Effect of prophylaxis or neratinib dose escalation on neratinib- associated diarrhea and tolerability in patients with HER2-positive early-stage breast cancer: phase II CONTROL trial

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Background

- Neratinib (NERLYNX®) is an irreversible pan-HER tyrosine kinase inhibitor that is approved in the US[1], Australia[2], and other countries[3,4] for the extended adjuvant treatment of adult patients with early-stage HER2-positive breast cancer following adjuvant trastuzumab-based therapy:
  - The ExteNET trial, which provided the basis for drug approval, showed that a 12-month course of neratinib after trastuzumab-based adjuvant therapy significantly improved invasive disease-free survival compared with placebo after 2 years (hazard ratio 0.66; 95% CI 0.49–0.90; p=0.008)[5] and 5 years (hazard ratio 0.73; 95% CI 0.57–0.92; p=0.008).[6]
- Neratinib has also been granted marketing authorization by the European Commission for the extended adjuvant treatment of adult patients with early-stage hormone receptor-positive HER2-positive breast cancer who are less than 1 year from the completion of prior adjuvant trastuzumab-based therapy.[7]
- Diarrhea is the main tolerability concern with neratinib and is common in the absence of proactive management:[5]
  - In ExteNET, where antidiarrheal prophylaxis was not mandated by the study protocol, grade ≥3 diarrhea occurred in 39.9% of patients (grade 4 diarrhea in one patient), and neratinib-associated diarrhea led to discontinuation of therapy in 16.8% of patients.[5]
  - In ExteNET, most grade 3 diarrhea events with neratinib were of short duration (i.e. median 2 days per event) and early onset, occurring within the first weeks of treatment (i.e. 75% of grade 3 diarrhea events occurred within the first 5 weeks of treatment), suggesting that early targeted preventive management with antidiarrheal prophylaxis is appropriate.[5,8]
  - These observations suggest that there may be some adaptation to the effects of neratinib, as higher-grade diarrhea occurs early and does not typically recur. Some patients may therefore acclimate to neratinib, which in turn may improve compliance.
- The CONTROL study is investigating the effectiveness of rationally structured antidiarrheal prophylaxis or neratinib dose escalation in the prevention and management of neratinib-associated diarrhea:[9]
  - Preclinical studies suggest that neratinib-related diarrhea may be multifactorial, involving inflammation,[10] bile acid malabsorption,[10] and possibly secretory mechanisms.[11]
  - To investigate these observations further, CONTROL included antidiarrheal prophylactic regimens with loperamide either alone or in combination with budesonide (a locally acting corticosteroid used for inflammatory gastrointestinal conditions) or colestipol (a bile acid sequestrant), as well as neratinib dose escalation.
- We report updated safety and tolerability findings from the CONTROL study.

Methods

- CONTROL (Clinicaltrials.gov NCT02400476) is an international multi-cohort, open-label, phase II study (Figure 1).

Patient population

- Adult patients with histologically confirmed HER2-positive stage I–IIIc breast cancer who had completed trastuzumab-based adjuvant therapy within the past 12 months or experienced side effects resulting in early discontinuation of trastuzumab-based adjuvant therapy were treated with neratinib for 1 year.
- Trastuzumab-based therapy included trastuzumab, trastuzumab-pertuzumab combination, and trastuzumab-emtansine (T-DM1).

Study treatment

- Patients were enrolled sequentially into separate cohorts investigating the following preventive strategies: 1) loperamide prophylaxis; 2) budesonide + loperamide prophylaxis; 3) colestipol + loperamide prophylaxis; 4) colestipol + loperamide prn; 5) neratinib dose escalation + loperamide prn (two cohorts).
- Treatment schedules for each cohort are presented in Figure 1.
- In addition to loperamide prn, treatment-emergent diarrhea was managed with neratinib dose interruptions and reductions, dietetic measures, and additional pharmacological agents depending on severity and as per standard of care.

Endpoints

- *Primary:* incidence of grade ≥3 diarrhea.
- *Secondary:* frequency distribution of maximum-grade diarrhea; incidence and severity of diarrhea; serious adverse events; adverse events of interest.

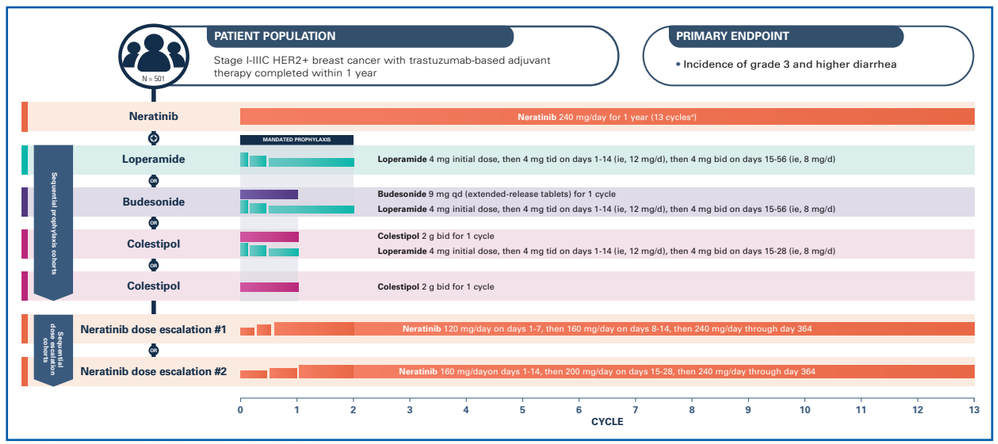
Statistical methods

- All analyses were descriptive and were performed in the safety population (defined as all patients who received ≥1 dose of neratinib). Data cutoff: August 26, 2019.

Results

- From February 2015 to August 2019, a total of 501 patients have been enrolled and dosed from 46 sites into the following cohorts: loperamide (n=137); budesonide + loperamide (n=64); colestipol + loperamide (n=136); colestipol + loperamide prn (n=104); and neratinib dose escalation + loperamide prn (n=60) [Table 1].
- Most patients (n=498; 99.4%) were women, with a median age of 52 (range 26–86) years and a median time from last trastuzumab dose to enrollment ranging from 2.5 to 4.1 months across all cohorts.
- As of August 26, 2019, study treatment had been completed or discontinued by 100% of patients in all cohorts except for the neratinib dose escalation cohort (38%).

Figure 1. CONTROL study design



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.

Table 1. Study overview

Variable	Loperamide (n=137)	Budesonide + loperamide (n=64)	Colestipol + loperamide (n=136)	Colestipol + loperamide prn (n=104)	Neratinib dose escalation + loperamide prn (n=60)
On neratinib treatment, n (%)	0	0	0	0	37 (61.7)
Completed 1 year of neratinib	76 (55.5)	51 (79.7)	97 (71.3)	75 (72.1)	11 (18.3)
Discontinued neratinib before 1 year (for any reason)	61 (44.5)	13 (20.3)	39 (28.7)	29 (27.9)	12 (20.0)
Median (range) neratinib treatment duration, months	11.63 (0.1–13.1)	11.96 (0.2–13.2)	11.94 (0–14.4)	11.96 (0.1–12.5)	9.99 (0.2–12.4)

Treatment-emergent diarrhea

- Compared with the ExteNET trial (historical control: 39.9%),[6] all preventive strategies reduced the incidence of grade ≥3 diarrhea, the primary study endpoint (Table 2).
- No grade 4 diarrhea was reported in the CONTROL study.

Table 2. Incidence of treatment-emergent diarrhea by worst grade

Outcome	Loperamide (n=137)	Budesonide + loperamide (n=64)	Colestipol + loperamide (n=136)	Colestipol + loperamide prn (n=104)	Neratinib dose escalation + loperamide prn (n=60)
Treatment-emergent diarrhea incidence, *N* (%)					
No diarrhea	28 (20)	9 (14)	23 (17)	5 (5)	2 (3)
Grade 1	33 (24)	16 (25)	38 (28)	33 (32)	24 (40)
Grade 2	34 (25)	21 (33)	47 (35)	31 (30)	25 (42)
Grade 3	42 (31)	18 (28)	28 (21)	35 (34)	9 (15)
Grade 4	0	0	0	0	0

Note: Each patient was counted only once in the highest grade category.

- Over the entire 12-month treatment period, for patients who experienced any grade 3 diarrhea, the median number of grade 3 diarrhea episodes is 1 or 2 (range, 1 to 17) across all cohorts (Table 3), with a median time to onset of 7 to 66 days across all cohorts.
- Over the entire 12-month treatment period, the median cumulative duration of grade 3 diarrhea ranged from 2 to 3.5 days across all cohorts (Table 3).
- Compared with the ExteNET trial (16.8%),[6] the proportion of patients who had diarrhea leading to neratinib discontinuation was decreased in all cohorts, with the exception of the mandatory loperamide only cohort (Table 3).

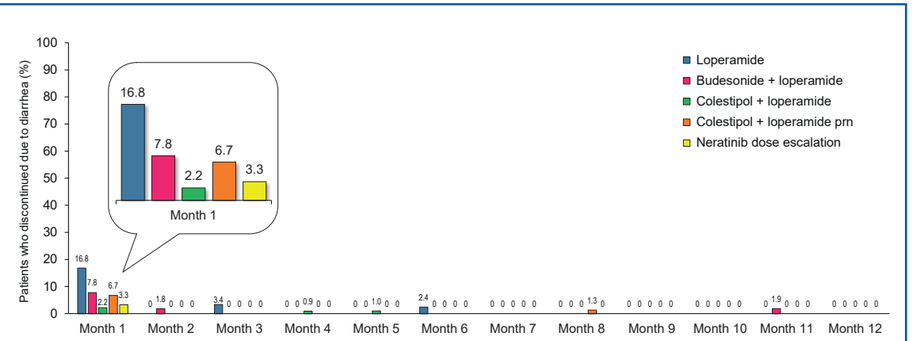
Table 3. Characteristics of treatment-emergent diarrhea

Outcome	Loperamide (n=137)	Budesonide + loperamide (n=64)	Colestipol + loperamide (n=136)	Colestipol + loperamide prn (n=104)	Neratinib dose escalation + loperamide prn (n=60)
Median diarrhea episodes/patient[a]					
Any grade	2	11	5	18	19
Grade ≥2[b]	2	3	2	4	4
Grade ≥3[b]	1	1	1	1	2
Median cumulative duration, days[c]					
Grade ≥2[b]	5.0	6.0	4.0	9.0	6.0
Grade ≥3[b]	3.0	2.5	3.5	3.0	2.0
Actions taken, *N* (%)					
Dose hold	20 (14.6)	12 (18.8)	23 (16.9)	16 (15.4)	7 (11.7)
Dose reduction	9 (6.6)	2 (3.1)	9 (6.6)	9 (8.7)	2 (3.3)
Discontinuation	28 (20.4)	7 (10.9)	5 (3.7)	8 (7.7)	2 (3.3)
Hospitalization	2 (1.5)	0	0	0	0

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

- The majority of discontinuations due to diarrhea in all cohorts occurred in the first month of treatment (Figure 2); after this period, all cohorts had a very low rate of treatment discontinuations.

Figure 2. Treatment-emergent diarrhea leading to discontinuation by month



No. of patients who discontinued due to diarrhea / Total No. of patients treated at the beginning of the month

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Loperamide	23/137	0/93	3/89	0/84	0/83	2/83	0/81	0/80	0/78	0/77	0/76	0/75
Budesonide + loperamide	5/64	1/57	0/54	0/53	0/53	0/53	0/53	0/53	0/53	0/53	1/53	0/51
Colestipol + loperamide	3/136	0/115	0/112	1/108	1/105	0/104	0/103	0/103	0/102	0/102	0/99	0/99
Colestipol + loperamide prn	7/104	0/86	0/85	0/84	0/82	0/81	0/80	1/79	0/79	0/76	0/76	0/74
Neratinib dose escalation	2/60	0/55	0/53	0/53	0/52	0/51	0/49	0/47	0/44	0/35	0/31	0/18

- The proportion of patients requiring neratinib dose holds and neratinib dose reductions due to diarrhea was lower in cohorts with loperamide + budesonide or colestipol and neratinib dose escalation (Table 3).
- Diarrhea events leading to hospitalization were rare; only 2 patients (1.5%) in the loperamide only group, were hospitalized (Table 3).
- The incidence of grade 3 diarrhea across all cohorts was similar in pertuzumab-naïve patients (27.6%) and in patients previously treated with pertuzumab (24.1%).

Table 4. Overall summary of TEAE

Event, *N* (%)	Loperamide (n=137)	Budesonide + loperamide (n=64)	Colestipol + loperamide (n=136)	Colestipol + loperamide prn (n=104)	Neratinib dose escalation + loperamide prn (n=60)
Any TEAE	137 (100.0)	64 (100.0)	136 (100.0)	104 (100.0)	60 (100.0)
Grade 3 or 4 TEAE	59 (43.1)	30 (46.9)	42 (30.9)	45 (43.3)	14 (23.3)
TEAE leading to discontinuation	56 (40.9)	11 (17.2)	20 (14.7)	17 (16.3)	7 (11.7)
TEAE leading to hospitalization	5 (3.6)	4 (6.3)	8 (5.9)	3 (2.9)	4 (6.7)
TEAE (all-grade ≥10% incidence)					
Diarrhea	109 (79.6)	55 (85.9)	113 (83.1)	99 (95.2)	58 (96.7)
Nausea	79 (57.7)	32 (50.0)	83 (61.0)	64 (61.5)	26 (43.3)
Constipation	78 (56.9)	48 (75.0)	94 (69.1)	39 (37.5)	19 (31.7)
Fatigue	73 (53.3)	34 (53.1)	65 (47.8)	41 (39.4)	28 (46.7)
Abdominal pain	36 (26.3)	12 (18.8)	26 (19.1)	27 (26.0)	13 (21.7)
Vomiting	36 (26.3)	16 (25.0)	43 (31.6)	25 (24.0)	8 (13.3)
Decreased appetite	27 (19.7)	11 (17.2)	24 (17.6)	26 (25.0)	8 (13.3)
Headache	26 (19.0)	12 (18.8)	20 (14.7)	24 (23.1)	13 (21.7)
Abdominal distension	21 (15.3)	5 (7.8)	22 (16.2)	15 (14.4)	7 (11.7)
Dizziness	19 (13.9)	6 (9.4)	21 (15.4)	20 (19.2)	6 (10.0)
Muscle spasms	15 (10.9)	8 (12.5)	14 (10.3)	15 (14.4)	9 (15.0)
Dyspepsia	12 (8.8)	10 (15.6)	16 (11.8)	13 (12.5)	7 (11.7)

Data are presented as n (%). No grade 3 or 4 constipation was reported. TEAE, treatment-emergent adverse event.

Other adverse events

- The overall safety profile of neratinib (other than diarrhea) with antidiarrheal prophylaxis was similar to that reported previously with neratinib,[6] apart from an increase in grade 1/2 constipation (Table 4).
- No grade 3 or 4 constipation, obstruction, or more serious sequelae from constipation were reported.
- Three patients experienced grade 4 treatment-emergent adverse events (sepsis, n=2; urinary tract infection, n=1; electrocardiogram QT prolonged, n=1). No fatal adverse events were reported in CONTROL.

Conclusions and future directions

- A rationally structured regimen of loperamide prophylaxis for one or two cycles reduces the incidence, severity, and duration of neratinib-associated diarrhea compared with that observed in the ExteNET trial.[6]
- Importantly, the addition of budesonide or colestipol to loperamide prophylaxis reduces the rate of neratinib discontinuation due to diarrhea, allowing patients to receive the efficacy benefits of 1 year of extended adjuvant neratinib therapy.
- While data for the neratinib dose-escalation cohort are not yet complete, the current findings, with only 2 months less median follow-up than the prior prophylaxis cohorts, are promising (grade 3 diarrhea, 15% incidence; discontinuation due to diarrhea, 3.3% incidence). Patient treatment is nearing completion.
- A second dose-escalation cohort evaluating neratinib (160 mg/day for 2 weeks, 200 mg/day for 2 weeks, then 240 mg/day thereafter) started enrolling earlier this year.
- Additional analyses are planned, including disease biomarkers and stool microbiome diversity. An interim analysis of health-related quality-of-life data, an exploratory study endpoint, has been presented previously.[12]

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