

Recombinant IL-21 (rIL-21) in Combination with Sorafenib: Preliminary Results from a Phase I/II Study in Patients with Metastatic Renal Cell Cancer (RCC)

Shailender Bhatia¹, Brendan D. Curti², Michael S. Gordon³, David I. Quinn⁴, Todd A. DeVries⁵, Naomi H. Hunder⁵, John A. Thompson¹

¹University of Washington/Seattle Cancer Care Alliance, Seattle, WA; ²Providence Medical Center, Portland, OR; ³Premiere Oncology of Arizona, Scottsdale, AZ; ⁴University of Southern California, Los Angeles, CA; ⁵ZymoGenetics, Inc., Seattle, WA

Introduction

Treatment paradigms for metastatic renal cell carcinoma (RCC) have changed considerably with the advent of targeted therapeutics. Tyrosine kinase inhibitors (TKIs) such as sunitinib and sorafenib have shown clinical benefit in patients with metastatic RCC, but durable responses continue to be elusive. Sunitinib used as first-line treatment has been shown to result in a median progression-free survival (PFS) of 11 months, with 27.5% partial response (PR) but 0% complete response (CR).¹ Sorafenib used as second-line treatment has resulted in a median PFS of 5.5 months, with 2% PR and 0% CR.²

Interleukin-21 (IL-21), a member of the common gamma-chain cytokine family, has been shown to enhance anti-tumor immunity through activation of cytotoxic T cells and natural killer (NK) cells. Unlike IL-2, IL-21 does not enhance proliferation of regulatory T cells. Recombinant IL-21 (rIL-21) is under development as a potential treatment for renal cell cancer and other tumors. In single-agent Phase I clinical studies, rIL-21 had a safety profile compatible with outpatient administration and was associated with anti-tumor activity in RCC.^{3,4} In these studies, rIL-21 was administered to 19 patients with RCC and measurable disease per RECIST. Of these patients, 4 had PR, 13 had stable disease (SD), and 2 had progressive disease (PD); duration of response was 5-18 months.

Combining two active agents with different mechanisms of action may improve outcomes in some patients. In preclinical studies, the combination of rIL-21 and sorafenib had additive effects on tumor shrinkage and prolonged survival in a murine RENCA model of RCC. A Phase I/II clinical study was initiated to further evaluate the safety and anti-tumor effects of this combination. Interim results from the Phase I dose escalation portion of this study are presented.

¹ Motzer RJ, Hutson TE, Tomczak P, et al. N Engl J Med 2007; 356(2): 115-124.

² Escudier B, Eisen T, Stadler WM, et al. N Engl J Med 2007; 356(2): 125-134.

³ Davis ID, Skrummsager BK, Cebon J, et al. Clin Cancer Res 2007; 13(12): 3630-3636.

⁴ Thompson JA, Curti BD, Redman BG, Weber JS, Agarwala SS, Sievers EL, J Clin Oncol, 2006 ASCO Annual Meeting Proceedings Part 1, Vol 24, No. 18S (June 20 Supplement), 2006: 2505.

Study Design

Phase I: Dose Escalation - ONGOING

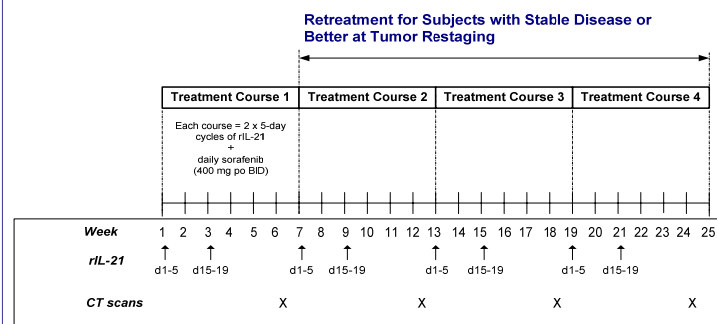
- Standard 3 + 3 escalation scheme to determine MTD
- 10, 30, and 50 µg/kg rIL-21 cohorts
- Open to patients receiving first- or second-line therapy

Phase II: Cohort Expansion - UPCOMING

- Endpoints: ORR, PFS, additional safety information
- Open to patients receiving second-line therapy with measurable disease per RECIST

Treatment

- Six-week treatment course consisting of two 5-day cycles of rIL-21 in combination with daily sorafenib
- Patients with SD or better eligible for repeated treatment courses
 - Dose escalation decision based on Treatment Course 1



ABSTRACT

Introduction. The development of multi-targeted tyrosine kinase inhibitors has changed treatment paradigms in metastatic renal cell cancer (RCC). However, durable responses continue to be elusive, except in a small subset of patients treated with high dose interleukin-2 (IL-2). Interleukin-21 (IL-21), an immunomodulatory cytokine with close homology to IL-2, has promising anti-tumor activity. A Phase I study of recombinant interleukin-21 (rIL-21) in patients with metastatic RCC or melanoma demonstrated its safety and tolerability and provided preliminary evidence of anti-tumor efficacy (Proc ASCO 2006; 24:2505). Based on encouraging preclinical evidence of an additive effect with rIL-21 and sorafenib, a Phase I/II dose-escalation study of this novel combination was launched in patients with metastatic RCC. We report the preliminary results of this multi-center study.

Methods. Patients with metastatic RCC of predominantly clear cell histology, ECOG status 0 or 1, and a maximum of one prior systemic therapy are being enrolled to receive a combination of sorafenib and rIL-21. Sorafenib is

Patient Characteristics

	N=13*
Gender	
Male	11
Female	2
Age, median (range)	63 years (48 to 77)
ECOG Performance Status Score	
0	12
1	1
Motzer risk	
Favorable	9
Intermediate	4
Prior nephrectomy	13
Prior treatments for metastatic disease	
None	7 (54%)
Any	6 (46%)
Sunitinib	2 (15%)
IL-2	2 (15%)
Other	2 (15%)

*Excludes two subjects withdrawn due to protocol violation; includes one subject not evaluable for dose escalation per protocol (received only 7 of 10 rIL-21 doses in Treatment Course 1)

Phase I Dose Escalation

Dose	Enrolled	1 protocol violation	1 not evaluable for dose escalation	1 DLT: Grade 3 hand-foot syndrome (off study)	Evaluable for Dose Escalation	Evaluable for Tumor Response
10 µg/kg	N=8	1	1	1	N=6	N=6
30 µg/kg	N=4	1	1	1	N=3	N=2
50 µg/kg*	N=3	1	1	1	N=3	N=2
Totals:	N=15				N=12	N=10

*Enrollment ongoing up to N=6 due to DLT

Safety Observations - Course 1

- Consistent with known rIL-21 and sorafenib safety profiles
- Majority of adverse events and lab abnormalities were Grade 1/2
- Grade 3 clinical adverse events related to rIL-21 and/or sorafenib:
 - Hand-foot syndrome (n=2), rash (n=1), intermittent fever (n=1), fatigue (n=1)
- Grade 3/4 laboratory abnormalities (without clinical symptoms):
 - Hypophosphatemia (n=7), hyponatremia (n=2), elevated lipase (n=3), elevated amylase (n=2), thrombocytopenia (n=1), hyperuricemia (n=1)

Hematology Lab Toxicities* - Course 1

	10 µg/kg (N=7)		30 µg/kg (N=3)		50 µg/kg (N=3)	
	Any Grade n (%)	Grade 3 n (%)	Any Grade n (%)	Grade 3 n (%)	Any Grade n (%)	Grade 3 n (%)
↓ Hemoglobin	3 (43)	-	2 (67)	-	3 (100)	-
↓ Platelets	5 (71)	-	2 (67)	-	3 (100)	1 (33)
↓ Lymphocytes	5 (71)	2 (29)	3 (100)	2 (67)	3 (100)	2 (67)
↓ Neutrophils	2 (29)	-	1 (33)	-	-	-

*No Grade 4 toxicities reported to date

Results

Non-Hematology Lab Toxicities - Course 1

	10 µg/kg (N=7)		30 µg/kg (N=3)		50 µg/kg (N=3)	
	Any Grade n (%)	Grade 3/4 n (%)	Any Grade n (%)	Grade 3/4 n (%)	Any Grade n (%)	Grade 3/4 n (%)
↑ ALT	2 (29)	-	3 (100)	-	2 (67)	-
↑ Bilirubin	2 (29)	-	2 (67)	-	2 (67)	-
↓ Albumin	5 (71)	-	3 (100)	-	3 (100)	-
↑ Amylase	2 (29)	1 (14)	-	-	1 (33)	1 (33)
↑ Lipase	4 (57)	1 (14)	1 (33)	1 (33)	1 (33)	1 (33)
↓ Phosphate	6 (86)	4 (57)	2 (67)	1 (33)	2 (67)	2 (67)
↓ Sodium	5 (71)	1 (14)	3 (100)	-	3 (100)	1 (33)

Adverse Events* - Course 1

	10 µg/kg (N=7)		30 µg/kg (N=3)		50 µg/kg (N=3)	
	Any Grade n (%)	Grade 3 n (%)	Any Grade n (%)	Grade 3 n (%)	Any Grade n (%)	Grade 3 n (%)
Rash	5 (71)	-	3 (100)	-	3 (100)	1 (33)
Fatigue	3 (43)	-	2 (67)	1 (33)	3 (100)	-
Chills	6 (86)	-	1 (33)	-	-	-
Pyrexia	4 (57)	1 (14)	1 (33)	-	2 (67)	-
Diarrhea	4 (57)	-	2 (67)	-	-	-
Hand-foot syndrome	4 (57)	1 (14)	1 (33)	1 (33)	-	-
Nausea	4 (57)	-	-	-	1 (33)	-

*Reported in ≥ 5 patients; No Grade 4 adverse events reported to date

Safety Observations - Repeat Treatment

- All patients who completed Treatment Course 1 have gone on to receive at least one additional treatment course
- No increase in toxicity seen with repeat treatment
 - Majority of adverse events and lab abnormalities Grade 1/2
 - No Grade 3 clinical adverse events related to rIL-21 + sorafenib

Completed Treatment Courses*

Total Number of Completed Courses	10 µg/kg (N=7) n	30 µg/kg (N=3) n	50 µg/kg (N=3) n
1	0	0	2
2	1	3	-
3	2	-	-
4	3	-	-

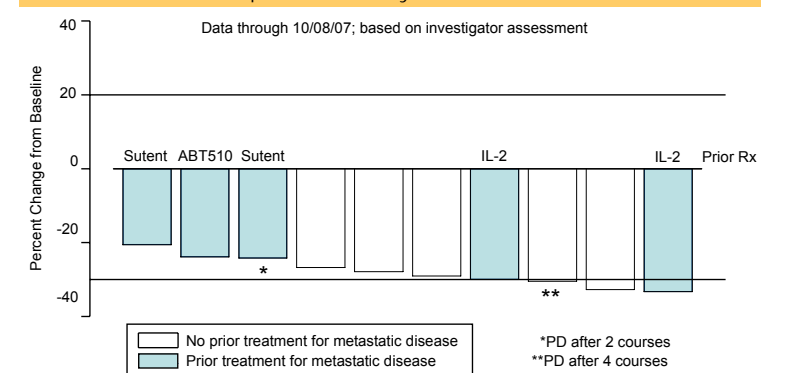
*Experience through 10/08/07

Sorafenib Exposure

		10 µg/kg (N=7) n	30 µg/kg (N=3) n	50 µg/kg (N=3) n
Sorafenib	No reduction	3	2	1
	Dose reduced	3	1	1
	Discontinued due to DLT	1	0	1

- Majority of dose reductions occurred during Treatment Course 1
- One patient in 10 µg/kg group decreased sorafenib dose during Treatment Course 3

Best Response on Study - rIL-21 + Sorafenib



Anti-tumor Response

Responses are investigator assessed, not yet confirmed by repeat scans

Subject Number	Dose Level (µg/kg)	1 st / 2 nd Line	Target Lesions	Target Lesions (n)	Baseline SLD (mm)	Response after Course 1	Response after Course 2	Response after Course 3	Response after Course 4
1002	10	1 st	Pancreas, lung, caval lymph nodes	3	59	SD	SD	PR	PD
1004	10	1 st	Chest wall, pleura, lung, adrenal	4	86	SD	SD	SD	SD
1005	10	2 nd Sunitinib	Chest lymph nodes	2	33	SD	PD	-	-
1006	10	2 nd Sunitinib	Retroperitoneal mass, liver, mesenteric nodes	5	325	SD	SD	SD	SD*
1007	10	1 st	Adrenal, lung	4	58	SD	SD	PR*	-
1008	10	1 st	Flank muscle nodules	2	71	SD	SD	SD*	-
1009	30	1 st	Spleen, thyroid	2	86	SD	SD*	-	-
1012	30	2 nd ABT510	Lung	2	46	SD	SD*	-	-
1013	50	2 nd IL-2	Lung	2	27	PR*	-	-	-
1014	50	2 nd IL-2	Retroperitoneal mass, hilum, lung	3	84	PR*	-	-	-

Legend: Yellow = Tumor shrinkage 0-20%, Orange = Tumor shrinkage 20-29%, Red = Tumor shrinkage ≥30%, Blue = Progressive disease

SLD = Sum of longest diameters

*Continuing on study

Summary

- Combination therapy with rIL-21 and sorafenib is well-tolerated by most patients.
- Encouraging anti-tumor activity was seen in both first- and second-line patients, including 4 unconfirmed PRs to date, and > 20% tumor shrinkage in 10 of 10 evaluable patients.
- The upcoming Phase II portion of this study is expected to provide more data on the safety and anti-tumor response associated with this therapy.

**Recombinant IL-21 (rIL-21) in Combination with Sorafenib:
Preliminary Results from a Phase I/II Study in Patients
with Metastatic Renal Cell Cancer (RCC)**

Bhatia S, Curti BD, Gordon MS, Quinn DI, DeVries TA, Hunder NH, Thompson JA

presented at the

**AACR-NCI-EORTC International Conference
San Francisco, CA**

October 2007