Trastuzumab emtansine in Asian patients with previously treated HER2-positive locally advanced or metastatic breast cancer: data from the phase 3 EMILIA study

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Background

- The phase 3 EMILIA study (NCT00829166) was initiated based on phase 1 and 2 data identifying the HER2-targeted antibody–drug conjugate trastuzumab emtansine (T-DM1) as an active therapy for HER2-positive advanced breast cancer previously treated with trastuzumab and chemotherapy[1–3]
  - The results of the EMILIA study demonstrated that T-DM1 significantly prolonged progression-free survival (PFS) and overall survival (OS) with less toxicity than lapatinib plus capecitabine, and led to the approval of T-DM1 in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane, separately or in combination[4,5]
- Here, we report a subgroup analysis of EMILIA data in Asian patients

Methods

- The randomized, open-label, phase 3 EMILIA study enrolled patients with centrally confirmed HER2-positive, unresectable, locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane
  - The subgroup of patients included in the current analysis was enrolled by study sites in the Asia region
- Patients received T-DM1 3.6 mg/kg IV every 3 weeks (q3w) or lapatinib 1250 mg/day orally (po) daily plus capecitabine 1000 mg/m^2 po twice daily, days 1–14, q3w
  - After the confirmatory analysis of OS was completed, patients in the lapatinib plus capecitabine arm were allowed to cross over to receive T-DM1
- PFS was determined by Independent Review Committee assessment
- The objective response rate (ORR) was determined using modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 in patients with measurable disease at baseline
- Adverse events (AEs) were graded according to Common Terminology Criteria for Adverse Events, version 3.0
- The Kaplan–Meier approach was used to estimate median PFS, OS, and duration of response for each treatment arm. A Cox proportional hazards model was used to estimate the hazard ratio between the two treatment arms (ie, the magnitude of treatment effect) and its 95% confidence interval (CI)
- An estimate of the ORR and its 95% CI (Blyth–Still–Casella) was calculated for each treatment arm
- Comparisons between data in the Asian and global patient populations are descriptive only

Results

Patients

- At the data cut-off date of January 14, 2012, 158 Asian patients were enrolled in EMILIA (~16% of the overall population)
  - Patients were from Republic of Korea (n=103), Taiwan (n=28), Singapore (n=22), Hong Kong (n=3) and The Philippines (n=2)
- Of these, 82 and 76 patients were randomized to T-DM1 and lapatinib plus capecitabine groups, respectively (efficacy evaluable)
  - 80 and 75 patients, respectively, were safety evaluable (ie, had been administered at least 1 dose of study drug)
- Baseline demographics and clinical characteristics were generally similar between Asian patients and the global population, except that Asian patients had lower median height and weight than the global population (**Table 1**)
  - Among Asian patients, those in the T-DM1 arm were more likely to have an Eastern Cooperative Oncology Group performance status of 1, visceral disease, and 3 or more metastatic sites than those in the lapatinib plus capecitabine arm (**Table 1**)

Table 1. Baseline demographics and clinical characteristics

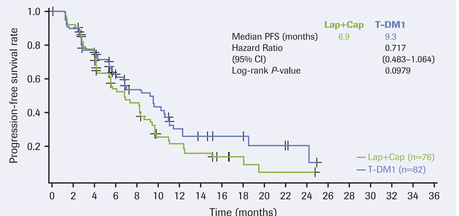
	Asian subgroup		Global population	
	T-DM1 (n=82)	Lapatinib + capecitabine (n=76)	T-DM1 (n=495)	Lapatinib + capecitabine (n=496)
Median age (range), years	51.5 (25.0–68.0)	51.0 (28.0–71.0)	53.0 (25.0–84.0)	53.0 (24.0–83.0)
Sex, n (%)				
Female	82 (100.0)	76 (100.0)	494 (99.9)	492 (99.2)
Male	0	0	1 (0.2)	4 (0.8)
Median height (range), cm	155.0 (144.0–173.0)	157.0 (140.0–165.0)	162.0 (134.6–185.0)	161.0 (140.0–185.0)
Median weight (range), kg	57.0 (43.0–86.0)	57.0 (37.2–96.2)	66.0 (43.0–133.0)	68.0 (37.2–221.0)
ECOG performance status, n (%)				
0	39 (47.6)	43 (56.6)	299 (60.6)	312 (63.9)
1	43 (52.4)	33 (43.4)	194 (39.4)	176 (36.1)
Median (range) LVEF by central assessment, %	62.6 (49.6–74.0)	60.4 (51.0–77.2)	61.5 (31.3–81.0)	60.9 (41.0–82.0)
Prior chemotherapy regimens for locally advanced or metastatic disease, n (%)				
0–1	46 (56.1)	44 (57.9)	304 (61.4)	305 (61.5)
>1	36 (43.9)	32 (42.1)	191 (38.6)	191 (38.5)
Disease involvement, n (%)				
Visceral	60 (73.2)	48 (63.2)	334 (67.5)	335 (67.5)
Non-visceral	22 (26.8)	28 (36.8)	161 (32.5)	161 (32.5)
Metastatic sites (independent review), n (%)				
1	31 (37.8)	25 (32.9)	143 (28.9)	151 (30.4)
2	23 (28.0)	26 (34.2)	155 (31.3)	156 (31.5)
3 or more	28 (34.1)	22 (28.9)	189 (38.2)	175 (35.3)
Missing	0	3 (3.9)	8 (1.6)	14 (2.8)

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LVEF, left ventricular ejection fraction; T-DM1, trastuzumab emtansine.

Efficacy

- At a median follow up of 13 months, median PFS was 9.3 vs 6.9 months with T-DM1 versus lapatinib plus capecitabine (hazard ratio [HR]=0.72; 95% CI: 0.48–1.06) in the Asian subgroup (**Figure 1**)
  - This is consistent with the median PFS seen in the overall population (9.6 vs 6.4 months; HR 0.65; 95% CI 0.55–0.77; $P<0.001$)[4]
- Objective response rates (modified RECIST v1.0) were 44.4% (95% CI: 31.9–57.5) and 38.7% (95% CI: 26.7–51.9) with T-DM1 versus lapatinib plus capecitabine, respectively
  - The median duration of response was 9.6 versus 6.9 months, respectively

Figure 1. Kaplan–Meier plot of PFS in the Asian subgroup (all-randomized patients)



No. at risk

Lap+Cap	76	68	55	33	28	13	11	8	5	3	1	1	1	0	0	0	0	0	0
T-DM1	82	71	59	39	26	21	13	9	7	6	4	3	2	0	0	0	0	0	0

CI, confidence interval; Lap+Cap, lapatinib plus capecitabine; PFS, progression-free survival; T-DM1, trastuzumab emtansine.

- Clinical response rates in the Asian subpopulation were consistent with those in the global patient population (**Table 2**)

Table 2. Clinical response in the Asian subgroup and global population

	Asian subgroup		Global population	
	T-DM1 (n=82)	Lapatinib + capecitabine (n=76)	T-DM1 (n=495)	Lapatinib + capecitabine (n=496)
Patients with measurable disease at baseline[a], n	63	62	397	389
ORR (95% CI), %	44.4 (31.9–57.5)	38.7 (26.7–51.9)	43.6 (38.6–48.6)	30.8 (26.3–35.7)
Median duration of response (95% CI), months	9.6 (4.8–NR)	6.9 (5.6–8.3)	12.6 (8.4–20.8)	6.5 (5.5–7.2)

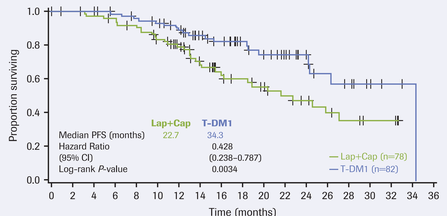
[a]Based on modified RECIST criteria, version 1.0
CI, confidence interval; NR, not reached; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors; T-DM1, trastuzumab emtansine

- At the second interim analysis, with a median follow up of 19 months, median OS was 34.3 versus 22.7 months with T-DM1 versus lapatinib plus capecitabine (HR=0.43; 95% CI: 0.24–0.77) in the Asian subgroup (**Figure 2**)

Safety

- The safety profile in Asian patients was generally similar to that in the global population (**Table 3**)
  - No new safety signals were noted in Asian patients
- However, the incidence of grade 3–4 thrombocytopenia was greater with T-DM1 than with lapatinib plus capecitabine, and consistently greater in the Asian subgroup than in the global population (**Table 3**)
- No differences between the Asian and global populations were observed for clinically significant hemorrhage (i.e., Grade ≥2; **Table 3**)

Figure 2. Kaplan–Meier plot of OS in the Asian subgroup (all-randomized patients)



No. at risk

Lap+Cap	76	75	73	71	67	59	49	38	30	26	22	18	15	11	6	4	4	0	0
T-DM1	82	79	78	74	71	68	63	49	43	33	28	21	15	10	8	4	2	1	0

CI, confidence interval; Lap+Cap, lapatinib plus capecitabine; OS, overall survival; T-DM1, trastuzumab emtansine.

Table 3. Overview of AEs

	Asian subgroup		Global population	
n (%)	T-DM1 (n=80)	Lapatinib + capecitabine (n=75)	T-DM1 (n=490)	Lapatinib + capecitabine (n=488)
Any AEs	78 (97.5)	74 (98.7)	470 (95.9)	477 (97.7)
Grade ≥3	48 (60.0)	41 (54.7)	200 (40.8)	278 (57.0)
AEs leading to discontinuation	5 (6.3)	L: 1 (1.3) C: 3 (4.0)	29 (5.9)	L: 37 (7.6) C: 46 (9.4)
Serious AEs	8 (10.0)	15 (20.0)	76 (15.5)	88 (18.0)
Thrombocytopenia[a]	42 (52.5)	1 (1.3)	149 (30.4)	14 (2.9)
Grade 1	3 (3.8)	1 (1.3)	34 (6.9)	9 (1.8)
Grade 2	4 (5.0)	0	47 (9.6)	4 (0.8)
Grade 3	28 (30.5)	0	55 (11.2)	0
Grade 4	7 (8.8)	0	13 (2.7)	1 (0.2)
Hemorrhage[a]	29 (36.3)	13 (17.3)	146 (29.8)	77 (15.8)
Grade 1	29 (36.3)	10 (13.3)	121 (24.7)	60 (12.3)
Grade 2	0	1 (1.3)	18 (3.7)	13 (2.7)
Grade 3	0	2 (2.7)	6 (1.2)	4 (0.8)
Grade 4	0	0	1 (0.2)	0
Hepatotoxicity				
Overall	28 (35.0)	21 (28.0)	152 (31.0)	123 (25.2)
Grade 1	10 (12.5)	6 (8.0)	52 (10.6)	43 (8.8)
Grade 2	9 (11.3)	13 (17.3)	57 (11.6)	57 (11.7)
Grade 3	9 (11.3)	2 (2.7)	41 (8.4)	23 (4.7)
Grade 4	0	0	2 (0.4)	0
Grade 3 AST increase	6 (7.5)	0	21 (4.3)	4 (0.8)
Grade 3 ALT increase	3 (3.8)	0	14 (2.9)	7 (1.4)
Total bilirubin ≥1.5 x ULN, ALT ≥2.5 x ULN, and AST ≥2.5 x ULN	1 (1.3)	1 (1.3)	10 (2.0)	5 (1.0)
Cardiotoxicity				
LVEF <50% and ≥15-point decrease from baseline	1 (1.3)	0	8 (1.6)	7 (1.4)

[a]Medical Dictionary for Regulatory Activities (MedDRA) preferred term
AEs, adverse events; ALT, alanine transaminase; AST, aspartate transaminase; LVEF, left ventricular ejection fraction; T-DM1, trastuzumab emtansine; ULN, upper limit of normal

- The incidence of hepatotoxicity events was broadly comparable in the Asian and global patient populations
  - Despite a higher number of transaminase-related AEs (elevations of alanine transaminase [ALT] and aspartate transaminase [AST]) with T-DM1 versus lapatinib plus capecitabine (**Table 3**), no grade 4 events were reported in the Asian subgroup
  - The percentage of patients with ALT and AST elevation with concurrent total bilirubin elevation was low in both the Asian and global populations
- No patients enrolled in Asian countries had an AE in the cardiac dysfunction category
- The number of patients with left ventricular ejection fraction (LVEF) of <50% and with a ≥15-point decrease from baseline was low in both treatment arms (**Table 3**)

Conclusions

- T-DM1 conferred a clinically meaningful PFS and OS benefit compared with lapatinib plus capecitabine in the Asian subgroup of patients with trastuzumab- and taxane-pretreated HER2-positive, locally advanced or metastatic breast cancer in the EMILIA study, which was generally consistent with that in the global population
- Although generally similar to the global safety profile, an increased incidence of grade 3–4 thrombocytopenia was noted with T-DM1 in the Asian subgroup, but there was no grade >1 hemorrhage and rates of treatment discontinuation due to AEs were low and similar between the treatment arms
- These data reinforce the favorable T-DM1 benefit-risk profile in Asian patients with mBC

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