NER-Tree study interim analysis of safety and patient-reported outcomes in patients with Human Epidermal Growth Factor Receptor 2 positive (HER2+) early breast cancer (EBC) treated with neratinib in China

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Background

Neratinib, an oral irreversible pan-HER tyrosine kinase inhibitor, was approved in 2020 in China for the extended adjuvant treatment of HER2+ early breast cancer (EBC) adult patients. The approval was based on the ExteNET trial showing significant iDFS benefit (absolute improvements of 2.3% and 2.5% at 2 and 5 years)[1,2]. It was included in the National Reimbursement Drug List in 2021. It has been successfully included in the national reimbursement drug list since 2021.[3]

In ExteNET, which did not mandate antidiarrheal prophylaxis, diarrhea was the most common grade 3 adverse event in the absence of primary diarrhea prophylaxis (neratinib arm: 40%, placebo: 2%); Grade 4 events were only reported in one patient from the neratinib group(<1%).[1] However, as demonstrated by the CONTROL study, diarrhea can generally be managed through adequate management, such as a dose escalation approach and loperamide.[4]

Pertuzumab and T-DM1 were approved in China for adjuvant use in 2018 and 2020, respectively, and are now reimbursed. This has shifted the treatment landscape significantly from that of the ExteNET study. The NER-Tree study aims to observe the treatment patterns, safety profile and patient-reported quality of life (QoL) of neratinib among HER2-positive early-stage breast cancer patients in the extended adjuvant setting in a contemporary treatment landscape in China. An interim analysis, including the characteristics, treatment patterns and safety profile of neratinib for the first 250 patients, was previously presented at ESMO Breast Cancer 2024 and ESMO 2024.[5,6]

Here we report safety data in the prespecified second interim analysis with all 500 patients included, focusing on diarrhea management and patient-reported outcomes. Here we report the corresponding safety data.

Study Objectives

The primary and secondary objectives are to describe the real-world treatment patterns with of neratinib as extended adjuvant treatment post anti-HER2 adjuvant therapy in HER2-positive early-stage breast cancer patients and to observe the safety of patients as extended adjuvant treatment in a real-world setting in China, respectively.

The exploratory objectives include describing invasive disease recurrence pattern and patient-reported quality of life.

Methods

NER-Tree is an ongoing, prospective, multi-center, non-interventional study (NCT05491057) that aims to enroll 500 patients with HER2+ early breast cancer (EBC) starting 1-year extended adjuvant neratinib after completion of an anti-HER2 based adjuvant treatment. Prespecified interim analyses are planned after the recruitment of 250 and 500 patients (Figure 1).

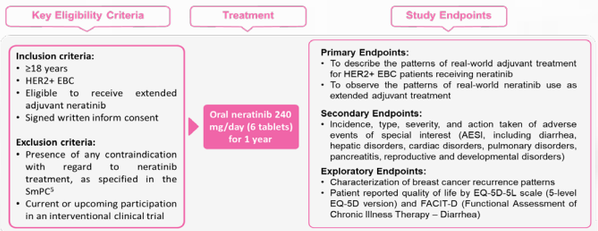


Figure 1

Results

Baseline Characteristics

As of 28 October 2024, 500 HER2-positive patients were enrolled and included in the analysis. (Table 1).

The median age of patients was 50.5 years. Over one-quarter (27.8%) of the patients had cT1 and 54.8% had cT2; 76.4% of patients were N+ and 89.0% had Stage II+ III tumors. A total of 328 patients (65.6%) were postmenopausal. At primary diagnosis, 55.0% of the patients had HER2+/hormone receptor-positive (HR+) tumors.

Table 1. Baseline characteristics

	HER2+ early-stage breast cancer with neratinib (N=500, %)
Median age, Years (range)	50.5 (25-77)
Menopausal status at baseline	
Postmenopausal	328 (65.6)
Pre-menopausal	171 (34.2)
Breast cancer stage category at initial BC diagnosis	
Stage 0	2 (0.4)
Stage I	24 (4.8)
Stage II	262 (52.4)
Stage III	183 (36.6)
Others (includes others and Tx)	29 (5.8)
T Stage	
T0	5 (1.0)
T1	139 (27.8)
T2	274 (54.8)
T3	34 (6.8)
T4	25 (5.0)
Others (includes others and not documented)	23 (4.6)
Nodal status at initial diagnosis	
N0	97 (19.4)
N1	218 (43.6)
N2	99 (19.8)
N3	65 (13.0)
Others (includes NX and not documented)	21(4.2)
Hormonal receptor status at initial diagnosis	
HER2+/HR+	275 (55.0)
HER2+/HR-	202 (40.4)
Others(includes not tested or documented)	23 (4.6)
Ki67 Positive	417 (83.4)
Adjuvant Treatment Regimens	
Trastuzumab	38 (7.6)
Trastuzumab + Pertuzumab	451 (90.2)
T-DM1	9 (1.8)

Overall Safety Results

Diarrhea (86.4%), nausea(18.2%), fatigue (15.6%), and decreased appetite (14.4%) were the most common AEs of any grade. Diarrhea was predominantly reported as Grade 1 or 2 (69.6%), while Grade 3 diarrhea was reported in 16.8% of the patients. No grade 4 diarrhea was observed (Figure 2).

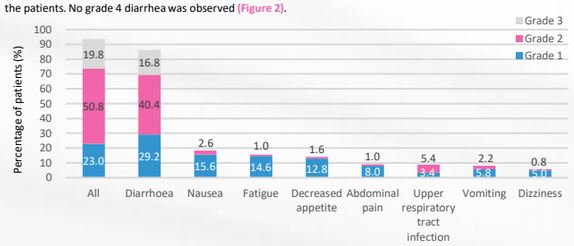


Figure 2. AEs occurring in at least 5% of patients in the safety population

Analysis of Diarrhea

The median time from the initiation of neratinib treatment to the onset of diarrhea was 3.0 days (interquartile range [IQR] 2.0,6.0). The cumulative duration of ≥grade 3 diarrhea was 5.0 days (IQR 1.0, 73.0).

Diarrhea was the most common adverse event leading to dose reduction (14.4% of cases vs. 18.2% for all adverse events combined), dose interruption (18.0% vs 33.6%), and permanent discontinuation(4.2% vs 6.8%) (Table 2).

Table 2. Summary of diarrhea in patients with neratinib treatment

	Neratinib (N=500)
Incidence of diarrhea [a]	N (%)
Any Grade	432 (86.4)
Grade 1-2 Diarrhea	348 (69.6)
Grade 1	146 (29.2)
Grade 2	202 (40.4)
Grade 3 Diarrhea	84 (16.8)
Time to onset of diarrhea, days (IQR)	3.0 days (2.0,6.0)
Cumulative duration of ≥grade 3 diarrhea	5.0 days (1.0, 73.0)
Diarrhea resulted in treatment modification or interruption (n,%)	
Dose reduction	72 (14.4)
Treatment interruption	90 (18.0)
Treatment permanent discontinuation	21 (4.2)

*No Grade 4 diarrhea was reported. [a] The worst grade of diarrhea per patient is counted.

Patients who initiated neratinib at <240 mg experienced a lower incidence of Grade 3 diarrhea compared to those who started at 240 mg (12.2% vs 26.1%) (Table 3).

Table 3. Subgroup Analyses of the Incidence of Diarrhea

	Grade 1 N (%)	Grade 2 N (%)	Grade 1-2 N (%)	Grade 3 N (%)
Dose of Neratinib				
Neratinib 240mg (N=165)	36 (21.8)	68 (41.2)	104 (63.0)	43 (26.1)
Neratinib < 240mg (N=335)	110 (32.8)	134 (40.0)	244 (72.8)	41 (12.2)
Molecular Subtypes				
HR-/HER2+ (N=207)	60 (29.0)	88 (42.5)	148 (71.5)	33 (15.9)
HR+/HER2+ (N=291)	86 (29.6)	113 (38.8)	199 (68.4)	51 (17.5)
Others (N=2)	0 (0)	1 (50.0)	1 (50.0)	0 (0)
Lymph Node Status				
N0 (N=116)	28 (24.1)	44 (37.9)	72 (62.1)	28 (24.1)
N1 (N=219)	69 (31.5)	81 (37.0)	150 (68.5)	35 (16.0)
N2 (N=95)	34 (35.8)	36 (37.9)	70 (73.7)	11 (11.6)
Adjuvant Treatment Regimens				
Trastuzumab (N=38)	12 (31.6)	13 (34.2)	25 (65.8)	3 (7.9)
Trastuzumab + Pertuzumab (N=451)	128 (28.4)	185 (41.0)	313 (69.4)	80 (17.7)
T-DM1 (N=9)	6 (66.7)	3 (33.3)	9 (100)	0 (0)

Anti-diarrheal Prophylaxis

Anti-diarrheal strategies were adopted at least once in 297 patients (59.4%), including drug prophylaxis (loperamide or other agents; 18.0%), dose escalation (28.0%), or a combination of both strategies (13.4%).

Compared to no prophylaxis (28.6%, 32/112), all strategies reduced the incidence of Grade ≥3 diarrhea: most substantially with the combination approach (9.6%, 10/104), followed by dose escalation (17.9%, 25/140) and drug prophylaxis alone (20.8%, 11/53) (Table 4).

Table 4. Anti-diarrheal prophylaxis and incidence of diarrhea

	Incidence of diarrhea, N (%) *			
	Grade 1 N (%)	Grade 2 N (%)	Grade 1-2 N (%)	Grade 3 N (%)
Dose escalation (N=140)	45 (32.1)	56 (40.0)	101 (72.1)	25 (17.9)
Drug prophylaxis (N=53)	10 (18.9)	20 (37.7)	30 (56.6)	11 (20.8)
Dose escalation and drug prophylaxis Combination (N=104)	28 (26.9)	36 (34.6)	64 (61.5)	10 (9.6)
No prophylactic measures (N=112)	26 (23.2)	48 (42.9)	74 (66.1)	32 (28.6)

*. 97 patients started neratinib at a dose <240 mg without a dose escalation strategy and were not included in the analysis of diarrhea prophylaxis.

Patient-reported Outcomes

Neratinib initiation induced concomitant transient deteriorations in patient-reported outcomes, peaking at Day 30 across all instruments. The EQ-5D-5L showed maximal declines in Health Status (-4.5) and Utility Index (-0.0492), while FACIT instruments revealed greater disease-specific impacts: FACIT-D Trial Outcome Index (fatigue/function) decreased by 10.31 points, FACIT-G Total (general QoL) by 4.85, and FACIT-D Total (breast cancer-specific) by 11.58. All metrics demonstrated progressive recovery through Day 60 toward near-baseline levels by Day 180 (Figure 3).

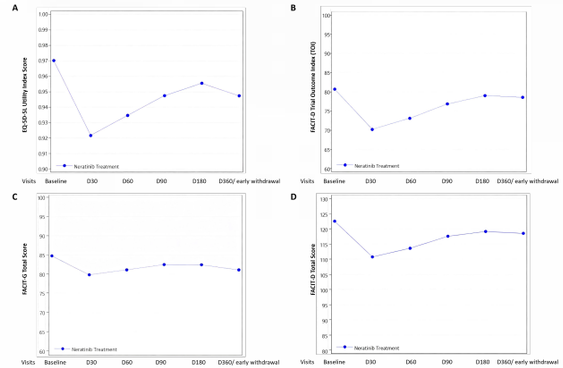


Figure 3. Evaluation of quality of life*

(A). The change in the mean value of the EQ-5D-5L questionnaire utility index score over time; (B). The change in the mean value of the FACIT-D Trial Outcome Index over time; (C). The change in the mean value of the FACIT-G Total Score of the FACIT-D questionnaire over time; (D). The change in the mean value of the FACIT-D Total Score over time.

*Evaluated in safety analysis set.

Conclusions

The safety profile of neratinib was manageable and consistent with previous reports, with no new safety signals identified. This study provides further insights on the pattern of diarrhea associated with neratinib and preventive anti-diarrheal measures.

Dose escalation and drug prophylaxis combined strategy was the most effective approach in reducing the incidence of Grade 3 diarrhea associated with neratinib.

Patient-reported outcomes showed an initial deterioration until Day 30 during neratinib treatment initiation, possibly related to the occurrence of treatment-emergent adverse events, followed by a functional/QoL recovery afterward.

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This study is sponsored by Pierre Fabre (Shanghai) Medical Co.,Ltd. Corresponding author: Jin Zhang (zhangjintjmuch1@163.com)