Treatment with monoclonal antibody cG250 (Rencarex®) in combination with IFNα-2a significantly prolongs survival in patients with metastatic renal cell cancer patients

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Introduction

cG250 (Rencarex®) is an IgG1 kappa light-chain chimeric monoclonal antibody that binds to carbonic anhydrase IX (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, astrocytes in the brain and to the spinal cord. Besides efficient bio-localization in RCC, it has been shown that cG250 can induce NK cells to kill tumor cells in vitro via antibody dependent cellular cytotoxicity (ADCC).

A phase II study with weekly administrations over 12 weeks in 36 metastatic RCC patients has shown that cG250 antibody alone is safe when given at a dose of 50 mg per week. Clinical response (WHO definition) was seen in 9 of 32 evaluated patients (28%). Median survival time was 15 months.

In a further phase II study cG250 was given weekly at a dose of 20 mg for 11 weeks in combination with bi-weekly low dose IL-2 to 35 patients with progressive RCC. Of 30 evaluable patients, 2 patients achieved partial remission and 7 patients stable disease for almost six months. Clinical response was seen in 23%. Median survival time was 22 months.

The current abstract updates the results of a combination therapy trial of cG250 with interferon α-2a in metastatic RCC patients and presents the latest survival data.

Study design

- Phase II, prospective, non-randomized, open-label, single arm, multi-center study
- A total of 32 patients were enrolled for a 12 week treatment (1 patient discontinued before therapy)
- At week 16 patients evaluated for response were stratified into 1) the extended treatment group of responders for additional 6 weeks of WX-G250 of previously progressive disease or progressive patients if further treatment considered clinically useful or, 2) the discontinued group.

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)

Patient selection

MAIN INCLUSION CRITERIA

- Stage IV renal cell carcinoma of documented clear cell histology, nephrectomized for primary tumor
- In progression at study entry
- 0 disease.
- Bi-dimensionally measurable disease with individual lesions ≤ 5 cm in diameter with at least one lesion of ≥ 1 cm
- Karnofsky performance status ≥ 80 %

MAIN EXCLUSION CRITERIA

- Known standard therapy 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

Objectives

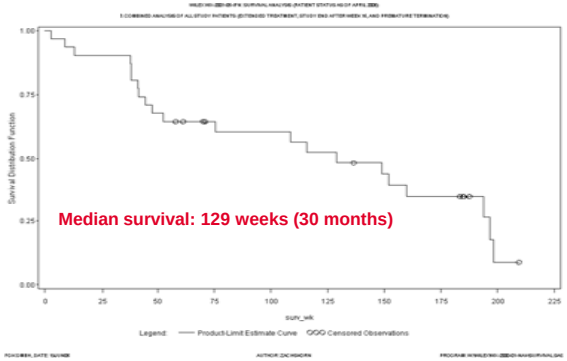
- Primary objectives: objective tumor response, toxicity
- Secondary objectives: immunogenicity (human anti-chimeric antibodies - HACA), biological activity (antibody dependent cellular cytotoxicity - ADCC), time to progression, overall survival

Results

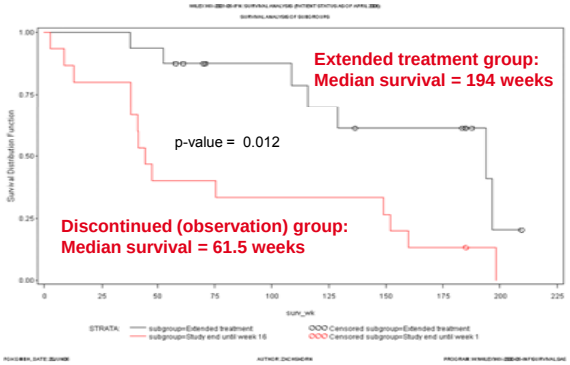
TUMOR RESPONSE

For tumor response assessment, CT scans at baseline, and weeks 16 and 22 were evaluated. Further CT scans at three monthly intervals after end of treatment were evaluated in cases of clinical response (stable disease or objective response). All images were evaluated by an independent radiologist. Twenty-six patients were evaluable for response to treatment. Two patients showed partial remission and 14 patients stable disease in week 16. One patient experienced a partial remission for at least 8 months. Nine patients had long durable disease stabilization (≥ 24 weeks). Clinical response, defined as objective response and stable disease ≥ 24 weeks, was obtained in 11 patients (42%).

Newest data show a median survival of 129 weeks (30 months).



Patients with **extended treatment** showed a median survival of 194 weeks whereas the patients who discontinued after week 16 experienced median survival of 61.5 weeks. This is a significant difference between both subgroups with a p-value of 0.012.



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.

HACA

Patient 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). HACA positive patient serum from a previous cG250 study was used as a positive control. No HACA was detected in any of the patients' sera tested.

SAFETY

- Six serious adverse events were seen in 5 patients; none were related to treatment with the antibody cG250 and all were due to tumor progression.
- The main side effects observed were constitutional symptoms (77.4%) commonly associated with IFN administration such as fever, chills, and flu–like syndromes). All were CTC toxicity grade 1 or 2 and reversible.
- Almost 30% of all adverse events occurred in the first study week in which only IFN-α was dosed (52/183 AEs).
- The administration of the study medication had no notable effect on hematological parameters.
- No allergic reactions were observed.

Conclusions

- cG250 in combination with IFN-α showed an encouraging extension of survival with a median overall survival of 30 months
- 42% of evaluated patients (11 out of 26) demonstrated clinical response (sum of patients with complete or partial responses and patients with stable disease lasting at least six months).
- Weekly administrations of 20 mg cG250 combined with low dose IFN-α were safe and well tolerated.
- No HACAs were detected during the administrations of the antibody.
- The demonstrated anti-tumor activity associated with a clinical benefit rate of 42% and a median survival of 30 months in this difficult-to-treat group of progressive metastatic renal cell carcinoma patients warrant further investigation

Results of phase II studies

Study	No. of Patients	Median Survival	2 y Survival
Phase II Monotherapy	36	15 months	41%
Phase II combination with LD IL-2	35	22 months	45 %
Phase II combination with LD IFN-α	31	30 months	57 %

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 (study code: Wilex-WX-2003-07-HR) or to clinical.trials@wilex.com.

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

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