Pyrotinib plus capecitabine for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases (PERMEATE): a multicentre, single-arm, two-cohort, phase 2 trial

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Summary

Background Patients with HER2-positive metastatic breast cancer have a high risk of developing brain metastases. Efficacious treatment options are scarce. We investigated the activity and safety of pyrotinib plus capecitabine in patients with HER2-positive metastatic breast cancer and brain metastases.

Methods We did a multicentre, single-arm, two-cohort, phase 2 trial in eight tertiary hospitals in China. Patients aged 18 years or older who had radiotherapy-naive HER2-positive brain metastases (cohort A) or progressive disease after radiotherapy (cohort B), with an Eastern Cooperative Oncology Group performance status of 0–2, received pyrotinib 400 mg orally once daily, and capecitabine 1000 mg/m^2 orally twice daily for 14 days, followed by 7 days off every 3 weeks until disease progression or unacceptable toxicity. The primary endpoint was confirmed intracranial objective response rate by investigator assessment according to the Response Evaluation Criteria In Solid Tumours (version 1.1). Activity and safety were analysed in patients with at least one dose of study drug. The study is ongoing, but recruitment is complete. The study is registered with ClinicalTrials.gov, NCT03691051.

Findings Between Jan 29, 2019, and July 10, 2020, we enrolled 78 women: 51 (86%) of 59 patients in cohort A and 18 (95%) of 19 patients in cohort B had previous exposure to trastuzumab. Median follow-up duration was 15·7 months (IQR 9·7–19·0). The intracranial objective response rate was 74·6% (95% CI 61·6–85·0; 44 of 59 patients) in cohort A and 42·1% (20·3–66·5; eight of 19 patients) in cohort B. The most common grade 3 or worse treatment-emergent adverse event was diarrhoea (14 [24%] in cohort A and four [21%] in cohort B). Two (3%) patients in cohort A and three (16%) in cohort B had treatment-related serious adverse events. No treatment-related deaths occurred.

Interpretation To our knowledge, this is the first prospective study showing the activity and safety of pyrotinib plus capecitabine in patients with HER2-positive breast cancer and brain metastases, especially in radiotherapy-naive population. This combination deserves further validation in a randomised, controlled trial.

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For the Chinese translation of the Abstract see **Online** for appendix 1

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Introduction

After treatment with trastuzumab, approximately 30–50% of patients with HER2-positive metastatic breast cancer develop brain metastases,[1–4] leading to poor outcomes. Although local therapy remains the mainstay treatment for brain metastases, including surgical resection, stereotactic radiotherapy, or whole-brain radiotherapy, recurrences are common within 6 to 12 months with a risk for neurocognitive impairment that brings great challenges to the management of brain metastases.[5–8]

An advantage of systemic therapy is to control both intracranial and extracranial metastatic lesions when drugs are effective. Median overall survival with chemotherapeutic drugs is about 11 months.[9] Standard monoclonal antibodies (trastuzumab and pertuzumab) yield unsatisfactory outcomes against brain metastases.[10] The HER2CLIMB study of tucatinib defined a novel treatment standard for patients with HER2-positive breast cancer and brain metastases.[11,12] The addition of tucatinib to the combination of trastuzumab and capecitabine improved intracranial progression-free survival by 5·7 months compared with trastuzumab and capecitabine alone, reduced the risk of intracranial progression or death by 68%, and improved overall survival.[12] These results suggest a pivotal role for small-molecule tyrosine kinase inhibitors to treat brain metastases.

Pyrotinib is an oral irreversible pan-HER receptor tyrosine kinase inhibitor targeting HER1, HER2, and HER4.[13] Results from the phase 3 PHOEBE and PHENIX studies have shown efficacy of pyrotinib in patients with HER2-positive metastatic breast cancer.[14,15] Two retrospective real-world studies showed the activity

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Research in context

Evidence before this study

We searched PubMed for articles of targeted therapy in patients with HER2-positive metastatic breast cancer and brain metastases up to Oct 20, 2021, with the search terms "monoclonal antibody OR antibody-conjugated drug OR tyrosine kinase inhibitor", "HER2-positive breast cancer", and "brain metastases" without any language restrictions. We excluded review articles and meta-analysis and identified eight phase 2 and one phase 3b (KAMILLA) trials. Lapatinib (NCT00263588), afatinib or combined with vinorelbine (LUX-Breast 3), neratinib (TBCRC 022), trastuzumab plus cabozantinib (NCT02260531), trastuzumab plus everolimus and vinorelbine (LCCC 1025), and pertuzumab plus high-dose trastuzumab (PATRICIA) showed low activity in patients with HER2-positive breast cancer and progressive brain metastases, with a CNS objective response rate around 10%. In the extension phase of the lapatinib study, patients who had progressed on lapatinib and received lapatinib plus capecitabine achieved a CNS objective response rate of 20%. Two cohorts treated with neratinib plus capecitabine from TBCRC 022 showed a CNS objective response rate of 49% by the composite criteria (primary endpoint) and 24% by the Response Assessment in Neuro-Oncology Brain Metastases criteria in lapatinib-naive cohort and 33% and 17% in lapatinib-treated cohort, respectively. The KAMILLA study of antibody–drug conjugate trastuzumab emtansine showed at least a 30% reduction in the sum of the largest diameters of brain target lesions in 42·9% of patients according to the Response Evaluation Criteria In Solid Tumours (RECIST; version 1.1). In the randomised HER2CLIMB study, addition of tucatinib to trastuzumab plus capecitabine improved the CNS objective response rate from 20·0% to 47·3% (by RECIST version 1.1) in patients with HER2-positive active brain metastases. However, it is still necessary to develop efficacious regimens for patients with HER2-positive breast cancer and progressive brain metastases. As for those with untreated brain metastases, only lapatinib plus capecitabine was investigated as first-line treatment in the LANDSCAPE study in 2013, with a CNS objective response rate of 57·1% per RECIST 1.1.

Added value of this study

To our knowledge, this 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, which separated patients into two cohorts based on the administration of radiotherapy for brain metastases. Our data showed that pyrotinib plus capecitabine is well tolerated and active for both intracranial and extracranial lesions, especially for patients with radiotherapy-naive brain metastases. Adverse events observed in our study were consistent with the known toxicity profile of pyrotinib plus capecitabine.

Implications of all the available evidence

The results of this phase 2 study provide evidence of promising antitumour activity and safety of pyrotinib plus capecitabine in patients with HER2-positive metastatic breast cancer and brain metastases, especially in those with radiotherapy-naive brain metastases. A large-scale randomised controlled trial is warranted.

with pyrotinib against brain metastases.[16–18] This PERMEATE study is the first prospective study to investigate the activity and safety of pyrotinib plus capecitabine in patients with HER2-positive metastatic breast cancer and brain metastases.

Methods

Study design and participants

See **Online** for appendix 2

This was an investigator-initiated, multicentre, single-arm, two-cohort, phase 2 trial done at eight qualified academic tertiary hospitals in China (appendix 2 p 1). Patients were included if they were aged 18 years or older; had pathologically confirmed HER2-positive (score 3+ by immunohistochemistry, or 2+ with gene amplification by fluorescence in-situ hybridisation) breast cancer; had brain metastases confirmed by MRI or enhanced CT (for patients with MRI contraindication); had at least one measurable brain lesion according to the Response Evaluation Criteria In Solid Tumours (RECIST; version 1.1); had an Eastern Cooperative Oncology Group performance status of 0–2; had a life expectancy of at least 6 months; and had adequate haematological, hepatic, renal, and cardiac function. Baseline laboratory tests required to assess eligibility included absolute neutrophil count, platelet count, haemoglobin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, serum creatinine, creatinine clearance, left ventricular ejection fraction, and Fridericia-corrected QT interval. Patients without previous radiotherapy were enrolled in cohort A, including those with new brain lesions after craniotomy without postoperative radiotherapy. Patients with progressive CNS disease after whole-brain radiotherapy or stereotactic radiotherapy were enrolled in cohort B. There was no limit on the number of previous therapy lines, but previous HER2 tyrosine kinase inhibitors and capecitabine were not allowed, except for patients with progression at least 6 (for metastatic disease) or 12 (as adjuvant therapy) months after discontinuation of a capecitabine-containing treatment. Concomitant bisphosphonates, mannitol, and corticosteroids were allowed if the corticosteroid dose (<2 mg/day dexamethasone or equivalent) was stable for at least 1 week before enrolment. Other concomitant anticancer drugs were not permitted. Full eligibility criteria are listed in the protocol (appendix 2 pp 21–22).

The study was done in accordance with the Declarations of Helsinki and Good Clinical Practice, and was approved by the ethics committee of each participating

centre. Written, informed consent was obtained from each patient.

Procedures

Patients in both cohorts received pyrotinib 400 mg orally once daily without breaks, and capecitabine 1000 mg/m² orally twice daily for 14 days, followed by 7 days off during each 21-day cycle. Treatment was continued until disease progression, intolerable toxicity, withdrawal of consent, or other reasons as determined by the investigator. Dose reductions and interruptions were allowed to manage adverse events. The dose of pyrotinib was permitted to be reduced stepwise from 400 mg to 320 mg to 240 mg. Dose reductions of capecitabine were permitted stepwise by 25%. Dose escalation was not allowed upon resolution of toxicity. Further details of dose adjustments are available in the protocol. Patients with progression isolated to the brain lesions per RECIST 1.1 would be withdrawn from the study, but could resume on study treatment after CNS local surgery or radiotherapy until the second progression at any site or death, at the discretion of the investigator.

Imaging examinations by enhanced MRI (or enhanced CT for patients with MRI contraindication) for intracranial lesions and CT or enhanced MRI for extracranial lesions were done at 6 weeks, and every 9 weeks thereafter. Subsequent imaging examinations were done using the same initial imaging method. Responses needed to be confirmed at next imaging examination. For patients without disease progression or death who discontinued the study treatment, subsequent imaging assessments were done every 3 months until disease progression, initiation of other anticancer therapies, or death. Response imaging was not centrally reviewed. Follow-up for overall survival was done every 3 months until death, loss to follow-up, or completion of the study. Physical examinations, blood routine and biochemical tests, and electrocardiogram were done every 3 weeks. Echocardiography, coagulation test, and urine and faecal tests were done every 6 weeks. Treatment-emergent adverse events were monitored before each drug administration and at each examination from the initiation of study treatment until 30 days after the last dose, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03).

Outcomes

The primary endpoint was CNS objective response rate, defined as the proportion of patients with the best intracranial response of confirmed complete or partial response according to RECIST 1.1, as assessed by the investigator.

Secondary endpoints were non-CNS objective response rate (proportion of patients with confirmed extracranial complete or partial response per RECIST 1.1), CNS disease control rate (proportion of patients with confirmed intracranial complete response, partial response, or stable disease per RECIST 1.1), duration of response (time from the first documented intracranial objective response to intracranial or extracranial disease progression in patients with confirmed response), progression-free survival (time from the first dose of study drug to disease progression or any-cause death), overall survival (time from the first dose of study drug to any-cause death), and safety.

Statistical analysis

Two separate Simon optimal two-stage designs were adopted to calculate the sample sizes of cohorts A and B. The null hypothesis of CNS objective response rate in cohort A was 47% and the alternative hypothesis was 65%, with one-sided α of 5% and power of 80%. In the first stage of cohort A, if ten or more of 18 patients had a CNS objective response, another 39 would be accrued to the second stage. If 33 or more of 57 patients achieved a CNS objective response, the study treatment would be deemed worthy of future study.

The null hypothesis of CNS objective response rate in cohort B was 20% and the alternative hypothesis was 40%, with one-sided α of 5% and power of 80%. In the first

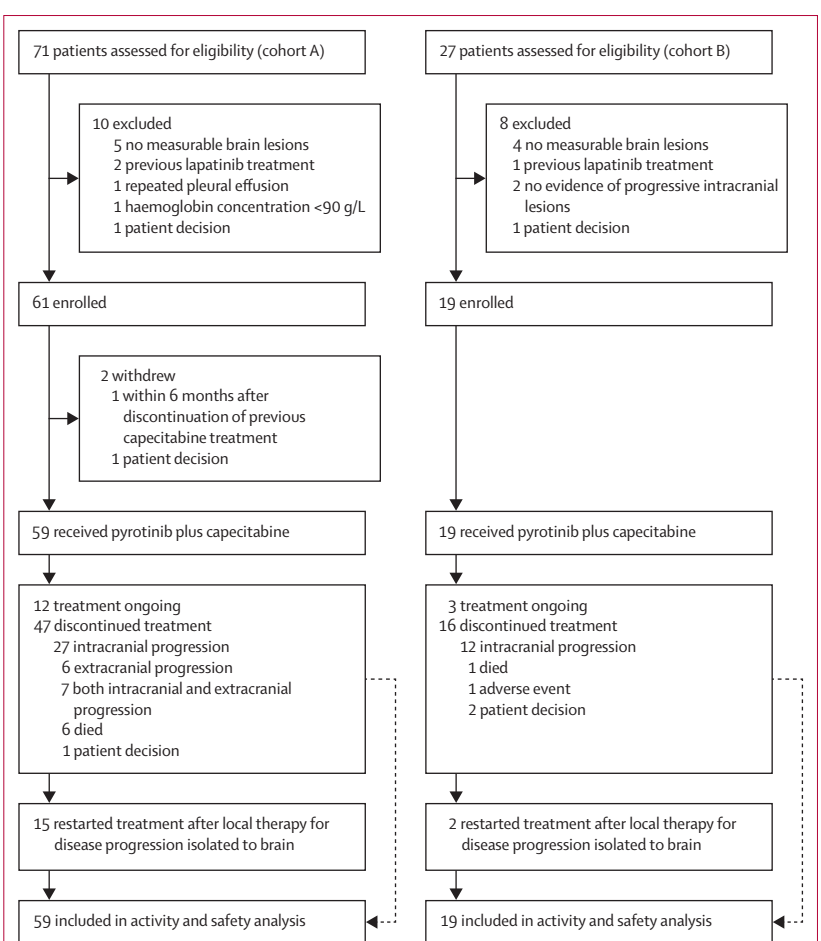

Figure 1: **Trial profile**

	Cohort A (n=59)	Cohort B (n=19)
Age, years	49·0 (42·0–55·0)	47·0 (38·0–56·0)
Eastern Cooperative Oncology Group performance status		
0	11 (19%)	1 (5%)
1	46 (78%)	15 (79%)
2	2 (3%)	3 (16%)
Time from breast cancer diagnosis to enrolment, months	27·5 (14·2–50·8)	43·5 (25·1–67·2)
Hormone receptor status		
ER positive, PgR positive, or both	33 (56%)	13 (68%)
ER and PgR 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 enrolment, months	9·2 (1·3–16·4)	22·1 (12·5–37·1)
Time from the completion of radiotherapy to enrolment, months	NA	10·4 (5·7–15·0)
Symptomatic brain metastases at enrolment	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
Previous CNS local therapy		
Surgery*	2 (3%)	0
Stereotactic radiotherapy	0	11 (58%)
Whole-brain radiotherapy	0	5 (26%)
Stereotactic radiotherapy and whole-brain radiotherapy	0	3 (16%)
None	57 (97%)	0
Previous HER2-directed therapy		
Trastuzumab	51 (86%)	18 (95%)
For advanced disease	24 (41%)	16 (84%)
As adjuvant or neoadjuvant 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 previous therapy lines in metastatic setting†		
0	21 (36%)	3 (16%)
1	29 (49%)	7 (37%)
2	5 (8%)	7 (37%)
≥3	4 (7%)	2 (11%)

Data are n (%) or median (IQR), unless otherwise stated. ER=oestrogen receptor. NA=not applicable. PgR=progesterone receptor. *Two patients with new CNS lesions after craniotomy without postoperative radiotherapy were included in cohort A. †Not including hormonal therapy.

Table 1: **Patient characteristics for each cohort**

stage of cohort B, if four or more of 13 patients had a CNS objective response, another 30 would be accrued to the second stage. If 13 or more of 43 patients achieved a CNS objective response, the study treatment would be deemed promising for radiotherapy-treated patients.

Pyrotinib is approved in China for HER2-positive metastatic breast cancer (Oct 12, 2018, and listed on national medical insurance on Jan 1, 2020), and many patients had been administered with pyrotinib before progression on radiotherapy and thus became ineligible for enrolment in cohort B. Therefore, the accrual was slow and enrolment was halted after 19 patients by investigators on Sept 30, 2020.

Activity and safety analyses were done in all patients with at least one dose of study treatment. Response would be deemed as not evaluable if it had not been confirmed before patient withdrawal from the study or by the data cutoff date. Continuous data were expressed as median (IQR), and categorical data were expressed as frequency (percentage). The 95% CIs of objective response rate and disease control rate were estimated using the Clopper-Pearson method. Median duration of response, progression-free survival, and overall survival were calculated using the Kaplan-Meier method, and their 95% CIs were estimated using the Brookmeyer-Crowley method.

Post-hoc comparisons of CNS objective response rate were done between subgroups by the size of intracranial target lesions (<2 cm or ≥2 cm), number of target lesions (one or two), primary resistance to trastuzumab (yes or no), hormone receptor status (positive or negative), number of previous therapy lines in metastatic setting (none, one, or two or more), and symptomatic brain metastases at enrolment (yes or no) in cohort A using the χ^2-square test or Fisher exact test, where appropriate. Primary trastuzumab resistance was defined as disease progression during trastuzumab treatment or within 12 months after the completion of trastuzumab treatment in the adjuvant setting, or disease progression within 6 months after the initiation of trastuzumab treatment for HER2-positive locally relapsed or metastatic breast cancer. Another post-hoc analysis was done for time to CNS response (time from the first dose of study drug to the first documented intracranial objective response in patients with confirmed response) using descriptive statistics. All activity data and adverse events were verified and analysed by the investigators, without a data safety monitoring board. All statistical analyses were done using SAS (version 9.4). This study is registered with ClinicalTrials.gov, NCT03691051.

Role of the funding source

The funder provided the study drug (pyrotinib) and participated in study design and data interpretation, but had no role in data collection, data analysis, or drafting of the report.

	Cohort A	Cohort B
Best CNS response, n	59	19
Complete response	7 (12%)	1 (5%)
Partial response	37 (63%)	7 (37%)
Stable disease	11 (19%)	4 (21%)
Progressive disease	2 (3%)	5 (26%)
Not evaluable	2 (3%)	2 (11%)
CNS objective response rate	44 (74·6%; 61·6–85·0)	8 (42·1%; 20·3–66·5)
CNS disease control rate	55 (93·2%; 83·5–98·1)	12 (63·2%; 38·4–83·7)
Median time to CNS response (IQR), months	1·3 (1·2–1·4)	1·5 (1·3–3·4)
Median duration of response (95% CI), months	12·5 (8·3–14·6)	7·7 (2·8–not reached)
Best non-CNS response, n	27	4
Complete response	2 (7%)	0
Partial response	17 (63%)	2 (50%)
Stable disease	5 (19%)	2 (50%)
Progressive disease	2 (7%)	0
Not evaluable	1 (4%)	0
Non-CNS objective response rate	19 (70·4%; 49·8–86·2)	2 (50·0%; 6·8–93·2)

Data are n (%) or n (%; 95% CI), unless otherwise stated.

Table 2: **Best response by cohort**

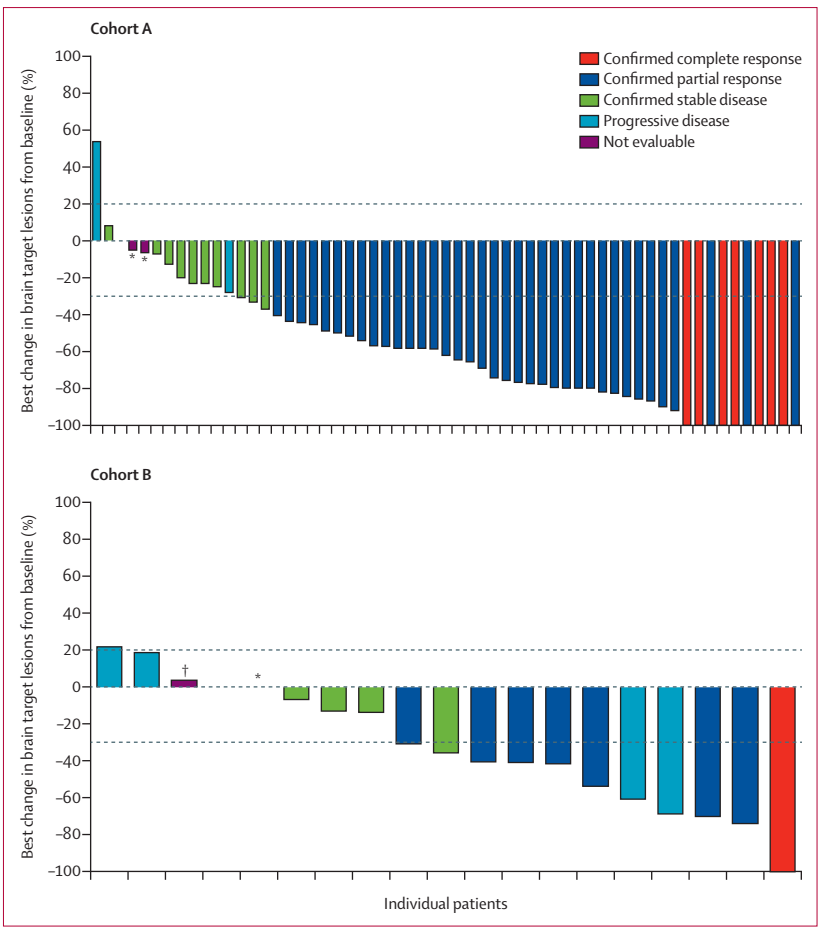

Figure 2: **Waterfall plot for best change in brain target lesions from baseline**

Dashed lines at 20% and –30% denote thresholds for progressive disease and partial response respectively, according to the Response Evaluation Criteria In Solid Tumours, version 1.1. *Two patients in cohort A had a stable disease, which had not been confirmed by the cutoff date and one patient in cohort B had a stable disease and withdrew from the study due to personal reason without confirmation of response; the final responses of three patients were deemed as not evaluable. †One patient in cohort B had a stable disease at first, but the radiographical response was not evaluable at subsequent three imaging examinations; this patient finally withdrew from the study due to personal reason, and the response was deemed as not evaluable.

Results

Between Jan 29, 2019, and July 10, 2020, 98 patients were screened for eligibility. Two additional patients had signed the informed consent and undergone screening examinations before confirmation of eligibility and formal enrolment of the 57th patient, therefore, 59 patients received study treatment in cohort A. 59 patients in cohort A and 19 in cohort B received pyrotinib plus capecitabine and were included in the activity and safety analyses (figure 1). Baseline characteristics are listed in table 1. 69 (88%) had previous exposure to trastuzumab; 51 (86%) of 59 patients in cohort A and 18 (95%) of 19 patients in cohort B. 65 (83%) of 78 patients had extracranial metastases; 52 (88%) of 59 patients in cohort A and 13 (68%) of 19 patients in cohort B. Cranial enhanced MRI was done at baseline and subsequent response assessments in 77 patients and cranial enhanced CT was done for one patient in cohort A who had previous cardiac surgery for tetralogy of Fallot and could not receive MRI examination. As of April 16, 2021, the median follow-up duration was 15·7 months (IQR 9·7–19·0). 12 (20%) of 59 patients in cohort A and three (16%) of 19 patients in cohort B were still on treatment. Median number of treatment cycles for pyrotinib was 16·0 (IQR 10·2–23·2) in cohort A and 8·1 (5·0–14·6) in cohort B. Median number of treatment cycles for capecitabine was 15·5 (9·3–23·0) in cohort A and 8·5 (5·0–14·7) in cohort B.

In cohort A, 13 (72%) of 18 patients had a CNS objective response (two with complete response and 11 with partial response) in the first stage, and the cohort proceeded to the second stage. Overall, the CNS objective response rate was 74·6% (95% CI 61·6–85·0; 44 of 59 patients) in cohort A with seven (12%) patients having a complete response (table 2 and figure 2A). Post-hoc subgroup analyses of CNS objective response rate in cohort A are shown in appendix 2 (p 2). In cohort B, six (46%) of 13 patients had a CNS objective response (one with complete response and five with partial response) in the first stage, and the cohort proceeded to the second stage. Two patients had a partial response in the second stage before the accrual was halted, and the overall CNS objective response rate in cohort B was 42·1% (95% CI 20·3–66·5; eight of 19 patients; table 2 and figure 2B). Median duration of response was 12·5 months (95% CI 8·3–14·6) in cohort A and 7·7 months (2·8–not reached) in cohort B. In a post-hoc analysis, the median time to CNS response was 1·3 months (IQR 1·2–1·4) in cohort A and 1·5 months (1·3–3·4) in cohort B (table 2).

As of April 16, 2021, 46 (78%) of 59 patients in cohort A and 13 (68%) of 19 patients in cohort B had disease progression or died. Median progression-free survival was 11·3 months (95% CI 7·7–14·6) in cohort A and 5·6 months (3·4–10·0) in cohort B (figure 3). 14 (24%) deaths in cohort A and two (11%) deaths in cohort B occurred, thus the overall survival was not yet mature. Median overall survival was not reached (95% CI 20·4–not reached) in cohort A and not reached (not reached–not reached) in cohort B. 34 (58%) of 59 patients in cohort A and 12 (63%) of 19 patients in cohort B came off study due to CNS progression, and seven in cohort A also had simultaneous extracranial progression. 17 (22%) of 78 patients (15 in cohort A *vs* two in cohort B) with progression isolated to the brain lesions continued the study treatment after CNS local therapy. Extracranial (non-CNS) objective response rate was 70·4% (95% CI 49·8–86·2; 19 of 27 patients) among patients with measurable extracranial disease in cohort A; two (7%) had a complete response (table 2). In cohort B, two (50·0%; 6·8–93·2) of four had a partial response (table 2). Six (10%) of 59 patients in cohort A came off study due to extracranial progression without simultaneous CNS progression.

Treatment-emergent adverse events are listed in table 3. The most common grade 3 treatment-emergent adverse events in cohort A were diarrhoea (14 [24%]), decreased white blood cell count (eight [14%]), and decreased neutrophil count (eight [14%]). One (2%) grade 4 anaemia was deemed treatment-related by the investigator, whereas the other grade 4 events (one [2%] blurred vision, one [2%] ventricular fibrillation, and one [2%] acute kidney injury) were deemed not related to the study treatment in cohort A. For cohort B, the most common grade 3 treatment-emergent adverse events were diarrhoea (four [21%]), decreased white blood cell count (three [16%]), and hypokalaemia (three [16%]). No grade 4 events were reported in cohort B. Two (3%) patients (one grade 4 anaemia and one grade 3 abdominal distension) in cohort A and three (16%) patients (one grade 3 anaemia, one grade 3 increased alanine aminotransferase, and one grade 2 vomiting) in cohort B had treatment-related serious adverse events, leading to hospitalisation. 14 (24%) deaths in cohort A and two [11%] deaths in cohort B occurred during the study or follow-up; nine (eight in cohort A and one in cohort B) occurred more than 30 days after the last dose (causes not recorded), and seven were deemed treatment emergent, which resulted from dyspnoea (one in cohort A), malnutrition leading to organ failure (one in cohort A), and disease progression leading to general physical health deterioration (four in cohort A and one in cohort B). No treatment-related deaths occurred.

Ten (17%) of 59 patients in cohort A and two (11%) of 19 patients in cohort B required a pyrotinib dose reduction to 320 mg, and one (2%) in cohort A had an additional reduction of pyrotinib to 240 mg because of vomiting. 12 (20%) patients in cohort A and four (21%) in cohort B required capecitabine dose reductions (appendix 2 p 3). One (5%) patient in cohort B discontinued the study treatment because of grade 2 oral mucositis, deemed possibly related to study drugs.

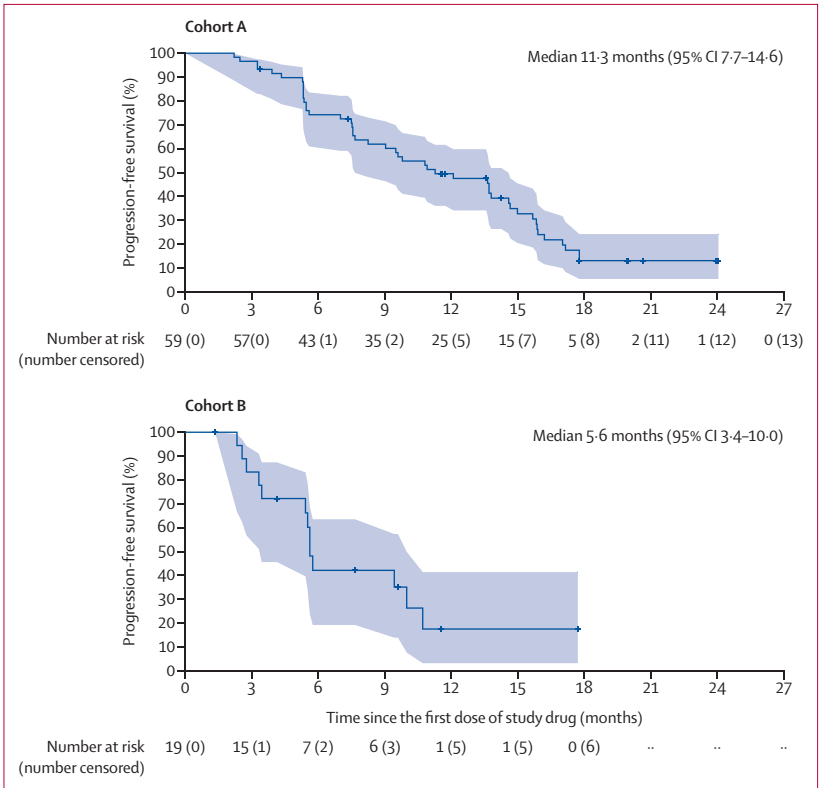

Figure 3: **Progression-free survival**
Shaded areas denote 95% CI. Crosses denote censored patients.

Discussion

To our knowledge, PERMEATE is the first prospective study to report the activity and safety of pyrotinib plus capecitabine in patients with HER2-positive metastatic breast cancer and brain metastases, which separated patients into two cohorts based on the administration of radiotherapy for brain metastases. Pyrotinib plus capecitabine resulted in a CNS objective response rate of 74·6% (95% CI 61·6–85·0) in cohort A and 42·1% (20·3–66·5) in cohort B. Median progression-free survival 11·3 months (7·7–14·6) in cohort A and 5·6 months (3·4–10·0) in cohort B. These results suggest the promising activity of pyrotinib plus capecitabine against brain metastases, especially for radiotherapy-naive population.

When PERMEATE was designed in 2018, the results of trastuzumab deruxtecan and tucatinib studies had not yet been published,[11,12,19] and phase 3 studies of pyrotinib plus capecitabine (PHOEBE[14] and PHENIX[15]) were still ongoing. The alternative hypothesis of CNS objective response rate in cohort A (65%) was based on the CNS objective response rate with lapatinib plus capecitabine (57% by RECIST [version 1.1]) in LANDSCAPE (n=44) and

overall objective response rate with pyrotinib plus capecitabine (78·5%) in a randomised phase 2 study (n=65).[20,21] The CNS objective response rate in patients with radiotherapy-naive brain metastases in this study was 74·6%, and the non-CNS objective response rate of 70·4% was similar with that of PHOEBE (68·6%) and PHENIX (67·2%),[14,15] suggesting the consistent activity of pyrotinib plus capecitabine in patients with CNS metastases and those with non-CNS metastases. Median progression-free survival in cohort A (11·3 months) was within the range of the median progression-free survival in PHOEBE (12·5 months) and PHENIX (11·1 months).[14,15] These results suggest that patients with HER2-positive metastatic breast cancer could potential have a survival benefit from pyrotinib plus capecitabine, regardless of the presence or absence of CNS metastases. However, these speculations made through cross-study comparisons need further validation.

Patients in cohort B were more heavily pretreated in the metastatic setting with higher drug resistance and had brain metastases progressing on previous local radiotherapy, resulting in lower response rate (42·1%). Similarly, the CNS objective response rate was 49% (by composite criteria[22]) or 24% (by Response Assessment in Neuro-Oncology Brain Metastases [RANO-BM] criteria[23]) with neratinib plus capecitabine in the lapatinib-naive cohort of TBCRC 022 (n=37),[24] and 47·3% (by RECIST version 1.1) with tucatinib plus trastuzumab and capecitabine in HER2CLIMB.[12] Intracranial response to systemic therapy is generally low in patients with progressive brain metastases. Greater understanding of the biology is needed to optimise the benefits for these patients. We are planning to analyse drug concentrations in cerebrospinal fluid and predictive biomarkers of clinical outcomes in future studies.

Most patients in PERMEATE had extracranial metastases. In a study of SEER database (n=206 913), patients with multiple extracranial metastases (bone, liver, and lung) showed a higher incidence of brain metastases than those with simple bone metastases (28·0% *vs* 8·6%), suggesting that visceral metastases are a risk factor for brain metastases.[25] According to the National Comprehensive Cancer Network guidelines, brain MRI screening is recommended only when patients have symptoms suspicious of intracranial metastases.[26] If closer brain surveillance can be done when patients have high-risk factors such as visceral metastases, the opportunity for early treatment of brain metastases will be greater. Both LANDSCAPE and cohort A in PERMEATE enrolled radiotherapy-naive populations, but the median progression-free survival was doubled with pyrotinib plus capecitabine compared with lapatinib plus capecitabine (11·3 months *vs* 5·5 months).[20] In addition to the superiority of pyrotinib over lapatinib confirmed by the PHOEBE trial,[14] early detection and control of brain metastases by investigators using MRI surveillance in patients with

	Cohort A (n=59)			Cohort B (n=19)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Diarrhoea	40 (68%)	14 (24%)	0	14 (74%)	4 (21%)	0
Palmar-plantar erythrodysesthesia syndrome	37 (63%)	5 (8%)	0	3 (16%)	2 (11%)	0
Anaemia	30 (51%)	4 (7%)	1 (2%)	9 (47%)	2 (11%)	0
Blood bilirubin increased	32 (54%)	2 (3%)	0	11 (58%)	0	0
Vomiting	31 (53%)	1 (2%)	0	9 (47%)	0	0
White blood cell count decreased	24 (41%)	8 (14%)	0	2 (11%)	3 (16%)	0
Nausea	25 (42%)	0	0	11 (58%)	0	0
Blood bilirubin conjugated increased	27 (46%)	1 (2%)	0	7 (37%)	0	0
Neutrophil count decreased	19 (32%)	8 (14%)	0	4 (21%)	2 (11%)	0
Blood bilirubin unconjugated increased	25 (42%)	0	0	8 (42%)	0	0
Hypokalaemia	16 (27%)	3 (5%)	0	5 (26%)	3 (16%)	0
Aspartate aminotransferase increased	18 (31%)	1 (2%)	0	7 (37%)	0	0
Hypertriglyceridemia	17 (29%)	3 (5%)	0	3 (16%)	1 (5%)	0
Anorexia	17 (29%)	1 (2%)	0	3 (16%)	0	0
Alanine aminotransferase increased	13 (22%)	1 (2%)	0	5 (26%)	1 (5%)	0
Urinary tract infection	14 (24%)	2 (3%)	0	2 (11%)	1 (5%)	0
Malabsorption	14 (24%)	0	0	2 (11%)	0	0
Fatigue	11 (19%)	0	0	5 (26%)	0	0
Headache	12 (20%)	0	0	3 (16%)	0	0
Abdominal distension	11 (19%)	1 (2%)	0	1 (5%)	1 (5%)	0
Mucositis oral	10 (17%)	1 (2%)	0	2 (11%)	0	0
Dyspepsia	8 (14%)	0	0	3 (16%)	0	0
Platelet count decreased	7 (12%)	1 (2%)	0	2 (11%)	0	0
Abdominal pain	7 (12%)	0	0	2 (11%)	0	0
Lymphocyte count decreased	7 (12%)	0	0	0	1 (5%)	0
Hypophosphataemia	3 (5%)	1 (2%)	0	2 (11%)	2 (11%)	0
Dizziness	6 (10%)	1 (1%)	0	0	0	0
Rash	7 (12%)	0	0	0	0	0
Fever	6 (10%)	0	0	0	0	0
Skin hyperpigmentation	6 (10%)	0	0	0	0	0
Blurred vision	0	1 (2%)	1 (2%)	1 (5%)	0	0
Electrocardiogram QT corrected interval prolonged	2 (3%)	1 (2%)	0	0	0	0
Dyspnoea	1 (2%)	1 (2%)	0	1 (5%)	0	0
Hyperuricaemia	0	1 (2%)	0	2 (11%)	0	0
Urine output decreased	0	1 (2%)	0	1 (5%)	0	0
Hypoproteinaemia	0	0	0	2 (11%)	0	0
Vertigo	0	0	0	2 (11%)	0	0
Insomnia	0	0	0	2 (11%)	0	0
Ventricular fibrillation	0	0	1 (2%)	0	0	0
Acute kidney injury	0	0	1 (2%)	0	0	0
Soft tissue infection	0	1 (2%)	0	0	0	0
Syncope	0	1 (2%)	0	0	0	0
Pneumonitis	0	1 (2%)	0	0	0	0
Thromboembolic event	0	1 (2%)	0	0	0	0
Cardiac disorder	0	1 (2%)	0	0	0	0
Hypoxia	0	1 (2%)	0	0	0	0
Ankle fracture	0	0	0	0	1 (5%)	0

Data are n (%). Grade 1–2 events occurring in at least 10% of patients and all grade 3 and 4 events are reported. Each patient was counted once for the highest grade of each event experienced.

Table 3: **Treatment-emergent adverse events by cohort**

trastuzumab-treated disease and visceral metastases might contribute to the prolongation of progression-free survival.

Monoclonal antibody-based breast cancer therapy (trastuzumab and pertuzumab) for brain metastases control remains unsatisfactory. Median progression-free survival with antibody–drug conjugate trastuzumab emtansine in patients with HER2-positive breast cancer and stable brain metastases was similar between EMILIA (5·9 months) and KAMILLA (5·5 months).[27,28] Some case series suggested the activity of trastuzumab emtansine in active brain metastases, but the median progression-free survival ranged from 5·0 to 6·1 months.[29,30] The subgroup analysis of DESTINY-Breast01 reported a median progression-free survival of 18·1 months with antibody–drug conjugate trastuzumab deruxtecan (n=24).[19] However, enrolment eligibility for this brain metastases subgroup included patients without brain lesions after previous CNS local therapy or those with stable brain lesions after radiotherapy. Data from trials of trastuzumab deruxtecan in active brain metastases are awaited (DESTINY-Breast12, DEBBRAH, and TUXEDO-1).

Consistent with LANDSCAPE and TBCRC 022,[20,24] CNS progression was the main reason for discontinuation of study treatment in our study, even if some patients also had simultaneous extracranial progression. This observation suggests that intracranial lesions are highly likely to show rapid resistance to systemic therapy, after HER2-targeted therapy, and more effective treatments for brain metastases are still needed.

The adverse events in our study were consistent with the known toxicity profile of pyrotinib plus capecitabine in previous clinical trials.[14,15] Diarrhoea, the most common treatment-emergent adverse event, was reversible with dose adjustments and treatment against diarrhoea (montmorillonite powder or loperamide), and did not cause discontinuation of treatment. The other grade 3 or higher treatment-emergent adverse events were also manageable.

This study had some limitations. First, this was a phase 2 study without control group. Second, only Chinese patients were enrolled. Evidence in other populations has not yet been confirmed. Third, response assessment was done by investigators only with no central review. Finally, as the enrolment of patients with brain metastases in clinical trials becomes common, the RANO-BM criteria are increasingly adopted to assess treatment response, with the incorporation of evaluating steroid use and neurological symptoms.[23] Also, we did not analyse response by RANO-BM criteria and did not assess quality-of-life or symptom improvement data. Long-term overall survival will be analysed in future reports.

In conclusion, pyrotinib plus capecitabine was well tolerated and active for both intracranial and extracranial lesions in patients with HER2-positive metastatic breast cancer and brain metastases, especially in those with radiotherapy-naive brain metastases. This combination might delay radiotherapy and provide survival benefits for patients. Further validation in a large-scale, randomised, controlled trial is warranted.

Contributors

MY conceived and designed the study. MY, QO, TS, JY, LiL, YS, CH, ZC, ZL, XY, HX, ZG, XL, FD, XC, JQ, and GZ recruited patients. MY, QO, TS, LN, JY, LiL, YS, CH, and ZC collected data. MY and LN verified the data in the study. All authors contributed to the analysis and interpretation of data. All authors contributed to the preparation and critically review of the manuscript. MY contributed to the study supervision. LN, MZ, and HL contributed to the administrative support. All authors approved the final version of manuscript for submission. All authors had full access to the raw data and the corresponding author had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Individual participant data (including data dictionaries) that underlie the results reported in this Article, after de-identification (text, tables, figures, and appendix 2), are available immediately and ending 3 years after 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 available in appendix 2.

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