Phase 1/2 Trial of Cirmtuzumab and Ibrutinib: Planned Analysis of Phase 1 CLL Cohorts

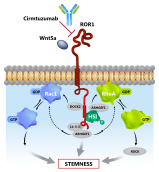
Michael Y. Choi, MD[1], William G. Wierda, MD, PhD[2], Hun Ju Lee, MD[2], Dimitrios Tzachanis, MD, PhD[1], Xen Ianopulos, MD, PhD[3], Deborah Jezior, BS[3], James Breitmeyer, MD, PhD[3], Catriona H.M. Jamieson, MD, PhD[1,4], Thomas J. Kipps, MD, PhD[1], CIRLL Study Group

[1]Moores Cancer Center, University of California, San Diego, La Jolla, CA; [2]MD Anderson Cancer Center, Houston, TX; [3]Oncternal Therapeutics, San Diego, CA; [4]Division of Regenerative Medicine, University of California, San Diego, La Jolla, CA

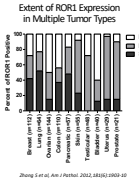
Introduction

ROR1 (Receptor tyrosine kinase-like Orphan Receptor 1) is an onco-embryonic protein that functions in embryonic skeletal, cardio-respiratory, and neurological development. It is detected in embryonic tissue, but not normal tissue in the adult.

ROR1 is a receptor for Wnt5a, and can induce activation of Rac1, RhoA, HS1 and other downstream targets to enhance cell proliferation, migration and stemness. Wnt5a levels are high in patients with chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL).



ROR1 is expressed by malignant cells in many cancers, including CLL and MCL. As such, it is an ideal drug target for cancer therapy.



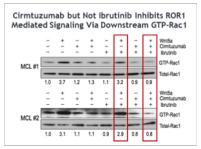
Zhong S et al, Am J Pathol. 2012;181(5):1903-10

Cirmtuzumab is a specific inhibitor of ROR1 signaling. It is a humanized IgG1 high affinity monoclonal antibody that binds the extracellular domain of human ROR1 and is distinct from other anti-ROR1 antibodies. It does not recognize normal adult tissues.

An earlier phase 1 trial in relapsed/refractory CLL showed it to safely inhibit ROR1 signaling, reverse stemness gene expression signatures of leukemic cells, and to prolong PFS with anti-CLL effects (Choi et al, Cell Stem Cell 2018).

ROR1-Wnt5a pathway remains active in ibrutinib treated MCL and CLL. In addition, inhibition of Bruton tyrosine kinase (BTK) in CLL cells increases dependence on ROR1 signaling.

Cirmtuzumab, in combination with ibrutinib, exert potent synergistic effects in both MCL and CLL (Yu et al, 2017, 2018).



Trial Design

This is a Phase 1/2 study of safety, pharmacokinetics, pharmacodynamics, and antitumor activity of the combination of cirmtuzumab and ibrutinib (C + I).

Part 1: Dose-finding in MCL and CLL

Cirmtuzumab: Weight-based and fixed dosing cohorts (N=3/cohort)

- 2, 4, 8 and 16 mg/kg per dose
- 300 mg and 600 mg per dose

Single agent cirmtuzumab in the first month to assess biomarkers, including receptor occupancy, followed by combination treatment of C + I.

Cirmtuzumab is administered IV, Q2W x 5 followed by monthly administration for a total duration of one year. Ibrutinib administered using FDA approved dosing for 48 weeks.

CLL results reported here. Full results of Part 1 for MCL will be reported separately.

Part 2: Expansion cohorts in MCL and CLL

Evaluation of the combination Cirmtuzumab + Ibrutinib to confirm the RDR.

Part 3 – Efficacy Evaluation in CLL

Randomized evaluation of the clinical activity and safety of Cirmtuzumab + Ibrutinib vs. Ibrutinib alone.

Main Eligibility Criteria

Inclusion

- Histological diagnosis of CLL/SLL or MCL
- No history of prior BTK-inhibitor therapy
- Presence of radiographically measurable disease
- Adequate bone marrow function, hepatic function, renal function and coagulation profile

Exclusions

- Transformation to an aggressive lymphoma
- CNS malignancy
- Severe cardiovascular or gastrointestinal disease
- Ongoing GvHD in those with prior hematopoietic progenitor transplants
- Prior solid organ transplantation
- Use of moderate or strong inhibitors of CYP3A4 within 7 days of onset of treatment with ibrutinib
- Bleeding diathesis

Selection of RDR in CLL Cohort

The recommended dose regimen (RDR) was selected based on an integrated analysis of:

- Safety (all doses cirmtuzumab: N=18)
- Clinical efficacy (≥24 weeks treatment: N=12)
- Pharmacokinetics and Pharmacodynamics (receptor occupancy)

After this analysis was completed, an RDR of 600 mg Cirmtuzumab + 420 mg Ibrutinib per dose was selected.

Characteristics of CLL Patients Evaluable for Efficacy (N=12)

Age (median and range)	69 (57-86)
IGH Variable Region	
- Unmutated	6
- Mutated	3
- Not Determined	3
Del17p	0
Del11q	3
Trisomy 12	3
No Previous Treatment	3
Relapsed/Refractory	9
- Median Prior Therapies (range)	2 (1-5)
- Prior Chemoimmunotherapy	3
- Prior Venetoclax	1
- Prior BCR antagonist	1

Cirmtuzumab Doses Administered

Cohort	Dose mg/kg	Average per group (mg)
	Weight based dosing	
1	2	156
2	4	309
3	8	713
4	16	1306
	Fixed dosing	
5		300
6		600

Safety

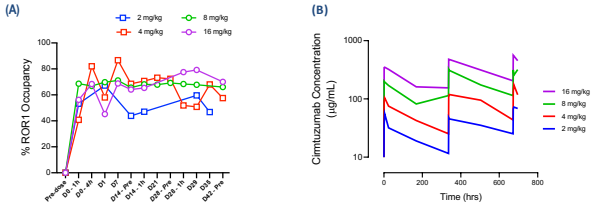
Summary of Most Frequent (≥10%) Treatment Emergent Adverse Events* by Preferred Term in the CLL cohort

	Overall	≥RDR	<RDR		Overall	≥RDR	<RDR
Preferred term	(N=18)	(N=9)	(N=9)	**Preferred term**	(N=18)	(N=9)	(N=9)
Subjects with at least one TEAE	*16 (88.9%)*	*7 (77.8%)*	*9 (100.0%)*				
Contusion	9	3	6	Myalgia	2	0	2
Arthralgia	6	2	4	Back pain	2	0	2
Fatigue	5	3	2	Pyrexia	2	1	1
Muscle spasms	4	2	2	Nausea	2	0	2
Diarrhoea	4	1	3	Dyspepsia	2	0	2
Upper respiratory tract infection	3	1	2	Gastrooesophageal reflux disease	2	1	1
Urinary tract infection	3	1	2	Sinusitis	2	1	1
Upper-airway cough syndrome	3	1	2	Dyspnoea	2	0	2
Insomnia	3	1	2	Nasal congestion	2	1	1
Atrial fibrillation	3	2	1	Vision blurred	2	1	1
Hypertension	3	2	1	Hyperkalaemia	2	1	1
Rash	2	1	1	Dizziness	2	0	2

*TEAE = Treatment Emergent Adverse Event on study (cirmtuzumab alone or cirmtuzumab + ibrutinib). Version 21.x of MedDRA was used to code AEs.
N = Number of subjects in the Safety Population. n = Number of subjects in the specific category. Percentages are calculated as 100 x (n/N).
Subjects reporting a particular adverse event (preferred term) more than once are counted only once by preferred term and System Organ Class.

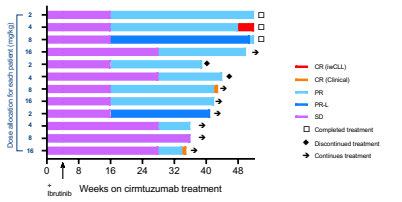
ROR-1 Receptor Occupancy and Pharmacokinetics

(A) Percent receptor occupancy (RO) for ROR-1 was evaluated by flow cytometry of PBMCs, using competitive versus non-competitive binding for ROR-1 on CLL cells. Good RO was observed across all doses, with less variability in the first 4 weeks of treatment in the higher dose groups (8 mg/kg and 16 mg/kg). Constant recycling of ROR1 causes an apparent less-than-maximal saturation when assessed by flow cytometry. (B) PK behavior for cirmtuzumab is consistent with that observed in the Phase 1a study.



Clinical Efficacy

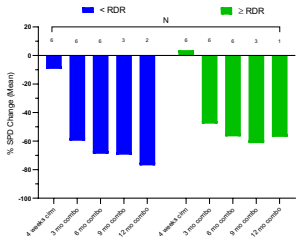
Responses in the CLL cohort of 12 evaluable patients based on investigator assessments



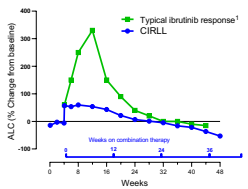
CR: Complete Response, iwCLL: International Working Group CLL criteria, CR(Clinical): Normalization of index lesions, lymphocyte count, and clinical parameters, bone marrow biopsy not performed (Rai et al., 2018), PR: Partial Response, PR-L: Partial Response with Lymphocytosis, SD: Stable disease

Two patients discontinued treatment. One patient due to worsening heart failure, unrelated to the combination treatment and one patient secondary to atrial fibrillation, pericardial effusion and tamponade, not attributed to cirmtuzumab.

Changes in the size of lymph nodes from baseline (RECIST) in the CLL cohort



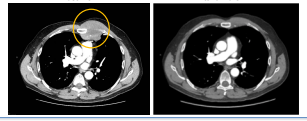
Percent change from baseline for absolute lymphocyte count (ALC) for the CLL cohort (N=12), suggesting a blunting in the lymphocytosis typically observed with ibrutinib single agent therapy



[1] Byrd et al, N Engl J Med 2013; 369:32-42

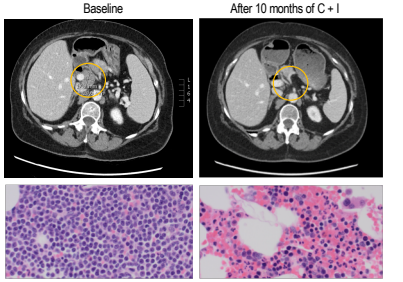
MCL Case

Six patients with MCL have also been treated in the CIRLL study, and their part 1 data will be reported separately. One patient treated experienced a complete response after 3 months of cirmtuzumab (2 mg/kg) + ibrutinib treatment, including complete resolution of a large mediastinal mass. The CR is sustained for 6+ months.

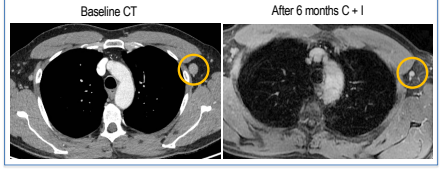


Clinical Cases

A CLL patient at the 4 mg/kg cirmtuzumab dose met iwCLL criteria for Complete Response after 10 months of combination treatment, with normalization of ALC counts and lymphadenopathy by CT scans, and no evidence for a lymphoid infiltrate or increased lymphocytes in the bone marrow (pre and on-treatment marrow biopsies shown at 400x).



A CLL Patient at 16 mg/kg had a clinical CR with normalization of lymphadenopathy by CT and MRI scans, and an ALC count in the normal range after 6 months of combination C + I treatment.



Conclusions and Future Directions

The Cirmtuzumab + Ibrutinib combination was well-tolerated. Adverse events were typical for patients receiving ibrutinib. No dose-limiting toxicities were attributed to cirmtuzumab.

On-treatment objective response rate (ORR) was 91.7% as of the data cutoff.

Three patients completed the one-year planned course. One out of these three patients met all iwCLL criteria for CR.

Two patients had clinical CR, with normalization of imaging and ALC in the normal range, pending marrow assessment.

Cirmtuzumab 600 mg + Ibrutinib 420 mg was selected as the RDR for CLL based on safety, efficacy, pharmacokinetic and pharmacodynamic measures.

600 mg per dose is a convenient way of dosing, and it is currently evaluated in Part 2 of the trial in CLL patients.

MCL accrual is ongoing, with preliminary data in the MCL cohort demonstrating one case of sustained efficacy and good tolerability of the combination.

REFERENCES

Choi, M. Y., et al. (2018). Phase I Trial: Cirmtuzumab Inhibits ROR1 Signaling and Stemness Signatures in Patients with Chronic Lymphocytic Leukemia. Cell Stem Cell 22(6): 951-959 e953. Rai K. R. & S. Stilgenbauer (2018) Evaluating response to treatment of chronic lymphocytic leukemia UpToDate, Apr 2019; Yu, J., et al. (2017). Cirmtuzumab inhibits Wnt5a-induced Rac1 activation in chronic lymphocytic leukemia treated with ibrutinib. Leukemia 31(6): 1333-1339. Yu, J., et al. (2018). Cirmtuzumab inhibits ibrutinib-resistant, Wnt5a-induced Rac1 activation and proliferation in mantle cell lymphoma. Oncotarget 9: 24731-24736

CIRRL (Cirmtuzumab + Ibrutinib for Relapsed Leukemia and Lymphoma) Investigators:
Jacqueline Barrientos, MD – Northwell Health / New Hyde Park, NY; Nicole Lamanna, MD – Columbia University / New York, NY; Tanya Siddiqi, MD – City of Hope / Duarte, CA; Philip Lerning, MD – The Christ Hospital / Cincinnati, OH; Alec Goldenberg, MD – MHONY (Manhattan Hematology Oncology Associates) / New York, NY; Iris Isufi, MD – Yale Cancer Center / New Haven, CT

E-mail: mychoi@ucsd.edu