Original Article

Patient-Reported Outcomes From KATHERINE: A Phase 3 Study of Adjuvant Trastuzumab Emtansine Versus Trastuzumab in Patients with Residual Invasive Disease After Neoadjuvant Therapy for Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer

PierFranco Conte, MD [1]; Andreas Schneeweiss, MD[2]; Sibylle Loibl, MD, PhD[3,4]; Eleftherios P. Mamounas, MD[5]; Gunter von Minckwitz, MD, PhD[3]; Max S. Mano, MD, PhD[6]; Michael Untch, MD, PhD[7]; Chiun-Sheng Huang, MD, PhD[8]; Norman Wolmark, MD[9]; Priya Rastogi, MD[9]; Veronique D'Hondt, MD, PhD[10]; Andrés Redondo, MD, PhD[11]; Ljiljana Stamatovic, MD, PhD[12]; Hervé Bonnefoi, MD[13]; Hugo Castro-Salguero, MD[14]; Hans H. Fischer, MD[15]; Tanya Wahl, MD[16]; Chunyan Song, MD[17]; Thomas Boulet, MS[18]; Peter Trask, PhD, MPH[17]; and Charles E. Geyer, Jr, MD[19]

BACKGROUND: The phase 3 KATHERINE trial demonstrated significantly improved invasive disease–free survival with adjuvant trastuzumab emtansine (T-DM1) versus trastuzumab in patients with HER2-positive early breast cancer and residual invasive disease after neoadjuvant chemotherapy plus HER2-targeted therapy. **METHODS:** Patients who received taxane- and trastuzumab-containing neoadjuvant therapy (with/without anthracyclines) and had residual invasive disease (breast and/or axillary nodes) at surgery were randomly assigned to 14 cycles of adjuvant T-DM1 (3.6 mg/kg intravenously every 3 weeks) or trastuzumab (6 mg/kg intravenously every 3 weeks). The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (QLQ-C30) and breast cancer module (QLQ-BR23) were completed at screening, at day 1 of cycles 5 and 11, within 30 days after study drug completion, and at 6- and 12-month follow-up visits. **RESULTS:** Of patients who were randomly assigned to T-DM1 (n = 743) and trastuzumab (n = 743), 612 (82%) and 640 (86%), respectively, had valid baseline and ≥1 postbaseline assessments. No clinically meaningful changes (≥10 points) from baseline in mean QLQ-C30 and QLQ-BR23 scores occurred in either arm. More patients receiving T-DM1 reported clinically meaningful deterioration at any assessment point in role functioning (49% vs 41%), appetite loss (38% vs 28%), constipation (47% vs 38%), fatigue (66% vs 60%), nausea/vomiting (39% vs 30%), and systemic therapy side effects (49% vs 36%). These differences were no longer |apparent at the 6-month follow-up assessment, except for role functioning (23% vs 16%). **CONCLUSION:** These data suggest that health-related quality of life was generally maintained in both study arms over the course of treatment. ***Cancer* 2020;126:3132-3139**.

KEYWORDS: ado-trastuzumab emtansine, antibody-drug conjugate, breast neoplasms, neoadjuvant therapy, patient-reported outcome, quality of life, T-DM1, trastuzumab.

INTRODUCTION

Patients with human epidermal growth factor receptor 2 (HER2)–positive breast cancer who have residual invasive disease after neoadjuvant therapy have higher rates of recurrence and death than those with a pathologic complete response.[1-5]

Corresponding Authors: PierFranco Conte, MD, Istituto Oncologico Veneto IRCCS, via Gattamelata 64, 35128 Padova, Italy (pierfranco.conte@unipd.it); Andreas Schneeweiss, MD, Im Neuenheimer Feld 460, 69120 Heidelberg, Germany (andreas.schneeweiss@med.uni-heidelberg.de).

[1]DiSCOG, University of Padova and Division of Medical Oncology 2, Istituto Oncologico Veneto, IRCCS, Padova, Italy; [2]National Center for Tumor Diseases, Heidelberg University Hospital and German Cancer Research Center, Heidelberg, Germany; [3]GBG, Neu-Isenburg, Germany; [4]Centre for Haematology and Oncology Bethanien, Frankfurt, Germany; [5]NSABP Foundation and Orlando Health University of Florida Health Cancer Center, Orlando, Florida; [6]Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil; [7]AGO-B and HELIOS Klinikum Berlin Buch, Berlin, Germany; [8]National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan; [9]NSABP Foundation and University of Pittsburgh, Pittsburgh, Pennsylvania; [10]Institut Régional du Cancer de Montpellier, Montpellier, France; [11]Hospital Universitario La Paz–IdiPAZ, Madrid, Spain; [12]Institute for Oncology and Radiology of Serbia, Belgrade, Serbia; [13]Institut Bergonié Unicancer and Bordeaux University, Bordeaux, France; [14]Grupo Medico Angeles, Guatemala City, Guatemala; [15]GBG and Evangelische Kliniken Gelsenkirchen, Gelsenkirchen, Germany; [16]Swedish Cancer Institute, Issaquah, Washington; [17]Genentech, Inc., South San Francisco, California; [18]F. Hoffmann-La Roche, Basel, Switzerland; [19]NSABP Foundation and Houston Methodist Cancer Center, Houston, Texas

The first 2 authors contributed equally to this article.

We thank Holly Strausbaugh and Laura Evans for medical writing support.

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.32873, **Received:** January 2, 2020; **Revised:** February 3, 2020; **Accepted:** February 12, 2020, **Published online** April 14, 2020 in Wiley Online Library (wileyonlinelibrary.com)

TABLE 1. Patients Completing at Least 1 Question on the EORTC QLQ-C30 and QLQ-BR23 at Each Assessment Time Point

	QLQ-C30		QLQ-BR23	
Assessment Time Point	Trastuzumab (n = 743)	T-DM1 (n = 743)	Trastuzumab (n = 743)	T-DM1 (n = 743)
Screening	632/743 (85)	655/743 (88)	630/743 (85)	655/743 (88)
Cycle 5	592/674 (88)	610/684 (89)	591/674 (88)	610/684 (89)
Cycle 11	528/613 (86)	529/636 (83)	527/613 (86)	528/636 (83)
Trastuzumab discontinuation	584/743 (79)	58/73 (79)[a]	584/743 (79)	58/73 (79)[a]
T-DM1 discontinuation	0/0 (0)	526/743 (71)	0/0 (0)	526/743 (71)
Follow-up month 6	446/621 (72)	496/667 (74)	446/621 (72)	496/667 (74)
Follow-up month 12	414/568 (73)	458/628 (73)	414/568 (73)	456/628 (73)

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; QLQ-BR23, Quality of Life Questionnaire breast cancer module; QLQ-C30, Quality of Life Questionnaire–Core 30; T-DM1, trastuzumab emtansine.
Data are presented as the number of patients with assessment/number of patients in treatment arm (%).
[a]Patients who discontinued T-DM1 because of adverse events and had switched to trastuzumab.

In the phase 3 KATHERINE trial, adjuvant treatment with trastuzumab emtansine (T-DM1), an antibody–drug conjugate composed of trastuzumab and the microtubule inhibitor emtansine, significantly lowered the risk of invasive disease recurrence compared with adjuvant trastuzumab in patients with residual invasive disease after neoadjuvant chemotherapy plus HER2-targeted therapy (hazard ratio, 0.50; 95% CI, 0.39-0.64; $P < .001$).[6] All-grade adverse events with at least a 10–percentage point increase in incidence in the T-DM1 arm compared with the trastuzumab arm were fatigue (49% vs 34%), nausea (42% vs 13%), platelet count decrease (29% vs 2%), aspartate aminotransferase increase (28% vs 6%), headache (28% vs 17%), alanine aminotransferase increase (23% vs 6%), epistaxis (21% vs 3%), peripheral sensory neuropathy (19% vs 7%), and dry mouth (14% vs 1%). The majority of these were grade 1 or 2. Compared with trastuzumab, patients receiving T-DM1 also had overall higher rates of grade ≥3 adverse events (26% vs 15%), serious adverse events (13% vs 8%), and adverse events leading to treatment discontinuation (18% vs 2%).

Patient-centered outcomes are well recognized as important treatment assessments across multiple disease states, including breast cancer. The International Consortium for Health Outcomes Measures recently identified an optimal set of patient-centered outcomes for patients with breast cancer.[7] These outcomes were broadly categorized as survival and cancer control (eg, treatment outcome measures, such as overall survival); disutility of care (eg, incidence and severity of acute adverse events); and degree of health (eg, overall well-being and patient functioning in a number of aspects of daily life). Degree of health measures are exclusively patient-reported. The Consortium recommended the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (QLQ-C30)[8] and the QLQ breast cancer module (QLQ-BR23)[9] for measuring cancer-specific and breast cancer–specific quality-of-life (QOL) outcomes in all patients regardless of treatment. Key categories identified for patients with breast cancer included overall well-being, physical functioning, emotional functioning, cognitive functioning, social functioning, pain, and fatigue as measured by the QLQ-C30, as well as sexual functioning and body image measured by the QLQ-BR23 (Table 1).

In the KATHERINE study, the patient-reported outcome (PRO) objective was to compare PROs between treatment arms using the QLQ-C30 and QLQ-BR23 to more fully characterize the clinical impact of adverse events associated with T-DM1 compared with trastuzumab. These PRO data are presented here.

MATERIALS AND METHODS

The KATHERINE study was a randomized, multicenter, open-label, phase 3 trial (NCT01772472/BO27938/NSABP B-50-I/GBG 77), the methods for which have been reported previously.[6] Briefly, eligible patients had histologically confirmed, HER2-positive, nonmetastatic, invasive primary breast cancer; had received taxane- and trastuzumab-containing neoadjuvant therapy (with or without anthracyclines) followed by surgery; and had residual invasive disease in the breast and/or axillary nodes at surgery. Patients were randomly assigned to receive up to 14 cycles of adjuvant treatment with trastuzumab (6 mg/kg intravenously every 3 weeks) or T-DM1 (3.6 mg/kg intravenously every 3 weeks). Both groups received adjuvant endocrine and radiation therapy per local standards of care. Patients who discontinued T-DM1 because of adverse events were permitted to switch to trastuzumab.

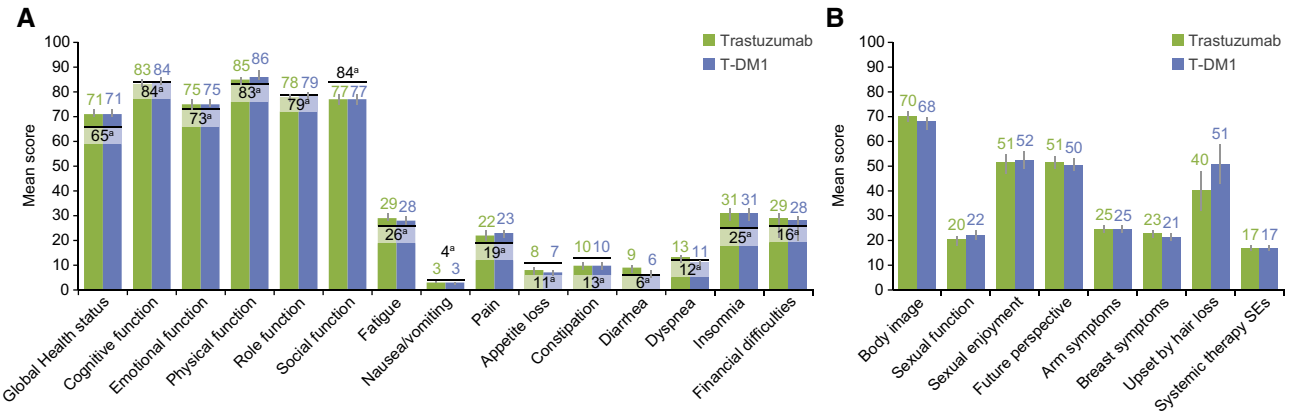

FIGURE 1. (A) Baseline QLQ-C30 and (B) QLQ-BR23 scale scores. The maximum possible score is 100. Horizontal lines over columns and associated numbers represent normative QLQ-C30 scores for patients with stage I/II breast cancer.[13] Vertical lines indicate 95% CIs. QLQ-BR23, Quality of Life Questionnaire breast cancer module; QLQ-C30, Quality of Life Questionnaire–Core 30; SE, side effect; T-DM1, trastuzumab emtansine.

PRO Assessments

The QLQ-C30 is a 30-item questionnaire that measures overall QOL (global health status [GHS]), 5 functional dimensions (physical, emotional, role, cognitive, and social), and additional symptoms and single items. Clinically meaningful deterioration from baseline thresholds for each item are outlined in Supporting Table S1. The QLQ-BR23 is a 23-item module evaluating functioning in several domains and symptoms specific to breast cancer and breast cancer treatment. For both instruments, a higher score on the function and global health scales is more favorable, indicating higher functioning or QOL, and a lower score on the single-item or symptom scale is more favorable, indicating a lower symptom level.

The QLQ-C30 and QLQ-BR23 were translated, as required, into the local language. Investigational site staff distributed questionnaires to patients, who were solely responsible for self-administering the questionnaires. Questionnaires were completed prior to completion of other study assessments and the study treatment at the site visit. Patients were asked to complete the QLQ-C30 and QLQ-BR23 at screening (baseline), at day 1 (prior to treatment) of cycles 5 and 11, within 30 days after study drug discontinuation, and at 6- and 12-month follow-up visits.

Statistical Analysis

Summaries of the compliance rates by treatment arm were obtained at each assessment time point. The compliance rate was defined as the number of patients who completed each assessment divided by the total number of eligible patients at that time point.

When scoring the QLQ-C30 and QLQ-BR23 questionnaires, if more than 50% of the constituent items were completed, a prorated score was computed, consistent with the scoring manuals and validation studies.[10] For subscales with fewer than 50% of the items completed, the subscale was considered to be missing. There was no data imputation. Summary statistics (mean, standard deviation, median, 25th and 75th percentiles, and range) of absolute scores and change from baseline scores of the QLQ-C30 and QLQ-BR23 subscales were summarized at each assessment time point for the 2 treatment arms. For the analyses of change in score from baseline and clinically meaningful deterioration, only patients with a baseline assessment and at least 1 postbaseline assessment were included in the analyses.

The proportion of patients who experienced a clinically meaningful deterioration (or worsening) in symptoms, in their function, or in GHS/QOL were summarized. Assessment of clinically meaningful deterioration in symptoms (score increase) and functions (score decrease) was based on the published thresholds reported by Cocks et al[11] for each applicable subscale (see Supporting Table S1). A clinically meaningful deterioration in GHS/QOL was defined as a decrease of ≥10 points, based on the thresholds reported by both Cocks et al[11,12] and Osoba et al.[13]

RESULTS

The KATHERINE study enrolled 743 patients in each arm (trastuzumab and T-DM1). Baseline and disease characteristics have been reported previously[6] and were similar

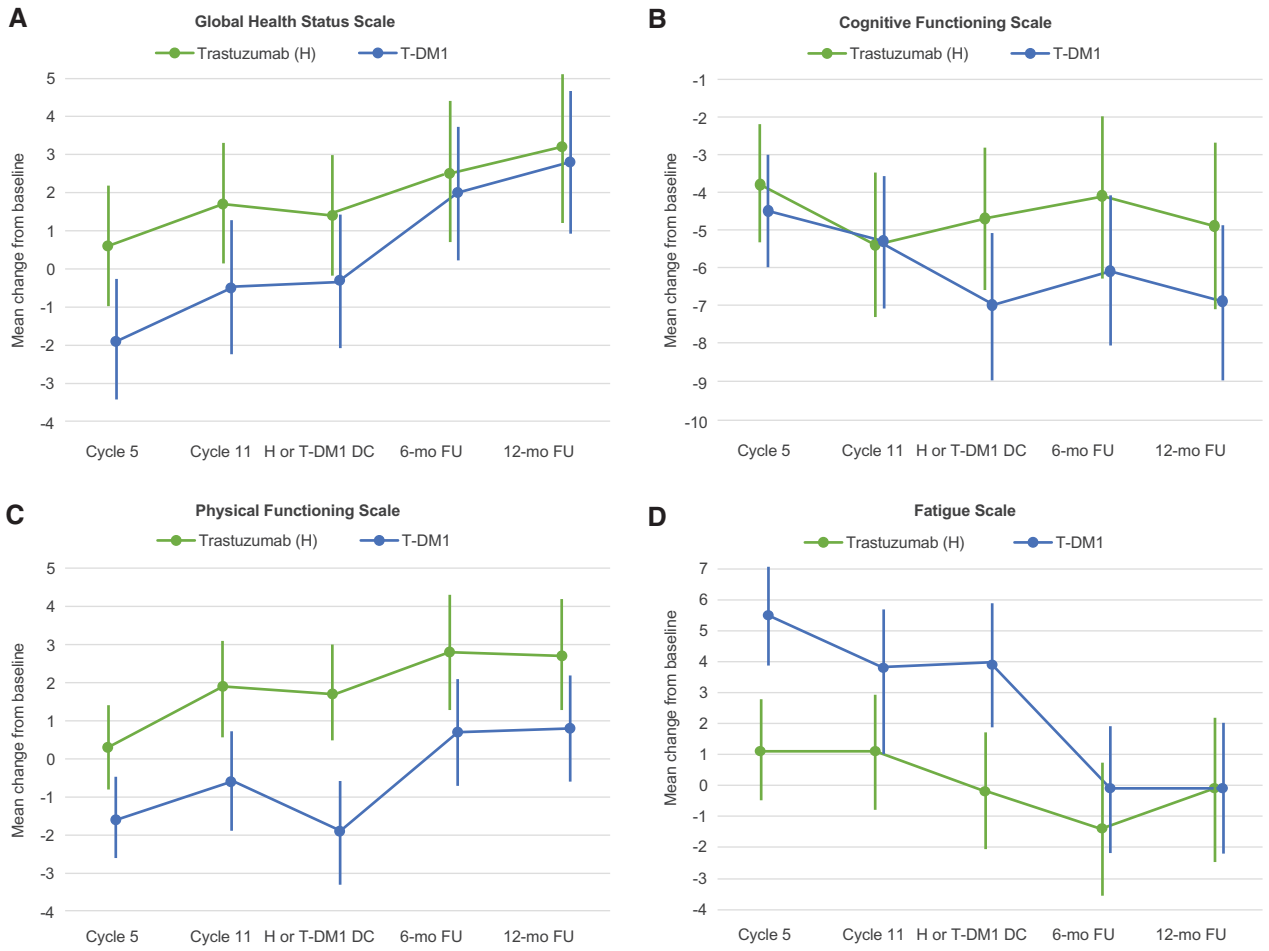

FIGURE 2. Mean change from baseline over time in QLQ-C30 scale scores for (A) global health status, (B) cognitive functioning, (C) physical functioning, and (D) fatigue. Patients who switched from T-DM1 to trastuzumab (n = 73) are not represented. Vertical lines indicate 95% CIs. DC, discontinuation; FU, follow-up; H, trastuzumab; QLQ-BR23, Quality of Life Questionnaire breast cancer module; QLQ-C30, Quality of Life Questionnaire–Core 30; T-DM1, trastuzumab emtansine.

in both treatment arms. A total of 612 (82%) patients in the trastuzumab arm and 640 (86%) patients in the T-DM1 arm had both a valid baseline and at least 1 post-baseline PRO assessment and were included in the analysis. Completion rates for the QLQ-C30 and QLQ-BR23 by time point are shown in Table 1. Of patients assessed at the 12-month follow-up visit, 73% submitted valid PRO assessments. Similar numbers of patients completed the QLQ-C30 and QLQ-BR23.

The mean baseline QLQ-C30 and QLQ-BR23 scale scores were similar in both treatment groups (Fig. 1). The mean scores for the QLQ-C30 function scales ranged from 75 to 86 points, reflecting moderate levels of functioning at baseline.[13,14] The mean baseline score for GHS was 71 in each group, reflecting a moderate level of overall QOL. Mean scores generally indicated low-to-moderate levels of disease- and treatment-related symptoms at baseline, with notably low baseline scores for nausea/vomiting, appetite loss, constipation, and diarrhea. The mean baseline QLQ-C30 scores for all scales were consistent with normative scores reported for patients with stage I/II breast cancer.[14]

Mean Change From Baseline

Similar mean changes from baseline in QLQ-C30 and QLQ-BR23 scores were generally observed in each treatment arm at most postbaseline assessments (Fig. 2 and Supporting Table S2). No mean change from baseline at any time point in either arm exceeded the threshold for a clinically meaningful deterioration. In the T-DM1 arm, the scales with the largest mean changes from baseline (ie, greatest deterioration) at cycles 5 and 11 were constipation,

TABLE 2. Patients Reporting a Clinically Meaningful Deterioration in Selected Scales at Any Assessment Time Point

	Trastuzumab (n = 743), n (%)	T-DM1 (n = 743), n (%)	Difference Between Arms, Percentage Points (95% CI)
QLQ-C30			
Evaluable patients[a]	612	640	—
GHS/QOL	255 (42)	290 (45)	4 (–2 to 9)
Function scales			
Cognitive functioning	346 (57)	386 (60)	4 (–2 to 9)
Physical functioning	206 (34)	247 (39)	5 (0 to 10)
Role functioning	253 (41)	315 (49)	8 (2 to 13)
Symptom scales and items			
Appetite loss	169 (28)	244 (38)	11 (5 to 16)
Constipation	233 (38)	300 (47)	9 (3 to 14)
Diarrhea	166 (27)	139 (22)	–5 (–10 to –1)
Dyspnea	249 (41)	286 (45)	4 (–1 to 9)
Fatigue	370 (60)	423 (66)	6 (0 to 11)
Nausea/vomiting	181 (30)	247 (39)	9 (4 to 14)
Insomnia	297 (49)	313 (49)	0 (–5 to 6)
Pain	327 (53)	372 (58)	5 (–1 to 10)
QLQ-BR23			
Symptom scales			
Hair loss			
Evaluable patients[a]	44	43	—
Any hair loss	15 (34)	12 (28)	–6 (–26 to 13)
Systemic therapy side effects			
Evaluable patients[a]	610	638	—
Patients with side effects	217 (36)	310 (49)	13 (8 to 18)

Abbreviations: GHS, global health status; QLQ-BR23, Quality of Life Questionnaire breast cancer module; QLQ-C30, Quality of Life Questionnaire–Core 30; QOL, quality of life; T-DM1, trastuzumab emtansine.
[a]Number of patients with valid baseline and at least one postbaseline assessment.

cognitive functioning, systemic therapy side effects, appetite loss, and fatigue. Mean scores generally returned to baseline levels after discontinuation of study treatment (Supporting Table S2). The scales with the greatest deterioration at follow-up months 6 and 12 were cognitive functioning, dyspnea, and constipation. However, as noted, these mean changes were less than the clinically meaningful deterioration thresholds for each scale. It should also be noted that for later time points, data are available only for patients who remained enrolled in the study.

Seventy-three patients discontinued T-DM1 because of adverse events and switched to trastuzumab. At the time of trastuzumab completion/early discontinuation, similar mean change scores were observed between patients who switched and patients who were randomly assigned to the trastuzumab arm, and these were less than the minimal clinically important difference across the 9 symptom scales (including financial difficulty) in the QLQ-C30 and the 4 symptom scales in the QLQ-BR23 (data not shown).

Clinically Meaningful Deterioration at Any Assessment

A higher proportion of patients in the T-DM1 arm reported a clinically meaningful deterioration during at least 1 assessment time point in the study in role functioning (49% vs 41%), appetite loss (38% vs 28%), constipation (47% vs 38%), fatigue (66% vs 60%), nausea/vomiting (39% vs 30%), and systemic therapy side effects (49% vs 36%) compared with patients in the trastuzumab arm (Table 2). A lower proportion of patients in the T-DM1 arm reported clinically meaningful deterioration in diarrhea during at least 1 assessment time point in the study compared with the trastuzumab arm (22% vs 27%). More than 50% of patients reported a clinically meaningful deterioration during at least 1 time point in fatigue (T-DM1 66%, trastuzumab 60%), cognitive functioning (T-DM1 60%, trastuzumab 57%), and pain (T-DM1 58%, trastuzumab 53%).

The proportions of patients reporting a clinically meaningful deterioration in the QLQ-C30 and QLQ-BR23 scales by assessment time are shown in Figure 3 and Supporting Table S3. By the 6-month follow-up assessment, the proportion of patients reporting a clinically meaningful deterioration in symptoms and function was similar in each arm, with the exception of role functioning, for which more patients in the T-DM1 arm had a clinically meaningful deterioration compared with the trastuzumab arm (23% vs 16%, respectively). This was maintained at the 12-month assessment.

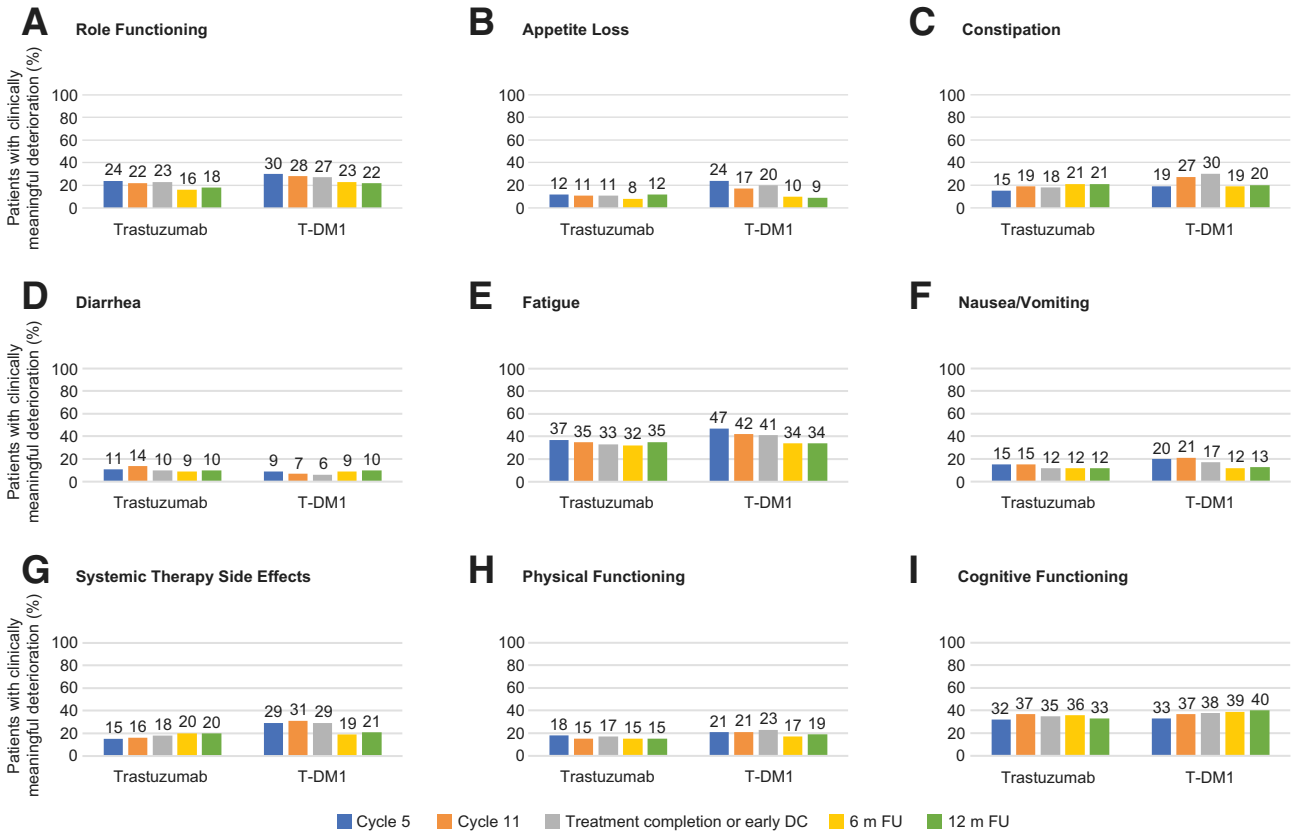

FIGURE 3. Proportion of patients reporting a clinically meaningful deterioration at each assessment point for (A) role functioning, (B) appetite loss, (C) constipation, (D) diarrhea, (E) fatigue, (F) nausea/vomiting, (G) systemic therapy side effects, (H) physical functioning, and (I) cognitive functioning. Data for all scales are shown in Supporting Table S2. DC, discontinuation; FU, follow-up; T-DM1, trastuzumab emtansine.

However, it should be noted that data are available only for patients who remained enrolled in the study.

DISCUSSION

The randomized, phase 3 KATHERINE trial demonstrated significantly improved invasive disease–free survival with adjuvant T-DM1 compared with trastuzumab in patients who had residual invasive disease following neoadjuvant chemotherapy plus HER2-targeted therapy.[6] Compared with trastuzumab, T-DM1 was associated with an increase in certain adverse events, including fatigue, nausea, decreased platelet counts, and increased liver enzymes. The current analysis demonstrated that despite the difference in adverse events, GHS and functioning were generally maintained in both arms over treatment. Mean scores showed a small deterioration from baseline in patient-reported treatment-related symptoms in both arms, but all were less than the clinically meaningful deterioration thresholds.

More than 50% of patients in both arms reported a clinically meaningful deterioration at some point in fatigue, cognitive functioning, and pain. More patients receiving T-DM1 reported clinically meaningful deterioration at some point in certain symptoms, including appetite loss, constipation, fatigue, and nausea/vomiting. This is consistent with adverse event reporting, demonstrating an increased incidence of these adverse events in the T-DM1 arm. Nonetheless, proportions of patients reporting a deterioration in treatment-related symptoms were similar for both groups by the 6-month follow-up visit in all scales but role functioning. It should be noted that data are only available from patients who completed the assessments at that time point; thus, data from patients who discontinued because of adverse events are not included.

Due to its composition of trastuzumab plus the cytotoxic agent emtansine, T-DM1 has been evaluated as a replacement for regimens consisting of an anti-HER2 agent plus a cytotoxic agent in HER2-positive breast

cancer. These trials have demonstrated superior QOL outcomes with T-DM1 compared with the conventional cytotoxic-containing regimens.[15-18] In the neoadjuvant setting, fewer impairments were reported on the QLQ-C30 or QLQ-BR23 among patients receiving T-DM1 plus pertuzumab compared with trastuzumab plus pertuzumab, docetaxel, and carboplatin in the phase 3 KRISTINE trial.[15] The KATHERINE study compared T-DM1 with a nonchemotherapy option. In this setting, a higher number of adverse treatment effects were expected with T-DM1 versus trastuzumab due to the chemotherapy component of the T-DM1 molecule. As reported with the primary results, patients receiving T-DM1 did experience a greater incidence of adverse events compared with patients receiving trastuzumab alone. However, the PRO measures demonstrated largely similar QOL between the treatment arms, and the clinically meaningful deterioration observed at some time points typically resolved within 6 months. The symptoms for which a greater proportion of patients receiving T-DM1 demonstrated clinically meaningful deterioration were largely consistent with the adverse events reported in the trial and the safety profile of T-DM1.[6]

The strengths of our analysis include the fact that the comparison of PRO outcomes using the QLQ-C30 and QLQ-BR23 was a prespecified objective of KATHERINE and that the QOL data were provided by >80% of patients during treatment and >70% of those remaining in follow-up at 6 months and 1 year. A limitation of this analysis is the open-label design of the KATHERINE study and the lack of data availability in T-DM1–treated patients who discontinued the study early because of adverse events.

In conclusion, adverse events associated with adjuvant T-DM1 appeared to have a minimal impact on patient-reported QOL. The mean change from baseline scores was generally similar between treatment arms and was below the clinically meaningful deterioration thresholds, suggesting that baseline levels of functioning and QOL were largely maintained over the course of treatment. While more patients in the T-DM1 arm reported clinically meaningful deterioration at some point in the study in several symptoms and functioning scales, by the 6-month follow-up assessment, the proportion reporting clinically meaningful deterioration was generally similar in each arm. These data from the KATHERINE study, together with the demonstrated superior efficacy of T-DM1 compared with trastuzumab in patients with HER2-positive residual invasive breast cancer after neoadjuvant chemotherapy and HER2-targeted treatment, support T-DM1 as the treatment option of choice in this setting.

FUNDING SUPPORT

This study was funded by F. Hoffmann–La Roche/Genentech.

CONFLICT OF INTEREST DISCLOSURES

PierFranco Conte has served on the speakers' bureau for AstraZeneca, Novartis, and Roche; has received research funding from Merck KGaA, Novartis, and Roche; and has received travel expenses from AstraZeneca, Celgene, and Novartis. Andreas Schneeweiss has received honoraria from AstraZeneca, Celgene, Lilly, MSD, Novartis, Pfizer, Roche, and Tesaro; has received research funding from AbbVie, Celgene, Molecular Partner, and Roche; has provided expert testimony for AstraZeneca and Roche; and has received travel expenses from Celgene and Roche. Sibylle Loibl has a pending patent (EP14153692.0) and her institution has received honoraria from Abbvie, Amgen, AstraZeneca, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Eirgenix, Lilly, Novartis, Pfizer, Puma, Roche, Samsung, Seattle Genetics; has received lecturing honoraria from Abbvie, Amgen, AstraZeneca, Celgene, Celltrion, Chugai, Novartis, Pfizer, prIME, Roche, Samsung, and Seattle Genetics; and has received research funding from Abbvie, Amgen, AstraZeneca, Celgene, Cepheid, Daiichi Sankyo, Myriad, Novartis, Pfizer, Roche, Teva, and Vifor. Eleftherios P. Mamounas has received honoraria from Biotheranostics, Daiichi Sankyo, Genentech/Roche, Genomic Health, and Merck; has served on the speaker's bureau for Genentech/Roche and Genomic Health; and has received research funding from the NSABP Foundation. Gunter von Minckwitz has owned stock in Cara GmbH and has received research funding from AbbVie, Amgen, AstraZeneca, Celgene, Pfizer, and Roche. Max S. Mano has owned stock in Biotoscana, Fleury, and Hypera; has received honoraria from Dasa, Lilly, Novartis, Oncologia Brasil, Pfizer, and Roche; has served as an advisor to AstraZeneca, Lilly, Novartis, Pfizer, and Roche; has been a principal subinvestigator for clinical trials from Lilly, Novartis, Pfizer, and Roche; and has received travel expenses from Roche. Michael Untch has received honoraria from PUMA biotechnology and Odonate and has received nonfinancial support from Odonate, and his institution has received fees from Abbvie, Amgen, AstraZeneca, Bristol Myers Squibb, Celgene, Clovis Oncology, Daiichi Sankyo, Eisai, Lilly Deutschland, Lilly Int., MSD Merck, Mundipharma, Myriad Genetics, Novartis, Pfizer, Pierre Fabre, Roche Pharma AG, Sanofi Aventis Deutschland, and Teva Pharmaceuticals and has received nonfinancial support from Abbvie, Amgen, AstraZeneca, Celgene, Clovis Oncology, Daiichi Sankyo, Eisai, Lilly Int., MSD Merck, Mundipharma, Myriad Genetics, Novartis, Pfizer, Roche Pharma AG, Sanofi Aventis Deutschland, and Teva Pharmaceuticals. Chiun-Sheng Huang has received research funding from AstraZeneca, Daiichi Sankyo, EirGenix, Eli Lilly, MSD, Novartis, OBI Pharma, and Pfizer; has received nonfinancial support from Amgen, AstraZeneca, and Pfizer; has served on advisory boards for Amgen, Eli Lilly, and Pfizer; has served on the speaker's bureau for Amgen, Novartis, and Pfizer; has received personal fees from Amgen, Eli Lilly, Novartis, and Pfizer; has received travel expenses from Amgen, Pfizer, and Roche; and has received speaker honoraria from Roche. Priya Rastogi has received travel expenses from AstraZeneca, Genentech/Roche, and Lilly. Veronique D'Hondt has received travel expenses from Roche. Andrés Redondo has received advisory board honoraria from Amgen, AstraZeneca, Clovis, Lilly, Pharmamar, Roche, and Tesaro-GSK; has received research funding from Eisai, Pharmamar, and Roche; and has received travel expenses from AstraZeneca, Pharmamar, Roche, and Tesaro-GSK. Ljiljana Stamatovic has served as an advisor to AstraZeneca, Novartis, Pfizer, and Roche; has served on the speakers' bureau for AstraZeneca, Novartis, Pfizer, and Roche; and has received travel expenses from Pfizer and Roche. Hervé Bonnefoi has received honoraria from Roche and has received travel expenses from Daiichi and Roche. Hans H. Fischer has received advisory board honoraria from AstraZeneca, Genomic Health, Pfizer, and Roche; has served on the speakers' bureau for AstraZeneca, Genomic Health, Pfizer, and Roche; has received travel expenses from Celgene; and has provided expert testimony for AstraZeneca, Genomic Health, Pfizer, and Roche. Chunyan Song is an employee and stockholder of Genentech/Roche. Thomas Boulet is an employee of F. Hoffmann–La Roche. Peter Trask is an employee and stockholder of Genentech/Roche. Charles E. Geyer, Jr, has received research support from Abbvie, AstraZeneca, and Genentech/Roche; has received travel expenses from AstraZeneca, Daiichi Sankyo, and Genentech/Roche; has received writing assistance from Abbvie and Genentech/Roche; and has received advisory board honoraria from Celgene and Myriad. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

PierFranco Conte: data collection; data interpretation; writing–original draft; writing–review and editing. **Andreas Schneeweiss:** data collection; data interpretation; writing–original draft; writing–review and editing. **Sibylle Loibl:** data collection; data interpretation; writing–review and editing. **Eleftherios P. Mamounas:** data collection; data interpretation; writing–review and editing. **Gunter von Minckwitz:** data collection; data interpretation; writing–review and editing. **Max S. Mano:** data collection; data interpretation; writing–review and editing. **Michael Untch:** data collection; data interpretation; writing–review and editing. **Chiun-Sheng Huang:** data collection; data interpretation; writing–review and editing. **Norman Wolmark:** data collection; data interpretation; writing–review and editing. **Priya Rastogi:** data collection; data interpretation; writing–review and editing. **Veronique D'Hondt:** data collection; data interpretation; writing–review and editing. **Andrés Redondo:** data collection; data interpretation; writing–review and editing. **Ljiljana Stamatovic:** data collection; data interpretation; writing–review and editing. **Hervé Bonnefoi:** data collection; data interpretation; writing–review and editing. **Hugo Castro-Salguero:** data collection; data interpretation; writing–review and editing. **Hans H. Fischer:** data collection; data interpretation; writing–review and editing. **Tanya Wahl:** data collection; data interpretation; writing–review and editing. **Chunyan Song:** data collection; data interpretation; writing–review and editing. **Thomas Boulet:** data collection; data interpretation; writing–review and editing. **Peter Trask:** data collection; data interpretation; writing–review and editing. **Charles E. Geyer, Jr:** data collection; data interpretation; writing–review and editing.

REFERENCES

1. Untch M, Fasching PA, Konecny GE, et al. Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups. *J Clin Oncol*. 2011;29:3351-3357.
2. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet*. 2014;384:164-172.
3. de Azambuja E, Holmes AP, Piccart-Gebhart M, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response. *Lancet Oncol*. 2014;15:1137-1146.
4. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet Oncol*. 2014;15:640-647.
5. Schneeweiss A, Chia S, Hickish T, et al. Long-term efficacy analysis of the randomised, phase II TRYPHAENA cardiac safety study: evaluating pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer. *Eur J Cancer*. 2018;89:27-35.
6. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med*. 2019;380:617-628.
7. Ong WL, Schouwenburg MG, van Bommel ACM, et al. A standard set of value-based patient-centered outcomes for breast cancer: the International Consortium for Health Outcomes Measurement (ICHOM) initiative. *JAMA Oncol*. 2017;3:677-685.
8. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85:365-376.
9. Sprangers MA, Groenvold M, Arraras JI, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. *J Clin Oncol*. 1996;14:2756-2768.
10. Fayers PM, Aaronson NK, Bjordal K, Curran D, Groenvold M. The EORTC QLQ-C30 Scoring Manual. 2nd ed. European Organisation for Research and Treatment of Cancer; 1999.
11. Cocks K, King MT, Velikova G, et al. Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *Eur J Cancer*. 2012;48:1713-1721.
12. Cocks K, King MT, Velikova G, Martyn St-James M, Fayers PM, Brown JM. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *J Clin Oncol*. 2011;29:89-96.
13. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol*. 1998;16:139-144.
14. Scott NW, Fayers PM, Aaronson NK, et al. EORTC QLQ-C30 reference values. Published July 2008. Accessed June 19, 2019. https://www.eortc.org/app/uploads/sites/2/2018/02/reference_values_manual2008.pdf
15. Hurvitz SA, Martin M, Jung KH, et al. Neoadjuvant trastuzumab emtansine and pertuzumab in human epidermal growth factor receptor 2-positive breast cancer: three-year outcomes from the phase III KRISTINE study. *J Clin Oncol*. 2019;37:2206-2216.
16. Welslau M, Diéras V, Sohn JH, et al. Patient-reported outcomes from EMILIA, a randomized phase 3 study of trastuzumab emtansine (T-DM1) versus capecitabine and lapatinib in human epidermal growth factor receptor 2-positive locally advanced or metastatic breast cancer. *Cancer*. 2014;120:642-651.
17. Hurvitz SA, Dirix L, Kocsis J, et al. 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*. 2013;31:1157-1163.
18. Perez EA, Barrios C, Eiermann W, et al. Trastuzumab emtansine with or without pertuzumab versus trastuzumab plus taxane for human epidermal growth factor receptor 2-positive, advanced breast cancer: primary results from the phase III MARIANNE study. *J Clin Oncol*. 2017;35:141-148.