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ORIGINAL ARTICLE

# Neratinib and ado-trastuzumab emtansine for pretreated and untreated human epidermal growth factor receptor 2 (HER2)-positive breast cancer brain metastases: Translational Breast Cancer Research Consortium trial 022☆

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**Background:** Treatment options for human epidermal growth factor receptor 2 (HER2)-positive breast cancer brain metastases (BCBMs) remain limited. We previously reported central nervous system (CNS) activity for neratinib and neratinib—capecitabine. Preclinical data suggest that neratinib may overcome resistance to ado-trastuzumab emtansine (T-DM1) when given in combination. In Translational Breast Cancer Research Consortium (TBCRC) 022's cohort 4, we examined the efficacy of neratinib plus T-DM1 in patients with HER2-positive BCBM.

**Patients and methods:** In this multicenter, phase II study, patients with measurable HER2-positive BCBM received neratinib 160 mg daily plus T-DM1 3.6 mg/kg intravenously every 21 days in three parallel-enrolling cohorts [cohort 4A—previously untreated BCBM, cohorts 4B and 4C—BCBM progressing after local CNS-directed therapy *without* (4B) and *with* (4C) prior exposure to T-DM1]. Cycle 1 diarrheal prophylaxis was required. The primary endpoint was the Response Assessment in Neuro-Oncology-Brain Metastases (RANO-BM) by cohort. The overall survival (OS) and toxicity were also assessed.

**Results:** Between 2018 and 2021, 6, 17, and 21 patients enrolled in cohorts 4A, 4B, and 4C. Enrollment was stopped prematurely for slow accrual. The CNS objective response rate in cohorts 4A, 4B, and 4C was 33.3% [95% confidence interval (CI) 4.3% to 77.7%], 35.3% (95% CI 14.2% to 61.7%), and 28.6% (95% CI 11.3% to 52.2%), respectively; 38.1%-50% experienced stable disease for $\geq$6 months or response. Diarrhea was the most common grade 3 toxicity (22.7%). The median OS was 30.2 [cohort 4A; 95% CI 21.9-not reached (NR)], 23.3 (cohort 4B; 95% CI 17.6-NR), and 20.9 (cohort 4C; 95% CI 14.9-NR) months.

**Conclusions:** We observed intracranial activity for neratinib plus T-DM1, including those with prior T-DM1 exposure, suggesting synergistic effects with neratinib. Our data provide additional evidence for neratinib-based combinations in patients with HER2-positive BCBM, even those who are heavily pretreated.

**Key words:** brain metastases, breast cancer, neratinib, T-DM1, ado-trastuzumab emtansine

## INTRODUCTION

Advanced breast cancer with overexpression of the human epidermal growth factor receptor 2 (HER2) encompasses 15%-20%[1] of breast cancers and is characterized by a higher risk of metastatic progression to the brain.[2-4] Up to half of patients with HER2-positive metastatic breast cancer will experience a brain recurrence, including brain-only relapses after treatment for early breast cancer.[5] Until recent years, evaluation of

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therapeutic agents for central nervous system (CNS) metastases was limited to small studies designed specifically for those with active CNS disease. Although international efforts have modestly improved the inclusion of patients with brain metastases in clinical trials,[6-8] the number of regimens with high-level evidence for CNS efficacy remains low. This includes three HER2-targeted tyrosine kinase inhibitors: lapatinib, neratinib, and tucatinib, which are included in the National Comprehensive Cancer Network compendium for the treatment of patients with HER2-positive breast cancer brain metastases (BCBMs).[9] Despite progress in this therapeutic space, BCBM remains a major cause of morbidity and mortality and persists as a substantial unmet clinical need.

Over the last decade, Translational Breast Cancer Research Consortium (TBCRC) 022 (https://ClinicalTrials.gov, NCT01494662) has evaluated the CNS efficacy of neratinib-based treatments in sequential cohorts (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2024.07.245). To date, we have reported the CNS activity of neratinib for progressive CNS disease [cohort 1, volumetric CNS objective response rate (ORR) = 8%],[10] within a limited preoperative experience (cohort 2),[11] and when administered with capecitabine (cohort 3, CNS volumetric ORR 49% in lapatinib naive and 33% in lapatinib treated).[12] Although the ORR was promising for capecitabine—neratinib, the median progression-free survival (PFS) was <6 months and gastrointestinal toxicity was common, with nearly one-third of patients experiencing grade 3 diarrhea despite loperamide prophylaxis. Thus the exploration of alternative neratinib partners was planned in additional study cohorts.

At the time of study design for cohort 4 of TBCRC 022, emerging data suggested CNS activity and safety for the antibody—drug conjugate (ADC) ado-trastuzumab emtansine (T-DM1), with postregistration clinical studies reporting CNS ORRs of 20%-44% using variable definitions of response.[13-19] Given T-DM1's promising efficacy, its favorable toxicity profile, and the presence of phase I data confirming the safety and preliminary extracranial efficacy of T-DM1 plus neratinib, the ADC was selected as the therapeutic partner for neratinib in cohort 4 of TBCRC 022. Further, experimental models have shown synergistic anticancer activity of neratinib plus T-DM1 through increased cellular internalization of ADCs with enhanced payload release and capacity to overcome T-DM1 resistance.[20,21] Finally, in preclinical models of HER2-positive BCBM, T-DM1 and neratinib resulted in more frequent and durable intracranial responses and prolonged survival compared with either agent alone.[22]

Herein, we present results from TBCRC 022 cohort 4, which evaluated the combination of neratinib plus T-DM1 in patients with HER2-positive BCBM.

## PATIENTS AND METHODS

### *TBCRC 022 cohort 4 eligibility*

Cohort 4 of TBCRC 022 (NCT01494662) was a multicenter, phase II, nonrandomized, open-label clinical trial with three simultaneously enrolled cohorts for patients with BCBM. The following centers participated: Dana-Farber Cancer Institute, Massachusetts General Hospital, Baylor College of Medicine, Johns Hopkins University, University of California (San Francisco), University of Michigan, University of Pittsburgh, Mayo Clinic (Minnesota), University of North Carolina, and Georgetown University. All participants signed informed consent forms approved by each site's institutional review board and the trial was conducted in accordance with the Declaration of Helsinki.

Eligible patients had HER2-positive BCBM and measurable CNS disease, defined by the presence of at least one parenchymal brain metastasis with the longest diameter of ≥10 mm. In cohort 4A, patients had not received prior CNS-directed treatments (i.e. no whole-brain radiation therapy, stereotactic radiosurgery, or surgical resection). In cohorts 4B and 4C, patients had to have CNS progression after prior receipt of CNS-directed therapies, either *without* previous exposure to T-DM1 (cohort 4B) or *with* any previous exposure to T-DM1 in any setting (cohort 4C; Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2024.07.245).

For cohorts 4A-C, there were no limits to the number of prior treatment lines or exclusions for specific treatments received, other than neratinib for cohorts 4A-C and T-DM1 for cohort 4B. Additional inclusion criteria were Eastern Cooperative Oncology Group performance status 0-2, adequate end-organ function, cardiac ejection fraction ≥50%, no escalation of steroids within a week before baseline brain imaging, and less than one seizure within 4 weeks of enrollment. Key exclusions were leptomeningeal disease (LMD) only, grade 2+ chronic diarrhea, or active hepatitis.

### *Treatment plan*

All cohort 4 patients received neratinib and T-DM1 per the established dosing from NSABP FB-10[21]: neratinib was administered at 160 mg orally once daily and T-DM1 was administered at 3.6 mg/kg intravenously, every 21 days.[21] Prophylaxis for diarrhea was mandated and provided during cycle 1, consisting of loperamide and colestipol per the CONTROL trial.[23] Neratinib and T-DM1 were continued until tumor progression, unacceptable toxicity, or patient/clinician preference. Patients were clinically evaluated every 21 days with a neurological/physical examination and laboratory evaluation. Participants underwent imaging every two cycles for the first 18 weeks, then every 3 cycles (with brain magnetic resonance imaging and computed tomography of the chest/abdomen/pelvis). Although we initially required treatments to be dispensed (neratinib) and administered (T-DM1) at participating centers, a study amendment in 2020 allowed for virtual study visits, local T-DM1 administration, and shipment of neratinib on a case-by-case basis, due to some patients' inability to travel during the coronavirus disease 2019 (COVID-19) pandemic.

### Clinical trial endpoints

The primary endpoint of TBCRC 022 was CNS-ORR for each cohort, according to the Response Assessment in Neuro-Oncology-Brain Metastases (RANO-BM).[24] CNS partial response (PR) required *all* of the following: ≥30% decrease in the sum longest diameter of CNS target lesions relative to baseline, stable/improved nontarget lesions, stable/improved neurological function, and no increases in steroid dosing for neurological symptoms. In addition, confirmation of PR or complete response (CR) ≥4 weeks later was required to deem either one of the best overall responses. CNS progression was defined by the presence of *any* of the following: ≥20% increase in the sum target lesion longest distance relative to nadir, presence of new lesions, worsening neurological symptoms, or increased steroid dosing. All participants' CNS imaging was assessed centrally by the Harvard Tumor Imaging Metrics Core (TIMC). If steroid dosing could not be confirmed or neurological status was not documented at any timepoint, CNS response was documented based on the remaining RANO-BM criteria, per guideline recommendations.[24]

Extra-CNS tumor response assessments were based on RECIST version 1.1,[25] with extra-CNS progression qualifying for therapy discontinuation. Non-CNS imaging evaluations were completed by the TIMC for Harvard Cancer Center institutions and by local assessment for other sites. The secondary endpoints were CNS volumetric response,[10,12,26] PFS and overall survival (OS), first site of disease progression, dose modifications, and toxicity based on the National Cancer Institute Common Terminology Criteria for Adverse Events v.4.0 criteria.

### Statistical assumptions

Each study cohort was independently evaluated for ORR by RANO-BM. In cohorts 4A and 4B, the target accrual was 20, which would have 80% power to reject an ORR of ≤30%, assuming a true ORR of 57% and a one-sided type I error of 0.05. In cohort 4C, the anticipated ORR was lower as a result of prior T-DM1 exposure; an ORR of ≥24% was considered promising (and an ORR of ≤5% was considered not promising). Cohort 4C used Simon's optimal two-stage design, with the first stage enrolling 10 patients. If at least one CNS response was observed, enrollment would continue for up to 14 more patients. In cohort 4C, the treatment combination would be deemed promising if at least 3 of 24 patients experienced a response. This design would yield a power of 90% and a type I error rate of 0.10 when the true ORR was 24%.

### Statistical methods

Patient characteristics were summarized using frequencies/percentages for categorical characteristics and medians/ranges for continuous variables. RANO-BM and volumetric CNS best responses were reported using percentages and Clopper Pearson (i.e. exact) 95% confidence intervals (CIs) separately for each cohort. Percent changes in the sum longest diameter and the sum volume CNS target lesions were graphically summarized using waterfall plots.

The Kaplan—Meier method was used to calculate the PFS and OS curves, median survival, and 12-month survival by cohort. In PFS analyses, a participant was considered to have an event if they had CNS progression, non-CNS progression, or died without a progression within two cycle lengths (42 days) after their last scan date. If a participant had multiple events (e.g. both CNS and non-CNS progression), the event (and corresponding date) for PFS analyses was whichever event happened first.

## RESULTS

### Patient characteristics

TBCRC 022 enrolled 6, 17, and 21 patients in cohorts 4A, 4B, and 4C between 7 November 2018 and 1 November 2021. We stopped enrollment due to slow accrual, after 30.0%, 85.0%, and 87.5% of anticipated participants enrolled in cohorts 4A, 4B, and 4C, respectively. Participant characteristics are displayed in Table 1. Across cohorts, median ages were 47-51 years, and three patients were documented to have LMD at baseline. The median number of prior therapy lines was 2.5, 1.0, and 3.0 (range 1-10), respectively; 11 (25.0%) had prior lapatinib, 2 (4.5%) had prior trastuzumab deruxtecan (T-DXd), and none had prior tucatinib. In cohorts 4B and 4C, 70.6% and 47.6% had stereotactic radiosurgery, whereas 70.6% and 52.4% had whole-brain radiation therapy, respectively.

### Treatment efficacy and survival outcomes

At the data cutoff (31 October 2023), the median follow-up for participants was 33 months, [interquartile range (IQR) 27-37 months] 28 months, (IQR 25-32 months), and 28 months, (IQR 25-28 months) for cohorts 4A, 4B, and 4C, respectively. Participants received a median number of 5 cycles (range 1-15 cycles, cohort 4A), 5 cycles (range 1-67 cycles, with 1 person still receiving treatment in cohort 4B), and 6 cycles (range 1-18 cycles, cohort 4C). The reasons for protocol therapy discontinuation are summarized in Table 2. Overall, the most common reason for treatment discontinuation was CNS progression/relapse ($n = 26$, 59.1%, across cohorts); five patients across cohorts (11.4%) stopped treatment due to toxicity.

The RANO-BM ORR was 33.3% (95% CI 4.3% to 77.7%) in cohort 4A, 35.4% (95% CI 14.2% to 61.7%) in cohort 4B, and 28.6% (11.3% to 52.2%) in cohort 4C. All responses were PRs except for one CR in cohort 4B. In addition, we observed four unconfirmed responses (one in cohorts 4A and 4B each and two in 4C). Table 3 summarizes the best CNS response by cohort, and a waterfall plot in Figure 1 demonstrates the maximal decrease in sum CNS disease diameter per RANO-BM criteria from baseline by cohort. All but seven participants experienced a decrease in their CNS tumor burden in the study. Among those with a RANO-BM response, 0 (0%, 95% CI 0% to 84.2%), 2 (33.0%, 95% CI 4.3% to 77.7%), and 2 (33.3%, 95% CI 4.3% to 77.7%)

**Table 1. Baseline characteristics by cohort**

| Characteristics | Cohort 4A ($n = 6$) | Cohort 4B ($n = 17$) | Cohort 4C ($n = 21$) |
|---|---|---|---|
| Age (years) | | | |
| Median | 51.0 | 48.0 | 47.0 |
| Range | 43.0-65.0 | 41.0-59.0 | 34.0-67.0 |
| Sex (female), *n* (%) | 6 (100.0) | 17 (100.0) | 20 (95.2) |
| Race, *n* (%) | | | |
| White | 4 (66.7) | 14 (82.4) | 20 (95.2) |
| African American or Black | 1 (16.7) | 0 (0.0) | 1 (4.8) |
| Asian | 0 (0.0) | 1 (5.9) | 0 (0.0) |
| Other | 1 (16.7) | 2 (11.8) | 0 (0.0) |
| Ethnicity, *n* (%) | | | |
| Hispanic or Latino | 1 (16.7) | 0 (0.0) | 0 (0.0) |
| Non-Hispanic | 5 (83.3) | 14 (82.4) | 20 (95.2) |
| Unknown | 0 (0.0) | 3 (17.6) | 1 (4.8) |
| CNS parenchymal (yes), *n* (%) | 6 (100.0) | 17 (100.0) | 21 (100.0) |
| CNS leptomeningeal (yes), *n* (%) | 0 (0.0) | 1 (5.9) | 2 (9.5) |
| Lung/Pleural (yes), *n* (%) | 1 (16.7) | 3 (17.6) | 6 (28.6) |
| Breast or chest wall (yes), *n* (%) | 2 (33.3) | 5 (29.4) | 1 (4.8) |
| Lymph node (yes), *n* (%) | 1 (16.7) | 2 (11.8) | 1 (4.8) |
| Liver (yes), *n* (%) | 3 (50.0) | 7 (41.2) | 3 (14.3) |
| Bone (yes), *n* (%) | 5 (83.3) | 9 (52.9) | 13 (61.9) |
| Soft tissue (yes), *n* (%) | 0 (0.0) | 2 (11.8) | 1 (4.8) |
| Number of non-CNS metastatic sites | | | |
| Median | 2.0 | 2.0 | 1.0 |
| Range | 0.0-5.0 | 0.0-6.0 | 0.0-2.0 |
| ER status, *n* (%) | | | |
| Negative | 1 (16.7) | 7 (41.2) | 11 (52.4) |
| Positive | 5 (83.3) | 8 (47.1) | 7 (33.3) |
| (Missing) | 0 (0.0) | 2 (11.8) | 3 (14.3) |
| Number of prior lines of chemotherapy | | | |
| Median | 1.5 | 1.0 | 3.0 |
| Range | 0.0-4.0 | 0.0-4.0 | 2.0-10.0 |
| Has the patient had prior surgery for CNS tumors? (yes, date of surgery), *n* (%) | 0 (0.0) | 7 (41.2) | 7 (33.3) |
| Prior SRS (stereotactic radiosurgery) (yes), *n* (%) | 1 (16.7) | 12 (70.6) | 10 (47.6) |
| Prior WBRT (yes), *n* (%) | 0 (0.0) | 12 (70.6) | 11 (52.4) |
| Number of neratinib cycles | | | |
| Median | 5.0 | 5.0 | 6.0 |
| Range | 1.0-15.0 | 1.0-67.0 | 1.0-18.0 |
| Number of ado-trastuzumab emtansine (T-DM1) cycles | | | |
| Median | 5.0 | 5.0 | 6.0 |
| Range | 1.0-15.0 | 1.0-67.0 | 1.0-18.0 |

Cohort 4A: naive to CNS-directed local treatments (though one patient was reported to have received stereotactic radiosurgery on further review); cohort 4B: previous CNS-directed local treatment and no prior T-DM1; cohort 4C: previous CNS-directed local treatment and prior T-DM1.
CNS, central nervous system; ER, estrogen receptor; SRS, stereotactic radiosurgery; T-DM1, ado-trastuzumab emtansine; WBRT, whole-brain radiation therapy.

patients in cohorts 4A, 4B, and 4C, respectively, experienced a CNS response for $\geq$6 months. The timing, duration of response, and progression events for all study participants are displayed in the swimmer plots in Figure 2 and Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2024.07.245. Of note, among those with LMD, the best responses were PR for $<$6 months ($n = 1$, 4C), progressive disease ($n = 1$, 4C), and stable disease for $<$6 months ($n = 1$, 4B).

CNS volumetric responses were observed for 3 participants (ORR 50%, 95% CI 11.8% to 88.2%), 5 participants (ORR 29.4%, 95% CI 10.3% to 56%), and 5 participants (ORR

**Table 2. Reasons for treatment discontinuation by cohort**

| Reasons | Cohort 4A ($n = 6$), *n* (%) | Cohort 4B ($n = 17$), *n* (%) | Cohort 4C ($n = 21$), *n* (%) |
|---|---|---|---|
| Off treatment reason | | | |
| CNS and non-CNS progression/relapse | 0 (0.0) | 0 (0.0) | 3 (14.3) |
| CNS progression/relapse | 3 (50.0) | 11 (64.7) | 12 (57.1) |
| Non-CNS progression/relapse | 1 (16.7) | 0 (0.0) | 3 (14.3) |
| Patient withdrew for other reasons | 1 (16.7) | 1 (5.9) | 2 (9.5) |
| Physician discretion | 0 (0.0) | 0 (0.0) | 1 (4.8) |
| Unacceptable toxicity | 1 (16.7) | 4 (23.5) | 0 (0.0) |
| Not applicable/Remains on therapy | 0 (0.0) | 1 (5.9) | 0 (0.0) |

CNS, central nervous system.

**Table 3. Best CNS response per the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria by cohort**

| Best response | Cohort 4A ($n$ = 6), $n$ (%); 95% CI | Cohort 4B ($n$ = 17), $n$ (%); 95% CI | Cohort 4C ($n$ = 21), $n$ (%); 95% CI |
|---|---|---|---|
| Objective response | 2 (33.3); 4.3% to 77.7% | 6 (35.3); 14.2% to 61.7% | 6 (28.6%); 11.3% to 52.2% |
| Clinical benefit[a] | 3 (50.0); 11.8% to 88.2% | 7 (41.2); 18.4% to 67.1% | 8 (38.1%); 18.1% to 61.6% |
| Complete response | 0 (0); 0% to 45.9% | 1 (5.9%); 0.1% to 28.7% | 0 (0%); 0% to 16.1% |
| Partial response | 2 (33.3); 4.3% to 77.7% | 5 (29.4%); 10.3% to 56% | 6 (28.6%); 11.3% to 52.2% |
| Stable disease | 2 (33.3); 4.3% to 77.7% | 7 (41.2%); 18.4% to 67.1% | 12 (57.1%); 34% to 78.2% |
| Stable disease for ≥6 months | 1 (16.7); 0.4% to 64.1% | 1 (5.9%); 0.1% to 28.7% | 2 (9.5%); 1.2% to 30.4% |
| Stable disease for <6 months | 1 (16.7); 0.4% to 64.1% | 6 (35.3%); 14.2% to 61.7% | 10 (47.6%); 25.7% to 70.2% |
| Unconfirmed partial response | 1 (16.7); 0.4% to 64.1% | 1 (5.9%); 0.1% to 28.7% | 2 (9.5%); 1.2% to 30.4% |
| Progression/Relapse | 0 (0); 0% to 45.9% | 0 (0%); 0% to 19.5% | 1 (4.8%); 0.1% to 23.8% |
| CNS progression from scan | 0 (0); 0% to 45.9% | 0 (0%); 0% to 19.5% | 1 (4.8%); 0.1% to 23.8% |
| CNS progression from clinical deterioration | 0 (0); 0% to 45.9% | 0 (0%); 0% to 19.5% | 0 (0%); 0% to 16.1% |
| Not assessable (radiologic inconsistencies or off treatment before follow-up imaging) | 2 (33.3); 4.3% to 77.7% | 4 (23.5%); 6.8% to 49.9% | 2 (9.5%); 1.2% to 30.4% |
| Off treatment before follow-up imaging done due to unacceptable toxicity or physician discretion (not assessable) | 0 (0); 0% to 45.9% | 3 (17.6%); 3.8% to 43.4% | 1 (4.8%); 0.1% to 23.8% |

CI, confidence interval; CNS, central nervous system.
[a]Clinical benefit is defined as complete response, partial response, or stable disease lasting at least 6 months.

23.8%, 95% CI 8.2% to 47.2%) in cohorts 4A, 4B, and 4C, respectively; two of these were CRs. Full volumetric data and waterfall plots for volumetric response are provided in Supplementary Table S1 and Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2024.07.245.

PFS and OS by cohort are shown in Supplementary Figures S4 and S5, respectively, available at https://doi.org/10.1016/j.annonc.2024.07.245, with PFS event types displayed in Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2024.07.245. In cohort 4A, the median PFS was 5.3 months [95% CI 4.5 months-upper confidence bound not reached (NR)], the median OS was 30.2 months (95% CI 21.9 months-NR), and the 12-month survival probability was 83.0% (95% CI 58% to 100%). In cohort 4B, the median PFS was 4.1 months (95% CI 2.7 months-NR), the median OS was 23.3 months (95% CI 17.6 months-NR), and the 12-month OS probability was 87.0% (95% CI 71.0% to 100%). In cohort 4C, the median PFS was 4.1 months (95% CI 2.7 months-NR), the median OS was 20.9 months (95% CI 14.9 months-NR), and the 12-month OS probability was 80% (95% CI 64% to 100%).

### *Safety and tolerability*

As all cohort 4 patients received the same protocol treatment, adverse events (AEs) deemed possibly, probably, or definitely attributable to treatment were summarized across cohorts (Table 4). Diarrhea was the most common grade 2 (31.8%) and grade 3 (22.7%) AEs reported; no grade 4 diarrhea was observed. Among the 10 (22.7%) experiencing grade 3 diarrhea, onset was documented at a median cycle number of 2 (range 1-5). One of these patients had two grade 3 diarrhea events during cycles 2 and 5, with the remaining nine having one grade 3 event documented. Fatigue was mostly grade 2 and reported by 12 (27.3%) of participants. One patient (2.3%) experienced grade 4 transaminitis; no treatment-attributed deaths were reported.

Dose modifications were aggregated across cohorts by agent. With regard to neratinib, 27 (61.4%) required one or more dose holds, with doses held at some point during 58 cycles across these 27 patients, 36 (62.1%) of which were for toxicity. Doses were held for a median of 7 (range 1-21) days, and 14 patients (31.8%; not mutually exclusive with the 27 having dose holds) required one or more dose reductions over a total of 17 cycles. All dose reductions were for toxicity. For T-DM1, 14 (31.8%) participants required one or more dose holds, with doses held for 27 cycles across these 14 patients, 15 (55.6%) of which were for toxicity. Doses were held for a median of 14 (range 6-21) days. Overall, 10 (22.7%) patients required one or more dose reductions over a total of 14 cycles, all of which were for toxicity.

## DISCUSSION

In cohort 4 of TBCRC 022, we evaluated the efficacy and safety of neratinib plus T-DM1 in patients with active HER2-positive BCBM. We observed intracranial activity across cohorts, including radiation-naive, heavily pretreated, and T-DM1-exposed patients, with 38.1%-50.0% experiencing stable disease for ≥6 months or response. Approximately one-third of participants experienced a PR, 33% of whom in cohorts 4B and 4C maintained a response for ≥6 months. Beyond response, the longer-term outcomes observed were also promising, with those in cohorts 4A-4C having an ≥80% probability of 12-month OS. However, our data also highlight the ongoing unmet therapeutic needs for this patient population, with a median observed PFS of 4.1-5.3 months across cohorts (though CIs were wide with a high degree of variability). Overall, our results provide further evidence for consideration of neratinib-based combinations

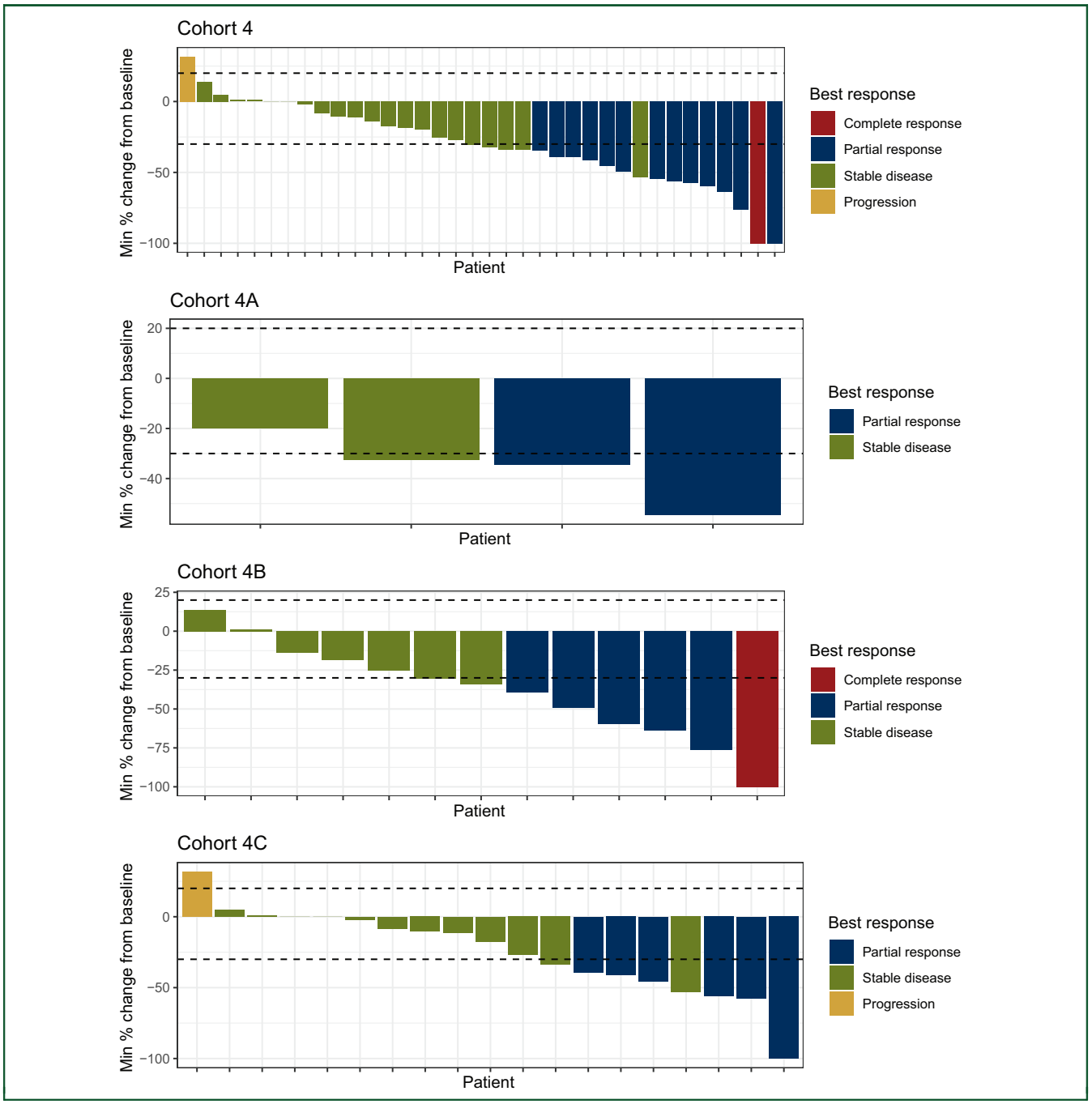


**Figure 1.** **Waterfall plots displaying the best Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) central nervous system responses observed in cohort 4 overall (panel A), cohort 4A (panel B), cohort 4B (panel C), and cohort 4C (panel D), among assessable patients.**

in patients with HER2-positive BCBM. Further, this is the first, prospective BCBM-dedicated trial of neratinib in combination with an agent other than capecitabine. Moreover, to our knowledge, this is the first trial to examine the activity of a T-DM1-inclusive combination after experiencing past progression on T-DM1.

Given the limitations of cross-trial comparisons with variable patient populations and differences in definitions for CNS response, understanding how our results compare with the existing data for T-DM1 in CNS disease is challenging. In the KAMILLA trial,[14] for example, the CNS-ORR was 42.9% with T-DM1 monotherapy by RECIST criteria, numerically higher than what was observed in our trial across cohorts. However, the CNS response analysis from KAMILLA was exploratory and ad hoc, all patients were T-DM1 naive, and the definition for CNS response differed from that reported here. In addition, with our non-randomized design, we cannot ascertain how neratinib impacted any activity that might be observed with T-DM1 monotherapy. However, it is notable that the magnitude of the CNS activity observed here is substantially higher than our previously reported efficacy for neratinib monotherapy (volumetric CNS ORR 8%),[10] even in T-DM1 pretreated patients, suggesting that neratinib may overcome prior T-DM1

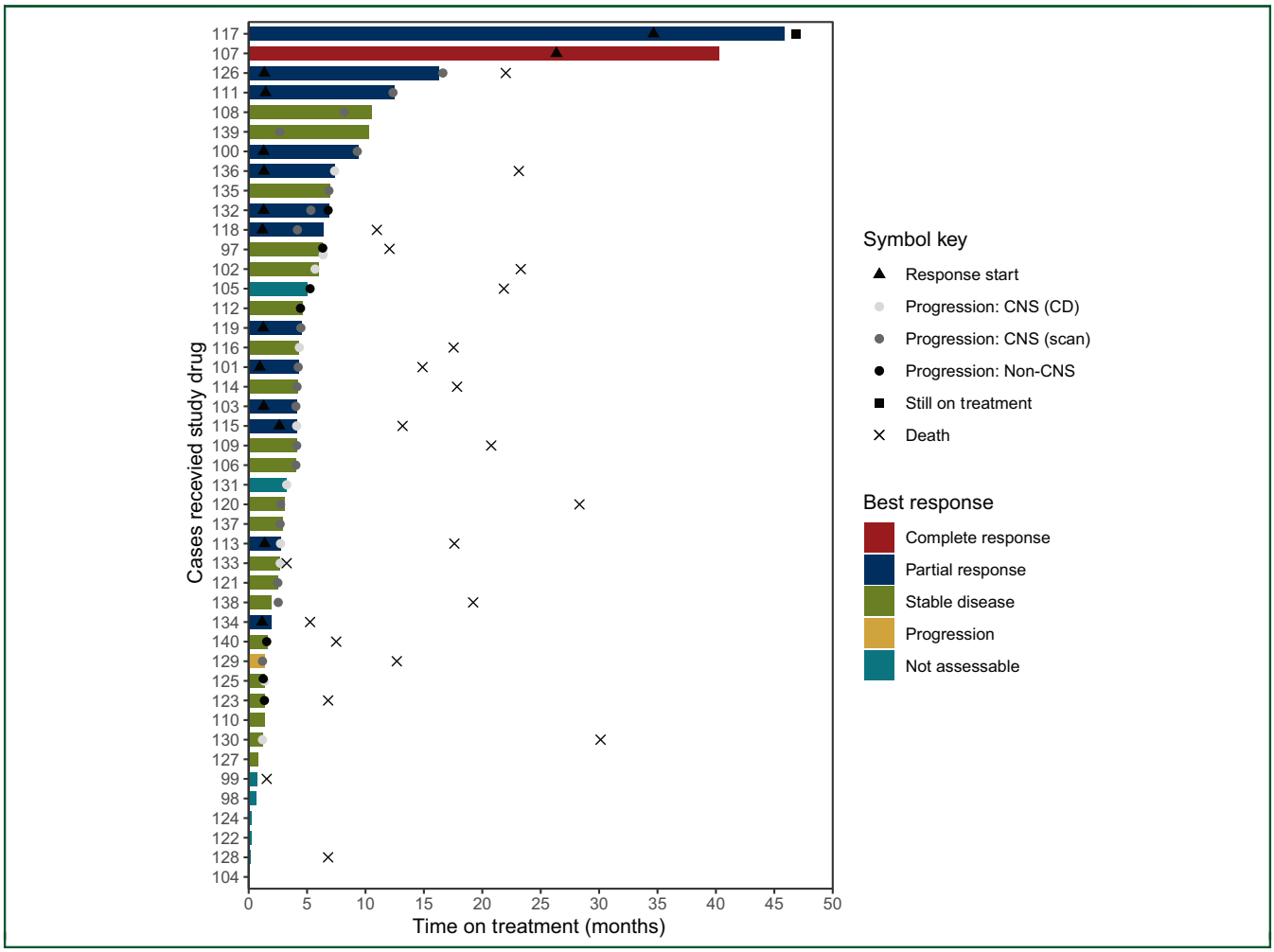


**Figure 2. Swimmer plot for cohort 4.**
CD, clinical deterioration; CNS, central nervous system.

resistance. These observations are consistent with data from preclinical models suggesting that concurrent treatment with irreversible pan-HER inhibitors may enhance receptor ubiquitination, ADC internalization, and treatment efficacy.[27]

Putting our results into further context, T-DM1 plus neratinib now adds to the growing list of combinations showing activity in clinical trials dedicated to those with HER2-positive BCBM.[12,28-30] For example, the HER2CLIMB trial demonstrated clinically meaningful activity of the triplet of tucatinib—capecitabine—trastuzumab compared with capecitabine—trastuzumab, with improved CNS-ORR (47.3% versus 20%, respectively) and longer OS [hazard ratio (HR) 0.60; median 21.6 versus 12.5 months, respectively].[31-34] HER2CLIMB-02 also recently reported initial results, demonstrating modestly improved outcomes when tucatinib was added to T-DM1 (versus T-DM1 alone) in patients with metastatic breast cancer, inclusive of those with BCBM (where PFS was 7.8 versus 5.7 months).[35] Currently, there are no available comparisons of T-DM1 plus neratinib versus T-DM1 plus tucatinib, which would better inform the optimal use of these combinations in the setting of CNS disease.

In addition, the ADC T-DXd has shown consistent activity in BCBM. In a recently presented pooled analysis for those with BCBM receiving T-DXd in the DESTINY-Breast01, 02, and 03 studies,[36] T-DXd demonstrated robust intracranial responses, with CNS ORR >45% regardless of having treated/stable or active BCBM at trial enrollment and a numerically longer CNS-PFS than comparator agents. These data are further supported by results from the DEBBRAH[37] and TUXEDO-1[38] studies and real-world case series.[39]

Overall, high-grade AEs in our trial were infrequent, with only one patient experiencing a grade 4 AE. However, despite primary prophylaxis with colestipol and loperamide, grade 3 diarrhea was experienced by nearly a quarter of study participants, similar to the rates seen in NSABP FB-10.[21] This may be partly due to clinician and participant discretion to stop prophylaxis as appropriate during cycle 1 or because the prophylaxis regimen was validated without T-DM1 and in the adjuvant setting.[23] Further, grade 3 diarrhea occurred at a median of cycle 2 and was observed through cycle 5, perhaps not prevented by early prophylaxis in some. It is possible that the onset and contributors to diarrhea in the metastatic setting are also affected by unique factors, and prolonged prophylaxis beyond cycle 1 or

**Table 4. Adverse events possibly/probably/definitely attributed to study therapy (cohorts 4A, 4B, and 4C combined)**

| Toxicity | Grade 2, *n* (%) | Grade 3, *n* (%) | Grade 4, *n* (%) | Total, *n* (%) |
|---|---|---|---|---|
| All toxicities | 17 (38.6) | 18 (40.9) | 1 (2.3) | 36 (81.8) |
| Diarrhea | 14 (31.8) | 10 (22.7) | 0 (0) | 24 (54.6) |
| Fatigue | 11 (25) | 1 (2.3) | 0 (0) | 12 (27.3) |
| Aspartate aminotransferase increased | 6 (13.6) | 4 (9.1) | 0 (0) | 10 (22.7) |
| Nausea | 7 (15.9) | 1 (2.3) | 0 (0) | 8 (18.2) |
| Alanine aminotransferase increased | 2 (4.6) | 2 (4.6) | 1 (2.3) | 5 (11.4) |
| Anorexia | 5 (11.4) | 0 (0) | 0 (0) | 5 (11.4) |
| Platelet count decreased | 4 (9.1) | 1 (2.3) | 0 (0) | 5 (11.4) |
| Vomiting | 4 (9.1) | 0 (0) | 0 (0) | 4 (9.1) |
| Abdominal pain | 3 (6.8) | 0 (0) | 0 (0) | 3 (6.8) |
| Dehydration | 1 (2.3) | 2 (4.6) | 0 (0) | 3 (6.8) |
| Dyspepsia | 3 (6.8) | 0 (0) | 0 (0) | 3 (6.8) |
| Gastroesophageal reflux disease | 3 (6.8) | 0 (0) | 0 (0) | 3 (6.8) |
| Hypokalemia | 0 (0) | 3 (6.8) | 0 (0) | 3 (6.8) |
| Mucositis oral | 3 (6.8) | 0 (0) | 0 (0) | 3 (6.8) |
| Anemia | 0 (0) | 2 (4.6) | 0 (0) | 2 (4.6) |
| Generalized muscle weakness | 2 (4.6) | 0 (0) | 0 (0) | 2 (4.6) |
| Peripheral sensory neuropathy | 1 (2.3) | 1 (2.3) | 0 (0) | 2 (4.6) |
| Acute kidney injury | 0 (0) | 1 (2.3) | 0 (0) | 1 (2.3) |
| Alkaline phosphatase increased | 1 (2.3) | 0 (0) | 0 (0) | 1 (2.3) |
| Bloating | 1 (2.3) | 0 (0) | 0 (0) | 1 (2.3) |
| Blurred vision | 1 (2.3) | 0 (0) | 0 (0) | 1 (2.3) |
| Colitis | 1 (2.3) | 0 (0) | 0 (0) | 1 (2.3) |
| Constipation | 1 (2.3) | 0 (0) | 0 (0) | 1 (2.3) |
| Creatinine increased | 0 (0) | 1 (2.3) | 0 (0) | 1 (2.3) |
| Dizziness | 1 (2.3) | 0 (0) | 0 (0) | 1 (2.3) |
| Dry mouth | 1 (2.3) | 0 (0) | 0 (0) | 1 (2.3) |
| Dry skin | 1 (2.3) | 0 (0) | 0 (0) | 1 (2.3) |
| Ejection fraction decreased | 1 (2.3) | 0 (0) | 0 (0) | 1 (2.3) |
| Epistaxis | 1 (2.3) | 0 (0) | 0 (0) | 1 (2.3) |
| Eye pain | 1 (2.3) | 0 (0) | 0 (0) | 1 (2.3) |
| Headache | 1 (2.3) | 0 (0) | 0 (0) | 1 (2.3) |
| Hyponatremia | 0 (0) | 1 (2.3) | 0 (0) | 1 (2.3) |
| Hypophosphatemia | 1 (2.3) | 0 (0) | 0 (0) | 1 (2.3) |
| Immune system disorders—other, specify | 1 (2.3) | 0 (0) | 0 (0) | 1 (2.3) |
| Infusion-related reaction | 1 (2.3) | 0 (0) | 0 (0) | 1 (2.3) |
| Nail infection | 1 (2.3) | 0 (0) | 0 (0) | 1 (2.3) |
| Noncardiac chest pain | 1 (2.3) | 0 (0) | 0 (0) | 1 (2.3) |
| Paronychia | 1 (2.3) | 0 (0) | 0 (0) | 1 (2.3) |
| Respiratory, thoracic, and mediastinal disorders | 1 (2.3) | 0 (0) | 0 (0) | 1 (2.3) |
| Sinus tachycardia | 1 (2.3) | 0 (0) | 0 (0) | 1 (2.3) |
| Skin/subcutaneous tissue disorders; others, specify | 1 (2.3) | 0 (0) | 0 (0) | 1 (2.3) |
| Urinary tract infection | 1 (2.3) | 0 (0) | 0 (0) | 1 (2.3) |

a dose escalation of neratinib might yield improved tolerability. Patient-reported gastrointestinal symptoms were collected during cycles 1-4 (data forthcoming) and will further inform questions on quality of life impact.

We acknowledge several study limitations. Although we observed promising activity of neratinib plus T-DM1, due to early trial closure during the COVID-19 pandemic, we could not fully carry out our preplanned estimations of statistical significance. In addition, because of the small sample size, we could not analyze potential determinants of intracranial response. In particular, due to the timing of study enrollment, no patient had received prior tucatinib and only a few had received prior T-DXd, limiting our evaluation of efficacy in patients exposed to these CNS-penetrating agents. However, we highlight that our trial assessed a novel combination of HER2-directed drugs delivered in efforts to overcome resistance in a cohort of patients with high medical need, multiple lines of prior therapy, and limited therapeutic options. Our results add to the growing list of active agents in this space, offering another therapeutic option in those with recurrent CNS progression.

In conclusion, we report promising CNS activity of neratinib plus T-DM1 in those naive to CNS treatments, or pretreated with neurosurgery, radiation, or T-DM1. Continued study of CNS-penetrant molecules and highly effective combinations will be critical to improve the outcomes in this therapeutic space, portending improved brain disease control and survival, along with better quality of life and neurological functioning. Further, efforts to define the optimal sequencing of regimens are warranted, particularly as the number of CNS-active regimens increases.

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## DISCLOSURE

RAF reports institutional funding for Puma (no salary support) for this trial and spousal equity in Firefly Health. KLS reports employment at AstraZeneca during 2023, current employment and stock ownership at Merck, institutional research funding from Pfizer, and spousal stock at AbbVie and Abbott Labs. AMB reports serving as a consultant for AstraZeneca, Pfizer, Novartis, Lilly, Genentech/Roche, Seagen (now Pfizer), Daiichi-Sankyo, Merck, Agendia, Sanofi, Puma, and Myriad; and research support from Agendia and AstraZeneca. CCOS reports research funding to Mayo Clinic from Eisai, Genentech, Bavarian Nordic, Sermonix, Seagen (now Pfizer), Tesaro, and Nference Inc.; and service on advisory boards for Seagen and AstraZeneca. CVP reports royalties for writing from UpToDate. JRN reports institutional research funding for SCALP from Paxman Coolers Ltd. NUL reports institutional research support from Genentech (and Zion Pharmaceutical as part of GNE), Pfizer, Merck, Seagen (now Pfizer), Olema Pharmaceuticals, and AstraZeneca; consulting honoraria from Puma, Seagen, Daiichi-Sankyo, AstraZeneca, Olema Pharmaceuticals, Janssen, Blueprint Medicines, Stemline/Menarini, Artera Inc. and Eisai; book royalties from UpToDate; and travel support from Olema Pharmaceuticals. All remaining authors have declared no conflicts of interest.

## DATA SHARING

The trial protocol and consent are available for sharing with interested investigators. The aggregated data used for the analyses in this manuscript are available upon request to the corresponding author. However, because the consent form did not include permission to share data from this study, we are not able to provide deidentified, individualized data to other researchers.

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