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REVIEW

Efficacy of tyrosine kinase inhibitors for the treatment of patients with HER2-positive breast cancer with brain metastases: a systematic review and meta-analysis

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Background: Brain metastases (BMs) are frequent events in patients with HER2-positive metastatic breast cancer (MBC) and are associated with poor prognosis. Small-molecule anti-HER2 tyrosine kinase inhibitors (TKIs) are promising agents for the treatment of BM. In this study, we assess the clinical outcomes of patients with HER2-positive MBC and BM treated with TKI-containing regimens compared with those treated with non-TKI-containing regimens.

Materials and methods: PubMed, Embase, Cochrane Library, and conference proceedings (ASCO, SABCS, ESMO, and ESMO Breast) were searched up to June 2021. The primary endpoint was progression-free survival (PFS) in patients with BM. Secondary endpoints included PFS in patients without BM and overall survival (OS). The study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Overall effects were pooled using random-effects models.

Results: This systematic review and meta-analysis included data from 2437 patients (490 with and 1947 without BM at baseline) enrolled in five trials assessing tucatinib-, lapatinib-, pyrotinib-, or afatinib-based combinations. A nonstatistically significant PFS benefit favoring TKI-containing regimens was observed in both patients with BM [hazard ratio (HR) 0.67, 95% confidence interval (CI) 0.41-1.12; $P = 0.13$] and without BM (HR 0.55, 95% CI 0.24-1.26; $P = 0.16$). Sensitivity analysis, excluding each study singly, demonstrated a significant PFS benefit favoring TKI-containing regimens in patients with BM after the exclusion of afatinib from the analysis (HR 0.56, 95% CI 0.35-0.90; $P = 0.016$). No statistically significant differences in OS were observed between the comparison groups.

Conclusions: A trend in PFS favoring TKI-containing regimens was observed in patients with BM. Sensitivity analysis including only trials that evaluated regimens containing tucatinib, lapatinib, or pyrotinib demonstrated a significant PFS benefit favoring TKI-containing regimens in patients with BM.

Key words: breast cancer, brain metastases, protein kinase inhibitors, HER2

INTRODUCTION

Breast cancer (BC) is the most common malignancy among women worldwide.[1] HER2 overexpression occurs in ∼15%-20% of all BCs. HER2 represents a negative prognostic factor, but it is a positive predictive factor of response to anti-HER2-targeting therapies, which have dramatically improved the survival of these patients across the past decades.[2]

Brain metastases (BMs) occur in up to 50% of patients with HER2-positive metastatic BC (MBC), and this incidence is increasing over the years,[3] mainly due to better systemic treatment and prolonged survival.[4] Despite recent treatment advances, BMs are still associated with a poor prognosis, with a median overall survival (OS) not exceeding 24 months in patients with HER2-positive MBC and BM. Central nervous system (CNS) has been traditionally considered as a unique sanctuary site for metastases, due to the tight junctions of the blood—brain barrier (BBB) that limit the diffusion into the brain parenchyma of effective drugs, especially those with a large molecular size, that is, monoclonal antibodies (e.g. trastuzumab, pertuzumab).[3,5] For this reason, small HER2-targeting

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molecules, such as the tyrosine kinase inhibitors (TKIs), have been investigated as a promising treatment strategy for patients with HER2-positive MBC and BM. TKI-based regimens have been incorporated into the management of patients with HER2-positive MBC, and are currently used in clinical practice.[6-8] However, while the treatment outcomes of patients without BM are largely determined by their extracranial activity, the outcomes of patients with BM are particularly influenced by the treatment's activity in the CNS.

The present systematic review and meta-analysis aimed to assess the clinical outcomes of patients with or without BM treated with TKI-containing regimens versus those treated with non-TKI-containing regimens.

MATERIALS AND METHODS

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[9] The complete protocol was prospectively registered on the International Prospective Register of Systematic Reviews (PROSPERO) website (ID: CRD42021252332).

Search strategy and data extraction

A systematic literature search was performed using PubMed, Embase, and Cochrane Library up to 20 June 2021. No date limits or language restrictions were used for the search of the databases. Conference proceedings from major oncology meetings (ASCO, SABCS, ESMO, and ESMO Breast) from 2019 up to June 2021 were also searched for eligibility. Updated OS results of the PHENIX trial presented in December 2021 were included in the analysis.

The search string included three main domains connected by the Boolean operator 'AND': (i) BC, (ii) class of agents (TKIs) and names of TKI agents, and (iii) randomized controlled trial (study type). Similar words and alternative spelling were used for each of these domains to widen the search. The search terms were adapted for use in each bibliographic databases using their specific controlled vocabulary, such as Medical Subject Headings (MeSH) terms. Full search strategies used for all databases are presented in the Supplementary Appendix, available at https://doi.org/10.1016/j.esmoop.2022.100501. Two investigators (GNM and DMB) independently screened records for inclusion. In case of disagreement, consensus was obtained after consultation with a third investigator (EdA).

When available, the following variables were extracted for each eligible study: first author, year and journal of publication, country, sample size, study design, TKI used, treatment associated with TKI, treatment used in the control arm, number of prior systemic therapies in the metastatic setting, CNS disease status at inclusion, prior local treatment for CNS, median follow-up, and progression-free survival (PFS) and OS for each treatment arm.

Study selection

Studies had to meet the following prespecified inclusion criteria: (i) randomized clinical trials (RCTs) including patients with HER2-positive MBC; (ii) comparison of systemic therapies with anti-HER2 TKI-containing regimens and non-TKI-containing regimens; and (iii) availability of data on PFS and OS in subgroups of patients with and without BM. For the purpose of this systematic review, the subgroup of patients with and without BM were defined according to the presence or absence of CNS involvement at the time of enrollment in each trial. Studies were excluded if separate outcomes for patients with and without BM were not reported, the control arm also contained an anti-HER2 TKI, or if a history of BM was an exclusion criterion of the trial. Whenever multiple publications were available for the same study, data were extracted from the one with the longest follow-up period for each endpoint.

Objectives

The primary objective of the study was to compare the efficacy of anti-HER2 TKI-containing regimens with non-TKI-containing regimens in patients with metastatic HER2-postive BC with BMs. The secondary objective was to compare of the efficacy of the aforementioned regimens between the subgroups of patients with and without BM at baseline.

Risk of bias assessment

The risk of bias (RoB) for each study included was assessed by two independent investigators (GNM and LD). The RoB was assessed using the Cochrane Risk of Bias tool version 2, which comprises five distinct domains regarding randomization process, deviations from intended intervention, missing outcome data, measurement of the outcome, and selection of the reported results.[10] Based on these assessments, each study was classified as having a low, high, or an unclear RoB.

Statistical analysis

A random-effect model was used to calculate global PFS and OS, reported as pooled hazard ratio (HR) with 95% confidence intervals (CIs). The pooled HR was considered statistically significant if the 95% CI did not include 1.0, with a P value <0.05 (two-sided). The Higgins I^2 index was computed to evaluate the heterogeneity between studies, with $>50\%$ considered as significant heterogeneity. To assess whether the pooled HRs estimates were stable or strongly dependent on one or few studies, sensitivity analyses were conducted by interactively recalculating the pooled HRs estimates after exclusion of each single study. Egger's test was applied to assess the occurrence of publication bias. All statistical analyses were conducted using Stata Software version 14.2 (StataCorp LLC, College Station, TX).

RESULTS

A total of 2305 records were identified from databases and conference proceedings using the predefined search criteria. After duplicate removal and title and abstract screenings, five RCTs including 2437 patients (490 with and 1947 without BM at baseline) were eligible for inclusion (Figure 1).

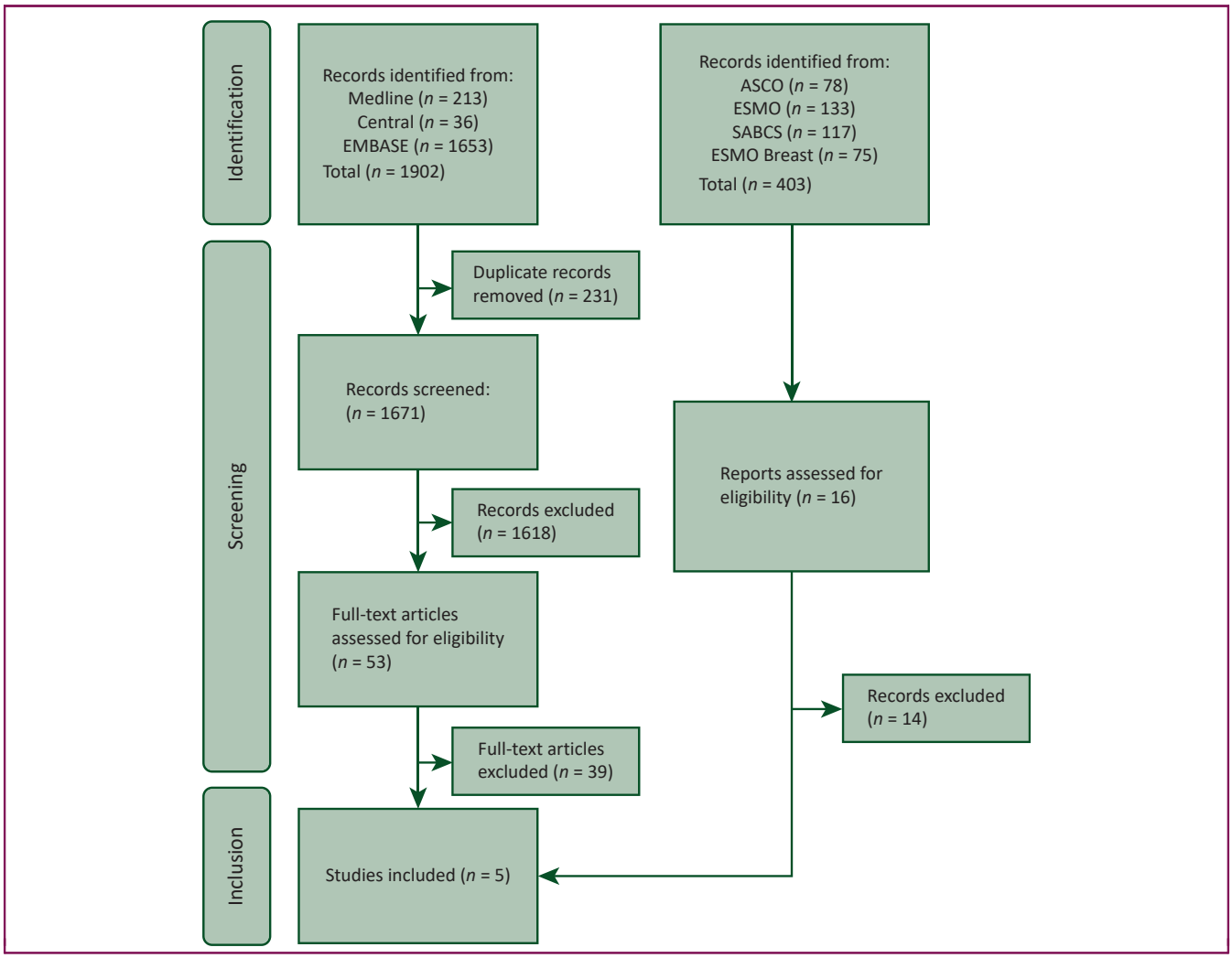

Figure 1. **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of retrieved studies.**

TKI-containing arms included tucatinib (HER2CLIMB[7]), lapatinib (EMILIA[11] and WJOG6110B/ELTOP[12]), pyrotinib (PHENIX[13]), or afatinib (LUX-Breast1[14]) in combination with cytotoxic chemotherapy with or without trastuzumab. Control arms included cytotoxic chemotherapy with or without trastuzumab or T-DM1. No trial evaluating neratinib met inclusion criteria due to lack of required data or to the presence of TKI in the control arm.[6,15,16] All trials allowed the inclusion of patients with stable and asymptomatic BM, while one (HER2CLIMB) also included patients with treated and progressing or untreated BM. The main characteristics of the included studies are summarized in Table 1.

Progression-free survival

Five studies including 490 patients with BM had PFS data available for the primary outcome analysis. A nonstatistically significant PFS trend favoring TKI-containing regimens was observed in patients with BM (HR 0.67, 95% CI 0.41-1.12; $P = 0.13$; Figure 2). Sensitivity analysis, excluding each study one by one (Table 2), demonstrated a significant PFS benefit favoring TKI-containing regimens in patients with BM after the exclusion of afatinib (Lux-Breast1), a non-HER2-specific TKI (HR 0.56, 95% CI 0.35-0.90; $P = 0.016$).

Four trials including 1084 patients without BM reported data on global PFS. Similarly, a nonstatistically significant PFS trend favoring TKI-containing regimens was observed in patients without BM (HR 0.55, 95% CI 0.24-1.26; $P = 0.16$; Figure 2). No statistically significant differences in global PFS within the subgroup of patients without BM were observed in the sensitivity analysis (Table 2).

Substantial heterogeneity was detected in the PFS analysis performed for patients with BM ($I^2 = 64.4\%$; $P = 0.024$) and without BM ($I^2 = 95.6\%$; $P < 0.001$). In a sensitivity analysis performed in the subgroup of patients with BM, the exclusion of LUX-Breast1 resulted in significant reduction in heterogeneity ($I^2 = 46.9\%$; $P = 0.13$; Table 2). However, the heterogeneity remained high ($I^2 > 50\%$) in the PFS analysis including patients without BM, even after excluding each study one by one (Table 2).

Overall survival

Four studies including 477 patients with BM reported OS and were included in the analysis (Figure 3). There was no

Table 1. Characteristics of the studies included in the meta-analysis

Study	EMILIA	LUX-Breast1	WJOG6110B/ ELTOP	HER2CLIMB	PHENIX
First author[a]	Krop[11]	Harbeck[14]	Takano[12]	Lin[42]/Curigliano[7]	Jiang[13]
Year of publication	2015	2016	2018	2020/2021	2021
Country/region	Worldwide	Worldwide	Japan	Worldwide	China
Phase	III	III	II	II	III
Patients, *n*	986	508[b]	86	612	279
With BM	95	60	13	291	31
Without BM	891	442	73	321	248
TKI regimen	Lapatinib + capecitabine	Afatinib + vinorelbine	Lapatinib + capecitabine	Tucatinib + trastuzumab + capecitabine	Pyrotinib + capecitabine
Non-TKI regimen	Trastuzumab + capecitabine	Trastuzumab + vinorelbine	Trastuzumab + capecitabine	Placebo + trastuzumab + capecitabine	Placebo + capecitabine
Median follow-up (months)	18.6	9.3	44.6	14	42.1 (for OS) NA for PFS
Prior anti-HER2 therapy, *n* (%)	891 (100)	508 (100)	86 (100)	612 (100)	279 (100)
Prior anti-HER2 TKI	—	—	—	34 (5.6%)	—
CNS status at inclusion	Treated, asymptomatic	Stable, asymptomatic	Asymptomatic	Untreated, treated, and stable, or treated and progressing	—

BM, brain metastasis; CNS, central nervous system; NA, not available; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
[a]First author of the publication from which data were extracted.
[b]In LUX-Breast1, six patients were excluded from the subgroup analysis.

statistically significant difference in OS between patients treated with TKI and those not treated with TKI (HR 1.13, 95% CI 0.54-2.37; $P = 0.740$). Sensitivity analysis showed no significant impact on OS after exclusion of each study one by one (Table 2). However, a trend of benefit in OS favoring TKI-containing regimens was observed after the exclusion of the EMILIA trial (HR 0.84, 95% CI 0.46-1.50; $P = 0.55$).

OS data were available for 1011 patients without BM included in three RCTs. Similarly, no significant differences in OS were detected between the two treatment regimens within the subgroup of patients without BM (HR 0.96, 95% CI 0.64-1.44; $P = 0.840$; Figure 3). Sensitivity analysis, excluding each study one by one, demonstrated a significant OS benefit favoring TKI-containing regimens in patients without BM after the exclusion from the analysis of afatinib (LUX-Breast1; HR 0.79, 95% CI 0.63-0.99; $P = 0.044$; Table 2).

Substantial heterogeneity was observed in OS analysis including patients with BM ($I^2 = 81.4\%$; $P = 0.001$) and without BM ($I^2 = 79.9\%$; $P = 0.007$). The heterogeneity remained high in the OS analysis including patients with BM, even after excluding each study one by one (Table 2). In the sensitivity analysis of OS with patients without BM, no heterogeneity was observed after the exclusion of LUX-Breast1 ($I^2 = 0$; $P = 0.481$; Table 2).

Risk of bias and publication bias

Overall, three studies included (HER2CLIMB, EMILIA, and LUX-Breast1) were considered to have an overall low RoB. The RoB in the randomization domain of the open-label WJOG6110B/ELTOP trial was considered to have some concerns due to the lack of information about the randomization process.[12] The PHENIX trial was considered to have a high RoB due to deviations from intended interventions as a consequence of the absence of information about the analysis used to estimate the effect of assignment to intervention.[13] A detailed RoB assessment for each study is reported in Supplementary Figure S1 and Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100501.

No statistically significant publication bias was observed for PFS analyses including patients with and without BM (Egger's tests: $P = 0.687$ and $P = 0.160$, respectively), or for OS analyses (Egger's tests: $P = 0.215$ and $P = 0.311$, respectively).

DISCUSSION

Systemic therapies have traditionally been underutilized for the treatment of BM due to their low CNS penetration and limited CNS activity.[17,18] In our systematic review and meta-analysis including 2437 patients enrolled in five RCTs, we observed a similar PFS and OS from anti-HER2 TKI-containing and non-TKI-containing regimens in patients with or without BM. Importantly, in the sensitivity analysis a statistically significant PFS benefit favoring TKI-containing regimens in patients with BM was observed after the exclusion from the analysis of afatinib (LUX-Breast1).[14] The same pattern was observed in the PFS and OS sensitivity analyses of patients without BM.

Afatinib is a non-HER2-specific TKI that failed to show a clear activity for the treatment of BC.[14,19] Indeed, despite the promising rational that a broader inhibition of the ErbB family could improve efficacy compared with trastuzumab in patients with a prior trastuzumab resistance, the LUX-Breast1 study showed no benefit of afatinib versus trastuzumab plus vinorelbine in HER2-positive MBC (HR 1.48, 95% CI 1.12-1.95).[14,20] Despite not being approved for the treatment of patients with MBC, the decision to keep LUX-Breast1 in our meta-analysis was based on the fact that it fulfilled all inclusion criteria and none of the exclusion criteria previously defined in the study protocol.

Thus considering only TKIs with proven activity for the treatment of BC (i.e. lapatinib, tucatinib, and

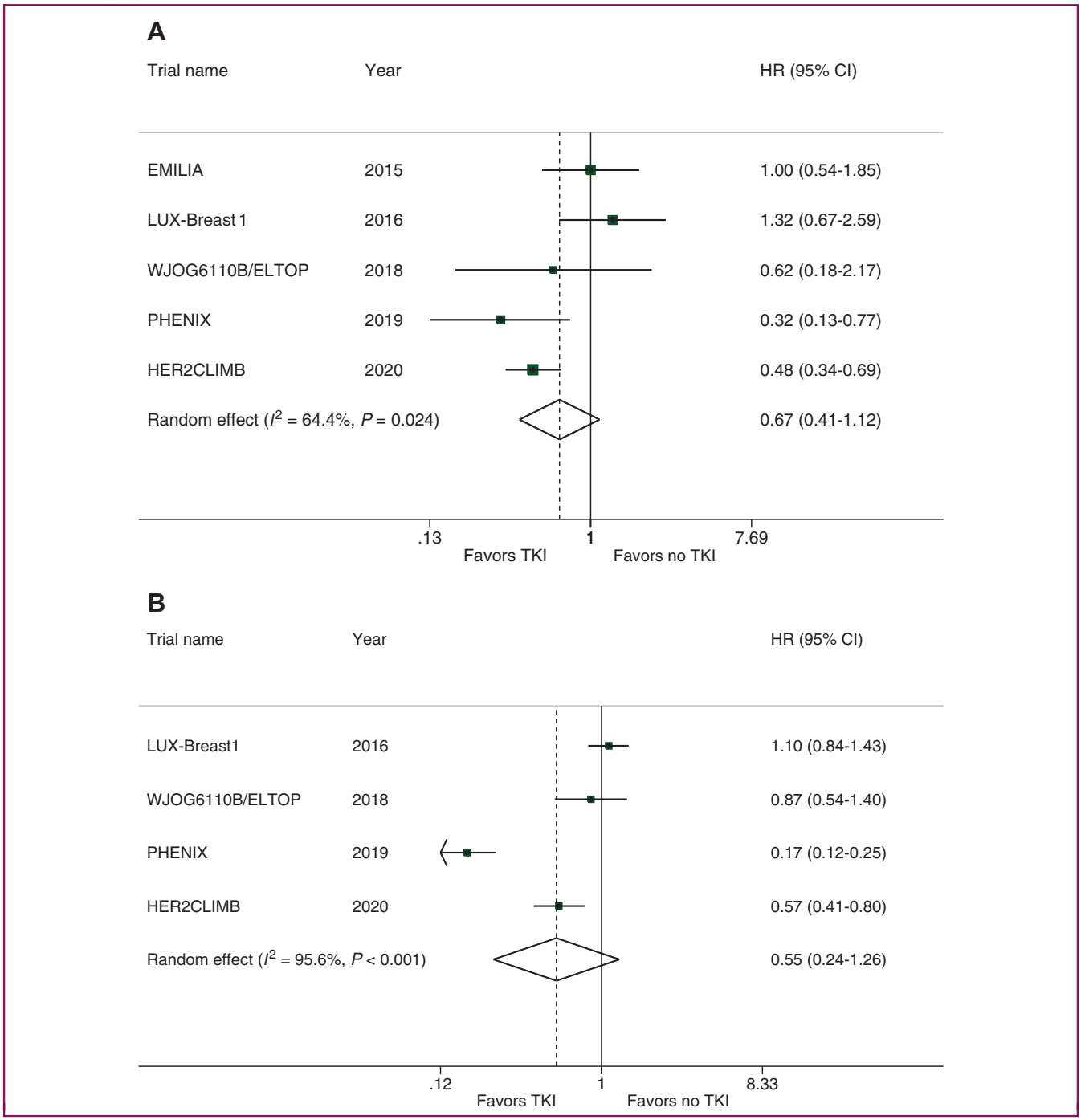

Figure 2. Forest plots for global progression-free survival for patients (A) with and (B) without brain metastases.
CI, confidence interval; HR, hazard ratio; TKI, tyrosine kinase inhibitor.

pyrotinib),[7,8,13] our data support the PFS benefit of TKIs in patients with BM. In addition to the included RCTs, other studies evaluating the individual CNS activity of each of these agents already suggested their efficacy for the treatment of BM, but often provided inconclusive results and different magnitudes of benefit. The single-arm phase II LANDSCAPE trial evaluated the combination of lapatinib and capecitabine in 45 patients with untreated BM and demonstrated an intracranial response rate of 65.9%.[21] Another phase II trial studying lapatinib-based therapy included 242 patients with CNS progression after cranial radiation and observed a CNS response rate of 20%.[22] A systematic review with pooled analysis that assessed the efficacy of lapatinib as single agent or in combination with capecitabine for the treatment of BM included data from 799 patients with BM enrolled in 12 studies.[23] In this study, a BM overall response rate of 21.4% was demonstrated, with pooled median PFS and OS of 4.1 (95% CI 3.1-6.7) and 11.2 (95% CI 8.9-14.1) months, respectively.[23]

Neratinib, an irreversible inhibitor of EGFR, HER2, and HER4,[24] is another TKI that demonstrated CNS activity in patients with MBC. In a phase II trial including 49 patients

Table 2. Sensitivity analysis, excluding each study one by one, for global PFS and OS for patients with and without brain metastases

PFS: Patients with brain metastases					
Study excluded	Random effect			I^2 (%)	I^2 *P* value
	HR	95% CI	*P* value		
EMILIA	0.60	0.33-1.10	0.097	64.5	0.037
LUX-Breast1	0.56	0.35-0.90	0.016	46.9	0.130
WJOG6110B/ELTOP	0.68	0.38-1.22	0.196	73.3	0.010
PHENIX	0.78	0.45-1.36	0.379	66.3	0.031
HER2CLIMB	0.77	0.42-1.42	0.405	55.7	0.079
PFS: Patients without brain metastases					
Study excluded	Random effect			I^2 (%)	I^2 *P* value
	HR	95% CI	*P* value		
LUX-Breast1	0.43	0.17-1.12	0.084	94.4	<0.001
WJOG6110B/ELTOP	0.48	0.17-1.37	0.169	96.9	<0.001
PHENIX	0.82	0.53-1.26	0.369	78.0	0.011
HER2CLIMB	0.55	0.16-1.83	0.327	97.0	<0.001
OS: Patients with brain metastases					
Study excluded	Random effect			I^2 (%)	I^2 *P* value
	HR	95% CI	*P* value		
EMILIA	0.84	0.46-1.50	0.550	62.0	0.072
LUX-Breast1	1.03	0.41-2.60	0.943	84.5	0.002
HER2CLIMB	1.51	0.77-2.97	0.232	54.4	0.112
PHENIX	1.29	0.49-3.40	0.612	87.6	<0.001
OS: Patients without brain metastases					
Study excluded	Random effect			I^2 (%)	I^2 *P* value
	HR	95% CI	*P* value		
LUX-Breast1	0.79	0.63-0.99	0.044	0.0	0.481
HER2CLIMB	1.01	0.52-1.96	0.965	88.3	0.004
PHENIX	1.10	0.67-1.80	0.713	82.0	0.018

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

with progressive BM, treatment with neratinib plus capecitabine resulted in a CNS response rate of 49% among lapatinib-naive patients, and 33% among those with prior exposure to lapatinib.[25] In the phase III NALA trial, patients with HER2-positive MBC, including 101 with stable or asymptomatic BM, were randomly assigned to neratinib plus capecitabine or lapatinib plus capecitabine.[6] Patients in the neratinib arm experienced improved PFS and CNS outcomes, but similar OS when compared with those treated with lapatinib.[26] Finally, in addition to their use as a treatment for established BM, there is growing interest in the use of TKIs such as neratinib as a means of preventing or delaying the occurrence of BM in patients with early[27] or metastatic[15] BC.

In the OS analysis of patients with BM, in addition to the aforementioned considerations about the LUX-Breast1 trial, data from the EMILIA study also significantly contributed to favor non-TKI-containing regimens. Notably, EMILIA was a randomized study comparing trastuzumab emtansine (T-DM1) with the combination of lapatinib and capecitabine in 991 patients with pretreated HER2-positive MBC that showed a significant PFS and OS improvement in patients treated with T-DM1 (HR 0.65, 95% CI 0.55-0.77 and HR 0.68, 95% CI 0.55-0.85, respectively).[8] In a retrospective, exploratory analysis of 95 patients with BM included in EMILIA, T-DM1 was associated with improved OS compared with capecitabine plus lapatinib.[11] These results might be explained by at least two main factors. First, patients with CNS metastases had significantly higher number of extracranial sites of metastatic disease in comparison with the intention-to-treat population (83.1% versus. 36.7% with $\geq$3 sites of metastatic disease in the CNS-positive and intention-to-treat populations, respectively),[11] which may have made the outcomes of patients with CNS involvement highly dependent on the better systemic control of the disease provided by T-DM1. Second, although it has been hypothesized that large molecules such as monoclonal antibodies and antibody—drug conjugates could have limited brain penetration, more recent studies support the opposite.[28-31] Interestingly, the presence of brain lesions may disrupt the BBB, which gets replaced by a blood—tumor barrier, characterized by a higher fenestration of the endothelium, allowing chemotherapy and anti-HER2-targeting agents to pass through and reach tumor cells.[32] Moreover, brain irradiation can increase the barrier permeability, as shown in preclinical[33] and clinical models.[34,35] Clinical evidence also supports increased BBB permeability in the presence of BM, as exemplified by recent data demonstrating remarkable CNS activity from antibody—drug conjugates. In the DESTINY-Breast03 study,

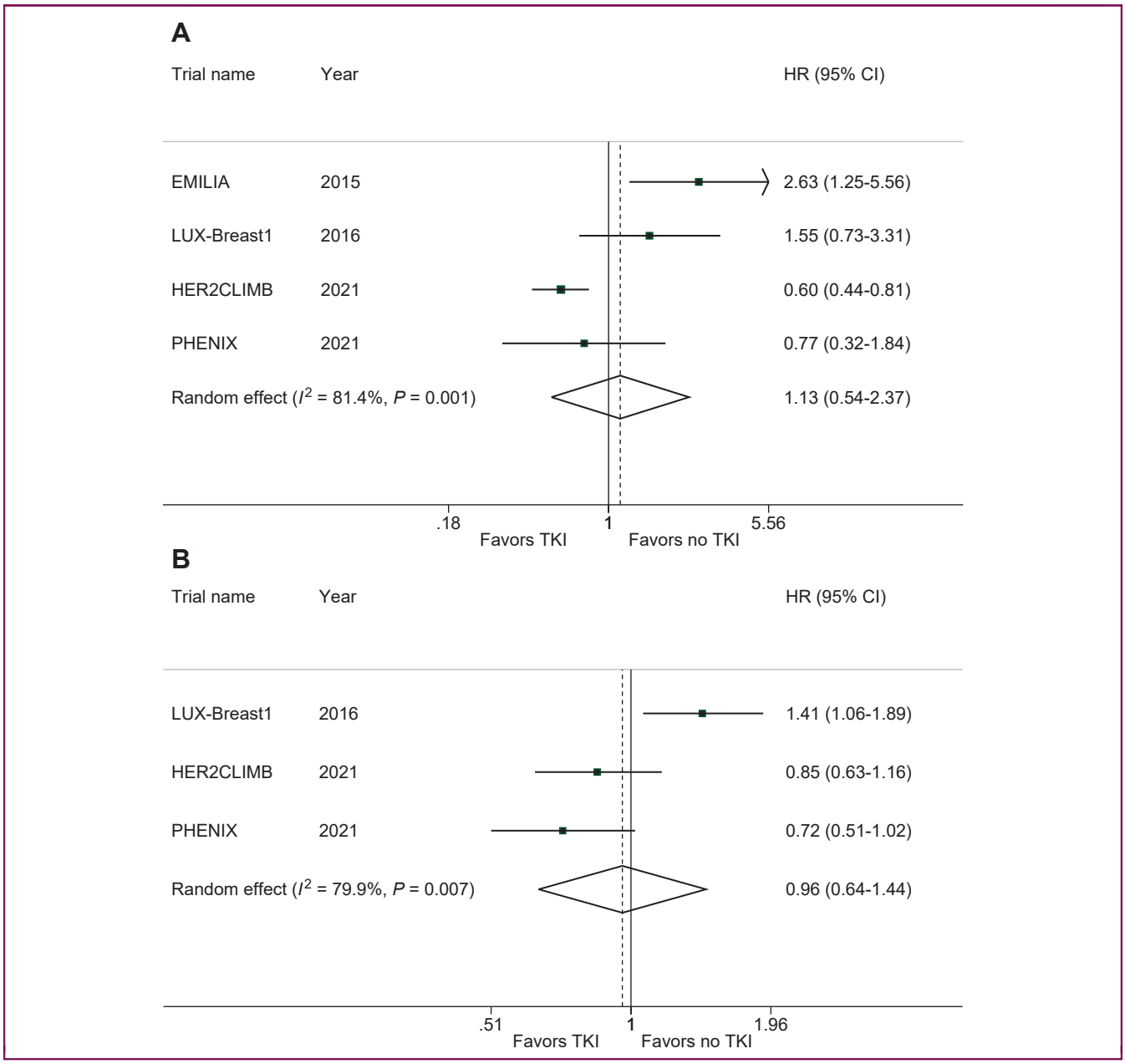

Figure 3. Forest plot for overall survival for patients (A) with and (B) without brain metastases.
CI, confidence interval; HR, hazard ratio; TKI, tyrosine kinase inhibitor.

trastuzumab deruxtecan (T-DXd) was compared with T-DM1 in patients with HER2-positive MBC previously treated with trastuzumab and demonstrated a significant increase in PFS favoring T-DXd.[36] Interestingly, in line with the overall study results, T-DXd also improved intracranial response (objective response rate 63.9% versus 33.3%) and PFS (median PFS 15 versus 3 months; HR 0.25, 95% CI 0.13-0.45) in patients with BM ($n = 82$).[31]

In our meta-analysis, all included trials allowed the inclusion of patients with stable and asymptomatic BM, with the exception of HER2CLIMB, which also included patients with progressing/untreated BM.[7] Based on the results of HER2CLIMB, the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) approved tucatinib in combination with trastuzumab and capecitabine for the treatment of patients with metastatic HER2-positive BC, including those with BMs, becoming the first FDA approval to specifically include patients with BMs in the indication statement.[18,37,38]

Our study has some limitations that should be considered when interpreting the results. First, this is this is not an individual patient-level data meta-analysis. Second, due to unavailability of data, we evaluated only PFS and OS as clinical outcomes, and not brain-specific outcomes. Of note, brain-specific outcomes are rarely reported in clinical trials and, often, their collection is not specified in study protocols, highlighting challenges in assessing brain-specific response to systemic therapies.[39] It would be of paramount importance to unify the definitions of brain-specific endpoints across clinical trials, particularly in the modern

era of target therapies.[39] By contrast, our study has the strength of being a large meta-analysis including a homogeneous population of 2437 patients with HER2-positive MBC from five RCTs that assessed the relevant topic of evaluating the efficacy of a class of agents (TKIs) in patients with BM, who have a dismal prognosis and represent a huge challenge of modern oncology.

Therapeutic advances achieved with multidisciplinary management of patients with BM may have increased their survival enough for them to experience the adverse effects of local therapies such as radiotherapy.[40] The recently reported increased CNS activities of systemic therapies[7,31] support the practice of treating patients with BM with systemic agents as an alternative to local therapies and have paved the way for the design of ongoing studies aimed at assessing potentially more effective therapeutic combinations, such as the TOPAZ trial (NCT04512261) evaluating tucatinib in combination with pembrolizumab and trastuzumab, and the HER2CLIMB-04 trial (NCT04539938) studying the combination of tucatinib with trastuzumab deruxtecan. These and other studies may drive changes in treatment paradigms and expand the role of systemic therapies in CNS disease control with the goal of achieving more effective and better tolerated treatment options for patients with a condition still associated with high morbidity and mortality. Finally, limited CNS activity of systemic therapies is not only determined by impaired drug delivery to the brain,[39] but also by differences in underlying tumor biology and tumor microenvironment.[40-42] Initiatives that aim to better understand the risk factors, clinical behavior, and biology of BM as proposed by some prospective trials and clinical research platforms (NCT04109131, NCT04030507, NCT03617341) will provide key elements for the development of new treatment strategies for patients with BM. The recent ESMO guidelines for MBC consider the use of some of these molecules as systemic therapies in case of BM.[41]

Conclusion

A trend in PFS favoring TKI-containing regimens was observed in patients with BM. Sensitivity analysis including only trials that evaluated regimens containing tucatinib, lapatinib, or pyrotinib demonstrated a significant PFS benefit favoring TKI-containing regimens in patients with BM, emphasizing the relevance of CNS involvement for the interpretation of the results of studies evaluating this class of agents.

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