

Imaging the effect of HSP90 inhibitor AUY922 on VEGF by means of 89Zr-bevacizumab PET. A side study to the phase I-II study with AUY922 in adult patients with advanced solid malignancies, or either HER2 or ER positive locally advanced or metastatic breast cancer: protocol CAUY922A2101.

Published: 29-07-2009

Last updated: 06-05-2024

To evaluate the effect of HSP90 inhibition by AUY922 on VEGF by means of 89Zr-bevacizumab PET. Primary endpoint: measurement of decreased VEGF compared to baseline. A decline is defined as a decrease of at least 30% in mean Standardized Uptake Value...

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

Summary

ID

NL-OMON33855

Source

ToetsingOnline

Brief title

89Zr-bevacizumab PET for imaging the effect of HSP90 inhibition

Condition

- Breast neoplasms malignant and unspecified (incl nipple)
- Breast disorders

Synonym

breast cancer, mammary carcinoma

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: Ministerie van OC&W, Novartis

Intervention

Keyword: bevacizumab, breast cancer, heat shock protein, PET imaging

Outcome measures**Primary outcome**

Measurement of decreased VEGF-levels compared to baseline, as a reflection of response to HSP90 inhibitor AUY922. A decline is defined as at least a 30% decrease of the mean SUV in a maximum of three lesions. These lesions will have a size of at least 2 cm (on the baseline CT), and will show the highest uptake on baseline 89Zr-bevacizumab scan (on which they are predefined).

Secondary outcome

Not applicable.

Study description**Background summary**

Angiogenesis, the formation of new blood vessels is a critical factor involved in the development and growth of tumors. New vasculature supplies the tumor with nutrients and oxygen, regulates disposal of metabolic waste products and provides route for metastatic spreading. An important factor involved in angiogenesis is vascular endothelial growth factor (VEGF). The VEGF production by tumor cells is thought to be regulated by hypoxemia, cytokines and cell differentiation. Over-expression of VEGF leading to angiogenesis, occurs in

many human tumor types, including breast cancer. Therefore, targeting angiogenesis is a rational approach in many cancer types. Inhibition of Heat Shock Protein (HSP) 90, is one way of achieving this. HSP90 is a molecular chaperone, involved in maintaining the conformation, stability, cellular localization and activity of several key oncogenic client proteins. It plays a central role in the basic power of cancer cells to adapt to various forms of stress. Client proteins of HSP90 include the regulator of VEGF expression hypoxia-inducible factor 1 α (HIF-1 α), HER2, hormone receptors, AKT, mutant p53, and so forth. HSP90 is constitutively expressed to 2- to 10-fold higher levels in cancer cells compared to their normal counterparts. Furthermore, HSP90 in tumor cells is present in active multi-chaperone complexes, conferring relative sensitivity to treatment with HSP90 inhibitors. Targeting multiple survival pathways by means of HSP90 inhibition may contribute to circumvention of resistance in cancer cells, to chemotherapeutics but also to trastuzumab and hormonal therapy. This has already been shown in a recent study, in which HSP90 inhibitor 17-allylamino-17-demethoxy-geldanamycin (17-AAG) was combined with trastuzumab in trastuzumab refractory patients. Tumor regression was reported in 4 of 25 of these heavily pre-treated patients.

HSP90 inhibition reduces angiogenesis by HIF-1 α inhibition and the consequent reduction of VEGF secretion. Decreased capillary density and vessel permeability was seen in xenograft models following HSP90 inhibitor AUY922. Moreover, a recent study demonstrated that the inhibition of HIF-1 α by means of HSP90 inhibitor 17-AAG, reduced VEGF secretion by 90% in a mouse model. These results demonstrate the potential to use local VEGF levels in the micro-environment of the tumor as a surrogate marker for early anti-angiogenic response on HSP90 treatment. Recently, measurement of these levels of VEGF in vivo was made possible in our institution. Bevacizumab, radiolabeled with ⁸⁹Zirconium (Zr) or ¹¹¹Indium (In), was used for VEGF visualization and quantification in a xenograft mouse model. Ex vivo biodistribution evaluation of the tracer showed tumor specific uptake, which could be measured quantitatively non-invasively. In a xenograft mouse model with a human ovarian A2780 tumor (which has a naturally high excretion of VEGF), we performed ⁸⁹Zr-bevacizumab imaging before and after intraperitoneal treatment with the HSP90 inhibitor AUY922. In vivo VEGF imaging demonstrated an impressive decrease (~70%) of VEGF levels in the tumor, as evaluated with ⁸⁹Zr-bevacizumab uptake. This demonstrates that VEGF is a rational read-out for HSP90 inhibition effect, and this response can be measured in vivo, by means of ⁸⁹Zr-bevacizumab imaging.

In conclusion, HSP90 inhibition is a new, promising treatment modality for cancer patients, particularly in the setting of resistance. A reliable read out system (biomarker) for the evaluation of early treatment effect is of great importance in the development of this treatment modality, and could contribute to customize this treatment for individual patients. So far, no reliable biomarker has been described for HSP90 effect. Visualizing the effect of HSP90 on VEGF secretion in vivo in the patient, by whole body ⁸⁹Zr-bevacizumab uptake, can be of great importance in this respect, and may contribute to

tailored made cancer treatment.

Study objective

To evaluate the effect of HSP90 inhibition by AUY922 on VEGF by means of ⁸⁹Zr-bevacizumab PET.

Primary endpoint: measurement of decreased VEGF compared to baseline. A decline is defined as a decrease of at least 30% in mean Standardized Uptake Value (SUV) in a maximum of three lesions.

Study design

This feasibility study is designed as a side study to the multicenter, international phase I-II trial with HSP90 inhibitor AUY922 (protocol CAUY922A2101), as part of the biomarker assessment. In protocol CAUY922A2101, section 4, the design of this phase I-II trial is described (p37, 38). Briefly, a dose-escalation study is performed according to phase I design in adult patients with advanced solid malignancies. This part is followed by a dose-expansion study according to a phase II design. In the latter part, breast cancer patients are enrolled that are either refractory to hormone- or trastuzumab treatment (both treatment arms, n=40 patients), on the maximal tolerated dose of AUY922 based on the phase I part of the study. Patients with ER positive, hormone therapy refractory breast cancer, will receive a ⁸⁹Zr-bevacizumab PET scan as part of the present side study protocol. To this end, a ⁸⁹Zr-bevacizumab PET scan will be performed before (baseline) and during treatment with HSP90 inhibitor AUY922.

A minimum of six and a maximum of 11 patients will be entered to evaluate whether the effect of HSP90 inhibition by AUY922 can be detected with a ⁸⁹Zr-bevacizumab PET scan (see statistical paragraph page 7).

Study burden and risks

In the present study, radioactive bevacizumab is used for PET scanning. The use of such a tracer means exposure to ionizing radiation. Twice, an infusion of radio active bevacizumab is administered: once before start of treatment and once during treatment with AUY922. The total additional radiation dose for the patient is 18 mSv at baseline, and 18 mSv at cyclus 1 (ICRP62, category III; comparable to 1,5 times a CT scan).

The tracer for this study is administered intravenously, which means an intravenous puncture. This puncture will be combined as much as possible with the punctures that are requested in the setting of the treatment with HSP90 inhibitor AUY922.

Contacts

Public

Universitair Medisch Centrum Groningen

Postbus 30.001
9700 RB Groningen
NL

Scientific

Universitair Medisch Centrum Groningen

Postbus 30.001
9700 RB Groningen
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

- patients with ER positive, hormone therapy refractory breast cancer
- participation in the phase I-II trial with HSP90 inhibitor AUY922 (in- and exclusion criteria for the study with AUY922 are described in protocol CAUY922A2101 -METc 2008.237-, section 5.1 and 5.2 (p 37-40).

Exclusion criteria

- no participation in the phase I-II trial with HSP90 inhibitor AUY922

Study design

Design

Study type: Observational non invasive

Masking: Open (masking not used)

Control: Uncontrolled

Primary purpose: Other

Recruitment

NL

Recruitment status: Recruitment stopped

Start date (anticipated): 08-02-2010

Enrollment: 11

Type: Actual

Ethics review

Approved WMO

Application type: First submission

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	EUCTR2008-005752-25-NL
CCMO	NL24929.042.08