Impact of neratinib on development and progression of central nervous system metastases in patients with HER2-positive metastatic breast cancer: Findings from the NALA, NEfERT-T, and TBCRC 022 trials

Ahmad Awada,[1] Adam Brufsky,[2] Cristina Saura,[3] Rachel A. Freedman,[4] Nancy U. Lin,[4] Judith Bebchuk,[5] Feng Xu,[5] and Sara A. Hurvitz[6]

[1]Institut Jules Bordet, Université Libre de Bruxelles, Bruxelles, Belgium; [2]Magee-Womens Hospital of UPMC, Pittsburgh, PA, USA; [3]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [4]Dana-Farber Cancer Institute, Boston, MA, USA; [5]Puma Biotechnology Inc, Los Angeles, CA, USA; [6]University of California, Los Angeles/Jonsson Comprehensive Cancer Center

#P2-20-01

Background

- Although HER2-directed therapies have improved the control of systemic disease and survival of patients with HER2-positive breast cancer, central nervous system (CNS) metastases present a clear unmet medical need:
  - Approximately one-half of patients with advanced breast cancer eventually develop brain metastases.[1,2]
  - Even though outcomes for patients with brain metastases from HER2-positive breast cancer have improved over time, recurrent CNS events remain a major cause of morbidity and adversely impact overall survival for many patients.[3]
  - Treatment options, particularly systemic approaches, remain limited.
- Neratinib (Nerlynx®; Puma Biotechnology Inc., Los Angeles, CA) is an irreversible small-molecule tyrosine kinase inhibitor of HER1, HER2 and HER4[4] that is licensed for use as extended adjuvant therapy in early HER2-positive breast cancer.
- Data from clinical trials in the advanced breast cancer setting – Neratinib Against Lapatinib in Advanced breast cancer (NALA),[5] NEfERT-T,[6] and Translational Breast Cancer Research Consortium (TBCRC) 022[3] – suggest that neratinib-based therapy has activity in patients with CNS metastases from HER2-positive breast cancer.
- We review the data from these three studies, with a specific focus on CNS outcomes, and report a combined analysis of survival outcomes in the presence or absence of a CNS response.

Methods

- Data from the following studies were included:
  - **NALA:** multicenter, randomized, controlled, open-label, phase III trial of neratinib plus capecitabine versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer previously treated with ≥2 HER2-directed regimens (ClinicalTrials.gov: NCT01808573);[5]
  - **NEfERT-T:** multicenter, randomized, controlled, open-label, phase II trial of neratinib plus paclitaxel versus trastuzumab plus paclitaxel in previously untreated metastatic HER2 positive breast cancer (ClinicalTrials.gov: NCT00915018);[6]
  - **TBCRC 022:** multicenter, open-label, phase II trial of neratinib plus capecitabine in patients with HER2-positive breast cancer and brain metastases (ClinicalTrials.gov: NCT01494662); efficacy data from cohort 3A (received no prior lapatinib) from this study are presented.[3]
- Details of the key eligibility criteria and treatments for each study are presented in Figure 1.

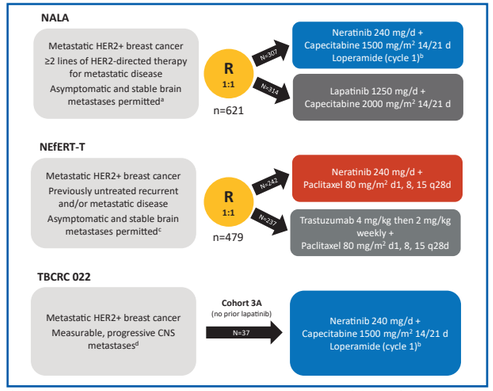
Study endpoints

- Endpoints, with CNS outcomes highlighted, for each of the studies are shown in Table 1.

CNS objective responses

- CNS objective response rates in patients with measurable CNS lesions at baseline were summarized for each individual study:
  - TBCRC 022 used composite criteria for determination of CNS objective response rate, which included volumetric measurements of target lesions, as well as lack of CNS progression, no worsening of neurologic status, or increase in corticosteroid dose;
  - In NALA and NEfERT-T, MRI brain scans were not required at baseline but performed at the discretion of the local investigator; CNS objective response rate was based on measurable target CNS lesions determined by the investigator based on RECIST v1.1.
- Progression-free survival (PFS) and overall survival (OS) were correlated with CNS objective response, when all three studies were combined.
  - A landmark analysis was used, i.e., all patients included were in the study for at least 16 weeks.

Figure 1. Study design: NALA, NEfERT-T and TBCRC 022



[a]Patients with asymptomatic metastatic brain disease who have been on a stable dose of corticosteroids for treatment of brain metastases for at least 14 days prior to randomization
[b]Mandatory loperamide prophylaxis: NALA – initial dose 4 mg, then 2 mg every 4 hours for 3 days, then loperamide 2 mg every 6–8 hours until the end of cycle 1; TBCRC 022 – loperamide 16 mg/day during cycle 1
[c]Patients with newly detected asymptomatic CNS metastases, a history of CNS metastases, or spinal involvement with cord compression were eligible provided that they were asymptomatic, had been treated definitively with surgery and/or radiation therapy, and had not received anticonvulsants or steroids within 4 weeks before study treatment
[d]CNS progression despite prior whole-brain radiotherapy, stereotactic radiosurgery, surgery, CNS-directed systemic therapy, or any combination was required for the study.
Abbreviations: CNS, central nervous system; d, day; q, every; R, randomization

Table 1. Study endpoints: NALA, NEfERT-T and TBCRC 022

	NALA	NEfERT-T	TBCRC 022
Primary	PFS (centrally confirmed) OS	PFS	**CNS ORR[a]**
Secondary	PFS (investigator-assessed) ORR[b] CBR[b] DoR	ORR[b] CBR[b] DoR	**CNS response (RANO-BM)[c]** PFS (centrally confirmed) Site of first progression Extracranial response
	Time to intervention for symptomatic CNS metastases	**Frequency of and time to symptomatic or progressive CNS lesions**	OS
	Safety Quality of life	Safety	Safety

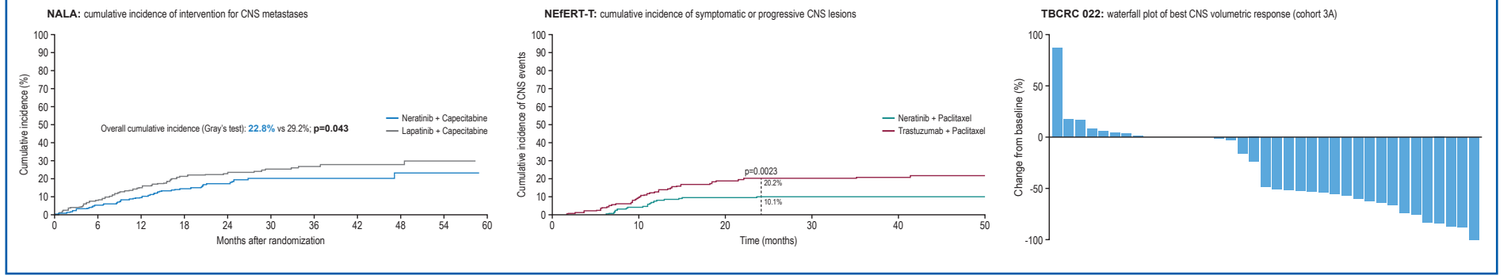
[a]TBCRC 022 used volumetric measurements for the determination of CNS ORR. Composite criteria of disappearance of all target lesions (complete response) or a 50% or greater reduction in the sum of CNS target lesion volumes (partial response), without progression of non-target lesions, new lesions, clear worsening of neurologic status, or increase in corticosteroid dose (for neurologic symptoms)
[b]RECIST v1.1 (NALA) and v1.0 (NEfERT-T) requiring confirmation
[c]Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria[4]
Abbreviations: CBR, clinical benefit rate; CNS, central nervous system; DoR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; RECIST, Response Evaluation Criteria in Solid Tumors

Results

NALA

- NALA met its primary objective, with a significant PFS benefit (HR 0.76; 95% CI 0.63–0.93; p=0.0059) and a trend towards improved OS with neratinib-capecitabine versus lapatinib-capecitabine (HR 0.88; 0.72–1.07; p=0.2086).
- Median treatment duration was 5.7 months for neratinib and 4.4 months for lapatinib.
- CNS endpoints favored neratinib-capecitabine:
  - Cumulative incidence estimated based on a competing risk model of time to interventions for symptomatic CNS disease was significantly lower with neratinib-capecitabine versus lapatinib-capecitabine (22.8% vs 29.2%, respectively; p=0.043) [Figure 2].
  - Fewer patients in the neratinib-capecitabine group (n=55, 18%) required interventions for symptomatic CNS disease versus lapatinib-capecitabine (n=75, 24%).

Figure 2. CNS outcomes: NALA, NEfERT-T and TBCRC 022



NEfERT-T

- Median PFS, the primary study endpoint, was 12.9 months in both study groups (HR 1.02, 95% CI 0.81–1.27; p=0.89).
- Median duration of treatment was 10.3 and 10.0 months for neratinib-paclitaxel and trastuzumab-paclitaxel, respectively.
- Estimated 2-year cumulative incidence of CNS progression by competing risks method was 10.1% with neratinib-paclitaxel and 20.2% with trastuzumab-paclitaxel (p=0.002) [Figure 2].
- Risk of CNS progression was reduced with neratinib-paclitaxel versus trastuzumab-paclitaxel based on a Cox proportional hazards model without considering competing risks (HR 0.45, 95% CI 0.26–0.78; p=0.0036).

TBCRC 022

- Composite CNS objective response rate was 49% (n=18) in cohort 3A; all responses were partial responses [Figure 2].
- Median number of 21-day treatment cycles initiated was 6 (range, 1–30).
- CNS responses by RANO-BM criteria were documented in 24% (n=9) of patients.

CNS objective responses

- Across all three studies, a total of 75 patients had measurable CNS lesions at baseline and were evaluable for CNS objective response rate:
  - 32 patients in NALA (neratinib-capecitabine, n=19; lapatinib-capecitabine, n=13);
  - 6 patients in NEfERT-T (neratinib-paclitaxel, n=3; trastuzumab-paclitaxel, n=3);
  - 37 patients in TBCRC 022.
- CNS objective responses were observed in all studies (Table 2).

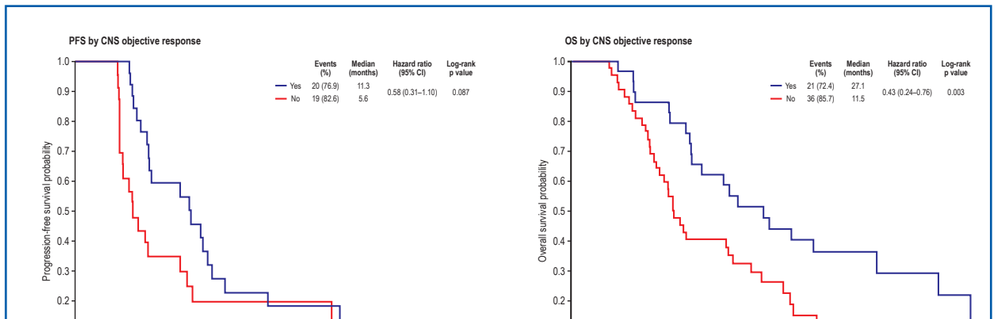
Table 2. CNS objective response rates (NALA, NEfERT-T and TBCRC 022)

CNS objective response rate, n (%)[a]				
NALA		NEfERT-T		TBCRC 022
Neratinib + capecitabine	Lapatinib + capecitabine	Neratinib + paclitaxel	Trastuzumab + paclitaxel	Neratinib + capecitabine
5/19 (26.3)	2/13 (15.4)	3/3 (100.0)	1/3 (33.3)	18/37 (48.6)

[a]One complete response in the NALA neratinib-capecitabine arm; all other responses were partial.

- CNS objective response was associated with improvements in both PFS (HR 0.58; 95% CI 0.31–1.10; p=0.087) and OS (HR 0.43; 95% CI 0.24–0.76; p=0.003) when data for all studies were combined (Figure 3).

Figure 3. Landmark analysis: PFS[a] and OS by CNS objective response (NALA, NEfERT-T and TBCRC 022)



[a]PFS for CNS and systemic disease.

Conclusions

- Neratinib demonstrated notable and consistent activity against CNS metastases in patients with HER2 positive breast cancer in two independent phase II studies and one phase III study,[3,5,6] with significant benefits for predefined CNS prevention endpoints first reported in NEfERT-T and replicated in NALA.[5,6]
- Analyses of patients with baseline CNS lesions demonstrated shrinkage of CNS lesions and promising CNS objective response rates with neratinib-based therapy in all 3 studies in different settings (i.e. progressive CNS metastases, asymptomatic and stable CNS metastases).
- Patients with CNS objective responses experienced longer PFS and OS than those without CNS objective responses.

References

1. Lin NU, et al. Clin Cancer Res 2013;19:6404–18.
2. Pestalozzi BC, et al. Lancet Oncol 2013;14:244–8.
3. Freedman RA, et al. J Clin Oncol 2019;37:1081–89.
4. Rabindran SK, et al. Cancer Res 2004;64:3958–65.
5. Saura C, et al. J Clin Oncol 2019;15(Suppl): abstract 1002 and oral presentation.
6. Awada A, et al. JAMA Oncol 2016;2:1557–64.
7. Lin NU, et al. Clin Cancer Res 2009;15:1452–9.
8. Lin NU, et al. Lancet Oncol 2015;16:e270–8.

Acknowledgements

Puma Biotechnology Inc. provided funding support for NALA, NEfERT-T and TBCRC 022, as well as editorial support by Miller Medical Communications. Funding support was also provided to the TBCRC by its foundation partners: the Breast Cancer Research Foundation and Susan G. Komen.

Presented at the San Antonio Breast Cancer Symposium (SABCS), Dec 10–14, 2019, San Antonio, Texas, USA