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 surgery (HER2+ directed adjuvant regimen – 35–55% of distant recurrences).1,2
- In the metastatic setting, 30–50% of patients develop CNS metastases, highlighting the need for new approaches for safe and effective CNS-directed treatments.3

Methods

- **Study design** – NALA was an international, randomized, multi-center, open-label, active-controlled, parallel-arms clinical trial (ClinicalTrials.gov, NCT01969387).4
- **Randomization** – Patients were randomly assigned 1:1 to receive neratinib plus capecitabine (N+C) or lapatinib plus capecitabine (L+C) if they had HER2+ positive metastatic breast cancer who had received ≥2 previous HER2-directed regimen for metastatic disease (Kaplan-Meier [HR] 0.76; 95% confidence interval [CI], 0.63–0.93; p=0.0059).
- **Assessments** – Tumor assessments were performed using MRI at CT at baseline and then every 6 weeks. Ad hoc CNS imaging was performed if clinically indicated by investigator assessment.
- **Primary Endpoint** – Tumor response was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
- **Secondary Endpoints** – Time to intervention for metastatic CNS disease; time to start of therapy for CNS disease; with interventions including anticancer medication, cancer-related radiation therapy, cancer-related surgical procedure, or concomitant medication therapy.
- **Statistical methods** – Time-to-event endpoints were analyzed using the Kaplan-Meier method, and log-rank test. Cox proportional hazards model was estimated for HR and 95% CI. Restriction mean survival time method was used as a sensitivity analysis to evaluate time to death from any cause, whichever occurred first (scan centrally read).

Results

- **Patient flowchart**
- **N+C**
  - Median age 54 (range, 25–75) years, 55 patients (57%) had an ECOG performance status of 0, and 20 (22%) had history of recent chemotherapy.
  - **L+C**
  - Median age 56 (range, 25–75) years, 55 patients (57%) had an ECOG performance status of 0, and 20 (22%) had history of recent chemotherapy.

- **N+C**
  - **N+C** patients randomized to study treatment, 101 (103.3%) had asymptomatic CNS metastases at baseline (N+C, n=51; L+C, n=50).
  - **L+C**
  - **L+C** patients randomized to study treatment, 101 (103.3%) had asymptomatic CNS metastases at baseline (L+C, n=51).

- **Within the CNS subgroup**
  - Mean age 54 (range, 25–75) years, 55 patients (57%) had an ECOG performance status of 0, and 20 (22%) had history of recent chemotherapy.

- **Time to intervention for CNS disease**
  - Median (95% CI), months; second CNS LMD event (in L+C) was 24.9 (95% CI) for neurosurgeries (p=0.074).

- **Overall survival**
  - Hazard ratio (95% CI)
  - Median (95% CI), months
  - N+C vs L+C, 19 (9.8) vs 15.4 (12.8); 51 vs 36, respectively.

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 (NEJ17-1, BCIRG-022, E2144), which showed improved CNS outcomes with neratinib in the treatment of HER2+ breast cancer and prevention of CNS metastases from HER2+ positive breast cancer subgroups.1,2,5
- A unique feature of NALA was the inclusion of patients with LMD, two of whom were treated with N+C with good outcomes:
  - One patient was reported with N+C in patients with LMD in the phase 2 BCIRG-022 study.6
  - Our findings support a role for neratinib as a systemic treatment option in the management of patients with HER2+ positive breast cancer metastases following anti-HER2-directed treatments.

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References


Figure 1. Tumor response in N+C and L+C patients

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

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