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Abstract #2511

Phase 1 Study of Cobomarsen (MRG-106) in Cutaneous T cell Lymphoma and HTLV-1 associated T cell Leukemia/Lymphoma

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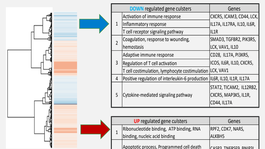
Background

Cobomarsen (MRG-106) miR-155-5p Inhibitor



		DOWN-regulated gene clusters	Genes
	1	Activation of immune response	CXCR5, ICAM3, CD44, LCK, IL17A, IL17RA, IL10, IL6R, IL1R
	2	T cell receptor signaling pathway	
	3	Coagulation, response to wounding, hemostasis	SMAD3, TGFBR2, PIK3R5, LCK, VAV1, IL10
	4	Adaptive immune response	CD28, IL17A, PI3KR5,
	5	Regulation of T cell activation	FOS, IL6R, IL1R, CXCR5,
	6	T cell costimulation, lymphocyte costimulation	LCK, VAV1
	7	Positive regulation of interleukin-6 production	IL6R, IL1R, IL1R, IL17A
	8	Cytokine-mediated signaling pathway	STAT3, TCIM4C, IL12RB2, CXCR5, MAP3K5, IL1R, CD44, IL17A

		UP-regulated gene clusters	Genes
	1	Ribonucleotide binding, ATP binding, RNA binding, nucleic acid binding	MYC, CDC, NAP1, ALDH3
	2	Apoptotic process, Programmed cell death	CASP3, TNFRSF9, BMP6, PPP2CC, MAP3K7
	3	Apoptotic signaling pathway	
	4	Immune response	IL5, IL4, IL13, GATA3,
	5	Cytokine-mediated signaling pathway	CCR7, VEGFA, SMAD7

- Cobomarsen is a chemically synthesized, phosphorothioate oligonucleotide, 14 nucleotides in length, that contains a mixture of deoxyribonucleotides and 2'-O, 4'-C-methylene-β-d-ribonucleotides (LNA)
- Genome-wide expression analysis demonstrates that cobomarsen regulates numerous genes implicated in cell cycle and apoptosis, consistent with the pharmacologic impact on cell survival
- A subset of these genes has been identified as potentially translatable biomarkers to monitor cobomarsen activity in clinical samples

Figure 1. Gene regulation in CD4+ T cells after treatment with PBS or cobomarsen.

Role of MicroRNA-155 in CTCL and ATLL

- miR-155 is overexpressed in CTCL skin lesions and is involved in tumor progression[1, 2, 3, 4]
- HTLV-1-specific transcription factor, Tax, promotes the proliferation and survival of virally-infected CD4+ lymphocytes[5]
- Tax activates miR-155 transcription and ATL tumor cells have been shown to have high miR-155 levels[5]
- JAK/STAT, NFκB and PI3K signaling pathways are regulated by miR-155 and are activated in CTCL and ATLL leading to uncontrolled clonal cell expansion[6, 7, 8, 9]

Cutaneous T Cell Lymphoma Efficacy and Safety

Gene Expression Changes with Intra-Tumoral Injection of Cobomarsen Correlate with Drug Levels in MF Lesion Biopsies

- Of 122 mRNA transcripts, two subgroups of genes were either commonly up or downregulated in cobomarsen treated biopsies
- Gene expression changes correlated with lesion drug levels including one saline treated lesion that had measurable drug levels

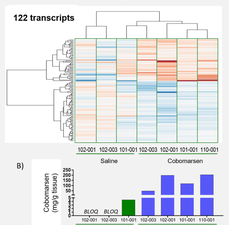


Figure 4.
A) Log2 fold-change in gene expression for drug or saline treated biopsy compared to pretreatment biopsy from the same biopsy in all 4 lesions.
B) Cobomarsen tissue concentration detected by mass spectrometry in each biopsy. BLOQ = below the level of quantitation

Cobomarsen Treatment Decreases Signaling Through Key CTCL Disease Pathways Including STAT and NFκB Pathways (Part A)

Figure 5.
IPA pathway analysis of the MRG-106 common signature of 122 genes. The analysis utilized the median expression of 4 MRG-106 treated lesions and the median of 3 saline-treated lesions.
Blue = predicted to be inactivated; orange = predicted to be activated

29 of 32 Patients (91%) have shown mSWAT Score Improvement after Systemic Cobomarsen Treatment

CTCL patients in IV infusion cohorts demonstrated most consistent mSWAT improvements

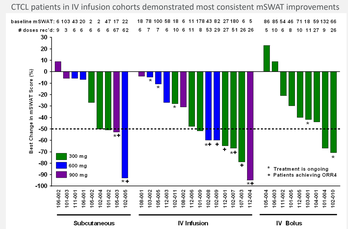


Figure 6. mSWAT score represents best score achieved while on study for 32 patients out of a total of 35 patients dosed as of the data cutoff (05 Apr 2018)

Quality of Life Improvement, as Measured by Skindex-29 Total Score, Occurs Predominantly in CTCL Patients who Received > 6 Doses of Cobomarsen

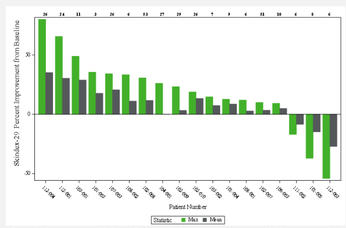


Figure 7. Maximal Improvement (% change from baseline) and Mean improvement (%change across the duration of study); evaluable patients (n=18) are those who had a baseline measure and participated in Part B of the study

Mean Duration of Response is 213 days as of data cutoff: 8 patients have reached an ORR4

- Patients typically reach a partial response after 1 to 2 cycles of cobomarsen
- 11 of 21 patients (52%) receiving > 1 month of cobomarsen achieved ≥50% mSWAT reduction
- 6 of 9 patients (67%) on cobomarsen monotherapy achieved ≥50% mSWAT reduction
- 7 patients continue treatment

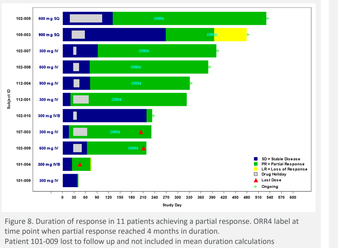


Figure 8. Duration of response in 11 patients achieving a partial response. ORR4 label at time point when partial response reached 4 months in duration.
Patient 101-009 lost to follow up and not included in mean duration calculations

- No serious adverse events (SAEs) attributed to cobomarsen
- Three SAEs, not attributed to cobomarsen, occurred in 1 patient
  - Hypercalcemia (Grade 4, Life-Threatening), Cellulitis (Grade 3, Severe), Orthopnea (Grade 1, Mild)
- Two dose-limiting toxicities (DLTs):
  - Grade 3 worsening pruritus, possible tumor flare, occurred twice in 1 patient at 900 mg SC and 300 mg IV infusion
  - Grade 3 tumor flare (300 mg IV bolus)

N= 41 (Parts A & B)	Total (n,%)	Grade 3	Grade 4
DLT	2 (5)	2 (5)	0 (0)
AE	36 (88)	17 (42)	5 (12)
Related AE	28 (68)	6 (15)	2 (5)
SAE	1 (2.5)	1 (2.5)	1 (2.5)
Related SAE	0 (0)	0 (0)	0 (0)

Table 3. Summary of safety in patients who received ≥ 1 dose of cobomarsen in Parts A and B (N=41) as of the safety data cutoff (05 Apr 2018)

AEs by preferred term, N (%)	Any grade*	Any grade attributed to cobomarsen	Grade 3-4	Grade 3-4 attributed to cobomarsen
Neutropenia	10 (24)	9 (22)	5 (12)	3 (7)
Fatigue	9 (22)	6 (15)		
Pruritus	9 (22)	1 (2.5)	1 (2.5)	1 (2.5)
Headache	7 (17)	2 (5)		
Lymphocyte count decreased	6 (15)	5 (12)	2 (7)	2 (7)
Injection site pain	6 (15)	6 (15)		
Anaemia	6 (15)	3 (7)		

Table 4. Most common AEs reported in ≥ 15% of patients who received at least one dose of cobomarsen (N=41) as of data coded on 30 Apr 2018

Study Design and Demographics

Cobomarsen: Multi-Part Phase 1 CTCL and ATLL Study (NCT02580552)

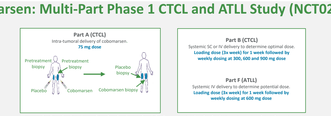


Figure 2. Study Design: Study designed with 6 parts to include intra-tumoral and systemic administration for 4 indications: CTCL, DLBCL, CLL, and ATLL. Parts C through E not shown.

	Part A	Part B	Total
Demographic	n = 6	n = 35	n = 41
Sex			
Male (n, %)	5 (83%)	24 (69%)	29 (71%)
Age			
Median years (range)	61 (50-64)	59 (21-85)	59 (21-85)
Race			
White/Caucasian	4 (67%)	27 (77%)	31 (76%)
Black	1 (17%)	5 (14%)	6 (15%)
Asian	0 (0%)	1 (3%)	1 (2%)
Other, specify	0 (0%)	2 (6%)	2 (5%)
Not reported	1 (17%)	0 (0%)	1 (2%)
Disease Stage at Screening			
Stage IA	0 (0%)	6 (17%)	6 (15%)
Stage IB	1 (17%)	10 (29%)	11 (27%)
Stage IIA	2 (33%)	3 (9%)	5 (12%)
Stage IIB	3 (50%)	11 (31%)	14 (34%)
Stage IIIA	0 (0%)	1 (3%)	1 (2%)
Stage IIIB	0 (0%)	4 (11%)	4 (10%)
Prior Systemic Therapies			
No. of Patient Reporting	6	32	38
Median no. (range)	4 (1-6)	4 (1-13)	4 (1-13)
Prior Skin Directed Therapies			
No. of Patient Reporting	6	32	38
Median no. (range)	4 (1-6)	3 (1-13)	3 (1-13)
Baseline mSWAT			
N	3	35	38
Median (range)	23 (3-96)	43 (2-180)	43 (2-180)

Table 1. Baseline characteristics of CTCL patients who received ≥ 1 dose of cobomarsen in Parts A and B (data cutoff 05 Apr 2018)

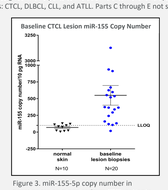


Figure 3. miR-155-5p copy number in baseline lesion biopsies from CTCL patients (Parts A and B) compared to normal skin biopsies from healthy donors

	Part F
Demographic	n = 3
Sex	
Male (n, %)	3 (100%)
Age	
Median years (range)	49 (47- 68)
Race	
Black	3 (100%)
Ethnicity	
Non-Hispanic	3 (100%)
ATL Type	
Leukemic ATLL	1 (33%)
Lymphomatous ATLL	2 (67%)
Prior Systemic Therapies	
No. Patients Reporting	3
Median no. (range)	4 (1-8)

Table 2. Baseline characteristics of ATLL patients enrolled in Part F (data cutoff 05 Apr 2018)

HTLV-1 Associated T Cell Leukemia/Lymphoma Efficacy and Safety

Cobomarsen Decreases Activation and Proliferation Status of Circulating Tumor Cells Leading to Stable Disease in Acute Leukemic Patient for > 6 Months

101-008: Acute leukemic disease diagnosed 14 Dec 2016

- Disease not well controlled with Zidovudine, Interferon alfa-2b, Lenalidomide or EPOCH chemotherapy
- Cobomarsen treatment (first dose 06 Nov 2017) has stabilized tumor cell counts in peripheral blood for over 6 months
- Cobomarsen treatment resulted in normalization of still enlarged lymph node after chemotherapy (1.0 to 0.8 cm) as measured by CT scan (31 Oct 2017 compared to 02 Jan 2018) which remains normal as of last CT scan on 09 May 2018
- No drug-related adverse events have been reported for this patient

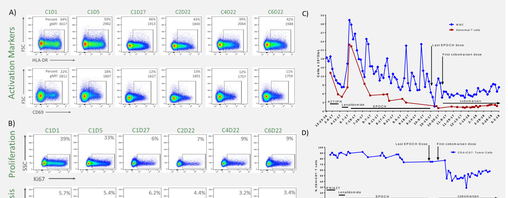


Figure 9
A and B) Flow cytometry assessment of activation, proliferation and apoptotic markers in circulating ATL cells isolated from patient 101-008 predose on C1D1 and over the course of treatment with cobomarsen
A) HLA-DR and CD69 expression on ATL peripheral tumor cells
B) Intracellular assessment of Ki67 and cPARP levels in ATL tumor cells.
C) Graphical representation of the absolute WBC and abnormal T cell counts for patient 101-008 since diagnosis in relation to treatment course.
D) Percent CD4+CD7- T cells in the circulating lymphocyte population since diagnosis.

Cobomarsen Decreases Activation and Proliferation Status of Circulating Tumor Cells Leading to Stable Disease in Lymphomatous Patient for > 5 Months

101-010: Lymphomatous disease diagnosed on 21 Apr 2017

- Extensive and bulky lymphadenopathy on initial CT scan was reduced significantly by CHOEP chemotherapy regimen completed in June 2017 on the 27 Nov 2017 scan
- Cobomarsen (first dose 11 Dec 2017) has maintained stable (1.0 to 1.1 cm) lymphadenopathy and peripheral blood tumor cell counts for 6 months
- Single related adverse event of nausea was reported which resolved within 24 hours
- Missed dose on 07 Mar 2017 was followed by increase in percent tumor cells in peripheral lymphocyte population that returned to prior levels after the following cycle of treatment

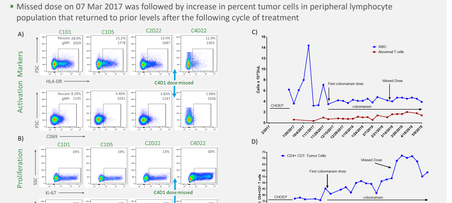


Figure 10:
A and B) Flow cytometry assessment of activation, proliferation and apoptotic markers in circulating ATL cells isolated from patient 101-010 predose on C1D1 and over the course of treatment with cobomarsen
A) HLA-DR and CD69 expression on ATL peripheral tumor cells
B) Intracellular assessment of Ki67 and cPARP levels in ATL tumor cells
C) Graphical representation of the absolute WBC and abnormal T cell counts for patient 101-010 since CHOEP therapy and subsequent cobomarsen treatment course
D) Percent CD4+CD7- T cells in the circulating lymphocyte population since CHOEP therapy

N = 3 (Part F)	Total (n, %)	Grade 3	Grade 4
DLT	0 (0)	0 (0)	0 (0)
AE	3 (100)	1 (33)	0 (0)
Related AE*	1 (33)	0 (0)	0 (0)
SAE	0 (0)	0 (0)	0 (0)
Related SAE	0 (0)	0 (0)	0 (0)

Table 5. Summary of safety in Part F as of 21 May 2018
* Grade 1 Nausea considered possibly related.

Grade 1	Grade 2	Grade 3
AST Increase (1)	Anorexia (1)	Hyperglycemia (1)
Diarrhea (2)	Neck pain (1)	
Cough (2)	Fatigue (1)	
Nasal Congestion (2)	Pain (hands and feet) (1)	
Nausea* (1)	Skin Infection (1)	
Skin Lesions (1)		
Chills (1)		
Dry Skin (1)		
Hypoglycemia (1)		

Table 6. All AEs reported in Part F where n = number of events as of 21 May 2018

Conclusions

- Cobomarsen is well-tolerated in CTCL and ATLL patients treated to date
  - No SAEs deemed related to study drug with two DLTs in two CTCLs patient (Grade 3 worsening pruritis and Grade 3 tumor flare)
- CTCL
  - 29 of 32 patients (91%) treated systemically with cobomarsen have shown mSWAT score improvement
  - 11 of 21 patients (52%) receiving > 1 month of cobomarsen achieved ≥50% mSWAT reduction
    - Mean duration of response is 213 days as of the cutoff date; 8 patients have reached an ORR4
  - Cobomarsen treatment resulted in durable improved quality of life, as measured by the Skindex-29 Total Score
- ATLL
  - Cobomarsen decreases the expression of activation markers and the proliferative index in ATL circulating tumor cells
  - Acute leukemic and lymphomatous ATLL patients maintained disease stabilization on cobomarsen for ≥ 6 months

References and Acknowledgments

1. Van Kester et al. 2011
2. Maj et al. Br J Derm 2012
3. Kopp et al. Cell Cycle 2013
4. Moyal et al. Exp Derm 2013
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