

Phase 1 Trial of Cobomarsen, an Inhibitor of miR-155, in Mycosis Fungoides

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BACKGROUND

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

- 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-ribose nucleotides (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

Role of MicroRNA-155 in CTCL

- Epigenetic alterations have been implicated in the pathogenesis of lymphomas and leukemias including CTCL
- miRNA profiling and RT-PCR discriminate CTCL and non-malignant inflammation with high accuracy
- miR-155 is overexpressed in CTCL skin lesions and is involved in tumor progression
- JAK/STAT, NFκB and PI3K signaling pathways are regulated by miR-155 and are activated in CTCL leading to uncontrolled clonal cell expansion

CLINICAL TRIAL DESIGN

Open-label, dose-ranging, multiple dose, study of intra-tumoral, subcutaneous, and intravenous administration of cobomarsen, an oligonucleotide inhibitor of microRNA miR155-5p, in subjects with CTCL, MF sub-type.

Primary Objective

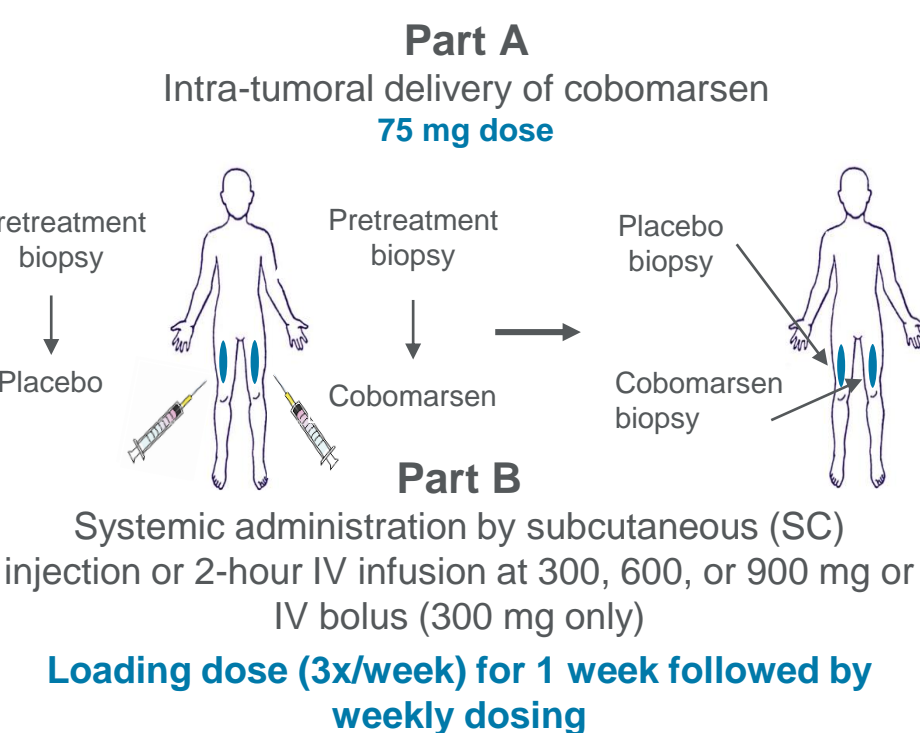
- To investigate the safety and tolerability of multiple intra-tumoral (IT), subcutaneous (SC), and intravenous (IV) administrations of cobomarsen

Secondary Objectives

- To characterize the pharmacokinetic profile, the recommended Phase 2 dose and route, and to evaluate the efficacy of cobomarsen in this population

Main Inclusion/Exclusion Criteria

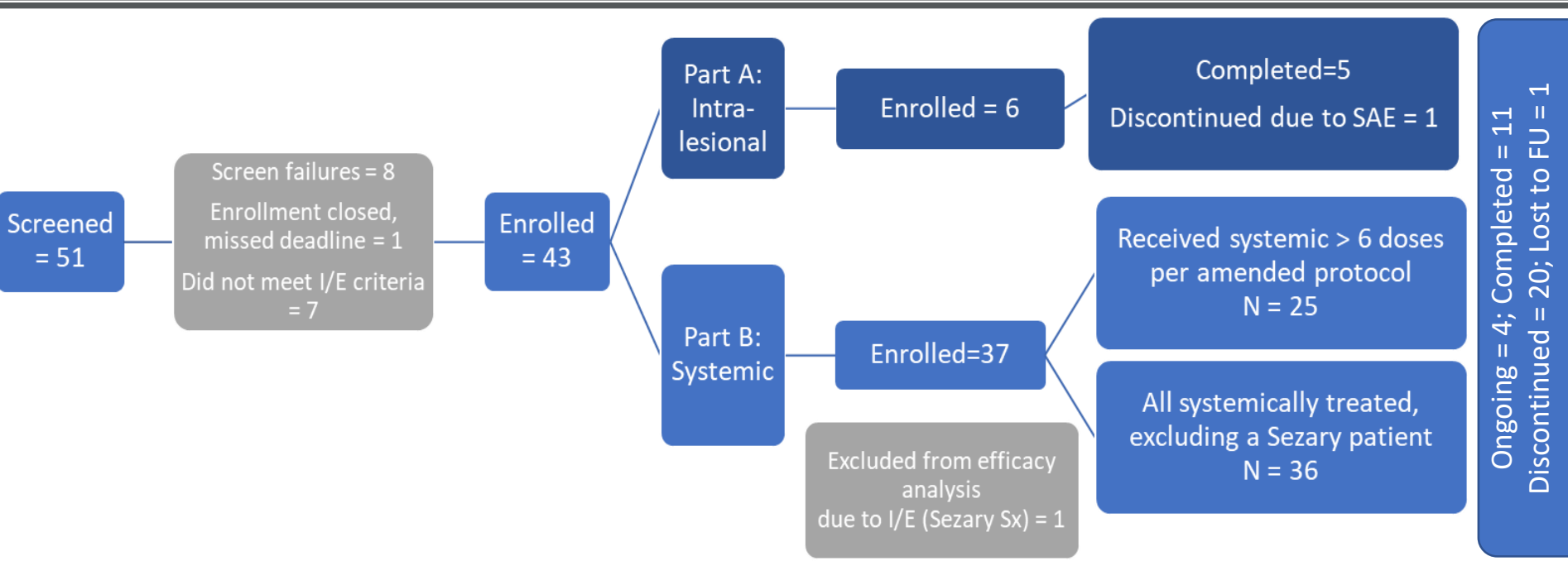
- Biopsy proven MF, Clinical Stage I-III, Large Cell Transformation included
- Subjects refractory to or intolerant to established therapy. Subjects could remain on stable doses of background therapy
- No evidence of clinically meaningful visceral, nodal or blood involvement related to CTCL
- No clinically significant laboratory, cardiac, renal, hepatic, or other medical conditions



Disease assessments

- Monthly Composite Assessment of Index Lesion Severity (CAILS) and Modified Severity Weighted Assessment Tool (mSWAT)
- Clinical signs and symptoms, safety laboratory, ECG, adverse event monitoring
- CT scans and flow cytometry at screening and when all criteria for a CR are met
- Monthly Quality of Life

CLINICAL TRIAL SUBJECT FLOW



BASELINE DEMOGRAPHICS

	Part A (Intra-tumoral)	Part B (Subcutaneous)			Part B (IV, 2 hr infusion)			Part B (IV Bolus)	Total
	N (%)	300mg	600mg	900mg	300mg	600mg	900mg	300mg	N (%)
Demographic	75mg (6)	300mg (3)	600mg (3)	900mg (3)	300mg (8)	600mg (8)	900mg (3)	300mg (9)	43
Sex									
Female	1 (17)	1 (33)	1 (33)	0 (0)	3 (38)	2 (25)	1 (33)	5 (56)	14 (33)
Male	5 (83)	2 (67)	2 (67)	3 (100)	5 (63)	6 (75)	2 (67)	4 (44)	29 (67)
Age Range									
18 - 45	0 (0)	0 (0)	2 (67)	0 (0)	2 (25)	0 (0)	1 (33)	0 (0)	5 (12)
46 - 65	6 (100)	3 (100)	1 (33)	3 (100)	5 (63)	6 (75)	1 (33)	4 (44)	29 (67)
> 65	0 (0)	0 (0)	0 (0)	0 (0)	1 (13)	2 (25)	1 (33)	5 (56)	9 (21)
Age									
N	6	3	3	3	8	8	3	9	43
Mean (SD)	59 (6)	57 (6)	41 (21)	62 (3)	52 (16)	62 (10)	59 (13)	65 (14)	58 (13)
Median	61	59	41	64	53	59	63	70	59
Min, Max	50,64	50,61	21,62	59,64	28,75	53,85	45,70	47,84	21,85
Race									
Asian	0 (0)	0 (0)	0 (0)	0 (0)	1 (13)	0 (0)	0 (0)	0 (0)	1 (2)
Black	1 (17)	0 (0)	1 (33)	0 (0)	2 (25)	2 (25)	0 (0)	1 (11)	7 (16)
Not reported	1 (17)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Other, specify	0 (0)	0 (0)	0 (0)	1 (33)	1 (13)	0 (0)	0 (0)	0 (0)	2 (5)
White/Caucasian	4 (67)	3 (100)	2 (67)	2 (67)	4 (50)	6 (75)	3 (100)	8 (89)	32 (74)
Ethnicity									
Hispanic	1 (17)	0 (0)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	2 (5)
Non-Hispanic	5 (83)	3 (100)	3 (100)	2 (67)	8 (100)	8 (100)	3 (100)	9 (100)	41 (95)

SAFETY

- No serious AEs have been attributed to cobomarsen. Eight serious adverse events (SAEs) have been reported in 4 subjects. These SAEs were either related to underlying disease (known complications of the CTCL patient population) or related to other comorbidities in these subjects, and unrelated to study treatment
- Thirty-nine subjects (90.7%) have reported at least 1 non-serious AE, for a total of 307 unique AEs
- The maximum severity of AEs has been Grade 1/Grade 2 (275 of 307 events [89.6%]) or Grade 3/Grade 4 (32 of 307 events [10.4%])
- Of the 32 Grade 3/Grade 4 events, 14 events in 6 subjects (all in Part B) were assessed to be related

AEs (SOC PT)	PART A (n = 6)		PART B (n = 37)		TOTAL (n = 43)	
	SAE	Grade 3/4	SAE	Grade 3/4	SAE	Grade 3/4
Neutropenia*				5		5
Lymphopenia		1		1		2
Hypophosphotemia		1		1		2
Leukopenia				2		2
Hyperuricaemia				2		2
Hypertriglyceridaemia				2		2
Tumor flare				2		2
Cellulitis	1	1			1	1
Sepsis			1	1	1	1
CPK increased		1			1	1
Hypercalcaemia	1	1			1	1
Hypokalaemia				1		1
Hyponatremia				1		1
Angina Pectoris			1	1	1	1
Coronary artery disease			1	1	1	1
Tumor pain				1		1
Erythema				1		1
Pruritus				1		1
Rash				1		1
Skin infection				1		1
Acute kidney injury				1		1
Palpitations				1		1
Orthopnea	1				1	
TOTAL	3	5	5	27	8	32

Table 1. Grade 3, Grade 4 and Serious Adverse Events, regardless of attribution, in patients who received ≥ 1 dose of cobomarsen in Parts A and B (N=43).

AE Table Worst Grade Occurring ≥ 10% of Subjects	Mono vs Combo Therapy Subjects		
	Mono n (%)	Combo n (%)	Total n (%)
Preferred Term	18 (18)	25 (25)	43 (43)
Fatigue	5 (28)	6 (24)	11 (26)
Neutropenia*	1 (6)	7 (28)	8 (19)
Pruritus	3 (17)	4 (16)	7 (16)
Nausea	2 (11)	5 (20)	7 (16)
Headache	4 (22)	3 (12)	7 (16)
Tumor flare	2 (11)	5 (20)	7 (16)
Injection site pain	2 (11)	4 (16)	6 (14)
Constipation	4 (22)	2 (8)	6 (14)
Diarrhoea	3 (17)	2 (8)	5 (12)
Blood creatine phosphokinase increased	2 (11)	3 (12)	5 (12)
Back pain	2 (11)	3 (12)	5 (12)
Upper respiratory tract infection	2 (11)	3 (12)	5 (12)

*Neutropenia is transient, mostly in subjects on concomitant medications that had Grade 1-2 neutropenia at baseline.

Table 2. Most common AEs reported in ≥ 10% of patients who received at least one dose of cobomarsen (N=43), either as monotherapy or in addition to stable doses of background therapy (combo).

IMMUNOPHENOTYPING

No Evidence of Immunosuppression in Subjects Treated with Cobomarsen for up to 23 Months

- No consistent or clinically significant changes in T or B cell subsets (including CD4, CD8, Treg, and B cells), or in monocytes or eosinophils
- NK cell counts increased in several patients treated with the highest cobomarsen dose (900 mg), though the relationship to drug administration is unclear with the small data set
- Subjects that had common infections (URI) during the study showed normal activated T and B cell expansion and contractions

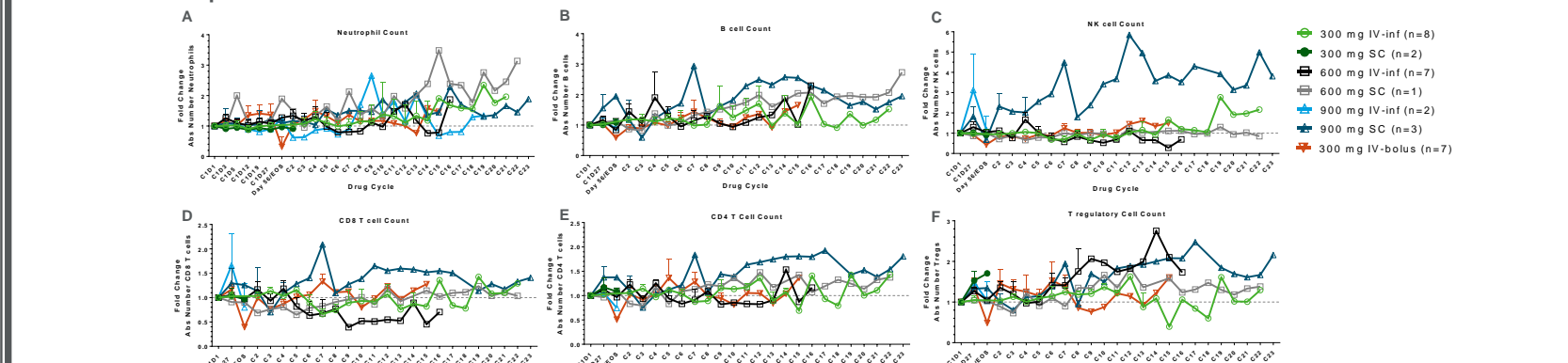


Figure 1. The absolute cell count was determined by CBC for neutrophils (A), and by flow cytometry for the major lymphocyte populations. B) B cells, C) NK cells, D) CD8 T cells, and E) CD4 T cells, and F) CD4+CD25+ T regulatory cells. The graphs depict fold change from baseline (C1D1) in cell count. The average fold change was calculated per cohort, legend indicates number of patients per cohort.

PHARMACOKINETICS

- Plasma concentration curves are multi-compartmental with a long terminal elimination phase
- Cobomarsen displays linear kinetics, with dose proportional increases in C_{max} and AUC across dose groups
- No evidence of accumulation at the highest doses tested for any route of administration
- Plasma trough values reach steady state in 12-16 weeks of dosing suggesting a terminal half life of approximately 2.5 to 3 weeks
- Increased trough values were observed in 3 patients that were later identified as having IgG anti-drug antibodies (ADAs); no effects on safety or efficacy were correlated with the presence of ADAs in these patients. 5 of 42 (12%) subjects subsequently screened were positive for ADAs

EFFICACY

Part A Lesion Biopsies Have Expected Gene Expression Changes and Lower Clonality After Cobomarsen Treatment Leading to Improved CAILS

- Subgroup of 122 mRNAs were modulated in common in lesion biopsy after cobomarsen treatment compared to a pre-treatment biopsy from the same lesion (Figure 2A)
- Modulated pathways include decreases in gene expression in key CTCL disease pathways (PI3K/AKT, JAK/STAT and NFκB pathways) as well as increased gene expression in pathways involved in apoptosis
- All evaluable Part A lesions directly injected with cobomarsen had improved CAILS scores (Fig. 2B) and decreased tumor cell clones when assessed by TCR sequencing on Study Day 9 (Figure 2C)

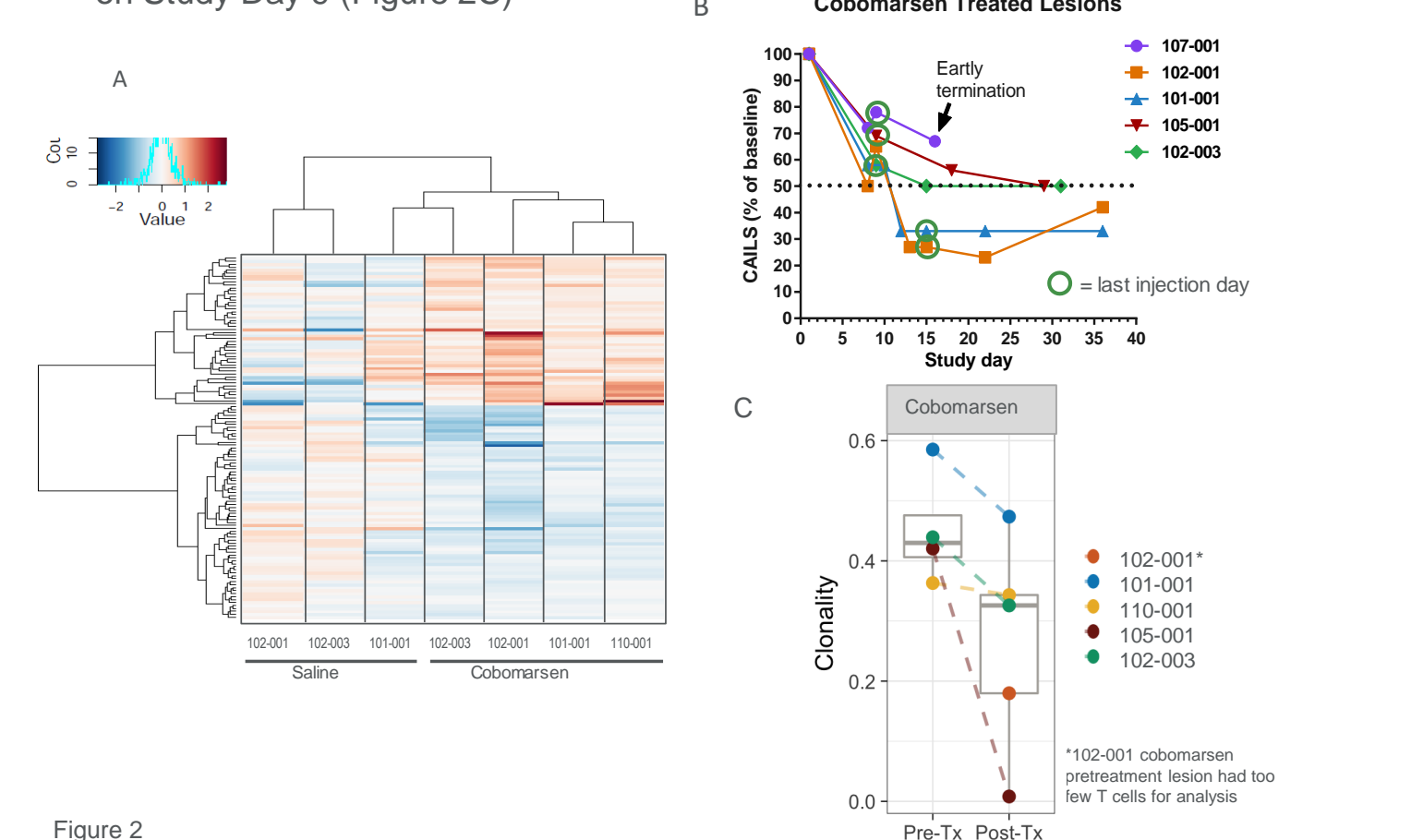


Figure 2. A) Log₂ fold-change in gene expression for drug or saline treatment vs. pretreatment for each individual biopsy. Shown are 122 genes regulated in the same direction by cobomarsen in all 4 lesions. Red = increased expression relative to the median for all samples; Blue = decreased expression relative to the median for all samples. B) The individual lesion Composite Assessment of Index Lesion Severity (CAILS) score was obtained by adding the severity score of each of the following categories: erythema, scaling, plaque elevation, and surface area. The change over time in CAILS scores (normalized to 100% at baseline) is presented graphically. C) VDJ Sequencing (T Cell Repertoire) completed at Adaptive Biotechnologies to identify oncogenic clone frequency for biopsies collected for Part A subjects pre-treatment or post-cobomarsen treatment on Day 9 (24 hours after the last dose). Clonality quantifies the extent of mono- or oligoclonal expansion by measuring the shape of the clone frequency distribution. Values can range from 0 to 1, where values approaching 1 indicate a nearly monoclonal population.

miR-155 Detection Decreases in Lesion Biopsies After Cobomarsen Treatment

- Pretreatment miR-155-5p expression levels quantitated by qPCR were elevated in the majority of CTCL patients compared to normal skin
- Highest levels of miR-155 were found in tumor lesions that had the highest density of neoplastic cells
- Intralesional and systemic cobomarsen treatment led to loss of miR-155 detection in the majority of subjects that was maintained up to 36 days post the last dose (EOS visit)

Five of Eight (63%) Subjects Treated with Cobomarsen Administered as a 300 mg IV-infusion Achieved a PR

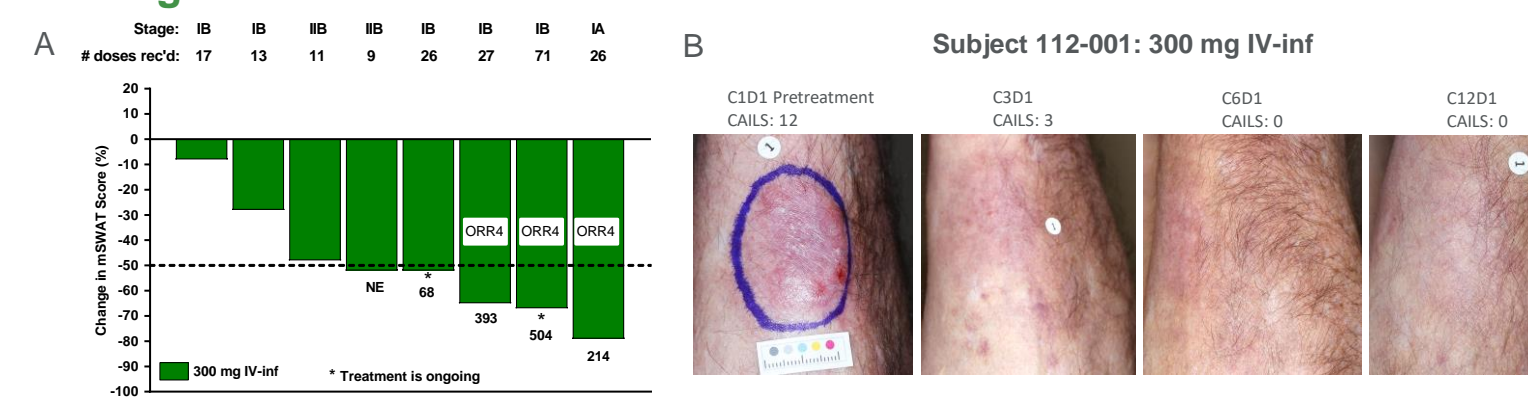


Figure 4. A) % change in mSWAT score represents best score achieved while on study for the 8 subjects in the 300 mg IV-infusion cohort. Duration of response (days) is indicated by the number below the bar for subjects achieving a PR. NE = Not Evaluable. B) Lesion photographs taken at baseline and over the course of cobomarsen treatment from subject 112-001 in the 300 mg IV-infusion cohort.

Thirty-three of Thirty-six Subjects (92%) Treated Systemically with Cobomarsen Have Shown mSWAT Score Improvement

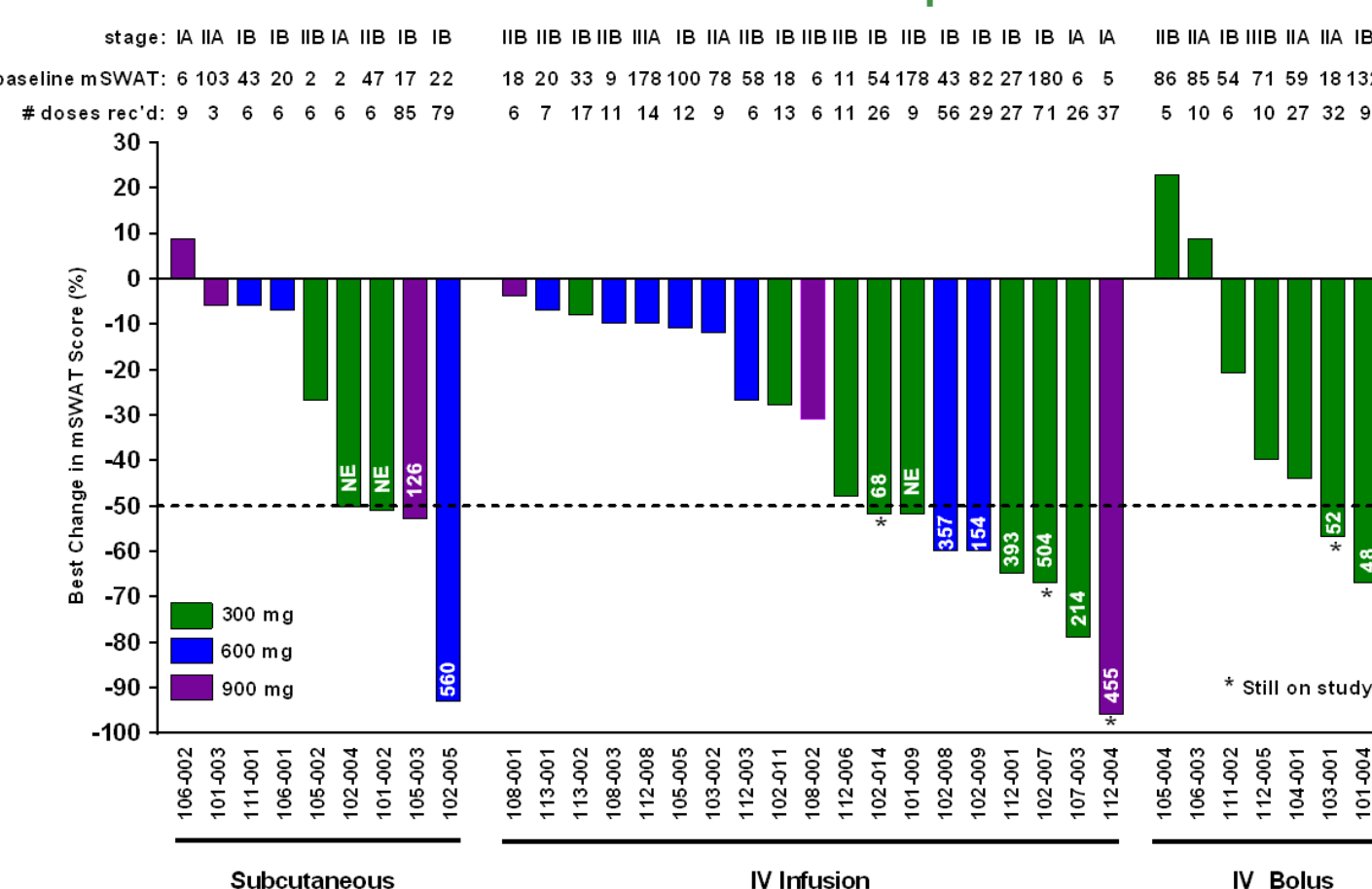
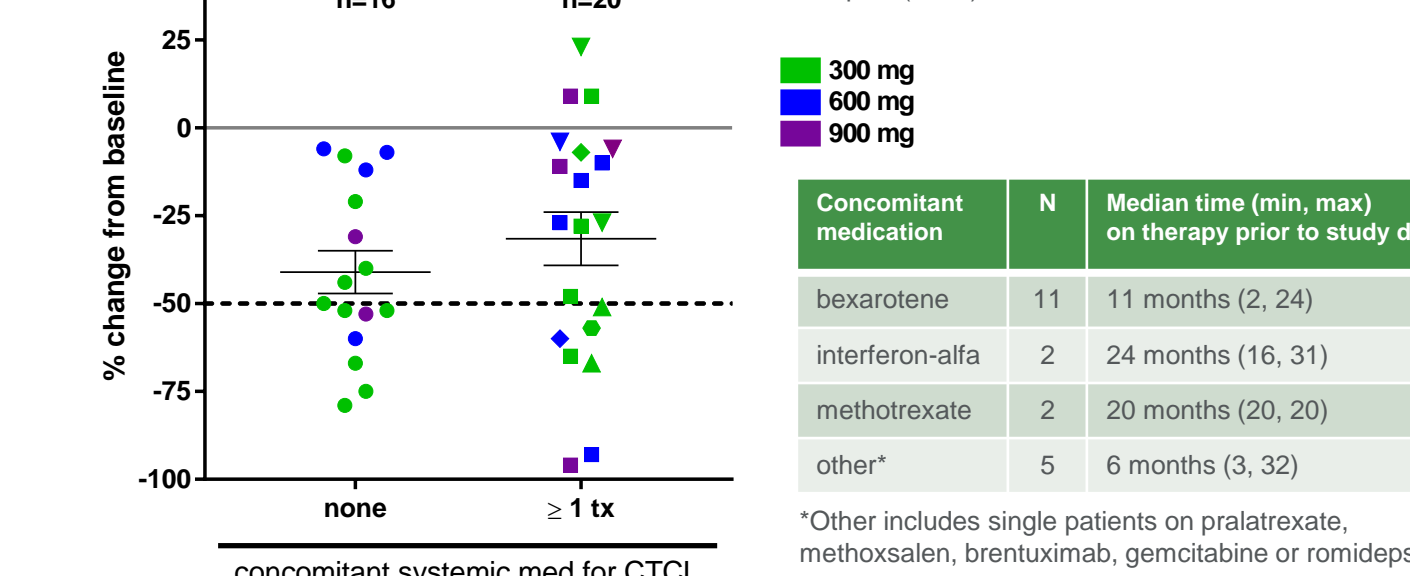


Figure 5. mSWAT score represents best score achieved while on study for 36 patients who had evaluable mSWAT scores as of the data cutoff (16OCT2018). Duration of response (days) as of 16OCT2018 for each evaluable patient achieving a 50% reduction in mSWAT score is shown in individual bar. NE = Not Evaluable; patients not allowed to continue on trial as per protocol or lost to follow up.

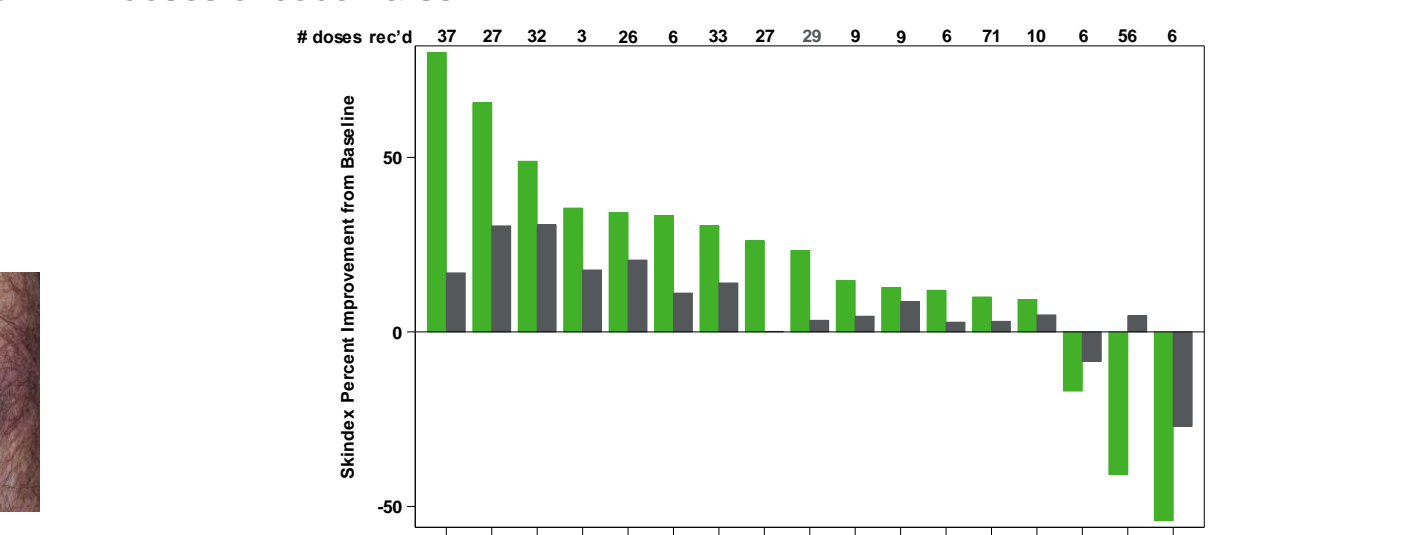
Cobomarsen has Similar Efficacy when Administered as Monotherapy or in Combination with Stable Regimens of Other CTCL Systemic Therapies

Figure 6. Percent change from baseline mSWAT score represents best score achieved while on study for subjects treated with cobomarsen as monotherapy (n=16) or in combination with other CTCL systemic therapies (n=20).



Quality of Life Improved as Measured by Skindex-29 Total Score

- Skindex-29 total score: maximal improvement and mean improvement throughout the duration of study (Figure 7)
- Quality of life (QoL) improvement occurs mostly in patients that received > 6 doses of cobomarsen



CONCLUSIONS

- Cobomarsen is well tolerated at doses ranging from 300-900 mg in CTCL. The doses studied after systemic administration appear to represent the top of the dose response curve
- 62% of subjects receiving more than 6 doses of the selected dose for phase II (300 mg IV infusion) had a partial response (PR)
- All evaluable subjects (n=5) showed improvement of lesions with direct cobomarsen injection. Target engagement and predicted pathway modulation was proven with IT injection
- 92% of subjects at any dose with systemic mode of administration showed improvement in mSWAT score
- 52% of subjects receiving more than 1 cycle (6 doses) had a partial response (≥50% reduction in mSWAT score)
- Responses are durable: 69% of the 13 subjects that achieved a PR maintained a response for at least 4 consecutive months (ORR4 based on mSWAT). Mean duration of response is 259 days (range: 48 - 560+ days)
- Quality of life, measured as mean Skindex-29 total score, improved in 88% of evaluable subjects throughout the study (N=17)
- PK is linear with a long terminal half-life (~2 1/2 to 3 weeks)

Acknowledgements and Disclosures

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