Impact of neratinib plus capecitabine on outcomes in HER2-positive metastatic breast cancer patients with central nervous system disease at baseline: Findings from the phase 3 NALA trial

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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).[1–3]
  - In the metastatic setting, 30–55% of patients develop CNS metastases, highlighting the need for multiple lines of safe and effective CNS-directed treatments.[4]
- Neratinib, an irreversible small-molecule pan-HER tyrosine kinase inhibitor, has demonstrated efficacy in both the prevention[5,6] and treatment[7–9] 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).[8]
  - Fewer interventions for CNS disease were required with N+C vs L+C (p=0.043).[8]
  - 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.[10]

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):[8]
  - Patients were randomly assigned (1:1) to neratinib 240 mg once daily plus capecitabine 750 mg/m^2 twice daily or lapatinib 1250 mg once daily plus capecitabine 1000 mg/m^2 twice daily orally.
  - Neratinib and lapatinib were given continuously, whereas capecitabine was administered on days 1–14 of a 21-day cycle.
  - Prophylactic antidiarrheal 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

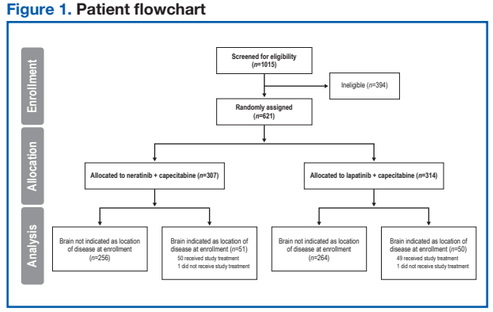
- Time-to-event endpoints were analysed using the Kaplan-Meier method, and treatment groups compared using a log-rank test and Cox proportional hazards model to estimate HR and 95% CI.
- Restricted mean survival time method was used as a sensitivity analysis for PFS and OS at predefined timepoints of 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)
Progression-free survival[a]			
Hazard ratio (95% CI)		0.66 (0.41–1.05)	
P-value		0.0741	
Restricted mean PFS[b], months	7.8		5.5
Difference, months		2.3	
Overall survival			
Hazard ratio (95% CI)		0.90 (0.59–1.38)	
P-value		0.6352	
Restricted mean OS[b], months	16.4		15.4
Difference, months		1.0	
CNS-specific outcomes			
Time to intervention for CNS disease			
12-month cumulative incidence[c], %	25.5		36.0
P-value		0.430	
CNS progression-free survival			
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.
[a]Independently adjudicated; [b]Restriction prespecified as 24 months for progression-free survival and 48 months for overall survival; [c]Percentage requiring intervention for CNS disease (competing risk model)

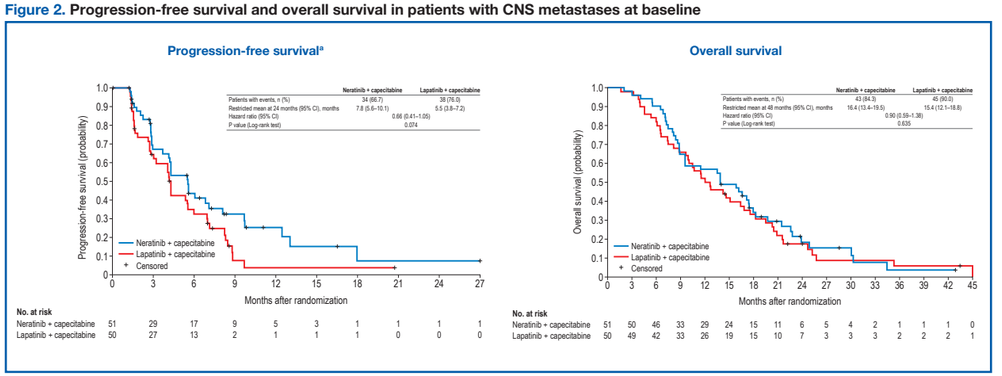
Leptomeningeal disease (LMD)

- 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

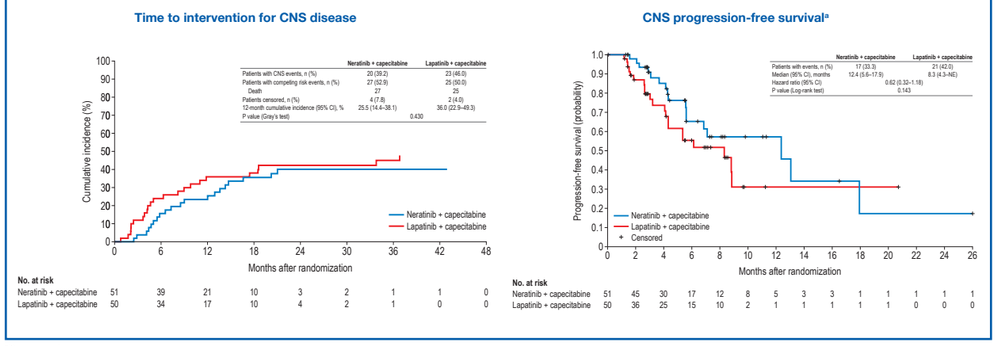
- Safety profile in patients with CNS metastases was consistent with that observed in the overall NALA safety population.[8]
- Diarrhea, nausea, vomiting, and palmar-plantar erythrodysesthesia syndrome were the most common adverse events.
- Common CNS adverse events (grade 1-4) included headache (N+C, 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.[8]

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



[a]Independently adjudicated.

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



[a]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 (NeRERT-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.[5–7,9]
- 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.[9]
- 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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