Pyrotinib plus capecitabine for patients with HER2-positive metastatic breast cancer and brain metastases (PERMEATE trial): overall survival results from a multicenter, single-arm, two-cohort, phase 2 trial

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Summary

Background The phase 2 PERMEATE study has shown the antitumor activity and safety of pyrotinib plus capecitabine in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer and brain metastases. In this report, survival results were updated with extended follow-up.

Methods Between January 29, 2019 and July 10, 2020, adult patients with HER2-positive metastatic breast cancer who had radiotherapy-naïve brain metastases (cohort A, n = 59) or progressive disease after radiotherapy (cohort B, n = 19) were enrolled and received pyrotinib (400 mg once daily) and capecitabine (1000 mg/m^2 twice daily on days 1–14 of each 21-day cycle) until disease progression or unacceptable toxicity. Secondary endpoints progression-free survival (PFS) and overall survival (OS) were updated, and post-hoc central nervous system (CNS)-PFS was analyzed. This study is registered with ClinicalTrials.gov (NCT03691051).

Findings As of February 2, 2023, the median follow-up duration was 30.9 months (interquartile range, 16.1–39.8). Median PFS was 10.9 months (95% confidence interval [CI], 7.6–14.6) in cohort A and 5.7 months (95% CI, 3.4–11.5) in cohort B. Median OS was 35.9 months (95% CI, 24.4-not reached) in cohort A and 30.6 months (95% CI, 12.6–33.3) in cohort B. Median CNS-PFS was 13.6 months (95% CI, 9.0–15.8) in cohort A and 5.7 months (95% CI, 3.4–11.5) in cohort B. Median OS was 34.1 months (95% CI, 21.7-not reached) for 14 patients with intracranial progression only in cohort A who restarted pyrotinib plus capecitabine after local radiotherapy.

Interpretation These data support further validation in a randomized controlled trial for the assessment of pyrotinib in combination with capecitabine as systemic therapy for patients with HER2-positive breast cancer and brain metastases.

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Research in context

Evidence before this study

We searched PubMed for phase 2 or 3 clinical trials of targeted therapy in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer and brain metastases up to July 20, 2024. The search terms used were "HER2-positive breast cancer", "brain metastases", and "monoclonal antibody OR trastuzumab OR antibody-conjugated drug OR T-DM1 OR T-DXd OR trastuzumab deruxtecan OR trastuzumab emtansine OR tyrosine kinase inhibitor OR lapatinib OR afatinib OR neratinib OR pyrotinib OR tucatinib" without language restrictions. For active (untreated or progressive) brain metastases, the median overall survival was 9.3–17.0 months with tyrosine kinase inhibitor plus chemotherapy, 21.4 months with tyrosine kinase inhibitor plus monoclonal antibody plus chemotherapy, 27.2 months with dual monoclonal antibodies, and not disclosed for trastuzumab deruxtecan.

Added value of this study

Our study is the first prospective study to report the activity and safety of pyrotinib plus capecitabine in full patients with HER2-positive metastatic breast cancer and brain metastases. The updated survival results suggest the durable survival outcomes with this combination therapy against active brain metastases.

Implications of all the available evidence

Our long-term results highlight the need of a large-scale randomized controlled trial to assess the effect of pyrotinib plus capecitabine on patients with HER2-positive metastatic breast cancer and brain metastases.

Introduction

Human epidermal growth factor receptor 2 (HER2)-positive breast cancer is an aggressive disease subtype, which accounts for 15%–20% of breast cancers.[1] The development and evolution of anti-HER2 therapies have resulted in dramatically prolonged survival of patients with HER2-positive metastatic breast cancer.[2–4] However, more than 30% of them will develop brain metastases during the disease course,[5,6] and traditional local radiotherapy or surgery brings limited survival benefits for this population, with a median overall survival (OS) of 3–14.5 months.[7–10]

In the past decade, new advances have been made in systemic therapy against brain metastases from HER2-positive breast cancer. Median OS reached 12.5 months for trastuzumab plus chemotherapy,[11] 9.3–17.0 months for tyrosine kinase inhibitor (TKI) plus chemotherapy,[12–14] 18.9 months for trastuzumab emtansine (T-DM1, an antibody-drug conjugate [ADC]),[15] 21.6 months for TKI plus trastuzumab and chemotherapy,[11] and 27.2 months for pertuzumab plus high-dose trastuzumab.[16] In terms of active (untreated or progressive) brain metastases, the exploratory analysis of the randomized HER2CLIMB trial showed that the addition of tucatinib (a highly selective TKI for HER2) to trastuzumab plus capecitabine significantly prolonged central nervous system (CNS) progression-free survival (PFS; 9.6 months vs 4.0 months; hazard ratio [HR], 0.34; 95% confidence interval [CI], 0.22–0.54) and OS (21.4 months vs 11.8 months; HR, 0.52; 95% CI, 0.36–0.77).[11] This combination has been recommended as preferred regimen by the National Comprehensive Cancer Network guideline.[17] Trastuzumab deruxtecan (T-DXd), a widely-discussed anti-HER2 ADC, has also shown preliminary data in patients with HER2-positive breast cancer and active brain metastases.[18–20]

The single-arm, two-cohort, phase 2 PERMEATE study investigated pyrotinib (a pan-HER receptor TKI targeting HER1, HER2, and HER4) plus capecitabine in HER2-positive metastatic breast cancer patients with radiotherapy-naive brain metastases (cohort A) or brain metastases progressing after radiotherapy (cohort B), which started in January 2019. The primary analysis was published in January 2022. The intracranial objective response rate (ORR) was 74.6% (44 of 59 patients) and 42.1% (eight of 19 patients) in cohorts A and B, and the median PFS was 11.3 months (95% CI, 7.7–14.6) and 5.6 months (95% CI, 3.4–10.0), respectively.[21] The toxicity profile was manageable and consistent with previous pivotal clinical trials.[22,23] Here we reported updated survival results of these two cohorts from PERMEATE.

Methods

Study design and participants

The participating centers and detailed eligibility criteria of this multicenter, single-arm, two-cohort, phase 2 trial were published previously.[21] Briefly, patients needed to have pathologically confirmed HER2-positive breast cancer, brain metastases with at least one measurable lesion per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1,[24] and an Eastern Cooperative Oncology Group performance status of 0–2. Cohort A recruited patients with radiotherapy-naive brain metastases, including those with new brain lesions after craniotomy without postoperative radiotherapy. Cohort B recruited patients with brain metastases that progressed after radiotherapy.

Ethics

The study was conducted in accordance with the Declarations of Helsinki and Good Clinical Practice. The study protocol was approved by the medical ethics committee of Henan Cancer Hospital (No. 2018160), Hunan Cancer Hospital (No. 2020KS [498]), Liaoning Cancer Hospital (No. 20200109), The First Affiliated Hospital of Xi'an Jiaotong University (No.XJTU1AF2019LSK-024-02), Qilu Hospital of Shandong University (No. [K]LS2019002), The Affiliated Hospital of Qingdao University (No. QYFYKYLL-531311920), Tianjin Medical University Cancer Institute & Hospital (No. E2020095), and Cancer Hospital of the University of Chinese Academy of Sciences (No. IRB-2020-5 [K]). This study is registered with ClinicalTrials.gov (Identifier: NCT03691051). Written informed consent was provided by each patient.

Procedures

Patients in both cohorts A and B were treated with oral pyrotinib (400 mg once daily) plus oral capecitabine (1000 mg/m^2 twice daily on days 1–14 of each 21-day cycle) until disease progression, intolerable toxicity, death, or withdrawal of consent. Dose adjustments were allowed to manage adverse events, as described previously.[21] Treatment was allowed to be restarted in patients with intracranial progression only per RECIST 1.1 after CNS local surgery or radiotherapy at the discretion of the investigator.

Details of imaging assessments were published previously.[21] OS was followed every 3 months.

Outcomes

The primary endpoint was intracranial ORR per RECIST 1.1,[24] as assessed by the investigator. Secondary endpoints included extracranial ORR, duration of response, intracranial disease control rate, PFS (time from the initiation of the study treatment to the first disease progression at any site or any-cause death), OS (time from the initiation of the study treatment to any-cause death), and safety. Most endpoints were previously reported.[21] In this paper, we reported updated PFS and mature OS.

Statistics

Sample size calculation was previously published.[21] Activity and safety analyses were performed in all patients who received at least one dose of study drug. Continuous data were expressed as median (interquartile range [IQR]), and categorical data were expressed as frequency (percentage). Median PFS and OS were calculated using the Kaplan–Meier method, and their 95% CIs were estimated using the Brookmeyer-Crowley method. Post-hoc comparisons of PFS and OS were performed between subgroups by hormone receptor status (positive or negative), symptomatic brain metastases at baseline (yes or no), size of intracranial target lesions (<2 cm or ≥2 cm), and primary trastuzumab resistance (yes or no) in cohort A using the univariable Cox proportional hazard model and 2-sided log-rank test. Symptomatic brain metastases were defined as presence of CNS symptoms, such as headache, nausea, vomiting, etc., requiring symptomatic treatment. Asymptomatic brain metastases were defined as the absence of CNS symptoms. Primary trastuzumab resistance was defined as disease progression during adjuvant trastuzumab treatment or within 12 months after completing adjuvant trastuzumab treatment, or disease progression within 6 months of starting trastuzumab treatment in the advanced setting. Post-hoc analyses of CNS-PFS (time from the initiation of treatment to the first intracranial progression or any-cause death) in both cohorts, and time from the first intracranial progression to the second progression at any site or any-cause death in patients from cohort A who had intracranial progression only and restarted pyrotinib plus capecitabine after local therapy were performed using the same methods as prespecified analyses of PFS and OS. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Role of the funding source

The funder provided the study drug (pyrotinib) and participated in the study design, data analysis, data interpretation, and preparation of the manuscript, but had no role in patient recruitment or data collection. The corresponding author had final responsibility for the decision to submit for publication.

Results

Patient characteristics

Between January 29, 2019 and July 10, 2020, a total of 78 female patients (59 in cohort A and 19 in cohort B) were enrolled and included for the survival analyses (Fig. 1). Baseline characteristics are shown in Table 1. Median age was 49.0 (IQR, 42.0–55.0) in cohort A and 47.0 (IQR, 38.0–56.0) in cohort B. Nineteen (32%) of 59 patients in cohort A and seven (37%) of 19 patients in cohort B had symptomatic brain metastases. Fifty-two (88%) of 59 patients in cohort A and 13 (68%) of 19 patients in cohort B had extracranial metastases.

As of February 2, 2023, the median follow-up duration was 30.9 months (IQR, 16.1–39.8). Two (3%) of 59 patients in cohort A and one (5%) of 19 patients in cohort B remained on treatment.

Efficacy

As of February 2, 2023, 56 (95%) of 59 patients in cohort A and 15 (79%) of 19 patients in cohort B experienced PFS events. Median PFS was 10.9 months (95% CI, 7.6–14.6) in cohort A and 5.7 months (95% CI, 3.4–11.5) in cohort B (Fig. 2). Thirty-three (56%) deaths in cohort A and 15 (79%) deaths in cohort B occurred. Median OS was 35.9 months (95% CI, 24.4-not reached) in cohort A

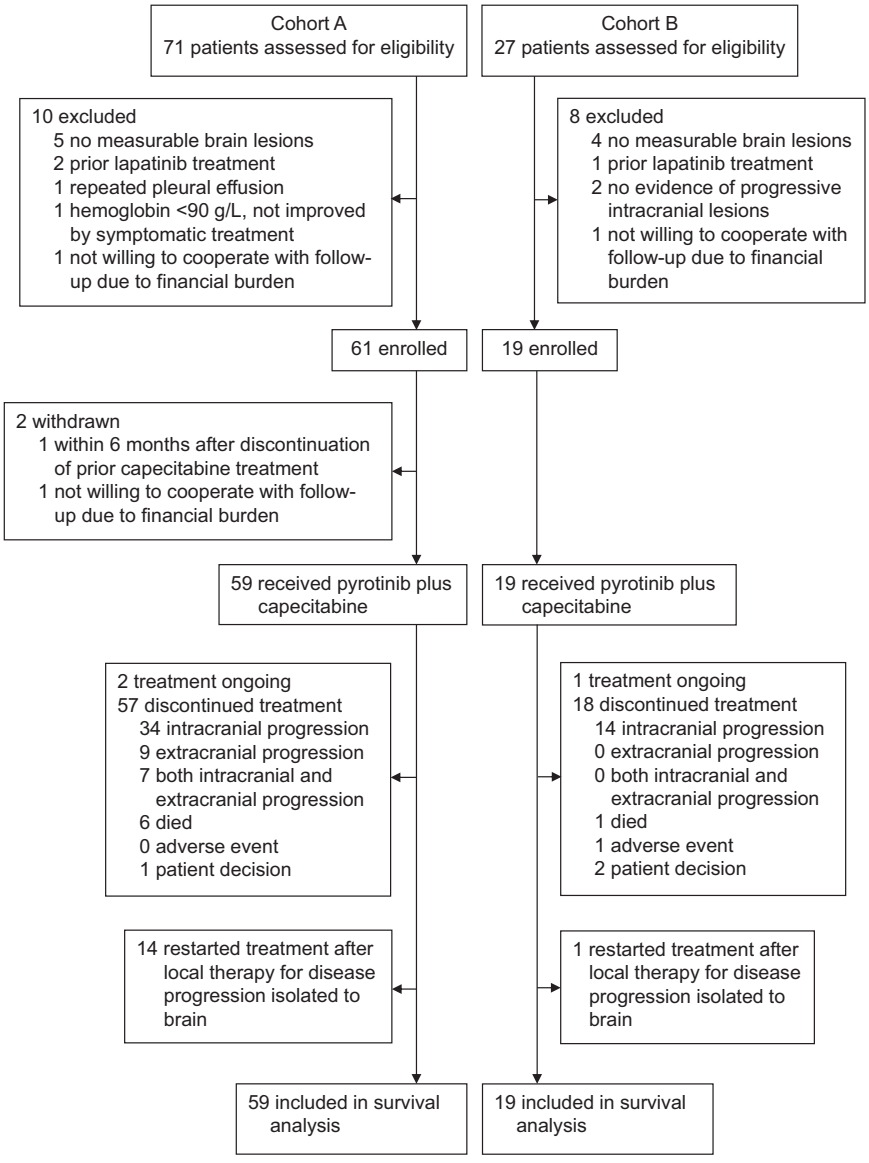

Fig. 1: **Trial profile**.

and 30.6 months (95% CI, 12.6–33.3) in cohort B (Fig. 3). Post-hoc subgroup analyses in cohort A showed that patients with asymptomatic brain metastases had longer median PFS than those with symptomatic brain metastases at enrollment (13.7 months [95% CI, 7.5–15.8] vs 9.4 months [95% CI, 5.4–10.9]; HR, 0.54 [95% CI, 0.30–0.97]; log-rank nominal P = 0.036). Patients without primary trastuzumab resistance had longer median PFS than those with primary trastuzumab resistance (12.0 months [95% CI, 7.6–17.0] vs 7.5 months [95% CI, 5.4–13.7]; HR, 0.52 [95% CI, 0.28–0.96]; log-rank nominal P = 0.032). Comparable median PFS was observed in subgroups by hormone receptor status or size of intracranial target lesions (Supplementary Fig. S1). No significant difference in median OS was found in these subgroups (Supplementary Fig. S2).

Forty-seven (80%) of 59 patients in cohort A and 15 (79%) of 19 patients in cohort B experienced CNS-PFS events. Median CNS-PFS was 13.6 months (95% CI, 9.0–15.8) in cohort A and 5.7 months (95% CI, 3.4–11.5) in cohort B (Fig. 4).

Further analyses in cohort A showed that the predominant site of the first progression in 50 patients with intracranial and/or extracranial progression was brain (41 [82%]), followed by liver (six [12%]) and lung (five [10%]). Twenty-eight (56%) of 50 patients received subsequent radiotherapy and systemic therapy, two (4%)

	Cohort A (n = 59)	Cohort B (n = 19)
Age (years), median (IQR)	49.0 (42.0–55.0)	47.0 (38.0–56.0)
ECOG performance status		
0	11 (19)	1 (5)
1	46 (78)	15 (79)
2	2 (3)	3 (16)
Time from breast cancer diagnosis to enrollment (months), median (IQR)	27.5 (14.2–50.8)	43.5 (25.1–67.2)
Hormone receptor status		
ER and/or PR positive	33 (56)	13 (68)
ER and PR negative	25 (42)	6 (32)
Unknown	1 (2)	0
Measurable disease status		
Measurable CNS disease only	32 (54)	15 (79)
Both CNS and extracranial measurable disease	27 (46)	4 (21)
Brain metastases		
Time from diagnosis to enrollment (months), median (IQR)	9.2 (1.3–16.4)	22.1 (12.5–37.1)
Time from the completion of radiotherapy to enrolment (months), median (IQR)	NA	10.4 (5.7–15.0)
Symptomatic brain metastases at enrollment	19 (32)	7 (37)
Site of metastases (not mutually exclusive)		
Parenchymal CNS disease	59 (100)	19 (100)
Lung	23 (39)	5 (26)
Liver	24 (41)	3 (16)
Bone	33 (56)	8 (42)
Breast or chest wall	17 (29)	3 (16)
Lymph nodes	17 (29)	3 (16)
Pleural effusion	5 (8)	1 (5)
Adrenal gland	4 (7)	0
Skin	2 (3)	0
Prior CNS local therapy		
Surgery[a]	2 (3)	0
SRT	0	11 (58)
WBRT	0	5 (26)
SRT and WBRT	0	3 (16)
None	57 (97)	0
Prior HER2-directed therapy		
Trastuzumab	51 (86)	18 (95)
For advanced disease	24 (41)	16 (89)
As (neo)adjuvant therapy	34 (58)	7 (37)
Both	7 (12)	5 (26)
Pertuzumab	1 (2)	1 (5)
Trastuzumab emtansine	0	3 (16)
BAT8001	0	1 (5)
None	8 (14)	1 (5)
Number of prior therapy lines in metastatic setting[b]		
0	21 (36)	3 (16)
1	29 (49)	7 (37)
2	5 (8)	7 (37)
≥3	4 (7)	2 (11)

Data are n (%), unless otherwise stated. IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; NA, not applicable; PR, progesterone receptor; CNS, central nervous system; SRT, stereotactic radiotherapy; WBRT, whole-brain radiotherapy; HER2, human epidermal growth factor receptor 2. [a]Two patients with new CNS lesions after craniotomy without postoperative radiotherapy were included in cohort A. [b]Not including hormonal therapy.

Table 1: **Baseline characteristics for each cohort.**

received radiotherapy alone, 11 (22%) received systemic therapy alone, six (12%) did not receive any subsequent treatment, and three (6%) had unknown information of subsequent treatment (Supplementary Table S1). For 30 patients who received first-line pyrotinib plus capecitabine followed by second-line radiotherapy with or without systemic therapy, the median OS was 39.5 months (95% CI, 29.0–45.6). Individual data for six patients who had progression isolated to the brain after first-line pyrotinib plus capecitabine and received second-line systemic therapy without radiotherapy are shown in Supplementary Table S2, and four of them reached an OS of more than 40 months. Fourteen patients in cohort A restarted pyrotinib plus capecitabine after CNS local radiotherapy for the first progression isolated to brain. Median PFS, time from the first intracranial progression to the second progression at any site or any-cause death, and OS for these 14 patients was 12.3 months (95% CI, 8.9–15.6), 12.3 months (95% CI, 6.1–19.7; Fig. 5), and 34.1 months (95% CI, 21.7-not reached).

Discussion

With a median follow-up of 30.9 months in PERMEATE, pyrotinib plus capecitabine resulted in a median OS of 35.9 months (95% CI, 24.4-not reached) in cohort A and 30.6 months (95% CI, 12.6–33.3) in cohort B, suggesting the durable survival benefit in patients with HER2-positive breast cancer and active brain metastases. Our results also indicate that retreatment with pyrotinib plus capecitabine after local radiotherapy for patients with intracranial progression only maybe feasible, with a median PFS of 12.3 months (95% CI, 8.9–15.6), median time from the first intracranial progression to the second progression at any site or any-cause death of 12.3 months (95% CI, 6.1–19.7), and

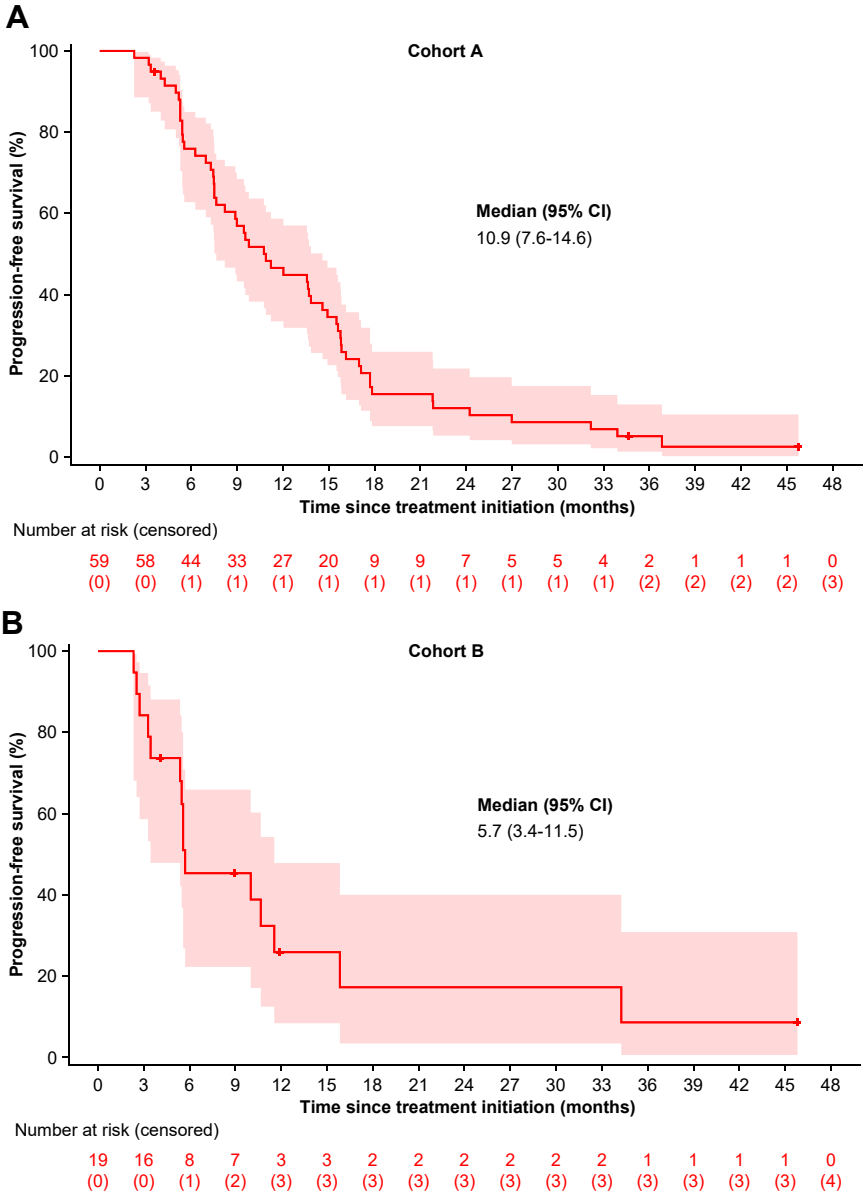

***Fig. 2:* Progression-free survival for (A) cohort A and (B) cohort B**. Shaded areas denote 95% CI. Crosses denote censored patients. CI, confidence interval.

median OS of 34.1 months (21.7-not reached) in cohort A, respectively.

The effect of TKI has been investigated in patients with HER2-positive breast cancer and active brain metastases for nearly two decades.[12–14,25] Recently, HER2-CLIMB successfully revealed the valuable contribution of tucatinib when added to trastuzumab plus capecitabine, which significantly prolonged the median OS by 9.6 months (21.4 months [n = 118] vs 11.8 months [n = 56]; HR, 0.52; 95% CI, 0.36–0.77) for active brain metastases.[11] Both HER2CLIMB and our data suggest the important role of TKI in this clinical setting. Despite the excellent OS results observed in PERMEATE, we need to acknowledge the fact that our study enrolled less heavily pre-treated patients compared with HER2-CLIMB. Twenty-one (36%) patients in cohort A and three (16%) in cohort B had no previous therapy in the metastatic setting, and pertuzumab and T-DM1 were barely used before enrollment in PERMEATE. All patients enrolled in HER2CLIMB had previously been treated with pertuzumab and T-DM1 in addition to trastuzumab, with a median previous therapy lines of 3

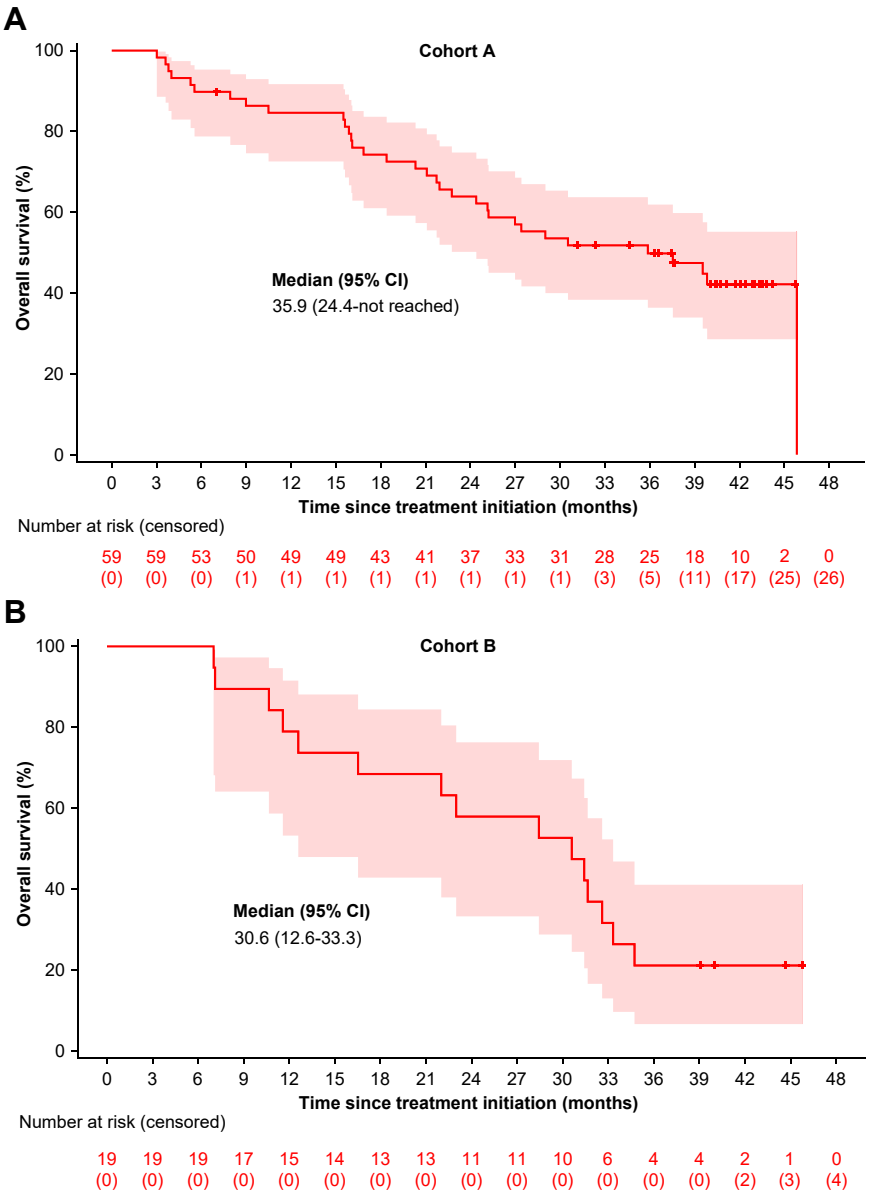

Fig. 3: **Overall survival for (A) cohort A and (B) cohort B**. Shaded areas denote 95% CI. Crosses denote censored patients. CI, confidence interval.

(range, 1–14) for metastatic cancer.[26] On the other hand, the phase 3 PHOEBE study showed a median OS of 39.4 months with pyrotinib plus capecitabine in patients with HER2-positive metastatic breast cancer without baseline brain metastases who had previously received trastuzumab and taxanes.[27] This suggests that patients with active brain metastases and those with non-CNS metastases can achieve consistent long-term survival benefits from pyrotinib plus capecitabine. Regarding other systemic therapies, the role of the ADC T-DXd against brain metastases has become a hot topic. However, only small trials (TUXEDO-1 [n = 15] and DEBBRAH [n = 13]) without mature OS data were published for active brain metastases.[18–20] Large-scale study results supporting the use of T-DXd in this setting are awaited. The explorations of ADC combined with TKI have also begun (TBCRC 022,[28] DESTINY-Breast 07,[29] TUCATEMEB [NCT05673928], and NCT05769010).

With the evolution of systemic therapy for control of brain metastases in patients with HER2-positive metastatic breast cancer, the sequencing of local therapy and systemic therapy may deserve reconsideration.

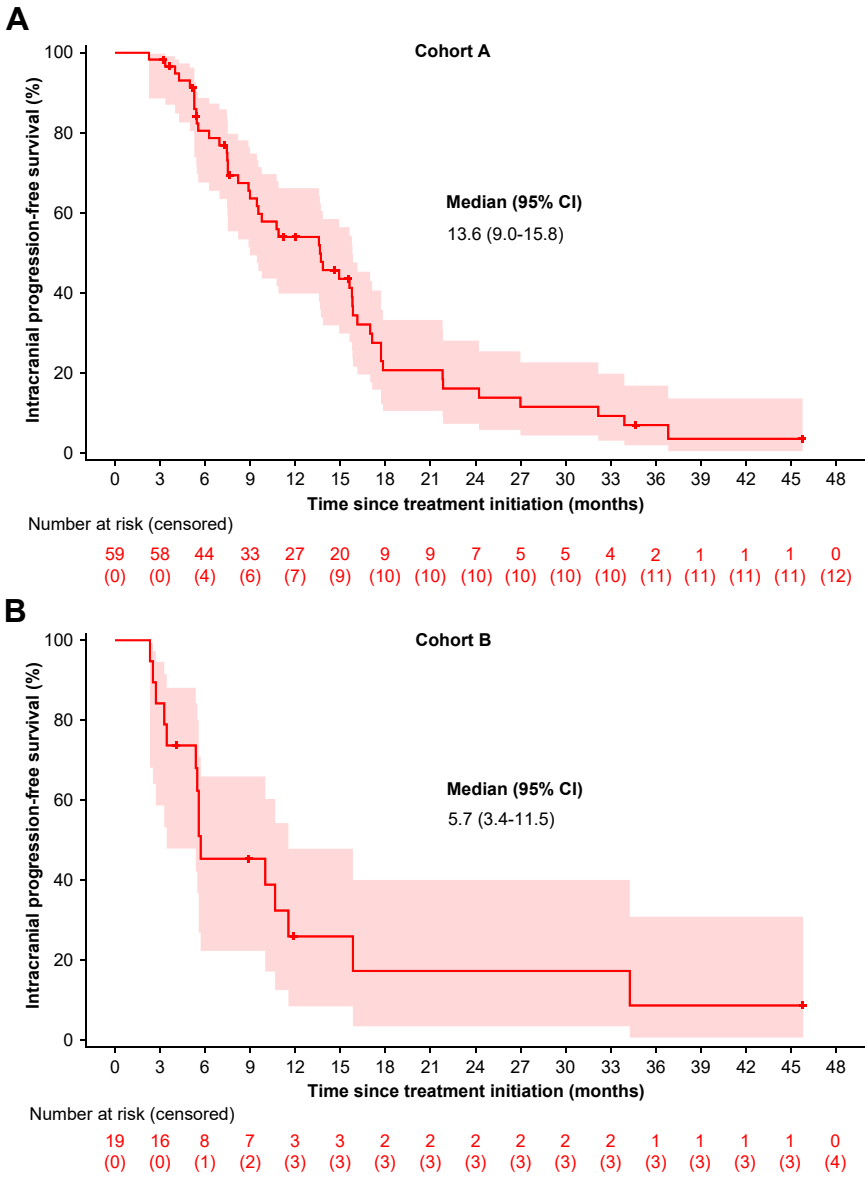

Fig. 4: **Intracranial progression-free survival for (A) cohort A and (B) cohort B**. Shaded areas denote 95% CI. Crosses denote censored patients. CI, confidence interval.

Interestingly, our results provided a small hint that the sequencing of treatment might not impact OS. Specifically, first-line pyrotinib plus capecitabine followed by second-line CNS local radiotherapy with or without systemic therapy resulted in a median OS of 39.5 months for 30 patients in cohort A. Median time from the completion of first-line radiotherapy to enrollment was 10.4 months and the median OS with second-line pyrotinib plus capecitabine was 30.6 months for 19 patients in cohort B. In our opinion, we propose the upfront use of effective systemic therapy to delay radiotherapy with the risk of cognitive impairment. Given the small sample size and non-randomization design, the optimal sequencing of systemic therapy and radiotherapy still needs further investigation. Recently, a phase 2 trial showed the potential of radiotherapy combined with pyrotinib plus capecitabine in 40 patients with HER2-positive breast cancer and active brain metastases, but the OS data were immature.[30] On the other hand, six patients in cohort A had progression isolated to the brain after first-line pyrotinib plus capecitabine and received second-line systemic therapy without radiotherapy. Their good prognosis prompts us to come up with a bold idea. If there exist both frontline

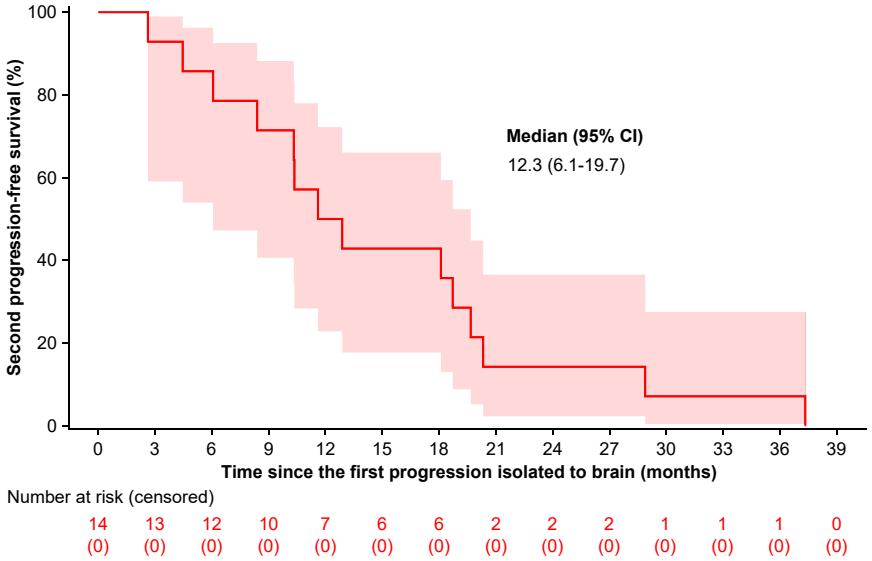

Fig. 5: **Time from the first intracranial progression to the second progression at any site or any-cause death for cohort A**. This post-hoc analysis was performed in 14 patients from cohort A who had intracranial progression only and restarted pyrotinib plus capecitabine after local radiotherapy. Shaded areas denote 95% CI. CI, confidence interval.

and later-line systemic therapies with potent intracranial antitumor activity, brain metastases may no longer be a special risk factor for reduced survival. The role of radiotherapy and other local therapies would be diminished in this systemic disease. This is a direction that demands persistent effort. We are exploring various potential systemic therapy options for patients with HER2-positive metastatic breast cancer and active brain metastases (NCT05357417 and NCT05769010).

Prospective evidence focusing on retreatment after progression in patients with HER2-positive advanced breast cancer is scarce. In cohort A, we allowed retreatment with pyrotinib plus capecitabine following radiotherapy for patients who developed intracranial progression only during the study period. The promising survival results in 14 patients indicate the feasibility of retreatment in this situation. However, we have to acknowledge that whether the subsequent survival benefits were attributed to radiotherapy alone or the combination of radiotherapy and retreatment with the study regimen could not be determined. HER2CLIMB explored the same retreatment scenario as our study, and the median time from the first intracranial progression to the second progression at any site or any-cause death was doubled with tucatinib plus trastuzumab and capecitabine compared to placebo plus trastuzumab and capecitabine (7.6 months [n = 21] vs 3.1 months [n = 9]).[31] Despite this supportive evidence on TKI retreatment, the small sample size warns us to carry out further validation in the future.

This study had some limitations. First, this was a phase 2 study without control arm. Second, the study treatment was evaluated in Chinese population only. Third, no patients received T-DXd after progression on pyrotinib plus capecitabine because T-DXd had not been approved for the treatment of HER2-positive metastatic breast cancer in China during the study period. Given that T-DXd has been considered the standard of care in most jurisdictions, this may limit the generalizability of our results but may also underestimate the OS data. Finally, the subgroup analyses were underpowered, which should be interpreted with cautions. Our nationwide Post-PERMEATE study (NCT05359120) is being conducted to observe the intracranial response, survival benefit, and safety of different treatment strategies (pyrotinib plus capecitabine, radiotherapy combined with concurrent pyrotinib plus capecitabine, or radiotherapy followed by a break for at least 3 months and sequential pyrotinib plus capecitabine) for the treatment of patients with HER2-positive advanced breast cancer and brain metastases in the real-world setting.

In conclusion, pyrotinib plus capecitabine shows the potential of long-term survival benefits in patients with HER2-positive metastatic breast cancer and brain metastases. Upfront use of this systemic therapy combination maybe a feasible strategy to delay radiotherapy. A large-scale randomized controlled trial is warranted to validate these findings.

Contributors

MY conceived and designed the study. MY, QO, TS, LN, JY, LLi, YS, CH, ZC, ZL, HL, MZ, LLiu, XY, HX, ZG, XL, FD, LZ, DD, XC, JQ, GZ, HZ, JW, HS, and YF recruited patients. MY, QO, TS, LN, JY, LLi, YS, CH, ZC, ZL, HL, MZ, LLiu, XY, HX, ZG, XL, FD, LZ, DD, XC, JQ, GZ, HZ,

JW, HS, and YF collected the data. All authors had full access to the raw data. MY and LN verified the underlying data. All authors contributed to the analysis and interpretation of data. All authors contributed to the preparation and critical review of the manuscript. MY contributed to the study supervision. LN, HL, and MZ contributed to the administrative support. All authors approved the final version of manuscript for submission.

Data sharing statement

Individual participant data (including data dictionaries) that underlie the results reported in this article, after de-identification (text, tables, figures, and Supplementary Materials) are available immediately and ending 3 years following article publication. Oncologists can gain access to the data from the corresponding author upon reasonable written request. After 3 years, data will be not available. The study protocol is provided with this paper.

Declaration of interests

MY declares support (funding) from Jiangsu Hengrui Pharmaceuticals and National Cancer Center Climbing Foundation Key Project of China. The other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102837.

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