

**TYPE OF CANCER:** Advanced Solid Malignancies  
**TYPE OF TRIAL:** Phase I  
**TRIAL SPONSOR:** Novartis

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### **STUDY SUMMARY**

A phase I dose escalation, multi-center, open-label study of AUY922 administered IV on a once-weekly schedule in adult patients with advanced solid malignancies including phase II expansion arms in patients with either HER2 positive or ER positive locally advanced or metastatic breast cancer

### **TREATMENT OVERVIEW**

- Each cycle is 28 days long
- AUY922 will be administered IV over 1 hour once every week
- Patients may continue to participate in the study unless they experience unacceptable toxicity or disease progression

### **PRETREATMENT ASSESMENT**

- Informed consent
- Demographics
- Inclusion/Exclusion Criteria
- Relevant medical history/ current medical conditions
- Diagnosis and extent of tumor
- Prior antineoplastic therapies
- Vital signs (weight, height, Performance status)
- Physical Examination
- Chest x-ray
- 12-lead ECG
- Cardiac imaging
- Hematology
- Coagulation
- Biochemistry
- Cardiac enzymes
- Urinalysis
- Radiological assessment of tumor
- FDG PET imaging
- FLT PET imaging
- Blood biomarkers
- Tumor biopsy
- Blood for metabolism genetics

## **ENTRANCE CRITERIA FOR PARTICIPATION IN TRIAL**

### *Inclusion Criteria*

1. Dose-escalation and MTD dose expansion arm: Patients with histologically confirmed, advanced malignant solid tumors whose disease has progressed on standard therapy or for whom no standard therapy exists.

Breast cancer phase II expansion arms only

a. Female patients with ER positive HER2 positive non-operable locally advanced or metastatic breast cancer must have:

- History of trastuzumab resistance, defined as either local or systemic disease progression on treatment with at least 8 weeks of a trastuzumab containing regimen.

- Received at least 1 but no more than 2 prior anti HER2 based regimens including at least 1 regimen containing trastuzumab. (Patients who develop metastases while receiving adjuvant or neo-adjuvant trastuzumab are eligible).

HER2 positive patients, tumor/s must demonstrate HER2 over-expression based on either:

- Immunohistochemistry (IHC) at the 3+ level, or

- IHC 2+ confirmed by fluorescence in-situ hybridization (FISH). Tumors tested by FISH must be positive by the specific FISH assay for the amplification of HER2.

b. Female patients with ER positive non-operable locally advanced or metastatic breast cancer who received standard sequence lines of endocrine therapy and whose disease has progressed on at least one line of endocrine therapy for advanced disease.

c. All patients with locally advanced or metastatic breast cancer (HER2+ or ER+) must have progression of the disease on at least 1 but no more than 2 lines of chemotherapy.

2. All patients must have at least one measurable lesion as defined by RECIST. Irradiated lesions are only evaluable for disease progression.

3. All patients must have progressive disease before entering to the study.

4. Patients who fulfill the following criteria will be eligible for PET assessments:

Indications: tumor types expected to have a high FDG uptake, such as breast, lung, GIST, melanoma & colorectal cancer.

- 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 with a tumor-muscle ratio  $\geq 2$ .

- Able to lie still and flat on the PET table.

5. Age  $\geq 18$  years.

6. World Health Organization (WHO) Performance Status of  $\leq 2$ .

7. Life expectancy of  $\geq 12$  weeks.

8. Patients must have the following laboratory values:

- Absolute Neutrophil Count (ANC)  $\geq 1.5 \times 10^9/L$

- Hemoglobin (Hgb)  $\geq 9$  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 within normal limits or correctable with supplements
  - Phosphorus within normal limits 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 albumin  $\geq 2.5g/dl$
  - Serum creatinine  $\leq 1.5 \times$  ULN or 24-hour clearance  $\geq 50$  ml/min
  - Negative serum pregnancy test. The serum pregnancy test must be conducted prior to the first administration of AUY922 ( $\leq 72$  hours prior to dosing) in all premenopausal women and women  $< 2$  years after the onset of menopause.
9. Able to sign informed consent and to comply with the protocol.

#### *Exclusion Criteria*

1. Patients with known CNS metastasis. Note: patients without clinical signs or symptoms of CNS involvement are not required to have a CT/MRI of the brain.
2. Prior treatment with any HSP90 or HDAC inhibitor compound.
3. Patient who received systemic anti-cancer treatment prior to the first dose of AUY922 within the following time frames:
  - Radiotherapy within 4 weeks
  - Palliative radiotherapy: within 2 weeks
  - Nitrosoureas, mitomycin and monoclonal antibodies, such as trastuzumab: within 6 weeks
  - Any continuous-dosing (i.e. daily dosing, every-other-day dosing, Monday-Wednesday- Friday dosing, weekly etc) of systemic anticancer treatment for which the recovery period is not known, or investigational drugs (i.e. targeted agents) within a duration of  $\leq 5$  half lives of the agent and their active metabolites (if any)
4. Patients who have recovered from side effects of previous systemic anticancer therapy to less than grade 2 CTCAE prior to the first dose of study treatment
5. Treatment with therapeutic doses of sodium warfarin (Coumadin). Low doses of Coumadin (e.g.  $\leq 2mg/day$  for line patency) are permitted.
6. Patients using medications that are substrates, inhibitors or inducers of CYP3A4, CYP2C8, CYP2C9 and CYP2C19 and cannot be switched or discontinued to an alternative drug prior to commencing AUY922 dosing need special consideration (please refer to Post-text supplement 2 and see Section 6.6.7 for further details).
7. Unresolved diarrhea  $\geq$  CTCAE grade 2.
8. Patients who do not have either an archival tumor sample available or are unwilling to have a fresh tumor sample collected at baseline.
9. Pregnant or lactating women.
10. Fertile women of childbearing potential (WCBP) not using adequate contraception (abstinence, oral contraceptives, intrauterine device or barrier

method of contraception in conjunction with spermicidal jelly or surgically sterile). Male patients whose partners are WCBP, not using adequate contraception.

11. Acute or chronic liver disease.

12. Acute or chronic renal disease.

13. Other concurrent severe and/or uncontrolled medical conditions (e.g. uncontrolled diabetes, active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with the protocol.

14. Cardiac exclusion criteria:

- History (or family history) of long QT syndrome.
- Mean QTc  $\geq$  450 msec on screening ECG.
- History of clinically manifest ischemic heart disease including myocardial infarction, stable or unstable angina, coronary arteriography or cardiac stress testing/imaging with findings consistent with coronary occlusion or infarction,  $\leq$  6 months prior to study start.
- History of heart failure or left ventricular (LV) dysfunction (LVEF  $\leq$  45%) by MUGA or ECHO.
- Clinically significant ECG abnormalities including one or more of the following: left bundle branch block (LBBB), right bundle branch block (RBBB) with left anterior hemiblock (LAHB). ST segment elevations or depressions  $>$  1mm, or 2nd (Mobitz II) or 3rd degree AV block.
- History of atrial fibrillation, atrial flutter or ventricular arrhythmias including ventricular tachycardia or Torsades de Pointes.
- Other clinically significant heart disease (e.g. congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen).
- Clinically significant resting bradycardia ( $<$  50 beats per minute).
- Patients who are currently receiving treatment with any medication which has a relative risk or prolonging the QTcF interval or inducing Torsades de Pointes (as listed in Post-text supplement 2) and cannot be switched or discontinued to an alternative drug prior to commencing AUY922 dosing.
- Obligate use of a cardiac pacemaker.

15. Known diagnosis of HIV infection (HIV testing is not mandatory).

16. Patients with known disorders due to a deficiency in bilirubin glucuronidation (e.g Gilbert's syndrome).

17. Patients with a history of another primary malignancy that is currently clinically significant or currently requires active intervention.

18. Patients unwilling or unable to comply with the protocol.