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Interim analysis (n=150) of the multi-national, prospective, non-interventional ELEANOR study observing real-life extended adjuvant treatment with neratinib in patients with HER2+ / HR+ early breast cancer (eBC)

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Background

- Therapies targeting the Human Epidermal Growth Factor Receptor 2 (HER2) in the neoadjuvant or (post-neo)adjuvant setting demonstrated a substantial benefit in patients with HER2-positive (HER2+) eBC. However, with longer follow-up, a considerable risk of local and distant disease recurrence still exists.[1]
- Neratinib is an irreversible pan-HER tyrosine kinase inhibitor registered in Europe as extended adjuvant treatment for adult patients with Hormone Receptor-positive (HR+), HER2+ eBC within one year after completion of adjuvant trastuzumab-based therapy („EMA-/Swissmedic-label population“).[2]
- The ExteNET study demonstrated clinically meaningful benefit for neratinib vs. placebo in this population, including significantly improved 5-year invasive disease-free survival (Δ5.1%, HR 0.58, 95% CI 0.41-0.82).[3] Exploratory post-hoc analyses showed more pronounced benefit for patients with non-pCR after neoadjuvant treatment[3] and patients who completed neratinib therapy (i.e., ≥11 months of treatment).[4]
- In ExteNET, diarrhea was the most common grade 3 adverse event (AE) in the absence of primary diar-rhea prophylaxis (neratinib arm: 39%, placebo: 1%; no grade 4 events).[3] However, as demonstrated by the CONTROL study, diarrhea can generally be managed through adequate prophylaxis and treatment management, including a dose escalation approach.[5,6]
- ELEANOR is the first non-interventional study to investigate real-world use of neratinib and its management after different pretreatments in the EMA-/Swissmedic-label population in Germany, Austria, and Switzerland (NCT04388384). As of April 2022, 222 patients have been included and patient enrollment is ongoing.

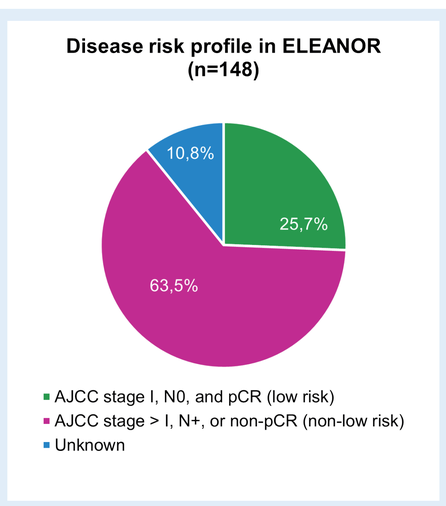

Figure 1: Disease risk profile in ELEANOR (ES). For 16 patients (10.8%), AJCC stage, nodal status, or pathological response to neoadjuvant therapy had not been documented at the time of data cutoff resulting in an “unknown” risk profile.

Legal entity responsible for the study & study funding:

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Methods

- ELEANOR is a prospective, longitudinal, observational study at approx. 100 sites.
- 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 neratinib treatment (i.e., intake for ≥75% of treatment days).
- **Secondary objectives** include the analysis of prior trastuzumab-based therapies (including pertuzumab and T-DM1), neratinib dosing and management, relapses, and safety / tolerability. In addition, patient-reported outcomes (PRO, including health-related quality of life) will be assessed for which CANKADO, a web-/application-based e-health solution, can be used optionally.
- Here, we report interim analysis results based on 150 patients (data cutoff 18th Nov. 2021, i.e., 3 months after enrollment of the 150th patient).
- 148 patients were enrolled at 50 centers (enrolled set [ES]). 137 patients fulfilled the in- and exclusion criteria and had at least one documented intake of neratinib (main analysis set [MAS]). 136 patients of the MAS had at least one post-baseline safety assessment documented (safety analysis set [SAF]).
- At the time of data cutoff, documentation in the eCRF was not locked and was partially incomplete. Data on treatment adherence, treatment management, and PROs were immature and will be reported in subsequent analyses.

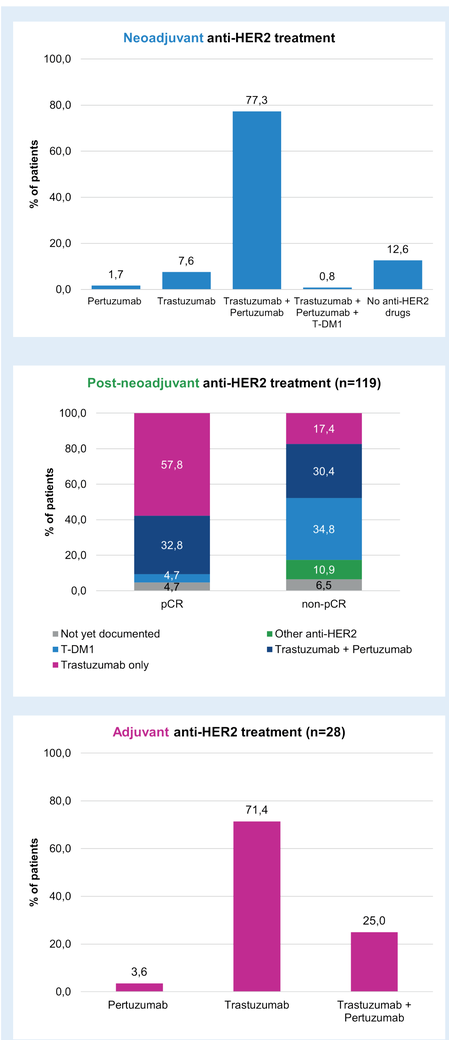

Figure 2: Anti-HER2 agents used in neoadjuvant (n=119), post-neoadjuvant (n=119), and adjuvant (n=28) pretreatment settings with/without chemotherapy (ES). For 6 patients, post-neoadjuvant treatment had not been documented yet. For 1 patient, data on previous treatment were missing at time of data cutoff. Top and bottom: bar charts show the proportion of patients by drug (combination) in relation to the number of patients in each pretreatment setting. Middle: Post-neoadjuvant anti-HER2 treatment by pathological response; other anti-HER2 drugs included other combinations or sequences of trastuzumab, pertuzumab, and/or T-DM1. pCR, pathological complete response; pCR, n=64; non-pCR, n=46, unknown or missing, n=9.

Results

Patient population

- **Table 1** summarizes the main demographic baseline characteristics in the enrolled set (ES).
- At primary diagnosis, 87.2% of patients presented with an invasive carcinoma of no special type and were mainly reported with a clinical stage cT1 (50.7%) and/or cN0 (61.5%). Half of tumors were graded G3 and 63.5% were Ki-67 high (**Table 2**).
- 63.5% of patients were at increased risk of disease recurrence (**Figure 1**).
- 18.9% of patients had upfront surgery followed by adjuvant treatment while 80.4% received neoadjuvant therapy. In the adjuvant setting, anti-HER2 treatment mostly consisted of trastuzumab only (71.4%), where-as in the neoadjuvant setting most patients received trastuzumab and pertuzumab (77.3%) (**Figure 2**).
- 57.8% of patients with pCR received trastuzumab only and 32.8% received trastuzumab plus pertuzumab in the post-neoadjuvant setting. For patients with non-pCR, T-DM1 was the most commonly used post-neoadjuvant treatment (34.8%), followed by trastuzumab plus pertuzumab (30.4%) (**Figure 2**).

Table 1: Demographic baseline characteristics (ES)

	ES, n=148
Median age, years (IQR)	**53.0 (45.0-60.0)**
Median BMI in kg/m² (IQR)	**26.6 (23.0-30.5)**
ECOG Performance Status, n (%)	
• 0	84 (56.8)
• 1	30 (20.3)
• 2	3 (2.0)
• Not evaluated / missing	31 (20.9)
Premenopausal at primary diagnosis, n (%)	**62 (41.9)**
Number of concomitant diseases, n (%)	
• 0	71 (48.0)
• 1	29 (19.6)
• 2	26 (17.6)
• ≥3	22 (14.9)

IQR, interquartile range

Table 2: Tumor characteristics at primary diagnosis (ES)

n (%)	ES, n=148
Clinical T-stage	
• cT1	75 (50.7)
• cT2	56 (37.8)
• cT3	6 (4.1)
• cT4	1 (0.7)
• cTX / missing	10 (6.8)
Clinical N-stage	
• cN0	91 (61.5)
• cN1[a]	37 (25.0)
• cN2	3 (2.0)
• cN3	2 (1.4)
• cNX / missing	15 (10.1)
AJCC stage	
• I	55 (37.2)
• II	58 (39.2)
• III	9 (6.1)
• Not determinable / missing	26 (17.6)
Tumor grade	
• G1	2 (1.4)
• G2	62 (41.9)
• G3	74 (50.0)
• GX / missing	10 (6.8)
Ki-67 status (local)[b]	
• High	94 (63.5)
• Low	41 (27.7)
• Unknown / missing	13 (8.8)
Pathological complete response (pCR) to neoadjuvant treatment (n=119)	**64 (53.8)**

[a] including one patient with cN1mi.
[b] High/Low classification according to the centers’ local standards

Neratinib treatment

- Median time from completion of previous trastuzumab-based therapy to start of neratinib treatment was 3.7 months (interquartile range [IQR]: 1.9 – 8.7 months, MAS).
- 92.0% of patients received endocrine treatment concomitant with neratinib.
- At time of data cutoff, 78 patients (56.9%) were still under neratinib treatment. Median treatment duration with neratinib was 10.3 months (IQR: 0.9 – 12.0 months).
- 11.7% of patients had completed treatment as per SmPC while treatment was prematurely discontinued due to adverse events in 16.1% or according to patients’ request in 10.9% of patients.

Safety

- 88.3% of patients received diarrhea prophylaxis at least once and 71.5% of patients had any kind of corrective diarrhea treatment (MAS).
- Non-serious and serious AEs were reported for 87.5% and 4.4% of patients, respectively. For 24.3% of patients, AEs grade ≥3 were reported. No fatal AE occurred (Safety Set, SAF).
- The most common AEs of any grade were diarrhea (77.9%), nausea (22.1%), and fatigue (19.1%). Diar-rhea grade 3 was reported for 25 (18.4%) patients and grade 4 diarrhea was reported for 2 patients.
- 50 (36.8%) patients started neratinib treatment at a daily dose lower than 240 mg with planned dose escalation (25.7%), due to patients’ request (2.9%), or for other reasons (5.9%). The incidence of grade ≥3 AE was 18.0% for patients who started at a lower daily dose as compared to 27.9% for patients starting at 240 mg/day and grade ≥3 diarrhea was observed less frequently (**Figure 3**).
- No relevant difference in the incidence of severe diar-rhea was observed between patients with different pretreatments.

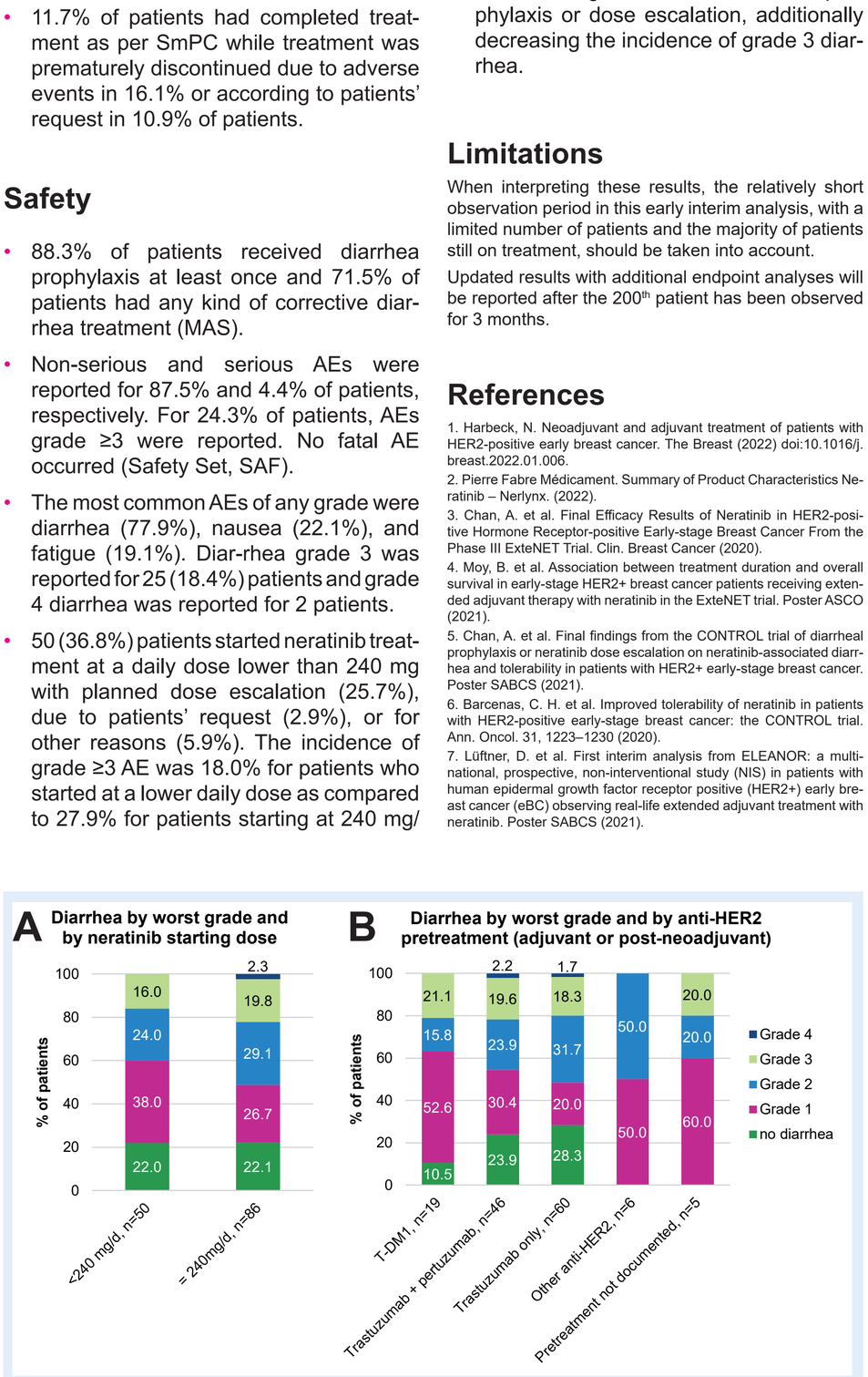

Figure 3: Incidence of diarrhea by worst grade and by (A) neratinib starting dose or by (B) adjuvant or post-neoadjuvant pretreatment (SAF). A, The proportion of patients by worst grade of diarrhea is reported in relation to the number of patients in the starting dose subgroups. B, The proportion of patients by worst grade of diarrhea is reported in relation to the number of patients in the pretreatment subgroups. For 5 patients, post-neoadjuvant pretreatment had not been documented yet. Other anti-HER2 drugs included other combinations or sequences of trastuzumab, pertuzumab and/or T-DM1

Conclusion

- The pattern of anti-HER2 pretreatment received by the patients in ELEANOR reflects the current treatment landscape for HER2+ eBC in Germany, Austria, and Switzerland.
- The proportion of patients with grade 3 diarrhea was lower if indirectly compared to the ExteNET study (18.4% vs. 39%).[3] This might be a result of increasing awareness towards the risk of diarrhea and increasing use of the dose escalation approach. A positive signal is the slight decrease of grade 3 diarrhea incidence, as compared to the previous ELEANOR interim analysis[7].
- These preliminary safety results emphasize the contribution of diarrhea management strategies, such as diarrhea prophylaxis or dose escalation, additionally decreasing the incidence of grade 3 diarrhea.

Limitations

When interpreting these results, the relatively short observation period in this early interim analysis, with a limited number of patients and the majority of patients still on treatment, should be taken into account.

Updated results with additional endpoint analyses will be reported after the 200th patient has been observed for 3 months.

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