PHASE 1/2 STUDY OF CIRMTUZUMAB* AND IBRUTINIB IN MANTLE CELL LYMPHOMA (MCL) OR CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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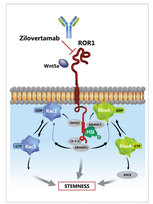
The new generic name (INN) for cirmtuzumab is zilovertamab

BACKGROUND

Front-line use of multi-agent therapies are typically successful in suppressing 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.*
- *Zilovertamab (cirmtuzumab) is a humanized monoclonal antibody designed to inhibit the tumor promoting activity of ROR1.*

*Formerly known as cirmtuzumab or UC-961



PHASE I/II STUDY DESIGN

Treatment naïve (TN) or Relapsed/Refractory (R/R) CLL/SLL or R/R MCL; prior BTK-inhibitor is allowed for MCL

PART 1 (in MCL & CLL)	PART 2 (in MCL & CLL)	PART 3 (in CLL)	PART 4 (in MCL)
DOSE-FINDING COHORT • At 2, 4, 8 & 16 mg/kg and 300 & 600 mg doses evaluated • Ibrutinib added after one month (420mg CLL, 560mg MCL qd po)	**DOSE-EXPANSION COHORT** • Confirm Recommended Dosing Regimen (RDR) of zilovertamab (600mg) + ibrutinib at approved dose (420mg CLL, 560mg MCL)	**RANDOMIZED EFFICACY** • Zilovertamab + ibrutinib vs ibrutinib • Randomization ratio: zilovertamab + ibrutinib : ibrutinib = 2:1 • Primary endpoint: Complete Response rate	**EXPLORATORY** • Zilovertamab + ibrutinib (refractory to prior BTKi therapy or have achieved an inadequate response (SD, PR) to prior ibrutinib therapy)
Enrolled *CLL n = 18* *MCL n = 12*	***CLL enrolled 16*** *MCL Phase 2 enrolling* *n = 19*	***Enrolled*** *n = 31*	***Open for Enrollment***

DEMOGRAPHY & DISEASE CHARACTERISTICS

Population: High-risk disease and heavily pre-treated

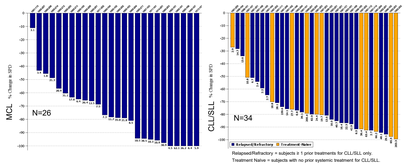
	MCL (N=31)	CLL TN or R/R (Parts 1 & 2) (N=34)
ECOG 0-1, n (%)	28 (90.3%)	34 (100.0%)
Received prior systemic regimens, n (%)	31 (100.0%)	22 (64.7%)
Median number of prior systemic regimens, n (range)	1 (1,4)	2.0 (1, 15)[x]
Prior BTK inhibitor, n (%)	5 (16.1%)[Ŧ]	0
Prior Transplant/Cell Therapy, n (%)	8 (25.8%)*	1 (2.9%)[ǂ]
Patient Disposition		
Evaluable* for Efficacy, n (%)	26 (83.9%)	34 (100.0%)
Ongoing, n (%)	17 (54.8%)	11 (32.4%)
Median Duration of Follow-up, months (95% CI)	12.4 (9.79, 17.23)	29.0 (27.64, 31.61)
Discontinued from Treatment, n (%)	14 (45.2%)	23 (67.6%)
Reason for Discontinuation		
Disease progression, n (%)	8 (25.8%)	1 (2.9%)
Adverse event, n (%)	1 (3.2%)	4 (11.8%)
Other[ǂ], n (%)	4 (12.9%)	17 (50.0%)
Death, n (%)	1 (3.2%)	1 (2.9%)

Data cut: 01OCT2021; [Ŧ]Prior BTK inhibitor = ibrutinib; *Median number of prior systemic regimens among previously treated patients (n=22). *Autologous stem cell transplant (n=8), Allogeneic stem cell transplant (n=1); CAR-T (n=1) patients could have received more than one; [ǂ]Autologous stem cell transplant (n=1).

RESULTS

Efficacy: Waterfall Plot of Best % Tumor Reduction from Baseline on zilovertamab + ibrutinib

• Marked reductions in tumor size observed in both MCL & CLL (TN or R/R)



SPD = Sum of the Products of the Diameters. # under bars represent baseline SPD. Data cut: 01OCT2021

Efficacy: Clinical Response to zilovertamab + ibrutinib

• High response rates and durable responses observed in both MCL and CLL

	MCL (N=26)	CLL TN or R/R (Parts 1 & 2) (N=34)
Overall Response Rate (ORR), n (%)	21 (80.8%)	31 (91.2%)
CR, n (%)	9 (34.6%)	2 (5.9%)
PR, n (%)	12 (46.2%)	29 (85.3%)*
SD, n (%)	3 (11.5%)	3 (8.8%)
PD, n (%)	2 (7.7%)	0
Median Duration of response, months (95% CI)	34.13 (13.67, 34.13)	33.5 (0.0, 33.5)**
Median Duration of follow-up, months (95% CI)	14.4 (11.38, 19.31)	29.0 (27.64, 31.61)

Data cut: 01OCT2021; Seven patients received prior stem cell transplant ± CAR-T therapy prior to enrolling in the study and achieved responses of 5 CRs, 2 PRs. Meanwhile, 2 CRs, 2 PRs, 1 SD were observed in the 5 patients that received prior ibrutinib treatment. * Include PR-Lymphocytosis; ** min, max.

MCL Subgroup Efficacy on zilovertamab + ibrutinib

	Overall (N=26)	Ki-67 ≥30% (N=13)	P53 Alterations (N=6)	>1 Prior Systemic Regimen (N=11)	Prior BTKi (N=5)	Prior SCT/CART (N=7)
Overall Response Rate (ORR), n(%)	21 (80.8%)	11 (84.6%)	5 (83.3%)	9 (81.8%)	4 (80.0%)	7 (100.0%)
CR, n (%)	9 (34.6%)	4 (30.8%)	1 (16.7%)	5 (45.5%)	2 (40.0%)	5 (71.4%)
PR, n (%)	12 (46.2%)	7 (53.8%)	4 (66.7%)	4 (36.4%)	2 (40.0%)	2 (28.6%)
SD, n (%)	3 (11.5%)	0	0	2 (18.2%)	1 (20.0%)	0
PD, n (%)	2 (7.7%)	2 (15.4%)	1 (16.7%)	0	0	0
Median Duration of Response, (95% CI)	34.13 (13.67, 34.13)	13.84 (13.67, NE)	13.84 (11.93,13.84)	2 prior line NR (1.51, NE) ≥3 prior line 34.13 (13.84, 34.13)	13.67 (11.93, NE)	34.13 (13.84, 34.13)

Data cut: 01OCT2021; NE – not evaluable; NR = not reached

CLL TN or R/R (Parts 1 & 2) Subgroup Efficacy on zilovertamab + ibrutinib

	Overall (N=34)	≥1 Prior Systemic Regimen (N=22)	RAI Stage ≥3 (N=9)	LDH > 250 U/L (N=15)
Overall Response Rate (ORR), n(%)	31 (91.2%)	20 (90.9%)	9 (100.0%)	13 (86.7%)
CR, n(%)	2 (5.9%)	2 (9.1%)	0	1 (6.7%)
PR*, n(%)	29 (85.3%)	18 (81.8%)*	9 (100.0%)	12 (80.0%)
SD, n(%)	3 (8.8%)	2 (9.1%)	0	2 (13.3%)
PD, n(%)	0	0	0	0
Median Duration of Response, (95% CI)	33.54 (0.0, 33.5)**	1 prior line NR (7.4, 28.0)** 2 prior line NR (2.8, 28.1)** ≥3 prior line 33.54 (19.57, 33.54)	NR (2.8, 27.6)*	NR (19.57, NE)

Data cut: 01OCT2021; NR – not reached; NE – not evaluable; * Include PR-Lymphocytosis; ** min, max

Efficacy CLL TN or R/R (Part 3): Clinical Response

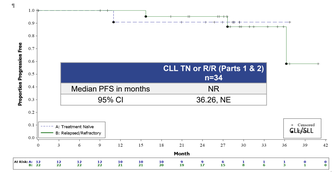
• High response rates and durable responses observed in both Part 3 arms

	Zilovertamab + Ibrutinib (N=15)	Ibrutinib (N=7)
Overall Response Rate (ORR), n (%)	14 (93.3%)	7 (100.0%)
CR, n (%)	0	0
PR, n (%)	14 (93.3%)	7 (100.0%)
SD, n (%)	1 (6.7%)	0
PD, n (%)	0	0
Median Duration of response, months (95% CI)	NR (0.0, 19.5)*	NR (8.30, NE)
Median Duration of follow-up, months (95% CI)	18.3 (16.47, 20.34)	19.3 (14.36, 23.79)
PFS median, months (95% CI)	NR (4.20, 24.75)*	NR (11.05, NE)
OS median, months (95% CI)	NR (12.85, 24.75)*	NR (13.08, 24.82)*

Data cut: 01OCT2021; * min, max

Progression Free Survival on zilovertamab + ibrutinib for TN and R/R CLL

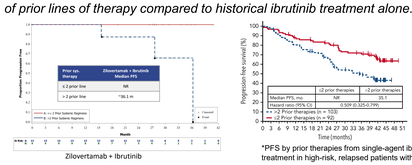
• Median PFS for CLL remains encouraging after median follow up of 29.0 months.



Data cut: 01OCT2021; 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; NR- not reached. NE – not evaluable

Progression Free Survival on zilovertamab + ibrutinib for R/R CLL by Prior Systemic Treatment

• Zilovertamab + ibrutinib demonstrates encouraging PFS based on number of prior lines of therapy compared to historical ibrutinib treatment alone.



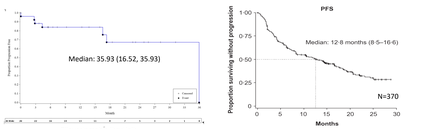
Zilovertamab + Ibrutinib

*PFS by prior therapies from single-agent ibrutinib treatment in high-risk, relapsed patients with CLL

Data cut: 01OCT2021; 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; NR- not reached. NE – not evaluable; *Byrd, Blood 2019

Progression Free Survival on zilovertamab + ibrutinib for MCL

• Zilovertamab + ibrutinib combination provides favorable PFS benefit compared to historical ibrutinib treatment alone.

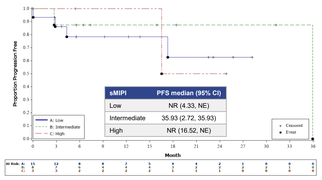


Zilovertamab + Ibrutinib

*Patient-level data from three single-agent ibrutinib studies

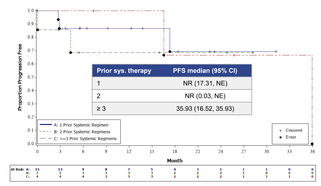
Data cut: 01OCT2021; PFS is defined as the time from the first dose to the time of objective disease progression or death from any cause, whichever occurs first; NR- not reached. NE – not evaluable; *Rule, British Journal of Haematology, 2017

Progression Free Survival on zilovertamab + ibrutinib for MCL by sMIPI Subtypes



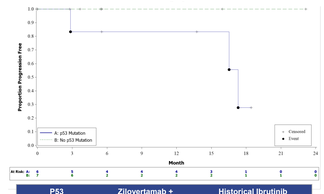
Data cut: 01OCT2021

Progression Free Survival on zilovertamab + ibrutinib for MCL by Prior Systemic Therapy



Data cut: 01OCT2021

Progression Free Survival on zilovertamab + ibrutinib for MCL by p53 Mutation

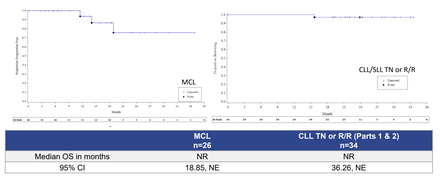


P53	Zilovertamab + Ibrutinib	Historical Ibrutinib (Rule, 2019*)
alterations	17.31 (2.85, NE)	4.0 (2.1, 8.3)
no alterations	NR (2.79, 23.15)*	12.0 (7.1, 15.6)

Data cut: 01OCT2021 *Rule, Hematologica, 2019

Efficacy: Overall Survival on zilovertamab + ibrutinib

• Median OS hasn't been reached for MCL and CLL patients after median follow up of 14.4 months and 29.0 months, respectively.



	MCL n=26	CLL TN or R/R (Parts 1 & 2) n=34
Median OS in months	NR	NR
95% CI	18.85, NE	36.26, NE

Data cut: 01OCT2021; Patients were considered evaluable for response if they had 1-dose of zilovertamab and had 1-post baseline tumor assessment. NR – not reached; NE – not evaluable

Safety MCL: Treatment Emergent AEs ≥20%

• Zilovertamab + ibrutinib generally well tolerated with AEs similar to ibrutinib alone. Most TEAEs Grades 1-2, hematologic adverse events infrequent.

MCL N=31	Overall	Grade 1-2	Grade ≥3
Fatigue	15 (48.4%)	11 (35.5%)	4 (12.9%)
Diarrhea	12 (38.7%)	11 (35.5%)	1 (3.2%)
Contusion	10 (32.3%)	10 (32.3%)	0
Cough	9 (29.0%)	9 (29.0%)	0
Dizziness	8 (25.8%)	8 (25.8%)	0
Myalgia	8 (25.8%)	7 (22.6%)	1 (3.2%)
Nausea	8 (25.8%)	8 (25.8%)	0
Stomatitis	8 (25.8%)	5 (16.1%)	3 (9.7%)
Treatment Emergent Hematological Laboratory Abnormalities			
Hemoglobin decrease	21 (67.7%)	18 (58.1%)	3 (9.7%)
Platelets decrease	20 (64.5%)	17 (54.8%)	3 (9.7%)
Neutrophils decrease	8 (25.8%)	5 (16.1%)	3 (9.7%)

Data cut: 01OCT2021; Patients are counted only once at the maximum grade observed after first dose of study medication.

Safety CLL (Part 1 & 2): Treatment Emergent AEs ≥20%

• Zilovertamab + ibrutinib well tolerated with AEs similar to ibrutinib alone

CLL N=34	Overall	Grade 1-2	Grade ≥3
Contusion	19 (55.9%)	18 (55.9%)	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	12 (35.3%)	11 (32.4%)	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%)
Onycholclasis	9 (26.5%)	9 (26.5%)	0
Rash	9 (26.5%)	9 (26.5%)	0
Cough	8 (23.5%)	8 (23.5%)	0
Dizziness	8 (23.5%)	8 (23.5%)	0
Gastroesophageal reflux disease	8 (23.5%)	8 (23.5%)	0
Haematuria	8 (23.5%)	8 (23.5%)	0
Headache	7 (20.6%)	7 (20.6%)	0
Hypercreatinaemia	7 (20.6%)	6 (17.6%)	1 (2.9%)
Palpitations	7 (20.6%)	7 (20.6%)	0
Thrombocytopenia	7 (20.6%)	6 (17.6%)	1 (2.9%)
Treatment Emergent Hematological Laboratory Abnormalities			
Hemoglobin decrease	25 (73.5%)	25 (73.5%)	0 (0.0%)
Platelets decrease	25 (73.5%)	24 (70.6%)	1 (2.9%)
Neutrophils decrease	16 (47.1%)	10 (29.4%)	6 (17.6%)

Data cut: 01OCT2021; Patients are counted only once at the maximum grade observed after first dose of study medication.

SUMMARY

- **Zilovertamab (formerly called cirmtuzumab or UC-961) is a humanized monoclonal antibody designed to inhibit the tumor promoting activity of ROR1**
- **Zilovertamab + ibrutinib generally well tolerated, safety profile similar to ibrutinib alone**
  - Grade 3/4 neutrophil decrease was only 9.7% with zilovertamab plus ibrutinib in MCL, compared to 29% for ibrutinib alone from its registration study
- **Encouraging response rates, particularly in patients with R/R disease**
  - CLL ORR 91.2% (31/34), CR 5.9% (2/34), PR 85.3% (29/34)
  - MCL ORR 80.8% (21/26), CR 34.6% (9/26), PR 46.2% (12/26)
- **Progression free survival favorable compared to historical ibrutinib alone**
  - MCL median PFS 36 months, CLL median NR
- **Encouraging efficacy in R/R MCL subsets traditionally difficult to treat with ibrutinib**
  - Landmark PFS of ~70% at 24 months regardless of number of prior therapies
  - 80% ORR (2 CR, 2 PR) for patients who received prior ibrutinib (n=5)
- **Study ongoing, investigating MCL BTKi resistance and consolidation**

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