A real-world prospective observational multi-national study in adult patients with breast cancer treated with extended adjuvant neratinib: interim results from the NERLYFE study

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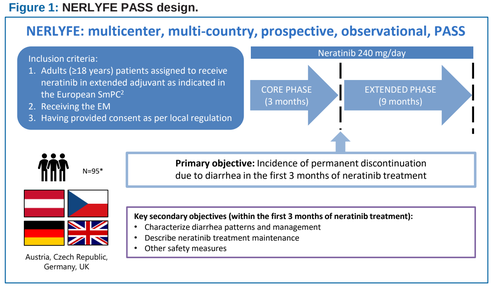
Introduction

- Although treatment with human epidermal growth factor receptor 2 (HER2)-targeted therapies in the (post-) neoadjuvant or adjuvant setting has improved the outcome of patients with HER2-positive (*HER2+*) early breast cancer (eBC), there remains a significant risk of disease recurrence in the longer term.[1]
- The pan-HER tyrosine kinase inhibitor neratinib was approved in Europe in 2018 as extended adjuvant therapy for hormone receptor-positive (HR+)/HER2+ eBC in patients who completed trastuzumab-based therapy less than one year ago.[2] The approved duration of neratinib therapy in Europe is 12 months (1 year) of continuous daily treatment.
- In the ExteNET trial, neratinib demonstrated a clinical benefit vs placebo, including significantly improved 5-year invasive disease-free survival (iDFS; Δ5.1%, hazard ratio [HR] 0.58, 95% confidence interval [CI] 0.41–0.82) in this population.[3] In the absence of mandatory diarrhea prophylaxis, neratinib-associated diarrhea was the most common adverse event (AE; Grade ≥3 in 40% of patients) in this study.[3]
- Neratinib is indicated in the EU for extended adjuvant treatment of adults with eBC, HER2+, hormone-receptor–positive who have completed prior trastuzumab-based adjuvant therapy.[2]
- When neratinib was approved, additional risk minimization measures (i.e., educational materials) were implemented as part of the risk management plan to prevent and minimize diarrhea through antidiarrheal prophylaxis, dietary changes, and neratinib dose modifications.[4]
- The real-world NERLYFE post-authorization safety study (PASS) assessed the effectiveness and safety of these measures in routine clinical practice.

Methods

- NERLYFE is a European, prospective, observational PASS (**Figure 1**).

Figure 1: NERLYFE PASS design.



BC, breast cancer; EM, extended adjuvant maintenance therapy; PASS, post-authorization safety study; SmPC, Summary of Product Characteristics (neratinib);[2] *Initially 368 patients were planned to be enrolled, then the protocol was amended to reduce the sample size to 95 patients.

- All patients provided informed consent as per local regulations. The study was approved by the local ethics committees.
- Here we report the results of the primary and key secondary endpoints (maintenance of neratinib treatment, pattern of diarrhea, other AEs) within the first 3 cycles of neratinib treatment (within 105 days of neratinib start date).

Results

Study population

- A total of 122 patients were enrolled between May 9, 2022, and September 30, 2024, from 35 active participating sites across Germany, Austria, Czech Republic, and the UK; 113 met eligibility criteria and were included in the safety analysis set (defined as patients who provided informed consent and received at least one dose of neratinib).
  - The majority of participants came from Germany (n=63) and the UK (n=44).
  - The study data cut-off date was December 31, 2024; this analysis was based on a data snapshot taken on February 11, 2025.
- At neratinib initiation, patients had a median age of 54.9 years and 99.1% were female **(Table 1).**

Table 1: Patient characteristics and tumor characteristics at initial diagnosis.

	Neratinib (n=113)
Patient characteristics	
Age, years, median (range)	54.9 (29.0–80.0)
Female sex, n (%)	112 (99.1)
Premenopausal status, n (%)	32 (28.6)
ECOG performance status, n (%)	n=76
0	65 (85.5)
1	10 (13.2)
2	1 (1.3)
Missing	37
Tumor characteristics	
Clinical AJCC stage, n (%)	n=112
I	47 (41.6)
II + III	65 (57.5)
Unknown	1 (0.9)
Tumor size, n (%)	n=112
T1	56 (50.0)
T2	46 (41.1)
T3	2 (1.8)
T4	8 (7.1)
Missing	1
Lymph nodes involved, n (%)	n=112
0	53 (47.3)
1–3	35 (31.3)
≥4	24 (21.4)
Missing	1
HER2 positive or amplified, n (%)	109 (97.3)
Negative	3 (2.7)
Missing	1
Receptor status, n (%)	n=112
HR positive	109 (97.3)
ER positive	109 (97.3)
PR positive	87 (77.7)
Missing	1

AJCC, American Joint Committee on Cancer; ECOG, European Cooperative Oncology Group; ER, estrogen receptor; HER, human epidermal growth factor receptor; HR, hormone receptor; PR, progesterone receptor.

Neoadjuvant and adjuvant therapies

- More than half of the patients (59.3%) received at least one prior neoadjuvant therapy; among these, most received at least one chemotherapy and at least one anti-HER2 therapy, most commonly trastuzumab + pertuzumab (76.2%; **Table 2**).
  - 38.8% of patients achieved a partial complete response (pCR) and 58.2% had residual disease (non pCR).
- The vast majority of patients were at high risk of relapse (80%; **Table 2**).
- All patients received at least one adjuvant or post neoadjuvant therapy, with 100.0% receiving an anti-HER2 therapy, most often trastuzumab only (55.8%) or T-DM1 (28.3%).

Table 2: Prior therapies and disease disease risk profile.

	Neratinib (n=113)
Previous therapy setting, n (%)[a]	
Adjuvant only	46 (40.7)
Neoadjuvant and post neoadjuvant	67 (59.3)
Prior neoadjuvant treatments, n (%)	
At least one neoadjuvant therapy	67 (59.3)
At least one chemotherapy	65 (97.0)
At least one endocrine therapy	2 (3.0)
At least one anti-HER2 therapy	63 (94.0)
Anti-HER2 therapy	
Trastuzumab only	12 (19.0)
Trastuzumab + pertuzumab	48 (76.2)
T-DM1	1 (1.6)
Other[b]	2 (3.2)
Duration of prior neoadjuvant anti-HER2 treatment, months, median [IQR]	3.5 [2.8; 3.5]
Response to neoadjuvant treatment, n (%)	
pCR	26 (38.8)
Non-pCR	39 (58.2)
Unknown	2 (3.0)
Disease risk profile, n (%)[c]	
Low	9 (8.0)
High	89 (78.8)
Unknown	15 (13.3)
Adjuvant/post-neoadjuvant treatments	
At least one adjuvant/post-neoadjuvant therapy, n (%)	113 (100.0)
At least one chemotherapy, n (%)	46 (40.7)
At least one endocrine therapy, n (%)	70 (61.9)
At least one anti-HER2 therapy, n (%)	113 (100.0)
Anti-HER2 therapy, n (%)	
Trastuzumab only	63 (55.8)
Trastuzumab + pertuzumab	12 (10.6)
T-DM1	32 (28.3)
Other[b]	6 (5.3)
Duration of adjuvant/post-neoadjuvant anti-HER2 treatment, months, median [IQR]	9.7 [8.6; 12.0]

[a]Includes anti-HER2 therapy and/or chemotherapy (excluding endocrine therapy); [b]Any other combination of trastuzumab, pertuzumab and T-DM1, including switches between agents; [c]Low risk = AJCC stage I and N0 and pCR; High risk = AJCC stage >I or node positive or non-pCR. AJCC, American Joint Committee on Cancer; HER, human epidermal growth factor receptor; IQR, interquartile range; pCR, pathological complete response; T-DM1, trastuzumab emtansine.

Neratinib treatment exposure

- At 3 months, >80% of patients were still being treated with neratinib. Among the 20 patients (18%) who discontinued neratinib prematurely, the main reason was diarrhea (13.3% of the safety population; **Table 3**).

Table 3: Neratinib treatment patterns and antidiarrheal concomitant therapies.

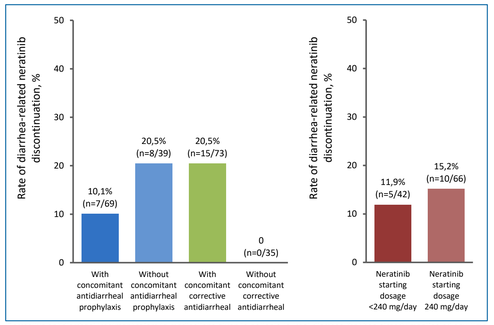
	Neratinib (n=113)
Time from completion of anti-HER2 therapy to initiation of neratinib, months, median (range)	2.4 (0.1–12.6)
Starting dosage of neratinib, n (%)	
240 mg/day	69 (61.1)
<240 mg/day	44 (38.9)
Duration of neratinib treatment, months, median (range)	3.5 (0.1–3.5)
Still on neratinib, n (%)	93 (82.3)
Discontinued neratinib, n (%)	20 (17.7)
Reasons for treatment discontinuation, n (%)	n=20
Diarrhea	15 (75.0)
Other AE/toxicity	4 (20.0)
Disease recurrence	0
Patient elected to withdraw from study	1 (5.0)
At least one treatment modification, n (%)[a]	68 (60.2)
Type of treatment modification, n (%)	n=68
Dose escalation[b]	36 (31.9)
Treatment interruption	33 (29.2)
Dose reduction	26 (23.0)
Dose increase	1 (0.9)
Reasons for treatment modification, n (%)[a]	n=134
Diarrhea	55 (41.0)
Other AE/toxicity	16 (11.9)
Dose escalation	36 (26.9)
Patient decision	13 (9.7)
Other	14 (10.4)
Concomitant antidiarrheal prophylaxis, n (%)[c]	71 (62.8)
Concomitant corrective antidiarrheal treatment, n (%)[d]	75 (66.4)

[a]Other than permanent treatment discontinuation. [b]Dose escalation was derived data when the starting dose is below 240mg with a subsequent dose increased in the subsequent weeks. [c]Antidiarrheal prophylaxis refers to treatment administered to prevent diarrhea before it occurs. [d]Corrective antidiarrheal treatment refers to medication given to patients for diarrhea that has already manifested any time during neratinib treatment. AE, adverse event.

Primary endpoint results

- In total, 15 of 113 patients (13.3%) discontinued treatment due to diarrhea within the first 3 months. For the primary endpoint analysis (**Figure 2**), among the 108 patients who have maintained neratinib treatment at 3 months or discontinued earlier due to diarrhea (base case), the rate of permanent discontinuation due to diarrhea within the first 3 months was 13.9% (15/108; 95% CI 7.4–20.4).
- Two sensitivity analyses were conducted:
  - In a best-case scenario, all 113 patients of the safety set were considered the denominator, leading to a discontinuation rate of 13.3% (15/113; 95% CI 7.0–19.5).
  - In a worse-case scenario, where 'other' reasons were combined with diarrhea-related discontinuations in the numerator, the rate of diarrhea-related discontinuation was 17.7% (20/113; 95% CI 10.7–24.7).

Figure 2: Rates of diarrhea-related neratinib discontinuation based on the use of antidiarrheal prophylaxis, corrective antidiarrheals, and the neratinib starting dose.



Corrective antidiarrheal treatment refers to medications given to patients to treat diarrhea that has already manifested any time during neratinib treatment, as opposed to prophylactic measures taken to prevent diarrhea before it occurs. Among patients having taken anti-diarrhoeal prophylactic treatments, the most frequently used was loperamide (98.6% of these patients).

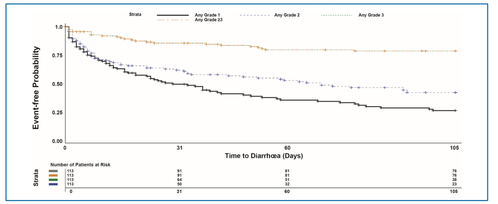
- The diarrhea-related discontinuation rate in the absence of concomitant antidiarrheal prophylaxis was double that when antidiarrheal prophylaxis was given (**Figure 2**).
- Neratinib was discontinued in 20.5% of patients given corrective antidiarrheal treatment, as per routine practice, and none without corrective antidiarrheal treatment discontinued neratinib.

Secondary endpoint results

Patterns of diarrhea

- Within the first 3 months of neratinib treatment, the proportion of patients with any grade of diarrhea was 87.6% and with Grade 3 diarrhea was 20.4%.
  - The median number of diarrhea events of any grade per patient was 3
  - Diarrhea events were mostly of Grade 1 severity (66.3%), 27.8% were Grade 2 and 5.9% were Grade 3.
  - No Grade 4 or 5 diarrhea events were reported.
- Overall, one diarrhea event (0.2%) was reported as serious by the investigators.
- Cumulative incidence of diarrhea by grade over time is shown in **Figure 3**.
  - Median time to the first diarrhea event of any grade was 7 days.
  - Median cumulative duration per patient for any diarrhea event was 23 days and for Grade 3 diarrhea was 12 days.

Figure 3: Cumulative incidence of diarrhea over time, by grade.



Patients without a diarrhea event were censored at 3 months (105 days) from treatment initiation if treatment was still ongoing or at treatment discontinuation date (if patient discontinued prior to 3 months from neratinib initiation.

- The rate of diarrhea (any grade/Grade 3) was slightly lower with antidiarrheal prophylaxis (85.9%/19.7%) versus without (90.5%/21.4%).
- A higher proportion of any diarrhea events were reported as resolved in the group that did not receive antidiarrheal prophylaxis compared with the group that received antidiarrheal prophylaxis (95.6% vs 83.5%, respectively).
- A higher percentage of Grade 3 diarrhea events were reported to cause neratinib discontinuation in the group without antidiarrheal prophylaxis compared with the antidiarrheal prophylaxis group (45.5% vs 8.3%, respectively) and the median cumulative duration of Grade 3 diarrhea was nearly half in patients who did versus did not receive antidiarrheal prophylaxis (6.5 vs 13.0 days, respectively).

Summary of all other AEs (other than diarrhea)

- 62 out of 113 patients (54.9%) reported at least one treatment-emergent AE (TEAE) with neratinib, mostly of Grades 1 (75.8%) and 2 (46.8%); Grade 3 TEAEs were reported in 12.9% of patients (no Grade 4 or 5 TEAEs were reported).
- Any grade TEAEs (other than diarrhea) occurring in ≥5% of patients were nausea (14.2%), vomiting (8.8%), upper abdominal pain (7.1%) and fatigue (6.2%); TEAEs leading to discontinuation of neratinib occurred in 8 patients (7.1%), mostly due to gastrointestinal disorders.
- Non-diarrhea treatment-related TEAEs of any grade occurred in 40 patients (35.4%); Grade 3 treatment-related TEAEs were reported in 5 patients (vomiting [n=2]; muscle spasms, nausea, mucosal ulceration and abnormal liver function [n=1 each]).
- Three patients reported serious AEs in the first 3 months of neratinib treatment:
  - GI disorders in 2 patients (Grade 2 constipation, Grade 3 nausea, Grade 3 vomiting).
  - Grade 3 fracture displacement in 1 patient.

Conclusions

- **Diarrhea-related neratinib treatment discontinuation within the first 3 months was 13.9% (primary endpoint). Concomitant antidiarrheal prophylaxis reduced the rate of diarrhea-related discontinuation from 20.5% to 10.1%. These real-world findings support the benefit of antidiarrheal prophylaxis (with loperamide).**
- **Overall, the interim results of the NERLYFE PASS conducted in Austria, the Czech Republic, Germany, and the UK support the use of neratinib for patients with HR+/HER2+ eBC in the real-world current landscape and show an overall safety profile consistent with the European prescribing information.[2]**

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Conflicts of interest

Rupert Bartsch has acted in an advisory role for AstraZeneca, Daiichi, Eisai, Eli Lilly, Gilead, Gruenenthal, MSD, Novartis, Pfizer, Pierre Fabre, Puma, Roche, Seagen, and Stemline; has received lecture honoraria from AstraZeneca, BMS, Daichi, Eisai, Eli Lilly, Gilead, Gruenenthal, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Seagen, and Stemline; and received research support from Daiichi, MSD, Novartis, and Roche.

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