Abstract #7556

Phase 1/2 Study of Cirmtuzumab and Ibrutinib in Mantle Cell Lymphoma (MCL) or Chronic Lymphocytic Leukemia (CLL)

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ASCO 2021
June 4-June 8, 2021
Virtual Meeting

UPDATE SINCE ABSTRACT

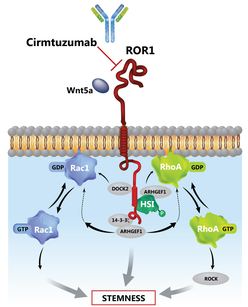
On 02FEB2021, we reported in this ASCO abstract, 82% ORR, 41% CR, 41% PR, 12% SD, and 6% PD in 17 evaluable relapsed/refractory MCL patients.

As of 16APR2021, we now report, 83.3% ORR, 38.9% CR, and 44.4% PR, 11.1% SD and 5.6% PD in 18 evaluable relapsed/refractory MCL patients.

BACKGROUND

Front-line use of multiagent therapy is commonly successful in suppressing disease manifestations for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and mantle cell lymphoma (MCL).

However, these diseases are incurable, and patients require further therapy for disease control.

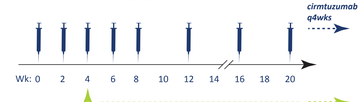


- ROR1 is an onco-embryonic tyrosine kinase receptor that is re-expressed at high levels on many solid and hematologic cancers including MCL and CLL, but not on normal adult tissues. ROR1 binds Wnt5a, resulting in increased tumor growth, survival, metastasis, cancer cell stemness and epithelial mesenchymal transition
- Cirmtuzumab is a humanized monoclonal antibody designed to inhibit the tumor promoting activity of ROR1

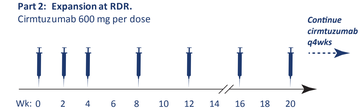
PHASE 1/2 STUDY DESIGN

Population: Relapsed/refractory (R/R) MCL or treatment naive or (R/R) CLL SLL with radiographically measurable disease and ECOG≤3; Prior BTK0inhibitor allowed

Part 1: Dose Escalation.
Cirmtuzumab 2, 4, 8, 16 mg/kg, 300 mg, 600 mg per dose



Part 2: Expansion at RDR.
Cirmtuzumab 600 mg per dose



- Conventional 3+3 design-Part 1
- Expansion-Part 2
- No DLTs; MTD not reached
- Phase 1 is complete
- RDR: 600 mg IV q2wks x3 then q4wks in combination with ibrutinib at approved doses per indication
- Phase 2 CLL/SLL randomized clinical trial (Part 3) has completed enrollment
- Phase 2 MCL Expansion (Part 2) enrolling new patients

ECOG = Eastern Cooperative Oncology Group, RDR = recommended dose regimen, MTD = maximum tolerated dose, DLT = dose limiting toxicity

DEMOGRAPHY AND CHARACTERISTICS

	MCL n=26	CLL/SLL n=34
Median age, years (min, max)	66.5 (45.0, 85.0)	68.0 (37.0, 86.0)
Male, n (%)	22 (84.6)	26 (76.5)
White, n (%)	19 (73.1)	29 (85.3)
ECOG 0-1, n (%)	23 (88.5)	34 (100)
Median time from diagnosis to study start (years)	1.87 (0.04, 9.15)	5.84 (0.03, 31.33)
Lymphocytosis at baseline, n (%)	3 (11.5)	22 (64.7)
Ki-67 ≥30%, n (%)	14 (70.0)^	N/A
sMIPI Intermediate/High, n (%)	4 (15.4)	N/A
RAI staging at baseline, ≥2, n (%)	N/A	29 (85.3)
LDH >250 U/L, n (%)	N/A	13 (38.2)
Received prior systemic treatments, n (%)	25 (96.2)	22 (64.7)
Median number of prior systemic treatments (range)	2 (1, 5)	2 (1, 15)
Number of prior systemic regimens >1, n (%)	13 (52.0)*	13 (59.0)*
Prior BTK inhibitor, n (%)	4 (15.4%)**	0
Prior transplant/cell therapy, n (%)	6 (23.1)##	1 (2.9)##

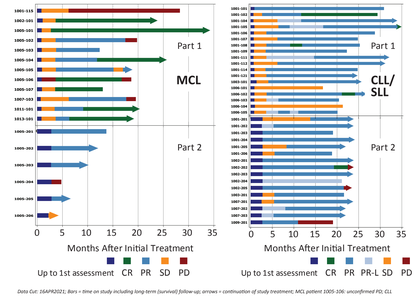
*Data Cut: 16APR2021; MCL patients include Parts 1 & 2; CLL patients include Parts 1 & 2; Lymphocytosis at baseline- ALC > 4 x 10⁹/L; N/A = not applicable; ^Percentage of Ki-67 is based on the number of subjects with Ki-67 % assessed; Ki-67 % was assessed in 76.9% (n=20/26) of MCL patients; sMIPI = Simplified Mantle Cell Lymphoma International Prognostic Index; LDH = lactate dehydrogenase; *Percentages of prior treatments are based on the number of subjects who had received prior treatments; ** prior BTKi = ibrutinib; # Autologous stem cell transplant (n=6), Allogeneic stem cell transplant (n=1); CAR-T (n=1) patients could have received more than one; ## Autologous stem cell transplant (n=1)*

PATIENT DISPOSITION

	MCL	CLL/ SLL
Patients enrolled, n	26	34
Safety population, n	26	34
Efficacy/Evaluable* population, n	18	34
Ongoing, n (%)	14	18
Median Duration of follow-up in months (95% CI)	8.5** (6.67, 14.37)	22.1 (17.63, 22.81)
Discontinued Treatment, n (%)	12 (46.2)	16 (47.1)
Reasons for Discontinuation#:		
• Objective disease progression, n (%)	4 (33.3)	1 (6.3)
• Clinical progression, n (%)	2 (16.7)	0
• Adverse event, n (%)	1 (8.3)	5 (31.3)
• Withdrawl of consent, n (%)	3 (25.0)	6 (37.5)
• Investigator Decision/New Treatment, n (%)	1 (8.3)	4 (25.1)
• Death	1 (8.3)	0

*Data Cut: 16APR2021; MCL patients include Parts 1 & 2; CLL patients include Parts 1 & 2; *Efficacy/evaluable population includes patients that received at least one dose of cirmtuzumab and had at least one post-baseline tumor assessment; ** Short median duration of follow-up secondary to newly enrolled patients with limited follow-up; # Percentages for reason for discontinuation are based on the number of patients who discontinued treatment*

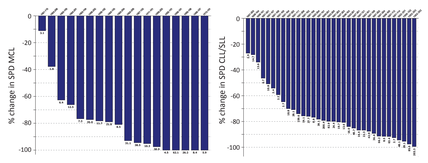
PATIENT OVERVIEW: SWIMMERS PLOT



Data Cut: 16APR2021; Bars = time on study including long-term (survived) follow-up; arrows = continuation of study treatment; MCL patient 1005-106: unconfirmed PD; CLL patients 1001-108, 1006-102, 1002-202: unconfirmed CR; CLL patient 1002-202: unconfirmed PD; CLL patient 1002-205: unconfirmed PD

EFFICACY

Waterfall Plot of Best % Tumor Reduction from Baseline SPD (cm^2)



Data cut: 16APR2021; MCL patients include Parts 1 & 2; CLL patients include Parts 1 & 2; Evaluable patients (n=18-MCL; n=34-CLL/SLL); SPD = sum of products of diameters; Number under bars represent baseline SPD

EFFICACY

CLINICAL RESPONSE RATES

	MCL Evaluable=18	CLL/SLL Evaluable=34
Overall Response Rate (ORR), n (%)	15 (83.3)	32 (94.1)
CR, n (%)	7 (38.9)	5 (14.7)
PR, n (%)	8 (44.4)	27* (79.4)
SD, n (%)	2 (11.1)	2 (5.9)
PD, n (%)	1 (5.6)	0
Clinical Benefit Rate, n (%)	17 (94.4)	34 (100)
Median Duration of Response in months (95% CI)	NE (11.93, NE)	NE

*Data cut: 16APR2021; MCL patients include Parts 1 & 2; CLL patients include Parts 1 & 2; Patients were considered evaluable for response if they had 1-dose of cirmtuzumab and had 1 post baseline tumor assessment; CR = complete remission, PR = partial remission, SD = stable disease, PD = progressive disease; ORR = number and percent of patients that achieved CR or PR; Clinical benefit rate = number of patients that achieved CR, PR or SD; NE = not estimable; *includes 1 PR with lymphocytosis*

MCL EFFICACY

CLINICAL RESPONSE RATES in Sub-Groups

	All MCL Evaluable=18	Ki-67 ≥30% n=9	1 prior systemic regimen n=9	>1 prior systemic regimen n=9
Overall Response Rate (ORR), n (%)	15 (83.3)	8 (88.9)	7 (77.8)	8 (88.9)
CR, n (%)	7 (38.9)	3 (33.3)	2 (22.2)	5 (55.6)
PR, n (%)	8 (44.4)	5 (55.6)	5 (55.6)	3 (33.3)
SD, n (%)	2 (11.1)	0	1 (11.1)	1 (11.1)
PD, n (%)	1 (5.6)	1 (11.1)	1 (11.1)	0
Clinical Benefit Rate, n (%)	17 (94.4)	8 (88.9)	8 (88.9)	9 (100)
Median Duration of Response in months (95% CI)	NE (11.93, NE)	13.84 (8.66, NE)	NE (11.93, NE)	NE (8.66, NE)
Median Time to First Response in months (95% CI)	2.79 (2.66, 2.79)	2.79 (2.66, 2.79)	2.79 (2.66, 2.85)	2.77 (1.84, 2.82)
Median Time to CR in months (95% CI)	2.79 (1.84, 8.20)	2.79 (2.66, 11.02)	6.84 (2.66, 11.02)	2.79 (1.84, 8.20)

*Data cut: 16APR2021; MCL patients include Parts 1 & 2; CLL patients include Parts 1 & 2; Patients were considered evaluable for response if they had 1-dose of cirmtuzumab and had 1 post baseline tumor assessment; CR = complete remission, PR = partial remission, SD = stable disease, PD = progressive disease; ORR = number and percent of patients that achieved CR or PR; Clinical benefit rate = number of patients that achieved CR, PR or SD; NE = not estimable; *includes 1 PR with lymphocytosis; Time to response analyses = Part 1 first scans were done at day 28, Part 2 first scans were done at 3 months*

MCL EFFICACY

PFS in Sub-Groups

	Median PFS in Months	95% CI
Overall (n=18)	NE	(16.52, NE)
Best Response of SD (n=2)	5.18	(NE)
Best Response of PR (n=8)	17.31	(16.52, NE)
Best Response of CR (n=7)	NE	(0.03, NE)
1 Prior Systemic Regimen (n=9)	NE	(2.85, NE)
>1 Prior Systemic Regimen (n=9)	NE	(0.03, NE)

Data cut: 16APR2021; MCL patients include Parts 1 & 2; CLL patients include Parts 1 & 2; PFS is defined as the time from the first dose to the time of objective disease progression or death from any cause, whichever occurs first; Patients were considered evaluable for response if they had 1-dose of cirmtuzumab and had 1 post baseline tumor assessment; CR = complete remission, PR = partial remission, SD = stable disease, NE = not estimable

MCL SAFETY

Treatment Emergent AEs ≥ 20% Incidence (regardless of causality)

	All Grades n (%)	Grades 1-2 n (%)	Grades ≥3 n (%)
N=26			
Fatigue	11 (42.3)	7 (26.9)	4 (15.4)
Diarrhea	9 (34.6)	8 (30.8)	1 (3.8)
Contusion	7 (26.9)	7 (26.9)	0
Dizziness	7 (26.9)	7 (26.9)	0
Nausea	7 (26.9)	7 (26.9)	0

Treatment Emergent Hematologic Laboratory Abnormalities

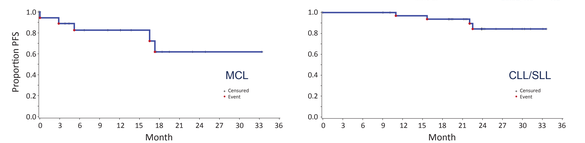
	All Grades n (%)	Grades 1-2 n (%)	Grades ≥3 n (%)
N=26			
Hemoglobin decreased	17 (65.4)	14 (53.8)	3 (11.5)
Neutrophils decreased	18 (69.2)	4 (15.4)	3 (11.5)
Platelets decreased	15 (57.7)	13 (50.0)	2 (7.7)

Data cut: 16APR2021; MCL patients include Parts 1 & 2; Patients are counted only once at the maximum grade observed after first dose of study medication

EFFICACY

Progression-free Survival (PFS)

	MCL n=18	CLL n=34
Median PFS in months	NE	NE
95% CI	16.52, NE	NE

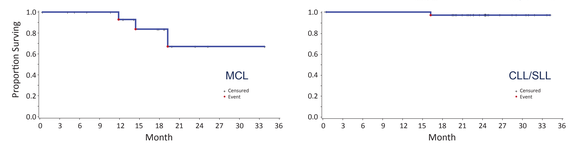


Data cut: 16APR2021; MCL patients include Parts 1 & 2; CLL patients include Parts 1 & 2; Evaluable patients (n=18-MCL; n=34-CLL/SLL); Patients were considered evaluable for response if they had 1-dose of cirmtuzumab and had 1 post baseline tumor assessment; PFS is defined as the time from the first dose to the time of objective disease progression or death from any cause, whichever occurs first; NE = not estimable

EFFICACY

Overall Survival

	MCL n=18	CLL n=34
Median OS in months	NE	NE
95% CI	14.03, NE	NE



Data cut: 16APR2021; MCL patients include Parts 1 & 2; CLL patients include Parts 1 & 2; Evaluable patients (n=18-MCL; n=34-CLL/SLL); OS is defined as the time from the first dose to the time of death from any cause; NE = not estimable

CLL SAFETY

Treatment Emergent AEs ≥ 20% Incidence (regardless of causality)

	All Grades n (%)	Grades 1-2 n (%)	Grades ≥3 n (%)
N=34			
Contusion	18 (52.9%)	18 (52.9%)	0
Hypertension	16 (47.1%)	9 (26.5%)	7 (20.6%)
Diarrhea	15 (44.1%)	13 (38.2%)	2 (5.9%)
Upper Respiratory Tract Infection	15 (44.1%)	15 (44.1%)	0
Fatigue	14 (41.2%)	14 (41.2%)	0
Arthralgia	11 (32.4%)	10 (29.4%)	1 (2.9%)
Dyspnea	10 (29.4%)	9 (26.5%)	1 (2.9%)
Muscle Spasms	10 (29.4%)	10 (29.4%)	0
Hypophosphatemia	9 (26.5%)	8 (23.5%)	1 (2.9%)
Onychoclasis	9 (26.5%)	9 (26.5%)	0
Rash	9 (26.5%)	9 (26.5%)	0
Cough	8 (23.5%)	8 (23.5%)	0
Gastroesophageal Reflux Disease	8 (23.5%)	8 (23.5%)	0
Hematuria	8 (23.5%)	7 (20.6%)	1 (2.9%)
Dizziness	7 (20.6%)	7 (20.6%)	0
Hypercreatinemia	7 (20.6%)	6 (17.6%)	1 (2.9%)

Treatment Emergent Hematologic Laboratory Abnormalities

	All Grades n (%)	Grades 1-2 n (%)	Grades ≥3 n (%)
N=34			
Hemoglobin decreased	25 (73.5)	25 (73.5)	0
Neutrophils decreased	16 (47.1)	10 (29.4)	6 (17.6)
Platelets decreased	24 (70.5)	24 (70.5)	0

Data cut: 16APR2021; CLL/SLL patients include Parts 1 & 2; Patients are counted only once at the maximum grade observed after first dose of study medication

SUMMARY

Cirmtuzumab is a humanized monoclonal antibody designed to inhibit the tumor promoting activity of ROR1

Phase 1 of study is complete in MCL & CLL

RDR of cirmtuzumab established

Efficacy is robust in high-risk and heavily pre-treated patients (including prior BTKi)
- **High response rates**
- **Favorable time to response**
- **Durable response times**
- **Encouraging PFS estimates signifying good disease control**

Safety profile is tolerable and consistent with ibrutinib alone

Phase 2 study in CLL completed enrollment; long-term follow-up awaited

Phase 2 in MCL is currently enrolling

Acknowledgement: Ibrutinib provided by Pharmacyclics LLC, an AbbVie Company