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.

Published: 24-09-2008
Last updated: 06-05-2024

Primary objective (dose escalation arm): To determine the MTD of AUY922 as a single agent.Primary objective (phase II): At the MTD two further arms will be expanded to assess response (breast cancer)

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON32784

Source
ToetsingOnline

Brief title
AUY922 in solid tumors and HER2+ or ER+ Metastatic Breast Cancer.

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Solid tumors and metastatic breastcancer

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma

Intervention

Keyword: AUY922, ER-positive, HER2- positive, metastatic breastcancer

Outcome measures

Primary outcome

Phase I: to determine the MTD of AUY922 as a single agent, administered once weekly. Estimation of the MTD will be based upon the estimation of the probability of DLT in cycle 1.

Phase II only (breast cancer)

Efficacy: responders (CR/PR), non-responders with stable disease for at least 6 months (SD * 6 months), progressive disease within 6 months from study start or others

Secondary outcome

* Safety: Type, frequency and severity of adverse events (CTCAE Version 3.0)

* Efficacy: In the dose-escalation arm response will be also assessed by RECIST.

* PK: Cmax, Tmax, AUC0-24 and AUC0-T

* PD: PET response, blood and tumor biomarkers at baseline and post-AUY922 dosing.

Study description

Background summary

AUY922 is a Heat shock protein (HSP) inhibitor. Heat shock proteins (HSP) are molecular chaperones that assist in the structural formation and folding of a wide variety of client proteins such as HER2 and ER. HSP90 is the most abundant molecular chaperone and is essential for cell survival.
AUY922 is an isoxazole that competitively inhibits the ATPase activity of HSP90. In doing so, the client proteins of HSP90 begin to undergo cellular degradation and the regulation of cell survival, proliferation and apoptosis are therefore affected. HSP90 is an important target for cancer chemotherapeutics because tumor cells, especially those with mutations, exist in a stressful environment and depend on HSP90 to grow and survive. For this reason, HSP90 inhibitors such as AUY922 are considered to be agents with significant therapeutic potential in a wide variety of tumor types.

Study objective

Primary objective (dose escalation arm): To determine the MTD of AUY922 as a single agent.

Primary objective (phase II): At the MTD two further arms will be expanded to assess response (breast cancer)

Study design

The study is designed as a phase I/II trial. During the phase I dose escalation component,
patients with advanced solid malignancies will be enrolled into cohorts to establish the MTD.
An adaptive Bayesian logistic regression model for dose escalation will guide the phase I dose escalation component to determine the MTD. Once the MTD has been confirmed, the cohort will be expanded to become the MTD expansion arm of the trial enrolling a total of 22 patients (advanced solid tumors) for safety and tolerability including patients from the MTD cohort.
The phase II component can start in parallel to the MTD expansion arm it will enroll only patients with locally advanced or metastatic breast cancer at the MTD and will have two arms: one for patients with HER2 positive disease and the other for those with ER positive disease.

Intervention

AUY922 administered intravenously, once weekly as single agent.

Study burden and risks

Side effects of AUY922.
The risks of taking blood and an intravenous catheter.
Risks of a tumor biopsy depend on the area of the biopsy.
Radiation exposure of CT-scan). The exposure to radiation in these scans is within the standard limits in this country.

Contacts

Public
Novartis

Raapopseweg 1
6824 DP Arnhem
NL
Scientific
Novartis

Raapopseweg 1
6824 DP Arnhem
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Breast cancer phase II expansion arms only
1a. Female patients with ER positive HER2 positive locally advanced non-operable metastatic

breast cancer with history of trastuzumab resistance
1b. Female patients with ER positive non-operable locally advanced or metastatic breast cancer who received endocrine therapy and whose disease has
progressed on at least one line of endocrine therapy for advanced disease.
2. At least one measurable lesion as defined by RECIST.
3. All patients must have progressive disease before entering to the study.
4. (WHO) Performance Status of * 2.
5. Life expectancy of * 12 weeks.
6. Patients must have the following laboratory values:
* Absolute Neutrophil Count (ANC) * 1.5 x 109/L
* Hemoglobin (Hgb) * 9 g/dl
* Platelets (plt) * 100 x 109/L
* Potassium, calcium, magnesium and phosphorus within normal limits or correctable with supplements
* Liverfunctiontests * 2.5 x Upper Limit of Normal (ULN) or * 5.0 x ULN if liver metastases are present
* bilirubin and creatinin * 1.5 x ULN or 24-hour clearance * 50 ml/min
* albumin * 2.5g/dl

Exclusion criteria

Main Exclusion criteria
1. CNS metastasis.
2. Prior treatment with any HSP90 or HDAC inhibitor compound.
3a. Radiotherapy within 4 weeks or palliative radiotherapy within 2 weeks
3b. Nitrosoureas, mitomycin and monoclonal antibodies, such as trastuzumab: within 6 weeks
3c. Systemic anticancer treatment for which the recovery period
is not known, or investigational drugs within a duration of * 5 half lives of the agent and their active metabolites (if any)
4. Patients who have not recovered from side effects of previous systemic anticancer therapy to less than grade 2 prior to the first dose of study treatment
5. Treatment with therapeutic doses of sodium warfarin (Coumadin). Low doses of Coumadin (e.g. * 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
7. Unresolved diarrhea * 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. Acute or chronic liver disease.
10. Acute or chronic renal disease.
11. Other concurrent severe and/or uncontrolled medical conditions
12. Clinical significant cardiac disease e.g:
* History of long QT syndrome or Mean QTc * 450 msec
* History of clinically manifest ischemic heart disease * 6 months prior to

study start.
* History of heart failure or left ventricular (LV) dysfunction (LVEF * 45%) by MUGA or ECHO.
* Clinically significant ECG abnormalities
* History of atrial fibrillation, atrial flutter or ventricular arrhythmias
* Clinically significant resting bradycardia (< 50 beats per minute).
* Any medication which has a relative risk or prolonging the QTcF interval or inducing Torsades de Pointes
* Pacemaker.
13. Patients with known disorders due to a deficiency in bilirubin glucuronidation
14. Patients with a history of another primary malignancy that is currently clinically significant or currently requires active intervention.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-12-2008
Enrollment:	11
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Geen
Generic name:	Geen

Ethics review

Approved WMO Date:	24-09-2008
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-10-2008
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-02-2009
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-07-2009
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-10-2009
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-10-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-10-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-09-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-10-2011

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-11-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2006-0027660-2-NL
ClinicalTrials.gov	NCT00526045AphaseIdoseescalation,multi-center,open-labelstudyof
CCMO	NL24551.042.08