Cirmtuzumab, a ROR1 Targeted Mab, Reverses Cancer Stemness, and Its Combination with Ibrutinib Is Safe and Effective: Planned Analysis of the *CIRLL* Phase 1/2 Trial for CLL and MCL

Abstract #1755

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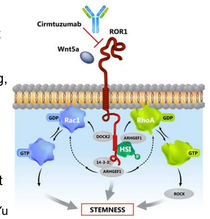
I. RATIONALE / BACKGROUND

- Receptor tyrosine kinase-like orphan receptor 1 (ROR1) is a cell surface expressed protein essential during fetal development but lost in adulthood. It is often re-expressed on many different cancers (but not normal cells), including chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), lung, breast and other NHL
- Cirmtuzumab is a humanized MAb that binds to ROR1 with high affinity and inhibits tumor cell signaling induced by its growth factor ligand Wnt-5a, preventing its activity on cancer cell survival.
- Preclinically, cirmtuzumab inhibits Wnt5a signaling and its effects on tumor differentiation, tumor cell proliferation, migration and survival. It reduces the viability of ibrutinib-resistant CLL and MCL cells and has synergistic activity with ibrutinib in preclinical models. (Yu et al., 2017; Yu et al., 2018)



- Cirmtuzumab, in a phase 1a trial, showed on-target inhibition of ROR1 signaling, reversal of cancer cell stemness, and clinical activity in the treatment of patients with CLL. (Choi et al., 2018)
- Hypothesis: The combination of cirmtuzumab and ibrutinib results in increased activity and deeper and more durable responses compared to ibrutinib, while maintaining the favorable safety profile of both agents.

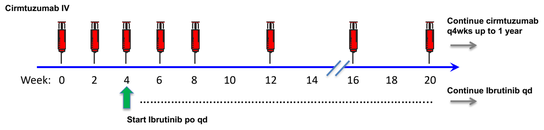
II. STUDY DESIGN

Patients with relapsed/refractory (R/R) or treatment-naïve (TN) CLL/SLL or R/R MCL who had measurable disease and were BTK-inhibitor naïve or had limited treatment were eligible to participate. (Entry criteria see ClinicalTrials.gov: NCT03088878). The study was designed in 3 parts

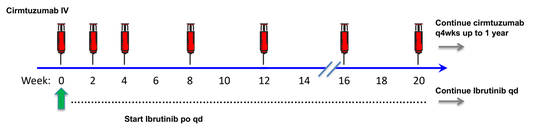
- **Part 1, Ph1 Dose Escalation of Cirmtuzumab:** Sequential patients (pts) were enrolled at increasing dose levels and standard indication specific doses of ibrutinib were initiated on Day 28. Enrollment completed: CLL/SLL, n= 18, MCL, n= 12
- **Part 2, Pt Expansion:** Following a review of safety and PK/PD data, a recommended dose regimen was chosen as cirmtuzumab 600mg IV per dose and ibrutinib at standard doses of 420mg for CLL/SLL or 560mg for MCL po qd. Pt Expansion was initiated to examine the combination regimen in a larger pts population. For CLL/SLL, Part 2 enrollment has completed n=16; for MCL, Part 2 is open and actively enrolling pts.
- **Part 3, Ph2 Randomized Cirmtuzumab/Ibrutinib vs. Ibrutinib alone in CLL/SLL**: Study was designed to determine efficacy of the combination regimen in a comparative study and is open and actively enrolling pts. Up to 90 pts who are either R/R or TN will be enrolled and assigned 2:1 to receive either cirmtuzumab (as shown in treatment schema figure for Part 2) and standard dose ibrutinib at 420mg po qd vs. ibrutinib alone.

Treatment Schema for Parts 1&2

Part 1: Dose Escalation, Sequentially enrolled/dosed pts at 2, 4, 8, 16 mg/kg x3 and then 300mg, 600mg x3, n= 18



Part 2: Patient Expansion, Enrolled/dosed pts at 600mg flat dose, n= 16



Patient Characteristics

	CLL/SLL	MCL
Age (years), n (pts)	34	12
Mean (Median)	67.5 (68.0)	61.4 (63.5)
Range	37.0 to 86.0	49.0 to 70.0
Gender, n (pts)	34	12
Male / Female	26 (76/5%) / 8 (23.5%)	10 (83.3%) / 2 (16.7%)
# Years since Diagnosis, n (pts)	33 (1 missing data)	12
Mean (Median)	8.1 (6)	3.9 (3.3)
Range	(0 – 31)	(0.4 – 9.2)
Prior Therapy, n (pts)	34	12
Treatment-Naive	12 (35%)	
Relapsed / Refractory	22 (65%)	12 (100%)
# Prior Systemic Regimens	# prior regimens: 56 Evaluable Pts: n= 22	# prior regimens: 22 Evaluable pts: n= 8
Regimens/pt: Mean (Median); Range	2.5 (2); 1 to 9	2.8 (2.5) 1 to 5
Regimens containing		
Chemotherapy	23 (41.1%)	19 (86.4%)
Biologics	50 (89.3%)	18 (81.8%)
PI3k or Bcl-2 inhibitors, Imids	9 (16.1%)	1 (4.5%)
Other (MCL only):		Auto-SCT (2), Allo-SCT (1), CAR-T (1)
Bone Marrow Involvement at Entry, n	34	8
	34 (100%)	4 (50%)

For MCL, N= 8 evaluable pts who have received combination therapy and have follow-up data.

III. CLINICAL RESULTS

Safety of Cirmtuzumab and Combination With Ibrutinib

- Cirmtuzumab was very well tolerated and adverse events considered at least possibly related were transient and grade 1 or 2. No DLTs or grade 3 possibly related events occurred.
  - Most common events possibly related to cirmtuzumab or the combination of cirmtuzumab/ibrutinib included fatigue, diarrhea, contusion
- Grade 3 events were only reported as at least possibly related to ibrutinib or the combination of ibrutinib and cirmtuzumab and consisted of adverse events previously reported for ibrutinib
- A total of 5 SAEs were reported that were considered potentially related to study agents, 4 in CLL/SLL pts and 1 in MCL. None were considered related to cirmtuzumab alone.
  - CLL/SLL: All 4 SAEs were considered related to ibrutinib. MCL: 1 SAE of infection was reported
  - Of the SAE cases: ≥ grade 3 events included Afib (2), pericardial hemorrhage (1), hyperkalemia (1), pneumonia (1)
- Overall, the addition of ibrutinib to cirmtuzumab was consistent with the AE profile reported for ibrutinib alone

Safety: Possibly Related AEs Reported in ≥10% Per Indication

CLL/SLL							
Preferred Term	Related to cirmtuzumab only		Related to ibrutinib only		Related to the combination of cirmtuzumab + ibrutinib		Overall N= 34
	Grade 1-2	Grade 3+	Grade 1-2	Grade 3+	Grade 1-2	Grade 3+	Any Grade
Subjects ≥1 Related TEAE	6 (17.6%)	0	20 (58.8%)	7 (20.6%)	11 (32.4%)	4 (11.8%)	29 (85.3%)
Contusion	0	0	8 (23.5%)	0	2 (5.9%)	0	9 (26.5%)
Nail Disorder	0	0	6 (17.6%)	0	0	0	6 (17.6%)
Muscle Spasm	0	0	10 (29.4%)	0	0	0	10 (29.4%)
Arthralgia	0	0	4 (11.8%)	0	0	0	4 (11.8%)
Diarrhea	0	0	9 (26.5%)	0	2 (5.9%)	1 (2.9%)	10 (29.4%)
Fatigue	3 (8.8%)	0	1 (2.9%)	0	6 (17.6%)	0	9 (26.5%)
Hematuria	0	0	4 (11.8%)	0	0	0	4 (11.8%)
Hypertension	0	0	3 (8.8%)	1 (2.9%)	0	0	4 (11.8%)

MCL							
Preferred Term	Related to cirmtuzumab only		Related to ibrutinib only		Related to the combination of cirmtuzumab + ibrutinib		Overall (N=12)
	Grade 1-2	Grade 3+	Grade 1-2	Grade 3+	Grade 1-2	Grade 3+	Any Grade
Subjects ≥1 Related TEAE	3 (25.0%)	0	5 (41.7%)	2 (16.7%)	4 (33.3%)	1 (8.3%)	9 (75.0%)
Diarrhea	1 (8.3%)	0	3 (25.0%)	0	2 (16.7%)	0	5 (41.7%)
Fatigue	1 (8.3%)	0	2 (16.7%)	1 (8.3%)	2 (16.7%)	0	6 (50.0%)
Contusion	0	0	4 (33.3%)	0	0	0	4 (33.3%)
Anaemia	0	0	1 (8.3%)	0	0	1 (8.3%)	2 (16.7%)
Neutropenia	0	0	1 (8.3%)	1 (8.3%)	0	0	2 (16.7%)

Note: Pts who reported separate Aes for ibrutinib or cirmtuzumab alone and also an AE related to the combination were counted separately within each category. However, this AE term would be counted once in the overall as a reported term per pt.
All Grade 3 events reported for either MCL or CLL/SLL (no grade 3 events attributed to cirmtuzumab alone): fatigue (1), neutropenia (3), anemia (1),staph infection (1), hypocalcemia (1), hyperkalemia (1), pericardial hemorrhage (1), hypertension (1), leukocytosis (1), myalgia (1), diarrhea(1), atrial fibrillation (2), pneumonia (1),

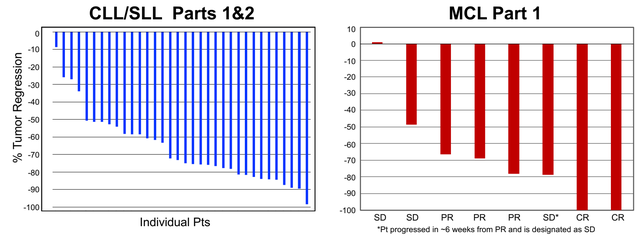
Efficacy of Cirmtuzumab / Ibrutinib

	Evaluable Pts N=	Overall Best Objective Response (CR & PR)*	Clinical Benefit (CR, PR, SD)	CR	PR	SD	PD
CLL/SLL	34 Parts 1&2	29 (85.3%)	34 (100%)	1** (3%)	28 (82%) 20 PR; 8 PR-L	5 (15%)	0
MCL***	8	5 (62.5%)	8 (100%)	2 (25%)	3 (37.5%)	3**** (37.5%)	0

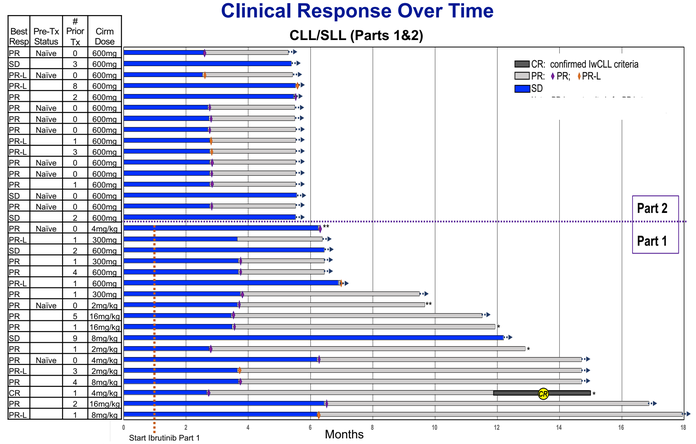
*Includes both confirmed and unconfirmed best responses as described below.
**At their most recent efficacy evaluations, there were 3 pts with Clinical CR, bone marrow biopsy not performed, (Rai 2018, UpTo Date) among the 28 pts with PR. These pts met CR criteria for tumor and lymphocyte reduction, normalization of lab criteria per iwCLL criteria but have unknown bone marrow (BM) status at this time (1 pt had a poor quality biopsy; 2 pts had evidence of CLL many months earlier). All have completed additional therapy and are awaiting repeat biopsies.
***MCL enrolled 12 pts but only 8 are evaluable with data following start of combination therapy.
****Of pts with SD, one remains stable with regressing disease >4 mos; two developed PD ~3 and 6 mos later. (Note: 1 SD pt achieved a PR but had progressive disease within 6 wks and was designated as a best response of SD)

For CLL: A PR was defined as 1) reduction of SPD ≥50%; 2) reduction of ALC ≥50%; 3) iwCLL criteria for Hgb and platelets; 4) if known, 50% reduction of enlarged spleen (by exam or based on normal of 13cm CT) or return to normal size ≤13cm. The first instance of meeting criteria were used to define PR (includes unconfirmed); if pt progressed within 8 wks of response, the response was called PD. A PR-L was defined as meeting the criteria for a PR but with a lymphocyte ct that did not decrease ≥50% or return to a normal value of 4000 (ALC, iwCLL CR criteria)

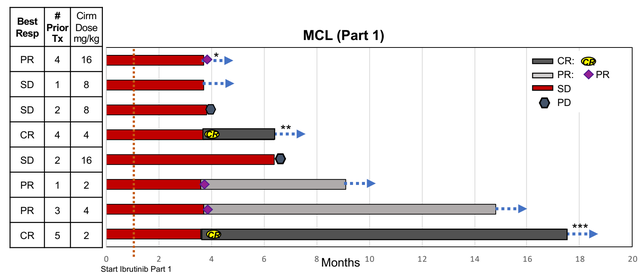
Tumor Regression: Maximal Change in SPD From Baseline



Clinical Response Over Time



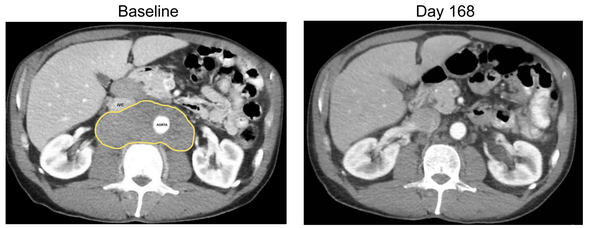
*Completed 1 year of planned therapy and did not join Extension. Based on follow-up visits and clinical assessments at 3 and, recently, 6 months post-study completion, PI reports that this pt remains well and continues to remain in remission >6 months off all therapy.
** Left study after experiencing SAEs considered unlikely related to cirmtuzumab but possibly related to ibrutinib (Afib, pericardial hemorrhage, pneumonia)



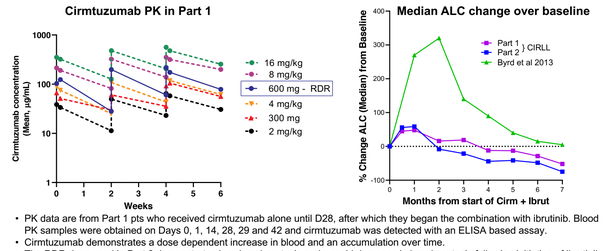
Note: Prior Therapy included, *auto-SCT; **auto-SCT and CAR-T; ***auto-SCT and allo-SCT

Rapid Response in Patient with Bulky Disease

- 66 y.o man with CLL/SLL dx in Dec2018 who enrolled and started on the study on 28Mar2019 and received cirmtuzumab 600mg IV/dose and ibrutinib 420 po qd. Tolerated Tx well with no cytopenias and only grade 1 AEs.
- Bulky tumor with retroperitoneal, pelvic, subcarinal and paravertebral masses, lymphocytosis at 50.4 k/µl, and marrow involvement. Achieved PR on Day 84 and confirmed on Day 168: Tumor masses baseline SPD 203.32 cm² → 2.82 cm² (largest residual node 1.3x1cm, all others <1cm) and lymphocyte ct 50.4 K/µl → normal 3.2 K/µl. Heme parameters normal. BM Bx was not interpretable; repeat pending. Pt is in a Clinical CR, bone marrow not done (included in PR total)

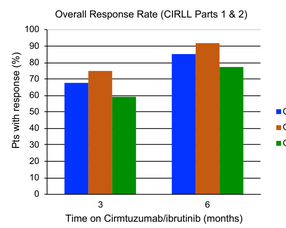


Cirmtuzumab RDR Dose And Clinical Effects

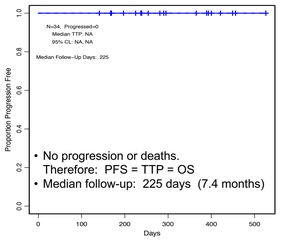


- PK data are from Part 1 pts who received cirmtuzumab alone until D28, after which they began the combination with ibrutinib. Blood PK samples were obtained on Days 0, 1, 14, 28, 29 and 42 and cirmtuzumab was detected with an ELISA based assay.
- Cirmtuzumab demonstrates a dose dependent increase in blood and an accumulation over time.
- The RDR dose used in Part 2 demonstrates less lymphocytosis and a rapid decrease in lymphocytosis following initiation of ibrutinib compared to historical data.

CLL/SLL Patients Receiving Cirmtuzumab/Ibrutinib Can Rapidly Achieve Clinical Responses

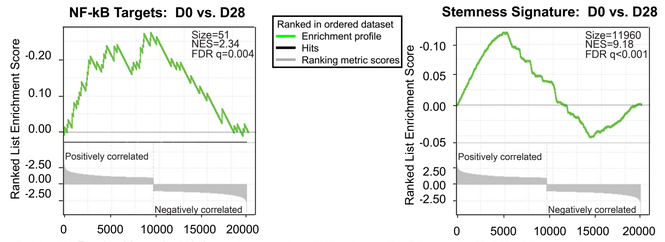


CLL/SLL Progression-Free Survival



- No progression or deaths.
  Therefore: PFS = TTP = OS
- Median follow-up: 225 days (7.4 months)

Reversal of NF-kB Target Genes and Cancer-Cell-Stemness Transcriptome Signature



- Peripheral blood mononuclear cells of 3 CLL samples were collected before therapy (Pre-Rx) and at day 28 (D28) of cirmtuzumab treatment. Negative isolation of CLL cells to more than 95% purity was performed before total RNA isolation. RNAseq data were analyzed as previously described (Choi MY et al., 2018). A gene set was considered significant when the false discovery rate (FDR) was less than 25%. The FDR q value was adjusted for gene set size and multiple hypothesis testing
- Gene Set enrichment analyses (GSEA; Subramanian et al., 2005) on the transcriptomes of 3 pts treated with cirmtuzumab on Part 1 were performed using paired pre- and post-treatment CLL cells at D28 (cirmtuzumab only, no ibrutinib). We evaluated pre and post-treatment differences in the expression of a gene set associated with stemness (Malta et al., 2018) as well as inflammation (NF-kB target genes) (Feuerhake et al., 2005). Transcriptome analyses of post-treatment leukemia cells demonstrated that treatment with cirmtuzumab led to a reversal in the gene expression signature associated with stemness and oncogenic dedifferentiation (Right panel, FDR q < 0.001). Notably, the GSEA of NF-kB target genes revealed that cirmtuzumab suppressed expression of NF-kB-target genes (Left panel, FDR q = 0.004) induced by ROR1-signaling (Chen et al., Blood 2019).

IV. Overall Conclusions

- The combination of cirmtuzumab plus ibrutinib is a well-tolerated and active regimen for pts with CLL or MCL. The time to response, depth, and duration of response are compelling for further development.
- In CLL/SLL, the combination achieved an overall best response rate of 85.3% (CR and PR) and Clinical Benefit (CR, PR, SD) of 100%. At their last evaluation, an additional 3 pts have achieved Clinical CR, bone marrow biopsy not performed, and a pt who achieved a CR remains in remission >6 months after completing the trial and stopping all therapy.
- In CLL/SLL pts treated with the combination therapy, results demonstrate an ability to generate rapid clinical responses with blunted lymphocytosis.
- Two R/R MCL pts (25% of evaluable pts) with aggressive or bulky disease achieved CRs. Both pts were heavily pre-treated. Both had previously received auto-SCT and later, one received an allo-SCT and the other, CAR-T therapy. Part 2 is enrolling.
- The inhibition of ROR1 signaling by cirmtuzumab was shown to down-regulate NF-kB-driven inflammation and Stemness signature as determined by gene expression analyses
  - Stemness has been noted to be increased in cases of CLL with acquired resistance to venetoclax (Ghia et al, ASH 2019 abstract 476). This group of pts with high unmet medical need may benefit from cirmtuzumab + ibrutinib.
- The efficacy of the combination of cirmtuzumab/ibrutinib is now being compared to single agent ibrutinib in a randomized phase 2 trial at a recommended dose level.
- ROR1 is expressed on a large number of other hematologic and solid cancers and encouraging preclinical and clinical data (e.g. breast) targeting these other indications with cirmtuzumab are emerging.