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ORIGINAL ARTICLE

# Trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer and brain metastases: exploratory final analysis of cohort 1 from KAMILLA, a single-arm phase IIIb clinical trial☆

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**Background:** Patients with brain metastases (BM) from human epidermal growth factor receptor 2 (HER2)-positive breast cancer represent a difficult-to-treat population. Trastuzumab emtansine (T-DM1) has shown potential activity in this subset of patients in small clinical series.

**Patients and methods:** KAMILLA is an ongoing, phase IIIb study of T-DM1 in patients with HER2-positive locally advanced/metastatic breast cancer with prior HER2-targeted therapy and chemotherapy. Patients received T-DM1 3.6 mg/kg every 3 weeks (intravenously) until unacceptable toxicity, withdrawal of consent, or disease progression. Tumor response and clinical outcomes in patients with baseline BM were evaluated in this *post hoc*, exploratory analysis. The main outcome measures were best overall response rate (complete response + partial response) and clinical benefit rate (complete response + partial response + stable disease lasting ≥6 months) by RECIST v1.1 criteria, progression-free survival, overall survival, and safety.

**Results:** Of 2002 treated patients, 398 had baseline BM. In 126 patients with measurable BM, the best overall response rate and clinical benefit rate were 21.4% [95% confidence interval (CI) 14.6—29.6] and 42.9% (95% CI 34.1—52.0), respectively. A reduction in the sum of the major diameters of BM ≥30% occurred in 42.9% (95% CI 34.1—52.0), including 49.3% (95% CI 36.9—61.8) of 67 patients without prior radiotherapy to BM. In the 398 patients with baseline BM, median progression-free survival and overall survival were 5.5 (95% CI 5.3—5.6) months and 18.9 (95% CI 17.1—21.3) months, respectively. The adverse event profile was broadly similar in patients with and without baseline BM, although nervous system adverse events were more common in patients with [208 (52.3%)] versus without [701 (43.7%)] baseline BM.

**Conclusion:** This exploratory analysis of patients with HER2-positive metastatic breast cancer and BM enrolled in a prospective clinical trial shows that T-DM1 is active and well-tolerated in this population. T-DM1 should be explored further in this setting.

**Trial registration:** ClinicalTrials.gov identifier: NCT01702571.

**Key words:** brain metastases, HER2-positive breast cancer, KAMILLA, metastatic breast cancer, T-DM1, trastuzumab emtansine

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☆Note: Interim results of a similar exploratory analysis of the KAMILLA study were presented at the San Antonio Breast Cancer Symposium, San Antonio, TX; 6—10 December 2016.



## INTRODUCTION

Patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer are at high risk for developing metastatic disease in the central nervous system (CNS), particularly of the brain.[1—3] Brain metastases (BM) are associated with poor outcomes,[4,5] and treatment options for patients with HER2-positive metastatic breast cancer (MBC) and BM are limited.[6] Accumulating evidence

indicates that systemic treatment that includes HER2-targeted agents may improve clinical outcomes in patients with HER2-positive MBC and BM; survival in such patients has been reported as approximately 11–30 months.[7–12]

Studies of the epidermal growth factor receptor/HER2-targeted tyrosine kinase inhibitors (TKIs) lapatinib and neratinib (alone or in combination with capecitabine), and the HER2-specific TKI tucatinib (in combination with trastuzumab and capecitabine), have reported activity in patients with HER2-positive MBC and BM.[7,10,13–17] Among other potentially active drugs in these patients, the antibody-drug conjugate trastuzumab emtansine (T-DM1) has been shown to improve overall survival (OS) in patients with trastuzumab-resistant advanced MBC and asymptomatic BM previously treated with radiotherapy, compared with lapatinib plus capecitabine.[11] Two small additional studies also provided signals of clinical activity for T-DM1 in patients with HER2-positive MBC and BM.[18,19]

KAMILLA (NCT01702571) is an ongoing, international, single-arm, open-label, phase IIIb study evaluating the safety and efficacy of T-DM1 in patients with previously treated, HER2-positive advanced breast cancer. The primary analysis found that T-DM1 was well tolerated and showed efficacy consistent with that reported in previous studies.[20] Here, we report the results of a *post hoc* exploratory analysis describing T-DM1 safety and efficacy in patients with and without baseline BM based on final cohort 1 data from KAMILLA.

## MATERIALS AND METHODS

### *Overall KAMILLA study: patients and study design*

The design of the ongoing, two-cohort KAMILLA study has been reported previously.[20] Cohort 1 had a target enrollment of 2000 patients; primary results have been reported.[20] To date, 182 patients have been enrolled in cohort 2, which includes only patients from Asian countries; follow-up is ongoing.

Eligible patients had received prior HER2-targeted therapy and chemotherapy, and had progressed on or after their most recent treatment of advanced breast cancer, or within 6 months of completing adjuvant therapy.[20] Patients with untreated, asymptomatic BM or controlled brain disease treated with radiotherapy >14 days before enrollment were eligible. 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 Used—Good Clinical Practice: Consolidated Guideline.

Participating patients received T-DM1 3.6 mg/kg every 3 weeks (intravenously) until unacceptable toxicity, withdrawal of consent, or disease progression.[20]

### *Exploratory analysis of patients with BM: outcomes and statistical methods*

The objective of this *post hoc* exploratory analysis of patients in cohort 1 was to evaluate T-DM1 clinical activity and safety in the subgroup of patients with BM at baseline. To minimize the bias of late responses in target CNS lesions following radiotherapy in patients with measurable baseline BM, T-DM1 clinical activity was also evaluated in subgroups defined by prior brain radiotherapy: <30 days before baseline, ≥30 days before baseline, or no radiotherapy. Information is also provided for patients who continued treatment with T-DM1 after disease progression.

Tumor assessments were made in accordance with RECIST version 1.1 at screening and every 12 weeks thereafter,[21] based on both target and non-target lesions in the body and brain. Tumor response definitions are provided in supplementary Methods, available at *Annals of Oncology* online. The Clopper-Pearson method was used to estimate the exact two-sided 95% confidence interval (CI) for proportions.

Follow-up for survival occurred every 6 months (±14 days) until death, loss to follow-up, or withdrawal of consent. Median progression-free survival (PFS) and OS were estimated using the Kaplan–Meier method. Definitions for PFS and OS are provided in supplementary Methods, available at *Annals of Oncology* online. The Brookmeyer-Crowley method was used to construct the two-sided 95% CI for median PFS and OS. Adverse events (AEs) were assessed throughout the study.

A univariate Cox proportional hazards model was used to explore the prognostic effect of brain involvement (yes versus no) at baseline on OS. In addition, an exploratory multivariable Cox proportional hazards model was employed to assess the association of other potential prognostic factors with OS and to adjust the BM effect for these factors. Estimates of hazard ratio (HR), with corresponding 95% two-sided CI and *P* value (based on the Wald test), were provided for covariates retained in the final Cox model. Further details on the multivariable Cox model are reported in supplementary Methods, available at *Annals of Oncology* online. Due to the exploratory nature of the analyses, no multiplicity adjustments were carried out.

## RESULTS

### *Patients*

In total, 2003 patients were enrolled in study cohort 1 between 12 November 2012, and 29 September 2014, and 2002 patients received treatment with T-DM1 (supplementary Figure S1A, available at *Annals of Oncology* online). At database lock (31 January 2017), median follow-up duration was 20.6 months (range 0–50).[20] Of the treated patients, 398 had baseline BM reported in the database (supplementary Figure S1B, available at *Annals of Oncology* online). Demographics and disease characteristics for the subgroups of patients with and without baseline BM were generally comparable (Table 1). However, numerically fewer patients with baseline BM had an Eastern Cooperative Oncology Group (ECOG) performance status of 0. Of the 398 patients with baseline BM, 126 (31.7%) had measurable BM designated as target lesions for the evaluation of treatment response. In this subset, 7.9% (10/126), 38.9%

**Table 1. Demographics and disease characteristics at baseline**

| | BM at baseline ($n$ = 398) | No BM at baseline ($n$ = 1604) |
|---|---|---|
| Median age, years (range) | 52 (28–83) | 55 (26–88) |
| ECOG performance status, *n* (%) | | |
| 0 | 192 (48.2) | 918 (57.2) |
| 1 | 174 (43.7) | 601 (37.5) |
| 2 | 32 (8.0) | 83 (5.2) |
| Hormone receptor status of the primary tumor, *n* (%) | | |
| ER- and/or PR-positive | 246 (61.8) | 986 (61.5) |
| ER- and/or PR-negative | 150 (37.7) | 603 (37.6) |
| Both unknown/not done | 2 (0.5) | 15 (0.9) |
| Stage IV disease at initial diagnosis,[a] *n* (%) | 122 (30.7) | 425 (26.5) |
| Median time since initial breast cancer diagnosis, years (range) | 4.8 (0–28) | 5.0 (0–53) |
| Median time since first metastasis, years (range) | 2.4 (0–25) | 2.6 (0–35) |
| Prior lines of treatment of metastatic disease, *n* (%) | | |
| None | 9 (2.3) | 18 (1.1) |
| 1L | 93 (23.4) | 474 (29.6) |
| 2L | 91 (22.9) | 355 (22.1) |
| 3L | 75 (18.8) | 283 (17.6) |
| 4L | 49 (12.3) | 152 (9.5) |
| ≥5L | 74 (18.6) | 242 (15.1) |
| Missing | 7 (1.8) | 80 (5.0) |
| Type of previous systemic cancer therapy (any setting),[b] *n* (%) | | |
| Chemotherapy | 395 (99.2) | 1603 (99.9) |
| Targeted therapy | 398 (100.0) | 1603 (99.9) |
| Endocrine therapy | 227 (57.0) | 946 (59.0) |
| Radiotherapy | 351 (88.2) | 1235 (77.0) |
| Previous anticancer therapy (any setting),[b] *n* (%) | | |
| Anthracyclines | 280 (70.4) | 1143 (71.3) |
| Taxanes | 373 (93.7) | 1473 (91.8) |
| Lapatinib | 237 (59.5) | 711 (44.3) |
| Trastuzumab | 392 (98.5) | 1584 (98.8) |
| Pertuzumab | 24 (6.0) | 65 (4.1) |
| Endocrine therapy | 225 (56.5) | 932 (58.1) |
| Prior brain radiotherapy (any setting), *n* (%) | 226 (56.8) | NA[c] |

1L, first-line; 2L, second-line; 3L, third-line; 4L, fourth-line; 5L, fifth-line; BM, brain metastases; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; NA, not applicable; PR, progesterone receptor.

[a] An additional 11 patients with baseline BM and 46 patients without baseline BM had unmeasurable metastases or unknown stage at breast cancer diagnosis.

[b] Patients could have received more than one type of prior therapy.

[c] Ninety-one patients had accounts of radiotherapy to the brain before study entry, but no documented BM lesions at baseline. Since no further information was available on the existence of BM lesions at baseline for these patients, they were included in the group of patients without BM at baseline.

(49/126), and 53.2% (67/126) had received brain radiotherapy <30 days before baseline, ≥30 days before baseline [median 8.4 months (interquartile range 5.0–13.8; range 1.0–45.3)], or had not received brain radiotherapy, respectively.

### Treatment exposure

Median duration of T-DM1 exposure was 4.9 months (range 0–44) in patients with baseline BM and 5.8 months (range 0–46) in those without.

### Overall tumor response in patients with RECIST Version 1.1 measurable BM at baseline

Of the 126 patients with measurable BM at baseline, 3 achieved a complete response and 24 achieved a partial response, corresponding to a best overall response (BOR) rate across all organs of 21.4% (27/126; 95% CI 14.6–29.6) (Figure 1A and B). An additional 27 patients experienced stable disease (SD) lasting ≥6 months, resulting in a clinical benefit rate of 42.9% (54/126; 95% CI 34.1–52.0) (supplementary Figure S2, available at *Annals of Oncology* online). A ≥30% reduction in the sum of the largest diameters of target brain lesions was observed in 42.9% (54/126; 95% CI 34.1–52.0) of patients, including those whose overall disease response was SD or progressive disease (PD) per RECIST version 1.1.

In the 126 patients with measurable BM, a ≥30% reduction in the sum of the largest diameters of target brain lesions was observed in 50.0% (5/10; 95% CI 18.7–81.3), 32.7% (16/49; 95% CI 20.0–47.6), and 49.3% (33/67; 95% CI 36.9–61.8) of patients who received brain radiotherapy <30 days before baseline, ≥30 days before baseline, and did not receive brain radiotherapy, respectively (Figure 1C). In these 54 patients with a ≥30% reduction in the sum of the largest diameters of target brain lesions, including 9 patients who continued T-DM1 beyond CNS progression, the median duration of exposure to T-DM1 was 9.5 months (range 0.8–43.5). Target lesion evolution over time for patients who did and did not receive radiotherapy is shown in Figure 2.

### Survival outcomes (overall population)

Median PFS was 5.5 months (95% CI 5.3–5.6) in patients with and 7.7 months (95% CI 6.8–8.1) in those without baseline BM (Figure 3A). In patients with BM, median PFS did not appear to be affected by line of treatment with T-DM1 (supplementary Figure S3, available at *Annals of Oncology* online).

Median OS was 18.9 months (95% CI 17.1–21.3) in patients with baseline BM and 30.0 months (95% CI 27.6–31.2) in those without (Figure 3B). Potential prognostic factors for OS were evaluated by exploratory Cox model (supplementary Table S1, available at *Annals of Oncology* online). In the univariate analysis, the presence of brain lesions at baseline was associated with decreased OS [estimated HR 1.68 (95% CI 1.46–1.93; $P < 0.0001$)]. In the multivariable Cox analyses, brain involvement at baseline remained a statistically significant variable. However, the adjusted BM effect estimate had a lower magnitude [estimated HR for adjusted BM effect 1.18 (95% CI 1.02–1.38; $P = 0.0268$)]; and several additional variables were found to be potentially associated with decreased OS, including older age, shorter time since diagnosis of metastatic disease, ECOG performance status ≥1, presence of liver metastases, greater number of metastatic sites, and greater lines of prior therapy for MBC.

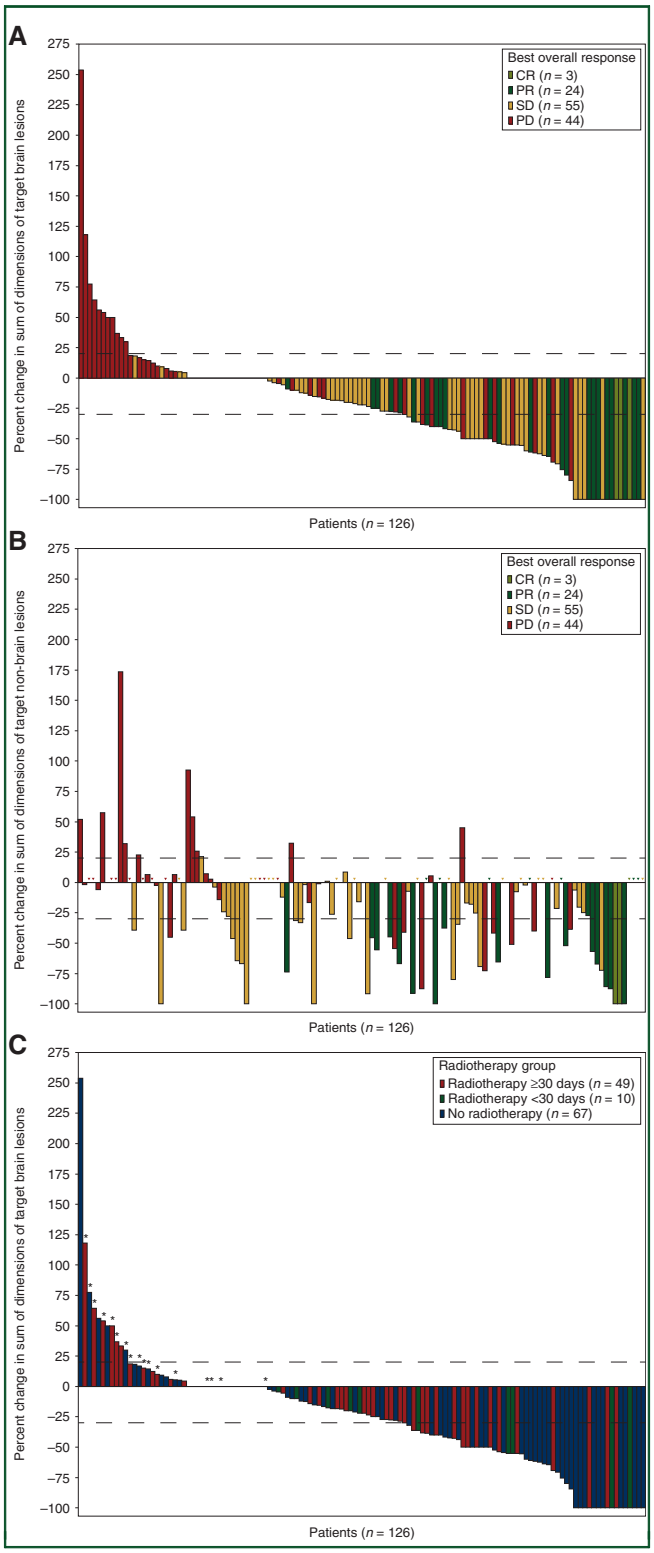


**Figure 1. Treatment response in brain and non-brain target lesions in patients with measurable brain metastases.**

(A) Percent change in sum of dimensions of target brain lesions. (B) Percent change in sum of dimensions of target non-brain lesions. (C) Percent change in sum of dimensions of target brain lesions by radiotherapy subgroup.

Bars are ordered in accordance with decreasing percent change in the sum of target lesion dimensions in brain metastases. Positive bars show growth in target lesions and negative bars indicate shrinkage. Color coding specifies the overall response per RECIST version 1.1 in panels (A) and (B), and by radiotherapy group in panel (C). The dotted lines correspond to a 20% increase or 30% reduction in the size of the target lesion(s).

### *Continued T-DM1 exposure in patients with new brain lesions*

A total of 269 patients experienced new brain lesions during T-DM1 treatment. These included 28.9% (115/398) of patients with baseline BM and 9.6% (154/1604) without baseline BM. KAMILLA allowed continuation of T-DM1 in patients with controlled systemic disease and new brain progression that was amenable to surgery and/or radiotherapy. Sixty-nine patients had investigator-reported continuation of T-DM1 treatment beyond brain progression, of whom 40 had baseline BM and 29 did not. The baseline demographics and disease characteristics of this subset of patients are summarized in supplementary Table S2, available at *Annals of Oncology* online. Among these patients, subsequent T-DM1 treatment administration data (post-progression) were available for 67 patients: the median duration of T-DM1 treatment post-progression was 6.2 months (range 0—37), with durations of 8.8 months (range 0—37) and 6.2 months (range 1—28) in patients with ($n = 39$) and without ($n = 28$) baseline BM, respectively.

### *Safety*

Any AEs and serious AEs were reported in 92.5% (368/398) and 28.4% (113/398) of patients with and in 93.1% (1494/1604) and 19.6% (314/1604) of patients without baseline BM, respectively. The incidence of individual all-grade AEs was generally similar between BM subgroups (supplementary Table S3, available at *Annals of Oncology* online); however, headache and vomiting occurred in a slightly higher percentage of patients with baseline BM and pyrexia occurred in a higher percentage of patients without baseline BM. Nervous system AEs were more common in patients with [$n = 208$ (52.3%)] versus without [$n = 701$ (43.7%)] baseline BM. The following individual serious AEs had a $\geq$1.0% difference between subgroups of patients with versus without BM, respectively: epilepsy [$n = 6$ (1.5%) versus $n = 2$ (0.1%)], seizure [$n = 6$ (1.5%) versus $n = 1$ (0.1%)], and brain edema [$n = 5$ (1.3%) versus $n = 1$ (0.1%)]. Grade $\geq$3 AEs occurring in $\geq$1% of all patients and patients with versus without BM are summarized in supplementary Table S4, available at *Annals of Oncology* online. Grade $\geq$3 CNS hemorrhage occurred in four patients with baseline BM (grade 3 intracranial hemorrhage, $n = 1$; grade 3 and 4 cerebral hemorrhage, each $n = 1$; and grade 4 hemorrhagic stroke, $n = 1$) and two patients without baseline BM (grade 3 and grade 5 intracranial hemorrhage, each $n = 1$).

Grade 5 AEs were reported in 3.5% ($n = 14$) of patients with baseline BM and 1.9% ($n = 31$) of patients without baseline BM. Among patients with baseline BM, brain edema was the only grade 5 AE reported in >1 patient

Triangles in panel B indicate patients with no change available (e.g. due to having no metastatic lesions outside of the brain). Asterisks in panel (C) indicate patients who progressed by the first tumor assessment.

BOR, best overall response; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.



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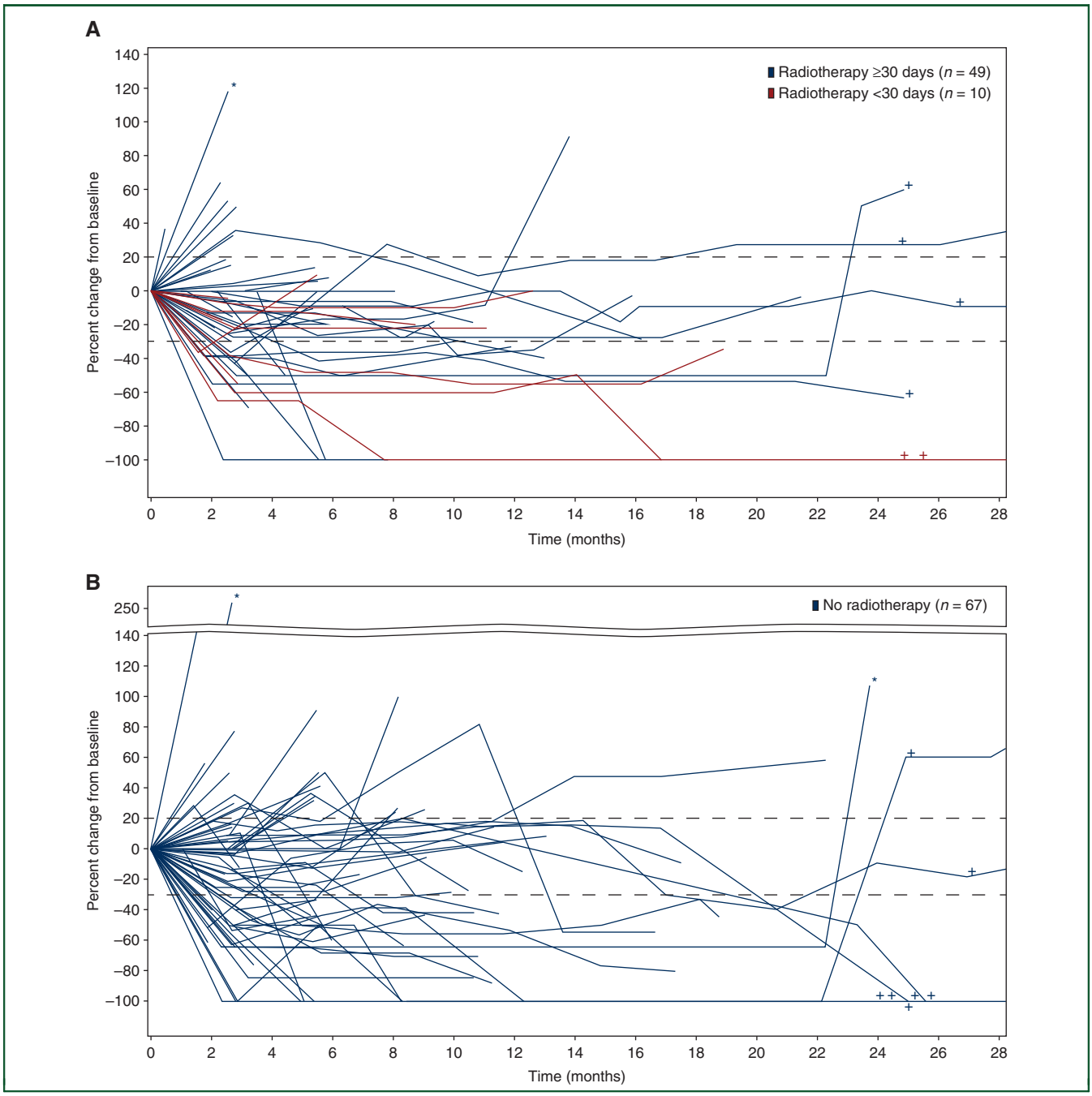


**Figure 2. Brain target lesion evolution over time for patients with measurable brain metastases at baseline.**
(A) Target lesion evolution in patients who received brain radiotherapy <30 days or ≥30 days before baseline. (B) Target lesion evolution in patients who did not receive radiotherapy before baseline.
One patient with radiotherapy and three patients without radiotherapy had a percent change from baseline greater than 100%, indicated with '*'. One patient without radiotherapy had a change from baseline of 120% with a last assessment at 33.2 months, outside of the plot area. The dotted lines correspond to a 20% increase or 30% reduction in the size of the target lesion(s). Six patients with radiotherapy and seven patients without radiotherapy had target lesion assessments after 24 months, indicated with '+'.

($n = 2$). Grade 5 AEs in >1 patient without baseline BM were renal failure ($n = 3$) and multiple organ dysfunction, sepsis, peritonitis, pneumonitis, and hepatic failure (each $n = 2$). Similar proportions of patients in each subgroup reported AEs as the primary reason for permanent treatment discontinuation [$n = 43$ (10.8%) and $n = 198$ (12.3%) in patients with and without baseline BM, respectively].

Among the 69 patients who continued T-DM1 treatment following progression in the brain, serious AEs were observed in 26.1% ($n = 18$). Seizure and confusional state [each $n = 2$ (2.9%)] were the only serious AEs reported in >1 patient. Median PFS from the start of T-DM1 in this subgroup was 10.9 months (95% CI 8.2—12.9).

## DISCUSSION

KAMILLA included the largest population to date of patients with HER2-positive advanced breast cancer and BM treated with T-DM1 in a prospective clinical trial ($n = 398$).

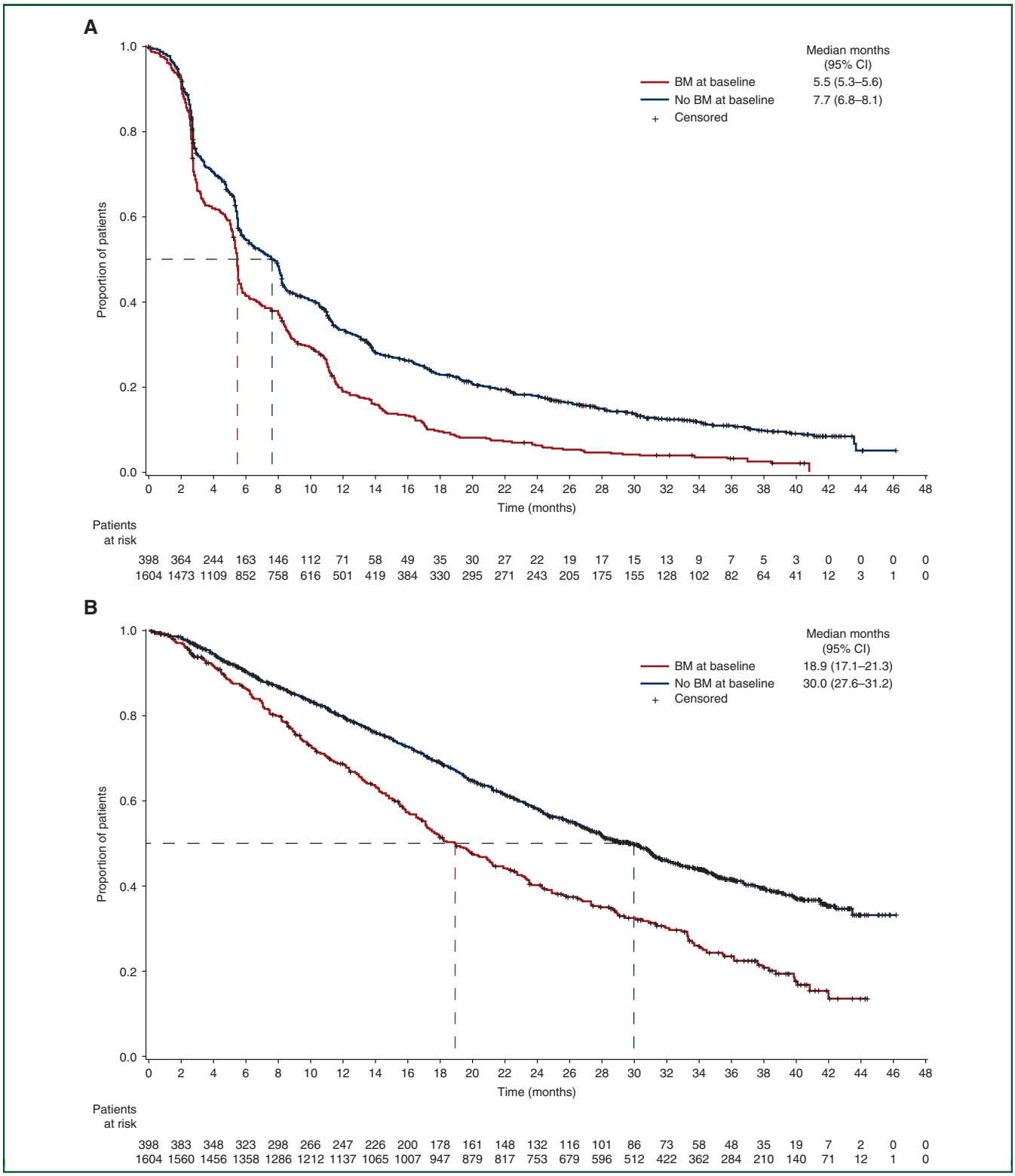


**Figure 3. Progression-free survival and overall survival in patients with and without brain metastases at baseline.**
(A) Progression-free survival. (B) Overall survival.
BM, brain metastases; CI, confidence interval.

Although KAMILLA was not specifically designed to address T-DM1 activity in this particular patient population, our *post hoc* analysis provides some interesting insights. First, in patients with measurable BM ($n = 126$), the BOR and clinical benefit rate were 21.4% and 42.9%, respectively. These figures can be considered clinically relevant in this heavily pretreated population. Second, 42.9% of these patients achieved a $\geq$30% reduction in the sum of major diameter of RECIST-evaluated BM, including patients with PD as the BOR. In this latter group of patients, eight also

showed a concomitant reduction in non-CNS target lesions (Figure 1B). Therefore, PD as BOR could have been due to the progression of non-target lesions (across all organs), the appearance of new lesions (across all organs), or significant clinical deterioration. Unfortunately, the data collected in KAMILLA do not provide the granularity needed to assess the pattern of disease progression in each patient. In the 67 patients without radiotherapy to target BM before study entry, 49.3% had a $\geq$30% reduction in the sum of the major diameters of BM. As this is unbiased by prior radiotherapy or other forms of local therapy to the brain, it represents the direct therapeutic effect of T-DM1 in BM. Because reduction in the size of BM is associated with improvements in neurological symptoms, it is possible (although not formally assessed) that patients with a BM response experienced clinically meaningful benefits on neurological end points; this interesting point warrants further research. Third, compared with patients without BM at study entry, patients with BM experienced reduced PFS and OS, underscoring the importance of continued research in this field. Fourth, patients with new brain lesions during treatment with T-DM1 may still benefit from continuation of T-DM1 after local treatment of BMs. When interpreting the encouraging PFS outcomes in this subset of patients, one must consider that these patients were selected for having SD or better outside of the CNS and progressing BMs that could have been managed with local treatment—a course of action aligned with current guidelines.[22] To our knowledge, this is the first descriptive report of outcomes in clinical trial participants who continued T-DM1 beyond isolated CNS progression. Finally, the overall safety profile for T-DM1 was generally similar between patients with and without baseline BM, although as expected, numerically more nervous system AEs were reported for the former. Overall, this analysis points to the potential of T-DM1 for the treatment of patients with HER2-positive MBC and BM.

Initial reports suggested that trastuzumab had little or no activity in the CNS due to difficulty penetrating the blood-brain barrier.[23] Therefore, much of the research in patients with HER2-positive MBC and BM has focused on small molecule TKIs, namely lapatinib, neratinib, and tucatinib.[7,10,13–17] Our reported median PFS, based on a large number of patients and events, is within the range of those described with lapatinib or neratinib plus capecitabine in patients with BM,[7,13] while the three-drug combination of tucatinib, trastuzumab, and capecitabine yielded superior median PFS in the HER2CLIMB trial.[17] In this trial, 75 patients had untreated, RECIST-measurable CNS metastases at baseline, and patients treated with the three-drug combination achieved an intracranial ORR of 47.3%.[24] Obviously, cross-trial comparisons should be taken with caution and may serve, at best, for hypothesis generation. Yet, antitumor activity for T-DM1 in BM from HER2-positive breast cancer is plausible and has supporting preclinical data. Despite similar drug tissue distribution, T-DM1, but not trastuzumab, significantly delayed the growth of metastases by inducing apoptosis and mitotic catastrophe in mouse models of HER2-positive MBC with BM.[25]

As they are *post hoc* and exploratory, the analyses reported here should be interpreted with caution and considered hypotheses-generating. KAMILLA used RECIST v1.1 to describe tumor response across all organs (CNS and non-CNS). As the recruitment of clinical trial participants with CNS metastases is becoming a research priority, limitations of RECIST v1.1 in correctly describing the CNS activity of systemic therapy have become evident.[26] The more recently proposed Responses Assessment Criteria for Brain Metastases (RANO-BM) criteria provide the means for evaluating treatment responses in patients with CNS metastases.[27] These include bicompartmental evaluation of PFS (CNS and non-CNS assessed separately and then combined for different definitions of PFS) and, more importantly, neurological deterioration and the correlative use of palliative steroid treatment.

Small patient numbers are another limitation to the interpretation of some analyses. For example, analyses of patients with radiotherapy $<$30 days before baseline and of patients who continued treatment after progression in the brain were based on small cohorts. Another potential limitation to the generalizability of our results is that only a small proportion (4.4%) of patients in KAMILLA had been exposed to pertuzumab before study entry. Pertuzumab plus trastuzumab and chemotherapy is the recommended first-line treatment of patients newly diagnosed with HER2-positive advanced breast cancer.[28] While controversy exists regarding the potential for reduced efficacy of T-DM1 in patients previously exposed to pertuzumab,[29–32] it is relevant to acknowledge that most patients in KAMILLA did not receive the current standard-of-care for first-line treatment of MBC.

Despite advances in the treatment of HER2-positive MBC, a notable unmet need remains for patients who also have BM. This exploratory subgroup analysis of KAMILLA represents the largest reported cohort of patients with HER2-positive MBC and BM treated with T-DM1 in a prospective setting. We observed clinically meaningful antitumor activity in patients with and without prior radiotherapy, suggesting that T-DM1 is active in this population and warrants further exploration.

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## DISCLOSURE

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## DATA SHARING

Qualified researchers may request access to de-identified patient level data through the Clinical Study Data Request platform (www.clinicalstudydatarequest.com) and will be provided with accompanying clinical study documentation (protocol and any associated amendments, annotated case report form, reporting and analysis plan, dataset specifications, and the clinical study report). Researchers requesting access to clinical study documentation only can do so via the following link: http://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing/clinical_study_documents_request_form.htm. Documents are made available on application, per scope and timing criteria as published on the Clinical Study Data Request platform.

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