A phase II trial with monoclonal antibody WX-G250 in advanced renal cell carcinoma

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Introduction

WX-G250 (cG250) is a IgG1 kappa light-chain chimeric monoclonal antibody that binds to a cell-surface antigen found on 95% of cells in clear cell renal cell carcinoma (RCC). The reactivity of cG250 with normal tissues is restricted to the gastric epithelium and the biliary ducts in the liver and in astrocytes in brain and spinal cord. Besides efficient biolocalization in RCC, it has been shown that cG250 can induce NK cells to kill tumor cells in vitro by antibody dependent cellular cytotoxicity (ADCC). In animals the murine G250 was effective in delaying growth of established grafted renal tumors.
A phase I dose escalation study with weekly administrations over 6-weeks per cycle has shown that the unconjugated antibody is safe at dose levels of 5, 10, 25 and 50 mg/m^2. In this study, patients received up to 9 cycles.
The current abstract describes results of a study conducted in advanced RCC patients treated with repeated doses of 50 mg cG250.

Study design

- Phase II, non-randomised, open-label, single arm, multicenter study
- Weekly doses of 50 mg over 12 weeks cG250, iv. administration by infusion over 30 min
- Possibility of extended treatment of another 8 weeks after the CT evaluation in week 16. For continuation patients needed to be objective responders or have stable disease
- Two stage design: part one with 32 evaluable patients, if at least 3 objective responses are seen, enrolment of another 22 patients

Objectives

- Primary objectives: objective tumor response, safety
- Secondary objectives: Immunogenicity (human anti-chimeric antibodies - HACA), biological activity (antibody dependent cellular cytotoxicity - ADCC)

Patient selection

INCLUSION CRITERIA

- Stage IV renal cell carcinoma, with documented clear cell histology, nephrectomized for primary tumor. Patient's status with respect to disease progression must be indicated at study entry. Patients with and without disease progression are eligible for enrolment
- Bidimensionally measurable disease with individual lesions < 5 cm in diameter with at least one lesion of ≥ 1 cm
- Karnofsky performance status ≥ 70 %
- Life expectancy > 28 weeks
- Laboratory values obtained ≤ 14 days prior to registration: Absolute neutrophil count (ANC) ≥ 2.0 x 10^9/d; Platelet count ≥ 100 x 10^9/dl; Hemoglobin > 6.5 mmol/ L (equals 10.5 g/dL); Total bilirubin < 1.5 x upper limit of normal (ULN); AST, ALT <3 x ULN (<5 x ULN if liver metastases present); Serum creatinine < 2x ULN

EXCLUSION CRITERIA

- Known standard therapy for the patients' disease that is potentially curative or definitely capable of extending life expectancy
- Any CNS metastases
- Patients with bone metastases only
- Pre-exposure to murine/chimeric antibody therapy
- Concurrent chemo-, immuno- or radiotherapy. Radiotherapy is permitted, if the tumor site is not foreseen for response assessment

Patient demographics

- 36 patients previously nephrectomized were enrolled, median age 64 years, 10 females, 26 males
- Thereof 14 patients were previously untreated for RCC and 22 patients were pretreated: 19 had received immuno-therapy, 2 prior radiation and one had been vaccinated with dendritic cells

Efficacy results

TUMOR RESPONSE

- 36 patients were enrolled of which 32 were evaluable, 4 discontinued within the first 4-5 weeks (1 due to protocol violation at inclusion, 3 with disease progression)
- Five patients initially progressive were stable after treatment and for over six months
- Two patients with progression at study entry showed tumor response with delayed onset after the end of the study: one complete response found in week 38 and one significant tumor reduction around 40% seen in week 44. Both patients had multiple pulmonary target lesions.

HACA

Patient's serum samples were taken weekly. Presence of human anti-chimeric antibodies (HACA) was tested using a sandwich-type ELISA with a linear dynamic range from 10-100 ng/ml (Limit of detection: 8.3 ng/ml, limit of quantification: 27 ng/ml). A HACA positive patient serum from a former study was used as a positive control.

- The ELISA gave no evidence for presence of HACA in any of the 36 patients.

ADCC

Immunophenotype and cytolytic activities of the peripheral blood mononuclear cells of 21 patients were analyzed and the proportion of NK-cells determined. To quantify the cG250-mediated ADCC on G250-positive RCC cells a ^{51}Cr release assay was performed. Positive and negative controls, as well as controls for LAK and NK-cytotoxicity were included.

- cG250 treatment had no effect on the proportion or activity of NK-cells in patient peripheral blood. One patient showed high levels of cG250-mediated ADCC which increased during treatment.
- The level of cG250-mediated ADCC was dependent on the individual patient: 42% of the patients had moderate to high ADCC whereas 33% showed no ADCC at all.
- There was no clear correlation between the proportion of NK-cells and the level of cG250-mediated ADCC.
- No correlation of levels of NK-cell related cytolytic activities and cG250 treatment results could be observed.

Safety results

- No patients with G250 related toxicity of grade 3 or 4
- One adverse event probably related to G250: nausea grade 1 for 2 days
- Refer to table below for toxicities (NCI-CTC) possibly related to cG250

	grade 1	grade 2	grade 3	grade 4
gastritis	----	1	----	----
vomiting	?	?	----	----
nausea	3	----	----	----
hypertension	2	----	----	----
hypotension	4	----	----	----
fatigue	2	----	----	----
mucositis	1	----	----	----

Conclusions

- Weekly administrations of 50 mg cG250 are safe and very well tolerated.
- Administrations of the antibody are non-immunogenic as no HACAs were detectable.
- WX-G250 showed anti-tumor activity with a delayed onset after the end of the study.
- No correlation between increased levels of NK-cell related cytolytic activities and cG250 treatment nor between the proportion of NK-cells and the level of cG250-mediated ADCC could be observed.

Future perspectives

Taking the above findings into account, a new study has been initiated investigating the combination of weekly administrations of 20 mg cG250 with low dose IL-2. At this non-toxic dose IL-2 is expected to increase the number and activity of NK cells. Another study recently started will evaluate the combination of 20 mg cG250 with low doses of Interferon alpha given three times a week.

Wilex

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