Synopsis acc ICH e3

Name of Sponsor/Company:

Radboud University Medical Centre

Name of Active Ingredient:

Girentuximab (cG250) labeled with 177 Lutetium

Title of Study:

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

Investigators:

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Study Locations:

Radboud UMC

Publication (reference):

https://pubmed.ncbi.nlm.nih.gov/26706103/

Study period (years):

Data of first enrollment:

1 August 2011

Date of end of trial:

3 August 2015

Phase of development:

Phase II

Objectives:

Primary objective of the trial was to determine the clinical efficacy of multiple doses of 177Lutetium-girentuximab (177Lu-cG250) at MTD in patients with advanced renal cancer using RECIST criteria.

Secondary objective was to assess the safety of treatment.

Methodology:

In total, 16 adult patients with metastatic clear cell renal cell carcinoma (ccRCC) were enrolled between August 2011 and April 2014 to participate in this Study if metastasis showed targeting of diagnostic imaging postinjection Indium 111 (111In)-girentuximab (185 MBq/10mg). After screening 2 patients were excluded from the study because known ccRCC lesions did not show any targeting at diagnostic imaging postinjection of indium 111 (111In)–girentuximab. 14 patients who showed targeting at scans postinjection of indium 111 (111In)–girentuximab were eligible for treatment with 177Lutetium-girentuximab.

Patients were eligible for a maximum of three treatment cycles with 177Lutetium-girentuximab if they did not show progressive disease (RECISTv1.1), had no grade 4 hematologic toxicities > 1wk and met the inclusion criteria prior to each cycle.

After treatment at each cycle patients were monitored for hematological toxicity and general toxicity during visits as follows, or more frequently:
- Wk 1: screening and injection 111In-cG250 (day 1) and 2 scans (day 2-4 and 5-7)
- Wk 2: injection 177Lu-cG250 and subsequent hospital admission for 1 night only
- Wk 3 until 8: Weekly visit UMCN for blood draw and physical exam.
- W 3 - 6: during fulminant hematological toxicity increased checks laboratory values
- Wk 12: CT-scan for evaluation of efficacy.
- Wk 13: blood draw and start of next cycle, if applicable.

Number of patients (planned and analyzed):

A Simon two-stage minimax design was used to calculate the no. of patients needed to reach a desirable response rate (RR) defined as at least Stable Disease (SD) by using RECIST v1.1. If RR >0.25 after the first cycle of treatment in the first 6 patients after 3 months, 14 patients had to be included. Desirable RR was set at 0.65 with alpha of 0.05 and beta of 0.10. Response was defined as at least SD on RECIST v1.1 evaluation after 3 months. After 6 patients RR was 0.5 so 14 patients were included.

Diagnosis and main criteria for inclusion:

Inclusion Criteria:
- Patients with proven advanced and progressive renal cell carcinoma of the clear cell type

- At least one evaluable lesion less than 5 cm
- Performance status: Karnowski > 70 %
- Laboratory values obtained less than 14 days prior to registration:
- White blood cells (WBC) > 3.5 x 109/l
- Platelet count > 100 x 109/l
- Hemoglobin > 6 mmol/l
- Total bilirubin < 2 x upper limit of normal (ULN)
- ASAT, ALAT < 3 x ULN (< 5 x ULN if liver metastases present)
- Serum creatinine < 2 x ULN
- Negative pregnancy test for women of childbearing potential (urine or serum)
- Age over 18 years
- Ability to provide written informed consent

Exclusion Criteria:
- Known metastases to the brain
- Untreated hypercalcemia
- 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. Limited field external beam radiotherapy to prevent pathological fractures is allowed,
when unirradiated, evaluable lesions elsewhere are present.
- Cardiac disease with New York Heart Association classification of III or IV
- Patients who are pregnant, nursing or of reproductive potential and are not practicing an effective
method of contraception
- Any unrelated illness, e.g. active infection, inflammation, medical condition or laboratory
abnormalities, which in the judgment of the investigator will significantly affect patients' clinical status
- Life expectancy shorter than 6 months.

Test product:

177Lutetium-girentuximab; other names: LUTETIUM-177 LABELED CHIMERIC MONOCLONAL ANTIBODYcG250; 177Lu-DOTA-cG250.

Dose:
In Cycle 1, 14 patients started treatment with 177Lutetium-cG250 at a dose level of 2405 MBq/m2.
In Cycle 2, 6 patients started treatment with 177Lutetium-cG250 at a dose level of 1805 MBq/m2.
None of the patients received Cycle 3.

Mode of administration: Intravenous use.

Duration of treatment: One single intravenous dosage per Cycle.

Reference therapy, dose and mode of admin: Not Applicable.

Criteria for evaluation:

Efficacy

Primary objective: To determine the clinical efficacy of multiple doses of 177Lutetium-girentuximab (177Lu-cG250) at MTD in patients with advanced renal cancer using RECIST v1.1 criteria.

Toxicity

Secondary objective: To determine the clinical toxicity of multiple doses of 177Lutetium-girentuximab (177Lu-cG250) at MTD in patients with advanced renal cancer.

Statistical Methods:

See above number of patients.

Summary – Conclusions:

Efficacy Results:

A total of 14 patients were treated with 177Lu-cG250 in Cycle 1. CT scans after 3 months showed that eight patients (57%) had stable disease (SD), five patients (36%) had progressive disease (PD) and one (7%) had a partial regression (PR).
Six of the nine patients with SD or PR were eligible to receive the second Cycle of treatment. The other 3 patients had to be excluded because of prolonged myelotoxicity. After the second cycle, continued SD was observed in four of six patients, one patient experienced PD and in one patient continued PR was observed, but none were eligible for retreatment due to prolonged thrombocytopenia.

Safety Results:

The treatment was generally well tolerated but resulted in grade 3–4 myelotoxicity in 13 of the 14 patients. The other patient developed grade 2 myelotoxicity. A total of 13 of 14 patients experienced mild (grade 1-2) general adverse events such as fatigue, anorexia, nausea, and diarrhea. Two patients had grade 3 general adverse events, 1 with fatigue and 1 with anorexia.

Conclusion:

In conclusion, radiotherapy with 177Lu-girentuximab resulted in disease stabilization in 9 of 14 patients with progressive metastatic ccRCC, but myelotoxicity prevented retreatment beyond the second cycle.
Further studies are warranted to evaluate if optimization of treatment e.g. by using personalized dosing, optimized combination with other treatment modalities or enhanced uptake of girentuximab in clear cell Renal Cell Carcinoma lesions with other drugs could help improving treatment strategies in Renal Cell Carcinoma lesions.

Date of report:

Aug 7th, 2024