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

Carlos H. Barcenas,[1] Sara A. Hurvitz,[2] Jack Di Palma,[3] Ron Bose,[4] Arlene Chan,[5] Jo Chien,[6] Cynthia Farrell,[7] Daniel Hunt,[7] Leanne McCulloch,[7] Amy Kupic,[7] Debu Tripathy,[1] Hope S. Rugo,[6] and the CONTROL Investigators

[1]MD Anderson Cancer Center, Houston, TX, USA; [2]University of California Los Angeles, CA, USA; [3]University of South Alabama College of Medicine, Mobile, AL, USA; [4]Washington University School of Medicine, St Louis, MO, USA; [5]Breast Cancer Research Centre–WA & Curtin University, Perth, WA, Australia; [6]University of California San Francisco Comprehensive Cancer Center, San Francisco, CA, USA; [7]Puma Biotechnology Inc., Los Angeles, CA, USA

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Background

- Neratinib (NERLYNX®) is an irreversible pan-HER tyrosine kinase inhibitor that is approved in the US[1] and Australia[2] for the extended adjuvant treatment of adult patients with early-stage HER2-positive breast cancer following adjuvant trastuzumab-based therapy.
- 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.[3]
  - The ExteNET trial,[4] 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)[1] and 5 years (hazard ratio 0.73; 95% CI 0.57–0.92; p=0.008).[5]
- Diarrhea is the main tolerability concern with neratinib and is common in the absence of proactive management:[4]
  - 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 1 patient), and neratinib-associated diarrhea led to discontinuation of therapy in 16.8% of patients.[4]
  - 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.[4,6]
  - 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 tolerability.
- 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:[7]
  - Preclinical studies suggest that neratinib-related diarrhea may be multifactorial, involving inflammation,[8] bile acid malabsorption,[8] and possibly secretory mechanisms.[9]
  - 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.

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 reductions and dose interruptions, 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.

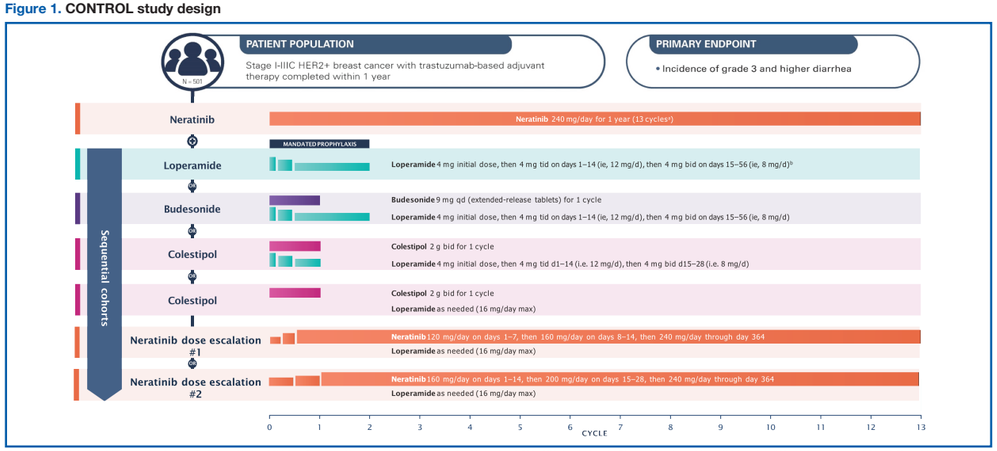
Statistical methods

- All analyses were descriptive and were performed in the safety population (defined as all patients who received ≥1 dose of neratinib).
- *Data cut-off:* April 8, 2019.

Results

- From November 2014 to April 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 April 2019, study treatment had been completed by 100% of patients in all cohorts except for the colestipol + loperamide prn (93.3%) and neratinib dose escalation + loperamide prn (0%) cohorts.

Figure 1. CONTROL study design



[a]Cycle = 28 days. [b]Under the original protocol, patients received loperamide 4 mg initial dose, 2 mg every 4 hours days 1–3, and 2 mg every 6 to 8 hours days 4–56 (n=28) before the "standard" loperamide regimen of 4 mg initial dose, 4 mg tid for 14 days and 4 mg bid days 14–56 was introduced (n=109).
Abbreviations: bid, twice a day; qd, once a day; tid, three times a day

Table 1. Study overview[a]

	Loperamide (n=137)	Budesonide + loperamide (n=64)	Colestipol + loperamide (n=136)	Colestipol + loperamide prn (n=104)	Neratinib dose escalation + loperamide prn (n=60)[b]
On neratinib treatment	0	0	0	7 (6.7)	52 (86.7)
Completed 1 year of neratinib	76 (55.5)	51 (79.7)	97 (71.3)	69 (66.3)	N/A
Discontinued neratinib before 1 year (for any reason)[c]	61 (44.5)	13 (20.3)	39 (28.7)	28 (26.9)	8 (13.3)
Median (range) neratinib treatment duration, months	11.6 (0.1–13.1)	12.0 (0.2–13.2)	11.9 (0–12.7)	11.9 (0.1–12.8)	5.6 (0.2–8.8)

Data are presented as n (%), unless otherwise stated.
[a]Data cut-off: April 8, 2019.
[b]Enrollment into this cohort is ongoing and data are preliminary.
[c]Reasons for discontinuation were adverse events, withdrawal by subject, disease relapse, investigator decision, non-compliance, lost to follow-up, and other.
N/A, not applicable.

Treatment-emergent diarrhea

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

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

	Loperamide (n=137)	Budesonide + loperamide (n=64)	Colestipol + loperamide (n=136)	Colestipol + loperamide prn (n=104)	Neratinib dose escalation + loperamide prn (n=60)
Any grade	109 (79.6)	55 (85.9)	113 (83.1)	99 (95.2)	57 (95.0)
Grade 1	33 (24.1)	16 (25.0)	38 (27.9)	32 (30.8)	26 (43.3)
Grade 2	34 (24.8)	21 (32.8)	47 (34.6)	34 (32.7)	24 (40.0)
Grade 3	42 (30.7)	18 (28.1)	28 (20.6)	33 (31.7)	7 (11.7)

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

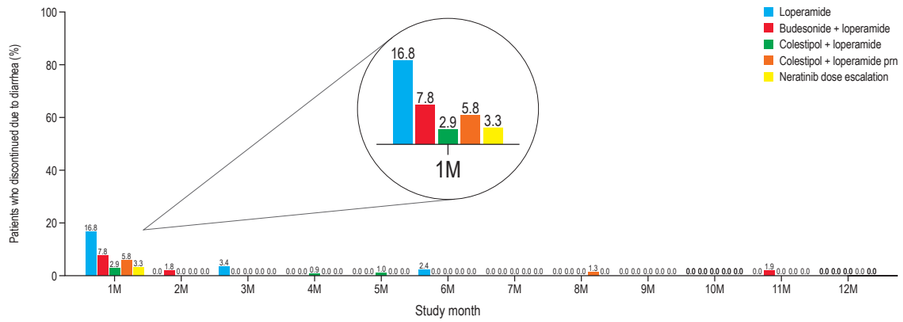
- In the CONTROL study, patients who experienced grade 3 diarrhea experienced a median of 1 or 2 (range, 1 to 17) diarrhea episodes across all cohorts for the entire 12-month treatment period (Table 3), with a median time to onset of 7 to 41 days across all cohorts.
- Median cumulative duration of grade 3 diarrhea ranged from 2.0 to 3.5 days over the 12-month treatment period across all cohorts (Table 3).
- The proportion of patients who had diarrhea leading to neratinib discontinuation was decreased compared with the ExteNET trial (16.8%)[4] in all cohorts, with the exception of the mandatory loperamide only cohort (Table 3).

Table 3. Characteristics of treatment-emergent diarrhea

	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[a]/ patient, n					
Any grade	2	11	5	16	11
Grade ≥2[b]	2	3	2	4	2
Grade 3[b]	1	1	1	1	2
Median cumulative duration,[c] days					
Grade ≥2[b]	5.0	6.0	4.0	10.0	3.0
Grade 3[b]	3.0	2.5	3.5	3.0	2.0
Actions taken, n (%)					
Dose hold	20 (14.6)	12 (18.8)	22 (16.2)	17 (16.3)	3 (5.0)
Dose reduction	10 (7.3)	2 (3.1)	9 (6.6)	11 (10.6)	3 (5.0)
Discontinuation	28 (20.4)	7 (10.9)	6 (4.4)	7 (6.7)	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.

Figure 2. Incidence of treatment discontinuations due to treatment-emergent diarrhea by month



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

	1M	2M	3M	4M	5M	6M	7M	8M	9M	10M	11M	12M
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	4/136	0/115	0/112	1/108	1/105	0/104	0/103	0/103	0/102	0/102	0/98	0/98
Colestipol + loperamide prn	6/104	0/86	0/85	0/83	0/81	0/80	0/79	1/78	0/78	0/74	0/74	0/72
Neratinib dose escalation[a]	2/60	0/54	0/47	0/43	0/41	0/39	0/26	0/20	0/8	0/0	0/0	0/0

[a]Note: attrition in the neratinib dose-escalation cohort was influenced by the fact that the cohort is still enrolling patients.

- 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 low rate of treatment discontinuations.
- 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 (range 0–1.5%) [Table 3].
- The incidence of grade 3 diarrhea across all cohorts was similar in pertuzumab-naïve patients (27.2%) and in patients previously treated with pertuzumab (24.2%).

Other adverse events

- The overall safety profile of neratinib (other than diarrhea) with antidiarrheal prophylaxis was similar to that reported previously with neratinib,[4] apart from an increase in grade 1/2 constipation (Table 4).

Table 4. Overall summary of TEAE

	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 3/4 TEAE	59 (43.1)	30 (46.9)	42 (30.9)	42 (40.4)	12 (20.0)
TEAE leading to neratinib discontinuation	56 (40.9)	11 (17.2)	21 (15.4)	16 (15.4)	3 (5.0)
TEAE leading to hospitalization	5 (3.6)	4 (6.3)	8 (5.9)	3 (2.9)	3 (5.0)
TEAE (all-grade ≥10% incidence)					
Diarrhea	109 (79.6)	55 (85.9)	113 (83.1)	99 (95.2)	57 (95.0)
Nausea	79 (57.7)	32 (50.0)	83 (61.0)	65 (62.5)	23 (38.3)
Constipation[a]	78 (56.9)	48 (75.0)	94 (69.1)	39 (37.5)	17 (28.3)
Fatigue	73 (53.3)	34 (53.1)	65 (47.8)	41 (39.4)	24 (40.0)
Vomiting	36 (26.3)	16 (25.0)	43 (31.6)	25 (24.0)	7 (11.7)
Abdominal pain	36 (26.3)	12 (18.8)	26 (19.1)	26 (25.0)	12 (20.0)
Decreased appetite	27 (19.7)	11 (17.2)	24 (17.6)	26 (25.0)	7 (11.7)
Headache	27 (19.7)	12 (18.8)	20 (14.7)	24 (23.1)	9 (15.0)
Abdominal distension	21 (15.3)	5 (7.8)	22 (16.2)	15 (14.4)	6 (10.0)
Dizziness	19 (13.9)	6 (9.4)	21 (15.4)	20 (19.2)	3 (5.0)
Muscle spasms	15 (10.9)	8 (12.5)	14 (10.3)	14 (13.5)	8 (13.3)
Dyspepsia	12 (8.8)	10 (15.6)	16 (11.8)	13 (12.5)	3 (5.0)

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

- No grade 3 or 4 constipation, obstruction or more serious sequelae from constipation were reported.
- There were two grade 4 treatment-emergent adverse events (sepsis, n=2), and no fatal adverse events 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.[4]
- 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.
- Data for the neratinib dose-escalation cohort included here are not yet complete, although early findings are promising (grade 3 diarrhea, 11.7%; discontinuation due to diarrhea, 3.3%). Patient enrollment 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) has recently started enrolling and did not have patients in the safety population as of the data cut-off.
- 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.[10]

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