Introduction

Neratinib, an irreversible pan HER tyrosine kinase inhibitor, is approved for both neoadjuvant/adjuvant treatment of early-stage breast cancer (HER2-overexpressed/amplified [HER2+] breast cancer) to following adjuvant trastuzumab therapy.1

The international, randomized, placebo-controlled phase III ExteNET trial2 tested the effectiveness of neratinib with or without anti-diarrheal prophylaxis for the treatment of HER2+ early-stage breast cancer who had completed trastuzumab-based (neo)adjuvant therapy (ClinicalTrials.gov: NCT02400476).

Methods

Study design and patients 

In ExteNET, an international, multicenter, randomized, double-blind, placebo-controlled phase III trial designed to compare neratinib versus placebo as an adjuvant therapy in patients (n=2407) aged 18 and over with early-stage HER2+ breast cancer who had completed trastuzumab-based (baseline therapy (ClinicalTrials.gov: NCT01377263).3

In CONTROL, a total of 240 patients were randomized to study treatment, i.e., fact-B (n=122), placebo (n=118).

In ExteNET: as of October 2018, a total of 968 patients have been enrolled (placebo, n=484; loperamide, n=484) and mean follow-up is 1 year of response to the FACT-B total score (0.95 confidence interval 0.42–0.48).

In CONTROL: baseline characteristics of the ExteNET and CONTROL study populations are shown in Table 1. Results

In ExteNET, all patients randomized to study treatment. Median duration of treatment was 11.6 months in the neratinib group and 12.0 months in the placebo group.

In CONTROL, all patients had completed study treatment. Median duration of treatment was 11.6 months in the neratinib group and 11.8 months in the placebo group.

In ExteNET, study treatment had been completed by 100% of patients in the loperamide and busidipine-loperamide cohorts, and 99% in the control and busidipine cohorts.

In CONTROL, all patients had completed study treatment: Median duration of treatment was 11.6 months in the neratinib group and 11.8 months in the placebo group.

In the CONTROL study:

• FACT-B total scores decreased from baseline in all cohorts; mean changes from baseline ranged from −0.5 to −4.1 points over the course of study treatment.

• In the cohorts that had completed follow-up (busidipine-loripamide), the largest decrease in FACT-B total score values were evident during months 3 and 6 followed by lower decrease.

• None of these changes reached clinically meaningful thresholds (−1.0 points) at any time point.

In the ExteNET study:

• FACT-B total scores decreased from baseline in all cohorts; mean changes from baseline ranged from −0.5 to −4.1 points over the course of study treatment.

• In the cohorts that had completed follow-up (busidipine-loripamide), the largest decrease in FACT-B total score values were evident during months 3 and 6 followed by lower decrease.

• None of these changes reached clinically meaningful thresholds (−1.0 points) at any time point.

In both ExteNET and CONTROL studies, mean changes from baseline in FACT-B physical well-being score (PWB) by visit are shown in Figure 1

In the CONTROL study:

• FACT-B total scores decreased from baseline in all cohorts through study treatment, with largest changes from baseline observed in the loperamide cohort.

• In the placebo and loperamide-coledipine cohorts, changes reached clinically meaningful thresholds at months 3 and 6, respectively, whereas changes did not reach these thresholds in any other cohort.

• Changes in FACT-B total scores at visit 1 (baseline) were –3.5 and −2.9 points for each FACT-B subscale. 9

In the ExteNET study:

• FACT-B total scores decreased from baseline in all cohorts; mean changes from baseline ranged from −0.5 to −4.1 points over the course of study treatment.

• In the cohorts that had completed follow-up (busidipine-loripamide), the largest decrease in FACT-B total score values were evident during months 3 and 6 followed by lower decrease.

• None of these changes reached clinically meaningful thresholds (−1.0 points) at any time point.

With the exception of the FACT-B PWB subscale, HRQoL changes in CONTROL and ExteNET at months 3 and 6 did not reach clinically meaningful thresholds in either or bothCONTROL or ExteNET.

In the CONTROL study:

• Changes in FACT-B PWB reached the CID threshold at most time points in the loperamide-coledipine-korporin cohorts and was greater than clinically meaningful thresholds (2‒3 points);9 changes were also evident in the placebo group.

• In the loperamide and coledipine-korporin cohorts, changes reached clinically meaningful thresholds at months 3 and 6, respectively, whereas mean changes were only observed early during treatment in the busidipine-loripamide cohort (month 3) and in the ExteNET neartinib group (month 1).

• Fewer patients in the busidipine-loripamide and coledipine-korporin cohorts discontinued treatment because of treatment-emergent adverse events compared with the loperamide-korporin and ExteNET neartinib groups, leading to a greater proportion of patients with HRQoL evaluations at later time points than in the other cohorts.

• This has helped to provide a more complete picture of HRQoL over time.

• Patient follow-up and enrichment in the coledipine-korporin and neartinib dose escalation cohorts in the CONTROL study are ongoing.

Conclusions

Extended therapy with neratinib with or without anti-diarrheal prophylaxis was associated with decreases in HRQoL during treatment.

While the FACT-B PWB total score at visit 1 (baseline) was −3.5 and −2.9 points for each FACT-B subscale, changes increased the CID threshold during months 3 and 6 only.

In the CONTROL study:

• FACT-B PWB values were observed in all CONTROL cohorts through study treatment, with largest changes from baseline observed in the loperamide cohort.

• In the loperamide and coledipine-korporin cohorts, changes reached clinically meaningful thresholds at months 3 and 6, respectively, whereas changes did not reach these thresholds in any other cohort.

• Changes in FACT-B total scores at visit 1 (baseline) were −3.5 and −2.9 points for each FACT-B subscale. 9

• In the CONTROL study:

• FACT-B total scores decreased from baseline in all cohorts; mean changes from baseline ranged from −0.5 to −4.1 points over the course of study treatment.

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