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HER2+/HR+ breast cancer patients at high risk of relapse derive benefit from extended adjuvant treatment with neratinib: an exploratory analysis from ExteNET study

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INTRODUCTION

Extended adjuvant therapy with neratinib after trastuzumab based therapy was investigated in the phase III ExteNET trial, in which 1 year of neratinib was shown to significantly improve invasive disease-free survival (iDFS) compared with placebo at the planned primary analysis time point of 2 years (hazard ratio, 0.66; 95% confidence interval [CI], 0.49-0.90; P 0.008)[1].The efficacy of neratinib was confirmed at the 5-year analysis (hazard ratio, 0.73; 95% CI, 0.57-0.92; P 0.008)[2].

The benefit of neratinib was more marked in predefined subgroups, including patients who initiated treatment within 1 year of completing prior trastuzumab compared with those who started treatment later, and among patients with hormone receptor-positive (HR+) versus hormone receptor-negative (HR-) disease[1-2].

Based on the findings from ExteNET, neratinib was approved by the European Medicines Agency in patients with HER2+/HR+ eBC who initiate treatment within 1 year (HR+/≤ 1 year) of completing trastuzumab-based therapy (EU label population)[3].

Randomized clinical trials, including ExteNET study, investigate general and representative patient populations, yet clinical decisions increasingly depend on the characteristics of individual patients. In this exploratory analysis of the ExteNET trial, we tested the efficacy of continuing with 1 year of neratinib after completing adjuvant trastuzumab therapy in breast cancer patients at high risk of relapse.

METHODS

For the purpose of our analysis, we tested invasive disease-free survival (iDFS) at 2 and 5 years in HR+/≤ 1-year patients included in ExteNET population based on Amendment 3 (Am3) definition in the study protocol, which ruled out patients with stage I or node negative disease, and those with pCR after neoadjuvant therapy, in order to enrich the population with patients at higher risk of recurrence.

All endpoints were analyzed using a 2-sided log-rank test to compare the 2 treatment groups, except for CNS recurrence for which Gray's method was used. Event-free rates were generated for all endpoints, except for CNS recurrence for which cumulative incidence was reported. The hazard ratio and the corresponding 2-sided 95% confidence interval were estimated using a Cox proportional hazards regression model. The proportion of subjects surviving free of recurrence as defined for iDFS were plotted for each treatment group using the Kaplan-Meier method.

References

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RESULTS

Baseline Patient Characteristics

Out of 1334 HR+/≤ 1 year BC patients initially recruited by ExteNET, 1056 (79%) were classified as at high risk according to baseline disease characteristics based on Am3 definition (high risk population) (Table 1).

Table 1: Baseline patient characteristics

	high risk population*		EU label population	
Patient Characteristics	**neratinib (N=531) n(%)**	**placebo (N=525)**	**neratinib (N=670) n(%)**	**placebo (N=664) n(%)**
Region				
Asia Pacific, East Europe and South	167 (31%)	162 (31%)	197 (29%)	195 (29%)
North America	170 (32%)	149 (28%)	237 (35%)	205 (31%)
Western Europe, Australia and South	194 (37%)	214 (41%)	236 (35%)	264 (40%)
Age (median [range])	51 (25-83)	50 (23-77)	51 (25-83)	51 (23-78)
Menopausal Status at Diagnosis				
Postmenopausal	252 (47%)	238 (45%)	320 (48%)	322 (49%)
Premenopausal	279 (53%)	287 (55%)	350 (52%)	342 (52%)
Nodal Status (IVRS) - 4 Categories				
0	0 (0%)	0 (0%)	130 (19%)	125 (19%)
1-3	330 (62%)	323 (62%)	339 (51%)	334 (50%)
>=4	201 (38%)	202 (38%)	201 (30%)	205 (31%)
Previous trastuzumab regimen				
Concurrent	325 (61%)	321 (61%)	411 (61%)	415 (63%)
Sequential	206 (39%)	204 (39%)	259 (39%)	249 (38%)
T Stage				
T1	149 (28%)	145 (28%)	218 (33%)	209 (32%)
T2	229 (43%)	214 (41%)	270 (40%)	250 (38%)
T3 and above	59 (11%)	52 (10%)	61 (9%)	65 (10%)
Unknown	94 (18%)	114 (22%)	121 (18%)	140 (21%)
Prior neo-adjuvant				
No	404 (76%)	377 (72%)	508 (76%)	472 (71%)
Yes	127 (24%)	148 (28%)	162 (24%)	192 (29%)
Pathological complete response (PCR) when prior neo-adjuvant				
No	116 (91%)	143 (97%)	131 (81%)	164 (85%)
Yes	0 (0%)	0 (0%)	17 (11%)	21 (11%)
Unknown	11 (9%)	5 (3%)	14 (9%)	7 (4%)
Duration of prior adjuvant trastuzumab therapy, months (median [range])	11.5 (1.4-29.1)	11.4 (1.4-24.0)	11.4 (1.4-29.1)	11.4 (1.4-24.0)
Time from last dose of trastuzumab to randomization, months (median [range])	2.8 (0.2-12.0)	3.1 (0.3-12.0)	3.07 (0.2-12.0)	3.30 (0.3-12.0)
Receiving Concomitant Endocrine Therapy				
N	32 (6%)	24 (5%)	38 (6%)	30 (5%)
Y	499 (94%)	501 (95%)	632 (94%)	634 (96%)
Concomitant Endocrine Therapy Type				
Anti-estrogen & aromatase inhibitor	21 (4%)	19 (4%)	29 (4%)	24 (4%)
Anti-estrogen only	266 (53%)	258 (52%)	340 (51%)	317 (48%)
Aromatase inhibitor only	210 (42%)	221 (44%)	259 (39%)	290 (44%)
Neither anti-oestrogen nor aromatase inhibitor	2 (0%)	3 (1%)	4 (1%)	3 (1%)

According to the EU label, all patients were HR+ and had prior trastuzumab use.

*based on Am3 definition. See methods section.

Efficacy

In the high risk population (HR+/≤ 1 year patient subgroup) based on Am3 definition, neratinib was associated with a 48% reduction in relative risk of recurrence at 2-years compared with placebo (HR 0.52, 95%CI 0.32-0.84) (Figure 1). This advantage was also seen at 5 years, with iDFS analysis showing a relative risk reduction by 39% (HR 0.61, 95%CI 0.42-0.88) (Figure 2). Results were consistent for secondary endpoints (Table 2).

Fig 1: 2-year iDFS in high risk population**

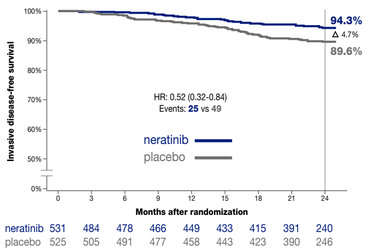


Fig 2: 5-year iDFS in high risk population**

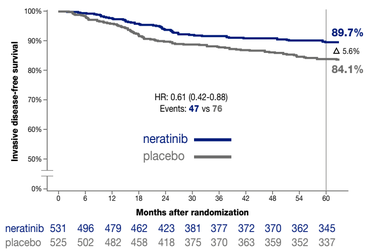


Table 2: Secondary endpoints results

Variable	High risk population**			
	Estimated 5-Year Event-Free Rates (%)			Hazard Ratio (95% CI)*
	neratinib (N=531)	placebo (N=525)	Absolute Difference	
iDFS	89.7	84.1	5.6	0.61 (0.42-0.88)
DFS-DCIS	89.4	83.6	5.8	0.60 (0.42-0.86)
DDFS	90.9	86.4	4.5	0.64 (0.43-0.95)
TTDR	91.1	87.0	4.1	0.66 (0.44-0.98)
	Cumulative incidence at 5 years			
CNS recurrence	0.86	2.20	-1.34	-
	Estimated 8-Year Event-Free Rates (%)			
OS	90.7	88.7	2.0	0.83 (0.56-1.22)

CI = confidence interval; DDFS = distant disease–free survival; DFS DCIS = disease-free survival including ductal carcinoma in situ; iDFS = invasive disease–free survival; TTDR = time to distant recurrence; CNS = central nervous system; OS = overall survival; CNS recurrence=time from randomization to CNS recurrence as first distant recurrence; *unstratified Cox proportional hazards model; **excluding nodal negative, PCR and Stage I.

Of note, the absolute benefit, in terms of iDFS at 2 (Figure 3A) and 5 years (Figure 3B) and of OS (Figure 3C), was notable for patients who did not achieve pCR upon neo-adjuvant treatment, with an absolute advantage with neratinib of 4.7%, 6.7% and 11.1%, respectively.

Fig 3A : 2-year iDFS in high risk no pCR population***

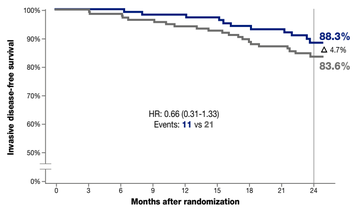


Fig 3B: 5-year iDFS in high risk no pCR population***

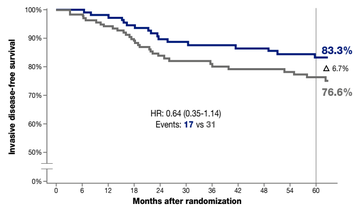
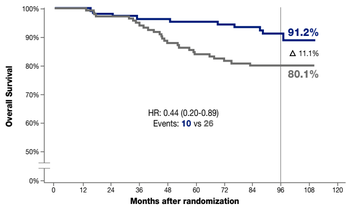


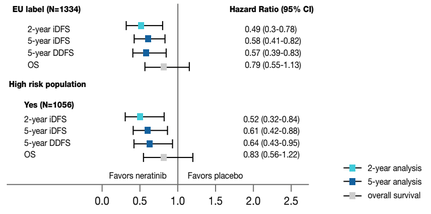
Fig 3C: OS in high risk no pCR population***



neratinib
placebo

***patients with unknown pCR status were removed.

Altogether, these results at 2, 5, and 8 years in the high risk patient population are comparable with the one reported in the full EU label population (Figure 4).
Notably, no significant interaction between risk categories, hormone receptor status, and use of neratinib was observed for the different endpoints, suggesting that the benefit derived by high risk patients resembled that derived by the whole ExteNET study population.



Safety

Safety analysis in the high risk population is consistent with the results in the full study population and with previously reported outcomes, with diarrhoea being the most frequent adverse event (38,6% of Grade 3), in the absence of protocol-mandated anti-diarrhoea prophylaxis. All other grade 3 adverse events in the neratinib group were each reported in 4% of patients or less.

CONCLUSIONS

Consistently with previously reported outcomes with neratinib in the EU label population, our results show that patients with HER2+/HR+ breast cancer with large primary tumors, lymph node involvement, and lack of response to neoadjuvant therapy are likely to derive meaningful and sustained benefit over time when treated with neratinib after standard trastuzumab-based therapy. The group of interest represents 79% of patients of the EU label.

These findings are in line with the existing international guidelines, recommending neratinib use for selected high risk patients, with appropriate diarrhoea prophylaxis and management[4].

Disclosures

- SDC has received fees for medical education from Novartis and Pierre-Fabre and is the recipient of the IG 20774 of Fondazione AIRC.
- FCO was a member of advisory board of GSK, Roche, AstraZeneca and Eli-Lilly. F.C. received speaker's fee by GSK, Roche, AstraZeneca, Eli-Lilly, Novartis, Amgen, Pfizer, MSD, BMS, Astellas, and Eli-Lilly.
- FCA, ED, JBT, RV are Pierre Fabre employees.
- The other authors declare no conflict of interest.

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