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Neratinib as Extended Adjuvant Treatment of HER2-Positive/HR-Positive Early Breast Cancer Patients in Germany, Austria, and Switzerland: Interim Results of the Prospective, Observational ELEANOR Study

Nadia Harbeck[a] Denise Wrobel[b] Matthias Zaiss[c] Jürgen Terhaag[d] Dagmar Guth[e] Andrea Distelrath[f] Mark-Oliver Zahn[g] Rachel Wuerstlein[a] Andreas Lorenz[h] Rupert Bartsch[i] Urs Breitenstein[j] Michael Schwitter[k] Marija Balic[l] Christian Jackisch[m] Volkmar Müller[n] Gabriel Rinnerthaler[o] Marcus Schmidt[p] Khalil Zaman[q] Timo Schinköthe[r] Anna Resch[s] Roberta Valenti[t] Diana Lüftner[u]

[a]Department of Obstetrics and Gynecology and CCC Munich, Breast Center, LMU University Hospital, Munich, Germany; [b]Sozialstiftung Bamberg Klinikum am Bruderwald, Bamberg, Germany; [c]Praxis fuer Interdisziplinaere Onkologie, Freiburg, Germany; [d]Rottal/Inn Clinic Eggenfelden, Eggenfelden, Germany; [e]Gyneco-Oncological Practice Dr. Guth, Plauen, Germany; [f]Praxisgemeinschaft Onkologie und Urologie, Wilhelmshaven, Germany; [g]MVZ Onkologische Kooperation Harz, Goslar, Germany; [h]Gyneco-Oncological Practice Dr. Lorenz, Hildburghausen, Germany; [i]Division of Oncology, Department of Medicine I, Medical University of Vienna, Vienna, Austria; [j]Divison of Oncology, Brust-Zentrum Zürich, Zurich, Switzerland; [k]Kantonsspital Graubünden, Chur, Switzerland; [l]Divison of Oncology, Department of Internal Medicine, Medical University Graz, Graz, Austria; [m]Department of Gynecology and Obstetrics, Klinikum Offenbach, Offenbach, Germany; [n]Department of Gynecology, University Hospital Hamburg-Eppendorf, Hamburg, Germany; [o]Department of Internal Medicine III, Paracelsus Medical University Salzburg, Salzburg, Austria; [p]Department of Gynecology, University Hospital Mainz, Mainz, Germany; [q]Breast Center, Lausanne University Hospital CHUV, Lausanne, Switzerland; [r]CANKADO Service GmbH, Kirchheim, Germany; [s]Pierre Fabre Pharma GmbH, Freiburg, Germany; [t]Pierre Fabre Medicament, Boulogne, France; [u]Immanuel Hospital Märkische Schweiz & Medical University of Brandenburg Theodor-Fontane, Brandenburg, Germany

Keywords

HER2-positive breast cancer · HR-positive breast cancer · Early breast cancer · Extended adjuvant treatment · Neratinib

Abstract

Introduction: Prognosis of patients diagnosed with HER2+ early breast cancer (eBC) has substantially improved, but distant recurrences impacting quality of life and survival still occur. One treatment option for extended adjuvant treatment of patients with HER2+/HR+ eBC is neratinib, available in Europe for patients who completed adjuvant trastuzumab-based therapy within 1 year. The ELEANOR study is investigating the real-world use of neratinib in Germany, Austria, and Switzerland. Results from an interim analysis of the first 200 patients observed for ≥3 months are reported. ***Methods:*** The primary objective of this

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karger@karger.com
www.karger.com/brc

Correspondence to:
Nadia Harbeck, nadia.harbeck@med.uni-muenchen.de

prospective, multicenter, observational study is to assess patient adherence to neratinib (defined as the percentage of patients taking neratinib on ≥75% prescribed days). Secondary objectives are patient characteristics and treatment outcomes. ***Results:*** At cut-off (May 2, 2022), a total of 202 patients had been observed for ≥3 months, with neratinib treatment documented for 187 patients (median age: 53.0 years; 67.9% at increased risk of disease recurrence). In total, 151 (80.7%) patients had received prior neoadjuvant treatment; of these, 82 (54.3%) patients achieved a pathologically complete response. Neratinib was initiated at a median 3.6 months after trastuzumab-based treatment, with 36.4% starting at a dose <240 mg/day. Treatment is ongoing for 46.0% of patients, with median treatment duration of 11.2 (interquartile range 0.9–12.0) months. Diarrhea was the most common adverse event (78.6% any grade, 20.3% grade ≥3); pharmacologic prophylaxis was used in 85.6% of patients. ***Conclusions:*** The pattern of anti-HER2 pretreatment observed reflected the current treatment for HER2+/HR+ eBC in Germany, Austria, and Switzerland. These interim results suggest that neratinib as an extended adjuvant is a feasible option after various anti-HER2 pretreatments and that its tolerability can be managed and improved with proactive diarrhea management.

Introduction

The prognosis of patients with human epidermal growth factor receptor 2 overexpressed/amplified (HER2+) early breast cancer (eBC) has substantially improved due to the introduction of targeted anti-HER2 therapies, such as trastuzumab [1–3], and the subsequent approval of neoadjuvant pertuzumab [4–7], post-(neo)adjuvant trastuzumab emtansine (T-DM1) for patients who do not achieve pathological complete response (non-pCR) [8], and extended adjuvant neratinib for patients with HER2+/hormone receptor-positive (HR+) tumors [9, 10]. Individualized treatment strategies have evolved, shifting towards neoadjuvant therapy and establishment of de-escalation and tailored dose-escalation approaches [11–14].

Therapy in the early setting aims to prevent loco-regional recurrence and development of distant metastases. Despite advances, up to 31% of patients are at risk of recurrence or death after 10 years, with a particularly high recurrence risk in those who are non-pCR after neoadjuvant treatment [3, 15]. In principle, patient prognosis is determined by tumor stage and biology and risk factors such as age and comorbidities [2, 3, 7, 8, 16]. Recurrence rates with HER2+/HR– eBC are higher in the 2 years post-randomization, while patients with HER2+/HR+ disease face a higher risk of late recurrences (years 5–9) [15].

Neratinib, an irreversible pan-HER tyrosine kinase inhibitor (TKI), is registered in Europe as extended adjuvant treatment for adults with HER2+/HR+ eBC who have completed adjuvant trastuzumab-based therapy within 1 year [17]. Twelve months of neratinib treatment after completion of post-(neo)adjuvant trastuzumab-based therapy switch the mode of action from extracellular HER2 blockade to intracellular pan-HER inhibition, offering additional risk reduction [10]. The ExteNET study demonstrated clinically meaningful benefit for neratinib versus placebo [18]. In this HR+ European Medicines Agency (EMA)/Swissmedic-label population, neratinib improved 5-year invasive disease-free survival (iDFS) by 5.1% overall (hazard ratio [HR] 0.58, 95% confidence interval [CI] 0.41–0.82) and 7.4% in patients who completed neratinib treatment (i.e., ≥11 months of treatment; HR 0.44, 95% CI 0.28–0.68) [10]. In addition, the 8-year overall survival was numerically improved in HR+ patients who were ≤1-year post-trastuzumab (HR 0.79, 95% CI 0.55–1.13) [10] and in those with HR+/centrally confirmed HER2+ disease (HR 0.65, 95% CI 0.41–1.03) [19]. A particularly high benefit was observed in the descriptive HR+ subgroup of non-pCR patients; the 5-year iDFS rate was improved by 7.4% (HR 0.60, 95% CI 0.33–1.07), and the 8-year overall survival rate was improved by 9.1% (HR 0.47, 95% CI 0.23–0.92) [10]; the 5-year iDFS rate was improved by 11.9% if neratinib treatment was completed (HR 0.42, 95% CI 0.19–0.83) [10, 20]. Of note, patients included in the ExteNET study had not received prior dual HER2-blockade and/or post-neoadjuvant T-DM1.

The tolerability of neratinib is consistent with other TKIs, with diarrhea as the most common adverse event (AE); however, in the ExteNET study, in the absence of specific recommended prophylaxis, grade ≥3 diarrhea was reported in 39% of neratinib patients [10], which is higher than that seen with other TKIs [21]. The CONTROL study investigated various prophylaxis and neratinib dose-escalation approaches and showed that frequency and severity of diarrhea can be improved over the ExteNET findings [22, 23]. All investigated strategies reduced rates of grade ≥3 diarrhea, with the lowest rate (13.3%) being achieved by a weekly dose-escalation strategy (120 → 160 → 240 mg over 2 weeks), diarrhea-associated discontinuations, and prolonged treatment durations.

The ELEANOR study aims to characterize the demographics, clinical characteristics, and treatment patterns of patients receiving neratinib in clinical practice in Germany, Austria, and Switzerland. The interim results of the ELEANOR study are presented here.

Materials and Methods

Study Design

This observational, prospective study is investigating the real-world use of neratinib in adult (≥18 years) female patients with HR+/HER2+ stage I–III breast cancer who completed adjuvant

Table 1. Patient characteristics at diagnosis in the main analysis set

Characteristic	*N* = 187
Median age, years (range)[a]	53.0 (22.0–81.0)
Ethnic group, *n* (%)	
Black	1 (0.5)
Caucasian	177 (94.7)
Other	9 (4.8)
Median (IQR) BMI, kg/m^2	26.0 (22.8–29.8)
Menopausal status (primary diagnosis), *n* (%)	
Premenopausal	82 (43.9)
Perimenopausal	14 (7.5)
Postmenopausal	91 (48.7)
Employment status, *n* (%)	
Employed full-time	56 (29.9)
Employed part-time	47 (25.1)
Unemployed, not disease related	12 (6.4)
Unemployed, disease related	26 (13.9)
Retired	39 (20.9)
Missing	7 (3.7)
ECOG performance status, *n* (%)	
0	133 (71.1)
1	47 (25.1)
2	3 (1.6)
Not evaluated	4 (2.1)
Clinical T-stage at primary diagnosis, *n* (%)	
cT0/cTis (DCIS)	1 (0.5)/2 (1.1)
cT1	23 (12.3)
cT1a/cT1b	2 (1.1)/12 (6.4)
cT1c	55 (29.4)
cT2	73 (39.0)
cT3	8 (4.3)
cT4/cT4d	1 (0.5)/1 (0.5)
cTX	9 (4.8)
Clinical N-stage at primary diagnosis, *n* (%)	
cN0/cN1mi	116 (62.0)/3 (1.6)
cN1	48 (25.7)
cN2	4 (2.1)
cN2a/b	1 (0.5)/1 (0.5)
cN3	1 (0.5)
cN3a	1 (0.5)
cNX	12 (6.4)
AJCC stage at primary diagnosis, *n* (%)	
TisN0M0	1 (0.5)
IA	69 (36.9)
IIA	55 (29.4)
IIB	26 (13.9)
IIIA	10 (5.3)
IIIB	2 (1.1)
IIIC	2 (1.1)
MX	11 (5.9)
TX/NX	11 (5.9)
WHO tumor grading at primary diagnosis, *n* (%)	
G1	3 (1.6)
G2	82 (43.9)
G3	92 (49.2)
GX	10 (5.3)
Ki67 status,[b] *n* (%)	
High	120 (64.2)
Low	54 (28.9)
Unknown	13 (7.0)

AJCC, American Joint Committee on Cancer; BMI, body mass index; c, clinical; DCIS, ductal carcinoma in situ; ECOG, Eastern Cooperative Oncology Group; G, grading; IQR, interquartile range; mi, micrometastasis; M, metastasis; N, lymph node; T, tumor; WHO, World Health Organization; X, status not determined. [a]At date of informed consent. [b]As per center standard definition.

trastuzumab-based therapy less than 1 year ago and decided to receive extended adjuvant neratinib according to the current summary of product characteristics [17].

Prior ethics committee approvals were obtained from participating sites. The study was registered at ClinicalTrials.gov (NCT04388384). Patients provided their written informed consent before enrollment.

Study Outcomes

The primary objective is to assess patient adherence to neratinib, defined as the proportion of patients who took neratinib on ≥75% of the prescribed treatment days. Secondary objectives include assessment of patient, disease, and tumor characteristics and previous treatments, as well as neratinib treatment patterns and management, disease relapse, patient-reported outcomes (PROs), reasons for treatment choice, physicians' and patients' satisfaction with treatment, health-related quality of life (QoL), and safety/tolerability. This pre-planned interim analysis reports patient, disease, and tumor characteristics, previous treatments, neratinib treatment patterns and management, disease relapse, and safety/tolerability.

Statistical Analysis

The main analysis set (MAS) was defined as all patients who met all inclusion criteria but none of the exclusion criteria, with at least one intake of neratinib documented, and who did not withdraw their consent to use the documented data, while the safety analysis set (SAS) was defined as all patients with at least one prescription of neratinib documented, for whom at least one safety assessment was obtained during treatment, and who did not withdraw their consent to use the documented data. The compliance set (CS) included all patients in the MAS for whom at least 1 patient calendar entry is available.

No formal database lock was performed before data analysis. Selective monitoring visits, regular central data monitoring, and validation were performed continuously during the study.

Descriptive statistics is used to present continuous variables (median, range, and interquartile range [IQR]) and categorical variables (number and percentage). Statistical analyses were conducted using SAS version 9.4.

Results

Patient Population

At the time of the pre-planned interim analysis, 202 of the 300 planned patients were enrolled ≥3 months prior to the cut-off date (May 2, 2022). Of these, 187 patients were included in the MAS and SAS; 178 patients were included in the CS (online suppl. Fig. S1; for all online suppl. material, see https://doi.org/10.1159/000533657).

In the MAS, median (range) age was 53.0 (22.0–81.0) years (Table 1); 55.1% of patients were employed; median (IQR) time from initial diagnosis to the start of neratinib treatment was 20.9 (18.0–23.7) months. Patients predominantly had clinical stages cT1 and cT2 (49.2% and 39.0%, respectively) or cN0/cN1mi and cN1 (63.6% and 25.7%, respectively). Correspondingly, 50.8% (n = 95) of patients were diagnosed with stage ≥II disease according to the American Joint Committee on Cancer (AJCC) staging system. Taken together, 67.9% of patients scheduled to

Table 2. Type of anti-HER2 treatment received in the neoadjuvant and adjuvant settings prior to neratinib

Setting (*n*/*N*, %)	Type of anti-HER2	*n* (%)
Neoadjuvant (151/187, 80.7%)	Trastuzumab + pertuzumab	127 (84.1)
	Trastuzumab	10 (6.6)
	Pertuzumab	2 (1.3)
	No anti-HER2	12 (7.9)
Post-neoadjuvant (151/187, 80.7%)[a,b]		
After pCR (82/151, 54.3%)	Trastuzumab	46 (56.1)
	Trastuzumab + pertuzumab	32 (39.0)
	Other anti-HER2[c]	2 (2.4)
	Not yet documented	2 (2.4)
After non-pCR (67/151, 44.4%)	Trastuzumab	7 (10.4)
	Trastuzumab + pertuzumab	17 (25.4)
	T-DM1	36 (53.7)
	Other anti-HER2	6 (9.0)
	Not yet documented	1 (1.5)
Adjuvant (no prior neoadjuvant) (36/187, 19.3%)	Trastuzumab	24 (66.7)
	Trastuzumab + pertuzumab	12 (33.3)

HER2, human epidermal growth factor receptor 2; pCR, pathological complete response; T-DM1, trastuzumab emtansine. [a]The post-neoadjuvant treatment was not documented for 4 patients. [b]pCR status was unknown in 2 patients. [c]"Other anti-HER2 treatments" included other combinations and/or sequences of trastuzumab, pertuzumab, and/or T-DM1.

receive neratinib were at increased risk of recurrence (defined as AJCC stage >I and/or lymph node involvement at diagnosis and/or non-pCR after neoadjuvant treatment); risk profiles were not assessable for 5.3% of patients. At the time of primary diagnosis, 49.2% of patients presented with World Health Organization tumor grade 3 and 64.2% of patients had high Ki-67 expression.

Thirty-six patients (19.3%) had upfront surgery and adjuvant treatment, while 151 (80.7%) patients received neoadjuvant treatment, of whom 82 (54.3%) achieved pCR. All 36 patients with upfront surgery received trastuzumab monotherapy (n = 24, 66.7%) or in combination with pertuzumab (n = 12, 33.3%; Table 2). In line with the current standard of care, anti-HER2 dual blockade with trastuzumab + pertuzumab (n = 127, 84.1%) was the most common neoadjuvant treatment. Patients who did not achieve pCR (n = 67, 44.4%) after neoadjuvant therapy predominantly received post-neoadjuvant T-DM1 (n = 36, 53.7%), while other patients received trastuzumab + pertuzumab (n = 17, 25.4%) or trastuzumab alone (n = 7, 10.4%). Patients who had a pCR (n = 82, 54.3%) commonly received post-neoadjuvant trastuzumab alone (n = 46, 56.1%) or with pertuzumab (n = 32, 39.0%).

In line with guidelines [11, 24], most patients (93.0%) received anti-hormonal treatment, either prior to or concomitantly with neratinib (online suppl. Table S1). Furthermore, 81% of patients had received prior radiotherapy.

Neratinib Treatment

Physicians' reasons for neratinib extended adjuvant treatment choice were efficacy (n = 118, 63.1%), safety (n = 27, 14.4%), physician's preference (n = 22, 11.8%), patient's preference (n = 15, 8.0%), QoL (n = 4, 2.1%), or other (n = 1, 0.5%). Median (IQR) time from the end of previous trastuzumab-based post-(neo)adjuvant therapy to neratinib initiation was 3.6 (1.8–7.3) months. In total, 119 (63.6%) patients started neratinib at an oral dose of 240 mg/day, whereas 68 (36.4%) patients started at lower doses, mostly at 120 (12.8%) or 160 (15.0%) mg/day.

At data cut-off, neratinib treatment was ongoing in 86 patients (46.0%), with 42 (22.5%) having completed 1 year of treatment. Neratinib was discontinued prematurely in 31 patients (16.6%) due to AEs, 19 (10.2%) due to their wishes, two (1.1%) due to disease recurrence, one (0.5%) due to concomitant disease, and six (3.2%) for other reasons (online suppl. Fig. S1). The median (IQR) treatment duration was 11.2 (0.9–12.0) months.

Disease Relapse

Three patients previously treated with neoadjuvant therapy had disease recurrence during the observation period, one with distant metastasis and two at the locoregional level.

Safety

In the SAS, any grade AEs and serious AEs were reported in 164 (87.7%) and 11 (5.9%) patients, respectively (Table 3); 48 (25.7%) patients experienced at least one grade ≥3 AE, irrespective of causality; no fatal AEs occurred. In patients who started neratinib at <240 mg/day, the occurrence of grade ≥3 AEs was 20.6% versus 28.6% for patients who started at 240 mg/day.

The most common AEs of any grade were diarrhea (n = 147, 78.6%), nausea (n = 38, 20.3%), and fatigue (n = 32, 17.1%). The most frequently reported AE of grade ≥3

Table 3. Adverse events (occurring in ≥5% of patients) by Common Terminology Criteria for Adverse Events (CTCAE) grade

Adverse events, *n* (%)	Any grade	Grade 1/2	Grade 3	Grade 4	Grade 5	Grade ≥3
Any TEAE	164 (87.7)	155 (82.9)	45 (24.1)	3 (1.6)	–	48 (25.7)
By MedDRA PT						
Diarrhea	147 (78.6)	127 (67.9)	36 (19.3)	2 (1.1)	–	38 (20.3)
Nausea	38 (20.3)	38 (20.3)	–	–	–	–
Fatigue	32 (17.1)	30 (16.0)	2 (1.1)	–	–	2 (1.1)
Abdominal pain upper	18 (9.6)	18 (9.6)	–	–	–	–
Headache	14 (7.5)	14 (7.5)	–	–	–	–
Rash	14 (7.5)	14 (7.5)	–	–	–	–
Muscle spasms	13 (7.0)	13 (7.0)	–	–	–	–
Vomiting	13 (7.0)	13 (7.0)	1 (0.5)	–	–	1 (0.5)
Constipation	12 (6.4)	12 (6.4)	–	–	–	–
Dry skin	12 (6.4)	12 (6.4)	–	–	–	–
Abdominal pain	10 (5.3)	10 (5.3)	–	–	–	–
Dry mouth	10 (5.3)	10 (5.3)	–	–	–	–
Epistaxis	10 (5.3)	10 (5.3)	–	–	–	–

MedDRA PT, Medical Dictionary for Regulatory Activities Terminology Preferred Term; TEAE, treatment-emergent adverse event.

was diarrhea (n = 38, 20.3%); 2 patients had grade 4 diarrhea. Most patients (85.6%) received diarrhea prophylaxis (timing of prophylaxis was unknown), mainly loperamide. Sixty-eight patients (36.4%) started neratinib at <240 mg/day with planned dose escalation; diarrhea prophylaxis was provided to 91.6% of patients starting neratinib at 240 mg/day and 75.0% of patients starting neratinib at <240 mg/day. Grade ≥3 diarrhea was observed less frequently in patients who started neratinib at a dose <240 mg (i.e., for whom an initial dose-escalation approach was chosen; 16.2% vs. 22.7%). No relevant difference in the incidence of severe diarrhea was observed between the various pretreatments (online suppl. Fig. S2). Diarrhea resulted in permanent discontinuation of treatment in 24 patients (12.8%), with 7/68 (10.3%) and 17/119 (14.3%) patients withdrawing from treatment after starting treatment at <240 and 240 mg/day, respectively.

Generally, patients who started neratinib at a lower dose had slightly longer treatment duration (median 11.7 [95% CI 4.0–12.0] months) compared with those who started at full dose (median 11.0 [95% CI 2.3–11.8] months), with 20.6% and 31.9% of patients permanently discontinuing treatment within the first 3 months, respectively (Fig. 1).

Discussion

To the best of our knowledge, ELEANOR is the first real-world study on neratinib use in Germany, Austria, and Switzerland and the management of treatment-related AEs according to current clinical standards.

Estimation of the recurrence risk is based on a combination of many factors, including patient demographics, tumor biology, and previous treatments. Employing a combination of AJCC tumor stage and response to neoadjuvant therapy to estimate the disease risk profile, as proposed by Amendment 3 of ExteNET [10], 67.9% of patients enrolled in ELEANOR so far were at increased risk of disease recurrence. The pattern of anti-HER2 pretreatment received by ELEANOR patients reflects the modern HER2+ eBC treatment landscape. Most patients received dual blockade in the neoadjuvant and/or adjuvant setting prior to neratinib. Of note, only 53.7% of patients with residual disease received T-DM1 in the post-(neo)adjuvant setting. This unexpectedly low proportion might be explained by the fact that T-DM1 was approved as adjuvant treatment in December 2019, which was only 6 months before the inclusion of the first patient in ELEANOR (July 2020). This means that post-(neo) adjuvant T-DM1 treatment was still ongoing in patients at the start of the ELEANOR study, and inclusion of patients pre-treated with T-DM1 was delayed accordingly. In line with this, the proportion of T-DM1-treated patients is steadily increasing at each interim analysis [25–27]. Remarkably, patients achieving a pCR after neoadjuvant therapy (43.9% of patients enrolled in ELEANOR) were also scheduled for neratinib treatment, clearly showing that additional factors, such as tumor size and nodal status [16], might be a reason for the choice of extended adjuvant treatment.

The tolerability profile of neratinib in ELEANOR is consistent with that observed in ExteNET [10]. Diarrhea was the most frequently reported AE, but prophylaxis (used by the majority of ELEANOR patients) appeared to

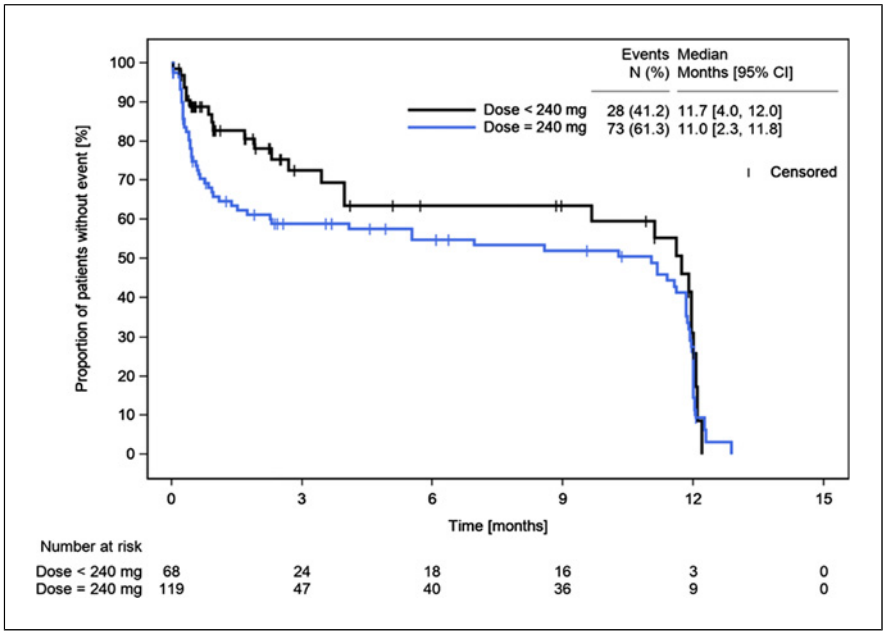

Fig. 1. Treatment duration by starting dose. CI, confidence interval.

reduce the risk of grade 3 diarrhea. With 20.3% of patients reporting grade ≥3 diarrhea and 78.6% reporting any grade, its occurrence in ELEANOR was lower than in ExteNET (39 vs. 94%, respectively) [10], and in the range of incidence and severity observed for other available TKIs [21]. This is likely the result of increasing awareness of diarrhea risk and more frequent use of anti-diarrheal strategies, including medical prophylaxis and a dose-escalation approach. About one-third of treating physicians started neratinib at a daily dose below the standard dose of 240 mg. In these patients, the proportion of patients with grade ≥3 diarrhea was lower than in those who had started neratinib treatment with the standard dose (16.2 vs. 22.7%). This is in line with the final analysis of the CONTROL study [23]; results show a substantial reduced incidence of grade 3 diarrhea in patients in whom medical prophylaxis or weekly dose escalation were employed as compared with ExteNET findings [10]. In fact, most ELEANOR patients also received anti-diarrheal treatment at least once during the documentation period. While encouraging, this interim analysis is limited by the relatively short observation period and the small patient number.

Conclusion

This second interim analysis of the ELEANOR study demonstrates the feasibility of extended adjuvant neratinib as a treatment option for HER2+/HR+ eBC in clinical practice settings, particularly for patients at increased risk of recurrence, and is independent of the type of anti-HER2 therapy received in the neoadjuvant setting. In this context, these results indicate that establishment of adequate treatment management strategies for neratinib, such as diarrhea prophylaxis or dose escalation, can markedly improve tolerability in high-risk HER2+/HR+ eBC. 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.

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Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study protocol was reviewed and approved by ethics committees from participating sites in Germany (Baden-Württemberg: F-2020-019), Austria (University of Wien: 1171/2020), and Switzerland (Kanton Zürich: 2021-00169). Patients provided written informed consent before enrollment.

Conflict of Interest Statement

Nadia Harbeck has received honoraria for lectures and/or consulting from Amgen, AstraZeneca, Daiichi Sankyo, Gilead, Lilly, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Sandoz, and

Seagen. Denise Wrobel has received honoraria from Novartis, Teva, Roche, and AstraZeneca and for lectures and travel grant from Roche, Novartis, and Pierre Fabre. Matthias Zaiss has received honoraria for lectures and/or consulting from AbbVie, AstraZeneca, BMS, Celgene, Eisai, Gilead, Hexal, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, and Vifor. Jürgen Terhaag has received funds from Aurikamed and registration fees from Lilly. Dagmar Guth has received fees for lectures and consulting from Amgen, Aristo, Astra Zeneca, Celgene, Gilead, Janssen, Lilly, Novartis, Pharma Mar, Pfizer, Ribosepharm, and Roche. Rachel Wuerstlein has acted as an advisor, consultant, or speaker for or received travel grant(s) from Agendia, Amgen, Aristo, AstraZeneca, Boehringer Ingelheim, Carl Zeiss, Celgene, Clovis Oncology, Daiichi-Sankyo, Eisai, Exact Sciences, Genomic Health, Gilead, Glaxo Smith Kline, Hexal, Lilly, Medstrom Medical, MSD, Mundipharma, Mylan, Nanostring, Novartis, Odonate, Paxman, Palleos, Pfizer, Pierre Fabre, Puma Biotechnology, Riemser, Roche, Sandoz/Hexal, Sanofi Genzyme, Seattle Genetics, Seagen, Tesaro Bio, Teva, Veracyte, and Viatris. Rupert Bartsch has received fees from AstraZeneca, Daiichi Sankyo, Eisai, Eli Lilly, Gilead, Grünenthal, MSD, Novartis, Pfizer, Pierre Fabre, Roche, and Seagen. Michael Schwitter has received personal fees from Pierre Fabre, Daiichi Sankyo, and Novartis. Marija Balic has received personal fees from Amgen, AstraZeneca, Daiichi Sankyo, Eli Lilly, Gilead, MSD, Novartis, Pierre Fabre, Pfizer, Roche, and Seagen; and research funding from AstraZeneca, Daiichi Sankyo, Eli Lilly, Novartis, Pierre Fabre, Pfizer, and Seagen. Christian Jackisch has received personal fees from AstraZeneca, Daiichi Sankyo, Exact Sciences, Eisai, Lilly, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Seagen, Art Tempi Communications, and Med Update. Volkmar Müller has received speaker honoraria from Amgen, AstraZeneca, Daiichi Sankyo, Eisai, GSK, Pfizer, MSD, Medac, Novartis, Roche, Teva, onkowissen, high5 Oncology, Medscape, Gilead, and Pierre Fabre; consultancy honoraria from Hexal, Roche, Pierre Fabre, Amgen, ClinSol, Novartis, MSD, Daiichi Sankyo, Eisai, Lilly, Sanofi, Seagen, and Gilead; institutional research support from Novartis, Roche, Seagen, and Genentech; travel grants from Roche, Pfizer, Daiichi Sankyo, and Gilead. Gabriel Rinnerthaler has received personal fees from Amgen, AstraZeneca, Daiichi Sankyo, Eli Lilly, Gilead, Merk, MSD, Novartis, Pfizer, Pierre Fabre, Roche, and Seagen. Marcus Schmidt has received personal fees from AstraZeneca, BioNTech, Daiichi Sankyo, Eisai, Lilly, MSD, Novartis, Pantarhei Bioscience, Pfizer, Roche, and SeaGen; institutional research funding from AstraZeneca, BioNTech, Eisai, Genentech, German Breast Group, Novartis, Palleos, Pantarhei Bioscience, Pierre Fabre, and Seagen; and holds patents for EP 2390370 B1 and EP 2951317 B1. Khalil Zaman has received honoraria from AstraZeneca, Daiichi, Eisai, Exact Sciences, Gilead, Lilly, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Seagen, Viatris, and Vifor; a member of the Executive Committee of the MINDACT trial; and a member of the Swiss Group for Clinical Research against Cancer (SAKK). Timo Schinköthe is the owner of CANKADO. Diana Lüftner has received honoraria for advisory board activities and/or presentations from Amgen, AstraZeneca, Eli Lilly, Gilead, GSK, high5md, Loreal, MSD, Mundipharma, Mylan, Novartis, onkowissen, Pfizer, Pierre Fabre, Roche, Teva, and Viatris. Anna Resch and Roberta Valenti are employees of Pierre Fabre. Andrea Distelrath, Mark-Oliver Zahn, Andreas Lorenz, and Urs Breitenstein have no conflicts of interest to declare.

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Author Contributions

All authors participated in the development of the manuscript and the decision to submit it for publication. The authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship, take responsibility for the integrity of the work, have given their approval for this version to be published, and have full confidence in the accuracy and integrity of the work and of other group authors.

Data Availability Statement

Data are available from the corresponding author on reasonable request and with the permission of Pierre Fabre GmbH.

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