78.7)	81.5 (48.8–116)	475 (270–665)	8.26 (5.38–13.3)	31.3 (11.5–55.1)
Asian	70 (11.3)	78.3 (57.4–98.0)	442 (290–576)	8.55 (6.24–12.4)	31.3 (19.2–44.9)
Others	62 (9.98)	89.9 (54.3–130)	518 (278–774)	7.62 (4.65–13.0)	27.8 (14.6–47.7)
Serum total trastuzumab					
White	489 (78.5)	89.2 (54.9–139)	1020 (371–2660)	5.00 (1.37–9.72)	42.3 (21.3–66.8)
Asian	69 (11.1)	81.1 (59.2–111)	702 (363–1290)	6.01 (2.79–9.92)	42.8 (21.8–62.3)
Others	65 (10.4)	90.1 (50.0–138)	862 (407–1850)	5.29 (1.93–8.85)	40.4 (23.5–67.8)
Plasma DM1					
White	488 (78.1)	5.02 (2.73–8.06)[b]	–	–	–
Asian	70 (11.2)	4.30 (2.24–7.83)[b]	–	–	–
Others	67 (10.7)	5.36 (3.14–9.06)[b]	–	–	–

AUC_{0-inf} area under the plasma concentration–time curve from time zero to infinity, *CI* confidence interval, *CL* clearance, *C_{max}* maximum concentration, *PK* pharmacokinetic, *T-DM1* trastuzumab emtansine, *V_{SS}* volume in steady state

[a] The number of patients for C_{max}

[b] Unit is ng/mL

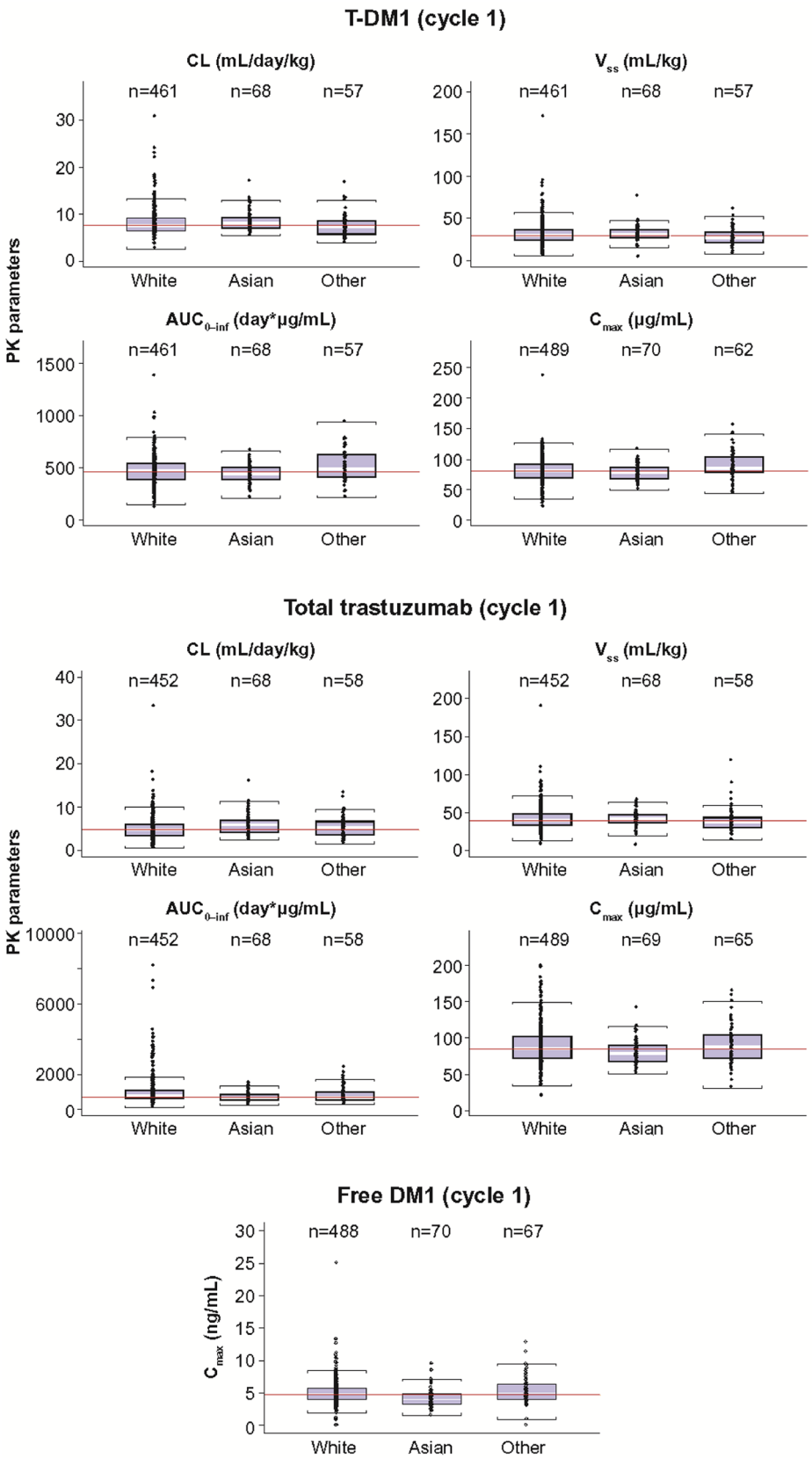

Fig. 1 *Box plots* for key pharmacokinetics parameters at cycle 1 for serum T-DM1, serum total trastuzumab, and plasma DM1 in patients with HER2-positive LABC or MBC administered T-DM1 3.6 mg/kg q3w. The median is represented by the *horizontal line in the middle of the box*. The *bottom* and *top* of the box plot represent the 25th and 75th percentiles (i.e., lower and upper quartiles, respectively). The *bars* extending from the box to the outermost data points represent 1.5 times the upper or lower interquartile range, if such observed values exist. The *orange line* indicates the median across all patients. AUC_{0-inf} area under the curve from time zero to infinity, *CL* clearance, C_{max} maximum concentration, *MBC* metastatic breast cancer, *LABC* locally advanced breast cancer, *PK* pharmacokinetic, *q3w* every 3 weeks, *T-DM1* trastuzumab emtansine, V_{SS} volume in steady state

Table 3 Bayesian post hoc pharmacokinetic parameter estimates and model-predicted steady state exposures after repeated dosing of T-DM1 3.6 mg/kg q3w by ethnicity

	Ethnic group		
	White	Asian	Others
Patients, *n* (%)	541 (80.6)	73 (10.9)	57 (8.49)
Mean (90 % CI)			
CL, L/day	0.691 (0.499–0.976)	0.647 (0.498–0.899)	0.783 (0.551–1.14)
V_c, L	3.11 (2.45–3.88)	2.80 (2.39–3.52)	3.37 (2.60–4.49)
$t_{1/2}$, day	4.92 (2.89–6.92)	4.11 (2.60–5.31)	5.67 (2.87–10.1)
AUC, day μg/mL	368 (250–516)	346 (246–428)	388 (249–531)
C_{max}, μg/mL	80.4 (66.3–99.2)	78.5 (67.6–88.4)	87.0 (72.5–107)
C_{trough}, μg/mL	2.34 (0.430–4.87)	1.89 (0.328–3.36)	2.32 (0.507–4.52)

AUC area under the curve, *CI* confidence interval, *CL* clearance, C_{max} maximum concentration, C_{trough} trough concentration, *q3w* every 3 weeks, $t_{1/2}$ half-life, *T-DM1* trastuzumab emtansine, V_c central volume of distribution

largely within the prediction interval generated from the final population pharmacokinetic simulation. These data suggest that the final population pharmacokinetic model could adequately predict the central tendency and variability of serum T-DM1 concentrations across the three ethnic groups (Fig. 2) and imply that T-DM1 pharmacokinetic profiles are consistent across different ethnic populations.

Ethnic assessment using pharmacokinetic data from Japanese patients

The pharmacokinetics of T-DM1 were evaluated in 42 Japanese patients from studies JO22591 ($n = 10$) and JO22997 ($n = 32$). In the phase I JO22591 study, patients received T-DM1 q3w at a dose of 1.8 mg/kg ($n = 1$), 2.4 mg/kg ($n = 4$), or 3.6 mg/kg ($n = 5$); all individuals enrolled in the phase II JO22997 study were treated with T-DM1 3.6 mg/kg q3w. Based on Bayesian post hoc pharmacokinetic parameter estimation in Japanese patients using the final population pharmacokinetic model, there were no apparent differences in key pharmacokinetic parameters (CL, V_c, AUC, and C_{max}) between Japanese and non-Japanese patients (Table 4). VPC plots showed that the observed pharmacokinetic profiles of the three doses of T-DM1 in Japanese patients were within the 90 % prediction interval generated from the final population pharmacokinetic simulation (Fig. 3).

Ethnic assessment using exposure–response analyses

The dataset used for the ethnic assessment of the relationship between exposure and efficacy was derived from the EMILIA study. Although 495 EMILIA study participants had been randomized to the T-DM1 3.6 mg/kg q3w treatment arm, pharmacokinetic data were available from only 307 patients [6]. There were no clear trends between observed T-DM1 exposure (i.e., observed cycle 1 AUC and C_{max}) and efficacy outcomes (PFS, OS, or ORR) following administration of T-DM1 3.6 mg/kg q3w in patients with HER2-positive LABC or MBC. However, there was a numerical trend of improved hazard ratios for PFS and OS by stratified T-DM1 model-predicted C_{min} quartiles, albeit with mostly overlapping 95 % confidence intervals [6]. Ethnicity (Asian vs. non-Asian) was not identified as a significant covariate for PFS, OS, or ORR.

For the exposure–safety analysis, pharmacokinetic data were available from 618 T-DM1-treated patients. Variations in T-DM1 AUC and C_{max} had no significant effect on the incidence of grade ≥3 hepatotoxicity or thrombocytopenia [24]. Ethnicity (Asian vs. non-Asian) was not identified as a significant covariate for the risk of experiencing grade ≥3 hepatotoxicity, but it was found to be a significant covariate for the risk of having grade ≥3 thrombocytopenia, with Asians appearing to have a higher risk than non-Asians [24], which could not be explained by the similar exposure observed between the two ethnic groups (Asian vs. non-Asian).

Discussion

This is the first publication to report an ethnic sensitivity assessment for an antibody–drug conjugate. As an antibody–drug conjugate, T-DM1 has a complex structure, with both large molecule (i.e., biologic) and small molecule (i.e., drug) characteristics. The ethnic sensitivity analyses described in this report incorporated both components into the assessment. Multiple analytes, including T-DM1 conjugate, total trastuzumab (sum of T-DM1 conjugate and unconjugated trastuzumab), and the cytotoxic agent DM1, were assessed. No apparent ethnic differences in the pharmacokinetics of T-DM1 conjugate, total trastuzumab, or DM1 were observed in patients with HER2-positive MBC participating in phase I–III clinical studies of single-agent

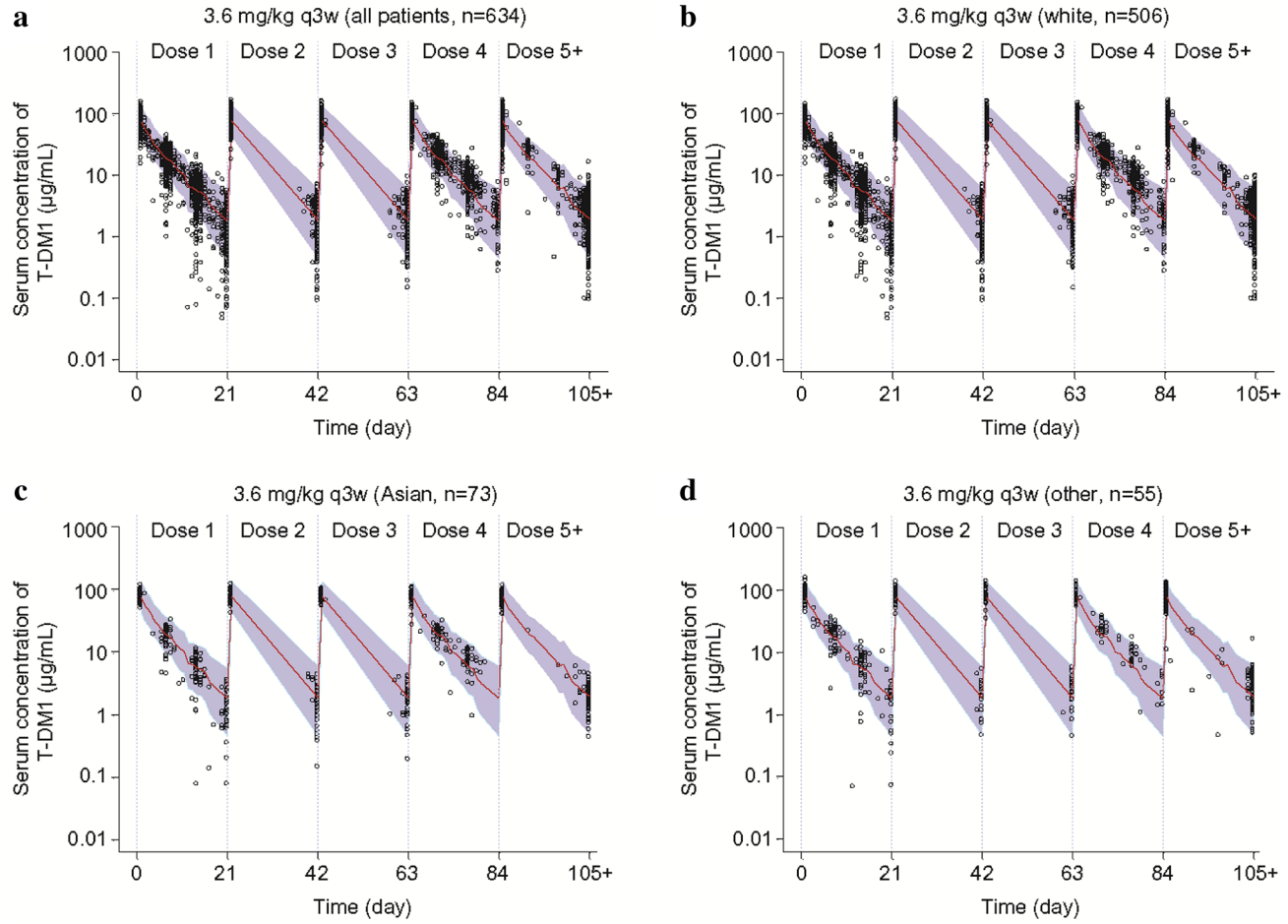

Fig. 2 VPC plots of T-DM1 serum concentration–time profiles for T-DM1 3.6 mg q3w for **a** all patients used to develop the final population pharmacokinetic model and for **b** white, **c** Asian, and **d** other ethnic subgroups. The *black points* are observed T-DM1 serum concentrations. The *red lines* are the median of the predicted concentrations by the final population pharmacokinetic model (a total of 1000 replicates of the trial were simulated using the observed covariates for each individual, the final population pharmacokinetic model parameter estimates, the estimated subject–subject random effects, and the residual error). The *blue shaded areas* are the spread (5th–95th percentile) of the predicted concentrations. Vertical lines are the time of dosing. *q3w* every 3 weeks, *T-DM1* trastuzumab emtansine, *VPC* visual predictive check

Table 4 Bayesian post hoc pharmacokinetic parameters of T-DM1 (estimated using the final population pharmacokinetic model) in Japanese and non-Japanese patients

	Mean (90 % CI)			
	C_{max}, µg/mL	AUC, day µg/mL	V_c, L	CL, L/day
Japanese patients ($n = 42$)	78.0 (61.9–91.2)	345 (216–425)	2.58 (2.09–3.16)	0.587 (0.439–0.795)
Non-Japanese patients ($n = 671$)	80.8 (66.8–99.4)	367 (248–514)	3.10 (2.45–3.91)	0.694 (0.499–0.995)

AUC area under the plasma concentration time curve, *CI* confidence interval, *CL* clearance, C_{max} maximum concentration, *T-DM1* trastuzumab emtansine, V_c central volume of distribution

T-DM1, indicating that T-DM1 is unlikely to be sensitive to ethnic factors with respect to pharmacokinetics.

Similar to monoclonal antibodies, T-DM1 is expected to undergo both target-mediated (HER2) and non-specific (partly Fc-mediated) proteolytic degradation [1, 25]. A trend of faster T-DM1 clearance (i.e., nonlinear pharmacokinetics) was observed at T-DM1 doses ≤1.2 mg/kg in the phase I dose escalation study (TDM3569g), but at doses ranging from 2.4 to 4.8 mg/kg q3w, T-DM1 exhibited linear pharmacokinetics [7]. Given that T-DM1 exhibited linear

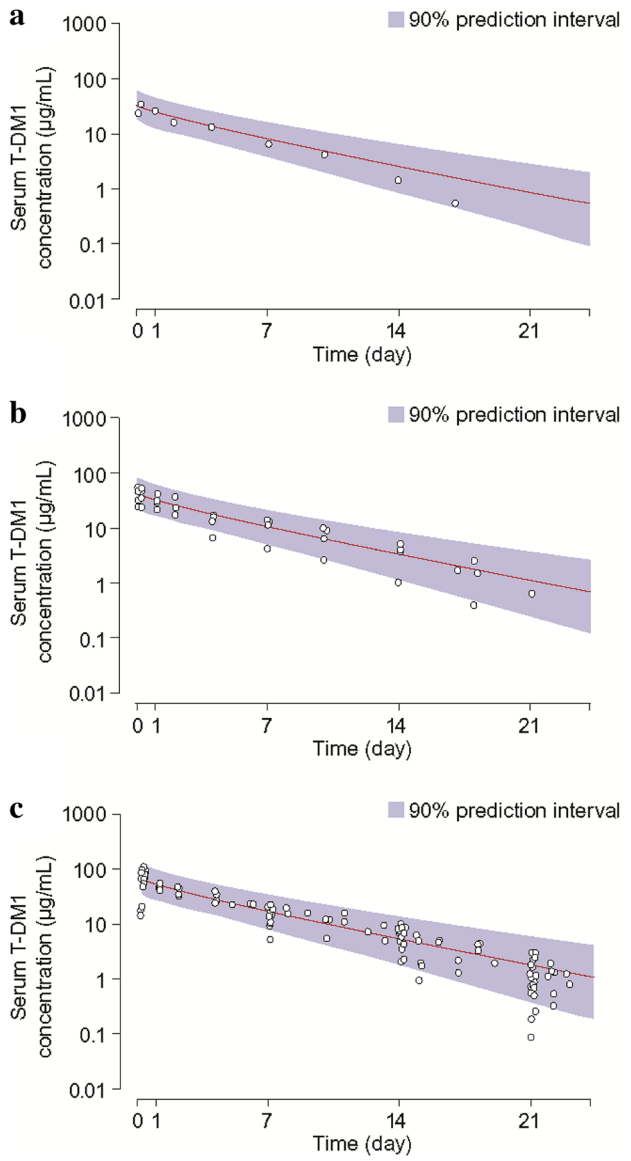

Fig. 3 Observed and 90 % prediction interval of serum T-DM1 concentrations at cycle 1 in Japanese patients administered T-DM1 **a** 1.8 mg/kg ($n = 1$), **b** 2.4 mg/kg ($n = 4$), or **c** 3.6 mg/kg ($n = 37$). The *shaded area* represents the 90 % prediction interval of serum T-DM1 concentrations predicted using the final population pharmacokinetic model for T-DM1. *Open circles* represent measured serum T-DM1 concentrations for each patient. *T-DM1* trastuzumab emtansine

pharmacokinetics at the clinically recommended dose regimen (3.6 mg/kg q3w), the pharmacokinetics of T-DM1 are unlikely to be affected by ethnic differences in HER2 expression. Notably, a population pharmacokinetic model of trastuzumab yielded similar findings [26]. Accumulating literature suggests that non-specific proteolytic degradation is unlikely to be affected by ethnicity as well [14, 15]. Moreover, since cytochrome P450 (CYP) enzymes are not involved in the catabolism of T-DM1 [27], ethnic polymorphisms in these isoenzymes are not anticipated to affect T-DM1 pharmacokinetics. This is supported by our clinical data: No apparent ethnic differences in T-DM1 exposure have been observed in patients with HER2-positive MBC across clinical studies.

DM1, the cytotoxic component of T-DM1, was detected at low levels in human plasma. Maximum systemic plasma concentrations of DM1 averaged ~6 ng/mL at the clinically recommended dose of T-DM1 (3.6 mg/kg q3w). The low systemic concentrations of DM1 may be due to its slow release from T-DM1 and its fast clearance after release. In vitro metabolism studies suggest that DM1 is metabolized mainly by CYP3A4 and to a lesser extent by CYP3A5 [28]. Ethnic differences in the disposition of CYP3A substrates, however, are poorly characterized and have not been consistently demonstrated [29]. Given substantial variations in the overall activity of CYP3A, the pharmacokinetics of DM1 are not expected to be sensitive to ethnicity. In line with this assumption, we found DM1 levels (i.e., C_{max}) after administration of T-DM1 3.6 mg/kg to be similar in Asian and white patients.

Given that T-DM1 is expected to primarily undergo deconjugation and proteolytic degradation with no significant involvement of CYP enzymes [1, 25, 27], the pharmacokinetics of T-DM1 are unlikely to be affected by concomitantly administered medications that are CYP inhibitors or inducers. In addition, DM1 is not a CYP inhibitor, CYP inducer, or P-glycoprotein inhibitor at clinically relevant concentrations [30]. DM1 is thus unlikely to be a perpetrator in altering the pharmacokinetics of concomitant medications. However, because DM1 is mainly metabolized by CYP3A4/5, there is potential for DM1 to be a victim of CYP3A inhibitors/inducers. Due to the potential increase in DM1 exposure, a conservative approach was adopted in T-DM1 labeling, which recommends that concomitant use of T-DM1 with strong CYP3A4 inhibitors be avoided [31]. However, exploratory analyses undertaken with data from the phase III EMILIA study demonstrated that concomitant administration of CYP3A inhibitors or inducers does not result in any noticeable change in the pharmacokinetics of either T-DM1 or DM1 [32]. Additionally, phase Ib/II studies have examined the use of T-DM1 in combination with docetaxel, paclitaxel, or pertuzumab [27, 33, 34]. The pharmacokinetics of T-DM1 and DM1 were not affected by the concomitant use of taxanes or pertuzumab. Moreover, the pharmacokinetics of docetaxel, paclitaxel, and pertuzumab were similar with and without co-administration of T-DM1 [27, 33, 34]. Based on these data, T-DM1 is not expected to have clinically relevant interactions with co-administered drugs and thus has low potential to exhibit ethnic sensitivity from a drug–drug interaction perspective.

We also evaluated the effect of ethnicity on treatment outcomes. Ethnicity (Asian vs. non-Asian) was not

identified as a covariate that would significantly impact efficacy outcomes (i.e., PFS, OS, and ORR) or the risk of grade ≥3 hepatotoxicity. However, ethnicity was found to be a significant covariate for the risk of grade ≥3 thrombocytopenia, with Asian patients appearing to have a higher risk than non-Asian patients. The apparent differences in risk could not be explained by similar T-DM1 exposure observed between the two ethnic groups, but could possibly be related to ethnic differences in baseline platelet counts. Platelet counts at baseline were lower in the 42 Japanese patients participating in the JO22591 and JO22997 studies than in the 671 non-Japanese patients used to develop the final population pharmacokinetic model. However, in an integrated safety analysis of 884 T-DM1-treated patients, the higher rate of grade ≥3 decreases in platelet count in Asians relative to non-Asians was independent of baseline platelet levels [23]. This is also consistent with our exposure–response analysis, which found ethnicity (Asian vs. non-Asian) to remain a statistically significant covariate for the risk of grade ≥3 thrombocytopenia even after adjusting for differences in baseline platelet counts [24]. Regardless of the cause, the increased risk of grade ≥3 thrombocytopenia does not appear to have serious clinical consequences, for in the integrated safety analysis, the incidence of grade 3–4 hemorrhage was similarly low in Asian and non-Asian patients [23]. Moreover, Asian patients with thrombocytopenia were able to continue treatment with—and derive benefit from—T-DM1 using the dose-adjustment rules recommended for the global population.

The present report summarizes the results from four complementary approaches used to evaluate ethnic sensitivity to T-DM1. NCA permitted us to directly compare differences in observed pharmacokinetic parameters for multiple analytes across ethnic groups. However, NCA requires frequent pharmacokinetic sampling; thus, patients with sparse pharmacokinetic collection (e.g., one or two post-dose samples) were excluded. In addition, comparisons based on NCA results may not be sensitive enough to detect small ethnic differences. In light of these limitations—and to mitigate the effects of potentially confounding factors (e.g., the typically lower body weight of Asian patients)—a population pharmacokinetic-based assessment of T-DM1 conjugate, the main analyte of interest, was performed. The results from the final population pharmacokinetic model indicated that ethnicity was not a statistically significant covariate for T-DM1 pharmacokinetics. VPC plots and comparison of Bayesian post hoc pharmacokinetic parameters across ethnic groups confirmed the results deriving from the population pharmacokinetic model. Ethnic sensitivity was also evaluated using pharmacokinetic data from two Japanese phase I/II studies that were not included in the final population pharmacokinetic model. VPC plots and comparison of Bayesian post hoc pharmacokinetic parameters demonstrated that the pharmacokinetics of T-DM1 conjugate were similar between Japanese and non-Japanese patients. Last, exposure–response analyses were used to assess the effect of ethnicity on efficacy and safety outcomes. Collectively, these four complementary approaches demonstrated good overall comparability across ethnic groups. Although a higher risk of grade ≥3 thrombocytopenia was seen in Asian patients, the data show that T-DM1 has a positive benefit–risk profile in Asian patients with HER2-positive MBC, thus supporting the use of the current clinical dosing regimen for T-DM1 (3.6 mg/kg q3w) in patient populations of different ethnicities.

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Compliance with ethical standards

Conflict of interest CL, BW, NC, and SG are employees of Genentech, Inc., and report stock ownership in Genentech, Inc. DL is an employee of Genentech, Inc., and reports stock ownership in Genentech, Inc., and F. Hoffmann-LaRoche. JJ is an employee of Genentech, Inc., and reports stock ownership in F. Hoffmann-La Roche and Lilly. YG is a consultant for Quantitative Solutions. KM and YI are employees of Chugai Pharmaceutical Co., Ltd. IN and ML are employees of Genentech, Inc., and report stock ownership in F. Hoffmann-La Roche. AS is an employee of F. Hoffmann-La Roche and reports stock ownership in F. Hoffmann-La Roche.

Statement of human rights The present analysis is based on data from eight phase I–III clinical trials. Each trial was approved by the relevant institutional review board at each site according to local clinical guidelines. These studies were conducted in accordance with ethical guidelines such as the Good Clinical Practice Guidelines laid down by the Declaration of Helsinki and other relevant local guidelines.

Statement of informed consent All patients from each clinical trial included in this analysis provided written informed consent.

References

1. Lewis Phillips GD, Li G, Dugger DL, Crocker LM, Parsons KL, Mai E, Blättler WA, Lambert JM, Chari RV, Lutz RJ, Wong WL, Jacobson FS, Koeppen H, Schwall RH, Kenkare-Mitra SR, Spencer SD, Sliwkowski MX (2008) Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. Cancer Res 68:9280–9290. doi:10.1158/0008-5472.CAN-08-1776
2. Junttila TT, Li G, Parsons K, Phillips GL, Sliwkowski MX (2011) Trastuzumab-DM1 (T-DM1) retains all the mechanisms of action of trastuzumab and efficiently inhibits growth of lapatinib insensitive breast cancer. Breast Cancer Res Treat 128:347–356. doi:10.1007/s10549-010-1090-x
3. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, Pegram M, Oh DY, Diéras V, Guardino E, Fang L, Lu MW, Olsen S, Blackwell K, EMILIA Study Group (2012) Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 367:1783–1791. doi:10.1056/NEJMoa1209124
4. Krop IE, Kim SB, González-Martín A, LoRusso PM, Ferrero JM, Smitt M, Yu R, Leung AC, Wildiers H, TH3RESA study collaborators (2014) Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast

cancer (TH3RESA): a randomised, open-label, phase 3 trial. Lancet Oncol 15:689–699. doi:10.1016/S1470-2045(14)70178-0
5. Girish S, Gupta M, Wang B, Lu D, Krop IE, Vogel CL, Burris III HA, LoRusso PM, Yi JH, Saad O, Tong B, Chu YW, Holden S, Joshi A (2012) Clinical pharmacology of trastuzumab emtansine (T-DM1): an antibody-drug conjugate in development for the treatment of HER2-positive cancer. Cancer Chemother Pharmacol 69:1229–1240. doi:10.1007/s00280-011-1817-3
6. Wang B, Jin J, Wada R, Fang L, Lu D, Guardino E, Swain S, Untch M, Girish S (2013) Exposure–efficacy relationship of trastuzumab emtansine (T-DM1) in EMILIA, a phase 3 study of T-DM1 vs capecitabine (X) and lapatinib (L) in HER2-positive locally advanced or metastatic breast cancer (MBC). J Clin Oncol 31(suppl). Abstract 644
7. Krop IE, Beeram M, Modi S, Jones SF, Holden SN, Yu W, Girish S, Tibbitts J, Yi JH, Sliwkowski MX, Jacobson F, Lutzker SG, Burris HA (2010) Phase I study of trastuzumab-DM1, an HER2 antibody-drug conjugate, given every 3 weeks to patients with HER2-positive metastatic breast cancer. J Clin Oncol 28:2698–2704. doi:10.1200/JCO.2009.26.2071
8. Lu D, Girish S, Gao Y, Wang B, Yi JH, Guardino E, Samant M, Cobleigh M, Rimawi M, Conte P, Jin JY (2014) Population pharmacokinetics of trastuzumab emtansine (T-DM1), a HER2-targeted antibody-drug conjugate, in patients with HER2-positive metastatic breast cancer: clinical implications of the effect of covariates. Cancer Chemother Pharmacol 74:399–410. doi:10.1007/s00280-014-2500-2
9. Ramamoorthy A, Pacanowski MA, Bull J, Zhang L (2015) Racial/ethnic differences in drug disposition and response: review of recently approved drugs. Clin Pharmacol Ther 97(3):263–273. doi:10.1002/cpt.61
10. Ozawa S, Soyama A, Saeki M, Fukushima-Uesaka H, Itoda M, Koyano S, Sai K, Ohno Y, Saito Y, Sawada J (2004) Ethnic differences in genetic polymorphisms of CYP2D6, CYP2C19, CYP3As and MDR1/ABCB1. Drug Metab Pharmacokinet 19(2):83–95
11. Yasuda SU, Zhang L, Huang SM (2008) The role of ethnicity in variability in response to drugs: focus on clinical pharmacology studies. Clin Pharmacol Ther 84(3):417–423. doi:10.1038/clpt.2008.141
12. CRESTOR [prescribing information]. Wilmington, DE: AstraZeneca; 2016
13. Zhang W, Yu B, He YJ, Fan L, Li Q, Liu Z, Wang A, Liu Y, Tan Z, Huang Y, Zhou H (2006) Role of BCRP 421C>A polymorphism on rosuvastatin pharmacokinetics in healthy Chinese males. Clin Chim Acta 373:99–103. doi:10.1016/j.cca.2006.05.010
14. Zhou H, Tsukamoto Y, Davis HM (2012) Should clinical pharmacokinetic bridging studies between Caucasian and Asian populations be required for approval of monoclonal antibodies? J Clin Pharmacol 52(8):1273–1276. doi:10.1177/009127001141119
15. Matsushima S, Huang Y, Suzuki H, Nishino J, Lloyd P (2015) Ethnic sensitivity assessment—pharmacokinetic comparability between Japanese and non-Japanese healthy subjects on selected mAbs. Expert Opin Drug Metab Toxicol 11(2):179–191. doi:10.1517/17425255.2015.990438
16. Beeram M, Krop IE, Burris HA, Girish SR, Yu W, Lu MW, Holden SN, Modi S (2012) A phase 1 study of weekly dosing of trastuzumab emtansine (T-DM1) in patients with advanced human epidermal growth factor 2-positive breast cancer. Cancer 118:5733–5740. doi:10.1002/cncr.27622
17. Burris HA 3rd, Rugo HS, Vukelja SJ, Vogel CL, Borson RA, Limentani S, Tan-Chiu E, Krop IE, Michaelson RA, Girish S, Amler L, Zheng M, Chu YW, Klencke B, O'Shaughnessy JA (2011) Phase II study of the antibody drug conjugate trastuzumab-DM1 for the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer after prior HER2-directed therapy. J Clin Oncol 29:398–405. doi:10.1200/JCO.2010.29.5865
18. Krop IE, LoRusso P, Miller KD, Modi S, Yardley D, Rodriguez G, Guardino E, Lu M, Zheng M, Girish S, Amler L, Winer EP, Rugo HS (2012) A phase II study of trastuzumab emtansine in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer who were previously treated with trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine. J Clin Oncol 30:3234–3241. doi:10.1200/JCO.2011.40.5902
19. Hurvitz SA, Dirix L, Kocsis J, Bianchi GV, Lu J, Vinholes J, Guardino E, Song C, Tong B, Ng V, Chu YW, Perez EA (2013) Phase II randomized study of trastuzumab emtansine versus trastuzumab plus docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. J Clin Oncol 31:1157–1163. doi:10.1200/JCO.2012.44.9694
20. Gupta M, Wang B, Carrothers T, Joshi A, LoRusso PM, Chu W, Shih T, Loecke D, Girish S (2011) Exposure-response analysis in patients with HER2-positive (HER2+) metastatic breast cancer (MBC) to assess the effect of T-DM1 on QTc prolongation. Clin Pharmacol Ther 89(suppl 1):S58. Abstract PII-64
21. Yamamoto H, Ando M, Aogi K, Iwata H, Tamura K, Yonemori K, Shimizu C, Hara F, Takabatake D, Hattori M, Asakawa T, Fujiwara Y (2015) Phase I and pharmacokinetic study of trastuzumab emtansine in Japanese patients with HER2-positive metastatic breast cancer. Jpn J Clin Oncol 45:12–18. doi:10.1093/jjco/hyu160
22. Masuda N, Ito Y, Takao S, Doihara H, Rai Y, Horiguchi J, Kohno N, Fujiwara Y, Tokuda Y, Watanabe J, Iwata H, Ishiguro H, Miyoshi Y, Matsubara M, Kashiwaba M (2012) A multicenter Phase 2 study (JO22997) evaluating the efficacy and safety of trastuzumab emtansine in Japanese patients with heavily pretreated HER2-positive metastatic breast cancer. Cancer Res 72(Suppl 24). Abstract P5-18-16. doi: 10.1158/0008-5472.SABCS12-P5-18-16
23. Diéras V, Harbeck N, Budd GT, Greenson JK, Guardino AE, Samant M, Chernyukhin N, Smitt MC, Krop IE (2014) Trastuzumab emtansine in human epidermal growth factor receptor 2-positive metastatic breast cancer: an integrated safety analysis. J Clin Oncol 32:2750–2757. doi:10.1200/JCO.2013.54.4999
24. Jin J, Wang B, Gao Y, Samant M, Li C, Song C, Swain S, Untch M, Girish S (2013) Exposure-safety relationship of trastuzumab emtansine in patients with HER2-positive locally advanced or metastatic breast cancer. J Clin Oncol 31(suppl). Abstract 646
25. Erickson HK, Park PU, Widdison WC, Kovtun YV, Garrett LM, Hoffman K, Lutz RJ, Goldmacher VS, Blättler WA (2006) Antibody-maytansinoid conjugates are activated in targeted cancer cells by lysosomal degradation and linker-dependent intracellular processing. Cancer Res 66:4426–4433
26. Quartino AL, Hillenbach C, Li J, Li H, Wada RD, Visich J, Li C, Heinzmann D, Jin JY, Lum BL (2016) Population pharmacokinetic and exposure-response analysis for trastuzumab administered using a subcutaneous "manual syringe" injection or intravenously in women with HER2-positive early breast cancer. Cancer Chemother Pharmacol 77(1):77–88
27. Lu D, Modi S, Elias A, Agarwal P, Yi J-H, Guardino AE, Althaus B, Girish S (2011) Pharmacokinetics (PK) of trastuzumab emtansine and paclitaxel or docetaxel in patients with HER2-positive MBC previously treated with a trastuzumab-containing regimen. Cancer Res 71(Suppl 24). Abstract P1-12-07. doi:10.1158/0008-5472.SABCS11-P1-12-07
28. Davis JA, Rock DA, Wienkers LC, Pearson JT (2012) In vitro characterization of the drug-drug interaction potential of catabolites of antibody-maytansinoid conjugates. Drug Metab Dispos 40:1927–1934. doi:10.1124/dmd.112.046169
29. Bjornsson TD, Wagner JA, Donahue SR, Harper D, Karim A, Khouri MS, Murphy WR, Roman K, Schneck D, Sonnichsen DS, Stalker DJ, Wise SD, Dombey S, Loew C (2003) A review and assessment of potential sources of ethnic differences in drug responsiveness. J Clin Pharmacol 43:943–967

30. Wong S, Bumbaca D, Yue Q, Halladay J, Kenny JR, Salphati L, Saad O, Tibbitts J, Khojasteh C, Girish S, Shen B-Q (2011) Non-clinical disposition, metabolism, and in vitro drug-drug interaction assessment of DM1, a component of trastuzumab emtansine (T-DM1). Mol Cancer Ther 10:A136. doi:10.1158/1535-7163.TARG-11-A136
31. Genentech. Ado-trastuzumab emtansine (KADCYLA) prescribing information. South San Francisco, CA: Genentech, Inc, 2015
32. Agarwal P, Wang B, Li C, Lu M, Kang B, Chernyukhin N, Girish S (2015) Assessment of the potential for drug-drug interactions between trastuzumab emtansine (T-DM1) and CYP3A inhibitors or inducers and the impact on its PK and safety. In: Presented at: ASPCT; 3–7 March 2015; New Orleans, LA. Abstract PII-027
33. Lu D, Burris HA 3rd, Wang B, Dees EC, Cortes J, Joshi A, Gupta M, Yi JH, Chu YW, Shih T, Fang L, Girish S (2012) Drug interaction potential of trastuzumab emtansine (T-DM1) combined with pertuzumab in patients with HER2-positive metastatic breast cancer. Curr Drug Metab 13:911–922
34. Lu D, Krop I, Modi S, Elias A, LoRusso P, Huang J, Girish S (2010) Pharmacokinetics (PK) of trastuzumab-DM1 (T-DM1) and paclitaxel (T) in patients with HER2-positive locally advanced or metastatic breast cancer (MBC) previously treated with a trastuzumab-containing regimen. Cancer Res 70(Suppl 24). Abstract P3-14-22. doi: 10.1158/0008-5472.SABCS10-P3-14