

## Background

- Central nervous system (CNS) metastases from HER2-positive breast cancer present a clinical challenge due to the limited availability of evidence-based treatments:
- In early-stage disease, the brain is a common first site of metastasis after current HER2-directed adjuvant regimens (~35–55% of distant recurrences).<sup>1-3</sup>
- In the metastatic setting, 30–55% of patients develop CNS metastases, highlighting the need for multiple lines of safe and effective CNS-directed treatments.<sup>4</sup>
- Neratinib, an irreversible small-molecule pan-HER tyrosine kinase inhibitor, has demonstrated efficacy in both the prevention<sup>5,6</sup> and treatment<sup>7-9</sup> of CNS metastases from HER2-positive breast cancer.
- In the recent phase 3 NALA trial:
  - Neratinib + capecitabine (N+C) significantly improved progression-free survival (PFS) compared with lapatinib + capecitabine (L+C) in patients with HER2-positive metastatic breast cancer who had received ≥2 previous HER2-directed regimens for metastatic disease (hazard ratio [HR] 0.76; 95% confidence interval [CI], 0.63–0.93; p=0.0059).<sup>8</sup>
  - Fewer interventions for CNS disease were required with N+C vs L+C (p=0.043).<sup>8</sup>
  - Intracranial overall response rate among patients with ≥1 target CNS lesion (n=32) was 26.3% with N+C vs 15.4% with L+C.<sup>10</sup>

## Objective

- We report efficacy and safety outcomes in the subgroup of patients from NALA who had CNS metastases at baseline, with a particular focus on CNS-specific endpoints.

## Methods

### Study design

- NALA was an international, randomized, multicenter, open-label, active-controlled, parallel-design study conducted in 28 countries (Clinicaltrials.gov: NCT01808573).<sup>8</sup>
- Patients were randomly assigned (1:1) to neratinib 240 mg once daily plus capecitabine 750 mg/m<sup>2</sup> twice daily or lapatinib 1250 mg once daily plus capecitabine 1000 mg/m<sup>2</sup> twice daily orally.
- Neratinib and lapatinib were given continuously, whereas capecitabine was administered on days 1–14 of a 21-day cycle.
- Prophylactic anti-diarrheal medication with loperamide was mandated in the N+C arm for the duration of cycle 1.

### Patients

- Patients with CNS metastases at baseline had treated or untreated disease in the 'brain' as assessed by the investigator at enrollment.
- Baseline MRI and screening for CNS metastases was not mandated; CNS imaging was performed if clinically indicated per investigator assessment.
- CNS-specific eligibility criteria were as follows:
  - Asymptomatic patients with metastatic brain disease, including leptomeningeal disease (LMD), on stable doses of corticosteroids (without dose limit) for brain metastases for ≥14 days prior to randomization were eligible;
  - Previous surgery and radiotherapy was permitted if completed within 28 days and 14 days, respectively, before starting study treatment;
  - Patients with progressive, symptomatic or unstable brain metastases were not allowed.

## Assessments

- Tumor assessments were performed using MRI or CT at baseline and then every 6 weeks; ad-hoc CNS imaging was performed if clinically indicated per investigator assessment.
- Tumor responses were evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
- Patients who discontinued treatment were contacted every 12 weeks to collect data concerning interventions for CNS disease, and for survival status.

## Endpoints

- Protocol-defined:
  - Independently adjudicated PFS and overall survival (OS).
  - Time to intervention for metastatic CNS disease: time from randomization to start of therapy for CNS disease, with interventions including anti-cancer medication, cancer-related radiation therapy, cancer-related surgery/procedure, or concomitant medication/therapy.
- Ad hoc:
  - CNS-PFS: time from randomization to disease progression in the brain or death from any cause, whichever occurred first (scans centrally read).

## Statistical methods

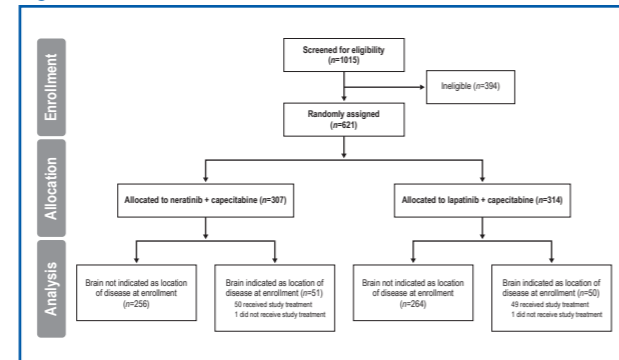
- Time-to-event endpoints were analysed using the Kaplan-Meier method, and treatment groups compared using a log-rank test and Cox proportional hazards model to estimate HR and 95% CI.
- Restricted mean survival time method was used as a sensitivity analysis for PFS and OS at predefined timepoints of 24 and 48 months, respectively.
- Cumulative incidence of interventions for metastatic CNS disease was analysed by competing risks analysis and tested via Gray's method.
- All analyses are descriptive without multiplicity adjustment.

## Results

### Patients

- Of 621 patients randomized to study treatment, 101 (16.3%) had asymptomatic CNS metastases at baseline (N+C, n=51; L+C, n=50) (Figure 1).
- Within the CNS subgroup:
  - Mean age 54 (range, 25–75) years, 58 patients (57.4%) had an ECOG performance status of 1, and 51 (50.5%) had hormone receptor-positive disease;

Figure 1. Patient flowchart



- Demographics and disease characteristics were generally well balanced between treatment groups and similar overall to the intention-to-treat population;
- 81 patients (80.2%) had received prior CNS-directed radiotherapy and/or surgery;
- 21 patients (20.8%) reported taking corticosteroids, and 10 patients (9.9%) reported taking anti-epileptics at baseline;
- 70 patients had baseline CNS scans that underwent retrospective central radiology review, 3 of whom had LMD (N+C, n=2; L+C, n=1). Baseline CNS scans were not available for the remaining 31 patients.
- Median duration of study treatment was 5.7 months (range, 0.4–28.6) for neratinib and 3.5 months (range, 0.5–20.8) for lapatinib.
- Study cut-off date: September 28, 2018.

## Efficacy

- Efficacy findings are summarized in Table 1 and Figures 2 & 3.

Table 1. Efficacy outcomes in patients with CNS disease at baseline

	CNS metastases at baseline (n=101)	
	N+C (n=51)	L+C (n=50)
<b>Progression-free survival*</b>		
Hazard ratio (95% CI)		0.66 (0.41–1.05)
P-value		0.0741
Restricted mean PFS <sup>b</sup> , months	7.8	5.5
Difference, months		2.3
<b>Overall survival</b>		
Hazard ratio (95% CI)		0.90 (0.59–1.38)
P-value		0.6352
Restricted mean OS <sup>b</sup> , months	16.4	15.4
Difference, months		1.0

## CNS-specific outcomes

	N+C (n=51)	L+C (n=50)
<b>Time to intervention for CNS disease</b>		
12-month cumulative incidence <sup>c</sup> , %	25.5	36.0
P-value		0.430
<b>CNS progression-free survival</b>		
Median, months	12.4	8.3
Hazard ratio (95% CI)		0.62 (0.32–1.18)
P-value		0.143

CI, confidence interval; CNS, central nervous system; L+C, lapatinib + capecitabine; N+C, neratinib + capecitabine.  
<sup>a</sup>Independently adjudicated; <sup>b</sup>Restriction prespecified as 24 months for progression-free survival and 48 months for overall survival; <sup>c</sup>Percentage requiring intervention for CNS disease (competing risk model)

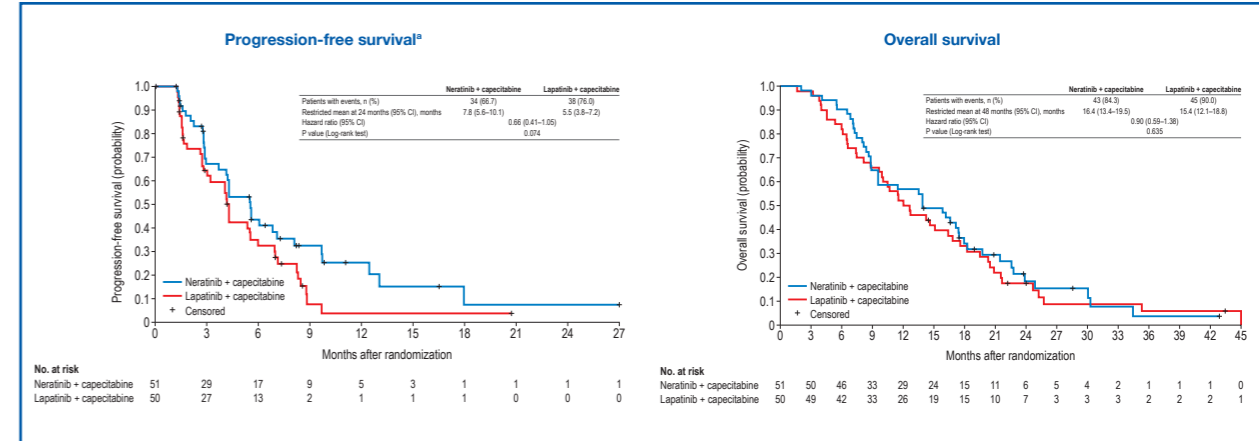
## Leptomeningeal disease (LMD)

- Among patients with LMD at enrollment (n=3):
  - Two patients treated with N+C had disease progression after 5.6 and 9.8 months, and OS times of 17.4 and 19.8 months, respectively;
  - One patient received L+C and had disease progression after 4.3 months and an OS of 6.5 months.

## Safety

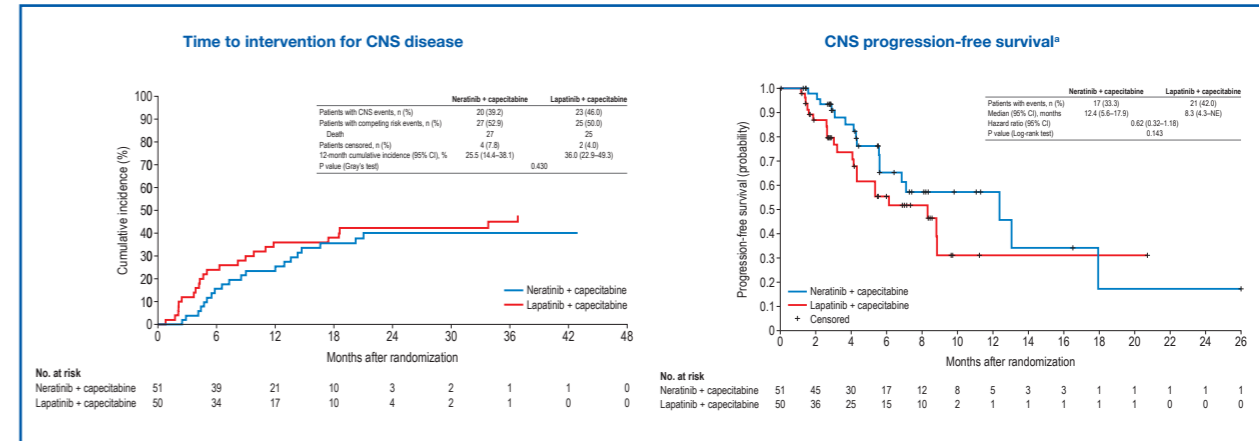
- Safety profile in patients with CNS metastases was consistent with that observed in the overall NALA safety population.<sup>8</sup>
- Diarrhea, nausea, vomiting, and palmar-plantar erythrodysesthesia syndrome were the most common adverse events.
- Common CNS adverse events (grade 1–4) included headache (N+C, 18% vs L+C, 29%), dizziness (18% vs 16%), hemiparesis (4% vs 4%), seizure (4% vs 4%), and gait disturbance (0% vs 8%).
- CNS events were slightly more common in the CNS subgroup than the overall NALA safety population.<sup>8</sup>

Figure 2. Progression-free survival and overall survival in patients with CNS metastases at baseline



\*Independently adjudicated.

Figure 3. CNS-specific outcomes in patients with CNS metastases at baseline



\*Scans centrally read

## Conclusions

- The data suggest an association between N+C and improved PFS and CNS outcomes in patients with CNS metastases from HER2-positive metastatic breast cancer compared with L+C in the phase 3 NALA trial:
  - Findings are consistent with three other prospective studies (NEFERT-T, TBCRC-022, ExteNET), which showed improved CNS outcomes with neratinib-based regimens in the treatment and prevention of CNS metastases from HER2-positive breast cancer.<sup>5-7,9</sup>
  - A unique feature of NALA was the inclusion of patients with LMD, two of whom were treated with N+C with good outcomes:
    - Similar findings were reported with N+C in patients with LMD in the phase 2 TBCRC-022 study.<sup>9</sup>
  - Our findings support a role for neratinib as a systemic treatment option in the management of patients with HER2-positive brain metastases following antibody-based HER2-directed therapies.

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