

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 BEZ235, administered orally on a continuous daily dosing schedule in adult patients with advanced solid malignancies including patients with advanced breast cancer

TREATMENT OVERVIEW

- Each cycle is 28 days long
- Patient should be seen by the physician at least every 2 weeks
- 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
- Bone Markers
- 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

[Dose escalation part and safety expansion arm]:

- Patients with histologically-confirmed, advanced unresectable solid tumors including CS patients who have progressed on (or not been able to tolerate) standard therapy or for whom no standard anticancer therapy exists.

[Efficacy expansion arm only]:

- Female patients with either hormone receptor positive (ER positive and/or PR positive) or HER2 positive advanced breast cancer (unresectable, locally advanced or metastatic).
- Patients with **hormone receptor positive** tumors must have progressed on the standard sequence lines of endocrine therapy for advanced (unresectable, locally advanced or metastatic) disease.
- Patients with **HER2 positive** tumors must have progressed on at least one anti-HER2 treatment for advanced (unresectable, locally advanced or metastatic) disease.
- **All breast cancer patients in the efficacy expansion arm** must have had at least 1 but not more than 2 prior lines of chemotherapy for advanced (unresectable, locally advanced or metastatic) disease.
- For the purpose of enrollment it is sufficient if the hormone receptor and HER2 expression status was assessed in an archival sample. In patients 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++: Confirmation by FISH needed
- IHC+: Confirmation by FISH needed if clinically patients were deemed to be HER2 dependent and were treated accordingly.

[Dose escalation and safety expansion arm]:

- at least one measurable or non-measurable lesion as defined by RECIST criteria for solid tumors

[Efficacy expansion arm only]:

- patients must have at least one measurable lesion as defined by RECIST criteria

[Dose escalation, safety and efficacy expansion arms]:

- Patients with Cowden Syndrome with a genetically confirmed and documented mutation of the susceptibility gene 10q22-23.
- Patients who fulfill the following criteria will be eligible for PET assessments:
 - Indications: tumor types known to have a high FDG uptake, such as breast, lung, GIST, melanoma, colorectal, lymphoma
 - At least one lesion must be measurable (>2cm)
 - To be eligible for follow-up scans, patients should have uptake of the tracer in at least one lesion where the tumor-muscle ratio is >2.
 - Able to lie still and flat on the PET table.
- Availability of a representative tumor tissue specimen. Archival tumor tissue is allowed.
- World Health Organization (WHO) Performance Status of ≤ 2
- Life expectancy of ≥ 12 weeks
- Patients must have the following laboratory values:
 - Absolute Europhile 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 or correctable with supplements
 - Total calcium (corrected for serum albumin) within normal limits or correctable with supplements
 - Magnesium \geq the lower limit of normal or correctable with supplements
 - Phosphorus \geq the lower limit of normal or correctable with supplements
 - 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
 - Amylase $< 1.5 \times$ ULN
 - Lipase $< 1.5 \times$ ULN
 - Fasting plasma glucose < 100 mg/dL (5.56 mmol/L)
 - 2 hour plasma glucose < 140 mg/dL (7.78 mmol/L) during a 75-g OGTT

- Hemoglobin A1C < 5.8%
- Negative serum pregnancy test within 48 hours before starting study treatment in women with childbearing potential

EXCLUSION CRITERIA

- Patients with a history of 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
- Fulminant disease
- Prior treatment with a PI3K inhibitor
- Lytic bone metastasis if the sole lesion of the patient is a bone metastasis
- Acute or chronic liver disease or renal disease
- Acute or chronic pancreatitis
- Patients with any peripheral neuropathy \geq CTCAE grade 2
- Patients with unresolved diarrhea \geq CTCAE grade 2
- Any of the following concurrent severe and/or uncontrolled medical conditions which could compromise participation in the study:
 - Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
 - LVEF < 45% as determined by MUGA scan or ECHO
 - Complete left bundle branch block
 - ST depression or elevation of \geq 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
 - Right bundle branch block + left anterior hemiblock (bifascicular block)
 - 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
 - Patients with diabetes mellitus, history of gestational diabetes mellitus
 - 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
- Patients with a history of photosensitivity reactions to other drugs
- Any of the following ophthalmological findings:
 - Patients with significant retinal disease. Mild retinal pigment epithelial changes are allowed but must be well documented in progress notes.
 - Any media opacity that prevents adequate examination of the fundus due to corneal, lenticular or vitreal changes

- Inability to perform the ophthalmic procedures required in this protocol
- Patients with moderate to severe posterior pole disease except if they have a normal Amsler grid
- Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity of worse than 1.0
- Any abnormality preventing reliable applanation tonometry in study eye(s)
- Severe previous visual acuity or field loss due to any cause
- Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of BEZ235 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection). Patients with unresolved diarrhea will be excluded as previously indicated
- Patients who have been treated with any hematopoietic colony stimulating growth factors (e.g. G-CSF, GM-CSF, erythropoietin) \leq 2 weeks prior to starting study drug
- 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
- Patients who are currently receiving treatment with calcium channel blockers
- Patients who are currently receiving treatment with therapeutic doses of warfarin sodium (Coumadin®)
- 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
- Patients who have 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) \leq 5 half lives prior to starting study drug or who have not recovered from side effects of such therapy
- 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
- 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 expansion stages in breast cancer, 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
- 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

- Women of childbearing 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. 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 childbearing potential, defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months), must have a negative serum pregnancy test \leq 48 hours prior to starting BEZ235.
- Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing is not mandatory)
- Patients with a history of another primary malignancy that is currently clinically significant, has potential for metastases or currently requires active intervention