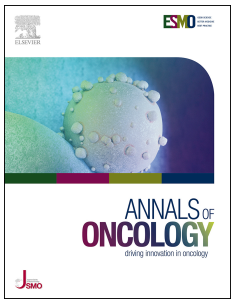

Improved tolerability of neratinib in patients with HER2-positive early-stage breast cancer: diarrheal toxicity in the CONTROL trial

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ORIGINAL ARTICLE

Improved tolerability of neratinib in patients with HER2-positive early-stage breast cancer: diarrheal toxicity in the CONTROL trial

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Running head: Prophylaxis of neratinib-associated diarrhea in HER2-positive breast cancer (80 characters max, including spaces)

Word count: 3557 words. Annals limit: 3500 words including references and tables/figures (150 words each)

ABSTRACT

Background: Neratinib is an irreversible pan-HER tyrosine kinase inhibitor approved for extended adjuvant treatment in early-stage HER2-positive breast cancer based on the phase III ExteNET study. In that trial, in which no anti-diarrheal prophylaxis was mandated, grade 3 diarrhea was observed in 40% of patients and 17% discontinued due to diarrhea. The international, open-label, sequential-cohort, phase II CONTROL study is investigating several strategies to improve tolerability.

Patients and methods: Patients who completed trastuzumab-based adjuvant therapy received neratinib 240 mg/day for 1 year plus loperamide prophylaxis (days 1–28 or 1–56). Sequential cohorts evaluated additional budesonide or colestipol prophylaxis (days 1–28) and neratinib dose escalation (DE; ongoing). The primary endpoint was the incidence of grade ≥3 diarrhea.

Results: Final data for loperamide (L; *n*=137), budesonide + loperamide (BL; *n*=64), colestipol + loperamide (CL; *n*=136), and colestipol + as-needed loperamide (CL-PRN; *n*=104) cohorts, and interim data for DE (*n*=60; completed ≥6 cycles or discontinued; median duration 11 months) are available. No grade 4 diarrhea was observed. Grade 3 diarrhea rates were lower than ExteNET in all cohorts and lowest in DE (L 31%, BL 28%, CL 21%, CL-PRN 32%, DE 15%). Median number of grade 3 diarrhea episodes was 1; median duration per grade 3 episode was 1.0–2.0 days across cohorts. Most grade 3 diarrhea and diarrhea-related discontinuations occurred in month 1. Diarrhea-related discontinuations were lowest in DE (L 20%, BL, 8%, CL 4%, CL-PRN 8%, DE 3%). Decreases in health-related quality of life did not cross the clinically important threshold.

Conclusions: Neratinib tolerability was improved with preemptive prophylaxis or DE, which reduced the rate, severity, and duration of neratinib-associated grade ≥3 diarrhea compared with ExteNET. Lower diarrhea-related treatment discontinuations in multiple cohorts indicate that proactive management can allow patients to stay on neratinib for the recommended time period.

ClinicalTrials.gov: NCT02400476.

Key words: neratinib, tyrosine kinase inhibitor, HER2-positive breast cancer, diarrhea prophylaxis, quality of life

Word count: 299 words **(limit 300 words)**

HIGHLIGHTS

- CONTROL trial investigated anti-diarrheal strategies including dose escalation in neratinib-treated patients with early HER2+ breast cancer
- Both preemptive prophylaxis and dose escalation reduced the rate, severity, and duration of grade ≥3 diarrhea compared with ExteNET
- Lower diarrhea-related discontinuations and dose reductions in multiple cohorts compared with ExteNET suggested improved tolerability
- Neratinib dose escalation is a particularly promising strategy as it eliminates mandatory prophylaxis and related side effects

INTRODUCTION

Neratinib, an irreversible pan-HER tyrosine kinase inhibitor,[1] is used for extended adjuvant treatment of early-stage HER2-positive breast cancer after trastuzumab-based adjuvant therapy; in the EU, neratinib is indicated for hormone receptor-positive HER2-positive patients who are less than 1 year from completion of prior adjuvant trastuzumab-based therapy. The multicenter, randomized, double-blind, placebo-controlled, phase III ExteNET trial showed that adjuvant therapy with neratinib after up to 1 year of trastuzumab therapy significantly improved invasive disease-free survival versus placebo after a median follow-up of 2 years (hazard ratio [HR] 0.67; 95% confidence interval [CI] 0.50–0.91; *P*=0.0091)[2] and 5 years (HR 0.73; 95% CI 0.57–0.92; *P*=0.008).[3] Diarrhea – the main toxicity associated with neratinib – is common in the absence of anti-diarrheal strategies and proactive management; in ExteNET, 40% of patients developed grade 3 diarrhea.[2] As most diarrhea events with neratinib occur early during treatment (median onset of grade ≥3 diarrhea 8 days),[3] structured intensive prophylaxis with loperamide during months 1–2 of neratinib treatment has been used to ameliorate diarrhea.[4] Preclinical studies suggest that neratinib-associated diarrhea may be caused by multiple factors with possible inflammatory and secretory etiologies. In a rat model of pan-HER neratinib-induced diarrhea, diarrhea was reduced with an anti-inflammatory agent or bile-acid sequestrant.[5]

The open-label, sequential-cohort, phase II CONTROL study is investigating the effect of different anti-diarrheal strategies on neratinib-associated diarrhea. Initial cohorts included loperamide prophylaxis alone or with budesonide (a locally acting corticosteroid used for inflammatory gastrointestinal conditions) or colestipol (a bile-acid sequestrant). Modified neratinib dosing regimens, including dose escalation, were subsequently investigated. Here, we report results of an interim analysis of safety and health-related quality of life (HRQoL) from the first five CONTROL cohorts: loperamide alone (L), budesonide + mandatory loperamide (BL), colestipol + mandatory loperamide (CL), colestipol + as-needed (PRN)

loperamide (CL-PRN), and neratinib dose escalation (DE). We used data on incidence, duration, and onset of diarrhea in ExteNET as a historical comparator.[2]

METHODS

CONTROL (PUMA-NER-6201; NCT02400476) is an ongoing international phase II safety study (Figure 1) designed to include the same patient population as the ExteNET trial (NCT00878709).[2] The study protocol was approved by the institutional ethics committee at participating sites. The study was performed in accordance with the 2008 Declaration of Helsinki. All patients provided written informed consent. Eligibility criteria are described in the supplementary Methods. One notable difference, mainly related to changes in the standard of care for HER2-positive disease, was that CONTROL patients were eligible if they had received prior pertuzumab or trastuzumab emtansine (T-DM1).

The study design included sequential mechanism-based interventions to reduce the incidence, severity, and duration of diarrhea where protocol-mandated treatment was implemented for the first 1–2 cycles of neratinib treatment. The study was initiated in 2015 with a loperamide alone cohort and is ongoing, with additional cohorts added sequentially on an approximately annual basis. All patients receive neratinib for 1 year (Figure 1). In the first cohort (L), patients received oral neratinib 240 mg/day (with or without endocrine therapy as indicated), with oral loperamide prophylaxis (4 mg, two tablets/capsules three times daily; supplementary Table S1) for the first two 4-week cycles and loperamide (≤16 mg/day) PRN after completion of loperamide prophylaxis. In the second cohort (BL), patients received neratinib 240 mg/day plus the locally acting oral anti-inflammatory budesonide (9 mg daily in the morning) on days 1–28 of cycle 1 plus loperamide prophylaxis in cycles 1–2 as described above (supplementary Table S2). A third cohort (CL) received neratinib 240 mg/day plus the oral bile-acid sequestrant colestipol (2 g orally twice daily) for the first cycle plus loperamide prophylaxis as described above and PRN thereafter. A fourth cohort (CL-PRN) received neratinib 240 mg/day plus colestipol (2 g bid) during the first cycle plus loperamide PRN. Finally, a fifth cohort (DE) is ongoing and was treated with escalating neratinib doses: 120 mg/day days 1–7, 160 mg/day days 8–14, and 240 mg/day thereafter;

loperamide was administered PRN (Figure 1). Commercially available loperamide, budesonide, and colestipol were provided by the study sponsor.

Treatment-emergent diarrhea was managed with standard pharmacological treatments (i.e. loperamide or diphenoxylate plus atropine), dietary measures (discontinuing lactose-containing products, drinking 8–10 large glasses of clear liquids/day, eating frequent small meals, low-fat regimen enriched with bananas, rice, apple sauce, and toast), and neratinib dose modifications (dose holds or reductions, according to a protocol-defined schedule; supplementary Tables S3–S5).

Patients were assessed in clinic on day 1 of cycles 1, 2, 3, 4, 7, and 10, and at the end of cycle 13. They also were contacted by telephone on days 1–3 after the first neratinib dose to inquire about diarrhea or potential adverse events (AEs) and to provide guidance on AE management. Patients were required to use a diary to record study medication intake. Patient-reported HRQoL was also assessed (supplementary Methods). Follow-up continued for 28 days after the last neratinib dose.

The primary objective of CONTROL was to characterize diarrhea incidence and severity in patients treated with neratinib plus different anti-diarrheal strategies, after prior treatment with trastuzumab. The primary endpoint was grade ≥3 treatment-emergent diarrhea incidence at any time during the study. Secondary endpoints included assessment of serious AEs, AEs of interest, and evaluation of diarrhea incidence and severity. Patient-reported HRQoL is an exploratory endpoint (supplementary Appendix). AEs were graded according to National Cancer Institute Common Terminology Criteria for AEs (version 4.0).

All safety analyses were descriptive and performed in the safety population (all patients who received ≥1 neratinib dose). HRQoL analyses were descriptive and performed in the quality of life (QoL) analysis population (all patients in the safety population with baseline and ≥1 post-baseline QoL assessments). Mean (±standard error) observed scores over time were calculated. Changes in HRQoL scores from baseline were considered clinically meaningful if greater than the previously reported lowest estimate for an 'important difference'.[6] ExteNET,

which included an analogous population but no protocol-mandated anti-diarrheal regimen,[2] was used for reference.

RESULTS

Between February 25, 2015, and October 21, 2019, when this interim analysis was performed, 501 patients from 50 sites in the USA, Canada, Australia, and Spain completed enrollment into five cohorts: L (*n*=137); BL (*n*=64), CL (*n*=136), CL-PRN (*n*=104), and DE (*n*=60). Baseline characteristics are summarized in Table 1.

All patients in the first four cohorts and 2/3 of patients (*n*=40/60) in the DE cohort had either completed or prematurely discontinued 1 year of neratinib treatment at the cutoff date (supplementary Table S6). The median duration (months) of neratinib treatment was similar across CONTROL cohorts (L [11.63, 0.76–11.96], BL [11.96, 11.79–12.02], CL [11.94, 8.48–11.99], CL-PRN [11.96, 8.25–11.99], DE [10.96, 8.25–11.99]) and compared with ExteNET (11.6, 2.48–11.93; supplementary Table S6). In the DE cohort, 56 of 60 patients (93%) had their neratinib dose escalated to 240 mg as planned at week 3; one additional patient escalated to 240 mg at week 4.

Treatment-emergent diarrhea

Diarrhea incidence and duration are summarized in Table 2 and supplementary Table S7. All preventive strategies reduced the rate of grade ≥3 diarrhea, the primary study endpoint, compared with ExteNET (40%). No grade 4 diarrhea was reported.

Grade 3 diarrhea was infrequently recurrent in CONTROL, as indicated by the median of 1 or 2 episodes per patient across all cohorts for the entire treatment period (Table 2). The median duration per grade 3 episode was 1–2 days; most episodes occurred in the first month of treatment (supplementary Table S8). The median cumulative duration of grade ≥3 diarrhea, defined as the sum of the durations of all episodes of grade ≥3 diarrhea, was 2–4 days.

The proportion of patients discontinuing neratinib due to an AE of diarrhea was 20% with L, 8% with BL, 4% with CL, 8% with CL-PRN, and 3% with DE, compared with 17% in ExteNET. Most diarrhea-related discontinuations (*n*=40/48 discontinuations; 83%) occurred

in the first month of treatment (Figure 2); after this period, all cohorts had low treatment discontinuation rates. Diarrhea events leading to hospitalization were rare (range 0–1.5%). Across cohorts, the incidence of grade 3 diarrhea was similar in pertuzumab-naïve patients (27%) and pretreated (25%) patients (supplementary Table S9).

Non-diarrhea adverse events

Other than diarrhea, the tolerability profile of neratinib in CONTROL was similar to previous reports for neratinib,[2] with the exception of an increase in grade 1/2 constipation (Table 3). No grade 3/4 constipation, obstruction, or more serious sequelae from constipation were reported. Three grade 4 AEs were reported, two of which were considered unrelated to treatment. Grade 3/4 AEs included one patient in the L cohort with urinary tract infection and sepsis in whom treatment was interrupted with no recurrence of events when restarted, one patient in the CL cohort who had grade 4 sepsis and discontinued treatment, and one patient in the DE cohort with grade 4 ECG QT prolongation, considered to be treatment related. Twelve patients had serious treatment-related AEs (supplementary Table S10). No fatal AEs were reported.

HRQoL

Patients in all five CONTROL cohorts experienced an early decrease from baseline in Functional Assessment of Cancer Therapy – Breast (FACT-B) total scores, apparent from month 2 (Figure 3). These changes did not meet the threshold for a clinically important difference (7–8 points) at any point in any cohort.[7]

DISCUSSION

Achieving a balance between treatment benefit and AEs is particularly important in early-stage breast cancer. In ExteNET,[3] grade 3 diarrhea occurred in 40% of patients without mandatory diarrhea prophylaxis, with 17% discontinuing treatment due to diarrhea. Improving tolerability by ameliorating neratinib-associated diarrhea is critically important to optimize compliance with the 12 months of neratinib treatment.

The CONTROL study demonstrates that neratinib tolerability can be improved with preemptive prophylaxis or dose escalation. All of the anti-diarrheal strategies reduced the rate, severity, and duration of neratinib-associated grade ≥3 diarrhea compared with ExteNET, including in patients with prior pertuzumab exposure. Fewer patients required neratinib dose reduction because of diarrhea (CONTROL 3–12% versus ExteNET 26%) and overall, fewer patients discontinued early, suggesting improved tolerability. These results, in particular cycle 1 discontinuation data, suggest that managing diarrhea early during neratinib treatment allows more patients to receive the potential efficacy benefits of 1 year's extended adjuvant neratinib therapy.

Nausea and constipation were the next most common treatment-emergent AEs in CONTROL. Dose escalation substantially lowered the rate of constipation, from 57% and 75% of patients in the L and BL cohorts, respectively, to 33% in the DE cohort, adding to the benefit of this approach. No events were severe or serious and few patients discontinued treatment because of constipation. It is important to balance neratinib-associated diarrhea and constipation avoidance, with patients being educated at the start of neratinib treatment regarding when to take and hold loperamide.

Patient-reported HRQoL assessments (FACT-B total scores) in CONTROL showed a transient decrease after month 1 of treatment, although these changes did not meet the threshold for a clinically important difference.[7] It is likely that diarrhea and constipation contribute to these observations, as these symptoms rapidly dissipated after month 1, staying low grade for patients remaining on study. A similar effect on HRQoL was observed

in ExteNET, with the most pronounced difference between neratinib- and placebo-treated patients observed at month 1.[6]

Some limitations of our study should be considered. This open-label study, conducted without a prospectively randomized control arm, was initially intended in 2015 to provide proof of principle for mandatory intensive loperamide prophylaxis; subsequent cohorts were included based on preclinical data regarding potential mechanisms and treatments for diarrhea, and HRQoL evaluations were included mid-study. Cohorts are being added sequentially over the course of approximately 5 years, allowing investigative sites to become proficient in managing treatment-emergent diarrhea, which is a possible confounding factor biasing the observed improved patient adherence over time. Although one-third of patients in the DE cohort are still on study, these patients have passed the point in time when most cases of neratinib-associated diarrhea or discontinuations are known to occur.

Considering the invasive disease-free survival benefit at 2 and 5 years with extended adjuvant therapy of neratinib following 1 year of trastuzumab in patients with HER2-positive disease, implementation of optimal patient education, dietary measures, and appropriate anti-diarrheal strategies are of key importance in minimizing the risk of diarrhea. These measures should be applied at neratinib onset and especially during the first 2 months of treatment, with the goal of allowing more patients to complete the 12-month course of adjuvant therapy, thereby reducing their risk of disease recurrence. All CONTROL cohorts had reduced rates of grade ≥3 diarrhea versus ExteNET and most had reduced treatment discontinuation rates due to diarrhea, thereby improving tolerability. Neratinib dose escalation is emerging as a particularly promising strategy as it eliminates mandatory prophylaxis and related side effects and appears to reduce the incidence of severe diarrhea to levels commensurate with other HER2-directed treatments (tucatinib[8], lapatinib[9], pertuzumab[10]).

In conclusion, this interim analysis of the CONTROL study suggests that proactively managing neratinib-associated diarrhea during month 1 of treatment may reduce the

incidence, severity, and duration of diarrhea, thereby lowering the rate of dose reductions and treatment discontinuations and improving long-term adherence. Given that neratinib is already approved for extended adjuvant use in early-stage breast cancer, the current findings are practice changing with immediate management implications, potentially resulting in more patients being able to complete therapy due to fewer side effects. A final report with dose-escalation cohorts will be forthcoming and other analyses are planned, including disease biomarkers and stool microbiome diversity.

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DATA SHARING

The authors declare that the data supporting the findings of this study are available within the article. The authors may be contacted for further data sharing.

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A. Chan: none.

APPENDIX 1. CONTROL STUDY INVESTIGATORS

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FIGURE LEGENDS

Figure 1. Treatment schedules by CONTROL cohort. Unless otherwise mandated, all patients received loperamide as needed (16 mg/day max) on days 1–364

[a]Cycle = 28 days. bid, twice daily; qd, once daily; tid, three times daily.

Figure 2. Treatment discontinuations relating to treatment-emergent diarrhea in ExteNET and CONTROL. BL, budesonide + loperamide; CL, colestipol + loperamide; CL-PRN, colestipol + as-needed loperamide; L, loperamide; DE, neratinib dose escalation.

Figure 3. Mean change from baseline in Functional Assessment of Cancer Therapy – Breast total scores for ExteNET and CONTROL cohorts: unadjusted scores. **Note:** A higher score indicates better quality of life. BL, budesonide + loperamide; CL, colestipol + loperamide; CL-PRN, colestipol + as-needed loperamide; L, loperamide; DE, neratinib dose escalation.

Figure 1.

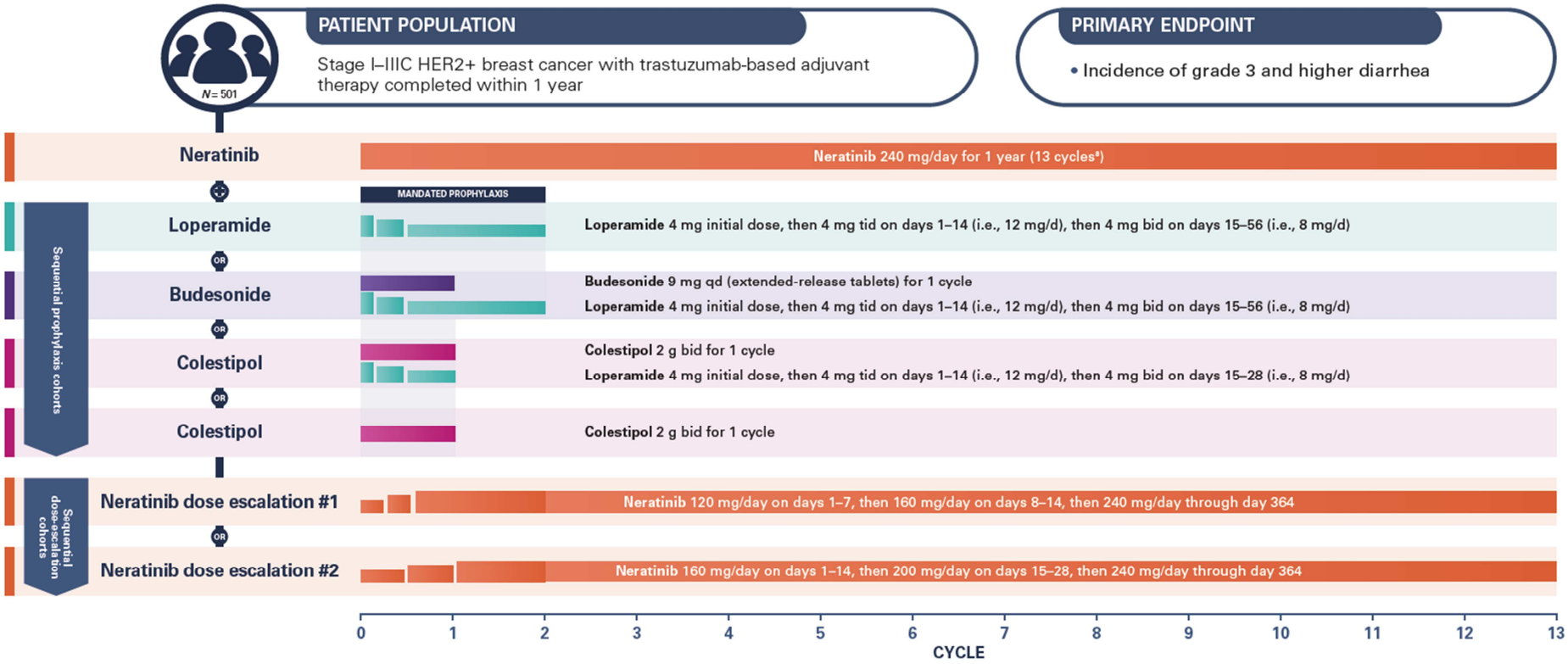
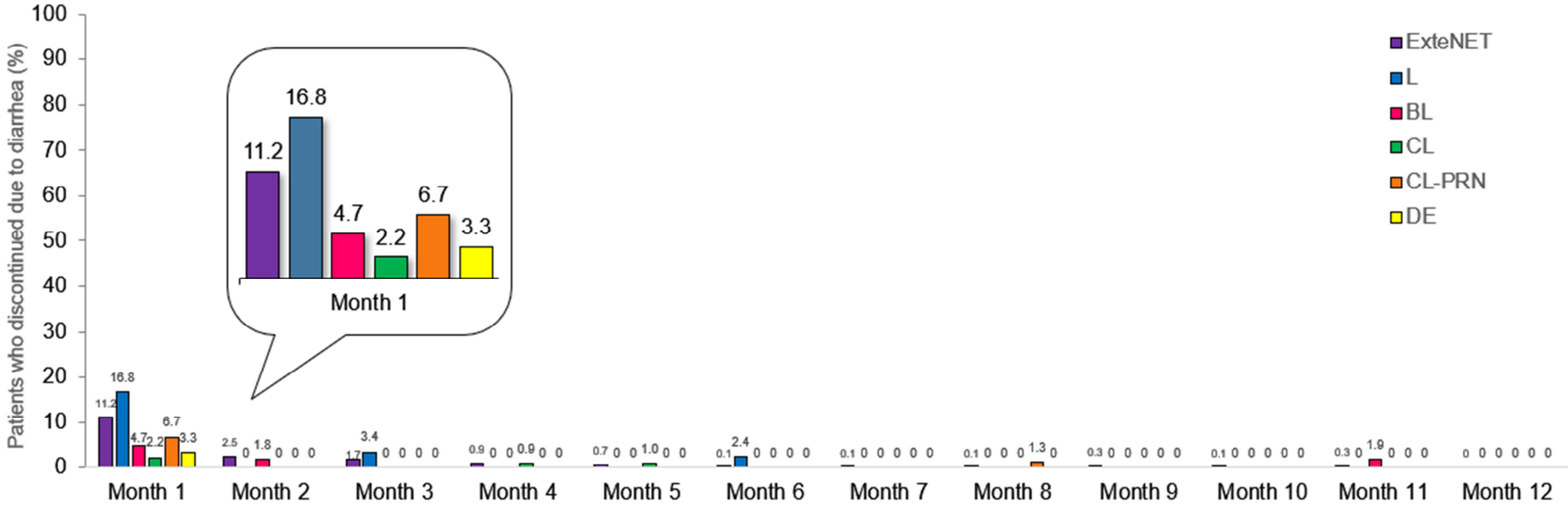

PATIENT POPULATION
Stage I–IIIC HER2+ breast cancer with trastuzumab-based adjuvant therapy completed within 1 year
N = 501
PRIMARY ENDPOINT
• Incidence of grade 3 and higher diarrhea
Neratinib
Neratinib 240 mg/day for 1 year (13 cycles[a])
MANDATED PROPHYLAXIS
Sequential prophylaxis cohorts
Loperamide
Loperamide 4 mg initial dose, then 4 mg tid on days 1–14 (i.e., 12 mg/d), then 4 mg bid on days 15–56 (i.e., 8 mg/d)
OR
Budesonide
Budesonide 9 mg qd (extended-release tablets) for 1 cycle
Loperamide 4 mg initial dose, then 4 mg tid on days 1–14 (i.e., 12 mg/d), then 4 mg bid on days 15–56 (i.e., 8 mg/d)
OR
Colestipol
Colestipol 2 g bid for 1 cycle
Loperamide 4 mg initial dose, then 4 mg tid on days 1–14 (i.e., 12 mg/d), then 4 mg bid on days 15–28 (i.e., 8 mg/d)
OR
Colestipol
Colestipol 2 g bid for 1 cycle
Sequential dose-escalation cohorts
Neratinib dose escalation #1
Neratinib 120 mg/day on days 1–7, then 160 mg/day on days 8–14, then 240 mg/day through day 364
OR
Neratinib dose escalation #2
Neratinib 160 mg/day on days 1–14, then 200 mg/day on days 15–28, then 240 mg/day through day 364
0 1 2 3 4 5 6 7 8 9 10 11 12 13
CYCLE

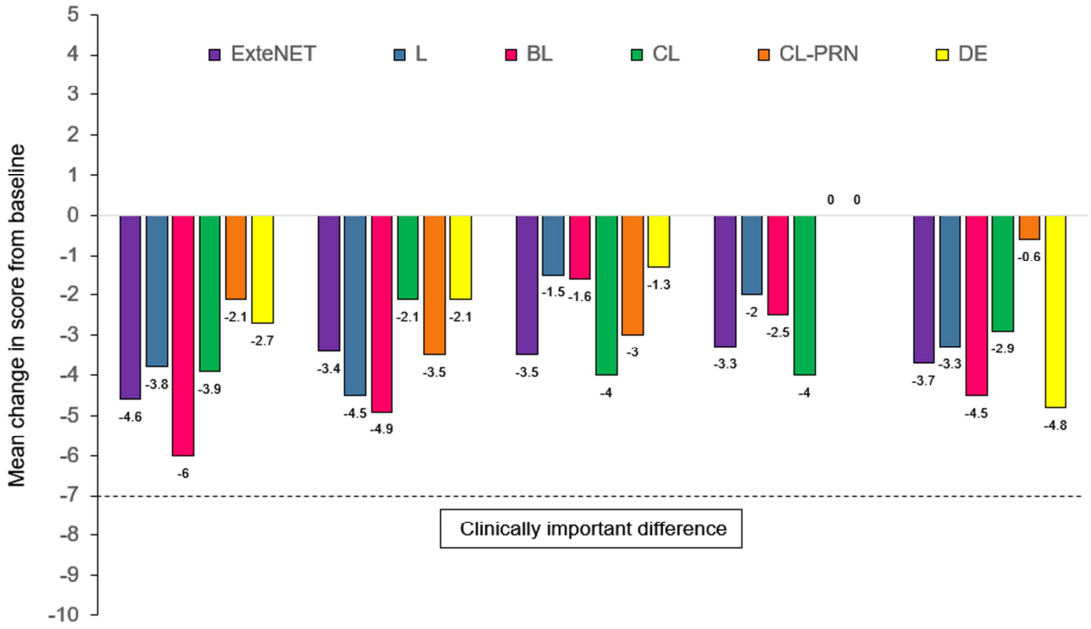
Figure 2.



No. of patients who discontinued due to diarrhea / Total No. of patients at risk

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
ExteNET	158/1408	29/1146	18/1074	9/1033	7/1006	7/971	1/935	1/924	3/911	1/888	3/873	0/863
L	23/137	0/93	3/89	0/84	0/83	2/83	0/81	0/80	0/78	0/77	0/76	0/75
BL	3/64	1/57	0/54	0/53	0/53	0/53	0/53	0/53	0/53	0/53	1/53	0/51
CL	3/136	0/115	0/112	1/108	1/105	0/104	0/103	0/103	0/102	0/102	0/99	0/99
CL-PRN	7/104	0/86	0/85	0/84	0/82	0/81	0/80	1/79	0/79	0/77	0/77	0/75
DE	2/60	0/55	0/53	0/53	0/52	0/51	0/49	0/48	0/47	0/35	0/32	0/30

Figure 3.



	Month 1	Month 3	Month 6	Month 9	Month 12
No. of patients					
ExteNET	1124	921	800	673	574
L	37	27	22	20	22
BL	59	56	51	50	49
CL	122	109	102	99	98
CL-PRN	93	82	76	72	72
DE	53	48	44	44	22

Table 1. Baseline characteristics of patients in the ExteNET and CONTROL studies

Characteristic	ExteNET (*n*=1420)	L (*n*=137)	BL (*n*=64)	CL (*n*=136)	CL-PRN (*n*=104)	DE (*n*=60)
Female, *n* (%)	1420 (100)	137 (100)	64 (100)	133 (98)	104 (100)	60 (100)
Median age (range), years	52 (25–83)	53 (30–86)	49 (29–78)	53 (26–78)	51 (33–77)	51 (29–76)
Menopausal status, *n* (%)						
Premenopausal	663 (47)	41 (30)	29 (45)	37 (27)	38 (37)	24 (40)
Postmenopausal	757 (53)	96 (70)	35 (55)	96 (71)	66 (63)	36 (60)
Not applicable	0	0	0	3 (2)	0	0
Hormone receptor status, %						
Positive (ER+ and/or PgR+)	816 (57)	103 (75)	46 (72)	103 (76)	81 (78)	48 (80)
Negative (ER– and PgR–)	604 (43)	34 (25)	18 (28)	33 (24)	23 (22)	11 (18)
Missing	0	0	0	0	0	1 (2)
Tumor stage at diagnosis, *n* (%)						
I	139 (10)	39 (28)	16 (25)	22 (16)	16 (15)	9 (15)
IIA/B	596 (42)	75 (55)	30 (47)	64 (47)	56 (54)	28 (47)
IIIA/B/C	444 (31)	20 (15)	15 (23)	37 (27)	24 (23)	17 (28)
IV	0	0	0	0	2 (2)	0
Unknown	241 (17)	3 (2)	3 (5)	13 (10)	6 (6)	6 (10)
Prior radiotherapy, *n* (%)	1130 (80)	94 (69)	45 (70)	97 (71)	70 (67)	49 (82)
Prior (neo)adjuvant therapy, %						
Trastuzumab	1420 (100)	136 (99)	62 (97)	134 (99)	102 (98)	60 (100)
Taxanes	1280 (90)	131 (96)	62 (97)	134 (99)	104 (100)	60 (100)
Anthracycline	1098 (77)	36 (26)	18 (28)	31 (23)	29 (28)	28 (47)
Pertuzumab	0	55 (40)	39 (61)	84 (62)	63 (61)	29 (48)
T-DM1	0	0	1 (2)	2 (1)	0	0
Median (range) duration of prior trastuzumab, months	11.5 (0.7–56.9)	11.5 (2.4–18.2)	10.8 (1.2–16.7)	10.9 (0.6–15.5)	10.9 (2.8–14.9)	10.7 (3.8–13.3)

Median (range) time since last trastuzumab dose, months	4.4 (0.2–30.9)	3.9 (0.1–12.1)	4.1 (0.5–12.1)	2.5 (0–12.0)	2.5 (0.5–12.0)	3.2 (0.5–20.2)
Median (range) duration of prior pertuzumab, months	–	3.5 (0–11.1)	3.5 (0–10.5)	3.5 (0–11.8)	3.5 (0–15.5)	3.8 (1.4–12.1)
Median (range) time since last pertuzumab dose, months	–	12.1 (3.3–22.3)	11.5 (2.6–20.0)	11.0 (0.6–20.0)	10.8 (1.4–20.5)	10.4 (0.8–20.2)

BL, budesonide + loperamide; CL, colestipol + loperamide; CL-PRN, colestipol + as-needed loperamide; DE, neratinib dose escalation; ER, estrogen receptor; L, loperamide; PgR, progesterone receptor; T-DM1, trastuzumab emtansine.

Table 2. Characteristics of treatment-emergent diarrhea in the ExteNET and CONTROL studies (safety population)

Outcome	ExteNET (*n*=1408)	L (*n*=137)	BL (*n*=64)	CL (*n*=136)	CL-PRN (*n*=104)	DE (*n*=60)
Treatment-emergent diarrhea incidence, *n* (%)						
No diarrhea	65 (5)	28 (20)	9 (14)	23 (17)	5 (5)	1 (2)
Grade 1	323 (23)	33 (24)	16 (25)	38 (28)	34 (33)	25 (42)
Grade 2	458 (33)	34 (25)	21 (33)	47 (35)	32 (31)	25 (42)
Grade 3	561 (40)	42 (31)	18 (28)	28 (21)	33 (32)	9 (15)
Grade 4	1 (<1)	0	0	0	0	0
Other grade ≥3 diarrhea events[a]						
Median episodes/patient (IQR)[b]	2 (1–3)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–3)	2 (1–2)
Median duration of episode, days (IQR)	2 (1–3)	2 (1–3)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–1)
Median time to first episode, days (IQR)	8 (4–33)	7 (5–13)	19 (7–45)	41 (7–189)	15 (8–47)	66 (21–82)
Median cumulative duration,[c] days (IQR)	5 (2–9)	3 (2–6)	3 (1–3)	4 (1–6)	2 (1–6)	2 (2–3)
Action taken, *n* (%)						
Dose hold	477 (34)	20 (15)	12 (19)	22 (16)	15 (14)	7 (12)
Dose reduction	372 (26)	10 (7)	3 (5)	10 (7)	12 (12)	2 (3)
Discontinuation	237 (17)	28 (20)	5 (8)	5 (4)	8 (8)	2 (3)
Hospitalization	20 (1)	2 (1)	0	0	0	0

[a]No grade 4 events were reported in the CONTROL study; 1 grade 4 event was reported in ExteNET. [b]Episode defined as one adverse event (using start and stop dates). [c]Defined as the sum of the durations of all episodes of diarrhea at that grade.

BL, budesonide + loperamide; CL, colestipol + loperamide; CL-PRN, colestipol + as-needed loperamide; DE, neratinib dose escalation; IQR, interquartile range; L, loperamide.

Table 3. Treatment-emergent non-diarrhea adverse events occurring in >10% of patients (all cohorts combined) in the ExteNET and CONTROL studies[a]

	ExteNET (*n*=1408)		L (*n*=137)		BL (*n*=64)		CL (*n*=136)		CL-PRN (*n*=104)		DE (*n*=60)	
Event, *n* (%)	**All grade**	**Grade 3/4[b]**	**All grade**	**Grade 3/4**	**All grade**	**Grade 3/4[b]**	**All grade**	**Grade 3/4**	**All grade**	**Grade 3/4[b]**	**All grade**	**Grade 3/4**
Nausea	605 (43)	26 (2)	79 (58)	1 (1)	32 (50)	0	83 (61)	2 (1)	64 (62)	3 (3)	27 (45)	0
Constipation	115 (8)	0	78 (57)	0	48 (75)	0	94 (69)	0	39 (38)	0	20 (33)	0
Fatigue	382 (27)	23 (2)	73 (53)	5 (4)	34 (53)	5 (8)	65 (48)	2 (1)	41 (39)	2 (2)	28 (47)	1 (2)
Abdominal pain	340 (24)	24 (2)	36 (26)	2 (1)	12 (19)	1 (2)	26 (19)	3 (2)	27 (26)	1 (1)	9 (15)	0
Vomiting	369 (26)	47 (3)	36 (26)	2 (1)	16 (25)	2 (3)	43 (32)	4 (3)	25 (24)	2 (2)	8 (13)	1 (2)
Decreased appetite	170 (12)	3 (<1)	27 (20)	0	11 (17)	0	24 (18)	1 (1)	26 (25)	0	8 (13)	0
Headache	278 (20)	8 (1)	26 (19)	0	12 (19)	0	20 (15)	0	24 (23)	0	13 (22)	0
Abdominal distension	73 (5)	4 (<1)	21 (15)	0	5 (8)	0	22 (16)	0	15 (14)	0	7 (12)	0
Dizziness	146 (10)	3 (<1)	19 (14)	0	6 (9)	0	21 (15)	0	20 (19)	0	8 (13)	0
Muscle spasms	159 (11)	1 (<1)	15 (11)	2 (1)	8 (13)	0	14 (10)	0	15 (14)	0	9 (15)	0
Dyspepsia	139 (10)	6 (<1)	12 (9)	0	10 (16)	0	16 (12)	0	13 (13)	0	7 (12)	0

[a]ExteNET adverse events were matched to those in >10% of all patients in CONTROL; there may have been additional adverse events in ExteNET that are not captured here.

[b]Grade 3 events only (no grade 4 events were reported in CONTROL).

BL, budesonide + loperamide; CL, colestipol + loperamide; CL-PRN, colestipol + as-needed loperamide; DE, neratinib dose escalation; L, loperamide.

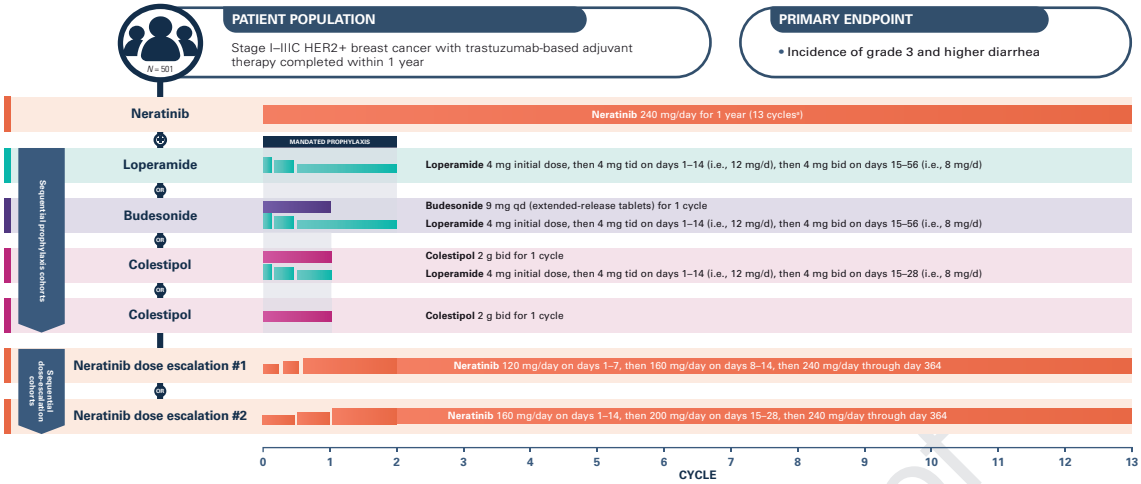
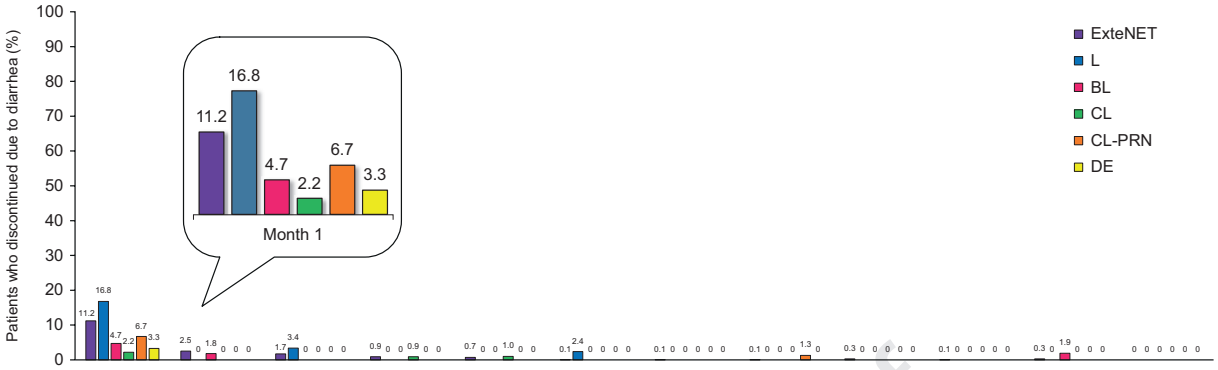


Figure 2



No. of patients who discontinued due to diarrhea / Total No. of patients at risk

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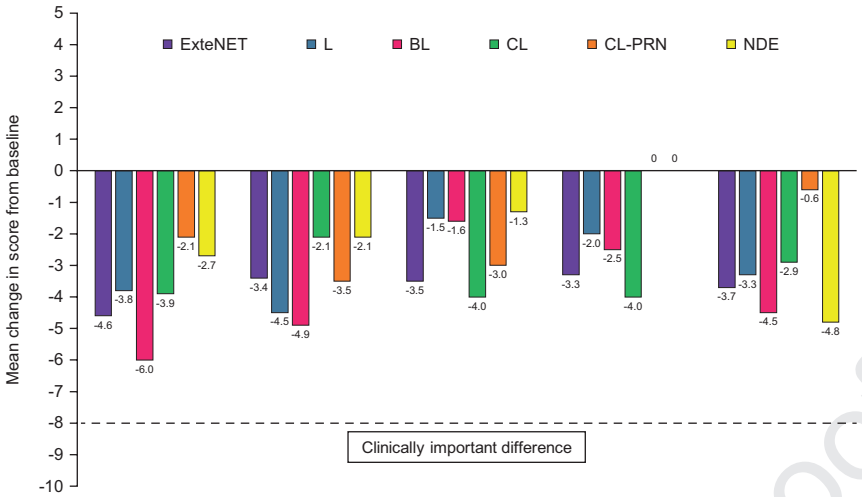
L	23/137	0/93	3/89	0/84	0/83	2/83	0/81	0/80	0/78	0/77	0/76	0/75
BL	3/64	1/57	0/54	0/53	0/53	0/53	0/53	0/53	0/53	0/53	1/53	0/51
CL	3/136	0/115	0/112	1/108	1/105	0/104	0/103	0/103	0/102	0/102	0/99	0/99
CL-PRN	7/104	0/86	0/85	0/84	0/82	0/81	0/80	1/79	0/79	0/77	0/77	0/75
DE	2/60	0/55	0/53	0/53	0/52	0/51	0/49	0/48	0/47	0/35	0/32	0/30

Figure 3



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