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

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To show the effect of the HSP90 inhibitor AUY922 on HER2 expression by means of 89Zr-trastuzumab PET scanning. Primary endpoint: measurement of decreased HER2 expression compared to baseline. A decline is defined as a decrease of at least 30% in...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Endocrine neoplasms benign
Study type	Observational non invasive

Summary

ID

NL-OMON33851

Source
ToetsingOnline

Brief title
89Zr-trastuzumab PET for imaging the effect of HSP90 inhibition

Condition

- Endocrine neoplasms benign
- Breast disorders

Synonym

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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,Patienten krijgen AUY922 door deelname aan de CAUY922A2101 studie (METc 2008.237);van Novartis.

Intervention

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

Outcome measures

Primary outcome

Measurement of decreased HER2 expression 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-trastuzumab scan (on which they are predefined).

Secondary outcome

not applicable

Study description

Background summary

Heat Shock Protein (HSP) 90 is a molecular chaperone, required for stability and function of signalling proteins that promote cancer cell growth and survival. 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 human epidermal growth factor receptor 2 (HER2), the hormone receptors, angiogenesis regulator hypoxia-inducible factor 1α (HIF-1α), 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. Unlike in normal cells, 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 patients. Biomarkers for the early prediction of response are increasingly important, for allocation of the right treatment to individual cancer patients and to support drug development. No biomarker is yet available for the early prediction of response to HSP90 inhibitors. Measurement of client proteins in peripheral blood mononuclear cells and tumor biopsies have so far not yielded consistent results. In vivo imaging of the effect of HSP90 inhibition on the expression on client proteins, is of great interest in this setting. It allows whole body imaging of multiple tumor lesions in a non invasive way, and can be repeated serially. The effect of HSP90 inhibitor 17-AAG on client protein HER2 was previously visualized by means of HER2 PET imaging in a xenograft mouse model. In line with these experiments, we could demonstrate early response to treatment with the HSP90 inhibitor AUY922, using 89Zr-trastuzumab microPET/CT imaging in a HER2 overexpressing xenograft mouse model. Imaging of patients with HER2 positive breast cancer has already been performed in our institution, with the SPECT tracer 111Indium-trastuzumab. This approach resulted in the detection of more lesions than conventional staging techniques. Currently also HER2 imaging with 89Zr-trastuzumab is operational in our institution. We developed the PET radiopharmaceutical because it is particularly suitable for quantification of tracer uptake. Preclinical data showed specific uptake of this PET tracer in the tumor (confirmed with histology), with low background uptake. 89Zr-trastuzumab imaging in humans showed excellent sensitivity for tumor lesions detected with conventional CT.
For HER2 positive metastatic breast cancer patients, HSP90 inhibition can possibly form a targeted drug modality, in addition to HER2 based treatment (with trastuzumab and lapatinib). Serial HER2 imaging with a PET tracer for HER2 quantification might serve as an early predictive biomarker for the effect of HSP90 inhibition. This is also the case in patients who are refractory to HER2 based treatment, as the expression of HER2 in their tumors is preserved.
In the present study, we will evaluate whether 89Zr-trastuzumab PET imaging can be used to evaluate early respondse to HSP90 inhibitor AUY922 (see for further information on the treatment with AUY922: protocol CAUY922A2101).

Study objective

To show the effect of the HSP90 inhibitor AUY922 on HER2 expression by means of 89Zr-trastuzumab PET scanning.
Primary endpoint: measurement of decreased HER2 expression 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 study is designed as a side study to the multicenter, international phase I-II trial with the 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 (p36, 37). Briefly, a dose-escalation study is performed according to phase I design. 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). Patients with HER2 positive, trastuzumab (and lapatinib) refractory breast cancer, will receive a 89Zr-trastuzumab PET scan as part of the present side study protocol. To this end, a 89Zr-trastuzumab PET scan will be performed before (baseline) and during treatment with the HSP90 inhibitor AUY922. A minimum of six patients and a maximum of 11 pattients is needed to evaluate whether the 89Zr-trastuzumab PET scan can be used for the detection of a decrease of HER2 expression, induced by HSP90 inhibition (see statistical paragraph, see page 7).

Study burden and risks

In the present study, radioactive trastuzumab is used for PET scanning. The use of such a tracer means exposure to ionizing radiation. Twice, an infusion of radio active trastuzumab 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.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- patients with HER2 positive, trastuzumab (and lapatinib) refractory breast cancer
- participation in the phase I-II trial with HSP90 inhibitor AUY922 (in- and exclusion criteriafor this 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):	19-02-2010
Enrollment:	11
Type:	Actual

Ethics review

Approved WMO

Date:	21-06-2010
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	EUCTR2008-005751-26-NL
CCMO	NL24928.042.08