UPDATE OF SURVIVAL DATA FOR TWO PHASE II STUDIES WITH MONOCLONAL ANTIBODY CG250 (RENCAREX®*) IN COMBINATION WITH IL-2 OR IFNα-2A IN METASTATIC RENAL CELL CARCINOMA 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 benefit was seen in 9 of 32 evaluated patients (28%). Median survival time was 15 months.

Two multi-center, open-label, prospective, single-arm phase I/II trials have been performed in combination with cytokines. 20 mg of cG250 was combined weekly with low dose (LD) Interleukin 2 (IL-2) or with LD interferon (IFN) α-2a respectively evaluating the safety and efficacy in patients with metastatic ccRCC.

This abstract provides updated survival and clinical data of these combination studies of LD cytokines with the monoclonal antibody cG250.

Study design

- Two Phase II, prospective, non-randomized, open-label, single arm, multi-center studies in patients with metastatic ccRCC.
- In the IL-2 combination trial 35 patients, in the IFNα-combination trial 31 patients were enrolled for 12 weeks of treatment.
- At week 16 patients were evaluated for response and stratified into 1) the extended treatment group for an additional 6 weeks of treatment (included non-response patients if further treatment considered clinically useful) or, 2) the progressive group with no further treatment.

Dosing

	cG250 i.v.	IFN-α s.c.	IL-2 s.c.
Week 1	None	Day 1-3-5 (each 3 MIU)	1.8 MIU daily, except for biw ekly pulses of 5.4 MIU/dayfor 3 cosecutive days)
Week 2-12	Day 1: 20 mg	Day 1-3-5 (each 3 MIU)	
For all patients w ith extension of treatment			
Week 17 22	Day 1: 20 mg	Day 1-3-5 (each 3 MIU)	1.8 MIU daily

Patient selection

MAIN INCLUSION CRITERIA

- Stage IV clear cell RCC, nephrectomized for primary tumor
- In progression at study entry
- 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 CNS metastases
- Patients with bone metastases only
- Lymphangiosis carcinomatosa
- Pre-exposure to murine/chimeric antibody therapy

Objectives

- Primary objectives: 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. In both studies patients had either low or intermediate risk based on modified Motzer criteria.

In the **IL-2 combination study** 30 patients were evaluable for response to treatment; in week 16 one patient showed a partial response (PR), 11 patients stable disease (SD). One patient experienced a partial remission for at least 95 weeks. 6 patients had long durable disease stabilization (≥ 24 weeks). Clinical benefit, defined as the sum of patients with a response and the sum of patients with SD ≥ 24 weeks, was obtained in 7 patients (23%).

In the **IFNα-combination study** 26 patients were evaluable for response to treatment; 2 patients showed a PR and 14 patients SD in week 16. One patient experienced a partial remission for at least 8 months. 9 patients had long durable disease stabilization (≥ 24 weeks). Clinical benefit, defined as the sum of patients with a response and the sum of patients with SD ≥ 24 weeks, was obtained in 11 patients (42%).

SURVIVAL

The **IL-2 combination trial** data show a median survival of 22 months with 45% of the 30 evaluable patients still alive after 2 years. (Figure1).

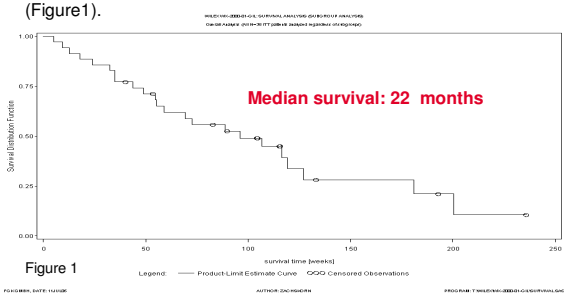

Figure 1

The extended treatment group receiving an additional 6 weeks of treatment showed a median survival of 41 months compared with 13 months in the non-response group. Patients receiving extended treatment with WX-G250 showed a significantly longer survival rate than the non-response patients (55% versus 25%; p=0.0062) (Figure 2).

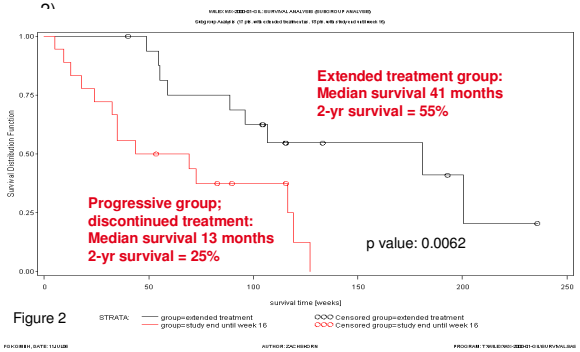

Figure 2

The overall median survival for patients in the **IFNα-combination study** was 30 months for the 31 patients treated with WX-G250 (Figure 3) with 57% of patients still alive after 2 years.

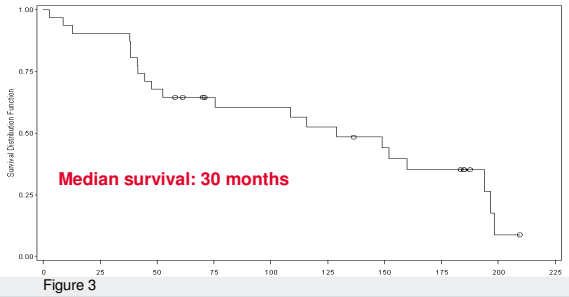

Figure 3

The response group receiving extended treatment showed a median survival of 45 months compared with 10 months in the non-response group. Patients receiving extended treatment with WX-G250 showed a significantly longer survival rate than the non-response patients (79% versus 30%; p=0.0083) (Figure 4).

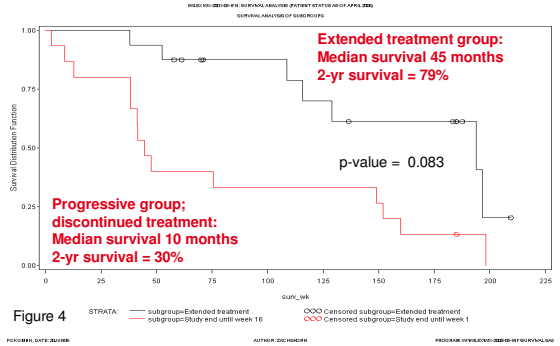

Figure 4

Results of phase II studies

Study	No. of Patients Evaluated	Response Rate (%)	Clinical Benefit Rate (%)	Median Survival (months)	2-Year Survival All Patients
WX-G250 monotherapy	36	3.1	28	15	41%
WX-G250 & IL-2	35	3.3	23	22	45%
WX-G250 & IFN-α	31	3.2	42	30	57%

Conclusion

- cG250 in combination with IL-2 and IFN-α showed an encouraging extension of survival with a median overall survival of 22 and 30 months respectively
- Weekly administrations of 20 mg cG250 combined with low dose cytokines were safe and very well tolerated.
- The demonstrated anti-tumor activity associated with a good clinical benefit rate and a prolonged median survival in this difficult-to-treat group of progressive metastatic renal cell carcinoma patients warrant further investigation

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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