cancers

MDPI

Article

Phase Ib Trial of Copanlisib, A Phosphoinositide-3 Kinase (PI3K) Inhibitor, with Trastuzumab in Advanced Pre-Treated HER2-Positive Breast Cancer "PantHER"

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Supplementary Materials:

Table S1. Inclusion and Exclusion criteria

Inclusion	Exclusion
• Adult women ≥ 18 years of age • Histologically confirmed HER2-positive breast cancer • Recurrent incurable or metastatic breast cancer • At least one measurable lesion according to RECIST criteria (Version 1.1). Patients with bone only disease are not eligible. • Patient has received at least one trastuzumab-based or T-DM1-based treatment regimen in the setting of metastatic disease or incurable locoregional recurrence. A trastuzumab based or T-DM1-based treatment regimen is considered as any treatment regimen that includes trastuzumab or T-DM1. • Disease progression during or following at least 1 prior trastuzumab-based or trastuzumab emtansine (T-DM1) based treatment regimen in the setting of metastatic disease or incurable locoregional recurrence. • ECOG performance status ≤ 2. • Availability of fresh tissue and/or archival tumour tissue at screening. • Adequate organ function including fasting glucose ≤120 mg/dL (≤ 6.0 mmol/L) if not diabetic or < 160 mg/dL (≤ 8.9 mmol/L) if diabetic • Left ventricular ejection fraction (LVEF), at or above the Institutions lower limit of normal, as determined by ECHO or MUGA • Patients must have recovered from clinically significant side effects associated with prior radiotherapy and chemotherapy with the exception of fatigue or neuropathy.	• Known breast cancer involvement of the brain, unless adequately controlled based on the clinical judgement of the treating physician. • Congestive heart failure > New York Heart Association (NYHA) class II. • Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months). Myocardial infarction less than 6 months before registration. • Uncontrolled arterial hypertension despite optimal medical management (per investigator's opinion). • Uncontrolled Type I or II diabetes mellitus. Defined as HbA1c > 8.5% as determined during screening laboratory assessments. • Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within 3 months before registration. • Non-healing wound, ulcer, or bone fracture. • Active, clinically serious infections > CTCAE Grade 2 (CTCAE v4.0). • known HIV, Hepatitis B, C or CMV positivity or uncontrolled intercurrent illnesses. • Patients with CMV PCR positive. • Patients with seizure disorder requiring medication • Patients with evidence or history of bleeding diathesis. Any haemorrhage or bleeding event ≥ CTCAE Grade 3 within 4 weeks prior to the start of study treatment.

	• Proteinuria of Grade 3 or higher (CTCAE v4.0). Patient will be excluded if > 2+ on urinalysis (unless 24 hr collection shows 24 h urinary protein < 3.5g/24hrs). • History or concurrent condition of interstitial lung disease of any severity, and/or severely impaired lung function (as judged by the investigator). • Concurrent diagnosis of pheochromocytoma. • Pregnant or breast-feeding patients. Women of childbearing potential must have a serum or urine pregnancy test performed a maximum of 7 days before start of treatment, and a negative result must be documented before start of treatment. • Unresolved toxicity higher than CTCAE Grade 1 attributed to any prior therapy/procedure, excluding alopecia, peripheral neuropathy, and bone marrow parameters. • Known hypersensitivity to any of the test drugs, test drug classes, or excipients in the formulation • Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results. • Any illness or medical conditions that are unstable or could jeopardize the safety of patients and their compliance in the study. • Patients permanently withdrawn from study participation will not be allowed to re-enter the study. • Excluded therapies included investigational drugs, immunosuppressive therapy, CYP3A4 inhibitors or inducers, anti- arrhythmic therapy apart from beta blockers and digoxin.

Table S2. Serious Adverse events in patients receiving the combination of copanlisib and trastuzumab.

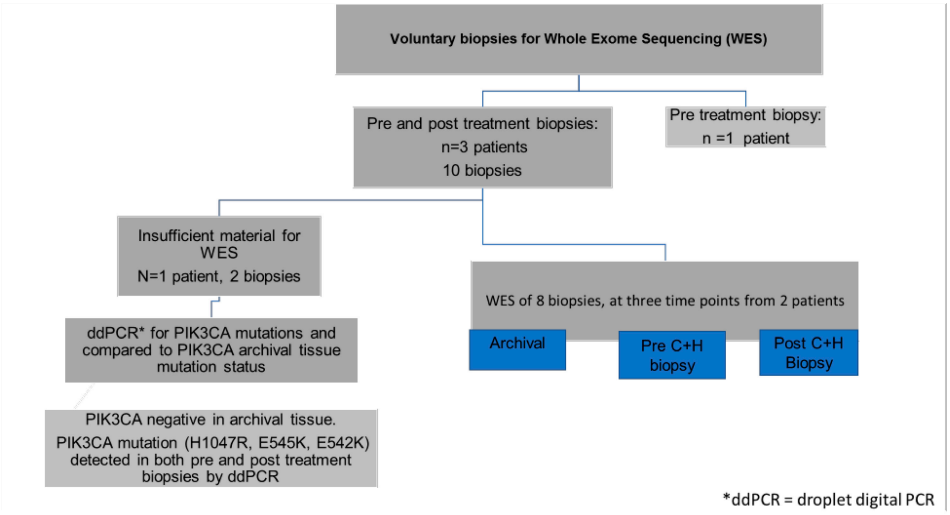
Serious Adverse Events N=11	**Dose Level 1 Copanlisib 45mg**	**Dose Level 2 Copanlisib 60mg**
Possibly Related	Abdominal Pain (n = 1) Lung Infection (n = 1)	-
Unrelated	Lung infection (n = 1) Urinary tract infection (n = 1) Infection (n = 1) Pleural effusion (n = 1) Seizure (n = 2)	Dyspnea (n = 1) Lymphangitis carcinomatosis (n = 1) Bile duct obstruction from tumour mass (n = 1),

Table S3. Plasma PIK3CA mutation status. The percentage of serial plasma samples with detectable PIK3CA mutation and the percentage of these with ≥ 500 copies/mL of mutant alleles for these

hotspot mutations H1047R, E542K and E545K are shown, as analysed by droplet digital PCR (ddPCR). Plasma samples were collected at baseline and every 2 weeks while on study for all patients.

Number of plasma ctDNA samples	**Tumour tissue PIK3CA**	PIK3CA H1047R ctDNA Plasma		PIK3CA E542K ctDNA Plasma		PIK3CA E545K ctDNA Plasma		Time on treatment (weeks)
		Mutant allele detectable	>500 copies/ml of mutant allele	Mutant allele detectable	>500 copies/ml of mutant allele	Mutant allele detectable	>500 copies/ml of mutant allele	
7	**E542K**	100%	14%	100%	57%	100%	43%	17
16	E545K	100%	19%	100%	0%	100%	100%	35
8	H1047R	100%	100%	87%	0%	100%	100%	16
7	H1047R	100%	100%	86%	0%	86%	43%	17
4	H1047R	100%	100%	75%	0%	100%	0%	7
3	H1047R	100%	100%	100%	0%	100%	33%	7
9	Wildtype	78%	11%	55%	0%	100%	67%	20
5	Wildtype	100%	80%	100%	0%	100%	40%	7
8	Wildtype	75%	63%	87%	0%	100%	63%	21
13	Wildtype	100%	54%	100%	0%	100%	31%	24
6	Wildtype	100%	0%	100%	0%	100%	67%	16
9	Wildtype	100%	22%	100%	0%	100%	44%	15

a.



b. (i)

Number of gene mutations present (%)	Patient X	Patient Y
Total gene mutations	324	772
At all timepoints	53 (16.4%)	71 (9.2%)
At diagnosis only (A)	82 (25.3%)	355 (46%)
Pre-copanlisib only (B)	105 (32.4%)	156 (20.2%)
Post-copanlisib only (c)	17 (5.3%)	98 (12.7%)
In A and B, but not C	59 (18.2%)	13 (1.68%)
In A and C, but not B	1 (0.3%)	4 (0.5%)
In B and C, but not A	7 (2.2%)	75 (9.7%)

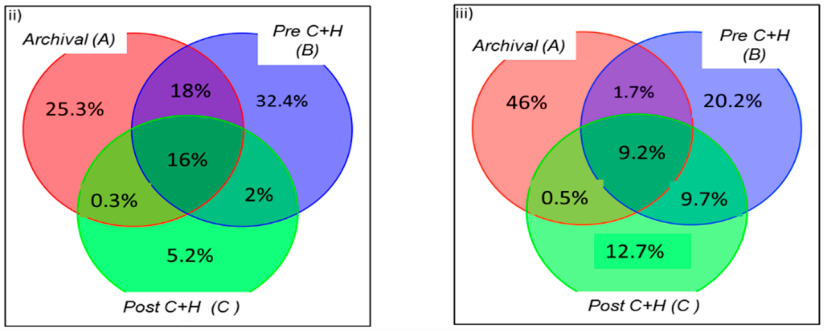


Figure S1. (**a**): Schematic diagram of tissue samples collected, and analysis performed. (**b**). (i) Comparison of somatic mutations present in three biopsies given by two participants at three different timepoints: (A) at diagnosis (B) pre-co-panlisib and trastuzumab and (C) at the time of disease progression on copanlisib and trastuzumab (C + H). (ii) Venn diagram of percentage of shared somatic mutation over 3 time points in Patient X. (iii) Venn diagram of percentage of shared somatic mutation over 3 time points in Patient Y..