Abstract

Varlitinib, a reversible small molecule tyrosine kinase inhibitor of the EGFR family (HER1, HER2 and HER4), showed potent anti-tumour activity in trastuzumab-resistant mouse xenograft breast cancer models and metastatic breast cancer (MBC) patients with trastuzumab-resistant, chemotherapy-refractory disease in phase 1. This open label study compared the efficacy and safety of varlitinib plus capcitabine (VC) versus lapatinib plus capcitabine (LC) in HER2+ MBC patients who failed prior trastuzumab therapy. The primary objective of the study was to assess percentage change in tumour size at week 12. Objective response rate (ORR) via RECIST, safety and drug exposure were also assessed as secondary endpoints. Patients who received at least one dose of study treatment were included in primary analysis. However, a sensitivity analysis for primary objective and ORR was performed in patients who remained on study for more than 30 days. From Oct 2014 to Aug 2016, 26 patients were randomized to the VC arm (400 mg BID) and 26 to the LC arm (1250 mg QD) in 16 sites across 6 countries. Percentage of tumour size reduction was numerically higher in VC than in LC (32.5% vs. 18.29%, one-sided p=0.133) and was similar to LC arm (45.5%), p=0.001.

Sensitivity analysis showed numerically superior ORR and statistically significant higher reduction of tumour size in VC compared to LC (60% vs. 45.5%, p=0.008; mean, 88.9% vs. 71.4%, one-sided p=0.057). All patients had at least 1 AE. Severe AEs were observed in 15 patients (54.2%) in the VC arm and 11 (42.3%) in the LC arm. Most common AE was diarrhoea (66.7% in the VC arm and were diarrhoea and palmar-plantar erythrodysesthesia syndrome in both 50% in the LC arm). All patients in the VC arm who experienced diarrhoea were controlled with standard dose of loperamide. Median intended exposure and percentage of intended dose were lower in the VC arm (84% vs. 90%, p=0.038) and 74.4% of patients were receiving dose more than once. Diarrhoea, reduction and treatment discontinuation were the LC arm (95.0 days). Sensitivity analysis showed a much greater tumour size reduction and improved ORR for VC arm when the analysis was performed for more than 30 days. Reduced intended exposure and dose intensity for the VC arm suggests a dose reduction of varlitinib may be considered compared with capcitabine for the 2nd line treatment of HER2+ MBC.

Background

• Approximately 20% of breast cancers have HER2 gene amplification and treatment with trastuzumab (Herceptin®) significantly prolongs progression-free and overall survival in patients with HER2- amplification.

• Involvement of other members of the HER family receptors in the tumour results in trastuzumab resistance. Agents blocking HER-family receptors have potential to overcome this resistance.

• Varlitinib, an orally active, potent small molecule tyrosine kinase inhibitor showing strong activity against HER1, HER2 and HER4, is a reversible, ATP-competitive inhibitor with non-selective potency in vitro.

• Varlitinib has been shown to be active in preclinical trastuzumab- and lapatinib-resistant tumour models and has been studied in over 350 patients with advanced malignancy showing good bioavailability and generally good tolerability.

Study Design

Tumour size reduction and ORR Per Protocol group (PP)

- Per protocol group included all randomised patients according to the treatment actually received, and excluding any patients with major deviations.

Percentage change from baseline in tumour size at week 12

Best overall tumour response (%)

- One patient in the VC arm had a complete response in her BC tumour but later developed a new bone metastasis and therefore is classified as PR.

- Five patients in VC arm were categorised as non-evaluable due to incomplete first cycle of treatment.

Waterfall plot of percentage change in tumour size

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Drug Exposure in Safety Set

- Intended exposure: a measure of the number of days that the patients was "on-treatment".

- Percentage of intended dose (PD): the percentage of the actual dose delivered relative to the intended dose until disease progression

Summary

A numerical advantage in favour of the varlitinib group was observed in the primary endpoint, tumour size, although the corresponding one-sided p-value did not reach statistical significance at the pre-specified alpha level (p = 0.132).

Sensitivity analysis revealed a statistically significant improvement in the primary endpoint, tumour size, for varlitinib compared to lapatinib (p = 0.075). Similarly, a sensitivity analysis of ORR showed a higher ORR for varlitinib group compared to lapatinib group, indicating a superiority to lapatinib when the combination was administered for more than 30 days.

Evaluations of safety of varlitinib was no specific or unexpected TEAEs after treatment.

- Varlitinib was well tolerated with diarrhoea as the most frequent AE, however, unlike other pan-HER inhibitors such as neratinib, varlitinib was adequately controlled with standard dose of loperamide according to label (no prophylaxis).

- Varlitinib had lower dose intensity compared with lapatinib, which suggests that a lower dose of varlitinib could be considered for varlitinib in combination with capcitabine in 2nd line metastatic breast cancer.

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References


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