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Background

- Despite modern human epidermal growth factor receptor (HER2)-directed treatment options, relevant recurrence risk persists in patients (pts) with extensive local disease and/or lack of pathologic complete response (pCR) to neoadjuvant therapy.^{1,2}
- Neratinib is approved in Europe for extended adjuvant therapy in adult pts with HER2+/hormone receptor positive (HR+) eBC who completed adjuvant trastuzumab-based therapy less than one year ago ("EMA-/Swissmedic-label population").³
- In this population, the ExteNET study demonstrated a 5.1% absolute improvement in 5-year invasive disease-free survival (iDFS) with neratinib compared to placebo (90.8% vs. 85.7%; hazard ratio 0.58 [95% confidence interval (CI), 0.41-0.82]).⁴ Exploratory post-hoc analyses demonstrated a more pronounced benefit in pts with residual disease (non-pCR) after neoadjuvant treatment and who completed neratinib therapy (i.e., ≥11 months of treatment) (iDFS, Δ11.9%, HR 0.42, 95% CI 0.19-0.83; overall survival, Δ13.2%, HR 0.29, 95% CI 0.10-0.68).⁵
- In ExteNET, diarrhea was the most common grade 3 adverse event (AE) in the absence of primary diarrhea prophylaxis (neratinib group: 39%, placebo: 1%; no grade 4 events).⁴ However, as demonstrated in the CONTROL study, diarrhea can be managed with adequate prophylaxis and treatment management, including a dose escalation approach.^{6,7}
- ELEANOR is the first non-interventional study of the real-world use and management (including dose escalation) of neratinib in the extended adjuvant setting in pts with HER2+/HR+ eBC in Germany, Austria, and Switzerland (NCT04388384) after completion of adjuvant trastuzumab-based therapy, including dual blockade with trastuzumab+pertuzumab or trastuzumab+emtansine (T-DM1).

Methods

- ELEANOR is a prospective, longitudinal, observational study.
- 300 adult female pts diagnosed with HER2+/HR+ eBC stage I – III, who ended trastuzumab-based adjuvant therapy less than one year ago, were planned to be enrolled in accordance with the EMA/Swissmedic product specifications³. Enrollment was completed on 5th May 2023. Treatment is administered according to local clinical practice.
- Primary objective** is to assess patient adherence to neratinib (i.e., neratinib intake for ≥75% of prescribed treatment days).
- Secondary objectives** focus on patient and tumor characteristics, prior trastuzumab-based treatments and neratinib treatment details, effectiveness, safety, patient-reported health-related quality of life, and physicians' evaluated treatment satisfaction.

Results

- Here, we report interim results based on 300 pts (enrolled set [ES]) enrolled at 66 sites and observed for a minimum of three months (data cut-off 5th August 2023).
- 286 pts met the eligibility criteria and had at least one documented dose of neratinib (main analysis set [MAS]). At least one post-baseline safety assessment was documented for 288 pts treated with neratinib (safety analysis set [SAF]).
- At the time of data cut-off, documentation in the electronic case report form (eCRF) was unlocked and partially incomplete.
- Here, the focus will be on patient and tumor characteristics, how neratinib treatment is managed, as well as preliminary effectiveness and safety of the neratinib treatment including physicians' evaluated treatment satisfaction.

Patient Population

- Table 1** summarizes the main patient baseline characteristics [MAS].
- Tumor characteristics at primary diagnosis, details on prior trastuzumab-based treatments and the disease risk profile are summarized in **Table 2** [MAS].

Therapeutic management prior to neratinib

- Overall, 37.4% (107/286) of pts received adjuvant/post-neoadjuvant trastuzumab monotherapy, 31.8% (91/286) received trastuzumab+pertuzumab, and 22.4% (64/286) received post-neoadjuvant T-DM1 (**Figure 1 A**). Anti-HER2 treatments by therapy setting (i.e., adjuvant or post-neoadjuvant) are depicted in **Figure 1 B**. In pts who had non-pCR following neoadjuvant treatment, 55.4% (62/112) received post-neoadjuvant T-DM1 (**Figure 1 C**) [MAS].

Neratinib treatment management

- The neratinib starting dose was <240 mg/day in 44.4% (128/288) of pts followed by a dose escalation in 84.4% (108/128) of pts (dose escalation strategy) [SAF].
- 86.8% (250/288) of pts received diarrhea prophylaxis [SAF].
- At data cut-off, 20.6% (59/286) of pts were still receiving neratinib treatment, while for 79.4% (227/286) of pts, end of neratinib treatment was documented. Thereof, 59.9% (136/227) had completed neratinib treatment as per SmPC, whereas neratinib treatment was discontinued because of adverse events in 25.1% (57/227) of pts, at the patient's wish in 9.3% (21/227) of pts, because of concomitant diseases or tumor relapse in 0.9% (2/227) each, and for other reasons in 4% (9/227) of pts (**Figure 2 A**) [MAS].
- Median neratinib treatment duration was 11.9 months (IQR: 4.1-12.0 months) [SAF].
- At the end of neratinib treatment, physicians' satisfaction rate was 86.4% (76/88) for safety (**Figure 2 B left**) [MAS]. The reasons for end of neratinib treatment for the corresponding patients are depicted in **Figure 2 B right** [MAS]. They differ slightly from the reasons documented for the overall MAS, with more pts completing treatment according to SmPC and fewer pts discontinuing treatment due to adverse events.

Effectiveness

- At an estimated median observation time of 14.0 months (IQR: 13.3-24.0 months), six pts (6/286, 2.1%) experienced a relapse (two distant recurrences). For four of them, relapse occurred while on neratinib treatment, while for two patients, relapse was documented in the follow-up period. In addition, one patient died (unknown reason of death) after starting neratinib treatment. The 12-month DFS rate was 97.4% (95% CI, 94.6-98.7) (**Figure 3**) [MAS].

Safety

- Treatment emergent adverse events (TEAEs) were consistent with the known safety profile of neratinib with grade ≥3 diarrhea observed in 20.1% (58/288) of pts. The incidence of grade ≥3 diarrhea by worst grade was less common in pts starting on a lower dose of neratinib (15.6% vs. 23.8%) (**Table 3**) [SAF].

Table 1: Patient baseline characteristics [MAS]

	MAS, N=286
Median age, years (IQR)	52.0 (44.0-60.0)
Median BMI in kg/m ² (IQR) (n=259)	25.9 (22.8-30.0)
ECOG Performance Status, n (%)	
• 0	205 (71.7)
• 1	58 (20.3)
• 2	5 (1.7)
• Not evaluated	13 (4.5)
• Missing	5 (1.7)
Premenopausal at diagnosis, n (%)	130 (45.5)
Number of concomitant diseases, n (%)	
• 0	131 (45.8)
• 1	61 (21.3)
• 2	44 (15.4)
• ≥3	50 (17.5)

IQR, interquartile range; MAS, main analysis set

Table 2: Tumor characteristics at primary diagnosis [MAS]

n (%)	MAS, N=286
WHO tumor type	
• Invasive carcinoma of no special type	246 (86.0)
• Invasive lobular carcinoma	16 (5.6)
• Other	16 (5.6)
• Missing	8 (2.8)
Clinical AJCC stage	
• Tis/N0/M0	1 (0.3)
• I	101 (35.3)
• II	127 (44.4)
• III	28 (9.8)
• Not determinable	21 (7.3)
• Missing	8 (2.8)
Tumor grading	
• G1	5 (1.7)
• G2	123 (43.0)
• G3	139 (48.6)
• GX	11 (3.8)
• Missing	8 (2.8)
Positive hormone receptor (i.e., estrogen receptor and/or progesterone receptor) status	286 (100)
Ki-67 status (local) ^a	
• High	180 (62.9)
• Low	78 (27.3)
• unknown / missing	28 (9.8)
Previous anti-neoplastic therapies ^b	
• Adjuvant	47 (16.4)
• Neoadjuvant	231 (80.8)
• Post-neoadjuvant ^c	227 (79.4)
• Missing	8 (2.8)
Pathological response to neoadjuvant treatment, N=231	
• pCR ^d	114 (49.4)
• non-pCR	113 (48.9)
• Missing	4 (1.7)
Disease risk profile ^e	
• Low risk	62 (21.7)
• Non-low risk	210 (73.4)
• Unknown	14 (4.9)

^aHigh/low classification according to the centers' local standards; ^b Including anti-HER2 therapy and/or chemotherapy; ^c For 4 pts post-neoadjuvant therapy was not documented (yet); ^dpCR, pathological complete response; ^e Low risk: AJCC stage I and N0 and pCR (in case of neoadjuvant treatment); non-low risk: AJCC stage > I or N+ or non-pCR (in case of neoadjuvant treatment). For 14 pts (4.9%), AJCC stage, nodal status, or pathological response to neoadjuvant therapy had not been documented at the time of data cutoff, resulting in an "unknown" risk profile. Patients with cN1mi were included in the non-low risk group. MAS, main analysis set

Table 3: Safety [SAF]^a

n (%)	SAF, N=288
TEAE ^b , any grade	263 (91.3)
• Grade ≥3 ^c	75 (26.0)
• Serious TEAEs	17 (5.9)
• Leading to discontinuation of neratinib	61 (21.2)
TEAEs in ≥10% of pts, any grade	
• Diarrhea	234 (81.3)
• Nausea	64 (22.2)
• Fatigue	57 (19.8)
Diarrhea by worst grade	
• Grade 1	95 (33.0)
• Grade 2	81 (28.1)
• Grade 3	57 (19.8)
• Grade 4	1 (0.3)
• Grade ≥3 by worst grade and by starting dose	58 (20.1)
• Neratinib starting dose <240 mg/day, N=128	20 (15.6)
• Neratinib starting dose =240 mg/day, N=160	38 (23.8)
• Leading to TEAE-induced treatment	183 (63.5)

^aData are retrieved from the AE form; ^b TEAE, treatment emergent adverse event; ^c No fatal TEAEs were reported. SAF, safety analysis set

Limitations

When interpreting the results of the interim analysis, the relatively short observation period with approximately 20% of pts still on treatment, should be taken into account. In addition, in real-world data collection, adverse events may be under-reported compared to interventional clinical trials. Final results of this study with additional endpoint analyses will be reported after the 300th patient has been observed for 13 months.

Legal entity responsible for the study & study funding:

Study sponsored by Pierre Fabre Pharma GmbH (Freiburg, Germany), Pierre Fabre Pharma Austria (Wels, Austria) and Pierre Fabre Pharma AG (Allschwil, Switzerland).

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Data were presented at ESMO Breast Cancer 2024^a and SABCS 2024^b.

19th St. Gallen International Breast Cancer Conference 2025

12-15 March, Vienna/Austria

Poster Number: P018

QR code

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Conclusion

- This preplanned interim analysis reflects the use of neratinib in a contemporary cohort of predominantly higher-risk pts with HER2+/HR+ eBC and after completion of pertuzumab- and T-DM1-containing adjuvant regimens in routine clinical practice in Germany, Austria, and Switzerland.
- Preliminary effectiveness data with a DFS rate at 12 months of 97.4% appears to be consistent with previous data.⁴
- The proportion of pts with grade ≥3 diarrhea was markedly lower when compared indirectly to the ExteNET study (20.1% vs. 39%).⁴ This may be a result of an increasing awareness of diarrhea risk leading to a more frequent use of diarrhea prophylaxis (86.8% of pts in ELEANOR) and implementation of the dose escalation approach (44.4% of pts in ELEANOR) with grade ≥3 diarrhea in 15.6% of pts who started treatment with a lower starting dose.
- The treating physicians were satisfied with the effectiveness and safety of the treatment with neratinib for the majority of pts.
- Final results, including updated data on effectiveness, will be presented in 2025.

