Final findings from the CONTROL trial of diarrheal prophylaxis or neratinib dose escalation on neratinib-associated diarrhea and tolerability in patients with HER2+ early-stage breast cancer

Arlene Chan,[1] Manuel Ruiz-Borrego,[2] Gavin Marx,[3] Adam Brufsky,[4] Jo Chien,[5] Michael Thirlwell,[6] Maureen Trudeau,[7] Ron Bose,[8] José A García-Sáenz,[9] Daniel Egle,[10] Barbara Pistilli,[11] Johanna Wassermann,[12] Kerry A Cheong,[13] Dieter Semsek,[14] Christian F Singer,[15] Daniel Hunt,[16] Navid Foruzan,[16] Leanne McCulloch,[16] Carlos H Barcenas[17]

[1]Breast Cancer Research Centre-WA, Perth & Curtin University, Nedlands, Australia; [2]Hospital Universitario Virgen del Rocio, Seville, Spain; [3]Sydney Adventist Hospital, Sydney, Australia; [4]Magee-Womens Hospital of UPMC, Pittsburgh, PA, USA; [5]University of California San Francisco, San Francisco, CA, USA; [6]McGill University Health Centre, Montreal, QC, Canada; [7]Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [8]Washington University School of Medicine, St. Louis, MO, USA; [9]Hospital Clínico San Carlos, Madrid, Spain; [10]University Frauenklinik Innsbruck, Innsbruck, Austria; [11]Gustave Roussy Cancer Center, Villejuif, France; [12]Hôpital Pitié-Salpêtrière, Paris, France; [13]Adelaide Cancer Centre, Adelaide, Australia; [14]Praxis am Diakonie Krankenhaus Onkologische Schwerpunktpraxis, Freiberg, Germany; [15]Medical University of Vienna, Vienna, Austria; [16]Puma Biotechnology Inc., Los Angeles, CA, USA; [17]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

#P5-18-02

Background

- Neratinib (NERLYNX®), an irreversible pan-HER tyrosine kinase inhibitor, is approved:[1]
  - As monotherapy for the extended adjuvant treatment of patients with early-stage HER2-positive (HER2+) breast cancer following adjuvant trastuzumab-based therapy.
  - In combination with capecitabine for patients with HER2+ metastatic breast cancer.
- Diarrhea is the most frequently reported on-target side effect associated with neratinib and is very 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 was an international, multi-cohort, open-label, phase 2 study designed to investigate preventive antidiarrheal prophylaxis (loperamide alone or in combination with budesonide or colestipol) or neratinib dose escalation (DE) for the prevention of neratinib-associated diarrhea.[4]
- All patients are off study, and the CONTROL trial is now complete.
- Data from the CONTROL prophylaxis and DE cohorts have been reported previously:
  - Final findings for the loperamide, budesonide and colestipol cohorts, and interim data for the DE cohorts, suggested that the 2-week (DE1) cohort resulted in the best diarrhea profile.[4,5]
  - An integrated tolerability assessment of CONTROL (including final DE1 data) suggested that the DE1 cohort improved tolerability versus other antidiarrheal strategies in CONTROL.[6]
- The 2-week (DE1) dose-escalation strategy from CONTROL has been incorporated into the US Package Insert.[7]

Objective

- This poster focuses on the final data for the 4-week escalation cohort (DE2) alongside the previously presented data for the 2-week escalation cohort (DE1).

Study design

Patients

- Patients ≥18 years of age with stage I–IIIc HER2+ breast cancer with trastuzumab-based adjuvant therapy completed within 1-year prior to study entry.

Treatment

- Patients received oral neratinib (240 mg/day for 1 year) after trastuzumab-based adjuvant therapy.
- Patients were enrolled sequentially into separate cohorts investigating:
  1. Mandatory loperamide prophylaxis.
  2. Budesonide + loperamide.
  3. Colestipol + loperamide.
  4. Colestipol + loperamide PRN.
  5. Neratinib DE1 (2-week escalation) + loperamide PRN.
  6. Neratinib DE2 (4-week escalation) + loperamide PRN.

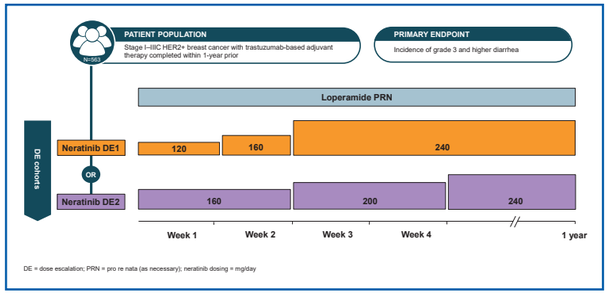
Rationale for neratinib DE cohorts

- There appears to be some adaptation to the effects of neratinib, as diarrhea occurs early and does not typically recur.[4] 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.[5]
- Employing a DE strategy also reduces the risk of additional side effects imposed by a mandatory anti-diarrheal prophylaxis regimen.
- Details on the DE1 (2-week escalation) and DE2 (4-week escalation) regimens are shown in Figure 1.

Safety evaluation

- Primary endpoint: incidence of grade ≥3 diarrhea.
- Adverse events were graded according to NCI CTCAE v4.0.

Figure 1. CONTROL trial DE cohorts: study schema



DE = dose escalation; PRN = pro re nata (as necessary); neratinib dosing = mg/day

Results

Patients and treatment

- A total of 563 patients were enrolled in CONTROL, including 60 in the DE1 and 62 in the DE2 cohort.
- In the DE1 cohort, 56 (93.3%) patients escalated the neratinib dose to 240 mg on schedule; one patient (1.7%) escalated to 240 mg 1 week later than the planned schedule.
- In the DE2 cohort, 47 (75.8%) patients escalated the 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%) escalated to 240 mg in later weeks.
- Overall, 48.3% and 54.8% of patients in DE1 and DE2, respectively, had received prior pertuzumab; 0% and 3.2%, respectively, had received prior T-DM1. No differences were noted in grade 3 diarrhea based on these prior therapies.
- Mean treatment durations in the DE1 and DE2 cohorts were 10.11 (SD 3.83) and 9.35 (SD 4.66) months, respectively.

Table 1. Patient disposition: CONTROL trial DE cohorts

	DE cohort 1 (n=60)	DE cohort 2 (n=62)
Patient disposition, n (%)		
Completed 1 year of treatment	47 (78.3)	46 (74.2)
Discontinued treatment prior to 1 year	13 (21.7)	16 (25.8)
Discontinued due to any AE	5 (8.3)	8 (12.9)
Discontinued due to diarrhea	2 (3.3)	4 (6.5)
Median duration of treatment, months	**11.96**	**11.94**
Q1–Q3	11.06–12.01	7.46–11.99
Range	0.2–12.4	0.3–14.5

Impact of DE on diarrhea

- Adoption of neratinib DE at the initiation of treatment, particularly the 2-week DE schedule (DE1), most markedly reduced the incidence, severity, and duration of neratinib-associated grade 3 diarrhea in CONTROL compared with ExteNET (Table 2):
  - Both DE strategies reduced the incidence of grade 3 diarrhea (DE1 13.3%; DE2 27.4%) compared with that observed in the ExteNET trial (historical control: 39.8%).[4,5] No grade 4 diarrhea was reported in any cohort.
  - The median cumulative duration of grade 3 diarrhea ranged from 2–2.5 days across the CONTROL DE study cohorts for the entire 12-month treatment period (compared with 5.0 days for ExteNET).[5]
  - The proportion of patients discontinuing neratinib because of diarrhea was decreased both DE cohorts (DE1 3.3%; DE2 6.5%) compared with ExteNET (16.8%).[5]

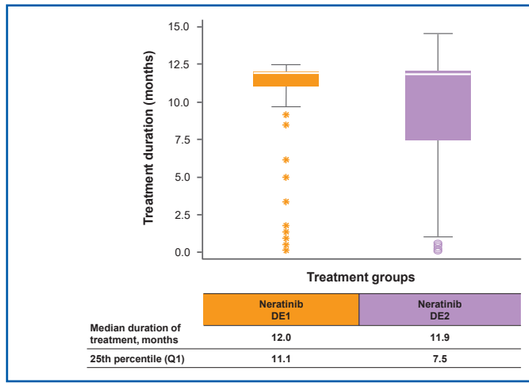
Table 2. Diarrhea characteristics: CONTROL trial DE cohorts

	DE cohort 1 (n=60)	DE cohort 2 (n=62)
Diarrhea, n (%)		
Grade 1	24 (40.0)	23 (37.1)
Grade 2	27 (45.0)	21 (33.9)
Grade 3	8 (13.3)	17 (27.4)
Grade 4	0	0
Median episodes of Grade 3 diarrhea, n	2	1
Median time to first onset of Grade 3 diarrhea, days	45	19
Median cumulative duration of Grade 3 diarrhea per patient, days	2.5	2
Discontinuations due to diarrhea, n (%)	2 (3.3)	4 (6.5)
Dose reductions due to diarrhea, n (%)	2 (3.3)	7 (11.3)
Dose holds due to diarrhea, n (%)	7 (11.7)	8 (12.9)
Hospitalizations due to diarrhea, n (%)	0	0

Impact of DE on treatment duration

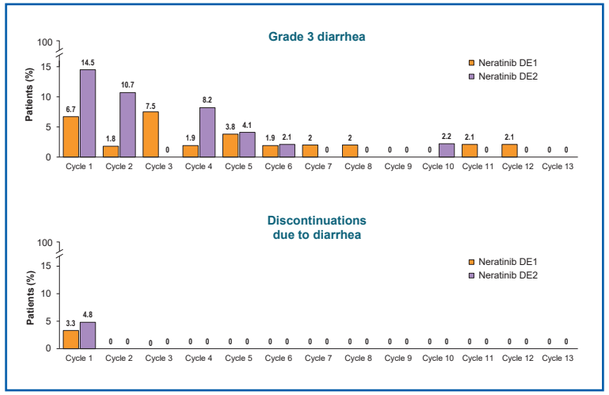
- Adoption of neratinib DE at the initiation of treatment, particularly the 2-week DE schedule (DE1), allowed patients to stay on treatment longer (Figure 2):
  - At least 75% of patients received neratinib longer than 11.06 months (Q1) in the DE1 cohort, compared with 7.46 months (Q1) in the DE2 cohort.
  - The median duration of treatment for the DE1 and DE2 cohorts are shown in Figure 2.
  - The mean duration of treatment was 10.11 months (SD 3.83) for DE1 and 9.35 months (SD 4.66) for DE2.
- Adoption of the neratinib DE1 schedule also appeared to reduce the rate of grade 3 diarrhea and treatment discontinuations due to diarrhea compared with the DE2 schedule (Figure 3).
- PRN loperamide was used in 93% of patients in DE1 and 100% of patients in DE2, with first use of loperamide occurring early in treatment (median of 5.5 days in DE1 and 4 days in DE2).

Figure 2. Treatment duration: CONTROL trial DE cohorts



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).

Figure 3. Grade 3 diarrhea and treatment discontinuations due to diarrhea: CONTROL trial DE cohorts



Conclusions

- Adoption of neratinib DE + loperamide PRN during the first 2 weeks of treatment (DE1 cohort) was associated with the lowest rate of grade 3 diarrhea during the trial compared with all other anti-diarrheal strategies investigated in CONTROL.
- The DE1 cohort also had the lowest rate of diarrhea-related discontinuations (3.3%) and dose holds (11.7%) compared with all previously mandated prophylaxis strategies investigated in CONTROL, the subsequent DE2 strategy, and also when compared with the neratinib arm in ExteNET.[2,3]
- These final findings from the CONTROL study show improved tolerability of neratinib with all diarrhea prophylaxis strategies and suggest that neratinib DE1 with loperamide PRN allows patients to stay on treatment longer and receive the full benefit of neratinib therapy.
- The US package label for neratinib includes loperamide prophylaxis and has recently been amended to include the DE1 strategy from CONTROL.[7]

References

1. U.S. Food and Drug Administration. NERLYNX® (neratinib) Prescribing Information.
2. Chan A, et al. Lancet Oncol 2016;17:367–77.
3. Mortimer J, et al. Breast Cancer Res 2019;21:32.
4. Barcenas CH, et al. Ann Oncol 2020;31:1223–30.
5. Ruiz-Borrego M, et al. Proc SABCS 2020 (abstract PS13-20).
6. Marx G, et al. Proc ASCO 2021 (abstract 536).
7. Puma press release. Available at: www.pumabiotechnology.com/pr20210701.html.

Acknowledgements and Disclosures

- The authors would like to thank all investigators, patients and their families for participating in the CONTROL study. We also thank Stefan Dyla and Pratiksha Patel of Puma Biotechnology Inc for statistical programming.
- CONTROL was sponsored by Puma Biotechnology Inc.
- Puma Biotechnology Inc. funded medical writing/editing assistance for this poster, which was provided by Miller Medical Communications Ltd.
- The presenting author, Arlene Chan, has no financial conflicts of interest to disclose.

Presented at the San Antonio Breast Cancer Symposium, San Antonio, TX, USA, December 7–10, 2021