The impact of neratinib with or without anti-diarrheal prophylaxis on health-related quality of life in HER2+ early-stage breast cancer: analyses from the ExteNET and CONTROL trials

Suzette Delaloge,[1] Sara Hurvitz,[2] Nancy Chan,[3] Ron Bose,[4] Rachel C. Jankowitz,[5] Michael Thirlwell,[6] István Láng,[7] Albert ten Tije,[8] Maureen Trudeau,[9] Cynthia Osborne,[10] Zhen-Zhou Shen,[11] Deepa Lalla,[12] Feng Xu,[12] Daniel Hunt,[12] Elizabeth Olek,[12] Leanne McCulloch,[12] Debu Tripathy,[13] Hope S. Rugo,[14] Jo Chien,[14] Arlene Chan,[15] Carlos H. Barcenas[13]

[1]Institut Gustave Roussy, Villejuif, France; [2]UCLA Hematology / Oncology Clinical Research Unit, Los Angeles, CA, USA; [3]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; [4]Washington University School of Medicine, St Louis, MO, USA; [5]Magee-Womens Hospital UPMC, Breast Center, Pittsburgh, PA, USA; [6]McGill University Health Centre Cedars Cancer Centre, Montreal, Quebec, Canada; [7]Orszagos Onkologiai Intezet "B" Belgyogyaszati osztaly, Budapest, Hungary; [8]Amphia Ziekenhuis, Breda, The Netherlands; [9]Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; [10]Texas Oncology, PA, Dallas, TX, USA; [11]Shanghai Cancer Center, Fudan University, Shanghai, China; [12]Puma Biotechnology Inc., Los Angeles, CA, USA; [13]MD Anderson Cancer Center, Houston, TX, USA; [14]University of California San Francisco Comprehensive Cancer Center, San Francisco, CA, USA; [15]BCRC WA Hollywood Private Hospital, Perth, WA, Australia

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Introduction

- Neratinib, an irreversible pan-HER tyrosine kinase inhibitor, is approved for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified (HER2+) breast cancer, to follow adjuvant trastuzumab-based therapy.[1]
  - The international, randomized, placebo-controlled phase III ExteNET trial (NCT00878709)[2] showed that 1 year of neratinib 240 mg/day after trastuzumab-based (neo)adjuvant therapy significantly improved 2-year invasive disease-free survival (iDFS) (hazard ratio 0.66; 95% confidence interval [CI] 0.49–0.90; p=0.008),[1] and also had a durable iDFS benefit after 5 years' follow-up (hazard ratio 0.73; 95% CI 0.57–0.92; p=0.008).[3]
  - Diarrhea is the main side effect of neratinib. In ExteNET, where antidiarrheal prophylaxis was not mandated by the study protocol, grade 1/2 diarrhea was reported in 55% and 34% of patients in the neratinib and placebo groups, respectively, and grade 3 diarrhea occurred in 40% and 2%, respectively.[2]
- As neratinib-induced diarrhea occurs early in the course of treatment, a structured high-dose regimen of loperamide prophylaxis given for 1–2 cycles has been introduced to better manage this side effect.[4,5]
  - The phase II CONTROL study investigated the effectiveness of anti-diarrheal prophylaxis with loperamide alone or in combination with budesonide or colestipol in the prevention of neratinib-associated diarrhea.[5]
- Both ExteNET and CONTROL assessed patient-reported outcomes using the Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B), a validated instrument for the assessment of health-related quality of life (HRQoL) in breast cancer.[6]
  - Preliminary HRQoL findings from the CONTROL study were presented in 2017.[5] We report more detailed and mature HRQoL data from CONTROL, and perform an indirect comparison of the HRQoL findings from the CONTROL and ExteNET studies.[7]

Methods

Study design and patients

- ExteNET is an international, multicenter, randomized, double-blind, placebo-controlled phase III trial designed to compare neratinib versus placebo as extended adjuvant therapy in patients (n=2840) aged ≥18 years with early-stage HER2+ breast cancer who had completed trastuzumab-based (neo)adjuvant therapy (ClinicalTrials.gov: NCT00878709).
- CONTROL (PUMA-NER-6201) is an international, multicenter, sequential-cohort, open-label, phase II study investigating the effectiveness of antidiarrheal prophylaxis with loperamide alone or in combination with an anti-inflammatory treatment (budesonide) or a bile acid sequestrant (colestipol) in patients (n=466) aged ≥18 years with early-stage HER2+ breast cancer receiving neratinib and who had previously completed trastuzumab-based (neo)adjuvant therapy (ClinicalTrials.gov: NCT02400476).
- Patient-reported HRQoL was an exploratory outcome in both studies.

Assessments

- HRQoL was assessed using FACT B, version 4.0, and EuroQoL 5-Dimensions 5-level version; data for the FACT-B are presented here.
- The FACT-B is a validated 37-item questionnaire with subscales assessing physical, social, emotional, and functional well-being, as well as a breast cancer-specific subscale. A higher score indicates better HRQoL.
- HRQoL questionnaires were completed electronically by patients in both studies:
  - *ExteNET*: at baseline and months 1, 3, 6, 9, and 12 (end of treatment),
  - *CONTROL*: at baseline, cycles 2 (month 1), 4 (month 3), 7 (month 6), 10 (month 9), and 13 (month 12; end of treatment).

Data analysis

- In ExteNET, HRQoL evaluations were performed in the safety population, defined as patients who received ≥1 dose of study treatment.
- In CONTROL, HRQoL evaluations were performed in the HRQoL analysis population, defined as patients who had received ≥1 dose of study treatment, and had a baseline HRQoL assessment and ≥1 post baseline HRQoL assessment.
- Changes from baseline in observed scores were summarized descriptively and plotted over time.
- Changes in scores from baseline were considered to be clinically meaningful if greater than the clinically important difference (CID) of 7–8 points for the FACT B total score[8] and 2–3 points for each FACT-B subscale.[9]

Results

- In ExteNET, a total of 2840 patients were randomized to study treatment (neratinib, n=1420; placebo, n=1420).
- In CONTROL, as of October 2018, a total of 466 patients have been enrolled (loperamide, n=137; budesonide-loperamide, n=64; and colestipol-loperamide, n=136); additional cohorts assessing colestipol-loperamide prn and the impact of neratinib dose escalation are enrolling (data not reported).
- Baseline characteristics for the ExteNET and CONTROL study populations are shown in Table 1.

Table 1. Baseline characteristics: ExteNET and CONTROL

	ExteNET		CONTROL		
Variable	Neratinib (n=1420)	Placebo (n=1420)	Loperamide (n=137)	Budesonide-loperamide (n=64)	Colestipol-loperamide (n=136)
Female, %	100	100	100	100	98
Median (range) age, years	52 (25–83)	52 (23–82)	53 (30–86)	49 (29–78)	53 (26–78)
<65 years, %	88	88	85	91	86
≥65 years, %	12	12	15	9	14
Race, %					
White	82	80	83	78	71
Black	2	3	8	8	7
Asian	13	14	6	6	10
Other	3	3	4	8	13
ECOG performance status, %					
0	93	92	90	89	84
1	7	8	10	11	15
Missing	0	0	0	0	2
Tumor stage at diagnosis, %					
I	10	11	29	25	16
IIA, B	42	40	55	47	47
IIIA, B, C	31	30	15	23	27
Missing/unknown	17	19	2	5	10
Prior (neo)adjuvant therapy, %					
Trastuzumab	100	100	99	97	99
Taxanes	90	90	96	97	99
Anthracycline	77	77	26	28	23
Pertuzumab	–	–	40	61	62
Median (range) time from last dose to enrollment, months					
Trastuzumab	4.4 (0.2–30.9)	4.6 (0.3–40.6)	3.9 (0.1–12.1)	4.1 (0.5–12.1)	2.6 (0.0–12.0)
Pertuzumab	–	–	12.1 (3.3–22.3)	11.5 (2.6–20.0)	11.0 (0.6–20.0)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Treatment exposure

- In ExteNET, all patients have completed study treatment. Median duration of treatment was 11.6 months in the neratinib group and 11.8 months in the placebo group.[2]
- In CONTROL, as of October 2018, study treatment had been completed by 100% of patients in the loperamide and budesonide-loperamide cohorts, and 95% of patients in the colestipol-loperamide cohort. Median duration of neratinib treatment was 11.6, 12.0, and 11.9 months, respectively.

Discontinuation rates

- In ExteNET, 28% of patients in the neratinib group and 5% of patients in the placebo group discontinued treatment because of treatment-emergent adverse events, and 17% and <1%, respectively, discontinued because of diarrhea.
- In CONTROL, 41% of patients in the loperamide cohort, 17% in the budesonide-loperamide cohort, and 15% in the colestipol-loperamide cohort discontinued treatment because of treatment-emergent adverse events, and 20%, 11% and 4%, respectively, discontinued because of diarrhea.

HRQoL

- In ExteNET, 2407 patients were evaluable for FACT B (neratinib, n=1171; placebo, n=1236).
- In CONTROL, 228 patients were included in the HRQoL population (loperamide, n=40; budesonide-loperamide, n=62; colestipol-loperamide, n=126).

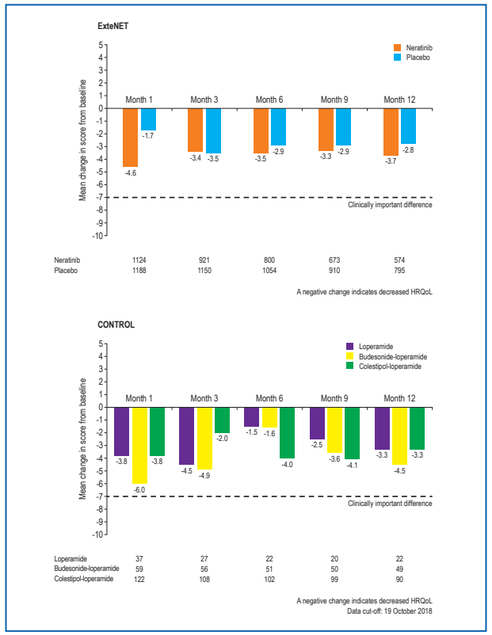
FACT-B completion rates

- In ExteNET, questionnaire completion rates were ≥85% from baseline to month 6 in both the neratinib and placebo groups; rates at later time-points were lower in both groups (69% to 79%) because of a protocol amendment (October 2011) that removed the requirement for HRQoL data collection.
- In CONTROL, questionnaire completion rates ranged from 76% to 100% across all time-points in the loperamide, budesonide-loperamide, and colestipol-loperamide cohorts.

FACT-B total scores

- Mean changes from baseline in FACT-B total scores by visit are shown in Figure 1.

Figure 1. Mean changes from baseline in FACT-B total scores by visit: ExteNET and CONTROL

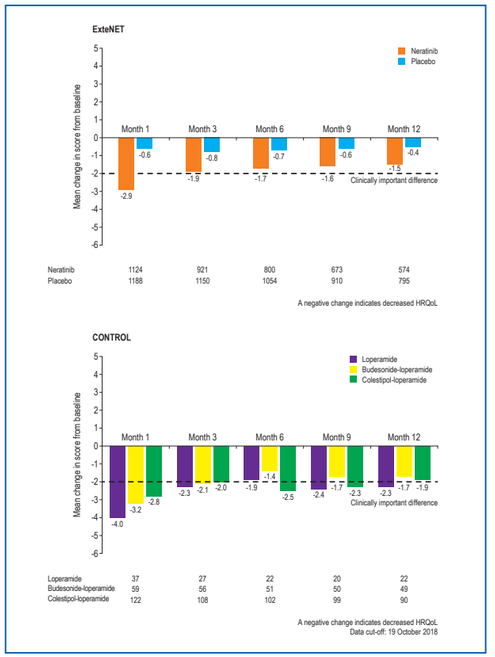


- In the ExteNET study:
  - A transient decrease in FACT-B total score was observed with neratinib at month 1 (mean change from baseline, –4.6 points) followed by recovery towards baseline.
  - Decreases were also evident in the placebo group, with mean changes from baseline ranging from –3.5 to –1.7 points during study treatment.
  - At month 3, mean changes from baseline were similar in neratinib and placebo arms. After month 3, neratinib arm had lower mean changes than placebo arm.
  - None of these changes reached clinically meaningful thresholds (7–8 points)[8] at any time point.
- In the CONTROL study:
  - FACT-B total scores decreased from baseline in all cohorts; mean changes from baseline ranged from –6.0 to –1.5 points over the course of study treatment.
  - In the cohorts that had completed follow-up (loperamide, budesonide-loperamide), the largest decreases in FACT-B total scores were evident during months 1 and 3 followed by lower decreases.
  - None of these changes reached clinically meaningful thresholds (7–8 points)[8] at any time point.

FACT-B physical well-being scores

- When all FACT-B subscales (n=5) were evaluated, physical well-being (PWB) was the only subscale where the CID threshold was crossed in both studies/trials.
- Mean changes from baseline in FACT-B PWB scores by visit are shown in Figure 2.
- In the ExteNET study:
  - In the neratinib arm, FACT-B PWB decreased at month 1 before improving at later visits
  - The mean change from baseline at month 1 with neratinib was –2.9 points and was greater than clinically meaningful thresholds (2–3 points);[9] changes at later time-points were all less than the CID threshold.

Figure 2. Mean changes from baseline in FACT-B physical well-being scores by visit: ExteNET and CONTROL



- In the CONTROL study:
  - Decreases in FACT-B PWB were observed in all CONTROL cohorts throughout study treatment, with largest changes from baseline observed at month 1.
  - In the loperamide and colestipol-loperamide cohorts, changes reached clinically meaningful thresholds (2–3 points)[9] at 4 out of 5 study visits, whereas in the budesonide-loperamide cohort, changes crossed the CID threshold during months 1 and 3 only.

Conclusions

- Extended adjuvant therapy with neratinib with or without anti-diarrheal prophylaxis was associated with decreases in HRQoL during treatment.
- While the FACT-B total score was lower at month 1, in subsequent time points, changes observed between neratinib and placebo arms were similar. Changes in the FACT-B total score did not cross the clinically important threshold at any time point in either CONTROL or ExteNET.
- With the exception of the FACT-B PWB subscale, HRQoL changes in other FACT-B subscales did not reach clinically meaningful thresholds in either CONTROL or ExteNET.
- Changes in FACT-B PWB reached the CID threshold at most time points in the loperamide and colestipol-loperamide cohorts (4 out of 5 visits), whereas meaningful changes were only observed early during treatment in the budesonide-loperamide cohort (months 1 and 3) and in the ExteNET neratinib group (month 1 only).
- Fewer patients in the budesonide-loperamide and colestipol-loperamide cohorts discontinued treatment because of treatment-emergent adverse events compared with the loperamide cohort and ExteNET neratinib group, leading to a greater proportion of patients with HRQoL evaluations at later months in these cohorts. This has helped to provide a more complete picture of HRQoL over time.
- Patient follow-up and enrollment in the colestipol-loperamide prn and neratinib dose escalation cohorts in the CONTROL study are ongoing.

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