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Original Research

Preservation of quality of life in patients with human epidermal growth factor receptor 2–positive metastatic breast cancer treated with tucatinib or placebo when added to trastuzumab and capecitabine (HER2CLIMB trial)



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Abstract *Aims:* In HER2CLIMB, tucatinib significantly improved progression-free and overall survival in patients with human epidermal growth factor receptor 2–positive (HER2+) metastatic breast cancer. We evaluated the impact of tucatinib on health-related quality of life (HR-QoL) in HER2CLIMB.

Methods: Patients were randomised 2:1 to tucatinib or placebo combined with trastuzumab and capecitabine. Starting with protocol version 7, the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) questionnaire and EQ visual analogue scale (VAS) were administered at day 1 of cycle 1, every two cycles during cycles 3–9, every three cycles during cycle 12 and thereafter and at each patient's 30-day follow-up visit.

Results: Among 364 patients eligible for HR-QoL assessment, 331 (91%) completed ≥ 1 assessment. EQ-VAS scores were similar for both arms at baseline and maintained throughout treatment. EQ-5D-5L scores were similar between the treatment arms, stable throughout therapy and worsened after discontinuing treatment. Risk of meaningful deterioration (≥ 7 points) on EQ-VAS was reduced 19% in the tucatinib vs. placebo arm (hazard ratio [HR]: 0.81; 95% confidence interval [CI]: 0.55, 1.18); the median (95% CI) time to deterioration was not reached in the tucatinib arm and was 5.8 months (4.3, -) in the placebo arm. Among patients with brain metastases ($n = 164$), risk of meaningful deterioration on EQ-VAS was reduced 49% in the tucatinib arm (HR: 0.51; 95% CI: 0.28, 0.93); the median (95% CI) time to deterioration was not reached in the tucatinib arm and was 5.5 months (4.2, -) in the placebo arm.

Conclusions: HR-QoL was preserved for patients with HER2+ metastatic breast cancer who were treated with tucatinib added to trastuzumab and capecitabine and maintained longer with tucatinib therapy than without it among those with brain metastases.

Clinical Trial Registration: NCT02614794

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1. Introduction

As our understanding of the molecular mechanisms of human epidermal growth factor receptor 2–positive (HER2+) breast cancer improves and targeted treatment strategies are developed, patients are living longer with this disease [1]. HER2+ metastatic breast cancer causes symptoms that impair health-related quality of life (HR-QoL), and treatment can exacerbate symptoms or lead to adverse events that further impact HR-QoL, including physical, emotional, caregiver and financial

burden [2]. As disease progresses and patients receive later lines of systemic therapy, this burden increases and survival and HR-QoL deteriorate further [3–6]. The burden is even greater for those with brain metastases because they have a worse prognosis and suffer from neurological symptoms and treatment-related adverse events, leading to further deterioration in HR-QoL [7–11]. In this setting of long-term therapy, reducing the impact of both illness and treatment on physical and psychosocial well-being takes on renewed importance [12]. Guideline-recommended treatments for

patients with HER2+ metastatic breast cancer are first-line trastuzumab plus pertuzumab and a taxane, followed by second-line trastuzumab emtansine (T-DM1) for patients who have disease progression [13,14].

For patients whose disease progresses after two lines of HER2-targeted therapy, there is no established consensus on the standard of care, and the treatment landscape is continually evolving. Besides trastuzumab and capecitabine, HER2-targeted tyrosine kinase inhibitors (TKIs) are often prescribed in combination with other chemotherapies [13,14]. However, tolerability can be an issue with the HER2-directed TKIs owing to off-target effects on the epidermal growth factor receptor (EGFR) receptor, resulting in high incidence of diarrhoea, including severe diarrhoea and skin toxicity [15,16].

Tucatinib is an oral TKI that is highly selective for the HER2 receptor, with minimal inhibition of other HER2 receptors, including EGFR [17]. Tucatinib is approved in combination with trastuzumab and capecitabine in the United States, the European Union and several other countries for patients with HER2+ metastatic breast cancer, including those with brain metastases, whose cancers have progressed on at least one (United States) or two (European Union) prior anti-HER2 regimens in the metastatic setting. In the pivotal HER2CLIMB trial, the combination of tucatinib, trastuzumab and capecitabine became the first regimen to demonstrate a statistically significant and clinically meaningful improvement in progression-free survival and overall survival among patients with HER2+ metastatic breast cancer who progressed on trastuzumab, pertuzumab and T-DM1, both with and without brain metastases [18]. The addition of tucatinib to trastuzumab and capecitabine was well tolerated, with adverse event rates similar to those observed with trastuzumab and capecitabine alone [18].

We evaluated the impact of adding tucatinib to a trastuzumab-capecitabine regimen on patient-reported HR-QoL in patients in the HER2CLIMB trial.

2. Methods

2.1. Study design

HER2CLIMB is a randomised, double-blind trial of tucatinib vs. placebo in combination with trastuzumab and capecitabine in patients with HER2+ metastatic breast cancer previously treated with trastuzumab, pertuzumab and T-DM1 [18]. Patients were randomly assigned 2:1 to receive either tucatinib (300 mg) or placebo orally twice daily, in combination with trastuzumab (6 mg/kg intravenously once every 21 days, with an initial loading dose of 8 mg/kg) and capecitabine (1000 mg/m² orally twice daily on days 1–14 of each 21-day cycle). In HER2CLIMB, 48% of participants had the presence or history of brain metastases at baseline, which included previously untreated, treated

stable, and treated and progressing brain metastases. Patients were stratified at randomisation based on the presence or history of brain metastases (yes or no), Eastern Cooperative Oncology Group performance status score (0 or 1) and region of world (US, Canada or rest of the world). All patients underwent contrast magnetic resonance imaging (MRI) of the brain at baseline, and those with brain metastases on the baseline scan underwent MRI of the brain every 6 weeks for 24 weeks and every 9 weeks thereafter.

The HER2CLIMB trial was conducted in accordance with regulatory requirements and International Conference on Harmonisation Good Clinical Practice guidelines. The protocol was approved by institutional review boards and ethics committees, as per the practice at each participating trial site, and informed consent was obtained for experimentation with human subjects.

2.2. HR-QoL assessments

Assessment of HR-QoL as an exploratory end-point was initiated with protocol version 7 on 30th August 2017, and therefore, it was only administered to patients enrolled after this date. Patients completed the HR-QoL questionnaire before treatment administration at day 1 of cycle 1, every two cycles during cycles 3–9, every three cycles starting at cycle 12 and beyond and at each patient's 30-day follow-up visit after stopping treatment (regardless of the number of cycles completed). For example, a patient who stopped treatment in cycle 5 would not have data reported at cycles 7 and 9 but would have data reported for 30-day follow-up.

The HR-QoL assessment tool was the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) questionnaire, which consists of five dimensions (mobility, usual activities, self-care, pain/discomfort and anxiety/depression), each rated on a 5-point scale (no problems, slight problems, moderate problems, severe problems and extreme problems) [19]. The EQ-5D-5L instrument also includes a visual analogue scale (EQ-VAS) in which patients rate their current overall health on a vertical visual analogue scale that ranges from 0 (worst imaginable health state) to 100 (best imaginable health state). Meaningful deterioration in HR-QoL was defined as a decrease in the EQ-VAS score from baseline of ≥ 7 points, based on a minimally important difference of 7 points as estimated by Pickard *et al.* [20]. EQ-5D-5L is validated for use in patients, with breast cancer [21–23], approved by the National Institute for Health and Care Excellence for calculating quality-adjusted life years and also can be used for economic evaluation of treatments in global pivotal trials.

2.3. Statistical analysis

The HER2CLIMB trial was not powered for statistical comparison of HR-QoL. We analysed EQ-5D-5L and

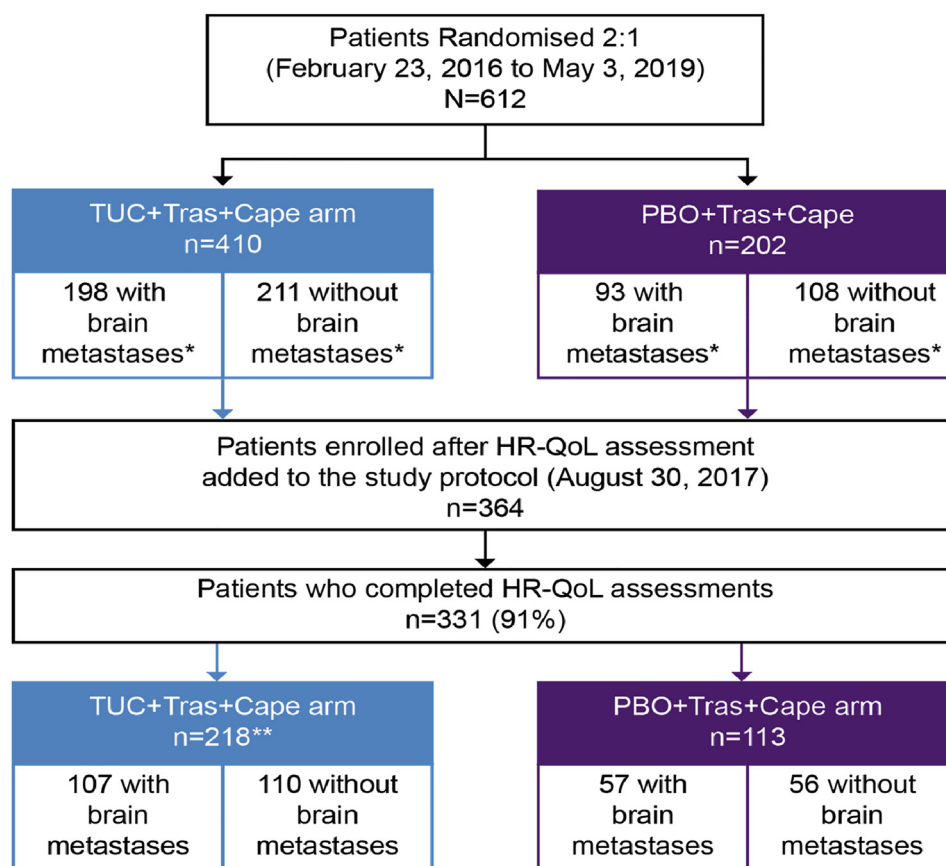


Fig. 1. CONSORT diagram of HER2CLIMB patients included in the HR-QoL analysis. TUC: tucatinib; Tras: trastuzumab; Cape: capecitabine; PBO: placebo. *Two enrolled subjects did not undergo baseline brain MRI, one randomised to tucatinib and one randomised to placebo. **One patient in the TUC arm was missing information regarding brain metastases. MRI: magnetic resonance imaging; HR-QoL: health-related quality of life.

Table 1
Demographic and disease characteristics of HER2CLIMB patients in the HR-QoL analysis.

Characteristic	All HR-QoL patients (N = 331)		HR-QoL patients with brain metastases (N = 164) ^a	
	Tucatinib combination (n = 218)	Placebo combination (n = 113)	Tucatinib combination (n = 107)	Placebo combination (n = 57)
Age, in years, median (range)	55 (22, 79)	54 (25, 76)	54 (22, 75)	52 (25, 75)
Female, n (%)	217 (99.5)	111 (98)	107 (100)	56 (98)
ECOG performance status, n (%)				
0	106 (49)	52 (46)	51 (48)	22 (39)
1	112 (51)	61 (54)	56 (52)	35 (61)
Stage at initial diagnosis, n (%)				
Stage 0–III	140 (64)	72 (64)	64 (60)	31 (54)
Stage IV	77 (35)	40 (35)	42 (39)	25 (44)
Not available	1 (0.5)	1 (1)	1 (1)	1 (2)
Histology, n (%)				
ER and/or PR positive	135 (62)	71 (63)	64 (60)	34 (60)
ER and PR negative	79 (36)	42 (37)	41 (38)	23 (40)
Other	4 (2)	0	2 (2)	0
Prior lines of therapy, median (range)				
Overall	4.0 (2, 11)	4.0 (2, 12)	4.0 (2, 11)	3.0 (2, 12)
Metastatic setting	3.0 (1, 11)	3.0 (1, 11)	2.0 (1, 11)	3.0 (1, 11)

Tucatinib combination: tucatinib, trastuzumab and capecitabine. Placebo combination: placebo, trastuzumab and capecitabine.

ECOG: Eastern Cooperative Oncology Group; ER: oestrogen receptor; PR: progesterone receptor; HR-QoL: health-related quality of life; MRI: magnetic resonance imaging.

^a Two enrolled subjects did not undergo baseline brain MRI, one randomised to tucatinib and one randomised to placebo.

EQ-VAS for all patients with HR-QoL data and based on the presence or absence of brain metastases. EQ-5D-5L domain scores and EQ-VAS scores were summarised by cycle for each treatment arm, with numerators representing the number of patients who completed the HR-QoL survey in that cycle and denominators representing the number of patients who completed the baseline survey and were still on treatment in that cycle. Time to meaningful deterioration on the EQ-VAS (defined as a ≥ 7 -point change from baseline [20]) was estimated using the Kaplan-Meier method; patients who did not have a ≥ 7 -point change were censored at the latest assessment before the data cut-off. The median time to deterioration and 95% confidence interval (CI) were computed for each treatment arm.

3. Results

HR-QoL data were available for 331 of 364 patients (91%) who enrolled in the HER2CLIMB trial after HR-QoL assessment was added to the protocol: 218 in the

tucatinib arm and 113 in the placebo arm (Fig. 1). Overall, this represents 54% (331 of 612) of all patients who were enrolled in HER2CLIMB. This population included 164 patients with brain metastases: 107 patients in the tucatinib arm and 57 patients in the placebo arm. Baseline demographic and disease characteristics were similar between all HR-QoL patients and the HR-QoL patients with brain metastases (Table 1) and consistent with those of the overall HER2CLIMB population [18]. These patients had a median of 4 (range: 2 to 12) lines of prior therapy overall and 3 (range: 1 to 11) lines of prior therapy in the metastatic setting (Table 1).

3.1. Outcomes in all patients

EQ-VAS scores were similar between treatment arms at baseline and were maintained throughout treatment in both arms (Fig. 2A). There was a 19% reduction in the risk of meaningful deterioration in HR-QoL in the tucatinib arm compared with the placebo arm (hazard ratio [HR]: 0.81; 95% CI: 0.55, 1.18); the median

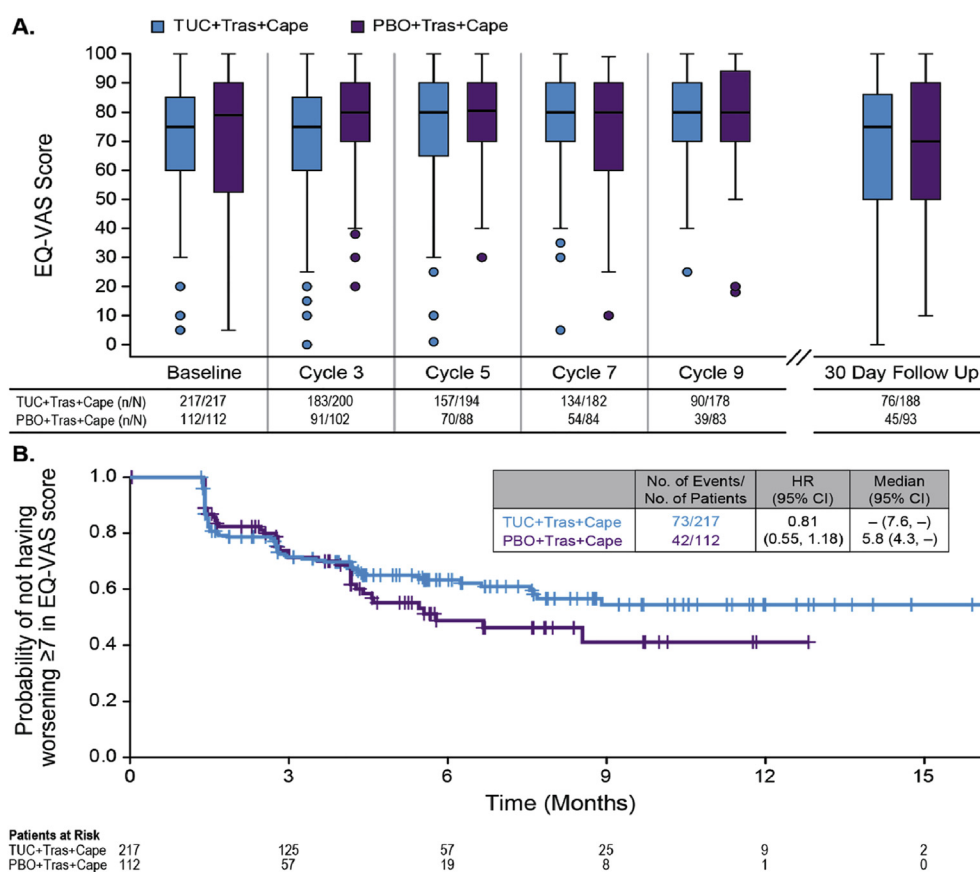


Fig. 2. Median EQ-VAS scores at baseline, on treatment and at 30 days after stopping treatment (A) and time to meaningful deterioration (≥ 7 points) in the EQ-VAS score (B) in all patients with HR-QoL data. TUC: tucatinib; trasTras: trastuzumab; Cape: capecitabine; PBO: placebo; VAS: visual analogue scale. Thirty-day follow-up represents 30 days after stopping treatment, regardless of the number of treatment cycles completed. The centre line within the box represents the median. The box represents the interquartile range. Error bars reflect minimum and maximum. Numerators are the number of patients who completed the HR-QoL survey in that cycle. Denominators are the number of patients who completed the baseline survey and were still on treatment. One patient each in the tucatinib arm and the placebo arm did not have EQ-VAS data available. HR-QoL: health-related quality of life; CI: confidence interval; HR: hazard ratio.

(95% CI) time to deterioration had not been reached in the tucatinib arm and was 5.8 months (4.3, –) in the placebo arm (Fig. 2B).

In all five EQ-5D-5L domains, most patients in both treatment arms reported only slight or no problems, and few patients reported moderate, severe or extreme problems while on therapy (Fig. 3A–E). The proportion of patients with slight or no problems was similar between treatment arms and remained stable throughout therapy. For each EQ-5D-5L domain, there was an increase in the proportion of patients reporting moderate, severe or extreme problems 30 days after stopping treatment (Fig. 3A–E). Overall, these increases were generally greater in the tucatinib arm than in the placebo arm.

3.2. Outcomes in patients with brain metastases

As in the overall HR-QoL population, EQ-VAS scores were similar for both treatment arms at baseline, were

maintained throughout treatment and were not different between treatment arms among patients with brain metastases (Fig. 4B). There was a 49% reduction in the risk of meaningful deterioration in HR-QoL in the tucatinib arm compared with the placebo arm (HR: 0.51; 95% CI: 0.28, 0.93); the median (95% CI) time to deterioration had not been reached in the tucatinib arm and was 5.5 months (4.2, –) in the placebo arm (Fig. 4B). For each EQ-5D-5L domain, there was an increase in the proportion of patients reporting moderate, severe or extreme problems 30 days after stopping treatment, with the exception of anxiety/depression in the placebo arm (Fig. 5A–E). Overall, these increases were generally greater in the tucatinib arm than in the placebo arm.

Outcomes for HR-QoL patients with no brain metastases are shown in Appendix A. EQ-VAS scores were maintained throughout treatment and were not different between treatment arms, and the risk of meaningful deterioration in HR-QoL was similar between treatment arms.

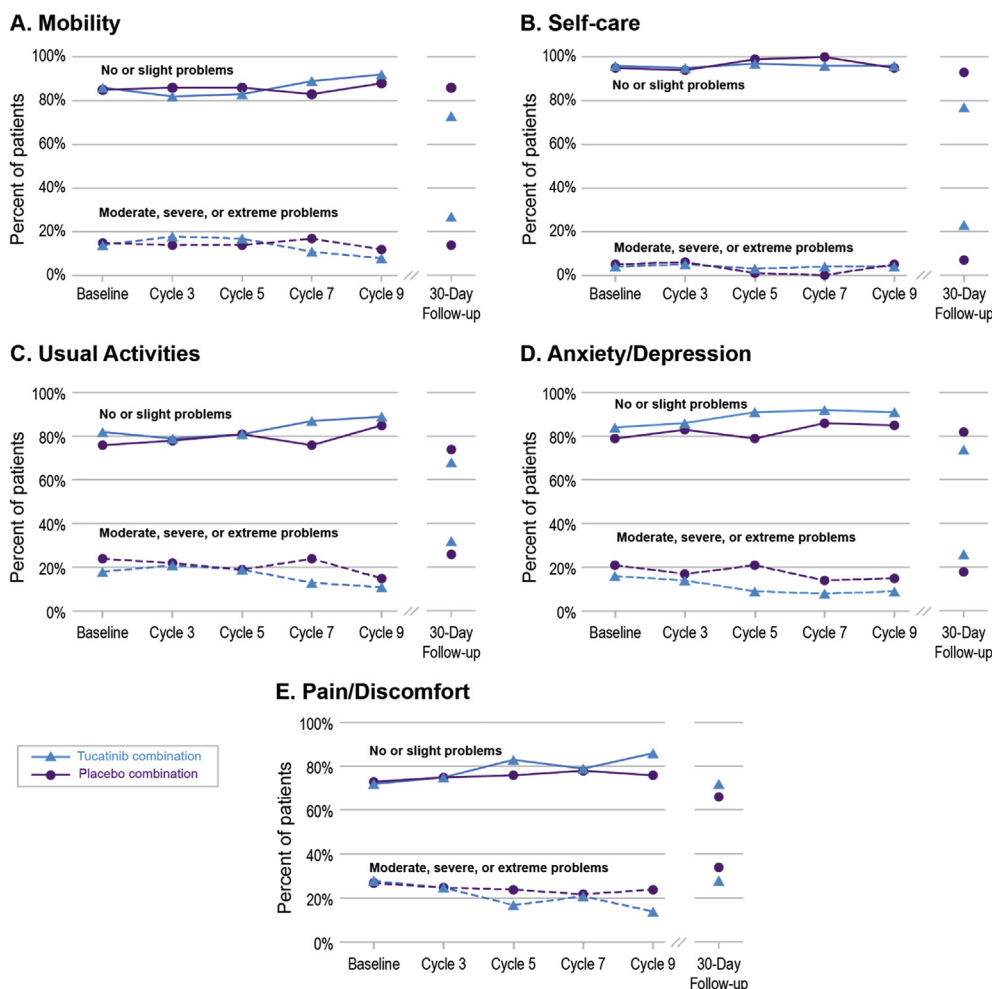


Fig. 3. EuroQol 5 Dimensions 5 levels (EQ-5D-5L) subscale responses at baseline, on treatment and at 30 days after stopping treatment in all patients with HR-QoL data: mobility (A), self-care (B), usual activities (C), anxiety/depression (D) and pain/discomfort (E). 30-day follow-up represents 30 days after stopping treatment, regardless of the number of treatment cycles completed. HR-QoL: health-related quality of life.

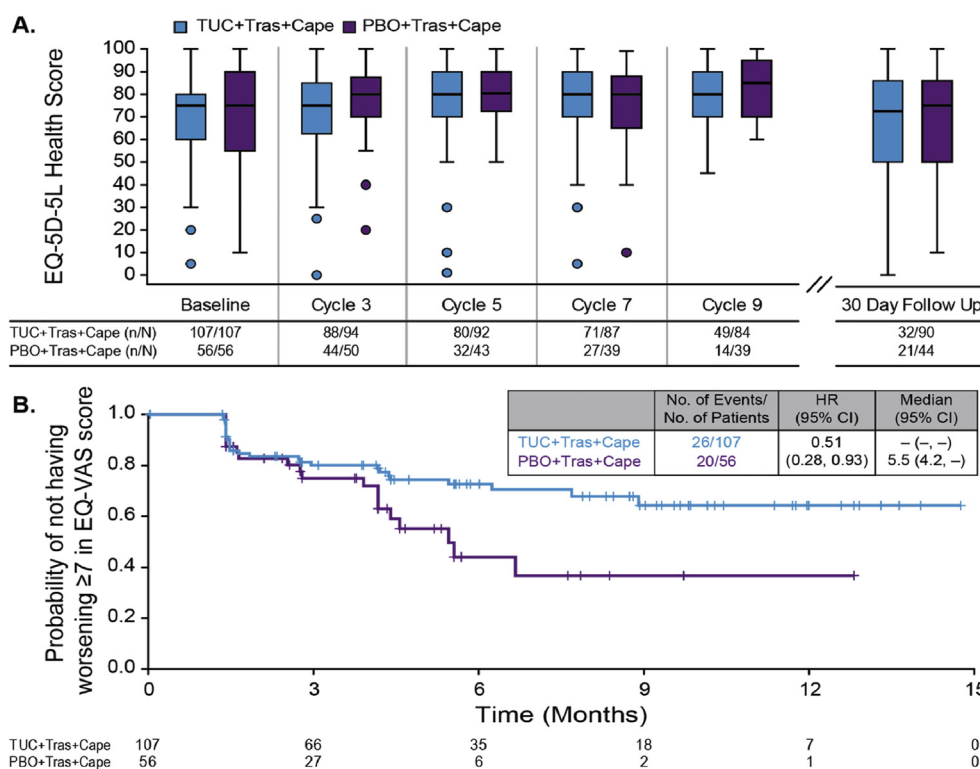


Fig. 4. Median EQ-VAS scores at baseline, on treatment, and at 30 days after stopping treatment (A) and time to meaningful deterioration (≥ 7 points) in the EQ-VAS score (B) in HR-QoL patients with brain metastases. TUC: tucatinib; trasTras: trastuzumab; Cape: capecitabine; PBO: placebo; VAS: visual analogue scale. Thirty-day follow-up represents 30 days after stopping treatment, regardless of the number of treatment cycles completed. The centre line within the box represents the median. The box represents the interquartile range. Error bars reflect minimum and maximum. Numerators are the number of patients who completed the HR-QoL survey in that cycle. Denominators are the number of patients who completed the baseline survey and were still on treatment. One patient each in the tucatinib arm and the placebo arm did not have EQ-VAS data available. HR-QoL: health-related quality of life; CI: confidence interval; HR: hazard ratio.

4. Discussion

In the HER2CLIMB trial, patients with HER2+ metastatic breast cancer, who had received at least two prior anti-HER2-directed regimens, reported preservation of overall HR-QoL when tucatinib was added to a trastuzumab and capecitabine regimen. Importantly, this durability of HR-QoL throughout the treatment course was reported in the context of a pivotal trial that demonstrated better progression-free survival and overall survival with the tucatinib regimen [18]. Furthermore, EQ-5D-5L domain scores worsened after patients stopped treatment to a greater degree among the tucatinib-treated patients. Taken together, these findings demonstrate that the tucatinib-trastuzumab-capecitabine regimen not only provides significant and clinically meaningful anticancer activity but also maintains HR-QoL.

Based on these findings, this triplet regimen has minimal impact on HR-QoL, which indicates that side-effects are not perceived as severe. Although diarrhoea, sometimes severe, is common with HER2-directed TKIs, [15,16], diarrhoea in HER2CLIMB patients was manageable with short courses of antidiarrheal medications (i.e., a median of three days per cycle) in

both the tucatinib and placebo arms [18]. Furthermore, preservation of HR-QoL with the tucatinib regimen was achieved without protocol-mandated use of prophylactic antidiarrheal medication.

Up to 50% of patients with HER2+ metastatic breast cancer will develop brain metastases, [24–27], and these patients have an increased likelihood of reduced HR-QoL compared with patients without brain metastases [8]. Patients with HER2+ breast cancer and brain metastases also continue to have a poor prognosis and impaired QoL, despite advances in HER2-targeted treatments [8]. Historically, patients with brain metastases, especially those with active (i.e., untreated or progressing) brain metastases, have not been included in clinical trials of treatments for HER2+ metastatic breast cancer. In recent years, the American Society of Clinical Oncology–Friends of Cancer Research Brain Metastases Working Group and the 2019 US Food and Drug Administration ‘Cancer Clinical Trial Eligibility Criteria: Brain Metastases—Guidance for Industry’ have advocated for inclusion of patients with both treated stable and active brain metastases in clinical trials to increase applicability to this population with high unmet need [28,29]. In this HR-QoL analysis from

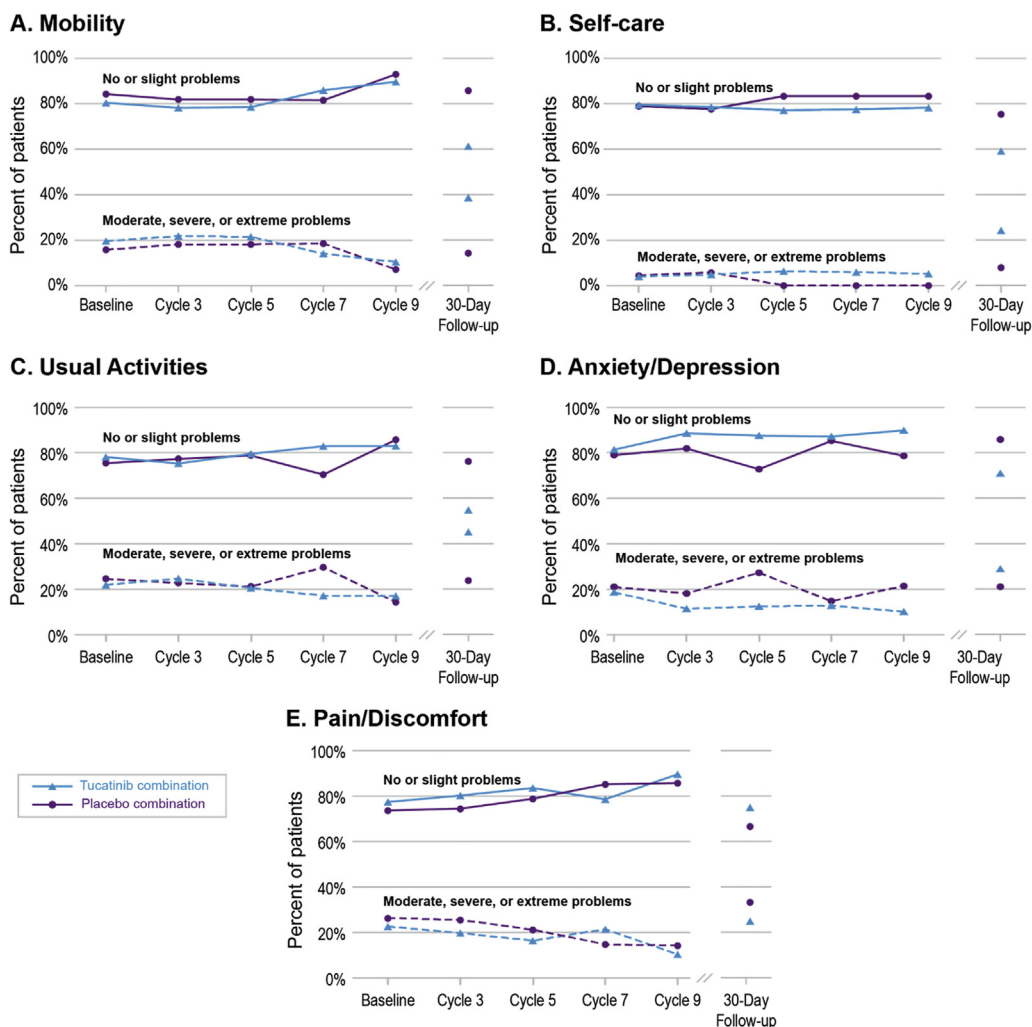


Fig. 5. EuroQoL- 5 Dimensions 5 levels (EQ-5D-5L) subscale responses at baseline, on treatment and at 30 days after stopping treatment in HR-QoL patients with brain metastases: mobility (A), self-care (B), usual activities (C), anxiety/depression (D) and pain/discomfort (E). Thirty-day follow-up represents 30 days after stopping treatment, regardless of the number of treatment cycles completed.

HER2CLIMB, nearly half of the patients had brain metastases, which was consistent with the overall HER2CLIMB population. To our knowledge, the combination of delayed progression, improved survival and prolonged HR-QoL seen in tucatinib-treated patients with brain metastases has not been shown with other HER2-directed therapies. With brain metastases in nearly half of the study population, these findings are likely to better reflect real-world outcomes than trials that excluded patients with brain metastases.

Although HER2CLIMB was a large, global, multi-centre study with good representation of patients with brain metastases, it was not powered for statistical comparison of HR-QoL end-points. Nonetheless, there was a trend towards better preservation of overall HR-QoL in the tucatinib arm than in the placebo arm. Although HR-QoL assessment was not part of the initial protocol, once implemented, 91% of enrolled patients completed at least one assessment and were eligible for analysis. And although <50% of subjects

completed the EQ-5D-5L at the 30-day follow-up visit (regardless of the number of treatment cycles), attrition was similar in both treatment arms. The lower patient numbers in cycles 7 and 9 reflect both missed assessments and fewer patients still on treatment during later cycles. We cannot rule out the possibility of attrition bias, whereby patients who felt well were perhaps more inclined to continue answering questionnaires throughout the study than those who did not feel well.

5. Conclusions

HR-QoL is increasingly recognised as a valuable end-point of cancer care by patients and their families, as well as prescribers, regulators and payers. In patients with HER2+ metastatic breast cancer, HR-QoL was preserved throughout treatment with tucatinib in combination with trastuzumab and capecitabine. In addition, among patients with brain metastases, HR-QoL was maintained longer with tucatinib than without it.

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Author contributions

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Conflict of interest statement

V.M. reports consultancy for Amgen, AstraZeneca, ClinSol, Daiichi Sankyo, Eisai, Genomic Health, Hexal, Lilly, MSD Oncology, Novartis, Pierre Fabre, Roche,

Seagen, Tesaro and Teva and research funding/grants from Novartis, Roche/Genentech and Seagen. A.W. reports corporate board membership for Andrew Wardley Limited, Manchester Cancer Academy and Outreach Research & Innovation Group Limited; consultancy for Accord Research, AstraZeneca, Athenex, Coleman Expert Network, Coleman Research, Daiichi Sankyo, Gerson Lehrman Group, Guidepoint Global, Lilly, MSD Oncology, NAPP Pharmaceuticals, Novartis, Pfizer and Roche; employment at the Christie NHS Foundation Trust and AstraZeneca (as of 11th January 2021); patents and royalties for Outreach Research & Innovation Group; speaker's bureau participation for AstraZeneca, Eisai, Lilly, Novartis, Pfizer and Roche; travel expenses from Daiichi Sankyo, MSD and Roche and other nonfinancial relationships with the Strategy Director for the Association of Cancer Physicians, Committee Member UK Breast Cancer Group, Committee Member NHS England and Chemo Clinical Reference Group, ESMO Breast Cancer Faculty and NCI Breast Research Group Chair. E.P. reports consultancy for Mylan, Novartis, Pfizer and R-Pharm; research funding/grants from AbbVie, Cascadian, Corcept Therapeutics, Genentech, Hoosier Cancer Research Network, Merck, Novartis and Seagen and travel expenses from Amgen, Genentech, Merck, Novartis and Tesaro. E.H. reports consultancy for AstraZeneca, Black Diamond Therapeutics, Boehringer Ingelheim, Daiichi Sankyo, Genentech/Roche, Lilly, Mersana, Novartis, Pfizer, Puma Biotechnology and Silverback Therapeutics; research funding/grants from AbbVie, AceraPharma, Aravive, ArQule, Arvinas, AstraZeneca, BerGenBio, Black Diamond Therapeutics, Boehringer, Clovis Oncology, Compugen, Curis, CytomX Therapeutics, Daiichi Sankyo, Deciphera, eFFECTOR, Eisai, EMD Serono, Fochon Pharmaceuticals, Fosun Orionov, Fujifilm, G1 Therapeutics, Pfizer, Puma Biotechnology, Radius Health, Regeneron, Rgenix, Seagen, Sermonix Pharmaceuticals, Silverback Therapeutics, Stemcentrx, Sutro Biopharma, Syndax, Syros Pharmaceuticals, Taiho Pharmaceutical, Takeda, TapImmune, Tesaro, Torque, Unum Therapeutics, Verastem, Zenith Epigenetics, Zymeworks, Genentech/Roche, H3 Biomedicine, Harpoon, Hutchison MediPharma, Immunogenics, InventisBio, Karyopharm Therapeutics, Leap Therapeutics, Lilly, Lycera, MacroGenics, MedImmune, Medivation, Mersana, Merus, Millennium, Molecular Templates, Novartis, NuCana and OncoMed and travel expenses from Amgen, AstraZeneca, Bayer, BMS, Clovis, Eisai, EMD Serono, Foundation Medicine, Genentech/Roche, Genentech, Genzyme, Guardant Health, Helsinn Therapeutics, Heron, Lilly, Medivation, Merck, Novartis, Pfizer, Roche, Sysmex and Tesaro. A.Z. reports consultancy for Novartis and Pfizer and travel expenses from Immunomedics. E.J. reports consultancy for Lilly, Novartis, Pfizer and Roche. F.B. reports consultancy and honoraria from

Lilly, Novartis, Lilly and Roche and travel expenses from Novartis. E.H.B. reports travel expenses from Pierre Fabre, Pfizer and Roche. A.B. reports corporate board membership for NanoTx Therapeutics; consultancy for AlaMab Therapeutics, NanoTx Therapeutics, Plus Therapeutics and Vascular Biogenics; equity ownership in NanoTx and Plus Therapeutics; honoraria from Vascular Biogenics; patents and royalties related to intellectual property interest in NanoTx Therapeutics; research funding/grants from Boston Biomedical, Immunomedics, Medicenna, Mirna Therapeutics, Threshold Pharmaceuticals, Upsher-Smith and Vascular Biogenics and travel expenses from Vascular Biogenics. L.C. reports speaker's bureau participation for Astellas, Ipsen and Janssen and other fees for Astellas, Bristol Myers Squibb, Ipsen, Novartis and Pfizer. C.F. reports honoraria from Pfizer, Bayer, Novartis, AstraZeneca, Merck, Astellas Pharma and Roche Canada; a consulting or advisory role for Genomic Health, Merck, AstraZeneca, Bayer and Odonate Therapeutics; speaker's bureau for Merck; research funding/grants to self from Bayer; research funding/grant to the institution from Astellas Pharma, AstraZeneca, Lilly, Merck, Novartis, Roche/Genentech, Sanofi, Pfizer, Janssen Oncology, Zymeworks, Seagen, Immunomedics, Bicycle Therapeutics and Sermonix Pharmaceuticals and travel expenses from Novartis and Roche. M.M.-M. reports advisory board membership for Pierre Fabre; grants for conference attendance from Roche, Pfizer and Lilly and expert testimony for Novartis, Roche and Eisai. H.T.A. reports advisory board membership for Bayer, BeiGene, Bicycle, BioNTech, iOnctura, Roche and Servier and employment at HCA Healthcare UK and Sarah Cannon. N.I. reports consultancy for Janssen, Merck, Novartis and Pfizer. S.A. reports speaker's bureau participation for Novartis, Pfizer, Puma, Daiichi/AstraZeneca, Merck and Seagen. M.C. reports consultancy for Sanofi and travel expenses from Novartis, Bristol Myers Squibb and Ipsen. T.P. reports research funding/grants from Merck, Pfizer and Seagen. E.S.-R. reports consultancy for Lilly and Mylan, research funding/grants from Susan G. Komen Victory Foundation and speaker's bureau participation for Mylan. D.C. reports consultancy for Daiichi Sankyo, GlaxoSmithKline, Novartis, Roche and Synthon; employment at Edinburgh Cancer Research Centre, Edinburgh, United Kingdom and research funding/grants from Daiichi Sankyo, GlaxoSmithKline, Novartis, Roche and Seagen (all funding is to his institution). G.C. reports consultancy from Bristol Myers Squibb, Lilly, Novartis, Pfizer, Roche, Seagen and Daiichi Sankyo; employment at the University of Milano, Istituto Europeo di Oncologia, IRCCS, Milano, Italy and speaker's bureau participation for Lilly, Pfizer, Roche, Seagen and Daiichi Sankyo. K.G. reports consultancy for AstraZeneca, Bristol Myers Squibb, Genentech, Genomic Health, Janssen, Lilly, Merck, Mylan, NanoString, Novartis,

Pfizer and Roche and research funding/grants from AstraZeneca, Bristol Myers Squibb, Pfizer and Roche. M.S. reports employment at Seagen Inc. and equity ownership in Seagen Inc. and Moderna Pharma. K.D. reports employment at Seagen Inc. and equity ownership in Seagen Inc. and Roche. J.R. and W.F. report employment at Seagen Inc. and equity ownership in Seagen Inc. M.B., S.C., M.C., E.C., L.F. and O.H. have declared no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejca.2021.05.025>.

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