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

Lee Soo-Chin[1], Chen Shin-Cheh[2], Dai Ming-Shen[3], Lee Guek Eng[4], Liu Chien-Liang[5], Chen Arlene[6], Chang Hsien-Kun[7], Tseng Ling-Ming[8], Chay Wen Yee[4], Chow Louis Wing Cheong[9], Peneyra Jhade Lotus[10],Rau Kun-Ming[11], Wang Hwei-Chung[12], Guancia Adonis A.[13], Head Michelle[14], Chiu Joanne Wing Yan[15], Robinson Bridget[16], McHale Mark[17], Barge Alan[17], Lindmark Bertil[17], McIntyre Nicola[17], Hsieh Chih-Yi[17]

[1]National University Cancer Institute, Singapore, Singapore, [2]Chang Gung Memorial Hospital, Taipei, Taiwan, [3]Tri-Service General Hospital, Taipei, Taiwan, [4]National Cancer Centre Singapore, Singapore, Singapore, [5]MacKay Memorial Hospital, Mackay Medical College, and Mackay Junior College of Medicine, Nursing, and Management, Taipei, Taiwan, [6]Breast Cancer Research Centre WA and Curtin University/ Western Australia & Curtin University, Nedlands, Australia, [7]Chang Gung Memorial Hospital, Taoyuan, Taiwan, [8]Taipei Veterans General Hospital, Taipei, Taiwan, [9]Unimed Medical Institute Limited, Hong Kong, Hong Kong PRC, [10]De La Salle Health Sciences Institute, Dasmarinas Cavite, Philippines, [11]Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan, [12]China Medical University Hospital, Taichung, Taiwan, [13]Dr. Pablo O. Torre Memorial Hospital, Bacolod City, Philippines, [14]Tauranga Hospital, Bay of Plenty, New Zealand, [15]Queen Mary Hospital, Hong Kong, Hong Kong PRC, [16]Christchurch Hospital, Christchurch, New Zealand, [17]ASLAN pharmaceuticals, Singapore, Singapore

Abstract

Varlitinib, a reversible small molecule tyrosine kinase inhibitor of the ErbB family (HER1 (EGFR), 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 capecitabine (VC) versus lapatinib plus capecitabine (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 Dec 2014 to Aug 2016, 24 patients were randomized to the VC arm (400mg BID) and 26 to the LC arm (1250mg QD) in 16 sites across 6 countries.

Percentage of tumour size reduction was numerically higher in VC than LC (-32.52% vs. -18.29%, one-sided p=0.132). ORR in the VC arm (40.9%) was similar to LC arm (45.5%), p=1.000.

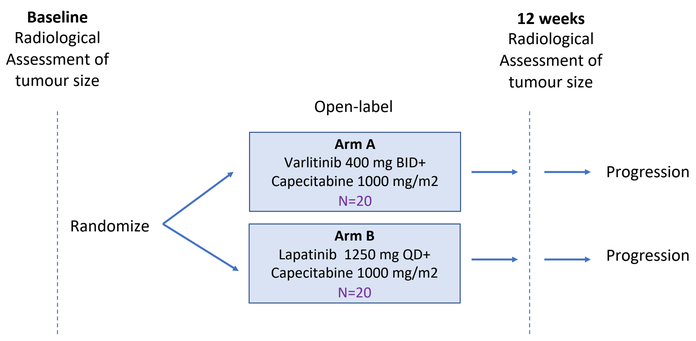
Sensitivity analysis showed numerically superior ORR and statistically significant higher reduction of tumour size in VC compared to LC (60% vs. 45.5%, p=0.508; mean, -36.4% vs.-17.8%, one-sided p=0.075). All patients had at least 1 AE. Severe AE(s) were observed in 13 patients (54.2%) in the VC arm and 11 (42.3%) in the LC arm.

The most common AE was diarrhea (66.7%) in the VC arm and were diarrhea and palmar-plantar erythrodysaesthesia syndrome (both 50%) in the LC arm. All patients in the VC arm who experienced diarrhea were controlled with standard dose of loperamide. Median intended exposure and percentage of intended dose were lower in the VC arm (115.5 days, 74.6%) indicating more frequent dose interruption, dose reduction and treatment discontinuation than the LC arm (135.0 days, 99.05%). Sensitivity analysis showed a much greater tumour size reduction and improved ORR for VC arm when the combination was administrated for more than 30 days. Reduced intended exposure and dose intensity for the VC arm suggests a dose reduction of varlitinib may be considered when combined with capecitabine for the 2nd line treatment of HER2$^+$ MBC.

Background

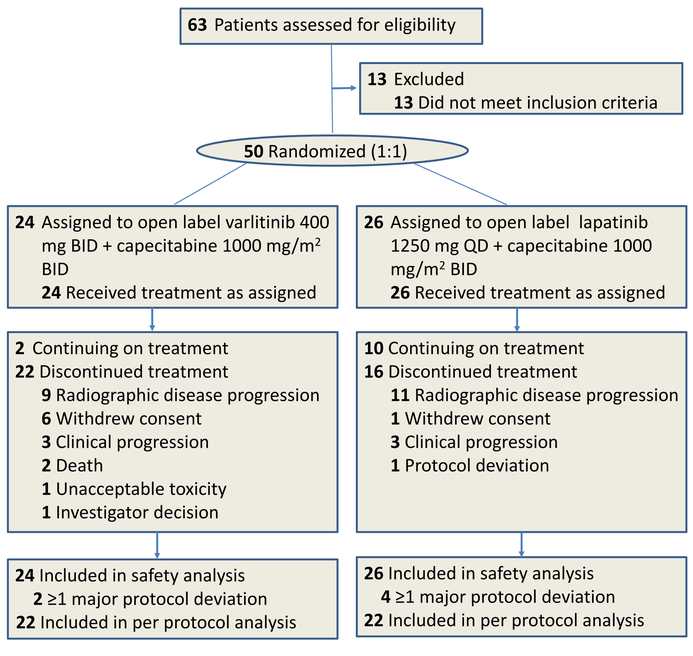
- Approximately 20% of breast cancers have HER2 gene amplification and treatment with trastuzumab (Herceptin®) significantly prolongs progression-free and overall survival in patients with HER-2 amplification.[1,2]
- Involvement of other members of the HER family receptors in the tumour results in trastuzumab resistance. Agents blocking all 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 nanomolar 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



- BID= twice daily; N = the number of evaluable patients at Week 12 in Phase 2A study; QD=once daily
- This study was conducted at 16 study centers in 6 countries (Australia, Hong Kong, New Zealand, Philippines, Singapore, and Taiwan).

Flow of Study Patient Disposition



Key eligibility criteria:

- Documented histological confirmation of breast cancer with HER2 overexpression or gene amplification (IHC 3+ or IHC 2+ with fluorescent/ chromogenic/silver *in situ* hybridization +) prior to study entry
- HER2 positive metastatic breast cancer that have **progressed on prior first-line treatment with trastuzumab in metastatic setting or who have relapsed within 1 year of treatment with trastuzumab in adjuvant setting**

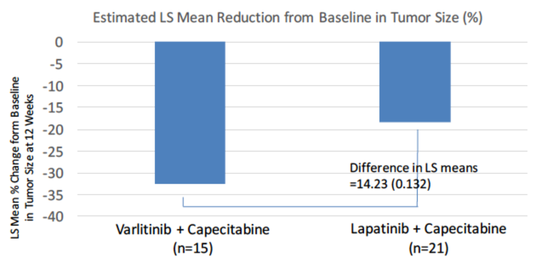
Demographic and Disease Characteristics

Characteristic		Varlitinib + Capecitabine (n = 24)	Lapatinib + Capecitabine (n = 26)	All Patients (N = 50)
Age, median (range) y		53.5 (29-83)	56.5 (33-79)	55.0 (29-83)
Female sex, No. (%)		24 (100)	26 (100)	50 (100)
Ethnic origin, No. (%)	Asian-Chinese	18 (75.0)	18 (69.2)	36 (72.0)
	Asian-other	3 (12.5)	4 (15.4)	7 (14.0)
	White	2 (8.3)	2 (7.7)	4 (8.0)
	Other	1 (4.2)	2 (7.7)	3 (6.0)
ECOG performance status, No. (%)	0	19 (79.2)	20 (76.9)	39 (78.0)
	1	3 (12.5)	6 (23.1)	9 (18.0)
	2	2 (8.3)	0	2 (4.0)
Breast cancer status, No. (%)	Recurrence	3 (12.5)	1 (4.8)	4 (8.0)
	Metastasis	21 (87.5)	25 (96.2)	46 (92.0)
HER2 IHC, No. (%)	1+	1 (4.2)	0	1 (2.0)
	2+	6 (25.0)	9 (34.6)	15 (30.0)
	3+	14 (58.3)	17 (65.4)	31 (62.0)
	Missing	3 (12.5)	0	3 (6.0)
HER2 FISH, No. (%)	Positive	10 (41.7)	12 (46.2)	22 (44.0)
	Not performed	14 (58.3)	14 (53.8)	28 (56.0)
Prior lines of palliative therapy, No. (%)	0	5 (20.8)	5 (19.2)	10 (20.0)
	1	14 (58.3)	13 (50.0)	27 (54.0)
	2	5 (20.8)	5 (19.2)	10 (20.0)
	3	0	1 (3.8)	1 (2.0)
	4	0	2 (7.7)	2 (4.0)
Trastuzumab in adjuvant setting, No. (%)	Yes	3 (12.5)	3 (11.5)	6 (12.0)
	No	21 (87.5)	23 (88.5)	44 (88.0)

Tumour size reduction and ORR Per Protocol group (PP)

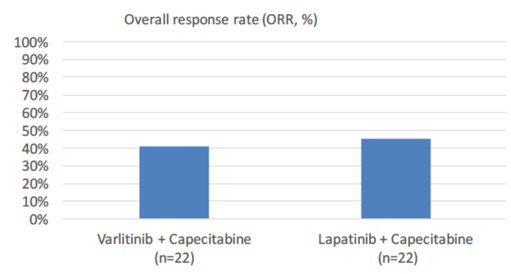
- Per-protocol group included all randomized patients according to the treatment actually received, and excluding any patients with major deviations.

Percentage change from baseline in tumour size at week 12



- LS mean was estimated from an ANCOVA, adjusted for baseline tumour size and the time from baseline scan to randomisation.

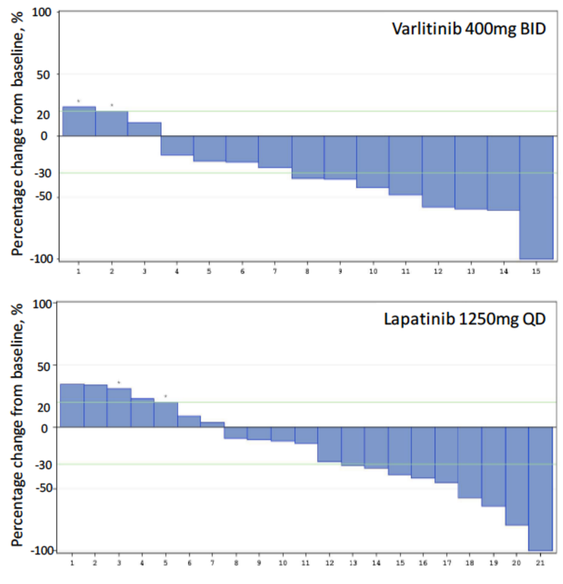
Best overall tumour response rate (%)



	CR	PR	Stable disease	Progressive disease
Varlitinib + Capecitabine (n=22)	0.0%	40.9%	27.3%	9.1%
Lapatinib + Capecitabine (n=22)	9.1%	36.4%	50.0%	4.5%

- One patient in the VC arm had a complete response in her BC tumour but later developed a new bone metastasis and therefore is classed as PR.
- Five patients in VC arm were categorized as non-evaluable due to incomplete first cycle of treatment.

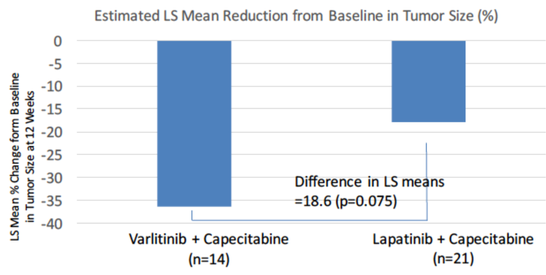
Waterfall plot of percentage change in tumour size



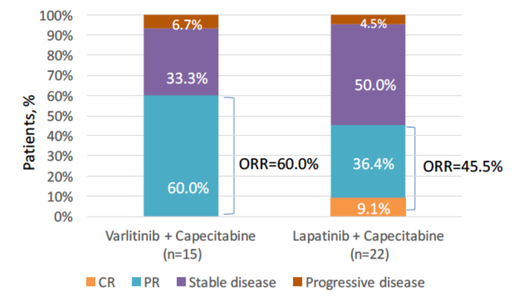
Tumour size reduction and ORR (Sensitivity Analysis)

- Sensitivity analysis was performed in patients who remained on study beyond the first 30 days. As such, the sensitivity analyses excluded 1 patient from the tumour size analysis, and 7 patients from the analysis of ORR. 4/7 patients withdrew from the VC arm for no stated reason. As this study was open label and lapatinib was provided whilst on study it was assumed that these patients withdrew because they were not randomized to the LC arm of the study.

Percentage change from baseline in tumour size at week 12



Best overall tumour response (%)



Treatment Emergent Adverse Events (TEAE) in Safety Set

- Safety set included all patients in the study who received at least 1 dose of randomized therapy. Patients were included in the safety set based on the treatment initially received.

Top three most frequent treatment emergent adverse events

Varlitinib + Capecitabine (n = 24)		Lapatinib + Capecitabine (n = 26)	
Diarrhea	66.7%	Diarrhea	50.0%
Nausea	54.2%	PPE syndrome	50.0%
Vomiting	41.7%	Rash	42.3%

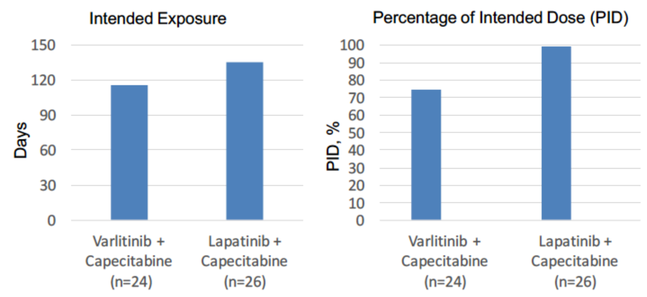
TEAE with CTCAE grade ≥ 3 reported in ≥ 10% of patients

Adverse Event	Varlitinib + Capecitabine (n = 24)	Lapatinib + Capecitabine (n = 26)	All Patients (N = 50)
Diarrhea	3 (12.5)	1 (3.8)	4 (8.0)
PPE syndrome	3 (12.5)	6 (23.1)	9 (18.0)
AST increased	3 (12.5)	0	3 (6.0)
Hypokalemia	3 (12.5)	0	3 (6.0)
Anemia	1 (4.2)	0	1 (2.0)
Hyponatremia	3 (12.5)	0	3 (6.0)

- Severe AE(s)= AE(s) with CTCAE grade ≥ 3

Drug Exposure in Safety Set

- Intended exposure: a measure of the number of days that the patients was "on-treatment"
- Percentage of intended dose (PID): 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 one-sided 10% 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 administrated for more than 30 days.
- Evaluation of safety of varlitinib revealed no specific or unexpected TEAEs after treatment.
- Varlitinib was well tolerated with diarrhea as the most frequent AE, however, unlike other pan-HER inhibitors such as neratinib, varlitinib was adequately controlled with standard dose of loperamine according to label (no prophylaxis).
- Varlitinib group had lower dose intensity compared with lapatinib, which suggests that a lower dose of varlitinib could be considered for varlitinib in combination with capecitabine in 2nd line metastatic breast cancer.

Acknowledgement

This study was sponsored by ASLAN Pharmaceuticals.

References

1. Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. NEJM 2012;366 (2):109-19.
2. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. NEJM 2001;344 (11):783-92.

Contact information:
- csilsc@nus.edu.sg;
- Chih-Yi.Hsieh@aslanpharma.com