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Clinical Trial

Safety of trastuzumab emtansine (T-DM1) in patients with HER2-positive advanced breast cancer: Primary results from the KAMILLA study cohort 1☆

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Abstract ***Background:*** Many patients with metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer (BC) are candidates for trastuzumab emtansine (T-DM1) treatment sometime in their disease history. KAMILLA evaluated safety of T-DM1 in patients with previously treated HER2-positive locally advanced or metastatic BC (advanced BC).

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Receptor, ErbB-2;
Receptor, epidermal growth factor;
Drug-related side effects and adverse reactions;
Malignant neoplasm of breast;
Clinical trial, Phase III

Methods: KAMILLA (NCT01702571) is a single-arm, open-label, international, phase IIIb safety study of patients with HER2-positive advanced BC with progression after prior treatment with chemotherapy and a HER2-directed agent for MBC or within 6 months of completing adjuvant therapy. Patients received T-DM1 (3.6 mg/kg every 3 weeks) until unacceptable toxicity, withdrawal or disease progression.

Results: Among 2002 treated patients, median age was 55 years (range, 26–88; 373 [18.6%] aged ≥65 years), 1321 (66.0%) received ≥2 prior metastatic treatment lines and 398 (19.9%) had baseline central nervous system metastases. Adverse events (AEs) and serious AEs occurred in 1862 (93.0%) and 427 (21.3%) patients, respectively. Grade ≥3 AEs occurred in 751 (37.5%) patients; the three most common (individual Medical Dictionary for Regulatory Activity terms) were anaemia (3.0%), thrombocytopaenia (2.7%) and fatigue (2.5%). Median progression-free survival (PFS) was 6.9 months (95% confidence interval [CI], 6.0–7.6). Median overall survival (OS) was 27.2 months (95% CI, 25.5–28.7). With increasing lines of prior advanced therapy (0–1 versus 4+), median PFS and OS decreased numerically from 8.3 to 5.6 months and from 31.3 to 22.5 months, respectively.

Conclusions: KAMILLA is the largest cohort of T-DM1–treated patients studied to date. Results are consistent with prior randomised studies, thereby supporting T-DM1 as safe, tolerable and efficacious treatment for patients with previously treated HER2-positive advanced BC.

1. Introduction

The antibody–drug conjugate trastuzumab emtansine (T-DM1) is approved for treatment of patients with human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer (MBC) who previously received trastuzumab and a taxane, separately or in combination [1–3]. Approval was based on results from the randomised, open-label, phase III EMILIA study of patients with HER2-positive advanced BC previously treated with trastuzumab and a taxane [4]. In EMILIA, patients treated with T-DM1 had significantly longer progression-free survival (PFS; median 9.6 versus 6.4 months with capecitabine plus lapatinib; $p < 0.001$) and overall survival (OS; median 30.9 versus 25.1 months; $p < 0.001$) and fewer grade ≥3 adverse events (AEs; 41% versus 57%).

The randomised phase III TH3RESA study also found that T-DM1 significantly improved PFS (median 6.2 versus 3.3 months with treatment of physicians choice [TPC]; $p < 0.0001$) and OS (median 22.7 versus 15.8 months; $p = 0.0007$) in patients with prior progression on ≥2 anti-HER2 regimens [5,6]. The incidence of grade ≥3 AEs was lower with T-DM1 (32%) compared with TPC (43%). T-DM1 was evaluated in the first-line MBC setting in the phase III MARIANNE study. In MARIANNE, PFS with T-DM1–containing regimens (T-DM1 alone [median PFS, 14.1 months] or T-DM1 plus pertuzumab [15.2 months]) was non-inferior but not superior to trastuzumab plus taxane (13.7 months) [7]. Current treatment guidelines include T-DM1 as a first-line treatment option for HER2-positive MBC patients considered unsuitable for treatment with the standard of care, pertuzumab, trastuzumab and a taxane [3,8].

Many patients with metastatic HER2-positive BC are candidates for T-DM1 treatment [3], underscoring the importance of thoroughly understanding T-DM1 safety and tolerability. A combined safety analysis of data from 884 T-DM1–treated patients found that grade ≥3 AEs were infrequent, typically asymptomatic and manageable [9]. The most commonly reported grade ≥3 AEs were laboratory abnormalities (thrombocytopaenia and elevated aspartate aminotransferase).

We report results of cohort 1 of the phase IIIb KAMILLA safety study. Notably, KAMILLA evaluated safety and efficacy of T-DM1 in 2002 patients with previously treated HER2-positive MBC, the largest cohort of T-DM1–treated patients studied so far. Unlike other studies, KAMILLA was designed with safety and tolerability as the primary objective, and enrolment criteria were less narrowly defined than those of a registration study, which may approximate the breadth of patients encountered in a 'real-life' target population.

2. Materials and methods

2.1. Study design

KAMILLA (NCT01702571) is an international, multicenter, single-arm, open-label, two-cohort, phase IIIb study. This study was undertaken in a post-marketing commitment with the European Medicines Agency. Cohort 1 included patients from 40 countries (planned enrolment: 2000 patients). The follow-up for cohort 1 is complete, and results are reported here. Cohort 2

includes patients from three Asian countries (185 enrolled patients); the follow-up is ongoing.

Study participants received single-agent T-DM1 (3.6 mg/kg every 3 weeks intravenously) until unacceptable toxicity, withdrawal of consent, disease progression, death or up to a maximum of 2 years after enrolment of the last patient. Dose reductions were based on T-DM1–prescribing information [1,2]. Tumour assessments for patients with measurable and non-measurable disease were made by investigators as per the Response Evaluation Criteria for Solid Tumors (RECIST), version 1.1, at screening and every 12 weeks thereafter during the treatment period through physical examination and computed tomography or magnetic resonance imaging, with the same radiographic procedure used to define measurable disease at the baseline and throughout the study. RECIST data were reviewed centrally to ensure consistent reporting. Patients who discontinued study treatment for reasons other than disease progression continued tumour assessments every 3–6 months until confirmed progression or study closure. Survival follow-up occurred every 6 months (±14 working days) until death, loss to follow-up or withdrawal of consent. AEs were assessed on an ongoing basis; assessment of treatment-related serious AEs continued up to 2 years after enrolment of the last patient.

2.2. Patients

Eligible patients were ≥18 years old with HER2-positive recurrent, metastatic or unresectable locally advanced BC. Patients had received a prior anti-HER2 agent and chemotherapy (prior taxane was not required) and had progressed on or after the most recent treatment or within 6 months of completing adjuvant therapy. Other key inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; left ventricular ejection fraction (LVEF) ≥50% by echocardiogram or multiple-gated acquisition scan; measurable and/or non-measurable disease and adequate organ function based on laboratory measurements. Key exclusion criteria included prior T-DM1 treatment, grade ≥3 peripheral neuropathy, treatment with any anticancer drug or biologic therapy ≤21 d or hormonal therapy ≤7 d before first study treatment, symptomatic central nervous system (CNS) metastases or CNS-limited metastatic disease (asymptomatic CNS metastasis or CNS disease treated with radiation therapy >14 d before enrolment was allowed), pregnancy or lactation, history of symptomatic congestive heart failure or serious cardiac arrhythmia requiring treatment and history of a decrease in LVEF <40% or symptomatic congestive heart failure with previous anti-HER2 treatment.

All patients provided written informed consent. The study was approved by the institutional review board at each site and was conducted in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use—Good Clinical Practice: Consolidated Guideline.

2.3. Outcomes and statistical analysis

The primary objective was to assess T-DM1 safety and tolerability. AEs were categorised using Medical Dictionary for Regulatory Activities (MedDRA) terminology and graded as per the National Cancer Institute Common Terminology Criteria for Adverse Events, v4.04. The safety population included all patients who received ≥1 dose of study medication. The intent-to-treat population included all enrolled patients. Safety data were summarised descriptively, and corresponding two-sided exact (Clopper–Pearson) 95% confidence intervals (CIs) were calculated. No formal statistical hypothesis tests were performed, and there were no adjustments for multiplicity of end-points.

Based on results obtained from the published combined safety analysis [9], thrombocytopaenia, hepatic events, haemorrhage, cardiac dysfunction (cardiotoxicity) and pneumonitis were predefined as AEs of interest. The incidence of these AEs was summarised by combining related MedDRA-preferred terms (eTable 1).

PFS and OS were assessed as secondary end-points. Time-to-event end-points were evaluated per standard statistical methodology and also in subgroups based on number of prior lines of treatment received.

The full trial protocol is available in the Appendix.

3. Results

3.1. Patients

Between November 12, 2012, and September 29, 2014, 2003 patients were enrolled in study cohort 1, of whom, 2002 received treatment with T-DM1 (safety population; Fig. 1). Median follow-up duration was 20.6 months (range 0–50) as of the cohort 1 database lock (January 31, 2017). Notably, 1321 patients (66.0%) received ≥2 prior treatments for MBC, 373 were aged ≥65 years (18.6%), 890 had an ECOG performance status ≥1 (44.4%; 115 [5.7%] with a performance status of 2) and 398 patients (19.9%) had a history of CNS metastases at the baseline (Table 1).

3.2. Safety

Median duration of T-DM1 exposure was 5.6 months (range 0–46). Few patients (87; 4.3%) experienced dose interruptions, but 450 (22.5%) patients had a dose reduction. Among 1913 patients who discontinued treatment, the most common reason was disease progression (n = 1495; 78.1%; Fig. 1). AEs were reported as

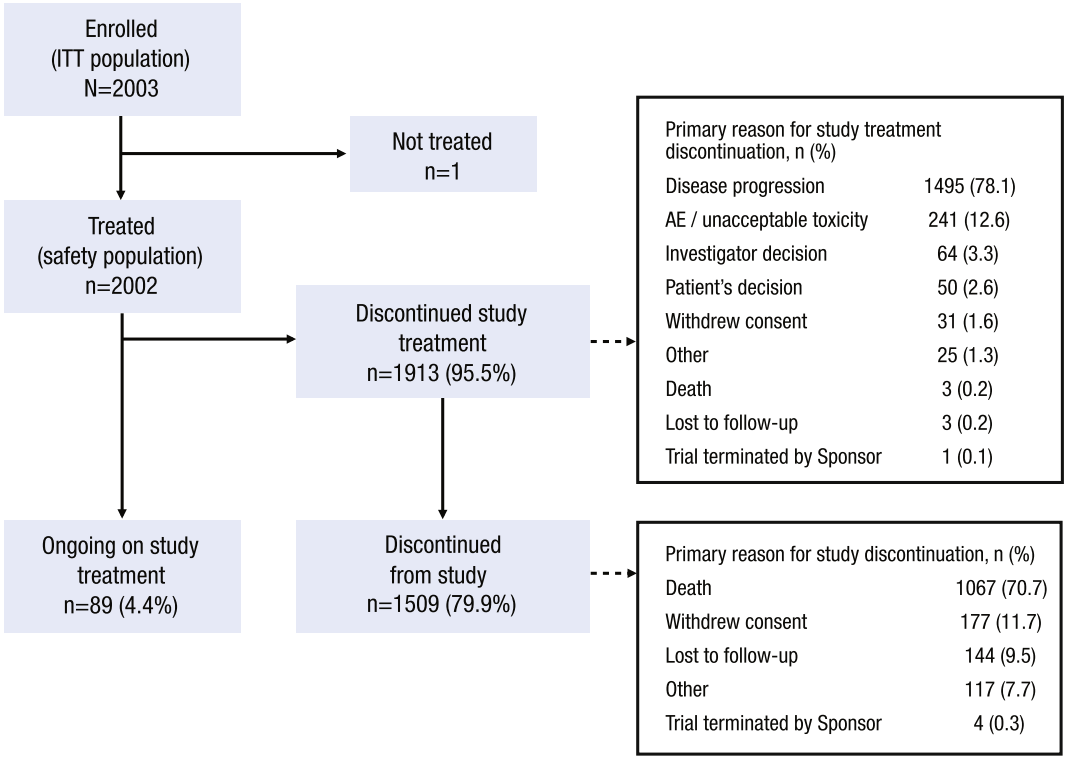

Fig. 1. Patient disposition. AE, adverse event; ITT, intent-to-treat.

the primary reason for treatment discontinuation in 241 (12.6%) patients. Among 237 (11.8%) patients with details available regarding AEs leading to treatment discontinuation, those in >0.5% of patients were thrombocytopaenia/platelet count decrease (45, 2.2% [95% CI, 1.64–3.00]) and blood bilirubin increased (24, 1.2% [0.77–1.78]).

Incidence of the primary end-point (grade ≥3 hepatic events, allergic reactions, thrombocytopaenia, haemorrhage events; grade ≥3 AEs related to T-DM1; all grade pneumonitis) was 23.1% (n = 462 [95% CI 21.2–25.0]). Overall, 1862 (93.0%) patients reported any AE (Table 2). Serious AEs occurred in 427 (21.3%) patients. Grade ≥3 AEs were reported in 751 (37.5%); 45 (2.2%) patients reported grade 5 events.

Grade 5 AEs considered related to T-DM1 included multiple organ dysfunction and brain oedema (two patients each) and sepsis, pneumonitis, pulmonary embolism, interstitial lung disease, respiratory failure, drug-induced liver injury, renal failure and acute kidney injury (one patient each). Worsening of preexisting brain radiation necrosis (unrelated to study treatment) occurred in one patient (grade 5 event).

Grade ≥3 thrombocytopaenia-related AEs occurred in 74 (3.7%) patients, and there were no grade 5 events (eTable 2). Grade ≥3 hepatic events occurred in 139 (6.9%) patients (six grade 5). Grade ≥3 haemorrhage-related AEs occurred in 46 (2.3%) patients (two grade 5). Grade ≥3 CNS haemorrhage occurred in six (0.3%) patients: three with intracranial haemorrhage (two grade 3 [one considered related to study drug], one grade 5 [unrelated]), two with cerebral haemorrhage (one grade 3 [related], one grade 4 [unrelated]) and one with haemorrhagic stroke (grade 4 [unrelated]). Cardiac dysfunction–related AEs (any grade) occurred in 54 patients (2.7%; 95% CI, 2.0–3.5), seven with grade 3 events and three with grade 4 events. Most patients (n = 1846, 92.2%) had an LVEF ≥50% during treatment; nine (0.4%) had an LVEF decrease from the baseline to <40%. Grade ≥3 pneumonitis-related AEs occurred in nine patients (0.4%), including four (0.2%) with grade 5 events (pneumonitis, n = 2; interstitial lung disease, n = 1; pulmonary fibrosis, n = 1).

The incidences of thrombocytopaenia defined as grade 3–4 platelet count decrease based on laboratory data, and haemorrhage-related AEs were cross-tabulated (eTable 3). Most haemorrhage events were not associated with grade ≥3 platelet count decrease (no grade 5 platelet count decreases). Of 66 patients (3.2%) with grade 3–4 platelet count decrease, 38 (57.6%) did not experience haemorrhage, 22 (33.3%) experienced a grade 1–2 haemorrhage and six (9.1%) experienced grade ≥3 haemorrhage (one grade 5 haemorrhage occurred in a patient with grade 3 platelet count decrease).

3.3. Efficacy

By data cut-off, median PFS was 6.9 months (95% CI, 6.0–7.6; Fig. 2A) and median OS was 27.2 months (95%

Table 1
Demographics and baseline characteristics.

Demographic and baseline characteristics	Safety population (N = 2002) N (%)
Sex, no. (%)	
Female	1988 (99.3)
Male	14 (0.7)
Age, years	
Median (range)	55.0 (26–88)
Age group, no. (%)	
<65 years	1629 (81.4)
≥65 years	373 (18.6)
≥75 years	101 (5.0)
Race, no. (%)	
Caucasian	1397 (69.8)
Black	21 (1.0)
Asian	72 (3.6)
Native American	41 (2.0)
Other[a]	471 (23.5)
ECOG status at screening, no. (%)	
0	1110 (55.4)
1	775 (38.7)
2	115 (5.7)
Missing	2 (0.1)
Measurable disease, no. (%)	
Measurable disease	1613 (80.5)
Non-measurable disease	390 (19.5)
Presence of visceral disease, no. (%)	
Visceral disease	1561 (78.0)
Absence of visceral disease	441 (22.0)
Brain metastases at baseline, no. (%)	398 (19.9)
Time since initial diagnosis, years	
Median (range)	5.0 (0–53)
Time since first metastasis, years[b]	
Median (range)	2.6 (0–35)
Presence of distant metastases at initial diagnosis, no. (%)	
M0	1398 (69.8)
M1	547 (27.3)
MX	41 (2.0)
Missing	16 (0.8)
ER/PR status at diagnosis, no. (%)	
ER and/or PR positive	1232 (61.5)
ER and PR negative	733 (36.6)
Unknown or not done	37 (1.8)
Prior number of treatment lines in the metastatic setting, no. (%)	
0–1	594 (29.7)
2	446 (22.3)
3	358 (17.9)
4 or more	517 (25.8)
Missing	87 (4.3)
Prior taxane exposure in any setting, no. (%)	1846 (92.2)

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; PR, progesterone receptor; TNM, tumour node metastases.
[a] Other: not applicable per local regulations, unknown, or missing.
[b] Based on available data from 1993 patients.

CI, 25.5–28.7; Fig. 3A). Median PFS and OS decreased numerically with increasing prior lines of therapy. In patients with 0–1 prior lines of therapy, median PFS was 8.3 months (95% CI, 8.0–9.2), whereas median PFS was 5.6 months (95% CI, 5.4–5.8) in patients with 4 + prior lines of therapy (Fig. 2B). Similarly, median OS was 31.3 months (95% CI, 28.3–34.8) in patients with 0–1 prior lines of therapy and 22.5 months (95% CI, 20.1–24.4) in patients with 4 + prior lines of therapy (Fig. 3B). Among 1613 patients with measurable disease at baseline, 73 and 400, respectively, achieved a complete or partial response, leading to an overall response rate of 29.3% (95% CI, 27.1–31.6).

4. Discussion

KAMILLA is the largest reported safety study of patients treated with T-DM1 (N = 2002). Our results show T-DM1 was tolerable with a manageable safety profile and no unexpected or new side-effects. The most common grade ≥3 AEs were anaemia, thrombocytopaenia, fatigue, gamma-glutamyltransferase increased and asthenia, each of which occurred in ≤3% of patients. While safety was the primary objective, patients were followed for approximately 2 years, allowing for mature PFS and OS estimates. Efficacy was consistent with earlier T-DM1 trials [4,5]. The longest PFS and OS occurred when T-DM1 was administered as second-line therapy, and PFS and OS decreased numerically with increasing numbers of prior treatment lines, consistent with the natural evolution of the disease.

Although cross-trial comparisons must be interpreted with caution, it is interesting to consider differences in the KAMILLA population compared with populations enrolled in prior trials (eTable 4). Subtle, but potentially important, differences from these other studies [4,5,9] include higher proportions of patients with symptomatic disease (e.g. ECOG = 2), hormone receptor–positive BC and visceral disease (compared with combined safety analysis [9] and EMILIA [4]) and a lower proportion of Asian patients. Furthermore, patients in EMILIA had ≤2 prior lines of metastatic treatment and patients in TH3RESA tended to be treated in the later line setting (67% had ≥4 prior lines), whereas KAMILLA included patients with a greater range of prior treatment lines. Most importantly, proportions of patients aged ≥65 years and those with baseline CNS metastases were both approximately twice as high as those reported in the safety analysis, EMILIA and TH3RESA. Given the KAMILLA sample size, these subsets included hundreds, rather than tens, of patients. An interim analysis from KAMILLA found that the overall safety profile of T-DM1 in patients with baseline CNS metastases was generally comparable with that observed in patients without baseline CNS metastases, and T-DM1 showed meaningful anti-tumour activity in patients with measurable baseline CNS metastases [10]. Interpretation of these findings should consider that patients with symptomatic CNS metastases or CNS-limited disease were excluded. In addition, when considering results from KAMILLA, note this was not a randomised study and there was no control arm.

Table 2
Summary of adverse events (N = 2002).

Adverse events	All grades		Grade 3–5		Serious adverse events	
	N	Percent (95% CI)	N	Percent (95% CI)	N	Percent (95% CI)
Any adverse event	1862	93.0 (91.80–94.09)	751	37.5 (35.39–39.68)	427	21.3 (19.55–23.19)
Drug discontinued due to adverse event[a]	237	11.8 (10.45–13.33)	NR		84	4.2 (3.36–5.17)
Adverse event individual MedDRA preferred terms						
Nausea	651	32.5 (30.47–34.62)	14	0.7 (0.38–1.17)	5	0.2 (0.08–0.58)
Fatigue	557	27.8 (25.87–29.84)	50[b]	2.5 (1.86–3.28)[b]	1	<0.1 (0.00–0.28)
Asthenia	494	24.7 (22.80–26.63)	35[b]	1.7 (1.22–2.42)[b]	3	0.1 (0.03–0.44)
Headache	455	22.7 (20.91–24.63)	22	1.1 (0.69–1.66)	1	<0.1 (0.00–0.28)
Epistaxis	405	20.2 (18.49–22.06)	5	0.2 (0.08–0.58)	7	0.3 (0.14–0.72)
Constipation	397	19.8 (18.10–21.65)	11	0.5 (0.27–0.98)	3	0.1 (0.03–0.44)
Pyrexia	347	17.3 (15.70–19.06)	7	0.3 (0.14–0.72)	13[c]	0.6 (0.35–1.11)[c]
Decreased appetite	321	16.0 (14.45–17.72)	13	0.6 (0.35–1.11)	2	0.1 (0.01–0.36)
Vomiting	305	15.2 (13.69–16.88)	28	1.4 (0.93–2.02)	17[c]	0.8 (0.50–1.36)[c]
Dry mouth	283	14.1 (12.64–15.74)	2	0.1 (0.01–0.36)	0	0 (0.00–0.18)
Arthralgia	266	13.3 (11.83–14.85)	3	0.1 (0.03–0.44)	2	0.1 (0.01–0.36)
Diarrhoea	254	12.7 (11.26–14.23)	16	0.8 (0.46–1.29)	4	0.2 (0.05–0.51)
Cough	220	11.0 (9.65–12.44)	2	0.1 (0.01–0.36)	0	0 (0.00–0.18)
Dyspnoea	218	10.9 (9.56–12.34)	34	1.7 (1.18–2.37)	7	0.3 (0.14–0.72)
Myalgia	205	10.2 (8.95–11.65)	1	<0.1 (0.00–0.28)	0	0 (0.00–0.18)
Anaemia	180	9.0 (7.77–10.33)	60[b]	3.0 (2.29–3.84)[b]	13[c]	0.6 (0.35–1.11)[c]
Thrombocytopaenia	175	8.7 (7.54–10.06)	55[b]	2.7 (2.08–3.56)[b]	11[c]	0.5 (0.27–0.98)[c]
GGT increased	85	4.2 (3.41–5.22)	44[b]	2.2 (1.60–2.94)[b]	1	<0.1 (0.00–0.28)
AST increased	139	6.9 (5.87–8.15)	30	1.5 (1.01–2.13)	3	0.1 (0.03–0.44)
ALT increased	88	4.4 (3.54–5.39)	29	1.4 (0.97–2.07)	2	0.1 (0.01–0.36)
Hypertension	96	4.8 (3.90–5.82)	24	1.2 (0.77–1.78)	0	0 (0.00–0.18)
Pneumonia	26	1.3 (0.85–1.90)	11	0.5 (0.27–0.98)	16[c]	0.8 (0.46–1.29)[c]
Urinary tract infection	164	8.2 (7.03–9.48)	12	0.6 (0.31–1.04)	11[c]	0.5 (0.27–0.98)[c]

Table shows all any grade adverse events that occurred in ≥10% of the safety population (N = 2002), all grade 3–5 adverse events that occurred in ≥1% of the population, and all serious adverse events that occurred in ≥0.5% of the population. Individual adverse event terms are based on MedDRA terminology.

CI, confidence interval; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; MedDRA, Medical Dictionary for Regulatory Activities; NR, not reported.

[a] An adverse event was reported as the reason for drug discontinuation for 237 patients. Four additional patients reported discontinuing T-DM1 due to an adverse events, without providing a corresponding adverse event.

[b] Five most common grade ≥3 adverse events.

[c] Serious adverse events occurring in >10 patients.

However, because inclusion criteria were less strictly defined than those of a registration study, there was greater breadth to the types of patients enrolled. Therefore, we speculate that our findings may approximate what might be observed in clinical practice.

AE reporting has been criticised, with suboptimal detailing of the incidence/type of clinically relevant AEs cited as a common shortcoming of many clinical trial publications [11–15]. These safety data from KAMILLA, together with published results from the previous safety analysis [9], provide comprehensive information for health-care practitioners making treatment decisions about T-DM1 in the clinic. The previous safety analysis found that thrombocytopaenia and increased ALT were the most commonly occurring AEs with T-DM1 [9]. To better understand any associations between T-DM1 and AEs of interest, thrombocytopaenia, hepatic events, haemorrhage and cardiac dysfunction were investigated by combining related AE terms (eTable 1). Importantly, as seen in the safety analysis [9], grade ≥3 thrombocytopaenia was rarely associated with grade ≥3 haemorrhage-related AEs (of 66 patients with grade 3–4 thrombocytopaenia, 38 had no haemorrhage, 22 had grade 1–2 haemorrhage and 6 had grade ≥3 haemorrhage; see eTable 3). One patient with grade 3 thrombocytopaenia also experienced a grade 5 haemorrhage, although these events did not occur at the same time. The rate of grade 5 AEs in KAMILLA (2.2%) was similar to that observed in both the T-DM1 (2%) and TPC (2%) arms of TH3RESA [5,6] and higher than that observed in EMILIA (T-DM1, 0.2%; capecitabine plus lapatinib, 0.8% [4]). Demographic similarities between the KAMILLA and TH3RESA studies (i.e. more patients with ECOG performance status ≥1 and multiple lines of prior therapy) suggest this might be the approximate rate of fatal events for a similar population in the clinical practice setting, regardless of treatment used.

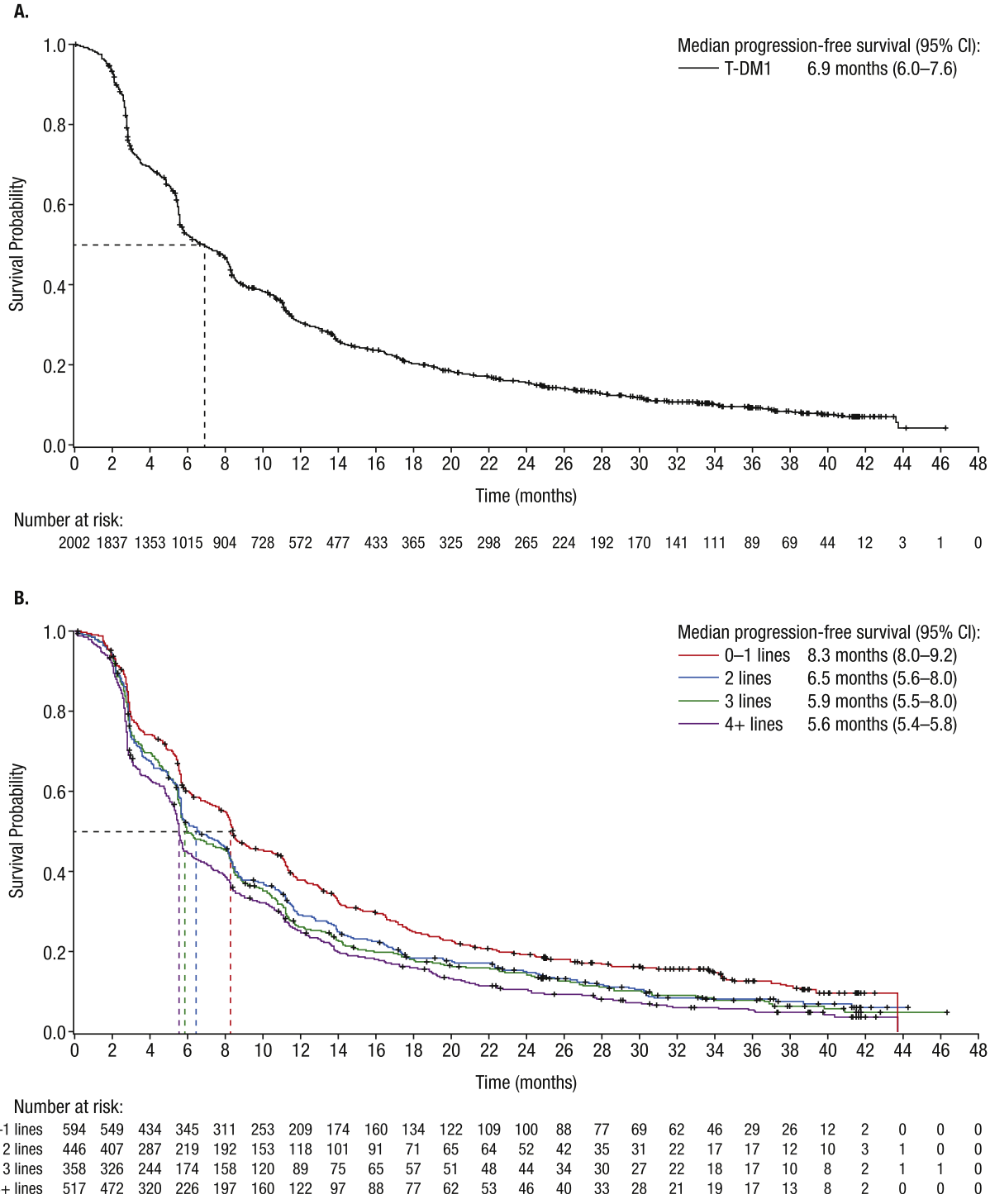

Fig. 2. PFS in the KAMILLA study population. (A) PFS in the ITT population. (B) PFS by number of lines of prior treatment. Of the intent-to-treat population (N = 2003), 1732 patients (86.5%) had a PFS event and 271 patients (13.5%) were censored. + Censored. CI, confidence interval; ITT, intent-to-treat; PFS, progression-free survival; T-DM1, trastuzumab emtansine.

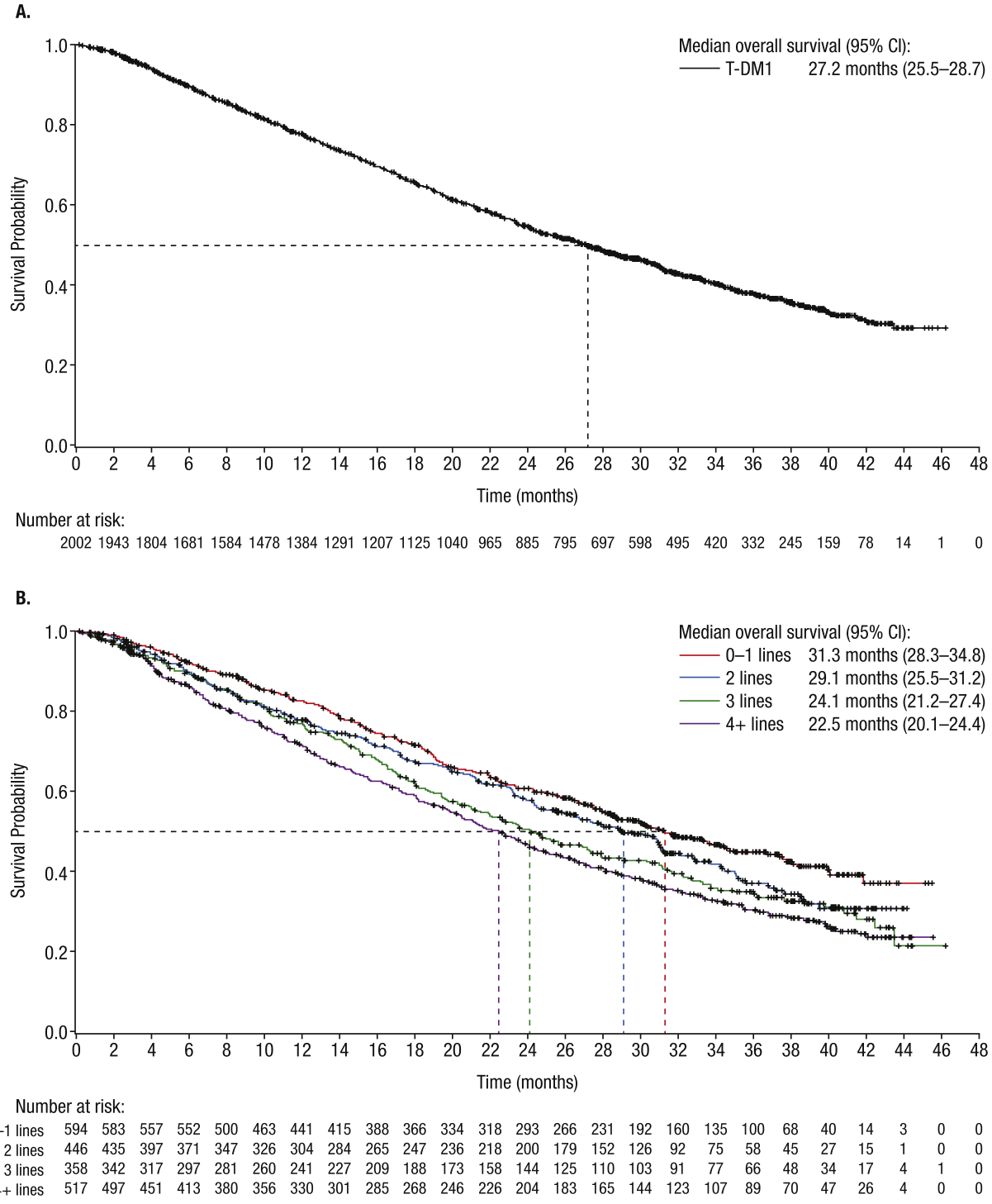

Fig. 3. Overall survival in the KAMILA study population. (A) Overall survival in the ITT population. (B) Overall survival by number of lines of prior treatment. Of the intent-to-treat population (N = 2003), 1072 patients (53.5%) had died and 931 patients (46.5%) were censored. + Censored. CI, confidence interval; ITT, intent-to-treat; NE, non-estimable; T-DM1, trastuzumab emtansine.

5. Conclusions

T-DM1 treatment across multiple lines of therapy was found to be safe, tolerable and efficacious with a manageable safety profile, based on results from this largest study reported to date of patients with previously treated HER2-positive MBC. Safety and efficacy were consistent with prior randomised studies [4,5]. Many patients receive treatment with T-DM1 in the MBC setting; we believe the size of the KAMILLA study and breadth of the patient population may make our findings more comparable with the experience of oncologists

prescribing T-DM1 in the clinical setting, compared with the more strictly defined setting of previous registration studies. T-DM1 is a standard of care for second- or higher-line treatment of HER2-positive advanced BC, and KAMILLA data support continued the use of T-DM1 as a therapy with a favourable safety profile for patients with previously treated disease.

Conflict of interest statement

F.M. has served on Speaker's Bureaus for F. Hoffmann-La Roche, AstraZeneca, and Novartis, and has received travel grants from AstraZeneca and Novartis. A.A. has served as a consultant/advisor for Bayer Hispania. R.W. has served as a consultant/advisor for and received research funding from F. Hoffmann-La Roche. S.D. has served as a consultant/advisor for Novartis, F. Hoffmann-La Roche and Pfizer; has received honoraria from Novartis and F. Hoffmann-La Roche; has received research funding from Novartis and Pfizer and has received travel support from F. Hoffmann-La Roche, Novartis and Amgen. J.B. has received honoraria from F. Hoffmann-La Roche. S.C.L. has served as a consultant/advisor for AstraZeneca; has received research funding from AstraZeneca, Amgen, BMS, F. Hoffmann-La Roche, Genentech and TESARO and has received travel support from F. Hoffmann-La Roche and Pfizer. N.I. is an employee of F. Hoffmann-La Roche. M.D. is an employee of F. Hoffmann-La Roche and owns stock in Novartis. N.L. is an employee of F. Hoffmann-La Roche and owns stock in F. Hoffmann-La Roche, Novartis, Idorcia and Johnson & Johnson. C.H.B. has received honoraria from Novartis, F. Hoffmann-La Roche/Genentech, Pfizer, GlaxoSmithKline, Sanofi, Boehringer Ingelheim and Eisai; has served as a consultant/advisor for Boehringer Ingelheim, F. Hoffmann-La Roche/Genentech, Novartis, Astellas Pharma, GlaxoSmithKline, Eisai and Pfizer and has received research funding from Pfizer, Novartis, Amgen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, F. Hoffmann-La Roche/Genentech, Lilly, Sanofi, Taiho Pharmaceutical, Mylan, Merrimack, Merck, AbbVie, Astellas Pharma, BioMarin, Bristol-Myers Squibb, Daiichi Sankyo, Abraxis BioScience, AB Science, Asana Biosciences, Medivation, Exelixis, ImClone Systems, LEO Pharma and Millennium. All authors received non-financial support from F. Hoffmann-La Roche in the form of medical writing support for this manuscript. N.Q-.T. and P.E. have no other conflicts of interest to disclose.

Role of the funding source

This work was supported by F. Hoffmann–La Roche, Ltd. The study was designed by the sponsor, F. Hoffmann-La Roche, Ltd., in collaboration with the trial steering committee. The sponsor funded the study, provided study drugs and was involved in the study design, data collection, data analysis, data interpretation and writing of this report. Data were analysed in collaboration with the authors, who are responsible for the completeness and accuracy of the data and analyses and for the fidelity of the study to the protocol. The first author prepared the initial draft of the manuscript, with support from a medical writer paid by the sponsor. All authors had full access to all study data, were involved in data analysis and interpretation, contributed to subsequent manuscript drafts and had final responsibility for the decision to submit this manuscript for publication.

Data statement

Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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Appendix A. Supplementary data

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