Bringing diarrhea under CONTROL: dose escalation reduces neratinib-associated diarrhea and improves tolerability in HER2-positive early-stage breast cancer

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Introduction

- Neratinib (Nerlynx®), an irreversible pan-HER tyrosine kinase inhibitor, is used for the extended adjuvant treatment of patients with early-stage HER2-positive (HER2+) breast cancer following adjuvant trastuzumab-based therapy and for patients with HER2+ metastatic breast cancer in combination with capecitabine.[1–7]
- Diarrhea, particularly in the first 1–2 months, is the main tolerability concern with neratinib and is common in the absence of proactive management.[5]
- In the ExteNET adjuvant trial, where no mandatory anti-diarrheal prophylaxis was used, the rate of grade 3 diarrhea was 40%, 34% of patients experienced at least 1 dose hold, and 17% of patients discontinued neratinib due to diarrhea.[5,8]
- The CONTROL trial (Figure 1) previously showed that pre-emptive antidiarrheal prophylaxis (loperamide alone or in combination with budesonide or colestipol) or neratinib dose escalation (DE) reduced the rate, severity, and duration of grade ≥3 diarrhea compared with that observed in ExteNET.[9]
- Currently, antidiarrheal prophylaxis is initiated with the first dose of neratinib and is used daily during the first 2 cycles of treatment.[1] Patients can also take antidiarrheal agents as needed during treatment.

Objectives

- To describe the complete data for the weekly DE cohort 1 (DE1; 60 patients) and interim data for the ongoing bi-weekly DE cohort 2 (DE2; 62 patients).
- Key results from previous cohorts studied in CONTROL[9] are also presented for select variables where relevant.

Neratinib dose-escalation cohorts

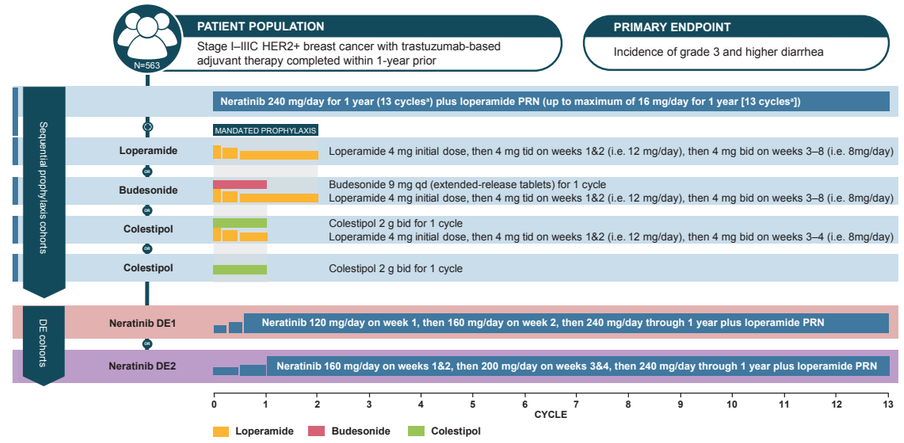
- There appears to be some adaptation to the effects of neratinib, as diarrhea occurs early and does not typically recur.[9] Consequently, a DE technique during the first weeks of therapy may allow patients to acclimate to neratinib, increasing tolerability and optimizing the management of treatment-related side effects.[9]
- In DE1 (weekly dose-escalation regimen), neratinib was administered 120 mg (daily during Week 1), 160 mg (daily during Week 2), and 240 mg (daily starting with Week 3 and up to 1 year), and loperamide was given as needed (not to exceed 16 mg/day) throughout the course of 1 year of neratinib treatment.[9]
- In DE2 (bi-weekly dose-escalation regimen), neratinib was administered 160 mg (daily during Weeks 1&2), 200 mg (daily during Weeks 3&4), and 240 mg (daily starting with Week 5 and up to 1 year) and loperamide was given as needed (not to exceed 16 mg/day) throughout the course of 1 year of neratinib treatment.[9]

Results

Patients and treatment

- As of 19 October 2020, all patients in DE1 (60 patients) were off study and data presented here are complete.
- DE2 enrollment is complete (62 patients). 24 (38.7%) patients have completed 1 year, 15 (24.2%) discontinued prior to 1 year, and 23 (37.1%) remain on treatment, all of whom have received at least 6 months of treatment.

Figure 1. CONTROL: overall study schema



[a]1 cycle = 28 days; bid = twice daily; DE = dose escalation; PRN = pro re nata (as necessary); qd = once a day; tid = three-times daily.

Table 1. Summary of patient disposition and diarrhea characteristics: DE cohorts

	DE cohort 1 (complete) (n=60)	DE cohort 2 (interim)[a] (n=62)
Patient disposition, n (%)		
Completed 1 year of treatment	47 (78.3)	24 (38.7)
Discontinued treatment prior to 1 year	13 (21.7)	15 (24.2)
Still on treatment	0	23 (37.1)
Median duration of treatment, months	11.96	9.17
Diarrhea, n (%)		
Grade 1	24 (40.0)	24 (38.7)
Grade 2	27 (45.0)	21 (33.9)
Grade 3	8 (13.3)	16 (25.8)
Days 1–7	0	3 (4.8)
Days 8–14	0	3 (4.8)
Days 15+	8 (13.3)	10 (16.1)
Grade 4	0	0
Median episodes of Grade 3 diarrhea, n	2	1
Median time to first onset of Grade 3 diarrhea, days	45	20
Median cumulative duration of Grade 3 diarrhea per patient, days	2.5	2
Discontinuations due to diarrhea, n (%)	2 (3.3)	3 (4.8)
Dose reductions due to diarrhea, n (%)	2 (3.3)	7 (11.3)
Dose holds due to diarrhea, n (%)	7 (11.7)	9 (14.5)

[a]Patients in DE2 still on treatment (October 19, 2020 datacut)

- The median treatment duration for DE1 was 11.96 (IQR 11.1–12.0) months.
- In the DE1 cohort, 55 (91.7%) patients escalated neratinib dose to 240 mg on schedule; one patient (1.7%) escalated to 240 mg 1 week later than the planned schedule.

Table 2. Key diarrhea outcomes (all CONTROL cohorts)

	Loperamide (n=137)	Budesonide + Loperamide (n=64)	Colestipol + Loperamide (n=136)	Colestipol + loperamide PRN (n=104)	Neratinib DE1 + loperamide PRN (n=60)	Neratinib DE2 + loperamide PRN* (n=62)
Grade 3 diarrhea, n (%)	42 (30.7)	18 (28.1)	28 (20.6)	33 (31.7)	8 (13.3)	16 (25.8)
Discontinuations due to diarrhea, n (%)	28 (20.4)	7 (10.9)	5 (3.7)	8 (7.7)	2 (3.3)	3 (4.8)

*October 19, 2020 datacut

- In the DE2 cohort, 48 (77.4%) patients escalated neratinib dose to 240 mg on schedule; two (3.2%) escalated to 240 mg ~1–2 weeks later than planned schedule, and two (3.2%) have not escalated to 240 mg and remain on treatment.
- Overall, 48% and 55% of patients in DE1 and DE2, respectively, had received prior pertuzumab; 0% and 3%, respectively, had received prior T-DM1.

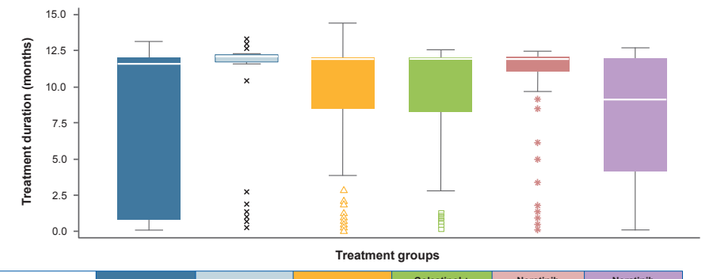
Dose-escalation cohorts

- There were no grade 4 diarrhea events. The incidence of grade 3 diarrhea was 13.3% in DE1 and 25.8% in DE2 (0% grade 3 diarrhea in DE1 vs 9.6% grade 3 diarrhea in DE2 occurring in the first 2 weeks).
- The median cumulative duration of grade 3 diarrhea over the entire 12-month treatment period was 2.5 days (range 1–6 days) for DE1 and 2 days (range 1–7 days) for DE2.
- In DE1 and DE2, 7 (11.7%) and 9 (14.5%) patients, respectively, had at least one dose hold while on study.
- In DE1 and DE2, 2 (3.3%) and 3 (4.8%) patients, respectively, discontinued neratinib because of diarrhea.

All CONTROL cohorts

- The lowest rates of both grade 3 diarrhea and discontinuation due to diarrhea were observed in DE1 (**Table 2**).
- At least 75% of patients in the DE1 cohort received neratinib longer than 11.07 months (**Figure 2**).
- Discontinuations primarily occurred early in treatment across all cohorts (**Figure 3**).

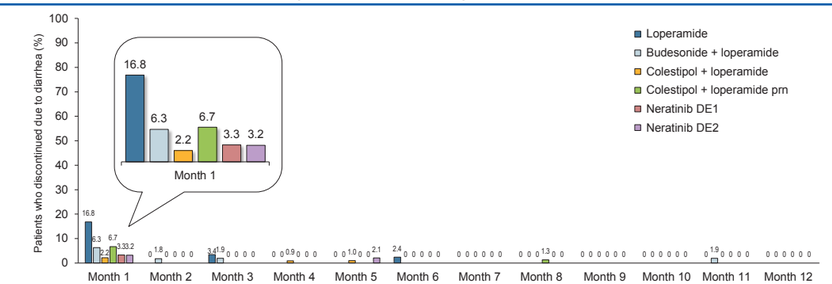
Figure 2. Treatment duration (all CONTROL cohorts)



Median duration of treatment, months	Loperamide	Budesonide	Colestipol	Colestipol + loperamide PRN	Neratinib DE1	Neratinib DE2*
	11.63	11.96	11.93	11.96	11.96	9.17
25th percentile (Q1)	0.76	11.79	8.48	8.25	11.06	4.27

*Oct 19 2020 data cut. Patients in the DE2 cohort are still on treatment.
The white line inside the box is the median. The lower edge of each solid box represents the 25th percentile (Q1), and the upper edge represents the 75th percentile (Q3). The upper and lower fences are the max and min observations within 1.5 inter quartile ranges (IQR). For example, at least 75% of patients received neratinib longer than 11.06 months (Q1) for the DE1 cohort, compared to 0.76 months (Q1) for Loperamide cohort.

Figure 3. Treatment discontinuations due to diarrhea (all CONTROL cohorts)



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	4/64	1/57	1/54	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	1/107	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	0/77	0/77	0/75
DE1	2/60	0/55	0/53	0/53	0/51	0/51	0/50	0/50	0/50	0/49	0/47	0/46
DE2	2/62	0/56	0/49	0/49	1/48	0/46	0/42	0/40	0/37	0/32	0/28	0/25

*October 19, 2020 datacut

Conclusions

- Adoption of neratinib dose escalation reduced the incidence, severity, and duration of neratinib-associated diarrhea in CONTROL compared with ExteNET:
  - The incidence of grade 3 diarrhea was low (13.3%) in DE1.
  - The median cumulative duration of grade 3 diarrhea was low (2.5 days) in DE1.
- DE1 was also associated with low rates of diarrhea-related discontinuations (3.3%) and dose holds (11.7%) compared with all previously mandated prophylaxis strategies investigated in CONTROL and compared with ExteNET.
- Taken together, these results show improved tolerability of neratinib with DE1 and suggest that DE1 combined with loperamide PRN allows patients to stay on neratinib longer, allowing them the opportunity to receive the full benefit of neratinib.
- DE2 is ongoing and complete data will be presented at a later date.

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