2023 NCODA Spring Forum, Indianapolis, IN, March 15–17, 2023 (poster previously presented at the San Antonio Breast Cancer Symposium®, December 6–10, 2022)

# Interim analysis (n=200) from ELEANOR: A multi-national, prospective, non-interventional study among patients with HER2+ and HR+ early breast cancer treated with extended adjuvant neratinib in the clinical routine

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## Background

- Neratinib is an irreversible pan-HER tyrosine kinase inhibitor registered in Europe as extended adjuvant treatment for adult patients with HER2+, Hormone Receptor-positive (HR+) early breast cancer (eBC) who completed adjuvant trastuzumab-based therapy within one year prior to start of neratinib (European Medicines Agency (EMA)/Swissmedic-label population).[1]
- The phase III ExteNET study demonstrated clinically meaningful benefit for neratinib vs. placebo in this population, including significantly improved 5-year invasive disease-free survival (˜5.1/, +5 0.58, 95/ &, 0.41 0.82).[2]
- In ExteNET, diarrhea was the most common grade 3 adverse event in the absence of primary diarrhea prophylaxis (neratinib arm: 39/, placebo: 1/; no grade 4 events).[2] However, as demonstrated by the CONTROL study, diarrhea can generally be managed through adequate prophylaxis and treatment management, including a dose escalation approach. [3,4]
- ELEANOR is the first non-interventional study (NIS) to collect real-world data on the use and treatment management of neratinib in the EMA/Swissmedic-label population in Germany, Austria, and Switzerland (NCT04388384). As of November 2022, 265 patients have been included and patient enrollment is ongoing.

## Methods

- ELEANOR is a prospective, longitudinal, observational study in Germany, Austria, and Switzerland.
- 300 adult female patients are planned to be enrolled in accordance with the EMA and Swissmedic Summary of Product Characteristics (SmPC) specifications. Treatment is performed according to local clinical routine.
- Primary objective is the proportion of patients that are adherent to neratiniE treatment (i.e., intaNe for 75/ of treatment da\s).
- Secondary objectives include the characterization of patients scheduled to receive neratinib, details on neratinib treatment, recurrences, safety/tolerability, and patient-reported outcomes (PRO, including health-related quality of life). CANKADO, an eHealth application can be used optionally by patients for PRO assessments.
- Here, we report results of the preplanned interim analysis based on 200 patients with a minimum follow-up of 3 months (data cut-off on May 2nd 2022).
- 202 patients were enrolled at 58 centers (enrolled set [ES]). 187 patients fulfilled the in-/exclusion criteria and had at least one documented intake of neratinib (main analysis set [MAS]). All patients of the MAS had at least one post-baseline safety assessment documented (safety analysis set [SAF]).
- At the time of data cutoff, no formal database lock was performed before this interim data analysis. Certain data including patient treatment adherence, effectiveness endpoints, and PROs were immature and will be reported in subsequent analyses.

**Table 1**
**Demographic baseline characteristics (Main analysis set)**

| | MAS, n=187 |
|---|---|
| **Median age, years (range)** | **53.0 (22.0-81.0)** |
| **Median BMI, kg/cm² (IQR)** | **26.0 (22.8-29.8)** |
| **ECOG performance status at inclusion, n (%)** | |
| • 0 | 133 (71.1) |
| • 1 | 47 (25.1) |
| • 2 | 3 (1.6) |
| • Not evaluated | 4 (2.1) |
| **Premenopausal at diagnosis, n (%)** | **82 (43.9)** |

IQR, interquartile range

**Table 2**
**Tumor characteristics at primary diagnosis (MAS)**

| n (%) | MAS, n=187 |
|---|---|
| **Clinical T-stage** | |
| • cT0/cTis (DCIS) | 1 (0.5)/2 (1.1) |
| • cT1[a] | 23 (12.3) |
| • cT1a/b | 2 (1.1)/12 (6.4) |
| • cT1c | 55 (29.4) |
| • cT2 | 73 (39.0) |
| • cT3 | 8 (4.3) |
| • cT4[a] | 1 (0.5) |
| • cT4d | 1 (0.5) |
| • cTX | 9 (4.8) |
| **Clinical N-stage** | |
| • cN0/cN1mi | 116 (62.0)/3 (1.6) |
| • cN1 | 48 (25.7) |
| • cN2a | 4 (2.1) |
| • cN2a/b | 1 (0.5)/1 (0.5) |
| • cN3 [a] | 1 (0.5) |
| • cN3a | 1 (0.5) |
| • cNX | 12 (6.4) |
| **AJCC stage** | |
| • Tis/N0/M0 | 1 (0.5) |
| • I | 69 (36.9) |
| • II | 81 (43.3) |
| • III | 14 (7.5) |
| • Not determinable / missing | 22 (11.8) |
| **Tumor grading** | |
| • G1 | 3 (1.6) |
| • G2 | 82 (43.9) |
| • G3 | 92 (49.2) |
| • GX | 10 (5.3) |
| **Ki-67 status (local) [b]** | |
| • High | 120 (64.2) |
| • Low | 54 (28.9) |
| • unknown / missing | 13 (7.0) |
| **Type of previous treatment** | |
| • Neoadjuvant | 151 (80.7) |
| • Post-neoadjuvant* | 147 (78.6) |
| • Adjuvant | 36 (19.3) |

[a] not further specified
[b] Ki-67 high/low classification according to the centers' local standards
* For 4 patients, post-neoadjuvant treatment had not been documented yet.

## Results

### Patient population

- **Table 1** summarizes the main demographic baseline characteristics in the MAS.
- At primary diagnosis, patients predominantly had clinical stages cT1 and cT2 (49.2/ and 39/, respectively) and/or cN0/cN1mi and cN1 (63.6/ and 25.7/, respectively). About half of tumors were G3 (49.2/) and 64.2/ had hi h i 67 (**Table 2**).
- 67.9/ of patients were at increased risk of disease recurrence (**Figure 1**).

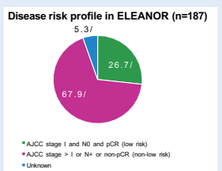


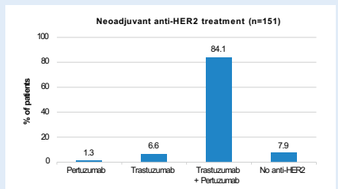

**Figure 1:** Disease risk profile in ELEANOR (MAS). Low risk: AJCC stage I and N0 and pCR (in case of neoadjuvant treatment); non-low risk: AJCC stage > I or N+ or non-pCR (in case of neoadjuvant treatment). For 10 patients (5.3/), AJCC stage, nodal status, or pathological response to neoadjuvant therapy had not been documented at the time of data cutoff, resulting in an "unknown" risk profile.

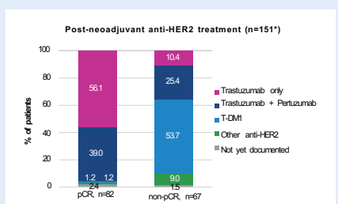
### Therapeutic management prior to neratinib

- 151 patients (80.7/) received neoadjuvant therapy, consisting of chemotherapy plus HER2-directed treatment in both settings while 36 patients (19.3/) had upfront surgery followed by adjuvant treatment. In the neoadjuvant setting most patients received trastuzumab and pertuzumab (84.1/), whereas in the adjuvant setting, anti-HER2 treatment mostly consisted of trastuzumab (66.7/) (**Figure 2**).
- 82 patients (54.3/) treated with neoadjuvant therapy had pathological complete response (pCR). In these patients, anti-HER2 targeted treatment was continued with trastuzumab in 56.1/ and with trastuzumab and pertuzumab in 39.0/ in the post-neoadjuvant setting. For patients with non-pCR (n=67, 35.8/), T-DM1 was the most commonly used post-neoadjuYant treatment (53.7/), followed by trastuzumab plus pertuzumaE (25.4/) (**Figure 2**).

### Neratinib treatment

- Efficacy was the most common reason for use of extended adjuYant treatment (63.1/) (**Figure 3**).
- Median time from completion of previous trastuzumab-based therapy to start of neratinib treatment was 3.6 months (IQR: 1.8 – 7.3 months, MAS).
- At the cut off date, extended adjuvant neratinib median treatment duration was of 11.2 months (IQR: 0.9–12.0 months, SAF).
- 92.5/ of patients received endocrine treatment concomitant with neratinib.
- Neratinib treatment had been documented for 187 patients, and at the time of data cutoff, 86 patients (46.0/) were still under neratinib treatment.
- 22.5/ of patients had completed treatment as per SmPC while treatment was discontinued in 16.6/ of patients due to adverse events, in 10.2/ the reason was "patient's wish" and in 4.8/ of patients due to other reasons.



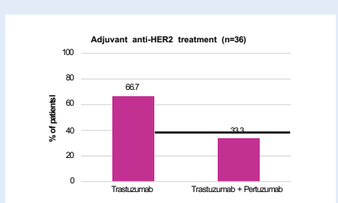




**Figure 2:** Anti-HER2 agents used in neoadjuvant (n=151), post-neoadjuvant (n=151), and adjuvant (n=36) pretreatment settings with/without chemotherapy (MAS). For 4 patients, post-neoadjuvant treatment had not been documented yet. Proportion of patients by drug (combination) in relation to the number of patients in each pretreatment setting. "Other anti-HER2 treatments" included other combinations and/or sequences of trastuzumab, pertuzumab and/or T-DM1.
* pCR status unknown in 2 patients

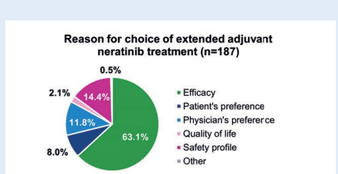



**Figure 3:** Reasons for choice of extended adjuvant neratinib treatment (MAS). The reason for treatment choice is documented in the eCRF by choosing one of the following answers: efficacy, patient's preference, physician's preference, quality of life, safety profile, comorbidities, or other.

### Safety

- Non-serious and serious treatment-emergent adverse events (TEAEs) were reported for 87.7/ and 5.9/ of patients, respectively. For 25.7/ of patients, TEAEs grade 3 were reported. No fatal TEAEs occurred (Safety Set, SAF, n=187).
- The most common TEAEs of any grade were diarrhea (78.6/), nausea (20.3/), and fatigue (17.1/). Grade 1/2 diarrhea was reported for 127 (67.9/), grade 3 diarrhea for 36 (19.3/) patients, and grade 4 diarrhea was reported for 2 patients (1.1/).
- 85.6/ of patients received diarrhea prophylaxis at least once and 68.4/ of patients had any kind of corrective diarrhea treatment (SAF).
- Previous anti-HER2 treatment did not influence neratinib diarrhea patterns (**Figure 4, A**).
- 68 patients (36.4/) started neratinib treatment at a daily dose lower than 240 mg with planned dose escalation. The incidence of grade 3 diarrhea was observed less frequently in patients starting at a lower neratinib dose (16.2 vs 21.0/) (**Figure 4, B**).

## Conclusion

- The results of this preplanned interim analysis reflect the current treatment landscape for HER2+ eBC in Germany, Austria, and Switzerland.
- The proportion of patients with grade 3 diarrhea was markedly lower when indirectly compared to the ExteNET study (20.3/ vs. 39/).[2] This might be a result of increasing awareness towards the risk of diarrhea as well as increasing use of diarrhea prophylaxis and the dose escalation approach.
- About 1/3 of physicians applied a dose escalation approach by starting neratinib treatment at <240 mg/day. In these patients, the incidence of grade 3 TEAEs and grade 3 diarrhea was lower as compared to patients starting at the standard dose, consistent with the results of the previous interim analysis.[5]
- Key findings of this interim analysis confirm that neratinib is used following adjuvant T-DM1 and pertuzumab+trastuzumab in the real-world clinical practice without new safety signals.

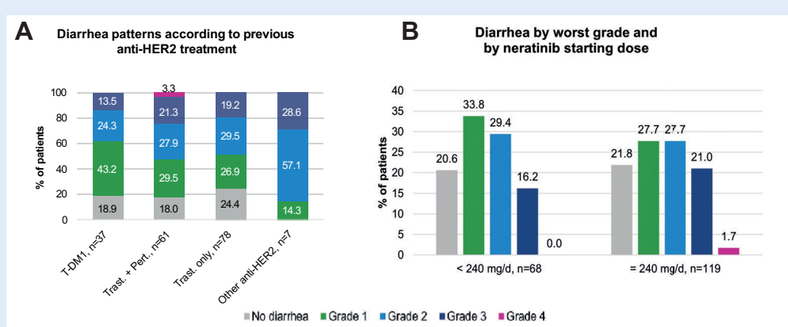



**Figure 4:** Diarrhea patterns according to previous anti-HER2 treatment (A) and diarrhea by worst grade and by neratinib starting dose (B) (SAF; n=187). Stacked bar charts in show the proportion of patients by worst grade of diarrhea reported, in relation to the number of patients in each pre-treatment subgroup. Other anti-HER2 therapies include other combinations of trastuzumab and/or pertuzumab and/or T-DM1. For 4 patients previous anti-HER2 treatment had not been documented yet.
Trast., Trastuzumab; Pert., Pertuzumab

### Limitations

Some key limitations are the relatively short observation period and small number of patients. Further study on use patterns of HER2-targeted agents in extended adjuvant neratinib patients is warranted given the relatively recent availability of most of the agents under study and small cohort sizes included in our analysis.

Updated results will be reported after the 300th patient has been observed for 3 months.


### References

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### 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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Poster number: P2-01-01