# Dose finding study of Varlitinib ± Trastuzumab with Carboplatin/Paclitaxel in advanced solid tumors

Abstract #2588

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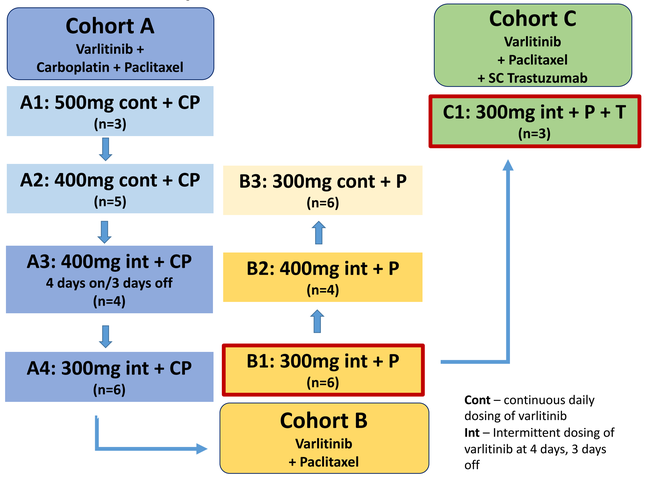
## BACKGROUND

- The HER family of tyrosine kinases are implicated in several malignancies.
- Varlitinib is a potent small molecule tyrosine kinase inhibitor of HER1/HER2/HER4.
- The recommended dose of Varlitinib is 500mg twice daily.

| | IC50 (nM) | | |
|---|---|---|---|
| Compound | HER1 | HER2 | HER4 |
| Varlitinib | 7 | 2 | 4 |
| Lapatinib | 10.8 | 9.2 | 367 |
| Neratinib | 92 | 59 | |
| Gefitinib | 27 | >3700 | |

## METHODOLOGY

- Aim: To determine the maximum tolerated dose and pharmacokinetics of Varlitinib (V) combination therapy. (NCT02396108)
- A 3+3 design was used in this Phase Ib trial.
- Eligibility: advanced cancer where treatment with weekly paclitaxel/carboplatin was indicated.
- There were 3 treatment cohorts, each in combination with V:
  - A: Carboplatin AUC2 (C) + Paclitaxel 80mg/m$^2$ (P) weekly
  - B: P 80mg/m$^2$ weekly
  - C: P + Subcutaneous Trastuzumab (T) 600mg 3 weekly
- Treatment was administered until disease progression or intolerable toxicity.




## PATIENT CHARACTERISTICS

| Demographics | N=37 |
|---|---|
| Gender | Male 6 (16.2%); Female 31 (83.7%) |
| Median age (yrs) | 56.8 (range 31.8 – 73.9) |
| Median lines of previous palliative systemic therapies | 3 (range 0-14) |
| Primary tumor site | |
| Breast | 28 (75.6%); HER2+ 20/28 (54% of entire cohort) |
| Cervix | 2 (5.6%) |
| Lung | 2 (5.6%) |
| Others | 5 (13.5%) |

## DOSE LIMITING TOXICITIES (DLT)

| Cohort | Number with DLTs | DLT in cycle 1 |
|---|---|---|
| A1 | 3/3 | G3 hyperbilirubinemia=1<br>Received <75% intended Varlitinib dose due to toxicities=2 |
| A2 | 3/5 | Febrile neutropenia = 3 |
| A3 | 2/4 | G3 hypophosphatemia= 1<br>G3 hyponatremia, G3 hypokalemia, intolerable G2 fatigue=1 |
| A4 | 2/6 | Febrile neutropenia = 1<br>G3 hypophosphatemia, G3 vomiting=1 |
| B1* | 0/6 | Nil |
| B2 | 2/4 | Febrile neutropenia =1<br>G3 transaminitis=1 |
| B3 | 4/6 | G3 diarrhea=1<br>G4 neutropenia >7days=1<br>Received <75% intended Varlitinib dose due to toxicities=2 |
| C1* | 0/3 | Nil |

*Only cohorts B1 and C1 were tolerable with no DLTs

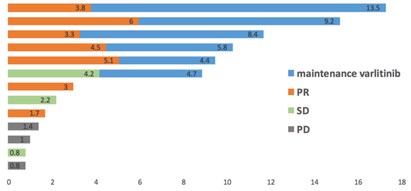
## EFFICACY

26/37 patients were evaluable for response

- 7 discontinued before cycle 2 due to toxicities, 1 died from suicide prior to cycle 2, 3 had yet to be evaluated for response at time of analysis.
- CR 1 (3.8%), PR 9 (34.6%), SD 11 (42.3%), PD 5 (19.2%),
- Median duration of response was 3 months (range 0.8 – 17.3m)

13/20 HER2+ metastatic breast cancer patients were evaluable for response

- 3 discontinued due to toxicities (in cohorts A4 & B2), 1 suicide prior to cycle 2, 3 yet to be evaluated,
- 6/20 were maintained on single agent Varlitinib for median 8 cycles (range 5-13) after chemotherapy completed.




## ADVERSE EVENTS

| Adverse Event | Any Grade | Grade 3-5 |
|---|---|---|
| Diarrhea | 25 (69.4%) | 2 (5.6%) |
| Fatigue | 24 (66.7%) | 4 (11.1%) |
| Neutropenia | 17 (47.2%) | 15 (41.7%) |
| Loss of appetite | 16 (44.4%) | 0 |
| Hyperbilirubinemia | 14 (38.9%) | 1 (2.8%) |
| Vomiting | 13 (36.1%) | 0 |
| Hypokalemia | 12 (33.3%) | 3 (8.3%) |
| Hyponatremia | 10 (27.8%) | 6 (16.7%) |
| Hypophosphatemia | 10 (27.8%) | 5 (13.9%) |
| Mucositis | 6 (16.7%) | 2 (5.6%) |
| Constipation | 5 (13.9%) | 0 |
| Anemia | 5 (13.9%) | 2 (5.6%) |
| Elevated AST | 4 (11.1%) | 1 (2.8%) |
| Febrile neutropenia | 4 (11.1%) | 4 (11.1%) |
| Thrombocytopenia | 4 (11.1%) | 1 (2.8%) |
| Pneumonitis | 2 (5.6%) | 2 (5.6%) |
| Perforated bowel | 1 (2.8%) | 1 (2.8%) |

## PHARMACOKINETICS

- Cmax, AUC and Clearance rates of paclitaxel were measured for patients in cohort A3, A4, B1.

| | | C1D1 | | | | C1D8 | | | |
|---|---|---|---|---|---|---|---|---|---|
| Cohort | | Tmax (h) | Cmax (ng/mL) | AUC (ng/mL*h) | Clearance (L/h) | Tmax (h) | Cmax (ng/mL) | AUC (ng/mL*h) | Clearance (L/h) |
| A3 (V 400mg int + CP) | Mean | 0.8 | 3357.5 | 5410.6 | 25 | 0.9 | 4065 | 7336.3 | 19.5 |
| | SD | 0.3 | 957.6 | 1141.3 | 5.86 | 0.3 | 1218.4 | 3711.0 | 10.2 |
| A4 (V 300mg int + CP) | Mean | 1.3 | 2470.8 | 5772.7 | 26.7 | 1 | 2730.4 | 6301.1 | 22.5 |
| | SD | 0.6 | 1103.7 | 1141.3 | 5.86 | 0.3 | 1218.4 | 3177.0 | 10.2 |
| B1 (V 300mg int + P) | Mean | 1.3 | 3137.5 | 5314.6 | 24.4 | 0.8 | 2942.5 | 5087.5 | 23.6 |
| | SD | 0.3 | 1406.1 | 1661.5 | 9.2 | 0.3 | 1150.8 | 1686.1 | 7.8 |

- Pharmacokinetics of paclitaxel were not significantly different between the V 400mg int and V 300mg int groups.
- Suggests that V did not interact significantly with the pharmacokinetics of paclitaxel.

## CONCLUSIONS

- The recommended dose of Varlitinib in combination with paclitaxel is 300mg BD administered intermittently.
- SC trastuzumab can be added safely.
- Promising efficacy of the combination was observed in HER2+ MBC with 30% patients experiencing prolonged disease control.
- Varlitinib with paclitaxel and SC trastuzumab is now being studied in HER2+ early breast cancers as a neoadjuvant regimen in a phase II trial.

## ACKNOWLEDGEMENTS

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