Dose escalation for mitigating diarrhea: Ranked tolerability assessment of antidiarrheal regimens in patients receiving neratinib for early-stage breast cancer

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Introduction

- Neratinib (Nerlynx®), an irreversible pan-HER tyrosine kinase inhibitor, is approved for extended adjuvant treatment of patients with early-stage HER2-positive (HER2+) breast cancer following adjuvant trastuzumab-based therapy and in combination with capecitabine for patients with HER2+ metastatic breast cancer.[1]
- Diarrhea is the most frequently reported on-target side effect associated with neratinib and is common in the absence of proactive management.[2]
- In the ExteNET adjuvant trial, where no mandatory anti-diarrheal prophylaxis was used, 40% of patients reported grade 3 diarrhea and 17% of patients discontinued neratinib due to diarrhea.[2,3]
- The CONTROL trial 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 the neratinib arm in ExteNET.[4]
- In the CONTROL trial, cohorts were enrolled sequentially, with no quantitative assessment or statistical comparison to determine the best regimen or to compare CONTROL with ExteNET.

Objectives

- To identify the best diarrhea mitigation strategy in the CONTROL trial.
- To compare the best CONTROL regimen with the neratinib treatment arm in ExteNET, in which diarrhea prophylaxis was not mandated.

Methods

Patients and treatment

- In CONTROL, patients ≥18 years of age with stage I–IIIc HER2+ breast cancer received neratinib (240 mg/day orally for 1 year) plus different antidiarrheal modalities: loperamide (L), L + budesonide (BL), L + colestipol (CL), colestipol + L as needed (CL-PRN), and neratinib DE (neratinib 120 mg/day on days 1–7, 160 mg/day on days 8–14, then 240 mg/day to day 365, + loperamide PRN) as previously described.[4] Cohorts that had completed follow up were included.
- In ExteNET, patients ≥18 years of age with stage I–III HER2+ breast cancer received neratinib 240 mg/day or matching placebo for one year.[2] No anti-diarrheal prophylactics were mandated.

Integrated tolerability assessment

- Clinical input was used to identify four domains that included 13 endpoints (Table 1).
- For each endpoint, a rank from 1 to 5 was assigned across the five CONTROL cohorts; lower scores indicate better results.
- The sum and mean of the ranks were calculated for each cohort. The cohort with the lowest sum and mean was deemed the best in terms of tolerability by this method.

Comparison of CONTROL DE cohort and ExteNET neratinib arm

- The best cohort in CONTROL and the ExteNET neratinib arm were compared descriptively.

Table 1. Integrated tolerability assessment of 13 endpoints

Domain	Endpoint
1. Diarrhea	1. Grade 3 diarrhea 2. Discontinuation due to diarrhea during first 3 months of treatment 3. Incidence of any-grade treatment-emergent diarrhea
2. Exposure	4. Treatment duration 5. Mean cumulative actual neratinib dose
3. Adverse events	6. TEAEs leading to treatment discontinuation 7. Grade 3 nausea 8. Grade 3 constipation 9. Grade 3 fatigue 10. Grade 3 vomiting 11. Grade 3 abdominal pain 12. Grade 3 decreased appetite
4. QoL	13. FACT-B mean change from baseline score at Month 1

QoL = Quality of Life. FACT-B: Functional assessment of Cancer Treatment – Breast. TEAE, treatment emergent adverse event.

Table 2. DE had the best overall tolerability ranking among the CONTROL cohorts

Endpoint [rank]	L (n=137)	BL (n=64)	CL (n=136)	CL-PRN (n=104)	DE (n=60)
1. Diarrhea, n (%)					
Grade 3 diarrhea[a]	30.7 [4]	28.1 [3]	20.6 [2]	31.7 [5]	13.3 [1]
Discontinuation due to diarrhea during first 3 months of treatment	19.0 [5]	9.4 [4]	2.2 [1]	6.7 [3]	3.3 [2]
Incidence of any-grade treatment-emergent diarrhea	79.6 [1]	85.9 [3]	83.1 [2]	95.2 [4]	98.3 [5]
2. Exposure					
Treatment duration, 25th percentile, months	0.76 [5]	11.79 [1]	8.48 [3]	8.25 [4]	11.06 [2]
Mean cumulative actual neratinib dose, mg	47253.72 [5]	66753.13 [2]	60846.18 [3]	58139.42 [4]	67364.00 [1]
3. Adverse events, n (%)[a]					
TEAEs leading to treatment discontinuation	40.9 [5]	17.2 [3]	16.2 [2]	17.3 [4]	13.3 [1]
Grade 3 nausea	0.7 [3]	0 [1.5]	1.5 [4]	2.9 [5]	0 [1.5]
Grade 3 constipation	0 [3]	0 [3]	0 [3]	0 [3]	0 [3]
Grade 3 fatigue	3.6 [4]	7.8 [5]	1.5 [1]	1.9 [3]	1.7 [2]
Grade 3 vomiting	1.5 [1]	3.1 [5]	2.9 [4]	1.9 [3]	1.7 [2]
Grade 3 abdominal pain	1.5 [3]	1.6 [4]	2.2 [5]	1.0 [2]	0 [1]
Grade 3 decreased appetite	0 [2.5]	0 [2.5]	0.7 [5]	0 [2.5]	0 [2.5]
4. QoL					
FACT-B Total Score mean change from baseline at month 1[c]	−3.8 [3]	−6.0 [5]	−3.9 [4]	−2.1 [1]	−3.0 [2]
Sum of ranks	44.5	42	39	43.5	26
Average rank	3.4	3.2	3.0	3.3	2.0
			Rank 1–1.5	**Rank 2**	**Rank 2.5–5**

FACT-B: Functional assessment of Cancer Treatment – Breast. TEAE, treatment emergent adverse event.
[a]No grade 4 events observed.

Quality of life

- Patients completed the Functional Assessment of Cancer Therapy – Breast (FACT-B) questionnaire.
- A 7–8 point change from baseline in FACT-B Total Score was considered a clinically meaningful difference.[5,6]

Results

Integrated tolerability assessment

- The CONTROL DE cohort ranked best among the five CONTROL cohorts (Table 2).

Comparison of CONTROL DE cohort and ExteNET neratinib arm

- Comparison of the CONTROL DE cohort and ExteNET neratinib arm showed better tolerability for CONTROL DE across all endpoints (Table 3).
- As illustrated in the radar plot (Figure 1), the orange area representing CONTROL DE data remains closer to the center – indicating better outcomes – in most dimensions compared with the blue shape, which represents the ExteNET arm.

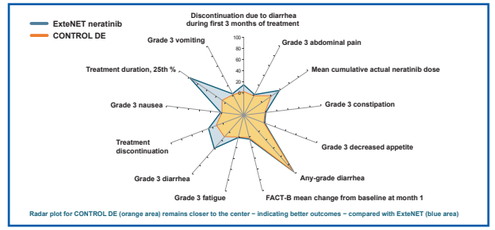
Table 3. Comparison of 13 endpoints between the ExteNET neratinib arm and CONTROL DE

Endpoint	ExteNET (n=1408)	CONTROL DE (n=60)
1. Diarrhea, n (%)		
Grade 3 diarrhea[a]	562 (39.9)	8 (13.3)
Discontinuation due to diarrhea during first 3 months of treatment	1204 (14.5)	2 (3.3)
Incidence of any-grade treatment-emergent diarrhea	1343 (95.4)	59 (98.3)
2. Exposure		
Treatment duration, 25th percentile, months	2.5	11.1
Mean cumulative actual neratinib dose, mg	54,193.9	67,364.0
3. Adverse events, n (%)[b]		
TEAEs leading to treatment discontinuation	388 (27.6)	8 (13.3)
Grade 3 nausea	26 (1.8)	0
Grade 3 constipation	0	0
Grade 3 fatigue	23 (1.6)	1 (1.7)
Grade 3 vomiting	47 (3.3)	1 (1.7)
Grade 3 abdominal pain	24 (1.7)	0
Grade 3 decreased appetite	3 (0.2)	0
4. QoL		
FACT-B Total Score mean change from baseline at month 1[c]	−4.6	−3.0

[a]1 patient had grade 4 diarrhea in ExteNET; no grade 4 diarrhea occurred in CONTROL.
[b]No grade 4 events observed.
[c]Higher scores indicate better QoL; larger changes from baseline indicate greater impact on QoL over the study period. Difference in score of 7–8 points considered clinically meaningful.[5,6]
DE = dose escalation; TEAE = treatment-emergent adverse event.

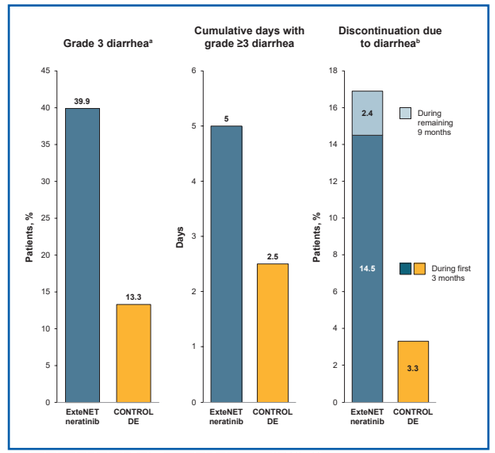
Results

Figure 1. Improved tolerability was seen with CONTROL DE versus the ExteNET neratinib arm (13 endpoints displayed)



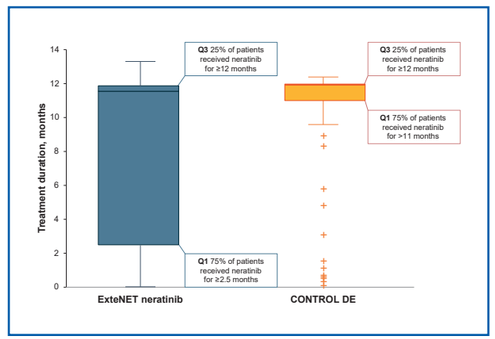
Radar plot for CONTROL DE (orange area) remains closer to the center – indicating better outcomes – compared with ExteNET (blue area)

Figure 2. An improved diarrhea profile was seen with CONTROL DE vs ExteNET neratinib arm



[a]1 patient had grade 4 diarrhea in ExteNET; no grade 4 diarrhea occurred in CONTROL.
[b]All discontinuations due to diarrhea occurred within the first 3 months of treatment in CONTROL DE cohort.

Figure 3. At least 75% of patients in CONTROL DE received neratinib for longer than 11.1 months



The lower edge of each box represents the 25th percentile (Q1), and the upper edge represents the 75th percentile (Q3). The line inside the box is the median and the symbols outside the whiskers are outliers. DE = dose escalation.

Results

Exposure

- Treatment duration in the CONTROL DE cohort was generally close to the planned 1 year of treatment (Figure 3):
  - At least 75% of patients in the CONTROL DE cohort received neratinib for longer than 11.1 months (Q1).
  - In contrast, treatment duration varied widely in the ExteNET neratinib arm.
- Mean cumulative dose of neratinib was higher in CONTROL DE vs ExteNET neratinib arm (Table 3).

Adverse events

- An improved or comparable adverse event profile was observed in the CONTROL DE cohort versus the ExteNET neratinib arm (Table 3).

Quality of life

- Decreases in health-related quality of life did not cross the clinically important threshold in either CONTROL DE or the ExteNET neratinib arm (Table 3).

Conclusions

- These analyses suggest that neratinib DE during the first 2 weeks of treatment improved tolerability further versus other antidiarrheal strategies in CONTROL.
- We observed the lowest rate of grade 3 diarrhea and an improved or comparable adverse event profile in the CONTROL DE cohort versus the ExteNET neratinib arm.
- These data also reveal greater compliance with neratinib DE in CONTROL (fewer early discontinuations, longer treatment duration, higher cumulative dose), as well as reduced impact on quality of life, suggesting improved tolerability versus the ExteNET neratinib arm.
- Neratinib DE may allow patients to stay on neratinib for the recommended time period, providing them the opportunity to receive the full benefit of treatment.

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