Efficacy and Safety of Recombinant Interleukin-21 (rIL-21) and Rituximab in Relapsed/Refractory Indolent Lymphoma

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INTRODUCTION

Rituximab in Relapsed/Refractory Indolent Non-Hodgkin's Lymphoma (NHL)

- Rituximab response rates between 36% and 57%, with median duration of response <1 year[1]
- Major mechanism of action believed to be antibody-dependent cell-mediated cytotoxicity (ADCC) mediated by natural killer (NK) cells
- Combination with agents that augment NK cell cytotoxicity may improve outcomes

Interleukin 21

- Common gamma chain cytokine with unique effects on innate and adaptive immunity
- Enhances ADCC by activation of NK cell cytolytic function
- Direct anti-tumor effects in malignant B-cells
  - Follicular lymphoma cells: promotes apoptosis[2]
  - Chronic lymphocytic leukemia cells: induces Granzyme B; sensitizes to apoptosis[3]; enhances rituximab- and fludarabine-mediated apoptosis[4]

Recombinant Interleukin 21 (rIL-21)

- In development as a potential new immunomodulatory cytokine
- In single-agent Phase 1 studies of rIL-21[5,6]
  - Safety profile consistent with outpatient administration
  - Demonstrated anti-tumor activity in metastatic renal cell carcinoma and melanoma

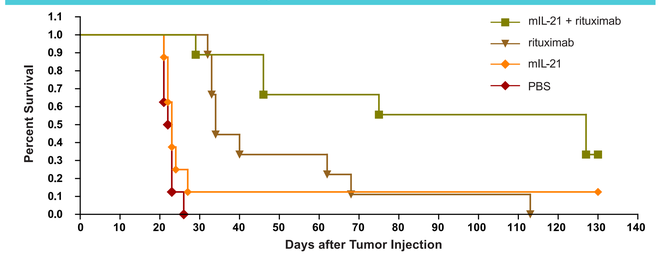
Preclinical Studies of IL-21 + Rituximab

- In murine lymphoma xenograft models, combination of murine IL-21 + rituximab led to prolonged survival compared to rituximab alone[7] (see figure below)

Phase 1 Study of rIL-21 + Rituximab in Patients with B-cell NHL

- Final results from Part 2 of a Phase 1 study looking at rIL-21 and rituximab in patients with relapsed/refractory indolent lymphoma are presented here

Effect of IL-21 + Rituximab in Mouse Xenograft Model



STUDY DESIGN

Primary Objective

- Determine the maximum tolerated dose (MTD) and evaluate the safety of rIL-21

Secondary Objectives

- Assess preliminary anti-tumor activity of rIL-21 + rituximab
- Characterize pharmacokinetics of rIL-21 in the presence of rituximab
- Evaluate immunogenicity of rIL-21 in the presence of rituximab

Part 1: Dose escalation

- Standard "3+3" design
- Fixed dose of rituximab: 375 mg/m² weekly, starting at Week 0
- Three dose levels of rIL-21 evaluated: 30, 100, or 150 µg/kg weekly, starting at Week 1

Part 2: Cohort expansion

- Up to 12 additional patients to be treated at MTD or dose recommended from Part 1, for a total of 15 patients treated at this dose level

Patient population

- Indolent CD20+ B-cell NHL
  - Grade 1, 2, or 3a follicular lymphoma
  - Marginal zone lymphoma
  - Small lymphocytic lymphoma
- Must have received at least 1 prior systemic therapy
  - Prior treatment with rituximab required for follicular lymphoma

Tumor response

- Investigator-assessed per Cheson criteria

Rituximab 375 mg/m² + rIL-21 IV Treatment Schedule

	Treatment Cycle 1							Treatment Cycle 2[a]					
Week	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**1**	**2**	**3**	**4**	**5**	**6**
Rituximab	✓	✓	✓	✓	✓			✓	✓	✓	✓		
rIL-21		✓	✓	✓	✓			✓	✓	✓	✓		
Tumor restaging							✓						✓

a Patients with stable disease (SD) or better were eligible for 1 repeat treatment cycle

Part 1: Dose Escalation (previously reported)[6]

- A total of 9 patients were treated (3 at 30 µg/kg, 3 at 100 µg/kg, and 3 at 150 µg/kg)
- 2 out of 2 patients who received Treatment Cycle 2 at 150 µg/kg experienced increased toxicity relative to Treatment Cycle 1; therefore, 100 µg/kg rIL-21 was selected for Part 2 (cohort expansion) of the study

RESULTS (Part 2: Cohort Expansion)

Patient Characteristics (N = 15[a])

Gender	
Male	11
Female	4
Age, median (range)	62 years (37–79)
Diagnosis	
Marginal zone B-cell lymphoma	1
Follicular lymphoma	5
Small lymphocytic lymphoma / chronic lymphocytic leukemia	9
Prior treatments for relapsed disease, median (range)	3 (1–10)
Patients with prior rituximab	14
Prior rituximab treatments, median (range)	2 (1–6)

a Includes 3 patients treated at 100 µg/kg in Part 1 of the study

Safety Observations

- Most adverse events (AEs) and laboratory abnormalities were Grade 1 or 2 in severity
- Grade 3 or higher AEs considered related to rIL-21 included the following:
  - Grade 3 rash (n=1)
  - Grade 3 pain in extremity (n=1)
  - Grade 3 arthralgia (n=1)
  - Grade 3 flu-like illness (n=1)
  - Grade 4 thrombocytopenia (n=1)
- One patient with a prior history of cardiac disease died on study after completing Treatment Cycle 1. Patient experienced Grade 4 acute myocardial infarction with subsequent stent placement complicated by cardiac arrest and device thrombosis. Patient subsequently developed acute respiratory failure and cardiac arrest leading to his death
- Serious adverse events considered related to rIL-21 occurred in 2 patients and included Grade 4 thrombocytopenia and events described above for the 1 patient death
- No patients developed antibodies to rIL-21 on study

Most Common Adverse Events[a] (N = 15)

	Any Grade n (%)	≥Grade 3 n (%)
Flu-like illness	11 (73)	1 (7)
Fatigue	9 (60)	1 (7)
Nausea	6 (40)	—
Pyrexia	6 (40)	—
Headache	5 (33)	—
Pruritus	4 (27)	—
Diarrhea	4 (27)	—
Dizziness	3 (20)	—
Insomnia	3 (20)	—
Night sweats	3 (20)	—
Pain in extremity	3 (20)	—
Constipation	3 (20)	—

a Reported in 5 or more patients

Most Common Laboratory Abnormalities[a] (N = 15)

	Any Grade n (%)	≥Grade 3 n (%)
Anemia	11 (73)	1 (7)
Thrombocytopenia	10 (67)	1 (7)
Hypoalbuminemia	10 (67)	—
Lymphopenia	10 (67)	4 (27)
Neutropenia	10 (67)	6 (40)
Leukopenia	9 (60)	2 (13)
Hypokalemia	6 (40)	—
Hypophosphatemia[b]	4 (29)	1 (7)
Hypocalcemia	3 (20)	—
Elevated AST	3 (20)	2 (13)

a Reported in 3 or more patients
b N=14; one patient (Subject 1007) did not have phosphate levels evaluated

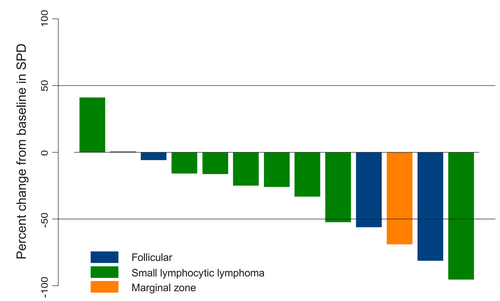
Anti-tumor Response

Best Response at Any Time on Study (N = 13)[a]

	Response	n (%)
ORR	(objective response rate)	5 (38%)
	CR (complete response)	1 (8%)[b]
	CRu (unconfirmed complete response)	1 (8%)
	PR (partial response)	3 (23%)
SD	(stable disease)	8 (62%)
PD	(progressive disease)	—

a Excludes 2 patients not evaluable for response
b Patient with small lymphocytic lymphoma/chronic lymphocytic leukemia. CR included no evidence of minimal residual disease in bone marrow as determined by high-sensitivity flow cytometry

Maximum Tumor Reduction on Study



One patient with follicular lymphoma and 1 patient with small lymphocytic lymphoma were not assessed for response

SPD = sum of the products of the 6 largest measurable disease diameters

Prior Response to Rituximab and Response on Study

Patient number	Diagnosis	Number of prior treatments	Number of prior rituximab therapies	Best response to last rituximab treatment /duration (months)	Best response to rIL-21 + rituximab	Disease status / duration of response (months)[a]
1005	FL	5	1	CR / 63	CRu	CRu / 11+
1007	SLL	6	3	unknown	PR	PR / <2
1008	MZ	3	1	PR / 4	PR	PR / 13+
1014	SLL	3	2	PR / 3	SD	unknown
1019	SLL	3	2	PR / 5	SD	unknown
1021	FL	2	2	PR / 13	—[b]	—[b]
1022	SLL	2	2	SD / 2	SD	unknown
1025	SLL	4	2	PD / —	SD	unknown
1026	FL	2	1	PR / 5	PR	PD / <5
1031	SLL	8	6	SD / 8	SD	unknown
1032	SLL	1	1	CR / 40	CR	CR / 3+[c]
1033	FL	10	6	SD / 6	SD	unknown
1034	SLL	3	1	PD / —	—[d]	—[d]
1035	SLL	1	1	PR / 6	SD	unknown
1036	FL	2	2	SD / 6	SD	unknown

CR = complete response; CRu = unconfirmed complete response; FL = follicular lymphoma; PR = partial response; SD = stable disease; SLL = small lymphocytic lymphoma
a As of 27 Feb 2008
b Patient received 4 doses of rIL-21 and died prior to restaging
c Included no evidence of minimal residual disease as determined by high-sensitivity flow cytometry
d Patient withdrew after 2 doses of rIL-21

rIL-21 Pharmacokinetics (Part 1 and Part 2)

- Cmax at 30 µg/kg was consistent with single-agent rIL-21 value[6]

ABSTRACT

Background IL-21 is a cytokine that activates NK and CD8+ T cells and can enhance antibody-dependent cellular cytotoxicity. This Phase 1, two-part dose-escalation study evaluated the combination of rIL-21 and rituximab in subjects with relapsed, indolent CD20+ B cell lymphomas who had received at least 1 prior course of systemic therapy. A dose of 100 µg/kg rIL-21 was selected for evaluation in an expanded cohort of 15 subjects in Part 2 of the study.

Methods Eligible subjects received weekly rituximab (375 mg/m²) on days –7, 0, 7, 14, and 21; and 100 µg/kg rIL-21 IV on days 0, 7, 14, and 21 of a 4-week treatment cycle. Safety, serum levels of rIL-21, and tumor response assessed by the investigator per Cheson criteria were evaluated. Subjects without disease progression at day 36 were eligible to receive a second cycle.

Results 15 subjects (5 follicular lymphoma, 9 small lymphocytic lymphoma/chronic lymphocytic leukemia, and 1 marginal zone lymphoma) were treated. The median number of prior regimens was 3 (range, 1–8); all subjects had prior rituximab (median number of prior courses, 2; range, 1–6). Last response to rituximab included CR in 2, PR in 6, SD in 2, PD in 3, and unknown in 2. Ten of 15 subjects completed 2 treatment cycles. Most adverse events (AEs) were Grade 1 or 2, and included flu-like symptoms, headache, and fatigue. Grade 3/4 AEs related to study drug consisted of Grade 4 chest pain in 1 subject with a history of cardiac disease who died secondary to stent restenosis, transient Grade 4 thrombocytopenia without bleeding in 1 subject, and Grade 3 rash in 1 subject. Lab abnormalities were generally Grade 1 or 2 and included anemia, thrombocytopenia, lymphopenia, neutropenia, hypoalbuminemia, and hypokalemia. Pharmacokinetic and immunogenicity assessments are in process. Overall best responses to date on study include 1 CR, 1 CRu, 3 PR (including 1 subject whose last response to rituximab lasted <6 months), 8 SD, and 2 unevaluable, for an overall response rate of 33% [95% CI = (12–62%)]. Two subjects with SD are still on study.

Conclusions Combination treatment with rIL-21 plus rituximab for up to two 4-week cycles is well tolerated and associated with clinical response, even in subjects heavily pre-treated with rituximab.

CONCLUSIONS

- Combination therapy with 100 µg/kg rIL-21 and rituximab was well tolerated by most patients
- Evidence of anti-tumor activity was seen in this heavily pretreated population, including 1 CR, 1 CRu, and 3 PRs
- Further Phase 2 studies investigating the combination of rIL-21 and rituximab in lymphoma, including small lymphocytic lymphoma and chronic lymphocytic leukemia, are under consideration

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