Extended adjuvant treatment of patients with HER2+ early breast cancer with neratinib: a multi-centric, prospective, non-interventional study (NIS) in Germany and Austria (ELEANOR)

Rupert Bartsch[1], Diana Lüftner[2], Marija Balic[3], Gabriel Rinnerthaler[4], Christian Jackisch[5], Volkmar Müller[6], Marcus Schmidt[7], Nadia Harbeck[8]

[1]Medizinische Universität Wien, Klinische Abteilung für Onkologie, AKH Wien, Austria; [2]Charité – Universitätsmedizin Berlin, Medizinische Klinik mit Schwerpunkt Hämatologie, Onkologie und Tumorimmunologie, Berlin, Germany; [3]Universitätsklinikum für Innere Medizin, Klinische Abteilung für Onkologie, Graz, Austria; [4]Universitätsklinikum Salzburg, Innere Medizin III, Salzburg, Austria; [5]Sana Klinikum Offenbach, Klinik für Gynäkologie und Geburtshilfe, Offenbach, Germany; [6]Universitätsklinikum Hamburg-Eppendorf, Klinik und Poliklinik für Gynäkologie, Hamburg, Germany; [7]Universitätsmedizin Mainz, Klinik und Poliklinik für Geburtshilfe und Frauengesundheit, Mainz, Germany; [8]LMU Klinikum München, Brustzentrum, Frauenklinik, München, Germany

BACKGROUND

- Neratinib is an irreversible pan-HER tyrosine kinase inhibitor (TKI) registered in Europe as extended adjuvant treatment for adult patients with early-stage Hormone receptor-positive (HR+), HER2-overexpressed/amplified (HER2+) breast cancer, who completed adjuvant trastuzumab-based therapy less than one year ago („EMA-label population").[1]
- Despite optimal (neo)adjuvant treatment, distant recurrences are still observed with longer follow-up.[2–5] The recurrence risk is particularly high for patients who do not achieve a pCR after neoadjuvant therapy.[6]
- The subgroup of HER2+/HR+ patients has a specific risk profile with a higher risk for late recurrence (>5 years after diagnosis).[7,8]
- In the EMA-label population, neratinib improved the 5-year invasive disease-free survival (iDFS) rate by 5.1% compared to placebo (90.8% vs. 85.7%; HR 0.58 [95% CI 0.41-0.82]) in the ExteNET study. The benefit was particularly high in the subgroup of patients without pCR after neoadjuvant therapy: improvement of 5-year iDFS-rate by 7.4% (85.0% vs. 77.6%; HR 0.60 [95% CI 0.33-1.07]).[9]
- Without systematic diarrhea prophylaxis, the most common grade 3 adverse event in the ExteNET study was diarrhea, a HER-TKI class effect (neratinib: 39%, median cumulative duration 5 days; placebo: 1%; no grade 4 events).[9]
- ELEANOR is the first non-interventional study (NIS) to investigate real-world use of neratinib and its treatment management after different pre-treatments in the EMA-label population in Germany and Austria.

METHODS

Study design and participants

- Prospective, longitudinal, multicenter, observational study
- 200 adult female patients in accordance with the European Medicines Agency (EMA) label and the Summary of product characteristics (SmPC) specifications for neratinib (i.e. HR+/HER2+ early breast cancer and end of trastuzumab-based therapy less than one year ago)
- Approx. 90 sites across Germany and Austria
- CANKADO, a web-/application-based e-health solution, can be optionally used for quality of life (QoL) documentation
- An equivalent study is currently being set up in Switzerland

Study Objectives

Primary Objective

Patient treatment adherence: Rate of patients who take neratinib on at least 75% of the prescribed treatment days, with the intake documented in a patient calendar

Secondary Objectives

- Patient and disease characteristics
- Prior trastuzumab-based therapies: Including pertuzumab and T-DM1
- Neratinib treatment: Dosages, dose modifications, and neratinib treatment management
- Optional: Patient-reported outcomes (PROs), including QoL, treatment satisfaction; optional use of CANKADO
- Disease recurrence
- Safety and tolerability

First Interim Analysis – Preliminary results

- An *ad hoc* preliminary baseline analysis was performed after the enrollment of the 50th patient (cut-off date: December 14th, 2020) focusing on patient and disease characteristics at diagnosis and prior trastuzumab-based therapies.
- The analysis population included the enrolled set (ES) and the main analysis set (MAS), see **Figure 1**.
- Descriptive statistics were used to analyze the data.
- Other data, including patient treatment adherence, neratinib treatment, PROs, and safety data were immature at the time of this analysis and will be reported later (planned regular interim analysis after inclusion of 100 patients).

References

1. Pierre Fabre Médicament. Summary of Product Characteristics Neratinib – Nerlynx (2020).
2. Perez, E. A. et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 32, 3744–3752 (2014). 3. Cameron, D. et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet Lond. Engl. 389, 1195–1205 (2017). 4. Piccart, M. Abstract GS1-04: Interim overall survival analysis of APHINITY (BIG 4-11): A randomized multicenter, double-blind, placebo-controlled trial comparing chemotherapy plus trastuzumab plus pertuzumab versus chemotherapy plus trastuzumab plus placebo as adjuv... | Cancer Research. SABCS 2019 Abstr-03 Oral Present. 5. von Minckwitz, G. et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N. Engl. J. Med. 380, 617–628 (2019). 6. Cortazar, P. et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet Lond. Engl. 384, 164–172 (2014). 7. Vaz-Luis, I. et al. Impact of hormone receptor status on patterns of recurrence and clinical outcomes among patients with human epidermal growth factor-2-positive breast cancer in the National Comprehensive Cancer Network: a prospective cohort study. Breast Cancer Res. BCR 14, R129 (2012). 8. Strasser-Weippl, K. et al. Long-term hazard of recurrence in HER2+ breast cancer patients untreated with anti-HER2 therapy. Breast Cancer Res. BCR 17, 56 (2015). 9. Chan, A. et al. Final Efficacy Results of Neratinib in HER2-positive Hormone Receptor-positive Early-stage Breast Cancer From the Phase III ExteNET Trial. Clin. Breast Cancer (2020).

RESULTS

Population

From July 2020 until December 2020, 50 patients were enrolled across 23 sites in Germany and Austria (ES), including hospitals and practices. 35 patients qualified for the MAS and 15 patients had not yet started treatment (**Figure 1**). The median observation time at cut-off date was 1.6 months (ES).

Demographic baseline characteristics (ES)

The median age was 54 years and 38% of patients were premenopausal at diagnosis. A total of 54% of patients were either full- or part-time employed. Demographic baseline characteristics are depicted in **Table 1**.

Disease characteristics at primary diagnosis (ES)

Almost 90% of tumors presented at diagnosis with a WHO grading of G2 (46%) or G3 (42%) and a clinical tumor classification of T1 (42%) or T2 (46%). A total of 66% of patients were free of lymph node involvement (cN0) (**Table 2**). For 47 patients, a surgical resection was documented (breast conserving surgery - 74.5 %, mastectomy - 25.5%) (**Figure 2**).

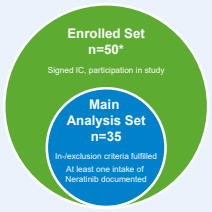
Prior trastuzumab-based therapies and pathological complete response (pCR) (ES)

68% of patients received neoadjuvant therapy, 26% started with adjuvant treatment (**Figure 3**). After neoadjuvant therapy (n=34 patients with documented neoadjuvant treatment), 55% of patients achieved a pCR (**Figure 4**). The dual blockade with trastuzumab and pertuzumab was administered in 83.3% of patients in the neoadjuvant setting (n=30 patients with documented drugs used in neoadjuvant setting). For 54% of patients, post-neoadjuvant therapy was already documented at the time of data cut-off, with the majority of patients being treated with trastuzumab monotherapy or the dual blockade (42.3% each, n=26 patients with documented drugs used in post-neoadjuvant setting). In the adjuvant setting, 76.9% received trastuzumab mono-therapy (**Figure 5**).

Neratinib treatment decision making and management

The main reason for neratinib treatment choice was efficacy (68%) (**Figure 6**). Diarrhea prophylaxis was performed in 91.4% patients (MAS). For a total of 88.6% of patients, the neratinib starting dose of 240 mg was chosen (**Table 3**).

Figure 1 – Analysis populations



IC, informed consent
*For 15 patients treatment start has not been documented yet.

Figure 2 – Surgery (ES)

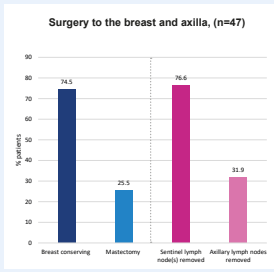
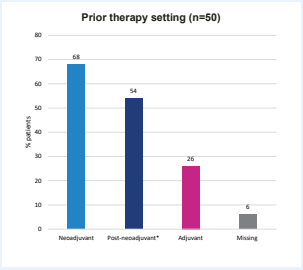
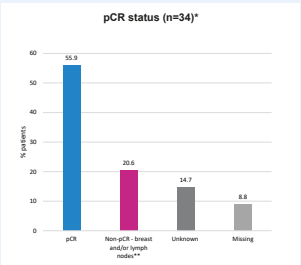


Figure 3 – Prior therapy setting (ES)



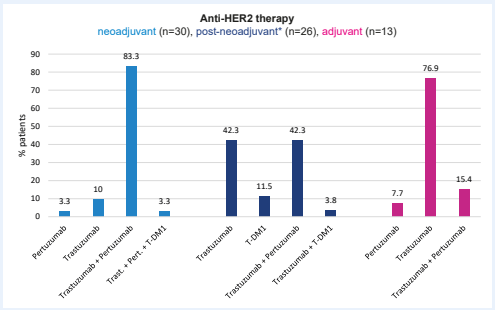
*At time of *ad hoc* preliminary analysis, documentation was not complete.

Figure 4 – pCR status after neoadjuvant therapy (ES)



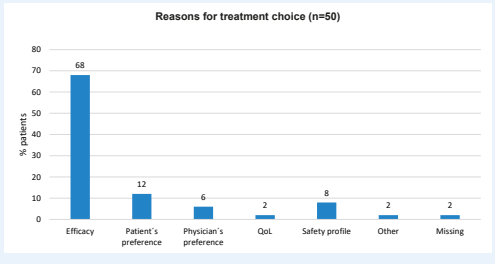
pCR, pathological complete response
* At time of *ad hoc* preliminary analysis, documentation was not complete.
**Non-pCR documented for breast and/or lymph nodes.

Figure 5 – Prior trastuzumab-based therapies (ES)



* At time of *ad hoc* preliminary analysis, documentation was not complete.

Figure 6 – Neratinib treatment decision (ES)



QoL, quality of life
The reason for choice of neratinib treatment is documented in the eCRF by choosing one of the possible answers: efficacy, patient's preference, physician's preference, QoL, safety profile, comorbidities, or other.

CONCLUSION

This preliminary *ad hoc* baseline analysis of the first 50 patients with extended adjuvant neratinib treatment who were included in the ELEANOR study depicts a young patient population with mainly node-negative disease and tumors <cT3 at diagnosis. Prior to neratinib, most patients received neoadjuvant and post-neoadjuvant treatment including trastuzumab and pertuzumab. More than half of the patients with neoadjuvant therapy achieved a pCR. The most common reason for neratinib treatment choice was "efficacy". Neratinib was mainly administered at the recommended starting dose of 240 mg and in combination with diarrhea prophylaxis.

The limited availability and immaturity of data at the time of this unscheduled analysis has to be taken into account when interpreting these preliminary data. Patient´s adherence to neratinib treatment, safety and QoL will be evaluated in the following analyses.

Table 1 – Demographic baseline characteristics (ES)

	N=50
Median age, years (IQR)	54.0 (44.0 – 60.0)
Median BMI (IQR), n=42	27.0 (23.1 – 31.7)
Employment status, %	
• Employed full-time	30.0
• Employed part-time	24.0
• Unemployed, not disease-related	4.0
• Unemployed, disease-related	10.0
• Retired	28.0
• Missing	4.0
ECOG Performance Status, %	
• 0	60.0
• 1	18.0
• 2	6.0
• Not evaluated / missing	10.0 / 6.0
Number of births, %	
• 0	14
• 1	30
• 2	48
• 3	6
• Missing	2
SARS-CoV-2 detected (virus or antibody), %	2
Median time from diagnosis to start of neratinib treatment, months (IQR), n=35	20.8 (18.4 – 27.0)
Premenopausal status at primary diagnosis, %	38

BMI, Body Mass Index; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group

Table 2 – Disease characteristics (ES)

%	N=50
WHO tumor type	
• Invasive carcinoma of no special type	82
• Invasive lobular carcinoma	6
• Other	8
• Missing	4
WHO tumor grading at primary diagnosis	
• G1	2
• G2	46
• G3	42
• Gx / missing	6 / 4
Clinical T-stage at primary diagnosis	
• cT1	42
• cT2	46
• cT3	2
• cTX / missing	6 / 4
Clinical N-stage at primary diagnosis	
• cN0 / cN1mi	66 / 2
• cN1	20
• cN3a	2
• cNX / missing	6 / 4
HER2 status at primary diagnosis	
• IHC +++	62
• FISH positive	14
• FISH pos. / IHC ++	10
• FISH pos. / IHC +++	2
• Unknown / missing	12
Ki67 status at primary diagnosis	
• High	48
• Low	30
• Unknown / missing	16 / 6

HER2, human epidermal growth factor receptor-2; IHC, immunohistochemistry; FISH, fluorescence *in situ* hybridization; Unknown/missing: At time of *ad hoc* preliminary analysis, documentation was not complete.

Table 3 – Neratinib treatment management (MAS)

%	N=35
Diarrhea prophylaxis performed* (documented on neratinib medication page)	
• Yes	91.4
• No	8.6
Neratinib start dose	
• 40 mg	2.9
• 120 mg	5.7
• 160 mg	2.9
• 240 mg	88.6

*at least once at any time

The study is funded by Pierre Fabre Pharma GmbH (Freiburg, Germany) and Pierre Fabre Pharma Austria (Wels, Austria).

Presented at 17th St. Gallen International Breast Cancer Conference, March 17 - 20, 2021

Poster number: P003