**Abstract**

**Background**

Lapatinib, a dual inhibitor of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2), is efficacious in treating HER2-positive metastatic breast cancer (mBC). However, drug resistance remains a major challenge. We aimed to determine whether combining lapatinib with varlitinib, a potent, reversible, selective EGFR inhibitor, could overcome HER2 resistance and improve survival in patients with HER2-positive mBC.

**Methods**

This was a 1:1 multicentre, open-label, randomized Phase 2 trial of varlitinib versus lapatinib in combination with capcitabine in patients with HER2+ metastatic breast cancer (mBC) who failed prior trastuzumab therapy. Eligible patients were randomized to receive varlitinib (60 mg twice daily; N = 120) or lapatinib (1000 mg once daily; N = 120) in combination with capcitabine (1250 mg/m² once daily). The primary endpoint was objective response rate (ORR) of the Treatment Emergent Adverse Events (SAF) group. Patients were followed up for one year after study therapy completion. Safety was assessed using the Common Terminology Criteria for Adverse Events version 4.03 and serious adverse events were assessed using the Medical Dictionary for Regulatory Activities version 15.0.

**Results**

The estimated sample size of this trial was 240 patients (120 in each arm). Of the 240 patients, 233 were evaluable for efficacy and safety analyses and the safety population included 240 patients. The overall ORR was 25.6% (95% CI 16.9–34.4%) in the varlitinib arm and 23.5% (95% CI 14.9–32.4%) in the lapatinib arm. The most common treatment-related adverse events in both arms were diarrhea (27.0% in varlitinib arm and 34.7% in lapatinib arm) and palmar-plantar erythrodysesthesia syndrome (PPE; 28.8% in varlitinib arm and 40.8% in lapatinib arm). In the varlitinib arm, the incidence of any grade 3 or 4 treatment-related adverse events was 13.5% (95% CI 6.3–21.5%) and 13.9% (95% CI 6.3–22.0%) for diarrhea and PPE, respectively. The safety analysis revealed no specific or unexpected deviations after both treatments. The most frequent adverse events were well-controlled with standard therapy. The median progression-free survival (PFS) was 12.5 months (95% CI 6.6–18.3) in the varlitinib arm and 10.0 months (95% CI 6.2–14.7) in the lapatinib arm. The primary endpoint analysis revealed no significant difference between the varlitinib and lapatinib arms.

**Conclusions**

This Phase 2 trial of varlitinib versus lapatinib in combination with capcitabine in patients with HER2+ metastatic breast cancer (mBC) who failed prior trastuzumab therapy.

---

**References**


---

**Contact information:** csilsc@nus.edu.sg, CH-B.R.Hank@alphanova.com

---

**TEAE with CTCAE grade 2 or higher**

- **Adverse Event**
  - **Varlitinib**
    - **Lapatinib**
    - **All Patients**

**Drug Exposure (SAF group)**

- **Intended exposure: a measure of the number of days that the patients were not exposed to the study drug.
  - **Percentage of intended dose (PD):** the percentage of the actual dose delivered relative to the intended dose until disease progression.

**Summary**

A Phase 2 trial of varlitinib versus lapatinib in combination with capcitabine in patients with HER2+ metastatic breast cancer (mBC) who failed prior trastuzumab therapy.

---

**Tumor size reduction and ORR Per Protocol Group (PP)**

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

**Percentage change from baseline in tumor size at week 12**

- **Complete responders**: patients who achieved a complete response and remained in complete response for at least 6 months.

**Best overall tumor response rate (%)**

- **Overall response rate**: the percentage of patients who achieved an objective response (complete or partial response).

**Treatment Emergent Adverse Events (SAF group)**

- **Safety set (SAE) included all patients in the study who received at least 1 dose of randomized therapy. Patients were included in the SAF based on the treatment actually received.

---

**Top three most frequent treatment emergent adverse events**

- **Varlitinib**:
  - **Lapatinib**:
  - **All Patients**

---

**Demographic and Disease Characteristics**

- **Variable**:
  - **Value**
  - **Statistics**

**Study Design**

- **Open-label Randomized Phase 2 Trial**

---

**Flow of Study Patient Disposition**

- **Patients assigned to treatment**:
  - **Cycle 1**: patients assigned to treatment.

---

**Key eligibility criteria:***

1. **Documented histological confirmation of breast cancer with HER2 overexpression or gene amplification (HC or HC in 2C with fluorescence in situ hybridization [FISH]) or positive HER2 IHC via HercepTest® prior to study entry.
2. **HER2 positive metastatic breast cancer that have progressed on prior first-line treatment with trastuzumab in metastatic setting or within 1 year of treatment with trastuzumab in adjuvant setting.**

---

**Multi-center open label, randomized Phase 2 trial of varlitinib versus lapatinib in combination with capcitabine in patients with HER2+ metastatic breast cancer (MBC) who failed prior trastuzumab therapy.**

---

**Background**

Lapatinib, a dual inhibitor of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2), is efficacious in treating HER2-positive metastatic breast cancer (mBC). However, drug resistance remains a major challenge. We aimed to determine whether combining lapatinib with varlitinib, a potent, reversible, selective EGFR inhibitor, could overcome HER2 resistance and improve survival in patients with HER2-positive mBC.

**Methods**

This was a 1:1 multicentre, open-label, randomized Phase 2 trial of varlitinib versus lapatinib in combination with capcitabine in patients with HER2+ metastatic breast cancer (MBC) who failed prior trastuzumab therapy. Eligible patients were randomized to receive varlitinib (60 mg twice daily; N = 120) or lapatinib (1000 mg once daily; N = 120) in combination with capcitabine (1250 mg/m² once daily). The primary endpoint was objective response rate (ORR) of the Treatment Emergent Adverse Events (SAF) group. Patients were followed up for one year after study therapy completion. Safety was assessed using the Common Terminology Criteria for Adverse Events version 4.03 and serious adverse events were assessed using the Medical Dictionary for Regulatory Activities version 15.0.

**Results**

The estimated sample size of this trial was 240 patients (120 in each arm). Of the 240 patients, 233 were evaluable for efficacy and safety analyses and the safety population included 240 patients. The overall ORR was 25.6% (95% CI 16.9–34.4%) in the varlitinib arm and 23.5% (95% CI 14.9–32.4%) in the lapatinib arm. The most common treatment-related adverse events in both arms were diarrhea (27.0% in varlitinib arm and 34.7% in lapatinib arm) and palmar-plantar erythrodysesthesia syndrome (PPE; 28.8% in varlitinib arm and 40.8% in lapatinib arm). In the varlitinib arm, the incidence of any grade 3 or 4 treatment-related adverse events was 13.5% (95% CI 6.3–21.5%) and 13.9% (95% CI 6.3–22.0%) for diarrhea and PPE, respectively. The safety analysis revealed no specific or unexpected deviations after both treatments. The most frequent adverse events were well-controlled with standard therapy. The median progression-free survival (PFS) was 12.5 months (95% CI 6.6–18.3) in the varlitinib arm and 10.0 months (95% CI 6.2–14.7) in the lapatinib arm. The primary endpoint analysis revealed no significant difference between the varlitinib and lapatinib arms.

**Conclusions**

This Phase 2 trial of varlitinib versus lapatinib in combination with capcitabine in patients with HER2+ metastatic breast cancer (MBC) who failed prior trastuzumab therapy.