Duration of extended adjuvant therapy with neratinib in early stage HER2-positive breast cancer after trastuzumab-based therapy: Exploratory analyses from the phase III ExteNET trial

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Introduction

- Neratinib (Puma Biotechnology Inc.) is an irreversible tyrosine kinase inhibitor of HER1, HER2 and HER4.[1]
  - ExteNET, an international, randomized, placebo-controlled phase III trial (N=2840), showed that a 1-year course of neratinib 240 mg/day after trastuzumab-based adjuvant therapy in women with early-stage HER2-positive breast cancer significantly improved invasive disease-free survival (iDFS) after a median follow-up of 2 years (hazard ratio 0.67; 95% confidence intervals [CI] 0.50–0.91; p=0.009).[2]
  - A prospectively planned sensitivity analysis after 5 years showed that iDFS improvements with neratinib were sustained and remained statistically significant compared with placebo (hazard ratio 0.73; 95% CI 0.57–0.92; p=0.008).[3]
- In the ExteNET trial, the rate of patient drop-out differed between groups, with more patients in the neratinib group ending treatment early (i.e. within 3 months), mainly because of adverse events occurring early during treatment.[2]
  - After 2 years of follow-up, the impact of early drop-outs on iDFS was investigated in a sensitivity analysis using imputed data and showed findings that were consistent with the primary analysis.[2]
  - Long-term follow-up data provided an opportunity to perform further analysis.
- This post hoc analysis of data from the ExteNET trial examined the efficacy and safety of neratinib among patients who ended treatment early (i.e. ≤3 months) as well as among those who remained on treatment longer (i.e. ≥11 months) after 5 years of follow-up.

Methods

Study design

- ExteNET is an ongoing multicenter, randomized, double-blind, placebo-controlled phase III trial (Clinicaltrials.gov identifier: NCT00878709).
  - Randomization was stratified by hormone receptor status (estrogen receptor [ER] and/or progesterone receptor [PR] positive *vs* ER and PR negative), prior trastuzumab regimen (administered concurrently *vs* sequentially with chemotherapy), and nodal status (0, 1–3, or ≥4 positive nodes).
- A protocol-specified sensitivity analysis of efficacy was performed after 5 years to evaluate the durability of effect of neratinib on efficacy; the findings from this analysis have been previously reported.[3]
  - The present exploratory analyses used the 5-year dataset from ExteNET.

Patients

- Women (N=2840) aged 18 years or older with histologically confirmed early-stage HER2-positive breast cancer without evidence of recurrence.
- Neo/adjuvant trastuzumab was completed up to 2 years (amended to 1 year) before randomization (81% of patients were randomized within 1 year of completing trastuzumab).

Treatment

- Neratinib 240 mg once daily or placebo orally for 1 year or until disease recurrence.
- Of note, antidiarrheal prophylaxis was not mandated by the study protocol.

Outcomes

- *Primary* – iDFS, defined as time from randomization to first occurrence of invasive ipsilateral tumor recurrence, invasive contralateral breast cancer, local/regional invasive recurrence, distant recurrence or death from any cause.
- *Secondary* – disease-free survival including ductal carcinoma in situ; time to distant recurrence; distant disease-free survival; central nervous system (CNS) recurrences; overall survival; and safety.

Statistical analysis

- The present analyses were exploratory.
- Patients in the neratinib group were categorized as follows:
  - ≤3 months of treatment (i.e. early discontinuation);
  - ≥11 months of treatment (i.e. an approximation for the median duration of treatment). In order to reduce guarantee-time bias,[4] patients who ended treatment because of disease recurrence before 11 months were also included in the ≥11 month subset. This group can be considered as "per protocol" patients who discontinued treatment due to disease recurrence or continued treatment to as close to the protocol-specified duration of 12 months.
  - The remaining patients (n=158), who received neratinib for >3 and <11 months, were excluded from the analysis as this subset was too small for reliable analysis.
- Efficacy and safety outcomes were presented for each neratinib subgroup and compared with the intention-to-treat (ITT) placebo group.
  - For time-to-event endpoints, Cox proportional hazards models were used to estimate hazard ratios (95% CIs), and Kaplan Meier methods were used to estimate event-free survival rates.
  - CNS recurrences were analyzed by the cumulative incidence competing risk method.
- As a sensitivity analysis, the analysis of iDFS was repeated after adjusting for key prognostic factors [i.e. time from last trastuzumab (≤1 *vs* >1 year), prior trastuzumab (concurrently *vs* sequentially with chemotherapy), age, menopausal status, nodal status, hormone receptor status, baseline performance status, radiotherapy, prior surgery, prior neoadjuvant therapy, region, race and histologic grade].
- Cut-off dates: March 2017 (efficacy data) and July 2014 (safety data).

Results

- The ITT population comprised 2840 patients (neratinib, n=1420; placebo, n=1420).
- The neratinib group was divided as follows:
  - Neratinib for ≤3 months (n=391).
  - Neratinib for ≥11 months (n=872), which included 858 patients who received neratinib for ≥11 months and 14 patients who ended treatment due to recurrence prior to 11 months.
- There were some imbalances between the two neratinib subgroups (≥10% difference) with regard to baseline characteristics (Table 1).
  - Patients who received neratinib for ≤3 months tended to be older, and were more likely to be enrolled from North American centers.

Efficacy

- The median duration of follow-up was 4.3 (interquartile range, 0.8–5.3) years in patients who received neratinib for ≤3 months, and 5.3 (interquartile range, 3.9–5.3) years in patients who received neratinib for ≥11 months.
- Patients who received neratinib for ≤3 months experienced a 15% reduction in the risk of iDFS relative to placebo (hazard ratio 0.85; 95% CI 0.57–1.24), whereas those who received neratinib for ≥11 months had a 32% relative risk reduction (hazard ratio 0.68; 95% CI 0.52–0.90) (Table 2).

Table 1. Baseline characteristics by duration of neratinib therapy

Characteristic	Neratinib			Placebo
	≤3 months (n=391)	≥11 months (n=872)	ITT (n=1420)	ITT (n=1420)
Median (IQR) age, years	55 (46–62)	51 (44–58)	52 (45–59)	52 (45–60)
<65 years	319 (82)	799 (92)	1247 (88)	1245 (88)
≥65 years	72 (18)	73 (8)	173 (12)	175 (12)
Region, n (%)				
North America	173 (44)	268 (31)	519 (370)	477 (34)
Western Europe, Australia and South Africa	140 (36)	298 (34)	487 (34)	532 (37)
Asia Pacific, East Europe and South America	78 (20)	306 (35)	414 (29)	411 (29)
Hormone receptor status, n (%)				
Positive	241 (62)	485 (56)	816 (57)	815 (57)
Negative	150 (38)	387 (44)	604 (43)	605 (43)
Nodal status, n (%)				
Negative	113 (29)	174 (20)	335 (24)	336 (24)
1–3 positive nodes	176 (45)	417 (48)	664 (47)	664 (47)
≥4 positive nodes	102 (26)	281 (32)	421 (30)	420 (30)
Prior trastuzumab regimen, n (%)				
Concurrent	247 (63)	530 (61)	884 (62)	886 (62)
Sequential	144 (37)	342 (39)	536 (38)	534 (38)

IQR = interquartile range; ITT = intention-to-treat

- The absolute iDFS benefit after 5 years was 0.7% among patients who received neratinib for ≤3 months and 3.3% among those who received neratinib for ≥11 months (Figure 1).
- Similar findings were observed when the analyses were adjusted for key prognostic factors: patients who received neratinib for ≤3 months experienced a 10% relative reduction in the risk of iDFS (adjusted hazard ratio 0.90; 95% CI 0.59–1.32), whereas those who received neratinib for ≥11 months had a 33% relative risk reduction (adjusted hazard ratio 0.67; 95% CI 0.50–0.88).

Table 2. iDFS by duration of neratinib therapy

(Sub)population	5-year iDFS rate, %				Hazard ratio (95% CI)
	n	Neratinib	n	Placebo	
≤3 months	391	88.4	1420	87.7	0.85 (0.57–1.24)
≥11 months	872	91.0	1420	87.7	0.68 (0.52–0.90)
Intention-to-treat	1420	90.2	1420	87.7	0.73 (0.57–0.92)[a]

CI = confidence interval; iDFS, invasive disease-free survival.
[a]Adjusted for stratification factors.

- Secondary efficacy outcomes also showed a trend towards improvement in both neratinib subgroups compared with placebo, although the benefits were consistently greater among patients who received neratinib for ≥11 months (Table 3).
- Overall survival data are not yet mature.

Figure 1. iDFS by duration of neratinib therapy

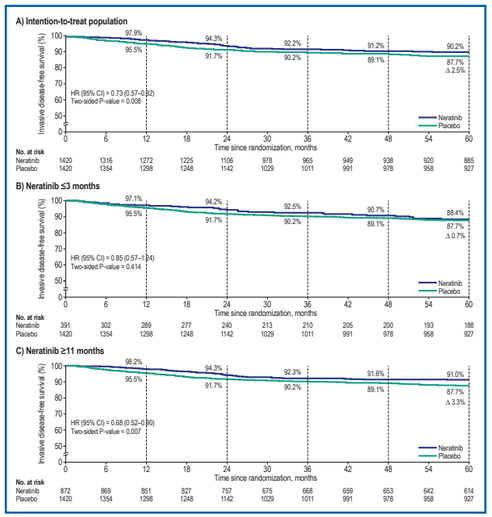

Table 3. Secondary efficacy endpoints by duration of neratinib therapy

	5-year event-free rate,[a] %				Hazard ratio (95% CI)
	n	Neratinib	n	Placebo	
DFS-DCIS					
≤3 months	391	87.5	1420	86.8	0.85 (0.57, 1.22)
≥11 months	872	90.7	1420	86.8	0.66 (0.50, 0.86)
Intention-to-treat	1420	89.7	1420	86.8	0.71 (0.56, 0.89)[b]
Distant disease-free survival					
≤3 months	391	90.9	1420	89.9	0.85 (0.54, 1.29)
≥11 months	872	91.9	1420	89.9	0.76 (0.56, 1.02)
Intention-to-treat	1420	91.6	1420	89.9	0.78 (0.60, 1.01)[b]
Time to distant recurrence					
≤3 months	391	90.9	1420	90.3	0.89 (0.56, 1.35)
≥11 months	872	92.2	1420	90.3	0.77 (0.57, 1.04)
Intention-to-treat	1420	91.8	1420	90.3	0.79 (0.60, 1.03)[b]
CNS recurrence					
≤3 months	391	1.12	1420	1.82	–
≥11 months	872	1.42	1420	1.82	–
Intention-to-treat	1420	1.30	1420	1.82	–

CI = confidence interval; CNS = central nervous system; DFS-DCIS = disease-free survival including ductal carcinoma in situ.
[a]Event-free rates for all endpoints, except for CNS recurrence for which cumulative incidence is reported.
[b]Adjusted for stratification factors

Safety

- A summary of the safety and tolerability profile of neratinib by duration of therapy is presented in Table 4.
  - Patients who received neratinib for ≤3 months were more likely to have experienced grade 3/4 treatment-emergent adverse events, particularly diarrhea, and to have discontinued treatment as a result of adverse events.
- In this patient subset, diarrhea that lead to discontinuation generally resolved shortly after stopping treatment (median 2 days, interquartile range, 1–4 days).

Table 4. Safety and tolerability summary by duration of neratinib therapy

	Neratinib			Placebo
	≤3 months (n=391)	≥11 months (n=872)	Safety population (n=1408)	Safety population (n=1408)
Any TEAE	371 (95)	859 (99)	1387 (99)	1240 (88)
Grade 3/4 TEAE	229 (59)	371 (43)	700 (50)	184 (13)
TEAE leading to:				
Treatment discontinuation	284 (73)	8 (<1)	388 (28)	76 (5)
Dose reduction	110 (28)	261 (30)	440 (31)	35 (3)
Hospitalization	25 (6)	44 (5)	93 (7)	75 (5)
Dose hold	188 (48)	345 (40)	629 (45)	187 (13)
Grade 3/4 TEAE (≥2.5% of patients)				
Diarrhea	186 (48)	314 (36)[a]	562 (40)[a]	23 (2)
Vomiting	35 (9)	8 (<1)	47 (3)	5 (<1)
Nausea	14 (4)	7 (<1)	26 (2)	2 (<1)
Fatigue	12 (3)	3 (<1)	23 (2)	6 (<1)
Abdominal pain	10 (3)	8 (<1)	24 (2)	3 (<1)
Dehydration	10 (3)	2 (<1)	13 (1)	1 (<1)

Data expressed as n (%). TEAE, treatment-emergent adverse event
[a]One grade 4 event.

Conclusions

- These exploratory analyses from the ExteNET trial suggest that:
  - Patients who discontinued neratinib early (i.e. ≤3 months) did so primarily because of adverse events, most commonly diarrhea, although these events generally resolved shortly after stopping treatment. There was a trend towards improved iDFS compared with placebo in this patient subset, although benefits from treatment were limited.
  - Patients who received neratinib for ≥11 months (i.e. those who followed protocol and continued treatment for ~12 months or discontinued treatment upon recurrence) appeared to derive greater benefit than was reported in the ITT population.
  - To reduce the risk of disease recurrences, early management is needed to allow patients to stay on therapy.
- Loperamide prophylaxis for one or two cycles has been shown to reduce the incidence, severity, and duration of neratinib-associated diarrhea in the phase II CONTROL study.[5]
  - The addition of budesonide, a locally acting corticosteroid, or colestipol, a bile acid sequestrant, to loperamide prophylaxis may help to further optimize the management of neratinib-related diarrhea and reduce discontinuations from therapy.[5]

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Acknowledgements

ExteNET was sponsored by Wyeth, Pfizer, and Puma Biotechnology Inc.
Puma Biotechnology Inc. funded the provision of editorial support provided by Miller Medical Communications.

Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, June 1–5, 2018, in Chicago, IL, USA