

Results of a phase I/II study with monoclonal antibody cG250 (Rencarex®) in combination with IFN α -2a in metastatic renal cell carcinoma patients



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Introduction

cG250 (Rencarex®) is a IgG1 kappa light-chain chimeric monoclonal antibody that binds to carbonic anhydrase IX (MN or G250 antigen), 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, murine G250 was effective in delaying growth of established xenograft renal tumors.

A phase II study with weekly administrations over 12 weeks in 32 metastatic RCC patients has shown that cG250 antibody alone is safe when given at a dose of 50 mg per week. Clinical benefit (objective responses (1) or stable disease (8) of at least six months) was seen in 9 of 32 patients (28%). Median survival time was 16 months.

In a further clinical phase II study cG250 was given weekly at 20 mg total dose in combination with low dose IL-2 for progressive patients. Of 30 evaluable patients, 3 patients achieved a partial remission and 4 patients a stable disease for almost six months. Clinical benefit was seen in 23%. Median survival time was 22 months.

The current abstract describes the study of a combination therapy trial of chimeric G250 with Interferon α -2a in metastatic RCC patients.

Study design

- Phase I/II, prospective, non-randomized, open-label, single arm, multi-center study
- Phase I part: 6 patients received cG250 once weekly i.v. (each infusion 20mg) and 3 MIU IFN- α three times a week s.c. In the first week of study treatment the patients received IFN- α alone in order to separately assess toxicity caused by IFN- α . The drug-related toxicity was assessed after 6 patients and found to be acceptable
- Phase II part: the 6 patients of the phase I part continued treatment for another 6 weeks (total treatment 12 weeks) and 25 additional patients (start of the phase II part) to a total number of 31 patients were enrolled for a 12 week treatment
- Patients showing response to tumor treatment at week 16, (objective response, stabilization of previously progressive disease, or progressive patients if further treatment was considered useful) were offered an additional treatment cycle of 6 weeks (18 weeks in total)

Patient selection

INCLUSION CRITERIA

- Stage IV renal cell carcinoma of documented clear cell histology, nephrectomized for primary tumor
- In progression at study entry
- Presence of pulmonary metastasis required for measurable disease. Metastases in any other organ except CNS may be present
- Bi-dimensionally measurable disease with individual lesions \leq 5 cm in diameter with at least one lesion of \geq 1 cm
- Karnofsky performance status \geq 80 %
- Life expectancy $>$ 26 weeks
- Laboratory values obtained \leq 14 days prior to registration: WBC \geq $3.0 \cdot 10^9$ /dl; Platelet count \geq $100 \cdot 10^9$ /dl; Hemoglobin \geq 6.2 mmol/L (equals 10 g/dl); Total bilirubin $<$ 1.5 x upper limit of normal (ULN); ASAT, ALAT \leq 3 x ULN (\leq 5 x ULN if liver metastases present); Serum creatinine \leq 2x ULN

EXCLUSION CRITERIA

- Known standard therapy for the patients' disease that is potentially curative or definitely capable of extending life expectancy
- Any metastatic lesion $>$ 5 cm in diameter
- Any CNS metastases
- Patients with bone metastases only
- Lymphangiosis carcinomatosa
- Pre-exposure to murine/chimeric antibody therapy
- IFN- α containing therapy within 3 months before first administration of study medication
- Any of the following within 4 weeks (6 weeks for mitomycin C or nitrosoureas) prior to the first dose of study agent: chemo-, immuno- or radiation therapy

Objectives

- Primary objectives: objective tumor response, toxicity
- Secondary objectives: immunogenicity (human anti-chimeric antibodies - HACA), biological activity (antibody dependent cellular cytotoxicity - ADCC), time to progression, overall survival

Dosing

	cG250 i.v.	IFN- α s.c.
Week 1	None	Day 1-3-5 (each 3 MIU)
Week 2-12	Day 1: 20 mg	Day 1-3-5 (each 3 MIU)
For all patients with extension of treatment		
Week 17-22	Day 1: 20 mg	Day 1-3-5 (each 3 MIU)

Results

TUMOR RESPONSE

For tumor response assessment, CT scans at baseline, week 16 and 22 were evaluated. Further CT scans were at three monthly intervals after end of treatment were evaluated in cases of clinical benefit (stable disease or objective response). All images were evaluated by an independent radiologist.

Twenty-six patients were assessable for response. Two patients showed a partial remission and 14 patients a stable disease in week 16. One patient experienced a PR for at least 8 months.

Nine patients remained with a long durable stabilization of their initially progressive disease: week 28, 34, 36, 37, 40, 41, 45, 47, 66+. Follow-up of response duration is still ongoing.

Clinical benefit, defined as objective response and SD \geq 24 weeks, was obtained in 11 patients (42%).

Median survival time has not been reached, as 18 patients are still alive. The data are too immature to assess effects on overall survival.

HACA

Patient's serum samples were taken at baseline and in weeks 2, 6, 10, 12 and 16. 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 cG250 study was used as a positive control.

None of the patient's sera tested showed any detectable HACA levels.

ADCC

Total blood count was stable in all of the investigated patients.

The level of ADCC was patient dependent and low in the majority of patients. A significant transient increase in ADCC activity was observed in a subgroup of patients without any evident correlation to e.g., clinical features. It is unclear whether the transient increase of ADCC activity was treatment related.

SAFETY

- Safety population consisted of 31 patients.
- Six serious adverse events were seen in 5 patients; none were related to treatment with the antibody cG250 but due to tumor progression.
- The main side effects observed were constitutional symptoms (77.4%) commonly associated with IFN administration (e.g. fever, chills, flu-like syndromes). These were CTC toxicity grade 1 or 2 and reversible.
- Almost 30% of all adverse events occurred in the first week of IFN- α dosing alone (52/183 AEs).
- The administration of the study medication had no notable effect on hematologic parameters.
- No allergic reactions were observed.

Conclusions

- Weekly administrations of 20 mg cG250 combined with IFN- α were safe and very well tolerated.
- No HACAs were detected during the administrations of the antibody.
- cG250 in combination with IFN- α showed clinical benefit (objective response or stable disease of at least six months) in 11 out of 26 evaluated patients (42%)
- The good tolerability of this treatment with cG250 and IFN- α showing anti-tumor activity together with a clinical benefit rate of 42% in this difficult-to-treat group of metastatic renal cell carcinoma patients warrant further investigation.

Results of phase II studies

Study	No. of Patients Evaluated	Objective Response Rate	Clinical Benefit Rate	Median survival
WX-2000-01-nak	32	3%	28%	16 months
WX-2000-04-gil	30	10%	23%	22 months
WX-2001-05-IFN	26	8%	42%	median not reached
Total Rencarex®	100	7%	31%	19 months

Phase III Trial Underway

A new clinical study has started to evaluate cG250 versus placebo in the adjuvant setting in patients at high risk of recurrence after recent nephrectomy.

For more information please refer the NCI homepage www.cancer.org (posting available from mid June 2004; study code: Wilex-WX-2003-07-HR) or to clinical.trials@wilex.com.

The IND number of this phase III study is BB-IND11346

