Clinical Activity of Cirmtuzumab, an Anti-ROR1 Antibody, in Combination with Ibrutinib; Interim Results of a Phase 1b/2 Study in Mantle Cell Lymphoma (MCL) or Chronic Lymphocytic Leukemia (CLL)

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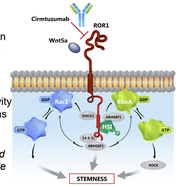
Update Since Abstract:

- *In Feb 2020, we observed and reported in this ASCO abstract, an 83% ORR, 33% (4) CR, 50% (6) PR in our 12 evaluable relapsed /refractory MCL patients.*
- ***As of 30April2020, we now report 7 of 12 (58%) relapsed/refractory MCL patients have achieved a CR, per Cheson criteria, including one patient with a complete metabolic response (CMR, PET-CT). The ORR remains 83%.***

I. RATIONALE / BACKGROUND

- ROR1 is an onco-embryonic tyrosine kinase receptor that is re-expressed at high levels on many hematologic and solid cancers but not on normal adult tissues. ROR1 binds Wnt5a, resulting in increased tumor growth and survival, cancer cell stemness and epithelial mesenchymal transition.
- Cirmtuzumab (Cirm) is a humanized monoclonal antibody designed to inhibit the tumor promoting activity of ROR1. In preclinical studies, Cirm has demonstrated anti-tumor activity as a single agent and has had at least additive effects when combined with agents such as BTK inhibitors. In this study, we examined the safety and efficacy of Cirm in combination with ibrutinib (Ibr) in MCL or CLL. (Yu et al., 2017; Yu 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.*



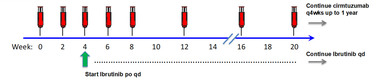
II. STUDY DESIGN

Patients with relapsed/refractory (R/R) MCL or R/R or treatment-naïve (TN) CLL/SLL who had measurable disease and who had limited or no prior BTK-inhibitor treatment were eligible to participate. Patients were adults ≥18 years, with ECOG <3, radiographically measurable disease and requiring therapy. (Entry criteria see ClinicalTrials.gov: NCT03088878). The study was designed in 3 parts:

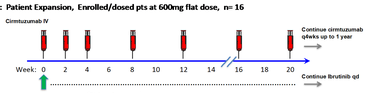
- **Part 1, Ph1 Dose Escalation of Cirmtuzumab:** Sequential patients (pts) were enrolled at increasing dose levels and standard indication specific doses of ibrutinib were initiated on Day 28. Enrollment completed: MCL, n= 12; CLL/SLL, n= 18.
- **Part 2, Expansion Cohort:** Following a review of safety and PK/PD data, a recommended dose regimen was chosen as cirmtuzumab 600mg IV per dose and ibrutinib at standard doses of 560mg for MCL or 420mg for CLL/SLL po qd. Pt Expansion was initiated to examine the combination regimen in a larger population. For CLL/SLL, Part 2 enrollment has been 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 actively enrolling CLL pts.

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

		MCL Part 1	CLL/SLL Parts 1&2
n (pts)		12	34
Age (years)	Mean (Median)	61.4 (63.5)	67.5 (68.0)
	Range	49.0 to 70.0	37.0 to 86.0
Gender	Male / Female	10 (83.3%) / 2 (16.7%)	26 (76.5%) / 8 (23.5%)
# Years since Dx	Mean (Median)	3.4 (2.5)	7.6 (5.5)
	Range	(< 1 yr to 9)	(<1 yr to 30)
Prior Therapy	Treatment-Naive	12 (35%)	12 (35%)
	Relapsed / Refractory	12 (100%)	22 (65%)
# Prior Systemic Regimens		**# Prior regimens: 31 Evaluable pts: n= 12**	**# Prior regimens: 57 Evaluable R/R Pts: n= 22**
Regimens/pt:	Mean (Median); Range	2.8 (2.5) 1 to 5	2.6 (2) 1 to 9
Regimens containing			
Chemotherapy		27 (87.1%)	23 (40.4%)
Biologics		27 (87.1%)	50 (87.7%)
PI3k or Btk-2 inhibitors, Imids		–	9 (15.8%)
Ibrutinib (1, 7, 10, 10 mo duration)		4 (12.9%)	
Stem Cell Transplant		Auto-SCT (5), Allo-SCT (1),	
CAR-T		CD19-CAR-T (1)	

MCL Expansion and CLL Part 3 Randomized Comparison are ongoing studies. Data are incomplete and these Study arms will only be included for safety analyses.

III. CLINICAL RESULTS

Safety of Cirmtuzumab and Combination With Ibrutinib

- Cirmtuzumab was very well tolerated in both MCL and CLL patients and adverse events considered at least possibly related were transient and grade 1 or 2. No DLTs or grade 3 events occurred that were possibly related to cirmtuzumab alone.
  - Most common events possibly related to cirmtuzumab or the combination of cirmtuzumab/ibrutinib included fatigue, diarrhea, contusion.
  - Reported neutropenia of any grade and regardless of assigned relationship to study agents occurred in 6 subjects (8.6%). Neutropenia is described as occurring in 50-60% of patients in the Imbruvica Prescribing information.
- 1 MCL and 9 CLL patients reported treatment related SAE events. SAEs were considered potentially related to ibrutinib or ibrutinib plus cirmtuzumab but none to cirmtuzumab alone.
  - Of the SAE cases reported for patients, grade 3 or higher events included Afib (5), pneumonia (3), pericardial hemorrhage (1), pleural effusion (1), pyrexia (1), hyperkalemia (1), GI hemorrhage (1), staph infection (1).
- Overall, the addition of cirmtuzumab to ibrutinib was without any new grade 3 or higher adverse events and was consistent with the AE profile reported for ibrutinib alone.

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

Incidence of Related Treatment Emergent Adverse Events in >1 Subject (>10%) in the MCL Safety Population

MCL (N=15) All Part1&2	Related to Cirm		Related to Ibrutinib		Related to combination of Cirm + Ibrut		Overall
Preferred Term	Grade 1-2	Grade 3+	Grade 1-2	Grade 3+	Grade 1-2	Grade 3+	Any Grade
Pts with ≥1 Related TEAE	4 (26.7%)	0	8 (53.3%)	3 (20.0%)	4 (26.7%)	1 (6.7%)	13 (86.7%)
Diarrhoea	1 (6.7%)	0	5 (33.3%)	0	2 (13.3%)	0	7 (46.7%)
Fatigue	1 (6.7%)	0	3 (20.0%)	2 (13.3%)	2 (13.3%)	0	7 (46.7%)
Contusion	0	0	4 (26.7%)	0	0	0	4 (26.7%)
Rash	0	0	2 (13.3%)	0	1 (6.7%)	0	3 (20.0%)
Nausea	0	0	1 (6.7%)	0	1 (6.7%)	0	2 (13.3%)
Anaemia	0	0	1 (6.7%)	1 (6.7%)	0	1 (6.7%)	2 (13.3%)
Neutrophil count decreased	0	0	1 (6.7%)	1 (6.7%)	0	0	2 (13.3%)
Platelet count decreased	0	0	2 (13.3%)	0	0	0	2 (13.3%)
Haematuria	0	0	2 (13.3%)	0	0	0	2 (13.3%)

Incidence of Related Treatment Emergent Adverse Events with an Incidence of >10% in the CLL Safety Population

CLL/SLL (N=55)	Related to Cirmt		Related to Ibrutinib		Related to combination Cirm + Ibrut		Overall
Preferred Term	Grade 1-2	Grade 3+	Grade 1-2	Grade 3+	Grade 1-2	Grade 3+	Any Grade
Pts with ≥1 Related TEAE	9 (16.4%)	0	28 (50.9%)	0	20 (36.4%)	0	46 (83.6%)
Contusion	0	0	14 (25.5%)	0	2 (3.6%)	0	15 (27.3%)
Diarrhoea	0	0	14 (25.5%)	0	2 (3.6%)	1 (1.8%)	15 (27.3%)
Fatigue	3 (5.5%)	0	4 (7.3%)	0	8 (14.5%)	0	14 (25.5%)
Hypertension	0	0	9 (16.4%)	2 (3.6%)	0	1 (1.8%)	12 (21.8%)
Muscle spasms	0	0	10 (18.2%)	0	0	0	10 (18.2%)
Onychoclasis	0	0	6 (10.9%)	0	1 (1.8%)	0	7 (12.7%)
Arthralgia	0	0	6 (10.9%)	1 (1.8%)	0	0	7 (12.7%)
Atrial fibrillation	0	0	2 (3.6%)	5 (9.1%)	0	0	7 (12.7%)
Nail disorder	0	0	6 (10.9%)	0	0	0	6 (10.9%)
Nausea	0	0	4 (7.3%)	0	3 (5.5%)	0	6 (10.9%)

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.

Disposition After Enrollment

Indication	Dosed	12 Weeks Combo Tx	24 Weeks Combo Tx	Completed 48 weeks Combo Tx	Extended Tx*	D/c'd*
CLL Part 1	18	18	18	16	6*	4
CLL Part 2	16	16	16	15	10	1
MCL Part 1	12	12	11	4	2	3

- Most patients have completed the planned 1 year on study. 6 CLL pts from Part 1 and 10 pts from Part 2 have chosen to enroll into extended therapy and continue combination treatment. Most MCL pts have completed 6 months of therapy; 2 have completed 1 year and enrolled into extended therapy.
- Reasons for discontinuations **during planned therapy**:
  - MCL Part 1: 3 discontinuations due to progressive disease – Days 140, 196, and 560.
  - CLL Part 1: 2 came off due to AE's (pericardial hemorrhage and pneumonia thought possibly related to ibrutinib); 1 sought alternative therapy; 1 required therapy for a pre-existing prostate cancer.
  - CLL Part 2: 1 discontinued due to an AE (arthralgias thought possibly related to ibrutinib).
  - COVID-19: One Part 3 CLL patient on ibrutinib alone was recently reported to have developed COVID-19 infection but is doing well. Two pts from Parts 1&2 extended therapy and one from Part 3 CLL have discontinued due to fear of contracting COVID-19 at the hospital. Sponsor has been working with the sites to minimize disruption of patient visits and treatments.
- MCL Part 2 and CLL Part 3 are ongoing and patients are not yet evaluable for efficacy. These data will be presented at a future meeting.

*Extended therapy refers to patients enrolled in Extended treatment arm to receive combination therapy beyond planned 1 year. D/c'd are patients discontinuing from the study for known reasons.

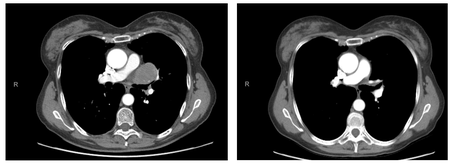
EFFICACY OF CIRMTUZUMAB / IBRUTINIB

	Evaluable Pts N=	Overall Best Objective Response (CR & PR)	Clinical Benefit (CR, PR, SD)	CR	PR	SD	PD
MCL	12	10/12 (83.3%)*	12 (100%)	7 (58.3%)*	3 (25%)	2 (16.7%)	0
CLL	34 Parts 1&2	30 (88.2%)	34 (100%)	1 (3%)	29 (85%) 25 PR; 4 PR-L	4 (12%)	0

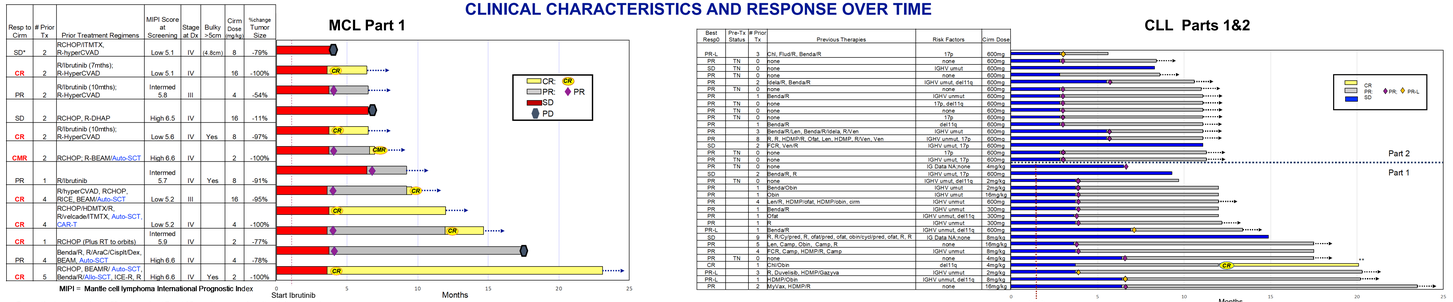
*CR and CMR determined by Cheson criteria. Data include one complete metabolic remission (CMR) by PET-CT; blinded review of bone marrow biopsy was indeterminant for tumor involvement.

Rapid Response in an MCL Patient with Bulky Disease

- 63yo female diagnosed with stage 4 MCL in 2017.
- Previous Therapy: R-Ibrutinib therapy followed by Hyper-CVAD alternating R-MTX-AraC for 3 cycles consolidation as part of a study. The patient achieved a complete metabolic response after having received 10.5 months of this ~13 month regimen.
- The patient developed progressive disease ~6.3 months later and enrolled in the cirmtuzumab plus ibrutinib study.
- Study Treatment regimen: cirmtuzumab 8 mg/kg for 1 month, followed by its combination with Ibrutinib.
- As shown in the CT images, the patient achieved a CR with rapid resolution of pulmonary lesions within 3 months of treatment with the combination of cirmtuzumab plus ibrutinib and remains in CR 3 months later.



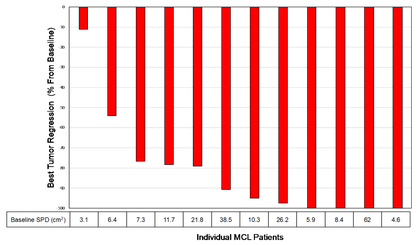
CLINICAL CHARACTERISTICS AND RESPONSE OVER TIME



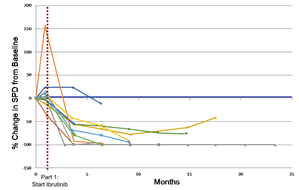
MIPI = Mantle cell lymphoma International Prognostic Index

Two patients who achieved CR had received 7 and 10 months or previous ibrutinib, respectively.

MCL Tumor Regression: Max Change From Baseline SPD

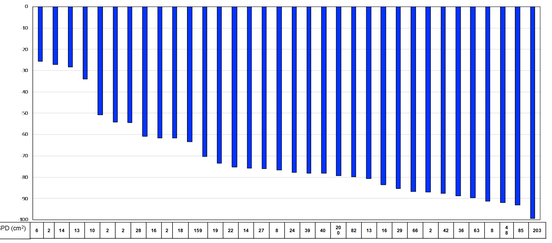


MCL: Individual % Change in SPD From Baseline

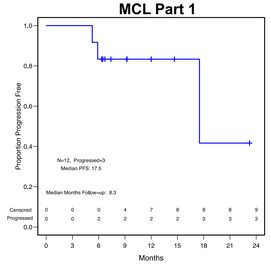


- The majority of patients had a rapid and sustained tumor regression over time.
- One pt had transient tumor growth at day 28 but then rapidly became a CR.

CLL Tumor Regression: Max Change From Baseline SPD



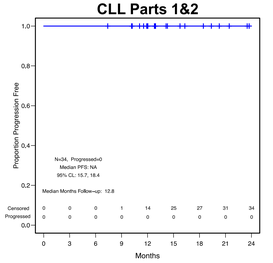
MCL Part 1



Progression−Free Survival

- MCL: With a median follow-up of 8.3 months, an initial median PFS of 17.5 months was observed. Note: only 2 patients have been on study >15 months.
  - Although numbers are small, the initial response rate and PFS appear to compare favorably with historical data. All R/R MCL patients had a PFS of 12.5 months on single agent ibrutinib, while those with >1 prior therapy receiving ibrutinib alone had a PFS of 10.3 months (Rule Haematologica 2019)
- CLL: With a median follow-up of 12.8 months, the median PFS has not yet been reached. There has been no PD reported for active patients on the study.

CLL Parts 1&2



IV. Overall Conclusions

MCL:

- The combination of cirmtuzumab plus ibrutinib is a well-tolerated and active regimen for patients. The time to response, depth, and duration of response are compelling for further development.
- Although only a limited number of patients are evaluable at this time, a high tumor response rate has been observed with an ORR of 83%, a CR rate of 58% and an initial median PFS of 17.5 months.
- Patients who had received 1-10 months of previous ibrutinib treatment responded well to the cirmtuzumab-ibrutinib combination, with 2 CRs and 2 PRs.
- Historical data have been published on single agent ibrutinib in a similar patient population: ORR 67% & CR rate 23% for ibrutinib in MCL with >1 prior lines of therapy in a pooled analysis across 3 third-party clinical studies (Rule Haematologica 2019).
- All patients have had relapsed / refractory disease and most had been heavily pre-treated, including 5 patients who had auto-SCT, 1 allo-SCT, and 1 CAR-T.
- Four of the patients, including two that achieved an early CR, had previously been treated with ibrutinib.
- The expansion cohort (part 2) is open and actively enrolling patients.

CLL/SLL:

- The combination achieved an overall best response rate of 88% (CR and PR) and Clinical Benefit (CR, PR, SD) of 100%. 1 patient has achieved a CR and has remained in remission for over 8 month off all CLL therapy; an additional 3 others have achieved deep PRs with normalization of tumor sites and blood but remain with either unknown or positive bone marrows.
- The efficacy of the combination of cirmtuzumab/ibrutinib is now being compared to single agent ibrutinib in a randomized Phase 2 trial using the recommended dosing regimen.

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