Effects of adding budesonide or colestipol to loperamide prophylaxis on neratinib-associated diarrhea in patients with HER2+ early-stage breast cancer: the CONTROL trial

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Background

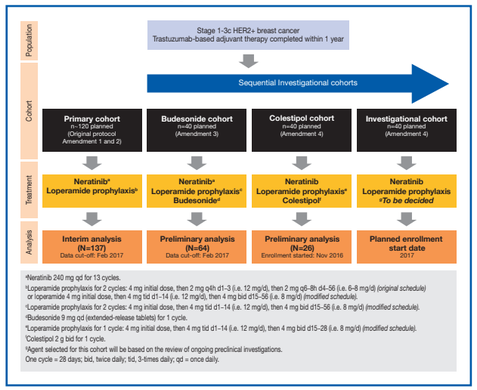
- Neratinib (Puma Biotechnology Inc.) is an irreversible pan-HER tyrosine kinase inhibitor.[1]
  - Results from the randomized, Phase III ExteNET study demonstrated that a 1-year course of neratinib after trastuzumab-based adjuvant therapy reduced the risk of disease recurrence or death by 33% relative to placebo after 2 years' follow-up in women with HER2-positive early-stage breast cancer.[2]
  - Patient follow-up is ongoing; the final 5-year efficacy analysis is anticipated in 2017.
- Diarrhea is the main toxicity of neratinib and is common in the absence of proactive management.[3]
  - In the ExteNET trial, where antidiarrheal prophylaxis was not protocol mandated:
    - Median duration of grade ≥3 diarrhea was 5 days;
    - Neratinib dose reductions and dose holds due to diarrhea occurred in 26.4% and 33.9% of patients, respectively.[2]
  - As most diarrhea events occur early during neratinib treatment, a structured (intensive) prophylactic regimen of loperamide given for 1–2 cycles has been introduced in all clinical trials of neratinib to better manage this toxicity.[3]
- Preclinical studies have suggested that neratinib-associated diarrhea may be multifactorial, including inflammatory, secretory and bile acid malabsorption etiologies. In a rat model of pan-HER TKI-induced diarrhea, a reduction in diarrhea was achieved with an anti-inflammatory or a bile acid resin.[4]
- CONTROL is an international, open-label, sequential cohort, phase II study investigating the effects of loperamide prophylaxis ± budesonide, a locally acting corticosteroid used for inflammatory gastrointestinal conditions, or the bile acid sequestrant colestipol, on neratinib-associated diarrhea.
- We report an interim analysis from the CONTROL study, and preliminary findings from the first investigational cohorts testing budesonide and colestipol.

Methods

Study design

- CONTROL (PUMA-NER-6201) is an international, open-label, phase II study (Clinicaltrials.gov identifier NCT02400476).

Figure 1. CONTROL study design and flowchart



[a]Neratinib 240 mg qd for 13 cycles.
[b]Loperamide prophylaxis for 2 cycles: 4 mg initial dose, then 2 mg q4h d1–3 (i.e. 12 mg/d), then 2 mg q6–8h d4–56 (i.e. 6–8 mg/d) (original schedule) or loperamide 4 mg initial dose, then 4 mg tid d1–14 (i.e. 12 mg/d), then 4 mg bid d15–56 (i.e. 8 mg/d) (modified schedule).
[c]Loperamide prophylaxis for 2 cycles: 4 mg initial dose, then 4 mg tid d1–14 (i.e. 12 mg/d), then 4 mg bid d15–56 (i.e. 8 mg/d) (modified schedule).
[d]Budesonide 9 mg qd (extended-release tablets) for 1 cycle.
[e]Loperamide prophylaxis for 1 cycle: 4 mg initial dose, then 4 mg tid d1–14 (i.e. 12 mg/d), then 4 mg bid d15–28 (i.e. 8 mg/d) (modified schedule).
[f]Colestipol 2 g bid for 1 cycle.
[g]Agent selected for this cohort will be based on the review of ongoing preclinical investigations.
One cycle = 28 days; bid, twice daily; tid, 3-times daily; qd = once daily.

Patient population

- Adults ≥18 years of age.
- Histologically confirmed stage 1–3c breast cancer.
- Documented HER2 overexpression or amplification determined locally.
- Completed trastuzumab-based adjuvant therapy, or experienced side effects resulting in early discontinuation, with last trastuzumab dose given >2 weeks and ≤1 year prior to enrollment.

Study treatments

- Details of treatment schedules are presented in Figure 1.
- Eligible patients were to receive:
  - Oral neratinib 240 mg/day for 1 year.
  - Oral loperamide prophylaxis for 2 cycles per one of two schedules:
    1. Original schedule (first protocol).
    2. Modified schedule to simplify dosing and improve efficacy (protocol amendments 1–4).
  - Oral budesonide for 1 cycle (protocol amendment 3).
  - Oral colestipol for 1 cycle (protocol amendment 4).
- Loperamide (≤16 mg/day) was given as needed after day 56 (after day 28 in the colestipol cohort).
- Treatment-emergent diarrhea was managed with dietetic measures and additional pharmacological treatments depending on grade (i.e. diphenoxylate plus atropine, octreotide, IV fluids, antibiotics).

Assessments

- Clinic visits were scheduled on day 1 of cycles 1, 2, 3, 4, 7 and 10, and treatment end.
- Patients were followed for 28 days after the last dose of neratinib.
- Adverse events were graded according to NCI-CTCAE (version 4.0).

Endpoints

- *Primary endpoint:* incidence of grade ≥3 diarrhea during neratinib treatment.
- *Secondary endpoints:* frequency distribution of maximum-grade diarrhea; incidence and severity of diarrhea by loperamide exposure; serious adverse events; adverse events of interest.
- *Exploratory endpoints:* patient-reported outcomes; biomarkers for disease recurrence.

Statistical methods

- *Primary endpoint:* incidence of grade ≥3 diarrhea during neratinib treatment.
- All analyses were descriptive and were performed in the safety population, defined as all patients who received ≥1 dose of neratinib.
- The ExteNET trial (neratinib arm), which included an analogous patient population but no protocol-mandated antidiarrheal prophylaxis,[2] was used as an historical control.

Results

- A total of 137 patients were included in the interim analysis of the loperamide cohort (original loperamide schedule, n=28; modified loperamide schedule, n=109).
- Sixty-four patients were included in the preliminary analysis of the actively enrolling budesonide cohort and 26 patients were included in the preliminary analysis of the recently started colestipol cohort (Figure 1).
- Baseline characteristics are presented in Table 1.

Table 1. Baseline characteristics

	CONTROL			ExteNET[2]
Variable	Loperamide cohort	Budesonide cohort	Colestipol cohort	Neratinib arm
N (at data cut-off)	137	64	26	1420
Female, %	100	100	96	100
Median age (range), years	53 (30–86)	49 (18–78)	51 (35–78)	52 (25–83)
Tumor stage at diagnosis,[a] %				
I	28.5	25.0	23.1	9.8
IIA, B	54.7	48.4	42.3	42.0
IIIA, B, C	14.6	21.9	30.8	31.2
Hormone receptor status, %				
Positive (ER and/or PR positive)	75.2	71.9	65.4	57.5
Negative (ER and PR negative)	24.8	26.6	30.8	42.5
Missing	0	1.6	3.8	0
Prior (neo)adjuvant therapy, %				
Trastuzumab	99.3	96.9	84.6	100.0
Taxanes	95.6	96.9	80.8	90.1
Anthracycline	26.3	28.1	19.2	77.3
Pertuzumab	40.1	60.9	50.0	–
Trastuzumab emtansine	0	1.6	3.8	–
Median (range) duration of prior trastuzumab, months	11.5 (2.4–18.2)	11.1 (1.2–15.0)	10.6 (0.6–12.0)	11.5 (0.7–56.9)
Median (range) time since last trastuzumab dose, months	3.9 (0.1–12.1)	4.3 (0.5–17.1)	2.3 (0–9.5)	4.4 (0.2–30.9)

ER, estrogen receptor; PR, progesterone receptor. [a]Unknown: loperamide cohort, n=2; budesonide cohort, n=3; ExteNET (neratinib arm), n=241.

Treatment-emergent diarrhea

- Incidence of grade ≥3 diarrhea, the primary study endpoint, was 30.7% (95% CI 23.1–39.1) with loperamide prophylaxis (loperamide cohort), 23.4% (95% CI 13.8–35.7) with loperamide prophylaxis plus budesonide (budesonide cohort) and 11.5% (95% CI 2.4–30.2) with loperamide prophylaxis plus colestipol (colestipol cohort) vs 39.9% without protocol-mandated loperamide prophylaxis in the ExteNET trial.
- There were also marked reductions in the median cumulative duration of diarrhea and in the median number of diarrhea episodes per patient with loperamide prophylaxis given with or without budesonide or colestipol vs ExteNET (Table 2).

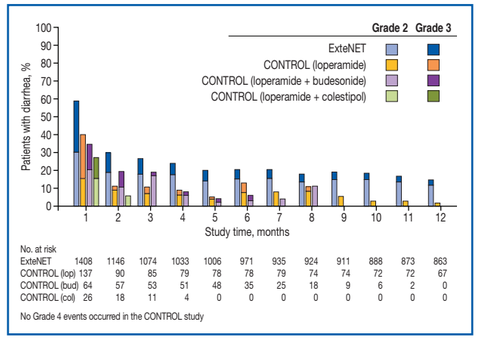
Table 2. Characteristics of treatment-emergent diarrhea

Study	CONTROL			ExteNET[2]
Antidiarrheal prophylaxis	Loperamide (original + modified)	Budesonide + loperamide	Colestipol + loperamide	Loperamide prn
N (at data cut-off)	137	64	26	1408
Diarrhea, %				
Any grade	77.4	79.7	57.7	95.4
Grade 1	24.1	26.6	30.8	22.9
Grade 2	22.6	29.7	15.4	32.5
Grade 3	30.7	23.4	11.5	39.8
Grade 4	0	0	0	0.1
Median cumulative duration of diarrhea, days				
Any grade	12.0	10.0	8.0	59.0
Grade ≥2	4.0	3.0	2.0	10.0
Grade ≥3[a]	3.0	2.0	2.0	5.0
Median episodes of diarrhea per patient, n				
Any grade	2.0	4.0	3.0	8.0
Grade ≥2	2.0	2.0	2.0	3.0
Grade ≥3[a]	1.0	1.0	2.0	2.0
Median duration of neratinib treatment, months	10.6	5.1	1.7	11.6
Tolerability related to neratinib diarrhea				
Neratinib dose hold due to diarrhea, %	14.6	14.1	7.7	33.9
Neratinib dose reductions due to diarrhea, %	7.3	1.6	3.8	26.4
Neratinib discontinuations due to diarrhea, %	20.4	9.4	0	16.8
Hospitalization due to diarrhea, %	1.5	0	0	1.4

[a]No grade 4 events in the CONTROL study; one grade 4 event in the ExteNET study.

- The proportion of patients requiring neratinib dose holds and dose reductions was also reduced with loperamide prophylaxis given with or without budesonide vs ExteNET.
- The occurrence and severity of diarrhea in the CONTROL study over the course of neratinib treatment showed a marked change from that observed in the ExteNET study (Figure 2):
  - ExteNET showed a profile for diarrhea that was chronic and characterized by higher-grade diarrhea (grades 2 and 3) that was highest in month 1 and still present in a larger proportion of patients in months 2–12.
  - In the CONTROL study cohorts, diarrhea was characterized by a lower percentage of high-grade diarrhea in month 1 and a much lower incidence in months 2–12.
  - There appears to be some adaptation to the effects of neratinib, as higher-grade diarrhea occurs early and does not typically recur.

Figure 2. Treatment-emergent grade 2 and 3 diarrhea by months: CONTROL vs ExteNET[2]



No Grade 4 events occurred in the CONTROL study

Potential factors contributing to diarrhea

- During the CONTROL study, there has been an increase in the proportion of patients previously treated with pertuzumab.
- Preliminary data show that budesonide decreases the incidence of grade 3 diarrhea in patients previously treated with pertuzumab.

Table 3. Incidence of grade 3 diarrhea by pertuzumab treatment status

	Prior pertuzumab treatment			
	Loperamide cohort		Budesonide cohort	
	Yes (n=55)	No (n=82)	Yes (n=39)	No (n=25)
Grade 3 diarrhea, %	38.2	25.6	10.3	36.0

Other adverse events

- Aside from diarrhea, the overall tolerability profile of neratinib with loperamide prophylaxis given with or without budesonide or colestipol was like that reported in the ExteNET trial, apart from an increase in grade 1/2 constipation (Table 4). No grade 3 or higher constipation has been observed to date.
- The incidence of other gastrointestinal events, i.e. nausea, vomiting, and abdominal pain, was similar in the CONTROL cohorts vs ExteNET.
- Aside from diarrhea, grade 3 adverse events were infrequent,the most frequently reported being fatigue (3.6%, 6.3%, 0%), abdominal pain (1.5%, 0%, 3.8%) vomiting (1.5%, 3.1%, 0%), ALT increased (0.7%, 3.1%, 0%) and dehydration (1.5%, 1.6%, 0%) in the loperamide, budesonide and colestipol cohorts, respectively.
- The only grade 4 events observed were sepsis and urinary tract infection (both unrelated events in the same patient); there were no fatal adverse events in the CONTROL study.

Table 4. Other common treatment-emergent adverse events (≥10% of CONTROL patients)

	CONTROL[1]			ExteNET[2,3]
Any-grade events, %	Loperamide cohort (n=137)	Budesonide cohort (n=64)	Colestipol cohort (n=26)	Neratinib arm (n=1408)
Constipation	56.2	70.3	65.4	8.2
Nausea	55.5	46.9	57.7	43.0
Fatigue	53.3	46.9	46.2	27.1
Vomiting	24.8	20.3	19.2	26.2
Abdominal pain	26.3	15.6	3.8	24.1
Decreased appetite	19.0	14.1	11.5	12.1
Headache	19.0	14.1	7.7	19.7
Dizziness	13.9	7.8	15.4	10.4
Dry mouth	13.1	9.4	11.5	3.3
Abdominal distension	15.3	4.7	3.8	5.2
Abdominal discomfort	5.1	3.1	11.5	–
Dyspepsia	8.0	14.1	3.8	9.9
Rash	3.6	17.2	11.5	15.0
Pyrexia	5.1	1.6	11.5	–

Conclusions

- By controlling early diarrheal events, effective diarrhea prophylaxis may help to improve the tolerability of neratinib, enhance long-term adherence to treatment, and ensure that the efficacy benefits of neratinib are realized.
- A structured loperamide prophylactic regimen, for one or two cycles and with or without the addition of either budesonide or colestipol for a single cycle, reduces the incidence, severity, and duration of neratinib-associated diarrhea compared with events observed in the ExteNET trial.
- The addition of colestipol to loperamide prophylaxis appears to offer an incremental decrease in diarrhea incidence and severity, and may further diminish the duration of diarrhea. The addition of colestipol may also improve tolerability as shown by the decreased number of neratinib dose holds, dose reductions, and discontinuations.
- An exploratory analysis revealed that budesonide may decrease the incidence of grade 3 diarrhea in patients previously treated with pertuzumab.
- Enrollment into the colestipol cohort is ongoing, and the final analysis of the CONTROL study will be performed when all patients have completed 12 months of neratinib therapy.

References

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