Association between treatment duration and overall survival in early-stage HER2+ breast cancer patients receiving extended adjuvant therapy with neratinib in the ExteNET trial

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Background

- Suboptimal adherence to systemic adjuvant therapy has been documented in a substantial proportion of patients with early-stage breast cancer.[1]
  - Non-adherence or early discontinuation from systemic adjuvant therapy is associated with higher disease recurrence and mortality.[2–5]
- Neratinib, an oral irreversible pan-HER tyrosine kinase inhibitor, significantly improves invasive disease-free survival (iDFS) when given as extended adjuvant therapy after trastuzumab-based therapy in patients with early-stage HER2-positive (HER2+) breast cancer based on findings from the phase 3 ExteNET trial:[6,7]
  - In ExteNET, the median duration of neratinib therapy was 11.6 (range, 0.0–13.3) months;[6] however, 28% of patients discontinued therapy early (≤3 months) primarily because of adverse events, most commonly diarrhea.[8]
  - Prior analyses from ExteNET have shown improved iDFS and distant disease-free survival (DDFS) in patients who completed the planned duration of neratinib therapy.[8,9]
  - Conversely, patients who discontinued therapy within the first 3 months experienced worse outcomes.[8,9]

Objectives

- To assess overall survival (OS) and other efficacy outcomes (iDFS, DDFS) in patients from ExteNET who completed neratinib therapy as planned.
- Data are reported for the intention-to-treat (ITT) population and subgroups at higher risk of relapse.

Methods

Study design

- ExteNET was a multicenter, randomized, double-blind, placebo-controlled phase 3 trial (Clinicaltrials.gov: NCT00878709), the design details of which have been described previously:[6]
  - Randomization was stratified by locally determined HR status (HR+ *vs* HR–), schedule of trastuzumab administration (sequential *vs* concurrent administration with chemotherapy), and nodal status (0, 1–3 or ≥4 positive nodes).
  - Patients were randomly assigned to oral neratinib 240 mg/day or placebo for 1 year; antidiarrheal prophylaxis was not mandated.

Patients

- Women with stage 1–3c HER2+ primary breast cancer who received locoregional treatment and completed trastuzumab-based adjuvant therapy (with or without prior neoadjuvant therapy) within 2 years of randomization were eligible.
- Recruitment was restricted in February 2010 (protocol amendment 3) to higher-risk patients with stage 2–3c disease, completion of trastuzumab within 1 year of randomization, and with residual disease post-neoadjuvant therapy (no pathologic complete response [no pCR]).

Statistical analysis

- In addition to the **ITT population,** analyses were also performed in:
  - **HR+/≤1-year (EU indication):** Patients with hormone receptor-positive (HR+) disease who initiated neratinib within 1 year after prior trastuzumab.
  - **HR+/≤1-year no pCR:** Patients from the HR+/≤1-year population with residual disease post-neoadjuvant therapy (no pCR).
- Completion of therapy was defined as ≥11 months of treatment or cessation of neratinib if recurrence occurred prior to 11 months.
  - Patients who ended neratinib therapy because of disease recurrence before 11 months were considered with those who 'completed therapy' to reduce guarantee-time bias.[10]
- For all groups, efficacy outcomes in patients who completed neratinib therapy were compared with placebo (all randomized patients).
  - iDFS, DDFS, and OS were analyzed using Kaplan-Meier methods; hazard ratios (HR) with 95% confidence intervals (CI) were estimated using Cox proportional-hazards models.
- All analyses are descriptive.
- Cut-off dates: March 2017 (5-year iDFS and DDFS) and July 2019 (8-year OS).

Results

Patients

- 2840 patients were randomly assigned to study treatment (1420 per group):
  - 1631 patients (57%) had HR+ disease, of whom 1334 (82%) initiated study treatment within 1 year of prior trastuzumab and comprised the HR+/≤1-year population.
  - 354 patients (27%) of the HR+/≤1-year population had received neoadjuvant therapy, of whom 295 patients had residual invasive disease (no pCR) at study entry.
  - Key baseline characteristics are presented in **Table 1**.

Table 1. Key baseline characteristics

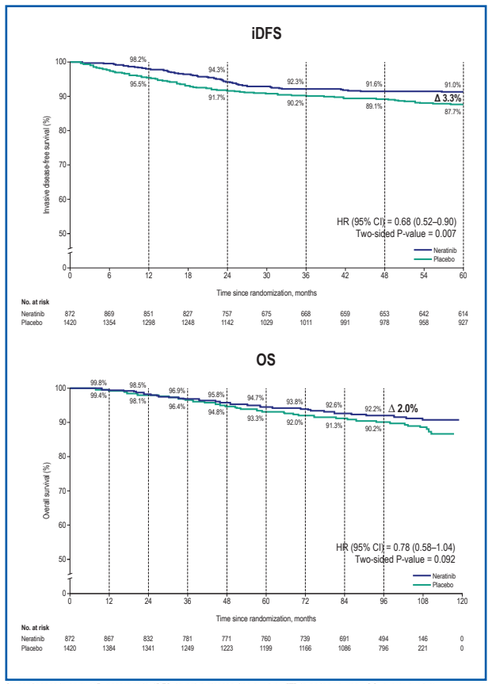
	ITT population		HR+/≤1-year[a] population (EU indication)		HR+/≤1-year no pCR[b]	
	Completed therapy[c] (N=872)	Placebo (N=1420)	Completed therapy[c] (n=402)	Placebo (n=664)	Completed therapy[c] (n=92)	Placebo (n=164)
Median age, years (range)	51 (26–83)	52 (23–82)	50 (26–83)	51 (23–78)	47 (30–65)	49 (26–76)
HR status, n (%)						
Positive	485 (56)	815 (57)	402 (100)	664 (100)	92 (100)	164 (100)
Negative	387 (44)	605 (43)	–	–	–	–
Nodal status, n (%)						
Negative	174 (20)	336 (24)	60 (15)	125 (19)	10 (11)	20 (12)
Positive	698 (80)	1084 (76)	342 (85)	539 (81)	82 (89)	144 (88)
Prior trastuzumab regimen, n (%)						
Concurrent	530 (61)	886 (62)	247 (61)	415 (63)	59 (64)	111 (68)
Sequential	342 (39)	534 (38)	155 (39)	249 (38)	33 (36)	53 (32)

HR, hormone receptor; HR+, hormone receptor-positive; ITT, intention-to-treat; pCR, pathologic complete response.
[a]HR+ and ≤1-year after prior trastuzumab; [b]HR+ and ≤1-year after prior trastuzumab with residual disease post-neoadjuvant therapy (no pCR); [c]Defined as ≥11 months of neratinib therapy or ended neratinib treatment due to disease recurrence.

Efficacy

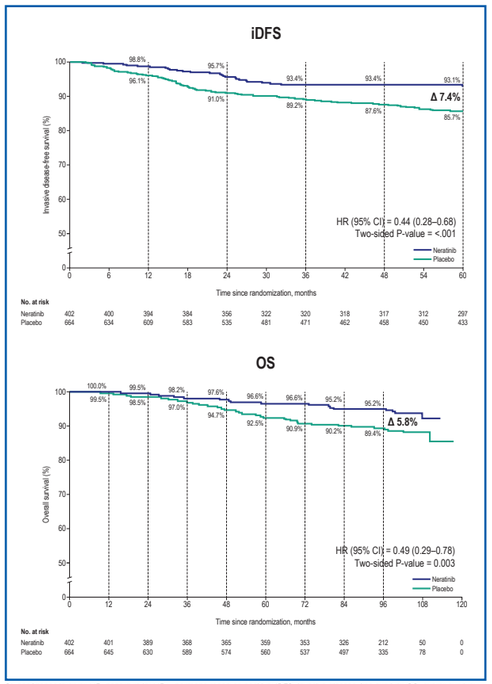
- Among patients who completed neratinib therapy, iDFS, DDFS and OS were improved versus placebo in each of the 3 groups (**Table 2 & Figures 1–3).**
- iDFS, DDFS and OS benefits were also greater in patients who completed neratinib therapy than in all randomized patients in each of the 3 groups (**Table 2**).
- For OS, after a median follow-up of 8.0 (range, 0–9.8) years:
  - In the ITT population, the HR for OS was **reduced from 0.95 to 0.78** upon completion of therapy
  - In the HR+/≤1-year population, the HR for OS was **reduced from 0.79 to 0.49** upon completion of therapy
  - In the HR+/≤1-year no pCR group, the HR for OS was **reduced from 0.47 to 0.29** upon completion of therapy.

Figure 1. iDFS and OS: Neratinib Completed Therapy[a] (ITT)



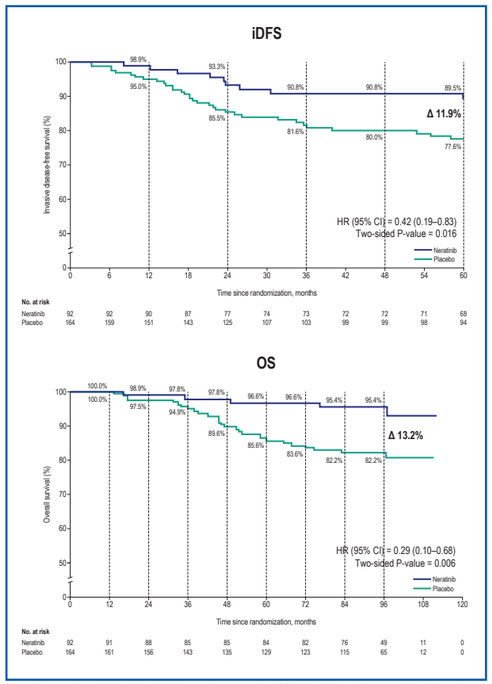
CI, confidence interval; HR, hazard ratio; iDFS, invasive disease-free survival; ITT, intention-to-treat; OS, overall survival.
[a]Defined as ≥11 months of therapy or ended treatment due to disease recurrence in the neratinib arm versus all randomized patients in the placebo arm.

Figure 2. iDFS and OS: Neratinib Completed Therapy[a] HR+/≤1-year;[b] EU indication



CI, confidence interval; HR, hazard ratio; HR+, hormone receptor-positive; iDFS, invasive disease-free survival; OS, overall survival.
[a]Defined as ≥11 months of therapy or ended treatment due to disease recurrence in the neratinib arm versus all randomized patients in the placebo arm; [b]HR+ and ≤1-year after prior trastuzumab.

Figure 3. iDFS and OS: Neratinib Completed Therapy[a] (HR+/≤1-year no pCR[b])



CI, confidence interval; HR, hazard ratio; HR+, hormone receptor-positive; iDFS, invasive disease-free survival; OS, overall survival; pCR, pathologic complete response.
[a]Defined as ≥11 months of therapy or ended treatment due to disease recurrence in the neratinib arm versus all randomized patients in the placebo arm; [b]HR+ and ≤1-year after prior trastuzumab with residual disease post-neoadjuvant therapy (no pCR).

Table 2. Efficacy summary

			5-year analysis				OS analysis	
	N		iDFS rate		DDFS rate		OS rate[a]	
Population or subgroup	**Neratinib**	**Placebo**	**Difference, %[b]**	**HR (95% CI)**	**Difference, %[b,8,9]**	**HR (95% CI)**	**Difference, %[b]**	**HR (95% CI)**
ITT population	1420	1420	+2.5	0.73 (0.57–0.92)[c]	+1.7	0.78 (0.60–1.01)[c]	–0.1	0.95 (0.75–1.21)[c]
Completed therapy[d]	872	1420	+3.3	0.68 (0.52–0.90)	+2.0	0.76 (0.56–1.02)	+2.0	0.78 (0.58–1.04)
HR+/≤1 year[e] (EU indication)	670	664	+5.1	0.58 (0.41–0.82)	+4.7	0.57 (0.39–0.83)	+2.1	0.79 (0.55–1.13)
Completed therapy[d]	402	664	+7.4	0.44 (0.28–0.68)	+5.9	0.49 (0.30–0.76)	+5.8	0.49 (0.29–0.78)
HR+/≤1 year no pCR[f]	131	164	+7.4	0.60 (0.33–1.07)	+7.0[g]	0.61 (0.32–1.11)	+9.1	0.47 (0.23–0.92)
Completed therapy[d]	92	164	+11.9	0.42 (0.19–0.83)	+10.9[h]	0.42 (0.18–0.88)	+13.2	0.29 (0.10–0.68)

CI, confidence interval; DDFS, distant disease-free survival; HR, hazard ratio; HR+, hormone receptor-positive; iDFS, invasive disease-free survival; ITT, intention-to-treat; OS, overall survival; pCR, pathologic complete response.
[a]OS analysis after a median follow-up of 8.0 years (range, 0-9.8); [b]Difference in event-free survival estimates (neratinib vs placebo); [c]Stratified by randomization stratification factors; [d]Defined as ≥11 months of therapy or ended treatment due to disease recurrence in the neratinib arm versus all randomized patients in the placebo arm; [e]HR+ and ≤1 year after prior trastuzumab; [f]HR+ and ≤1 year after prior trastuzumab with residual disease post-neoadjuvant therapy (no pCR); [g]5-year DDFS rate estimates: 86.8% (neratinib) vs 79.8% (placebo); [h]5-year DDFS rate estimates: 90.7% (neratinib) vs 79.8% (placebo).

Discussion

- These descriptive findings suggest that patients with early-stage HER2+ breast cancer who receive the recommended duration of extended adjuvant therapy with neratinib of 1 year may have improved outcomes.
  - Completion of planned neratinib was associated with improvements in iDFS, DDFS and OS in all groups evaluated.
- Optimal anti-diarrheal management to minimize diarrhea and increase likelihood of completing planned treatment is recommended (as observed in the recent phase 2 CONTROL trial; NCT02400476).[11,12]

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