REVIEW OF THE MONOCLONAL ANTIBODY cG250 (RENCAREX®) ALONE OR 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 (CAIX), a cell-surface antigen found on 95% of cells in clear cell renal cell carcinoma (ccRCC).

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 ccRCC, it has been shown that cG250 can induce natural killer (NK) cells to kill tumor cells in vitro via antibody dependent cellular cytotoxicity (ADCC).

Three multi-center, open-label, prospective, single-arm phase I/II trials were completed. cG250 was given either as monotherapy or in combination with low dose (LD) Interleukin-2 (IL-2) or Interferon (IFN)α-2a.

This poster reports updated survival and clinical data from these three studies with c G250.

Study design

- Three Phase I/II, prospective, non-randomized, open-label, single arm, multi-center studies in patients with metastatic ccRCC.
- In the monotherapy 36 patients were included for treatment, in the IL-2 combination trial 36 patients (1 pat. was never treated), and in the IFNα-combination trial 32 patients for 12 weeks of treatment (also here 1 patient was never treated).
- At week 16 and 22 patients were evaluated for response and stratified into

  1) the extended treatment group for an additional 8 weeks of treatment in the monotherapy study, or 6 weeks in the combination trials (included non-responsive patients if further treatment was considered clinically useful) or,

  2) the progressive group with no further treatment.

Treatment

	Mono cG250 i.v.	Combo cG250 i.v.	IFN-α s.c.	IL-2 s.c.
Week 1	d1q8: 50 mg	None	d1-3-5 (each 3 MIU)	1.8 MIU daily, and biweekly pulses of 5.4 MIU/day for 3 consecutive days
Week 2-12	d1q8: 50 mg	d8q8: 20 mg	Day 1-3-5 (each 3 MIU)	
	For all patients with extension of treatment:			
	Wk 17-24:	Wk 17-22	Wk 17-22	Wk 17-22

Patient selection

MAIN INCLUSION CRITERIA

- Stage IV ccRCC, nephrectomized for primary tumor
- Progressive disease 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

CT scans were evaluated for tumor response at baseline, and in weeks 16 and 22. In the presence of clinical response CT scans were evaluated at three month intervals after the end of treatment by an independent radiologist. In all studies patients had either low or intermediate risk based on modified Motzer criteria.

In the **monotherapy** trial 32 of 36 patients were evaluated for response to treatment, eleven of which showed stable disease (SD) in week 16. One patient experienced a minor response in week 44 and another patient a complete response (CR) in week 38. Clinical benefit, defined as CR + PR + [SD ≥ 24 weeks], was obtained in 28% (9/28) of the patients.

In the **IL-2 combination study** 30 of 35 patients were evaluable. In week 16 one patient showed a partial response (PR), and 11 patients showed stable disease (SD). One patient experienced a partial remission for at least 95 weeks and 6 patients had durable disease stabilization lasting 24 weeks or longer. Clinical benefit was obtained in 23% (7/30) of the patients.

In the **IFNα-combination study** 26 of 31 patients were evaluable for response to treatment. Two patients showed a PR and 14 patients SD in week 16. One patient experienced a partial remission for at least 8 months and 9 patients had long durable disease stabilization (≥ 24 weeks). Clinical benefit was obtained in 42% (11/26) of the patients.

Survival

The **monotherapy trial** showed a median overall survival of 15 months with 41% of the 32 evaluable patients still alive after 2 years. (Figure1).

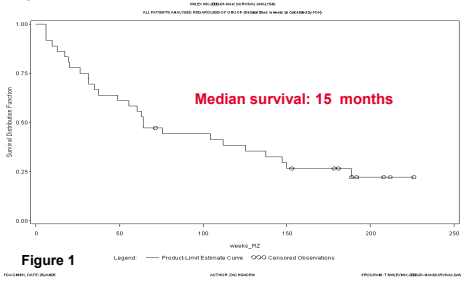

Figure 1

The extended treatment group (additional 8 weeks of treatment) showed a median survival of 39 months, compared to 10 months in the discontinued group. Patients receiving extended treatment with cG250 showed a significantly longer survival rate than the non-response patients (70% versus 26%; p=0.01). (Figure 2).

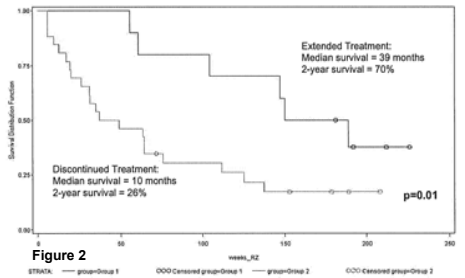

Figure 2

The **IL-2 combination trial** data show a median overall survival of 22 months with 45% of the 30 evaluable patients still alive after 2 years. (Figure 3).

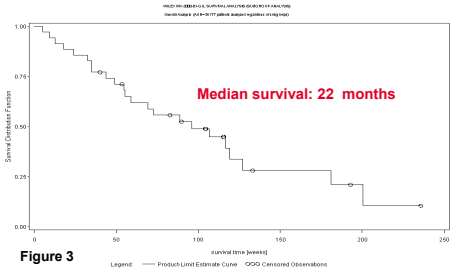

Figure 3

The extended treatment group (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 4).

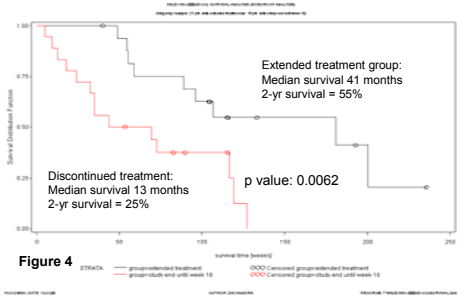

Figure 4

The overall median survival for patients in the **IFNα-combination study** was 30 months for the 31 patients treated with WX-G250 (Figure 5) with 57% of patients still alive after 2 years.

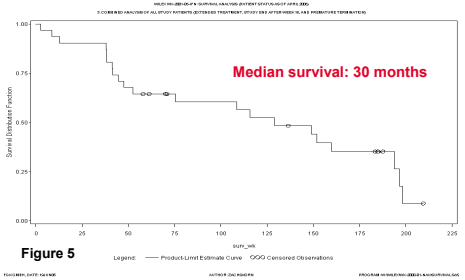

Figure 5

The patients receiving extended treatment showed a median survival of 45 months compared with 10 months in the non-extended group. Patients receiving extended treatment with cG250 showed a significantly longer survival rate than the non-response patients (79% versus 30%; p=0.0083) (Figure 6).

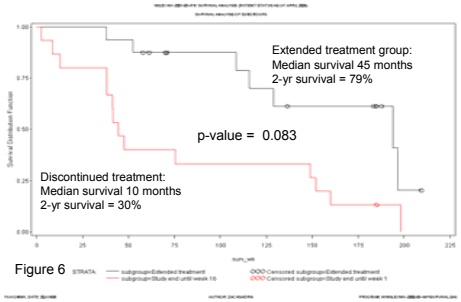

Figure 6

Results of phase II studies

Study	No. of Patients	Response Rate*	Clinical Benefit Rate (%)	Median Survival Rate (mo)	2-Year Survival Rate All Patients
WX-G250 monotherapy	36	3.1	28	15	41%
WX-G250 IL-2	36	3.3	23	22	45%
WX-G250 &IFN	32	3.8	42	30	57%
*based on evaluated patients					

Conclusion

- cG250 both alone and in combination with IL-2 and IFN-α showed an encouraging extension of survival with a median overall survival of 15, 22 and 30 months respectively.
- Weekly administrations of 50mg or 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

An international, randomized, placebo-controlled phase III clinical study is evaluating cG250 vs. 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.

Study IND number: BB-IND11346

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