PHASE II STUDY OF LUTETIUM-177 LABELED CHIMERIC MONOCLONAL ANTIBODY cG250 (177Lu-DOTA-cG250) IN PATIENTS WITH ADVANCED RENAL CANCER

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Primary objective:- To determine the clinical efficacy of multiple doses of 177Lu-DOTA-cG250 at MTD in patients with advanced renal cancer using RECIST criteriaSecondary objectives:- To determine the toxicity of the treatment as defined by NCI...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON33866

Source
ToetsingOnline

Brief title
Phase 2 radioimmunotherapy in M+ RCC

Condition

- Renal and urinary tract neoplasms malignant and unspecified
- Renal disorders (excl nephropathies)

Synonym
kidney cancer, radioimmunotherapy

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: 177Lu-DOTA-cG250, Metastatic Renal Cell Carcinoma, Monoclonal Antibody cG250, Radioimmunotherapy

Outcome measures

Primary outcome

Determine the clinical efficacy of multiple doses of 177Lu-DOTA-cG250 at MTD in

patients with advanced renal cancer using RECIST criteria

Secondary outcome

Determine the toxicity of the treatment as defined by NCI Common Terminology

Criteria for Adverse Events (CTCAE v3.0)

Determine the targeting and dosimetry of 111In-DOTA-cG250 in patients with

advanced renal cancer, as a surrogate for 177Lu-DOTA-cG250

Study description

Background summary

Renal Cell Carcinoma (RCC) is the most common malignancy arising in the kidney. In the US alone, each year 51,000 people are diagnosed with RCC and 13,000 people die from the disease. Thirty percent of patients with RCC will present with metastatic disease, whereas of the other 70% treated by nephrectomy, 30-40% will eventually relapse (1). RCC is known as a chemotherapy and radiation resistant tumor (2;3). Treatment modalities for metastasized disease include immunotherapy with interferon-α and interleukin-2. Response rates, however, are low in the range of 5-25% and side-effects are significant (4;5). Recently, the use of angiogenesis inhibitors Sorafenib and Sunitinib have been introduced for treatment of this disease. And although response rates are high

(partial responses up to 30%), no patient thus far has been cured using these new substances and again, side-effects are common and often severe in nature (6;7). So although advances have been made in the management of metatastic RCC, there is still a need for a more effective treatment.
Chimeric monoclonal antibody (mAb) G250 (cG250) is a high-affinity (Ka = 4 x 109 M-1) chimeric, IgG1 mAb, reactive with carbonic anhydrase IX (8-10), a transmembraneous glycoprotein (11-13). Studies showed an almost ubiquitous expression (>90%) of G250-antigen in clear cell RCC (ccRCC), being the most prominent histologic type of RCC (80% of cases). Expression in normal tissues has been evaluated extensively and it has shown to be restricted to the gastrointestinal mucosa (stomach, ileum, proximal and middle colon) and gastrointestinal related structures (intra- and extrahepatic biliary system, pancreas) (10;14).
The chimeric form of the mAb was designed to allow multiple administrations, since the murine form of G250 induced Human Anti Mouse Antibodies (HAMA) in all patients even at very low protein doses (<1 mg) (8).
Various clinical studies have been performed with mAb cG250. In a protein dose-escalation study focal uptake of 131I-labeled cG250 in RCC lesions was found to be extremely high (up to 0.52 %ID/g) (8;15). In the subsequent activity dose-escalation study in progressive ccRCC patients with 131I-cG250 a Maximum Tolerated Dose (MTD) of 2220 MBq/m2 was found. In this study 12 patients with progressive metastatic disease were treated; in one patient stable disease was achieved and in another a partial response was noted (9). These findings led to a phase I/II study where patients were treated with 131I-cG250 at the MTD found in the previous study. After 3 months patients were retreated with 131I-cG250, the MTD of this 2nd injection was found to be 1665 MBq/m2 (=75% of the first dose). Although no objective responses were seen, stabilisation of previously progressive disease was noted in 4 of 16 (25%) patients treated at the optimal dose level (16).
In radioimmunotherapy (RIT) experiments in xenografted nude mice, tumor growth was delayed more effectively with 177Lu-cG250 (185 days) than with 131I-cG250 (25 days) (17). Moreover, an intrapatient comparison revealed higher uptake of cG250 labeled with the residualizing radionuclide 111In as compared to 131I-cG250 (18), indicating that higher radiation doses could be guided to tumor lesions when cG250 was labeled with a residualising radionuclide such as 177Lu or 90Y (17).

Study objective

Primary objective:
- To determine the clinical efficacy of multiple doses of 177Lu-DOTA-cG250 at MTD in patients with advanced renal cancer using RECIST criteria

Secondary objectives:
- To determine the toxicity of the treatment as defined by NCI Common Terminology Criteria for Adverse Events (CTCAE v3.0)
- To determine the targeting and dosimetry of 111In-DOTA-cG250 in patients with

advanced renal cancer, as a surrogate for 177Lu-DOTA-cG250
- To determine progression-free survival of study patients

Study design

This is a Phase II study using 177Lu-DOTA-cG250 for treatment of patients with advanced renal cell carcinoma. Patients will be treated at the previously determined MTD of 2405 MBq/m2 177Lu-DOTA-cG250. If patients respond to therapy (objective tumor response or stabilization of previously progressive disease) they are eligible for a maximum of three treatment cycles. The disease status of patients will be monitored during each cycle for 13 weeks with imaging, biochemical and hematologic tests. CT scans will be carried out at baseline and 12 weeks after each treatment, for response assessment.
For a detailed description see study protocol pages 5 and 6 or the study flow chart in the protocol.

Intervention

not applicable

Study burden and risks

Burden of the study per cyclus:
- Week 1: screening and injection 111In-cG250 (day 1) and 2 scans (day 2-4 and 5-7)
- Week 2: injection 177Lu-cG250 and subsequent hospital admission for 1 night only
- Week 3 until 8: Weekly visit UMCN for blood draw and physical examination
- Week 3 until 6: during fulminant hematological toxicity increased checks laboratory values
- Week 12: CT-scan
- Week 13: evaluation CT-scan and blood draw

Risks:
- First days post-injection 177Lu-cG250: fatigue, nausea and malaise (lasts on average 1 week and is ubiquitous)
- Week 3 until 6: Hematological toxicity, for which possible extra checks laboratory values (lasts on average 2 weeks and on this dose level in the phase I study no patients had to be admitted for transfusions)
- On multiple cycles with cG250 injections possible HACA formation, although no allergic reactions have been noted

Contacts

Public
Universitair Medisch Centrum Sint Radboud

Geert Grooteplein-Zuid 10
6525 GA Nijmegen
NL
Scientific
Universitair Medisch Centrum Sint Radboud

Geert Grooteplein-Zuid 10
6525 GA Nijmegen
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients with proven advanced and progressive renal cell carcinoma of the clear cell type
Performance status: Karnofsky > 70 %
Adequate bone marrow function
Age over 18 years

Exclusion criteria

Known metastases to the brain
Metastatic disease limited to the bone
Pre-exposure to murine/chimeric antibody
Chemotherapy, external beam radiation, immunotherapy or angiogenesis inhibitors within 4

weeks prior to study.
Life expectancy shorter than 6 months.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-08-2011
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Rencarex
Generic name:	cG250

Ethics review

Approved WMO Date:	04-01-2010
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-08-2010
Application type:	First submission

Review commission: CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2008-004548-35-NL
CCMO	NL25943.091.09