Sponsor

Novartis

Generic Drug Name

Buparlisib

Therapeutic Area of Trial

Advanced solid malignancies

Approved Indication

Investigational

Protocol Number

CBKM120X2101

Title

A Phase IA, multicenter, open-label dose escalation study of BKM120 (buparlisib), administered orally, in adult patients with advanced solid malignancies.

Phase of Development

Phase 1A

Study Start/End Dates

24-Nov-2008 (first patient first visit) to 22-Sep-2011 (Interim analysis CSR cut-off date CSR cut-off date)

Study Design/Methodology

This was a multicenter, open-label dose-escalation study including a maximum tolerated dose (MTD) dose-expansion arm in patients with advanced solid tumors. Oral buparlisib was administered once daily on a continuous schedule. Patients were treated until disease progression, unacceptable toxicity, investigator's decision to discontinue treatment, or patient refusal.

All evaluable patients included in each dose cohort were to be assessed for decision making on dose escalation.

A cohort could be expanded at any dose level below MTD for further elaboration of safety, pharmacokinetic and/or pharmacodynamic parameters as required.

An adaptive Bayesian logistic regression model (BLRM) for dose escalation with overdose control was employed to guide the dose escalation part to determine the MTD. Before a drug dosage could be declared to be the MTD, at least 21 evaluable patients were required, with at least six evaluable patients treated at the MTD.

Once the MTD was declared, the MTD cohort was expanded to enroll at least 22 and up to 65 patients (including the patients treated at the MTD from the dose-escalation cohort) with advanced solid tumors. There was a particular interest to enroll patients with breast, colorectal, ovarian or endometrial cancer, including at least eight patients with paired fresh

biopsies (pre- and post-treatment). In this MTD expansion cohort, patients were pre-screened for molecular alterations of *PIK3CA* (mutation and/or amplification) and/or *PTEN* (mutation and/or null/low protein expression).

In order to characterize the apparent oral terminal elimination half-life (T1/2) of buparlisib, a terminal elimination half-life assessment cohort was introduced within the MTD expansion arm.

Centres

Five centers in four countries: Spain (1), Unites States (1), Canada (1), and Netherlands (2).

Publication

Bendell JC, Rodon J, Burris HA, de Jonge M, Verweij J, Birle D, Demanse D, De Buck SS, Ru QC, Peters M, Goldbrunner M, Baselga J., Phase 1 dose-escalation study of BKM120, and oral pan-Class I PI3K inhibitor, in patients with advanced solid tumors, J Clin Oncol. 2012 Jan 20;30(3):282-90.

Outcome measures

Primary endpoint:

Incidence rate of DLT in the first cycle of each dose level was the primary variable for the primary objective to establish the MTD level.

Secondary variables:

- Efficacy endpoints
  - Preliminary efficacy of buparlisib in patients with advanced solid tumors using overall response (CR or PR), stable disease (SD) and progressive disease (PD) categories.
  - Tumor marker levels such as prostate-specific antigen (PSA), carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9, soluble mesothelin peptides, as relevant for the respective cancer type, if any, as potential surrogate indicators of efficacy
- Safety endpoint
  - The assessment of safety was based mainly on the type and frequency of adverse events (AEs) and on the number of laboratory values that fell outside of pre-determined ranges.
- Pharmacokinetic (PK) endpoint
  - Plasma concentration of buparlisib and basic PK parameters (e.g. Cmax, Tmax, AUC0-last) and the apparent oral terminal elimination half-life (T1/2) of buparlisib
- Biomarker endpoints
  - Percentage of patients by dose at which >50% and >80% inhibition of phospho-Akt (p-Akt) and phospho-S6 (p-S6) (ribosomal protein) (as indicated by change in the level of phosphorylated protein) was observed in tumor and skin, post-treatment versus pre-treatment
  - Percentage of patients by dose at which a change of >2x in coefficient of variation was observed for circulating markers (angiogenic markers and the cellular death markers M30/M65)

- Percentage of patients by dose at which the proportion of Ki-67 positive cells in tumor tissue was ≤ 2% and ≤ 5% post-treatment
- Percentage of patients by dose at which the proportion of apoptotic cells (e.g., by evaluation of PARP cleavage) in tumor tissue increased ≥ 30% post-treatment versus pre-treatment
- Percentage of patients in which an altered molecular status was detected for markers related to PI3K signaling (e.g. mutations, deletion, loss/enhanced protein expression or activation)
- Percentage of patients by dose in whom significant changes were determined for glucose, insulin & C-peptide levels in blood, post-treatment versus pre-treatment

Test Product (s), Dose(s), and Mode(s) of Administration

Buparlisib hard gelatin capsules were supplied to the investigators at dose strengths of 0.5 mg, 2.5 mg, 10 mg, and 50 mg. The starting dose was set at 12.5 mg/person orally once daily at approximately the same time each day (preferably in the morning) as a continuous administration. Buparlisib was to be ingested two hours following food intake and was to be taken with a glass of water and consumed over as short a time as possible.

Statistical Methods

MTD and Dose-limiting toxicity (DLT): The primary objective of the dose escalation part of the study was to determine the MTD of single agent buparlisib. The corresponding primary analysis method was an adaptive Bayesian logistic regression model guided by the escalation with overdose control (EWOC) principle. All information available regarding the dose-toxicity curve of buparlisib was summarized in a prior distribution. For this study, the information included pre-clinical data on buparlisib. This prior distribution was then updated after evaluation of each cohort of patients with the DLT data from the current trial. Once updated, a dose recommendation was based on posterior summaries for each dose, including the mean, median, standard deviation, 95%-credibility interval, and the interval probabilities for under-dosing, targeted, excessive, and unacceptable toxicity for intervals:

- [0,16%) under-dosing
- [16%,33%) targeted toxicity
- [33%,60%) excessive toxicity
- [60, 100%] unacceptable toxicity

Following the principle of dose escalation with overdose control after each cohort of patients, the recommended dose was the one with the highest posterior probability of DLT in the target interval [16%,33%) among the doses fulfilling the overdose criterion that there was less than 25% chance of either excessive or unacceptable toxicity. The recommendations of the BLRM were shared with the clinical trial team and investigators at each planned Dose Escalation Teleconference.

The DLT assessment period comprised the first cycle of treatment (28 days).

Efficacy: The efficacy analysis was performed using the Full Analysis Set. The efficacy endpoints were derived from the overall response at each assessment based on modified RECIST 1.0 criteria. The analysis was primarily based on the outcome of the investigator review.

Progression-free survival and Overall survival were displayed using Kaplan-Meier curves according to the categories: patients treated at doses greater than or at the MTD, and patients treated at doses below the MTD.

The Disease control rate and Objective response rate were summarized in terms of percentage rates.

The sum of the longest diameters (SLD) across lesions was listed, summarized and graphically presented by treatment group along with the relevant variable (e.g., disease indication, biomarkers).

FDG-PET response was assessed using SUVmax changes ≥ 25% in accordance with the EORTC guidelines.

Data on tumor markers relevant for the respective cancer type (e.g., CA19-9, CEA and prostate-specific antigen (PSA), etc.) were listed.

Safety: The assessment of safety was based mainly on the type and frequency of AEs and on the number of laboratory values that fell outside of pre-determined normal ranges. Other safety data (e.g., ECGs, vital signs, and special tests) were also presented. Except for summaries of DLTs, for which the dose determining set was used, all safety analyses were based on the safety set.

Pharmacokinetics: The following PK endpoints were analyzed: plasma concentration of buparlisib and basic PK parameters (e.g. Cmax, Tmax, AUC0-last) and the apparent oral terminal elimination half-life (T1/2) of buparlisib.

Biomarkers: For selected biomarkers, raw values as well as change from Baseline and/or pre-dose evaluations were summarized by means of descriptive statistics at each post baseline assessment. Summaries of percentage of change from Baseline by treatment at the predefined threshold were generated. In some cases, analytical validation of the chosen assay could not be confirmed. In these cases data were listed only and not used for the descriptive statistical analysis.

Study Population:

Inclusion Criteria

- **Dose escalation or terminal elimination half-life assessment cohort (TEC):**
  Patients with histologically-confirmed, advanced unresectable solid tumors who had progressed on (or not been able to tolerate) standard therapy or for whom no standard anticancer therapy existed.

  MTD expansion arm (excluding the terminal elimination half-life assessment cohort):
  Patients with histologically-confirmed, advanced unresectable breast, colorectal, ovarian or endometrial cancer, who had progressed on (or not been able to tolerate) standard therapy or for whom no standard anticancer therapy existed. Patients with other solid tumors could be included after mutual agreement with the Sponsor. Documented progression as per RECIST criteria on the last line of therapy was required before entering the study. Only patients with mutated tumor *PIK3CA*, mutated *PTEN*, or null/low PTEN protein expression were eligible.
- At least one measurable or non-measurable lesion as defined by RECIST criteria for

solid tumors.

- Patients who fulfilled the following criteria were eligible for FDG-PET assessment:
  - Indications: tumor types known to have a high FDG uptake, such as breast, lung, GIST, melanoma, colorectal, ovarian and endometrial cancer.
  - To be eligible for follow-up scans, patients were to have FDG uptake with a tumor-background ratio ≥ 2 in at least one lesion ≥ 2 cm at Baseline.
  - Ability to lie still and flat on the imaging table.
- Availability of a representative tumor tissue specimen. Archival tumor tissue was allowed.
- Age ≥ 18 years.
- World Health Organization (WHO) performance status of ≤ 2.
- Life expectancy of ≥ 12 weeks.
- Patients were required to meet the following laboratory criteria:
  - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L.
  - Hemoglobin ≥ 9 g/dL.
  - Platelets ≥ 100 x 10^9/L.
  - Potassium within normal limits.
  - Total calcium (corrected for serum albumin) within normal limits.
  - Magnesium ≥ the lower limit of normal.
  - AST and ALT ≤ upper limit of normal (ULN) (or ≤ 2.5 x ULN if liver metastases were present).
  - Serum bilirubin ≤ ULN (or ≤ 1.5 x ULN if liver metastases were present; or total bilirubin ≤ 3.0 ULN with direct bilirubin within normal range in patients with well documented Gilbert syndrome).
  - Serum creatinine ≤ 1.5 x ULN or 24-hour clearance ≥ 50 mL/min.
  - Serum amylase ≤ ULN.
  - Serum lipase ≤ ULN.
  - Serum triglycerides ≤ 500 mg/dL.
  - Fasting plasma glucose ≤ 140 mg/dL (7.8 mmol/L).
  - Negative serum pregnancy test within 72 hours before starting study treatment in all pre-menopausal women and women <12 months after the onset of menopause.
- Able to sign informed consent and to comply with the protocol.

Exclusion Criteria

- Patients with a history of primary central nervous system tumors or brain metastases or who had signs/symptoms attributable to brain metastases and had not been assessed with radiologic imaging to rule out the presence of brain metastases. **The following exception applied to the MTD dose-expansion part only**: Patients with treated brain metastases that were asymptomatic and had been clinically stable for three months were eligible for the study.
- Prior treatment with a PI3K inhibitor.
- Presence of acute or chronic liver disease, renal disease or pancreatitis.

- Patients with any peripheral neuropathy CTCAE grade ≥ 2.
- As per Protocol Amendment 4, patients with the following mood disorders as judged by the Investigator or a psychiatrist, or as result of patient's mood assessment questionnaire:
  - Medically documented history of or active major depressive episode, bipolar disorder (I or II), obsessive-compulsive disorder, schizophrenia, a history of suicidal attempt or ideation, or homicidal ideation (immediate risk of doing harm to others).
  - CTCAE grade ≥ 3 anxiety.
- The psychiatric judgment, if available, overruled the mood assessment questionnaire result/investigator judgment.
- Patients with unresolved diarrhea CTCAE grade ≥ 2.
- Any of the following concurrent severe and/or uncontrolled medical conditions that could compromise safe participation in the study:
  - Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
    - Left ventricular ejection volume (LVEF) <45% as determined by Multiple Gated Acquisition (MUGA) scan or ECHO.
    - ST depression or elevation of ≥ 1.5 mm in two or more leads.
    - Congenital long QT syndrome.
    - History or presence of ventricular arrhythmias or atrial fibrillation.
    - Clinically significant resting bradycardia (<50 beats per minute).
    - QTc >480 ms on screening ECG.
    - Complete left bundle branch block.
    - Right bundle branch block + left anterior hemiblock (bifascicular block).
    - Unstable angina pectoris ≤ 3 months prior to starting study drug.
    - Acute myocardial infarction ≤ 3 months prior to starting study drug.
    - Other clinically significant heart disease such as congestive heart failure requiring treatment or uncontrolled hypertension (please refer to WHO-ISH guidelines).
  - Patients with clinically manifested diabetes mellitus (i.e. treated and/or with clinical signs), history of gestational diabetes mellitus, or corticosteroid-induced diabetes mellitus.
  - Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g., uncontrolled hypertriglyceridemia [triglycerides >500 mg/dL], active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with the protocol.
- Impairment of gastrointestinal (GI) function or GI disease that could significantly alter the absorption of buparlisib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
- Patients who had been treated with any hematopoietic colony-stimulating growth factors (e.g., G-CSF, GM-CSF) ≤ 2 weeks prior to starting study drug. Erythropoietin or

darbepoetin therapy, if initiated before enrollment, could be continued.

- Patients receiving medication with a potential to prolong the QT interval or to induce Torsades de Pointes, unless the treatment could be stopped, discontinued or switched to a different medication prior to starting on the study drug.
- Patients receiving treatment with therapeutic doses of warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulant.
- Patients who had received corticosteroids ≤ 2 weeks prior to starting study drug or who had not recovered from the side effects of such treatment.
- Patients who had received chemotherapy, targeted therapy or immunotherapy ≤ 4 weeks (6 weeks for nitrosourea or mitomycin-C) prior to starting study drug or who had not recovered from side effects of such therapy
- Patients who had received any continuous-dosing (i.e. daily dosing, ever-other-day dosing, Monday-Wednesday-Friday dosing weekly etc.) therapeutic modalities or investigational drug (excluding monoclonal antibodies) ≤ 5 half-lives prior to starting study drug or who had not recovered from side effects of such therapy.
- Patients who had received wide field radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting study drug or who had not recovered from side effects of such therapy.
- Patients who had undergone major surgery ≤ 2 weeks prior to starting study drug or who had not recovered from side effects of such therapy.
- Women of child-bearing potential and fertile males were required to practice highly effective contraceptive measures during and after stopping treatment (as defined and specified in the protocol).
- Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing was not mandatory).

Participant Flow

Patient disposition by treatment dose

Disposition Reason	12.5 mg N=1 n (%)	25 mg N=2 n (%)	50 mg N=5 n (%)	80 mg N=11 n (%)	100 mg N=55 n (%)	150 mg N=4 n (%)	TEC 100 mg* N=5 n (%)	All patients N=83
Patients treated								
Treatment discontinued	1 (100)	2 (100)	5 (100)	11 (100)	53 (96.4)	3 (75.0)	5 (100)	80 (96.4)
Treatment ongoing[1]	0	0	0	0	2 (3.6)	1 (25.0)	0	3 (3.6)
Primary reason for end of treatment								
Adverse Event(s)	0	0	0	2 (18.2)	13 (23.6)	1 (25.0)	3 (60.0)	19 (22.9)
Death	0	0	1 (20.0)	1 (9.1)	2 (3.6)	0	0	4 (4.8)
Disease progression	1 (100)	2 (100)	3 (60.0)	8 (72.7)	35 (63.6)	2 (50.0)	2 (40.0)	53 (63.9)
Subject withdrew consent	0	0	1 (20.0)	0	3 (5.5)	0	0	4 (4.8)

*terminal elimination half-life assessment cohort
1. Patients ongoing at the time of the data cut-off

Demographic and other baseline characteristics

Demographic summary by treatment

Demographic variable	12.5 mg N=1	25 mg N=2	50 mg N=5	80 mg N=11	100 mg N=55	150 mg N=4	TEC 100 mg N=5	All patients N=83
Age (Years)								
n	1	2	5	11	55	4	5	83
Mean	63.00	57.50	53.40	54.36	57.20	55.75	47.80	56.04
SD		12.021	4.561	10.614	10.361	20.614	18.199	11.198
Median	63.00	57.50	52.00	55.00	56.00	55.00	52.00	55.00
Min	63.0	49.0	49.0	40.0	37.0	37.0	30.0	30.0
Max	63.0	66.0	60.0	72.0	78.0	76.0	73.0	78.0
Age group (Years) – n (%)								
<40	0	0	0	0	4 (7.3)	2 (50.0)	2 (40.0)	8 (9.6)
40 to <50	0	1 (50.0)	1 (20.0)	3 (27.3)	8 (14.5)	0	0	13 (15.7)
50 to <60	0	0	3 (60.0)	5 (45.5)	20 (36.4)	0	2 (40.0)	30 (36.1)
60 to <70	1 (100)	1 (50.0)	1 (20.0)	2 (18.2)	18 (32.7)	0	0	23 (27.7)
≥ 70	0	0	0	1 (9.1)	5 (9.1)	2 (50.0)	1 (20.0)	9 (10.8)
Gender – n (%)								
Male	1 (100)	1 (50.0)	2 (40.0)	2 (18.2)	22 (40.0)	2 (50.0)	3 (60.0)	33 (39.8)
Female	0	1 (50.0)	3 (60.0)	9 (81.8)	33 (60.0)	2 (50.0)	2 (40.0)	50 (60.2)
Predominant race – n (%)								
Asian	0	0	0	1 (9.1)	0	0	0	1 (1.2)
Black	0 (0.0%)	1 (50.0)	1 (20.0)	0 (0.0%)	0	0	0	2 (2.4)
Caucasian	1 (100)	1 (50.0)	4 (80.0)	10 (90.9)	54 (98.2)	3 (75.0)	5 (100)	78 (94.0)
Other	0	0	0	0	1 (1.8)	1 (25.0)	0	2 (2.4)
Ethnicity - n (%)								
Hispanic/Latino	0	0	1 (20.0)	4 (36.4)	37 (67.3)	3 (75.0)	0	45 (54.2)
Other	1 (100)	2 (100)	4 (80.0)	7 (63.6)	18 (32.7)	1 (25.0)	5 (100)	38 (45.8)
Height (cm)								
n	1	0	4	11	54	4	5	79
Mean	188.00		166.00	167.55	165.56	171.00	174.20	166.96
SD			3.367	9.427	8.309	6.683	13.682	9.022
Weight (kg)								
n	1	2	5	11	55	4	5	83
Mean	104.00	87.00	65.20	73.12	68.82	71.25	79.20	70.77
SD		25.456	6.943	15.583	14.659	8.617	12.007	14.851
Weight group (kg) – n (%)								
<55	0	0	1 (20.0)	1 (9.1)	10 (18.2)	0	0	12 (14.5)
55 to <75	0	1 (50.0)	4 (80.0)	5 (45.5)	28 (50.9)	2 (50.0)	1 (20.0)	41 (49.4)
≥ 75	1 (100)	1 (50.0)	0	5 (45.5)	17 (30.9)	2 (50.0)	4 (80.0)	30 (36.1)
BMI (kg/m^2)								
n	1	0	4	11	54	4	5	79
Mean	29.40		23.18	26.25	25.11	24.35	26.08	25.25
SD			2.164	6.439	4.856	2.307	2.852	4.777
BMI group (kg/m^2) – n (%)								
<30	1 (100)	0	4 (80.0)	8 (72.7)	45 (81.8)	4 (100)	5 (100)	67 (80.7)
≥ 30	0	0	0	3 (27.3)	9 (16.4)	0	0	12 (14.5)

Missing	0	2 (100)	1 (20.0)	0	1 (1.8)	0	0	4 (4.8)
BSA (m^2)								
n	1	0	4	11	54	4	5	79
Mean	2.30		1.75	1.85	1.79	1.85	1.98	1.81
SD			0.100	0.207	0.220	0.129	0.217	0.218
Median	2.30		1.80	1.80	1.80	1.85	2.10	1.80
Min	2.3		1.6	1.5	1.3	1.7	1.6	1.3
Max	2.3		1.8	2.1	2.3	2.0	2.1	2.3
WHO Performance Status – (%)								
0	1 (100)	2 (100)	3 (60.0)	6 (54.5)	20 (36.4)	4 (100)	0	36 (43.4)
1	0	0	2 (40.0)	5 (45.5)	34 (61.8)	0	5 (100)	46 (55.4)
2	0	0	0	0	1 (1.8)	0	0	1 (1.2)

Disease history at the time of study entry by treatment

	12.5 mg N=1	25 mg N=2	50 mg N=5	80 mg N=11	100 mg N=55	150 mg N=4	TEC 100 mg N=5	All patients N=83
Primary site of cancer – n (%)								
Lung	0	0	0	1 (9.1)	3 (5.5)	0	0	4 (4.8)
Liver	0	0	0	0	1 (1.8)	0	0	1 (1.2)
Head and neck	0	0	0	0	1 (1.8)	0	1 (20.0)	2 (2.4)
Pancreas	0	0	0	0	2 (3.6)	0	0	2 (2.4)
Prostate	0	0	1 (20.0)	0	1 (1.8)	0	0	2 (2.4)
Oral cavity	0	0	0	0	0	0	1 (20.0)	1 (1.2)
Stomach	0	0	0	0	0	0	1 (20.0)	1 (1.2)
Small intestine	0	0	0	0	1 (1.8)	0	0	1 (1.2)
Colon	1 (100)	1 (50.0)	3 (60.0)	3 (27.3)	14 (25.5)	1 (25.0)	0	23 (27.7)
Rectum	0	0	0	0	6 (10.9)	0	2 (40.0)	8 (9.6)
Breast	0	0	0	1 (9.1)	19 (34.5)	1 (25.0)	0	21 (25.3)
Ovary	0	0	0	1 (9.1)	2 (3.6)	0	0	3 (3.6)
Kidneys	0	0	0	0	0	1 (25.0)	0	1 (1.2)
Thyroid	0	0	0	1 (9.1)	0	0	0	1 (1.2)
Gall bladder	0	0	0	1 (9.1)	0	0	0	1 (1.2)
Other	0	1 (50.0)	1 (20.0)	3 (27.3)	5 (9.1)	1 (25.0)	0	11 (13.3)
Details of tumor histology/cytology – n (%)								
Adenocarcinoma	1 (100)	1 (50.0)	4 (80.0)	8 (72.7)	27 (49.1)	1 (25.0)	2 (40.0)	44 (53.0)
Papillary serous	0	0	0	1 (9.1)	0	0	0	1 (1.2)
Invasive ductal carcinoma	0	0	0	0	11 (20.0)	1 (25.0)	0	12 (14.5)
Serous adenocarcinoma	0	0	0	0	1 (1.8)	0	0	1 (1.2)
Clear cell adenocarcinoma	0	0	0	0	1 (1.8)	1 (25.0)	0	2 (2.4)
Undifferentiated carcinoma	0	0	0	1 (9.1)	0	0	0	1 (1.2)
Glioblastoma multiforme	0	1 (50.0)	0	0	0	0	0	1 (1.2)
Small cell (neuroendocrine) carcinoma	0	0	0	0	1 (1.8)	0	0	1 (1.2)
Melanoma	0	0	0	1 (9.1)	0	0	1 (20.0)	2 (2.4)
Gastrointestinal stromal tumor	0	0	0	0	1 (1.8)	0	1 (20.0)	2 (2.4)

Carcinoid	0	0	1 (20.0)	0	1 (1.8)	0	0	2 (2.4)
DCIS (ductal carcinoma in situ)	0	0	0	0	1 (1.8)	0	0	1 (1.2)
Other	0	0	0	0	11 (20.0)	1 (25.0)	1 (20.0)	13 (15.7)
Histologic grade – n (%)								
Well differentiated	0	0	0	0	5 (9.1)	0	0	5 (6.0)
Moderately differentiated	0	1 (50.0)	2 (40.0)	1 (9.1)	19 (34.5)	0	2 (40.0)	25 (30.1)
Poorly differentiated	1 (100)	0	1 (20.0)	4 (36.4)	9 (16.4)	0	0	15 (18.1)
Undifferentiated	0	0	1 (20.0)	1 (9.1)	0	0	0	2 (2.4)
Unknown	0	1 (50.0)	1 (20.0)	5 (45.5)	22 (40.0)	4 (100)	3 (60.0)	36 (43.4)
Stage at initial diagnosis – n (%)								
Stage 0	0	0	0	0	1 (1.8)	0	0	1 (1.2)
Stage I	0	0	0	0	2 (3.6)	0	2 (40.0)	4 (4.8)
Stage I b	0	0	0	1 (9.1)	0	0	0	1 (1.2)
Stage I c	0	0	0	0	2 (3.6)	0	0	2 (2.4)
Stage II	0	0	0	1 (9.1)	5 (9.1)	0	0	6 (7.2)
Stage II a	0	0	0	0	7 (12.7)	0	0	7 (8.4)
Stage II b	1 (100)	0	0	0	3 (5.5)	0	0	4 (4.8)
Stage III	0	0	0	2 (18.2)	7 (12.7)	0	2 (40.0)	11 (13.3)
Stage III a	0	0	0	1 (9.1)	4 (7.3)	0	0	5 (6.0)
Stage III b	0	0	1 (20.0)	0	7 (12.7)	1 (25.0)	0	9 (10.8)
Stage IV	0	1 (50.0)	4 (80.0)	4 (36.4)	16 (29.1)	3 (75.0)	1 (20.0)	29 (34.9)
Stage IV a	0	0	0	0	1 (1.8)	0	0	1 (1.2)
Stage IV b	0	0	0	2 (18.2)	0	0	0	2 (2.4)
Missing	0	1 (50.0)	0	0	0	0	0	1 (1.2)
Current stage of cancer – n (%)								
Stage III	0	0	0	1 (9.1)	0	0	0	1 (1.2)
Stage III b	0	0	0	0	1 (1.8)	0	0	1 (1.2)
Stage IV	1 (100)	1 (50.0)	5 (100)	8 (72.7)	52 (94.5)	4 (100)	5 (100)	76 (91.6)
Stage IV a	0	0	0	0	1 (1.8)	0	0	1 (1.2)
Stage IV b	0	0	0	2 (18.2)	0	0	0	2 (2.4)
Missing	0	1 (50.0)	0	0	1 (1.8)	0	0	2 (2.4)
Time since diagnosis of primary site to first dose of drug (months)								
n	1	2	5	11	55	4	5	83
Mean	47.5	53.1	60.7	51.3	58.8	31.8	65.0	56.7
SD		49.53	53.88	34.50	51.96	37.58	48.25	47.99
Median	47.5	53.1	24.7	48.2	41.2	14.3	53.9	41.2
Min	48	18	20	15	7	11	22	7
Max	48	88	132	126	266	88	139	266
Time from first diagnosis to first relapse (months)								
n	1	2	5	11	54	4	5	82
Mean	28.9	35.1	34.5	21.7	28.1	12.6	15.5	26.3
SD		45.49	30.19	17.32	27.85	6.85	11.48	25.52
Median	28.9	35.1	13.0	15.5	18.6	10.9	9.6	16.9

Min	29	3	12	3	3	7	8	3
Max	29	67	72	55	142	22	35	142
Time from first diagnosis to most recent recurrence/relapse (months)								
n	1	2	5	11	55	4	5	83
Mean	46.9	52.1	57.6	49.8	55.3	29.9	62.5	53.8
SD		48.97	50.63	34.76	50.72	37.51	47.77	46.86
Median	46.9	52.1	24.5	47.3	39.1	12.3	49.0	39.1
Min	47	17	19	13	5	9	20	5
Max	47	87	120	125	265	86	136	265
Metastases reported – n (%)								
No	0	0	0	1 (9.1)	2 (3.6)	0	0	3 (3.6)
Yes	1 (100)	2 (100)	5 (100)	10 (90.9)	53 (96.4)	4 (100)	5 (100)	80 (96.4)
Parameters measured only in patients with breast cancer								
Estrogen Receptor Status (ER) – n (%)								
Negative	0	0	0	0	4 (7.3)	0	0	4 (4.8)
Positive	0	0	0	1 (9.1)	15 (27.3)	1 (25.0)	0	17 (20.5)
Progesterone Receptor Status (PR) – n (%)								
Negative	0	0	0	0	8 (14.5)	0	0	8 (9.6)
Positive	0	0	0	1 (9.1)	10 (18.2)	1 (25.0)	0	12 (14.5)
HER2 protein expression level – n (%)								
Negative	0	0	0	1 (9.1)	12 (21.8)	1 (25.0)	0	14 (16.9)
Positive	0	0	0	0	4 (7.3)	0	0	4 (4.8)
Receptor status – n (%)								
HER2 Positive and Hormone receptor Positive	0	0	0	0	3 (5.5)	0	0	3 (3.6)
HER2 Positive and Hormone receptor Negative	0	0	0	0	1 (1.8)	0	0	1 (1.2)
HER2 Negative and Hormone receptor Positive	0	0	0	1 (9.1)	9 (16.4)	1 (25.0)	0	11 (13.3)
Triple Negative	0	0	0	0	3 (5.5)	0	0	3 (3.6)

Summary statistics of mutational status of tumor

Activation of PI3K pathway – mechanism	**12.5 mg N=1**	**25 mg N=2**	**50 mg N=5**	**80 mg N=11**	**100 mg N=55**	**150 mg N=4**	**TEC 100 mg N=5**	**All patients N=83**
PIK3CA mutation	0	0	0	3 (27.3)	12 (21.8)	0	0	15 (18.1)
PTEN Null or low	1 (100)	1 (50.0)	3 (60.0)	1 (9.1)	15 (27.3)	0	0	21 (25.3)
PIK3CA mutation or PTEN null/low [1]	1 (100)	1 (50.0)	3 (60.0)	4 (36.4)	26 (47.3)	0	0	35 (42.2)
Unknown [2]	0	1 (50.0)	1 (20.0)	0	7 (12.7)	0	2 (40.0)	11 (13.3)

1. Patients with at least one of the following: *PI3KCA* mutation, PTEN Null or low expression. PTEN Null was defined as PTEN IHC=0. PTEN Low was defined as PTEN IHC ≤ 50.
2. Patients with at least one information missing for whom footnote (1) does not apply.

Outcome measures

Analysis of MTD

Summary of posterior distribution of DLT rates at time of MTD declaration

	Posterior probabilities (%) that Pr(DLT) is in interval:					Quantiles		
Dose (mg)	0-0.16	0.16-0.33	0.33-1	Mean	SD	2.5%	50%	97.5%
5.0	0.999	0.001	0.000	0.009	0.019	0	0.001	0.067
12.5	0.996	0.004	0.000	0.018	0.027	0	0.007	0.099
25.0	0.989	0.011	0.000	0.034	0.037	0.001	0.021	0.134
50.0	0.940	0.060	0.000	0.073	0.049	0.009	0.063	0.191
70.0	0.817	0.182	0.001	0.113	0.054	0.031	0.106	0.236
80.0	0.696	0.302	0.003	0.136	0.056	0.047	0.13	0.262
90.0	0.533	0.459	0.007	0.161	0.059	0.064	0.155	0.29
100.0	0.364	0.614	0.022	0.187	0.063	0.081	0.181	0.326
110.0	0.233	0.703	0.064	0.215	0.071	0.095	0.208	0.369
120.0	0.150	0.709	0.142	0.242	0.080	0.107	0.235	0.419
130.0	0.102	0.655	0.243	0.271	0.092	0.117	0.261	0.476
150.0	0.056	0.504	0.440	0.325	0.118	0.134	0.312	0.592
170.0	0.036	0.385	0.579	0.376	0.142	0.148	0.359	0.695
200.0	0.022	0.272	0.706	0.442	0.171	0.165	0.424	0.809

Summary of posterior distribution of DLT rates at end of study

	Posterior probabilities (%) that Pr(DLT) is in interval:					Quantiles		
Dose (mg)	0-0.16	0.16-0.33	0.33-1	Mean	SD	2.5%	50%	97.5%
5.0	1.000	0.000	0.000	0.007	0.014	0	0.001	0.051
12.5	0.999	0.001	0.000	0.013	0.021	0	0.005	0.075
25.0	0.998	0.002	0.000	0.025	0.028	0	0.015	0.103
50.0	0.985	0.015	0.000	0.056	0.038	0.007	0.049	0.147
70.0	0.942	0.058	0.000	0.089	0.041	0.026	0.084	0.182
80.0	0.884	0.116	0.000	0.109	0.042	0.041	0.104	0.202
90.0	0.769	0.231	0.000	0.130	0.043	0.058	0.126	0.226
100.0	0.586	0.413	0.001	0.153	0.047	0.074	0.149	0.256
110.0	0.398	0.595	0.007	0.178	0.054	0.087	0.174	0.295
120.0	0.261	0.701	0.038	0.204	0.064	0.098	0.198	0.346
130.0	0.177	0.718	0.106	0.231	0.077	0.107	0.222	0.405
150.0	0.096	0.612	0.293	0.284	0.106	0.121	0.269	0.531
170.0	0.060	0.488	0.451	0.335	0.134	0.134	0.313	0.647
200.0	0.036	0.356	0.608	0.403	0.168	0.149	0.376	0.779

Efficacy results

Best overall response

Summary of best overall response on RECIST as per investigator assessment

	12.5 mg N=1 n %	25 mg N=2 n %	50 mg N=5 n %	80 mg N=11 n %	100 mg N=55 n %	150 mg N=4 n %	TEC 100 mg N=5 n %	All patients N=83 n %
Best overall response								
Complete response (CR)	0	0	0	0	0	0	0	0
Partial response (PR)	0	0	0	0	1 (1.8)	0	0	1 (1.2)
Stable disease (SD)	1 (100.0)	1 (50.0)	1 (20.0)	6 (54.5)	22 (40.0)	1 (25.0)	1 (20.0)	33 (39.8)
Progressive disease (PD)	0	0	3 (60.0)	3 (27.3)	28 (50.9)	2 (50.0)	2 (40.0)	38 (45.8)
Unknown	0	1 (50.0)	1 (20.0)	2 (18.2)	4 (7.3)	1 (25.0)	2 (40.0)	11 (13.3)
Overall response rate (CR or PR)	0	0	0	0	1 (1.8)	0	0	1 (1.2)
90% Confidence interval*	[0.0; 95.0]	[0.0; 77.6]	[0.0; 45.1]	[0.0; 23.8]	[0.1; 8.3]	[0.0; 52.7]	[0.0; 45.1]	[0.1; 5.6]
Disease control rate (CR or PR or SD)	1 (100.0)	1 (50.0)	1 (20.0)	6 (54.5)	23 (41.8)	1 (25.0)	1 (20.0)	34 (41.0)
90% Confidence interval*	[5.0; 100.0]	[2.5; 97.5]	[1.0; 65.7]	[27.1; 80.0]	[30.5; 53.8]	[1.3; 75.1]	[1.0; 65.7]	[31.8; 50.6]

Progression-free survival

Analysis of Progression-free survival (PFS) based on investigator assessment using Kaplan-Meier method - patients at and above MTD vs. patients below MTD

	Below MTD N=19	At and above MTD N=59
No. of PFS events	17 (89.5%)	43 (72.9%)
Progression	13 (68.4%)	42 (71.2%)
Death	4 (21.1%)	1 (1.7%)
Censored	2 (10.5%)	16 (27.1%)
Kaplan-Meier estimates (%) of PFS rate [95% CI] at:		
2 months	53 [29, 77]	46 [32, 59]
6 months	18 [0, 36]	24 [11, 37]
Median PFS (days) [95% CI]	87 [55, 113]	57 [50, 106]
25th percentile PFS (days) [95% CI]	55 [6, 87]	34 [30, 50]
75th percentile PFS (days) [95% CI]	113 [87, 224]	148 [93, 249]

Patients in the terminal elimination half-life cohort were not included in the analysis of PFS

FDG-PET

Summary statistics for percentage change from Baseline in SUVmax and metabolic response from FDG-PET

FDG-PET scan time	Statistics	12.5 mg N=1	25 mg N=2	50 mg N=5	80 mg N=11	100 mg N=55	150 mg N=4	TEC 100 mg N=5	All patients N=83
Percentage change from Baseline SUVmax C1D28	n	0	1	2	6	39	3	1	52
	Mean		-38.23	-0.60	-7.18	-20.69	-36.19	-3.95	-19.27
	SD			0.018	20.416	18.720	15.200		19.286
	Median		-38.23	-0.60	-10.21	-23.24	-36.35	-3.95	-19.93
	Min		-38.2	-0.6	-27.0	-63.8	-51.3	-4.0	-63.8
	Max		-38.2	-0.6	29.1	14.6	-20.9	-4.0	29.1

Metabolic response at C1D28	CMR	0	0	0	0	0	0	0	0
	PMR	0	1 (50.0%)	0	1 (9.1%)	17 (30.9%)	2 (50.0%)	0	21 (25.3%)
	SMD	0	0	2 (40.0%)	4 (36.4%)	23 (41.8%)	1 (25.0%)	2 (40.0%)	32 (38.6%)
	PMD	0	0	0	1 (9.1%)	0	0	0	1 (1.2%)
	Unknown	1 (100.0%)	1 (50.0%)	3 (60.0%)	5 (45.5%)	15 (27.3%)	1 (25.0%)	3 (60.0%)	29 (34.9%)
Percentage change from Baseline SUVmax C2D28	n	1	1	2	3	21	1	1	30
	Mean	-5.31	-9.45	-1.70	-8.13	-13.80	-12.27	-30.71	-12.51
	SD			12.156	11.041	27.422			23.599
	Median	-5.31	-9.45	-1.70	-11.20	-13.40	-12.27	-30.71	-10.75
	Min	-5.3	-9.5	-10.3	-17.3	-60.9	-12.3	-30.7	-60.9
	Max	-5.3	-9.5	6.9	4.1	40.0	-12.3	-30.7	40.0
Metabolic response at C2D28	CMR	0	0	0	0	0	0	0	0
	PMR	0	0	0	0	8 (14.5%)	0	1 (20.0%)	9 (10.8%)
	SMD	1 (100.0%)	1 (50.0%)	2 (40.0%)	3 (27.3%)	13 (23.6%)	1 (25.0%)	1 (20.0%)	22 (26.5%)
	PMD	0	0	0	0	2 (3.6%)	0	0	2 (2.4%)
	Unknown	0	1 (50.0%)	3 (60.0%)	8 (72.7%)	32 (58.2%)	3 (75.0%)	3 (60.0%)	50 (60.2%)

Safety Results

Adverse events, regardless of study drug relationship, by primary system organ class

	12.5 mg N=1 n (%)	25 mg N=2 n (%)	50 mg N=5 n (%)	80 mg N=11 n (%)	100 mg N=55 n (%)	150 mg N=4 n (%)	TEC 100 mg N=5 n (%)	All patients N=83 n (%)
Adverse events								
Adverse events, regardless of study drug relationship	**1 (100)**	**2 (100)**	**5 (100)**	**11 (100)**	**55 (100)**	**4 (100)**	**5 (100)**	**83 (100)**
Adverse events suspected to be treatment-related	1 (100)	2 (100)	4 (80.0)	9 (81.8)	54 (98.2)	4 (100)	3 (60.0)	77 (92.8)
Primary system organ class								
Gastrointestinal disorders	1 (100)	1 (50.0)	4 (80.0)	8 (72.7)	50 (90.9)	4 (100)	5 (100)	73 (88.0)
General disorders and administration site conditions	1 (100)	0	4 (80.0)	9 (81.8)	46 (83.6)	2 (50.0)	5 (100)	67 (80.7)
Metabolism and nutrition disorders	1 (100)	2 (100)	2 (40.0)	8 (72.7)	36 (65.5)	3 (75.0)	3 (60.0)	55 (66.3)
Psychiatric disorders	0	1 (50.0)	2 (40.0)	6 (54.5)	32 (58.2)	2 (50.0)	2 (40.0)	45 (54.2)
Nervous system disorders	0	2 (100)	3 (60.0)	8 (72.7)	28 (50.9)	2 (50.0)	1 (20.0)	44 (53.0)
Skin and subcutaneous tissue disorders	0	1 (50.0)	1 (20.0)	5 (45.5)	29 (52.7)	3 (75.0)	3 (60.0)	42 (50.6)
Musculoskeletal and connective tissue disorders	1 (100)	2 (100)	3 (60.0)	5 (45.5)	20 (36.4)	2 (50.0)	2 (40.0)	35 (42.2)

Investigations	0	1 (50.0)	0	3 (27.3)	26 (47.3)	1 (25.0)	2 (40.0)	33 (39.8)
Respiratory, thoracic and mediastinal disorders	0	1 (50.0)	1 (20.0)	3 (27.3)	15 (27.3)	1 (25.0)	3 (60.0)	24 (28.9)
Infections and infestations	1 (100)	0	2 (40.0)	3 (27.3)	15 (27.3)	2 (50.0)	0	23 (27.7)
Vascular disorders	0	0	0	1 (9.1)	9 (16.4)	0	1 (20.0)	11 (13.3)
Eye disorders	0	0	0	1 (9.1)	8 (14.5)	1 (25.0)	0	10 (12.0)
Hepatobiliary disorders	0	0	0	1 (9.1)	7 (12.7)	0	2 (40.0)	10 (12.0)
Blood and lymphatic system disorders	0	0	0	0	7 (12.7)	1 (25.0)	0	8 (9.6)
Renal and urinary disorders	0	0	1 (20.0)	0	6 (10.9)	1 (25.0)	0	8 (9.6)
Cardiac disorders	0	0	0	2 (18.2)	4 (7.3)	0	0	6 (7.2)
Ear and labyrinth disorders	0	0	0	0	4 (7.3)	0	0	4 (4.8)
Immune system disorders	0	0	0	1 (9.1)	2 (3.6)	1 (25.0)	0	4 (4.8)
Reproductive system and breast disorders	0	0	0	1 (9.1)	1 (1.8)	0	2 (40.0)	4 (4.8)
Injury, poisoning and procedural complications	0	0	0	0	3 (5.5)	0	0	3 (3.6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	0	0	0	1 (25.0)	0	1 (1.2)

10 Most frequently reported AEs, regardless of study drug relationship, overall by preferred term n (%)

Preferred term	12.5 mg N=1 n (%)	25 mg N=2 n (%)	50 mg N=5 n (%)	80 mg N=11 n (%)	100 mg N=55 n (%)	150 mg N=4 n (%)	TEC 100 mg N=5 n (%)	All patients N=83 n (%)
Nausea	0	1 (50.0)	1 (20.0)	3 (27.3)	27 (49.1)	3 (75.0)	3 (60.0)	38 (45.8)
Decreased appetite	0	2 (100)	1 (20.0)	5 (45.5)	22 (40.0)	2 (50.0)	3 (60.0)	35 (42.2)
Asthenia	0	0	2 (40.0)	1 (9.1)	26 (47.3)	2 (50.0)	0	31 (37.3)
Diarrhea	0	0	0	2 (18.2)	25 (45.5)	2 (50.0)	1 (20.0)	30 (36.1)
Hyperglycemia	1 (100)	0	1 (20.0)	4 (36.4)	19 (34.5)	3 (75.0)	0	28 (33.7)
Rash	0	1 (50.0)	1 (20.0)	3 (27.3)	18 (32.7)	2 (50.0)	1 (20.0)	26 (31.3)
Constipation	0	0	3 (60.0)	1 (9.1)	18 (32.7)	2 (50.0)	1 (20.0)	25 (30.1)
Fatigue	1 (100)	0	2 (40.0)	4 (36.4)	14 (25.5)	0	3 (60.0)	24 (28.9)
Vomiting	0	1 (50.0)	0	3 (27.3)	14 (25.5)	2 (50.0)	2 (40.0)	22 (26.5)
Stomatitis	0	0	0	4 (36.4)	15 (27.3)	0	2 (40.0)	21 (25.3)

Serious Adverse Events and Deaths

Summary of deaths and adverse events - Safety set

Category	12.5 mg N=1 n (%)	25 mg N=2 n (%)	50 mg N=5 n (%)	80 mg N=11 n (%)	100 mg N=55 n (%)	150 mg N=4 n (%)	TEC 100 mg N=5 n (%)	All patients N=83 n (%)

All deaths	0	0	3 (60)	3 (27.3)	21 (38.2)	1 (25.0)	1 (20)	29 (34.9)
Adverse events (AEs)	1 (100)	2 (100)	5 (100)	11 (100)	55 (100)	4 (100)	5 (100)	83 (100)
AEs suspected to be drug-related	1 (100)	2 (100)	4 (80)	9 (81.8)	54 (98.2)	4 (100)	3 (60)	77 (92.8)
Grade 3-4 AEs	0	1 (50)	4 (80)	8 (72.7)	36 (65.5)	4 (100)	4 (80)	57 (68.7)
Suspected to be drug-related grade 3-4 AEs	0	1 (50)	0	3 (27.3)	25 (45.5)	3 (75.0)	1 (20)	33 (39.8)
Serious adverse events (SAEs)	0	0	4 (80)	4 (36.4)	23 (41.8)	4 (100)	1 (20)	36 (43.4)
SAEs suspected to be drug-related	0	0	0	1 (9.1)	7 (12.7)	3 (75.0)	0	11 (13.3)
AEs leading to discontinuation	0	0	1 (20)	2 (18.2)	13 (23.6)	1 (25.0)	3 (60)	20 (24.1)
AEs, suspected to be drug-related, leading to discontinuation	0	0	0	1 (9.1)	11 (20)	1 (25.0)	1 (20)	14 (16.9)
Others significant AEs								
AEs requiring dose interruption and/or reduction	1 (100)	1 (50)	3 (60)	7 (63.6)	42 (76.4)	2 (50)	1 (20)	57 (68.7)

Other Relevant Findings

None

Date of Clinical Trial Report

28 August 2012

Date Inclusion on Novartis Clinical Trial Results Database

20 September 2012

Date of Latest Update