Sponsor

Novartis

Generic Drug Name

BGT226

Therapeutic Area of Trial

Advanced solid malignancies

Approved Indication

Investigational

Study Number

CBGT226A2101

Title

A phase I/II, multi-center, open-label study of BGT226, administered orally in adult patients with advanced solid malignancies including patients with advanced breast cancer.

Phase of Development

Phase I/II

Study Start/End Dates

05-Dec-2007 to 09-Mar-2010, Early termination date 30-Nov-2009

Study Design/Methodology

This was an open-label, single-arm, multi-center dose escalation study of oral BGT226 administered once-a-day 3-times a week in adult patients with advanced solid malignancies.

Centers

5 centers in three countries – Canada (1), Spain (1), United States (3)

Publication

None

Objectives

Primary objective(s)

To determine the maximum tolerated dose (MTD) of BGT226 as a single agent administered orally once-a-day 3-times a week to adult patients with advanced solid tumors, whose disease has progressed despite standard therapy or for whom no standard anticancer therapy exists.

Secondary objective(s)

To assess the safety and tolerability of BGT226 treatment.

To assess the preliminary efficacy of BGT226 in patients with advanced solid tumors during the dose-escalation,

To characterize the single and multiple-dose pharmacokinetic (PK) profiles of oral BGT226 given once-a-day 3-times a week with respect to the parent drug in plasma.

To assess changes between pre- and post-treatment Biomarker markers. Multiple potential biomarkers relevant to PI3K signaling modulation have been incorporated into this study to explore the effect of BGT226 at the molecular level and on clinical outcome.

To assess the tumor metabolic response by FDG-PET imaging, pre and post-treatment in all patients.

To assess treatment-related biologic effect of BGT226 by pre and post-treatment, non-invasive imaging (DCE-MRI) to measure the effect of BGT226 on the vascular perfusion and vessel permeability of tumors in those patients with liver metastasis.

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

Oral capsules of BGT226 were administered at dose strengths 2.5 mg, 5 mg, 25 mg and 75 mg and dosed on a flat scale of mg/day.

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

Not applicable

Criteria for Evaluation

MTD:

The determination of the MTD was based upon the frequency of DLT in the first cycle for patients in the dose determining-set (DDS). The MTD was estimated based on the recommendation of the adaptive Bayesian model, also taking into account further available safety and tolerability information.

Efficacy:

Response and progression evaluations were performed according to RECIST v1.0 and were based on radiologic techniques (CT or MRI imaging, or by physical examination) obtained at tumor evaluations.

Safety:

Safety assessments consisted of monitoring and recording of all adverse events, serious adverse events, discontinuations from study drug, and deaths. They also included regular monitoring of hematology, blood chemistry, coagulation, fasting insulin/glucose, cardiac enzymes and urine and regular assessments of vital signs, ECGs and physical examination. Adverse events were assessed according to the CTCAE version 3.0.

Pharmacokinetics and Biomarkers:

Pharmacokinetics:

Blood samples for BGT226 plasma concentration-time profiles were collected on all patients of the study on Day 1 and Day 8 of Cycle 1 and Day 1 of Cycle 2 and pre-dose samples on Day 1 of every subsequent cycle.

Biomarkers:

Tumor tissue samples were collected for investigating BGT226 effects on molecular signaling and tumor cell responses, as well as potential biomarkers predictive of efficacy. Tumor biopsy tissue obtained pre - and on-treatment was analyzed for the mutational status of genes relevant to PI3K/mTOR signaling and for markers such as p-Akt (Ser473), p-S6 (Ser240/244) and Ki-67. Paraffin embedded tissue obtained pre- and on-treatment from skin biopsies were analyzed for p-S6 (Ser240/244). Blood samples were collected to investigate treatment related changes in markers relevant to PI3K signaling and drug effect such as circulating angiogenic molecules, markers indicators of cellular responses (e.g. apoptosis, necrosis, circulating tumoral cells) and/or to identify genetic alterations that may predict efficacy (e.g. PTEN germline mutations).

Statistical Methods

An adaptive 2-parameter Bayesian logistic regression model (BLMR) guided by the escalation with overdose control (EWOC) principle was used in the dose-escalation part. All preclinical data currently available about the dose-toxicity curve of BGT226 were summarized in a prior distribution. This prior was updated after each cohort with the DLT data in the dose-determining-set. The Full Analysis Set (FAS) was the primary set of patients for all efficacy analyses, consisting of all patients receiving at least one dose of study drug. The safety set was the primary set of patients or all safety related endpoints except determination of the dose-DLT relationship, consisting of all patients receiving at least one dose of study drug and having at least one valid post-baseline safety assessment. The DDS was the primary set of patients to be used in the BLMR, consisting of all patients from the safety set who met the requirements of minimum exposure to BGT226 and had sufficient safety evaluations during cycle 1 or discontinued earlier due to DLT within cycle 1.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

Male or female patients = 18 years with histologically-confirmed, advanced solid tumors including Cowden Syndrome (CS) patients with solid tumors, at least one measurable or non-measurable lesion as defined by response evaluation criteria in solid tumors (RECIST),

whose disease has progressed despite standard therapy (or who are intolerant of such therapy) or for whom no standard therapy exists.

Life expectancy of = 12 weeks and World Health Organization (WHO) Performance Status of = 2

Exclusion criteria

Patients with known primary central nervous system tumors or brain metastases or who have signs/symptoms attributable to brain metastases and have not been assessed with radiologic imaging to rule out the presence of brain metastases.

Prior treatment with a PI3K inhibitor. Patients who are currently receiving treatment with calcium channel blockers.

Acute or chronic liver disease or renal disease or pancreatitis.

Patients with any peripheral neuropathy = CTCAE grade 2.

Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of BGT226 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, unresolved diarrhea = CTCAE grade 2, malabsorption syndrome, or small bowel resection).

Number of Subjects

A total of 57 patients were enrolled in the dose-escalation part of the study and have received at least one dose of study drug, all 57 patients had discontinued from the study. Disease progression was the most frequent reason for the discontinuation (89.5%) in the study. Overall four patients (7.0%) discontinued from the study due to adverse event, and two patients (3.5%) withdrew consent and discontinued from the study.

Demographic and Background Characteristics

The minimal age of enrolled patients was 23.0 years, the maximal age 82.0 years. The majority of patients were <65 years old (70.2%), female (57.9%), Caucasian (96.5%), and with WHO performance status =1 (94.7%).

Demographic summary by treatment group for the FAS:

	2.5 mg N=5	5 mg N=4	10 mg N=4	20 mg N=3	40 mg N=8	80 mg N=9	100 mg N=13	125 mg N=11	All patients N=57
Age (years at baseline)									
Mean (n)	53.6 (5).	66.3 (4)	54.8 (4)	62.3 (3)	59.6 (8)	60.6 (9)	59.1 (13)	52.9 (11)	58.1 (57)
Sex – n (%)									
Male	2 (40.0%)	1 (25.0%)	1 (25.0%)	0	3 (37.5%)	3 (33.3%)	10 (76.9%)	4 (36.4%)	24 (42.1%)
Female	3 (60.0%)	3 (75.0%)	3 (75.0%)	3 (100 %)	5 (62.5%)	6 (66.7%)	3 (23.1%)	7 (63.6%)	33 (57.9%)
Race n									

(%)									
Black	1	0	0	0	0	0	1 (7.7%)	0	2 (3.5%)
Caucasian	4 (80%)	4 (100%)	4 (100%)	3 (100 %)	8 (100%)	9 (100%)	12 (92.3%)	11 (100%)	55 (96.5%)
WHO performance status									
0	2 (40.0%)	1 (25.0%)	2 (50.0%)	1 (33.3%)	3 (37.5%)	5 (55.6%)	10 (76.9%)	4 (36.4%)	28 (49.1%)
1	3 (60%)	3 (75.0%)	1 (25.0%)	2 (66.7%)	4 (50.0%)	4 (44.4%)	3 (23.1%)	6 (54.5%)	26 (45.6%)
2	0	0	1 (25.0%)	0	1 (12.5%)	0	0	1 (9.1%)	3 (5.3%)

Primary Objective Result(s)

Three patients with confirmed DLTs were observed in the 125 mg cohort (CTC grade 3 diarrhea, CTC grade 3 vomiting, and CTC grade 3 diarrhea and vomiting). With three DLTs out of 11 evaluable patients at the 125 mg dose and no DLTs seen in the 33 evaluable patients at doses between 2.5 and 80 mg, the model indicated that 125 mg was the dose that maximized the targeted toxicity while meeting the overdose criteria as specified in the protocol. Therefore the 125 mg dose was declared as the MTD. Due to the chronic nature and difficulties of managing the CTC grade 1-3 (depending on the patient) nausea, vomiting and diarrhea observed at this dose level, the 100 mg dose was then explored. The 100 mg dose was better tolerated than the 125 mg with no DLT, and was declared as the clinically recommended dose.

Secondary Objective Result(s)

Efficacy results

The best overall response as per investigators and central review, from the start of the treatment with BGT226 was stable disease (SD) (defined as at least one SD assessment > 6 weeks after start of treatment and not qualifying for CR or PR) in a total of 17 (29.8%) patients with 95% CI (18.4%, 43.4%) and in 18 (31.6%) patients with 95% CI(19.9%, 45.2%), respectively.

Safety results

All the patients enrolled in the study experienced at least one AE (regardless of causality) during the study. The three most frequently reported AEs regardless of causality and dose were nausea (78.9%), diarrhea (68.4%), and vomiting (57.9%).

Most patients (87.7%) experienced at least one AE suspected to be related to BGT226 during the study. The most frequently reported AEs suspected to be related to BGT226 were nausea (68.4%; of which were 3.5% CTC grade 3 or 4), diarrhea (61.4%; of which were 12.3% CTC grade 3 or 4), vomiting (49.1%; of which were 3.5% CTC grade 3 or 4) and fatigue (19.3%; of which none were grade 3 or 4). There were no significant hematology abnormalities or biochemistry abnormalities observed in this study. Most hematologic and biochemistry abnormalities were CTC Grade 1 or 2 in severity. No > grade 1 fasting plasma glucose was observed in any patient in this study.

Adverse events overall and most frequent events (>10% in all patients group), regardless of study drug relationship – by treatment group (Safety analysis set)

Preferred term	2.5 mg	5 mg	10 mg	20 mg	40 mg	80 mg	100 mg	125 mg	All patients
	N=5	N=4	N=4	N=3	N=8	N=9	N=13	N=11	N=57
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	5 (100)	4 (100)	4 (100.0)	3 (100.0)	8 (100.0)	9 (100.0)	13 (100.0)	11 (100.0)	57 (100.0)
Nausea	3 (60.0)	2 (50.0)	1 (25.0)	3(100.0)	6 (75.0)	8 (88.9)	12 (92.3)	10 (90.9)	45 (78.9)
Diarrhoea	1 (20.0)	1 (25.0)	1 (25.0)	2 (66.7)	4 (50.0)	8 (88.9)	12 (92.3)	10 (90.9)	39 (68.4)
Vomiting	2 (40.0)	0	2 (50.0)	1 (33.3)	4 (50.0)	5 (55.6)	10 (76.9)	9 (81.8)	33 (57.9)
Decreased appetite	1 (20.0)	1 (25.0)	2 (50.0)	2 (66.7)	1 (12.5)	1 (11.1)	8 (61.5)	3 (27.3)	19 (33.3)
Fatigue	1 (20.0)	3 (75.0)	0	0	1 (12.5)	5 (55.6)	6 (46.2)	3 (27.3)	19 (33.3)
Anaemia	2 (40.0)	1 (25.0)	1 (25.0)	1 (33.3)	2 (25.0)	2 (22.2)	2 (15.4)	3 (27.3)	14 (24.6)
Abdominal pain	1 (20.0)	1 (25.0)	1 (25.0)	1 (33.3)	1 (12.5)	1 (11.1)	4 (30.8)	2 (18.2)	12 (21.1)
Back pain	1 (20.0)	2 (50.0)	0	0	1 (12.5)	2 (22.2)	1 (7.7)	1 (9.1)	8 (14.0)
Dyspnoea	1 (20.0)	0	2 (50.0)	0	1 (12.5)	1 (11.1)	1 (7.7)	2 (18.2)	8 (14.0)
Arthralgia	0	1 (25.0)	1 (25.0)	0	2 (25.0)	1 (11.1)	2 (15.4)	0	7 (12.3)
Asthenia	1 (20.0)	1 (25.0)	0	1 (33.3)	0	1 (11.1)	0	3 (27.3)	7 (12.3)
Pyrexia	1 (20.0)	1(25)	0	0	1 (12.5)	0	2 (15.4)	2 (18.2)	7 (12.3)
Abdominal pain upper	0	0	0	0	0	0	4 (30.8)	2 (18.2)	6 (10.5)
Constipation	0	0	1 (25.0)	1 (33.3)	0	0	1 (7.7)	3 (27.3)	6 (10.5)
Headache	2 (40.0)	0	0	0	1 (12.5)	1 (11.1)	2 (15.4)	0	6 (10.5)
Lymphopenia	1 (20.0)	2 (50.0)	1 (25.0)	1 (33.3)	0	0	1 (7.7)	0	6 (10.5)

Serious Adverse Events and Deaths

Four patients died within 28 days after the last dose of the study drug: 2.5 mg one patient, 40 mg one patient, 100 mg one patient, and 125 mg one patient. All the deaths were due to disease progression and not suspected to be related to study drug. No patient died while on BGT226 treatment.

Ten patients (17.5%) experienced a SAE. Three events (diarrhea, nausea, and vomiting) in one patient, were considered by the investigator to be related to BGT226. The other SAEs were considered to be not study drug related as per investigator.

Deaths, other serious or clinically significant adverse events or related discontinuations (Safety analysis set)

	2.5 mg	5 mg	10 mg	20 mg	40 mg	80 mg	100 mg	125 mg	All patients
	N=5	N=4	N=4	N=3	N=8	N=9	N=13	N=11	N=57
Death	1 (20.0)	0	0	0	1 (12.5)	0	1 (7.7)	1 (9.1)	4 (7.0)
SAE(s)	2 (40.0)	0	1 (25.0)	0	1 (12.5)	1 (11.1)	2 (15.4)	3 (27.3)	10 (17.5)
DLT(s)	0	0	0	0	0	0	0	3 (27.3)	3 (5.3)
Nausea	0	0	0	0	0	0	0	0	0
Vomiting	0	0	0	0	0	0	0	2 (18.2)	2 (3.5)
Diarrhea	0	0	0	0	0	0	0	2 (18.2)	2 (3.5)
Discontin-ued due to SAE(s)	0	0	0	0	0	1 (11.1)	0	1 (9.1)	2 (3.5)
Discontin-ued due to DLT(s)	0	0	0	0	0	0	0	1 (9.1)	1 (1.8)

Other Relevant Findings

BGT226 was rapidly absorbed after oral administration, with mean peak plasma levels (Cmax) occurring at 1 to 4 hours post dose. Cmax was found to be in the lower nanogram range. Also, overall drug exposure over a dosing interval (AUC0-48) was found to be low, even at the higher doses tested. There was no significant drug accumulation of BGT226 in plasma upon repetitive dosing on a once-a-day 3-times weekly dosing schedule.

At doses higher than 80 mg significant inhibition of the PI3K pathway could be shown as determined by post-treatment measurement of pS6 levels in the skin of patients. Available data from tumor samples of patients (from six patients in doses up to 40mg) suggested that BGT226 treatment may also inhibit the PI3K pathway in patient tumors. The pharmacodynamic changes were however overall inconsistent.

No correlation seemed to exist between tumor metabolic response in FDG-PET and efficacy response in CT. No conclusions could be drawn from the available DCE-MRI data.

Date of Clinical Trial Report 01 Oct 2010
Date Inclusion on Novartis Clinical Trial Results Database 10 Nov 2010
Date of Latest Update