

TYPE OF CANCER: Advanced Solid Malignancies
including Advanced Breast Cancer
TYPE OF TRIAL: Phase I/II
TRIAL SPONSOR: Novartis

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STUDY SUMMARY

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

TREATMENT OVERVIEW

- Each cycle is 28 days long
- Patients should be seen by the physician weekly in the first 2 months, then biweekly
- Patients may continue to participate in the study unless they experience unacceptable toxicity or disease progression.

PRE-TREATMENT ASSESSMENTS

- WHO Performance Status
- Chest X-Ray
- Fasting Insulin & C-peptide
- 2-hr 75-g OGTT
- ECG
- FDG-PET
- Skin Biopsy
- Informed Consent
- Demography
- Inclusion/Exclusion Criteria
- Relevant Medical History/Current Medical Conditions
- Diagnosis and extent of cancer
- Prior antineoplastic therapy
- Height
- Weight
- Vital Signs
- Physical Exam (including skin rash)
- Eye Exams (ERG)
- Hematology
- Coagulation
- Biochemistry
- Fasting Plasma Glucose

- Urine dipstick test for glucose monitoring
- Hemoglobin A1C & fructosamine
- Urinalysis and 24-Hour urine collection (if clinically indicated)
- Serum Pregnancy Test for WCBP
- Cardiac Imaging
- Prior and concomitant medications
- Adverse Events
- Response assessments (CT or MRI)
- Skin assessments for CS patients only (by photographic documentation with ruler)
- Blood for CTCs
- Blood for plasma angiogenic biomarker analysis
- Blood for retrospective germline mutational analysis of the PTEN gene
- Pharmacogenetic blood sample (optional)
- Fresh (on-study) tumor biopsy for pharmacodynamic, mutational and exploratory biomarker analysis (if available)

ENTRANCE CRITERIA FOR PARTICIPATION IN TRIAL

INCLUSION CRITERIA

1. [Dose-escalation part]:

Patients with histologically-confirmed, advanced solid tumors including CS patients with solid tumors, whose disease has progressed despite standard therapy (or who are intolerant of such therapy) or for whom no standard therapy exists.

[Dose-expansion part]:

- MTD dose-expansion arm:

with histologically-confirmed, advanced solid tumors, including CS patients with solid tumors, whose disease has progressed despite standard therapy (or who are intolerant of such therapy) or for whom no standard therapy exists

- Breast Cancer dose-expansion arms Arm A (ER-positive and/or PR-positive advanced BC) Female patients with histologically confirmed, hormone receptor-positive (ER positive and/or PR positive), unresectable, locally advanced or metastatic breast cancer whose disease has progressed on the standard sequence lines of endocrine therapy.
 - Patients with pre- or perimenopausal hormonal status should have received either aromatase inhibitor with LHRH agonists or SERMs/SERDs with or without an LHRH agonist
 - Patients with postmenopausal hormonal status should have received an aromatase inhibitor and SERMs or SERDs.

Patients must have progressed on at least 1 line of hormonal therapy for advanced disease and received at least 1 but not more than 2 lines of chemotherapy. Patients must be progressing on the last line of therapy received prior to study entry.

Arm B [HER2-positive advanced BC]:

Female patients with histologically confirmed HER2 positive (including patients who are hormone receptor positive) unresectable, locally advanced or metastatic breast cancer who have:

- Received at least 2 prior anti-HER2 containing regimens including trastuzumab and lapatinib. Patients who received adjuvant or neo-adjuvant trastuzumab are eligible. In these patients, they must have subsequently received a lapatinib containing regimen and progressed after their last anti-HER2-containing regimen as first or second line therapy for advanced disease.
- History of trastuzumab or lapatinib resistance, defined either local or systemic disease progression on treatment with at least 8 weeks of a trastuzumab or lapatinib containing regimens, whichever is the last regimen received.

Patients must have progressed on at least 1 line but not more than 2 lines of chemotherapy. Patients must be progressing on the last line of therapy received prior to study entry.

The analysis of the preliminary efficacy of BGT226 in arms A and B will follow a multinomial two-stage design.

Breast cancer patients who do not meet the criteria for Arms A and B will be included into the MTD dose-expansion arm provided that they meet eligibility criteria for this arm.

For the purpose of enrollment it is sufficient if the hormone receptor and HER2 expression status was assessed in an archival sample. In patients on the breast cancer dose-expansion arms from whom no historical data are available, the hormone receptor and HER2 expression status must be newly determined in tumor biopsies.

For the determination of the hormone receptor status, both IHC and biochemical measurement are acceptable.

The following rules should be used for the assessment of the HER2 expression status:

- IHC +++: IHC results, if obtained with standard IHC methods, is acceptable
- IHC++ or IHC+: Confirmation by FISH (Fluorescence in situ hybridization) is required. Tumors tested by FISH must be positive by the specific FISH assay for the amplification of HER2.

Cowden Syndrome patients with breast cancer, with a genetically confirmed and documented mutation of the susceptibility gene 10q22-23, will be included to Arm A or Arm B according to the hormone receptor positive or HER2-positive status. HER2+ and hormone receptor-positive patients should be included into the HER2+ arm provided that they meet other eligibility criteria.

2. [Dose-escalation part and MTD dose-expansion arm]: at least one measurable or non-measurable lesion as defined by RECIST criteria for solid tumors [Breast cancer dose-expansion arms]: patients must have at least one measurable lesion as defined by RECIST criteria (Post-text Supplement 1) for solid tumors.

3. Patients who fulfill the following criteria will be eligible for FDG-PET assessments:

- Indications: tumor types known to have a high FDG uptake, such as breast, lung, GIST, melanoma, colorectal, lymphoma.
- To be eligible for follow-up scans, at baseline patients should have uptake of the tracer in at least one lesion where the tumor-muscle ratio is >2 .
- Ability to lie still and flat on the PET table.

4. Patients who fulfill the following criteria will be eligible for DCE-MRI assessments:

- At least one liver lesion with a minimal diameter of 3.0 cm (in case a liver biopsy is performed, a second liver lesion is necessary for DCE-MRI assessment)
- Ferromagnetic metal implant approved as safe for use in MR scanner. Some types of aneurysm clips, shrapnel are not allowed, no pacemaker.
- Patient should fit into the machine (e.g patients with obesity or suffering from uncontrollable claustrophobia should not perform DCE-MRI assessments)

5. For patients on the breast cancer dose-expansion arms: Availability of an archival tumor sample. Patient who would have been eligible for the breast cancer dose-expansion arms,

MTD dose-expansion arm.

6. Age ≥ 18

7. World Health Organization (WHO) Performance Status of ≤ 2

8. Life expectancy of ≥ 12 weeks

9. Patients must have the following laboratory values:

- Absolute Neutrophil Count (ANC) $\geq 1.5 \times 10^9/L$
- Hemoglobin (Hgb) ≥ 9 g/dl
- Platelets (plt) $\geq 100 \times 10^9/L$
- Potassium within normal limits (WNL) or correctable with supplement to WNL prior to study treatment start
- Total calcium (corrected for serum albumin) within normal limits (WNL) or correctable with supplement to WNL prior to study treatment start
- Magnesium within normal limit (WNL) or correctable with supplement to WNL prior to study treatment start
- Phosphorus within normal limit (WNL) or correctable with supplement to WNL prior to study treatment start
- AST/SGOT and ALT/SGPT $\leq 2.5 \times$ Upper Limit of Normal (ULN) or $\leq 5.0 \times$ ULN if liver metastases are present
- Serum bilirubin $\leq 1.5 \times$ ULN
- Serum creatinine $\leq 1.5 \times$ ULN or 24-hour clearance ≥ 50 mL/min
- Serum amylase \leq ULN
- Serum lipase \leq ULN
- Urine amylase within normal limits in patients with serum triglycerides ≥ 500 mg/dL
- Adrenal function tests (basal serum cortisol, renin, DHEAS) within normal limit

- Negative serum pregnancy test within ≤ 72 hours before starting study treatment in all pre-menopausal women and women < 2 years after the onset of menopause.

10. Ability to sign informed consent and to comply with the protocol

EXCLUSION CRITERIA

1. 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
2. Prior treatment with a PI3K inhibitor
3. For patients on the breast cancer dose-expansion arms: Lytic bone metastasis if the sole lesion of the patient is a bone metastasis (patients has to have at least one measurable lesion according to RECIST criteria)
4. Acute or chronic liver disease or renal disease
5. Acute or chronic pancreatitis
6. Patients with any peripheral neuropathy \geq CTCAE grade 2
7. Patients with unresolved diarrhea \geq CTCAE grade 2
8. Any of the following concurrent severe and/or uncontrolled medical conditions which could compromise participation in the study:
 1. Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
 - LVEF $< 45\%$ as determined by MUGA scan or ECHO
 - ST depression or elevation of ≥ 1.5 mm in 2 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 > 460 msec on screening ECG

- Unstable angina pectoris \leq 3 months prior to starting study drug
 - Acute myocardial infarction \leq 3 months prior to starting study drug
 - Other clinically significant heart disease such as congestive heart failure requiring treatment or uncontrolled hypertension
2. Patients with diabetes mellitus or history of gestational diabetes mellitus or steroid-induced diabetes mellitus
 3. Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g. active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with the protocol
9. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of BGT226 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection). Patients with unresolved diarrhea will be excluded as previously indicated
 10. Patients who have been treated with any hematopoietic colony-stimulating growth factors (e.g., G-CSF, GM-CSF) \leq 2 weeks prior to starting study drug. Erythropoietin or darbepoetin therapy, if initiated before enrollment, may be continued
 11. Patients who are currently receiving treatment with medication that has the potential to prolong the QT interval or inducing Torsades de Pointes (Post-text Supplement 2), and the treatment cannot either be discontinued or switched to a different medication prior to starting study drug
 12. Patients who are currently receiving treatment with calcium channel blockers
 13. Patients who are currently receiving treatment with therapeutic doses of warfarin sodium (Coumadin®). Patients using medications known to be metabolized by CYP3A4/5, CYP 2D6 and P-gp will need special considerations (please refer to Post-text Supplement 2 and Section 6.6.4 for further details)
 14. Patients who have received chemotherapy, targeted therapy or immunotherapy \leq 4 weeks (6 weeks for nitrosourea, mitomycin-C, or monoclonal antibodies) prior to starting study drug or who have not recovered from side effects of such therapy

15. Patients who have received any continuous-dosing (i.e. daily dosing, every-other-day dosing, Monday-Wednesday-Friday dosing weekly etc) therapeutic modalities or investigational drug (excluding monoclonal antibodies) \leq 5 half lives prior to starting study drug or who have not recovered from side effects of such therapy
16. Patients who have received corticosteroids \leq 2 weeks prior to starting study drug or who have not recovered from the side effects of such treatment
17. Patients who have received wide field radiotherapy \leq 4 weeks or limited field radiation for palliation \leq 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy. For the breast cancer patients, the site of radiotherapy should not be the only site of measurable disease unless there is evidence of disease progression at this site prior to entry on this study
18. Patients who have undergone major surgery \leq 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy
19. Women of child-bearing potential who are pregnant or breast feeding or adults of reproductive potential not employing an effective method of birth control. Barrier contraceptives must be used throughout the trial in both sexes and one month after the end of treatment. Oral, implantable, or injectable contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective for this study (refer to Post-text Supplement 2 for a list of substrates of cytochrome P450 isoenzymes). Women of child-bearing potential, defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 24 consecutive months (i.e., who has had menses any time in the preceding 24 consecutive months), must have a negative serum pregnancy test \leq 72 hours prior to starting BGT226.
20. Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing is not mandatory)
21. Patients with a history of another primary malignancy that is currently clinically significant, has potential for metastases or currently requires active intervention.
22. Any progressive eye disease that could lead to severe loss of visual acuity or visual field loss during the study period.
23. Patients with thyroid disease requiring treatment