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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 early-stage HER2-positive (HER2+) breast cancer following adjuvant trastuzumab-based therapy and for HER2+ metastatic breast cancer (3rd line). In the ExteNET trial (no mandatory prophylaxis), the rate of grade 3 diarrhea was 40%, 34% of patients experienced ≥1 dose hold, and 17% of patients discontinued due to diarrhea. The phase 2 CONTROL trial showed that pre-emptive antidiarrheal prophylaxis or neratinib dose escalation (DE) reduced the rate, severity, and duration of neratinib-associated grade ≥3 diarrhea compared with ExteNET.

Methods: Patients ≥18 years with stage I–IIIc HER2+ breast cancer received neratinib (240 mg/day for 1 year) after trastuzumab-based adjuvant therapy. There are 2 dose-escalation cohorts: DE1 (neratinib 120 mg/day on days 1–7, 160 mg/day on days 8–14, then 240 mg/day to day 365) + loperamide as needed (PRN); and DE2 (neratinib 160 mg/day on days 1–14, 200 mg/day on days 15–28, then 240 mg/day to day 365) + loperamide PRN. Adverse events were graded per NCI-CTCAE v4.0. Primary endpoint: incidence of grade ≥3 diarrhea. Data cut-off: October 19, 2020.

Results: Complete data for DE1 and interim data for the ongoing DE2 are presented. All 60 patients in DE1 were off study and 23/62 (37.1%) patients remained on treatment in DE2. Median treatment duration: DE1 12.0 months; DE2 9.2 months. Incidence of grade ≥3 diarrhea: DE1 13.3%; DE2 25.8%. Median cumulative duration of grade 3 diarrhea over 12-month treatment period: DE1 2.5 days; DE2 2 days. Dose holds due to diarrhea: DE1 7 patients (11.7%); DE2 9 patients (14.5%). Discontinued neratinib because of diarrhea: DE1 2 (3.3%) patients; DE2 3 (4.8%) patients.

Conclusions: Adoption of neratinib DE reduced the incidence, severity, and duration of neratinib-associated diarrhea in CONTROL compared with ExteNET. DE1 was also associated with

low rates of diarrhea-related discontinuations and dose holds compared with all previously mandated prophylaxis strategies investigated in CONTROL and with ExteNET. 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.