

MRG106-11-101

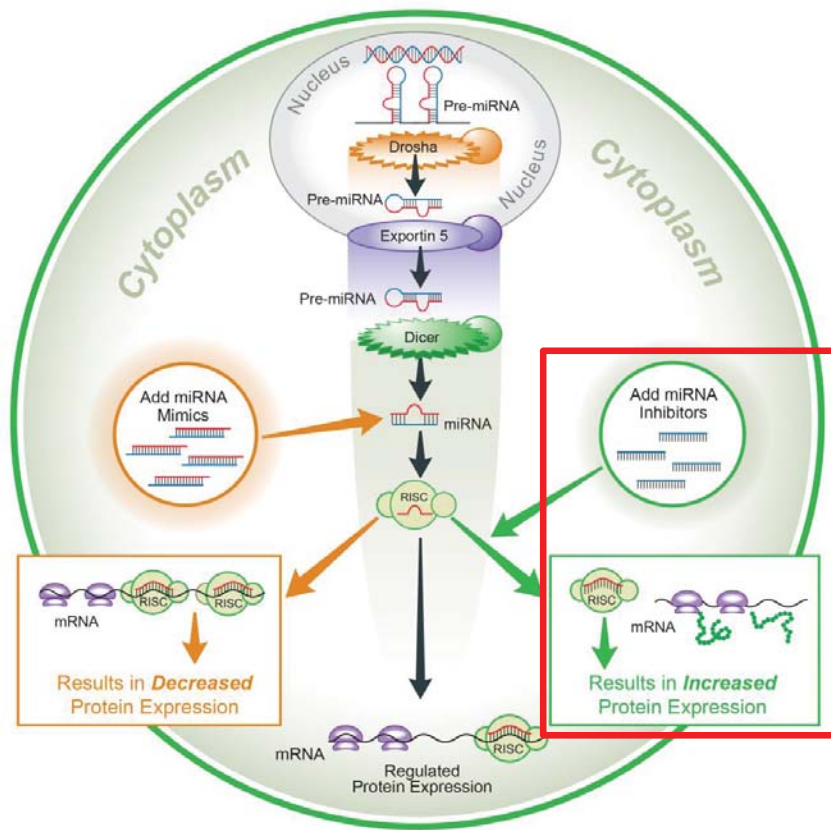
A Phase I Clinical Trial of Cobomarsen in Patients with ATLL

Preliminary Results

19th International Congress HTLV 2019

Lima, Peru


microRNA Therapeutics Regulate Systems Biology to Modify Disease




- microRNA-targeted therapy is focused on disease modification by restoring homeostasis to dysregulated processes
- microRNAs regulate complex biological systems
- microRNA-targeted therapies are intrinsically focused on disease-relevant pathways
- microRNA therapeutics particularly suited for complex, multigenic disorders

Cobomarsen 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



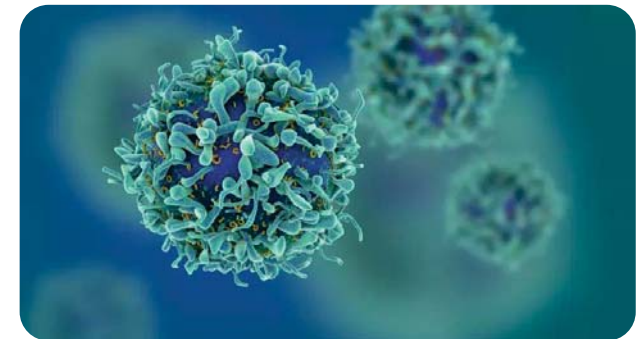
Genome-wide expression analysis demonstrates that cobomarsen regulates numerous genes implicated in cell cycle and apoptosis, consistent with the pharmacologic impact on cell survival



A subset of these genes has been identified as potentially translatable biomarkers to monitor cobomarsen activity in clinical samples

ATLL/HTLV-1 Epidemiology

- Adult T-cell leukemia/lymphoma (ATLL) is a mature, peripheral T-cell neoplasm caused by human T-cell leukemia virus type 1 (HTLV-1)
- HTLV-1 establishes lifelong latency in human T cells (50-70 years) before development of ATLL
- Malignant transformation leading to ATLL occurs in HTLV-1–infected individuals with a cumulative lifetime risk of 2.1% for women and 6.6% for men
- The median survival time for acute ATLL subjects is reported from 4.1 to 8.3 months, approximately 10 months for lymphomatous ATLL and 27 to 67 months for chronic unfavorable ATLL



Arch Pathol Lab Med 2014;138-282
Blood Advances, 2018 (March27); 2(6)

The Role of miR-155 in ATLL

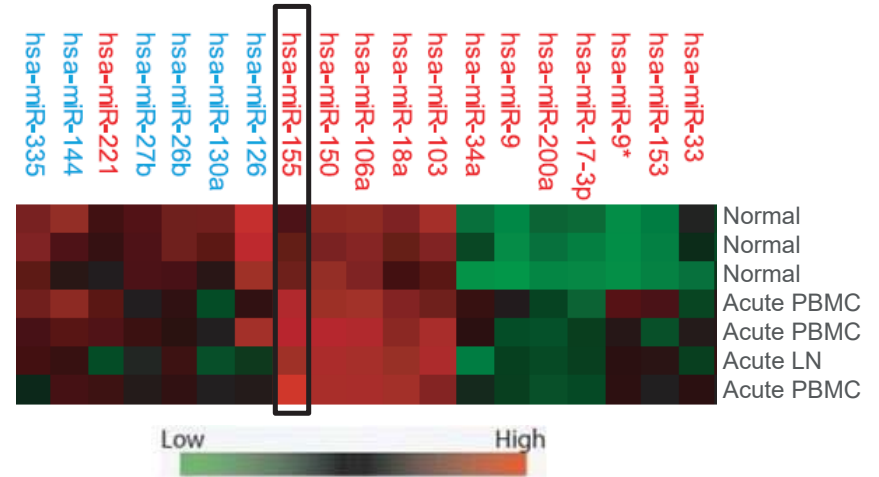
- miR-155 upregulation has been reported in HTLV-1 cell lines and *ex vivo* tumor cells from ATLL patients^{1,2}
- Increased expression of miR-155-5p enhances the growth of HTLV-1 infected T-cells

¹ Bellon et al. Blood. 2009

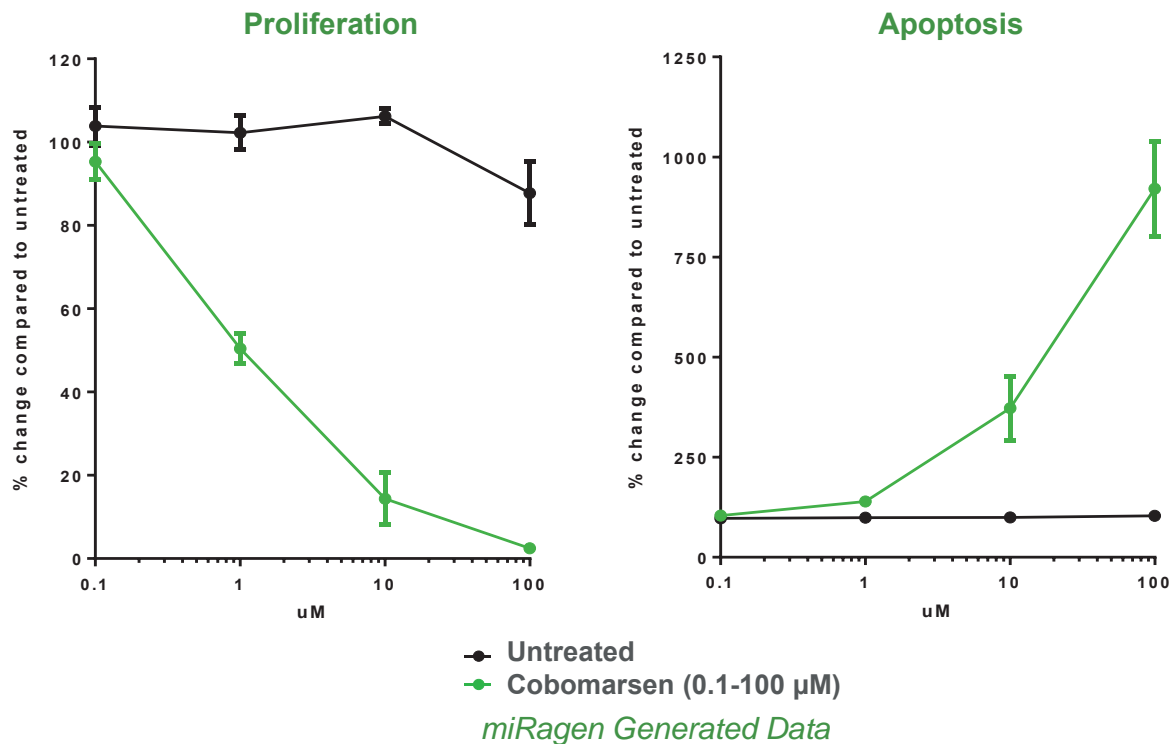
² BeSeto et al. Br J Haematol. 2018

³ Yeung et al. Cancer Res. 2008

miR-155 is upregulated in patient PBMCs or lymph biopsy (n=4)³



Cobomarsen Reduces Proliferation and Induces Apoptosis in a Dose-Dependent Manner in an ATLL Cell Line



- miR-155 expression is increased in HuT102 cells (HTLV-1+ ATLL line) (miRagen data)
- Cobomarsen inhibits cellular proliferation and induces apoptosis *in vitro*

**Phase I Clinical
Trial of MRG-106
(Cobomarsen) in
ATLL, DLBCL
and CLL**

**Interim Efficacy in ATLL and
Therapy Effects of
Cobomarsen on Immunologic
and Tumor-Associated Markers**

Data Cutoff: March 15, 2019

Overall Trial Design

- Open-label, dose-ranging, multiple dose study of subcutaneous or intravenous administration of cobomarsen in subjects with HTLV-1 associated ATLL, acute, lymphomatous, chronic, and smouldering subtypes
- Subjects receive 3 loading doses the first week of Cycle 1 followed by weekly dosing until subject becomes intolerant, develops clinically significant side effects, or progresses
- Safety Review Committee (SRC) comprised of study investigators and sponsor reviews the safety of enrolled subjects to assess dose-limiting toxicities, dose escalation, or dose de-escalation
- Primary objective is to determine safety and tolerability of cobomarsen in patients with ATLL
- Secondary and exploratory outcomes include pharmacokinetics (PK), clinical efficacy and effect on biomarkers of cell proliferation and activation

Subject Characteristics and Disposition

9 Patients Enrolled: 89% Black, 67% Male; Median Age of 49 Years

| Subject ID | ATLL Type at Diagnosis ¹ | ATLL Presentation at Screening | Relapse or Partial Remission ² | % Abnormal Lymphocytes at Screening ³ | Lymph Nodes at Screening CT Scan/PET | Dose (mg) | Days Since last TX | Duration of Cobomarsen Tx (Days) | Disposition ⁴ |
|----------------------|-------------------------------------|--|---|--|--------------------------------------|-----------|--------------------|----------------------------------|--------------------------|
| 101-008 | Acute | Acute | Partial Remission | 9% | Normal | 600 | 21 | 500 | Ongoing |
| 101-010 | Lymphomatous | Lymphomatous | Partial Remission | 14% | Normal | 600 | 46 | 465 | Ongoing |
| 101-012 | Lymphomatous | Lymphomatous | Partial Remission | 10% | Normal | 600 | 108 | 186 | Ongoing |
| 101-014 | Lymphomatous | Lymphomatous | Partial Remission | 15% ⁵ | Normal | 600 | 28 | 136 | Discontinued |
| 119-001 ⁶ | Chronic Unfavorable | Chronic unfavorable | Partial Remission | None | Abnormal | 600 | 450 ⁷ | 274 | Ongoing |
| 101-011 | Lymphomatous | Lymphomatous | Relapsing | Not Done | Abnormal | 600 | 219 | 10 | Discontinued |
| 102-012/ 102-015 | Acute | Lymphomatous transformation, mostly skin | Relapsing | 9% | Not Done | 600 | 21 | 92 | Discontinued |
| | | | | 26% | Normal | 600 | 30 | 43 | Discontinued |
| 118-001 | Smouldering | Aggressive, LCT, mostly skin | Relapsing | 0.3% | Abnormal | 600 | 31 | 24 | Discontinued |
| 119-002 | Chronic Unfavorable | Acute | Relapsing | 45% | Abnormal | 900 | 469 | 18 | Discontinued |

¹ PI diagnosis verified by miRagen

² Per miRagen assessment of disease status at screening

³ The percentage ATLL tumor cells of WBCs at screening prior to cobomarsen treatment. Any numbers reported were determined by flow cytometry performed locally at the clinical site and tumor cells were defined phenotypically as CD3+ CD4+ CD8- CD25+ CD7- CD26-

⁴ Subjects discontinued due to disease progression

⁵ Data from historical control, not screening date

⁶ Subject 119-001 had extensive skin, lymph and blood involvement at diagnosis. Abnormal cells were not quantified by flow cytometry, but visual blood smear only on C3D22

⁷ Subject continued to receive AZT/VPA as antiviral therapy while on cobomarsen. Last dose of Alemtuzumab was 15 months (450 days) prior to initiation of cobomarsen

Safety Summary of Cobomarsen in ATLL Cohort

No deaths while on cobomarsen treatment

No dose limiting toxicities (maximum tolerated dose not yet established) and no discontinuation from trial due to related AEs

4 SAEs in 3 subjects due to disease progression (unrelated to drug)

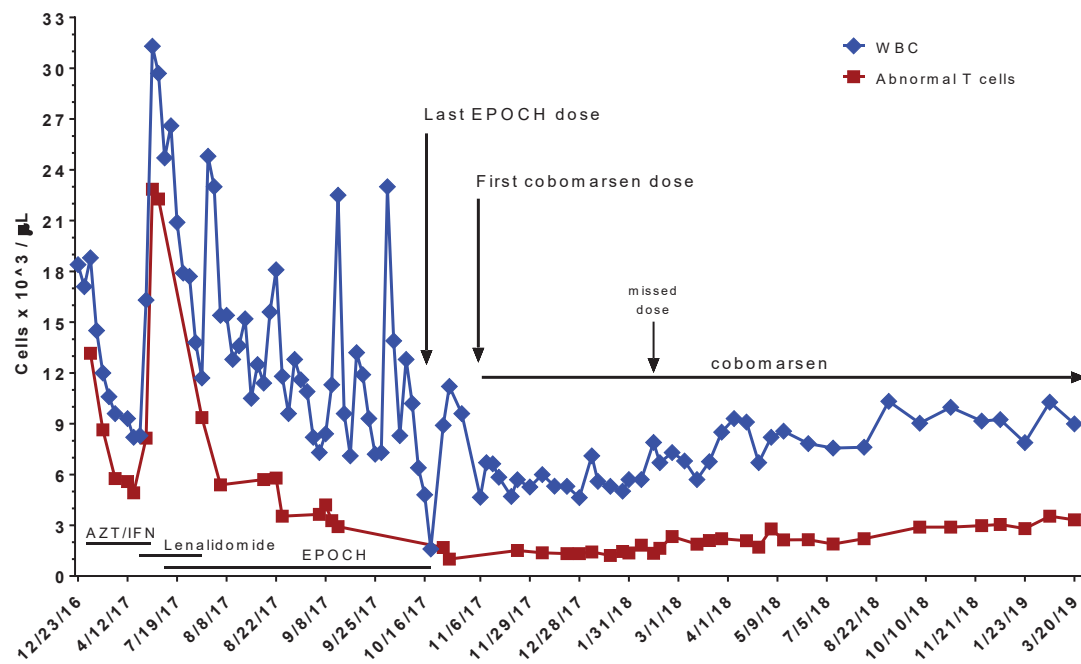
No related grade 3 or grade 4 AEs

No significant hematological events

Most common (in more than 2 subjects) related AEs (all grade 1 and 2) were diarrhea and nausea

Case Study in Acute ATLL Subject 101-008 in Partial Remission

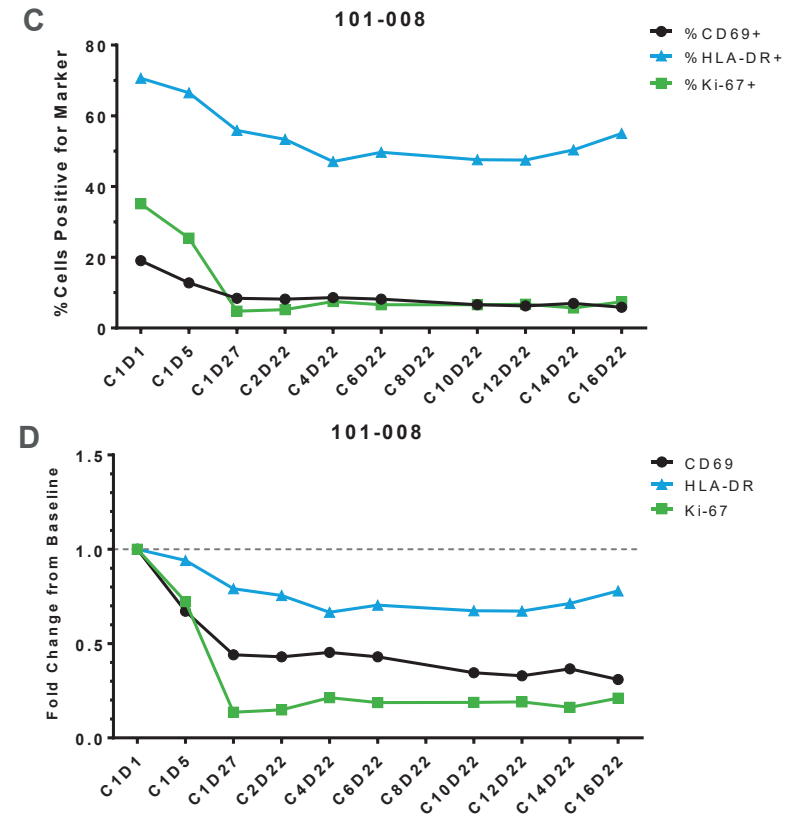
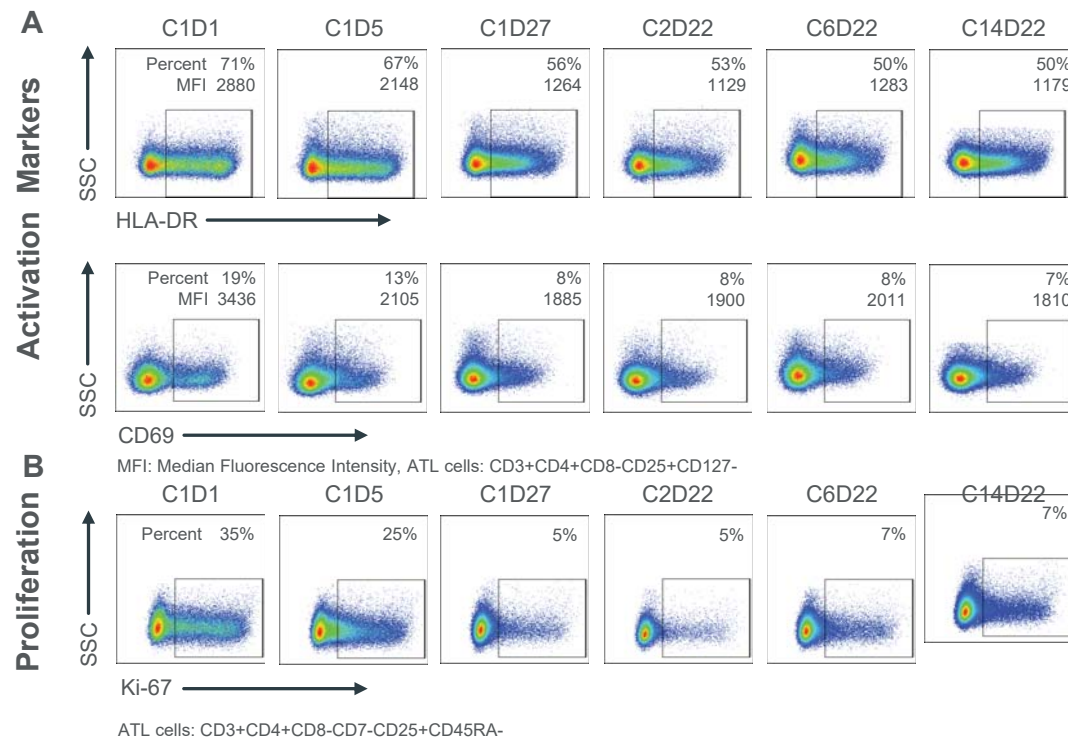
- Diagnosed in Dec 2016 with acute ATLL
- Relapsed after treatment with zidovudine, interferon alfa-2b, lenalidomide and EPOCH chemotherapy
- Cobomarsen treatment was initiated on Nov 2017; cobomarsen monotherapy resulted in stable peripheral WBC counts for over 16 months
- Cobomarsen treatment resulted in normalization of enlarged lymph node after chemotherapy (1.0 to 0.8 cm) as measured by CT scan (Oct 2017 compared to Jan 2018) that remain normal as of last imaging in Nov 2018
- Subject remains on treatment and has completed Cycle 18, missing only 1 dose, due to sciatic pain (Cycle 4 Day 15)



Graphical representation of the absolute WBC and abnormal T cell counts (CD4+ CD7- CD25+ CD26-) for subject 101-008 since diagnosis in relation to treatment course.

Cobomarsen Decreases Activation and Proliferation Status of Circulating Tumor Cells in ATLL Subject 101-008

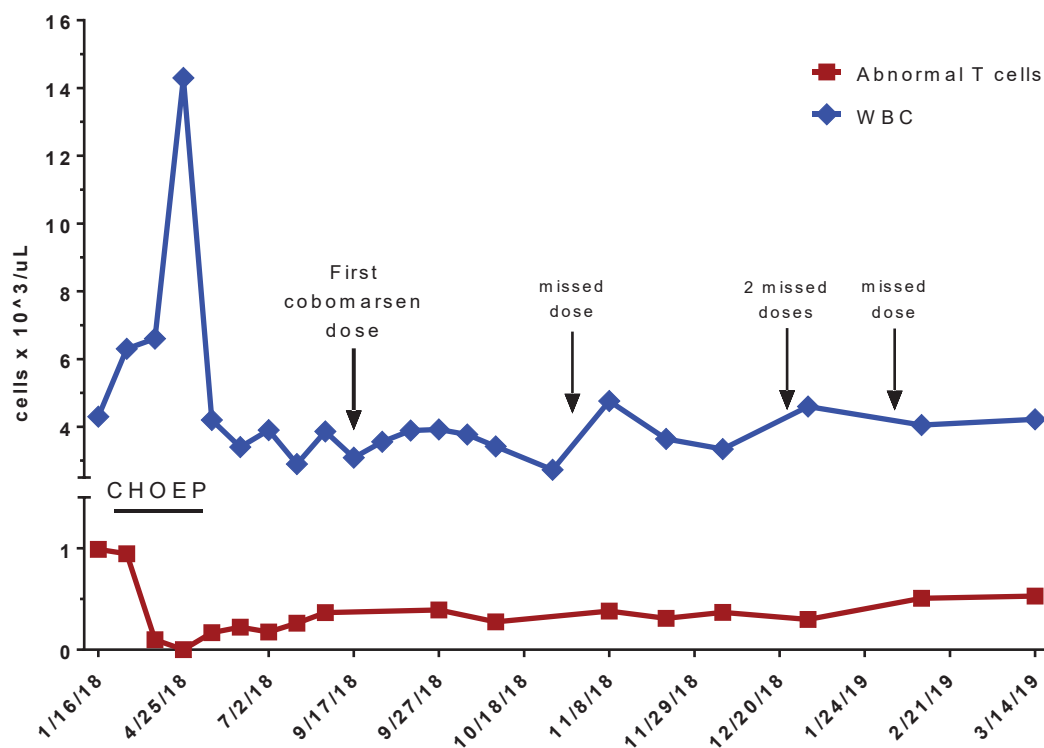
Representative Subject with Acute ATLL (101-008)



Flow cytometric assessment of A) activation, HLA-DR and CD69, and B) proliferation, Ki-67, marker expression in circulating ATL cells for subject 101-008 over the course of cobomarsen treatment. MFI – median fluorescence intensity C) The percentage of ATL cells positive for each biomarker and D) the fold change from baseline (C1D1) is graphed over the course of cobomarsen treatment.

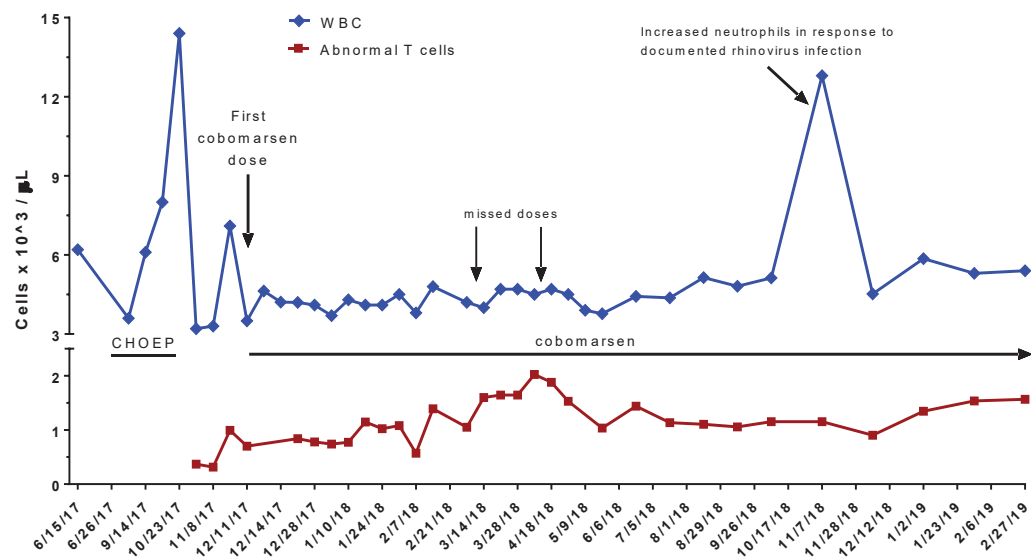
Case Study in Acute ATLL Subject 101-012 in Partial Remission

- Diagnosed in December 2017 with ATLL, lymphomatous sub-type
- Subject received 6 cycles of CHOEP therapy from January to May 2018 and had a complete response based on CT scan but persistent peripheral ATLL cells by flow cytometry
- CT scan at screening was normal
- Cobomarsen first dose on September 2018
- Subject has completed Cycle 6 and continues to receive treatment; Subject has missed 4 doses (shown in graph)
- CT scans have remained normal over the course of treatment (last scan performed in January 2019)
- LDH values for this subject were all within normal range



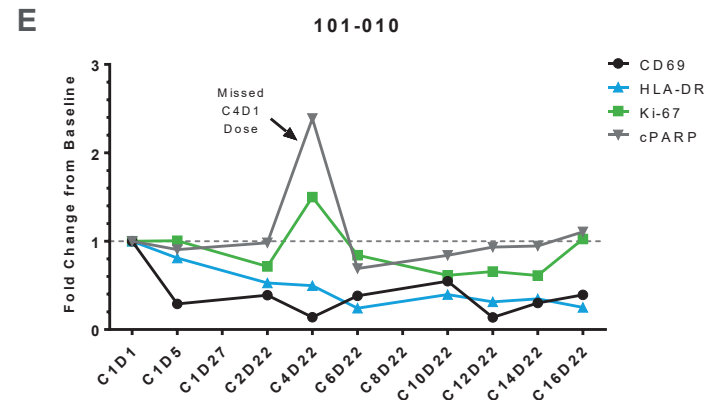
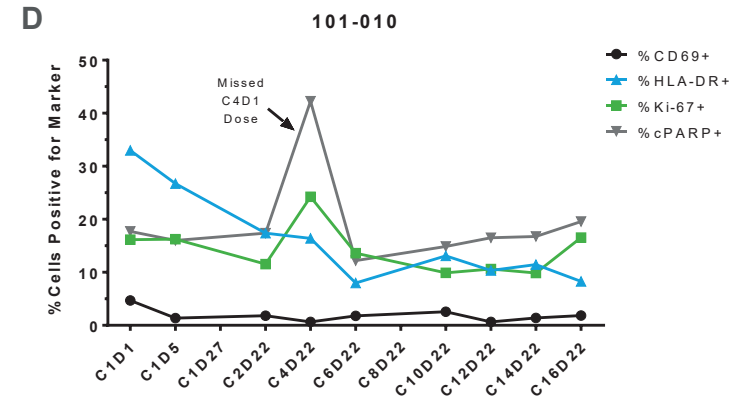
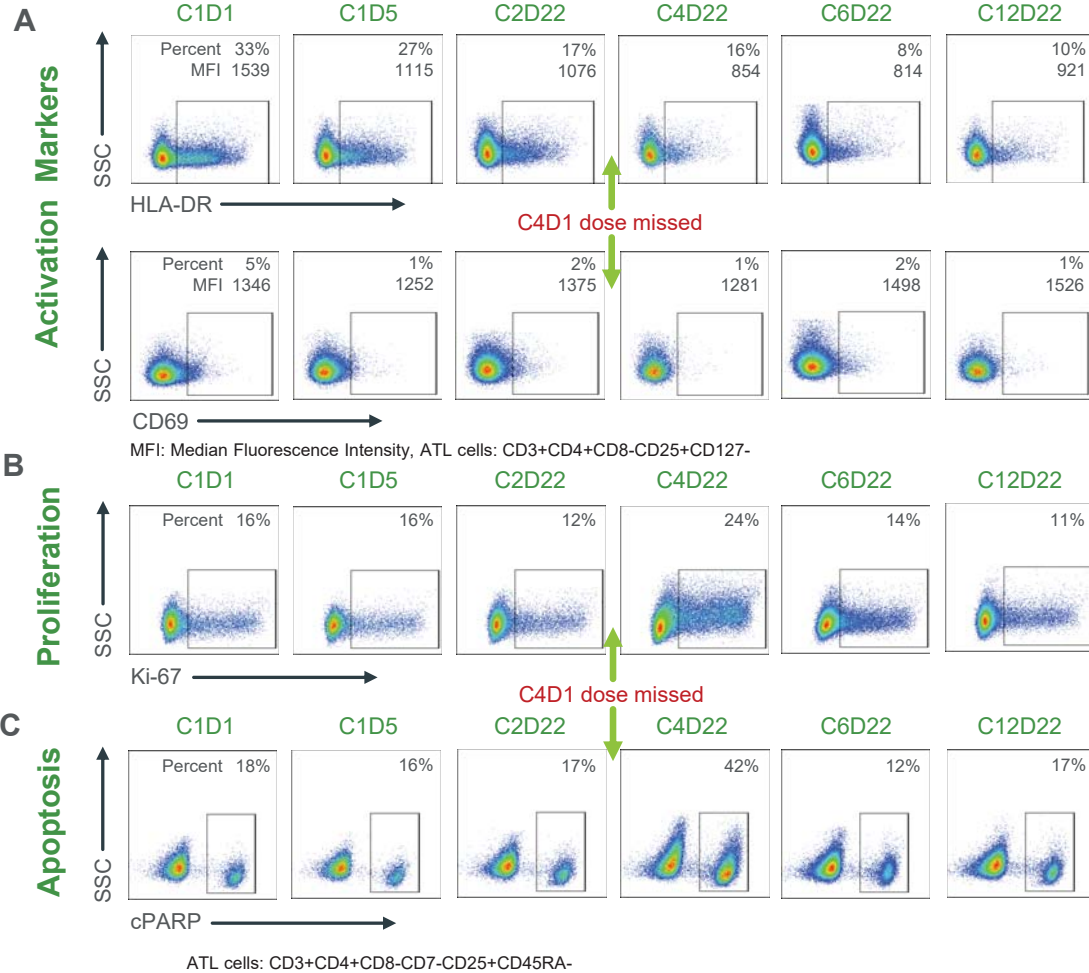
Case Study in Lymphomatous ATLL Subject 101-010 in Partial Remission

- Diagnosed in April 2017 with lymphomatous ATLL
- Extensive and bulky lymphadenopathy on initial CT scan was reduced by 6 cycles of CHOEP chemotherapy completed in June 2017
- Restaging PET scan showed resolution of adenopathy but with increased splenic uptake; Flow cytometry at the end of treatment showed 20% ATLL cells in peripheral blood
- After starting cobomarsen in Dec 2017, the stable lymph node size and peripheral blood tumor cell counts have been maintained for 15 months; Recent CT scan in November 2018 is now normal (resolution of splenic lesion)
- Subject has completed Cycle 16 and continues treatment
- Subject missed 2 doses of cobomarsen (Cycle 4 Day 1 and Cycle 5 Day 8)
- Rhinovirus infection in November 2018 showed a normal immune response as an increase in neutrophil count



Graphical representation of the absolute WBC and abnormal T cell counts (CD4+ CD7- CD25+ CD26-) for subject 101-010 since diagnosis in relation to treatment course.

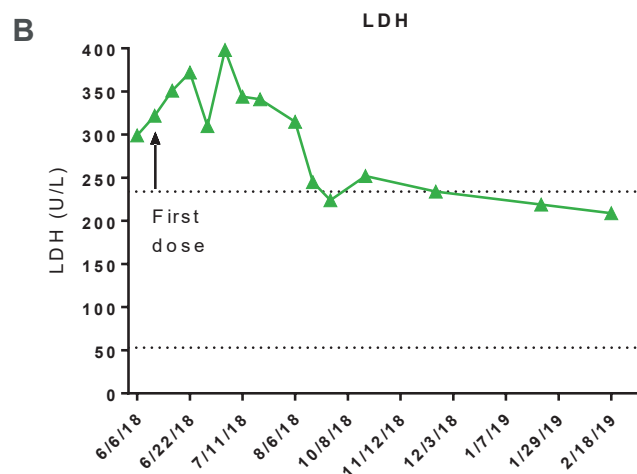
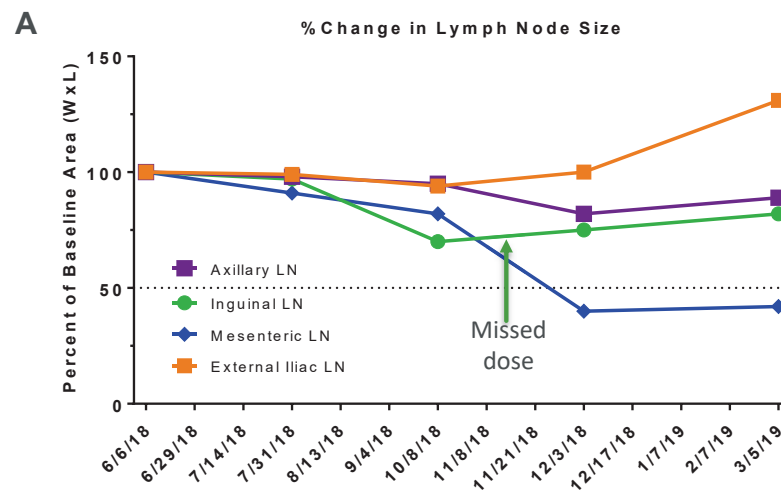
Cobomarsen Decreases Activation and Proliferation Status of Circulating Tumor Cells in Lymphomatous ATLL Subject 101-010



Flow cytometric assessment of: A) activation, HLA-DR and CD69; B) proliferation, Ki-67; C) apoptosis, cPARP, marker expression in circulating ATL cells for subject 101-010 (MFI – median fluorescent intensity); D) The percentage of ATL cells positive for each biomarker; and E) the fold change from baseline (C1D1) is graphed over the course of cobomarsen treatment.

Case Study in Chronic Unfavorable (Residual Nodal Disease at Screening) ATLL Subject 119-001 in Partial Remission

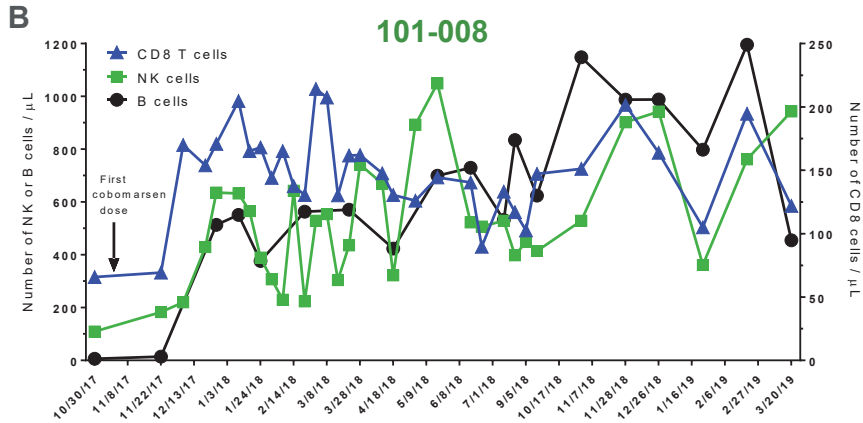
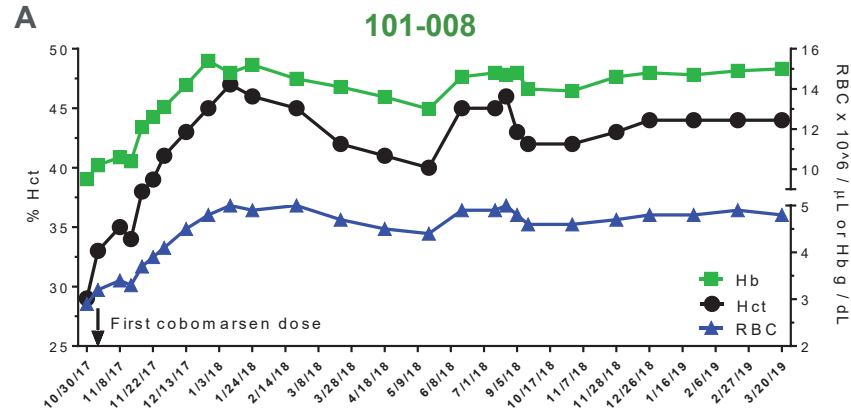
- Diagnosed in June 2013 with ATLL, chronic unfavorable sub-type, with aggressive disease involving skin, blood and lymph nodes
- Failed and relapsed after many therapies and was finally stabilized on Alemtuzuma; Subject was switched to, and maintained on, AZT/VPA and remained stable with residual abnormal nodes for 15 months
- In first 10 months of cobomarsen treatment there were no opportunistic infections; CT scans showed stable disease with mesenteric nodes clearly decreasing in size; LDH decreased and remains in normal range
- Continues to receive treatment and has completed Cycle 10



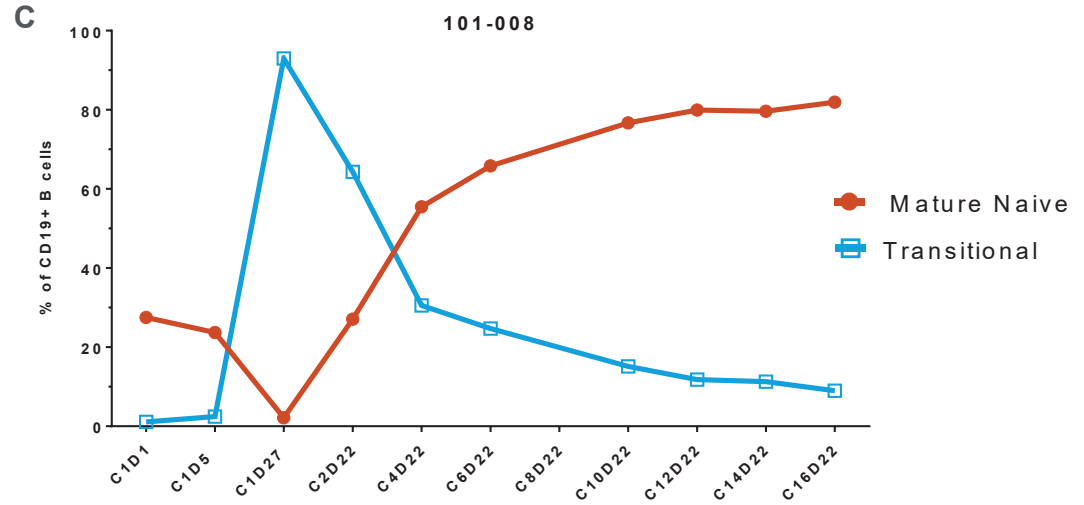
A) The percent change in size of 4 lymph nodes over the course of Cobomarsen treatment for subject 119-001. The size refers to area (width x length) as measured by CT scans.

B) The concentrations of LDH in blood over the course of treatment.

Cobomarsen Allows For Rapid Bone Marrow Recovery Following Chemotherapy and Does Not Inhibit B Cell Maturation In 4 Subjects



A) Hemoglobin (Hb, g/dL), Hematocrit (Hct, percentage), and Red Blood Cell (RBC, cells x 10⁶/μL) lab values are shown for subject 101-008 who underwent recent (21 day washout period) EPOCH chemotherapy. Flow cytometric assessments for B) CD8 T cells, NK cells, and B cells, reported as number of cells per μL for subject 101-008.

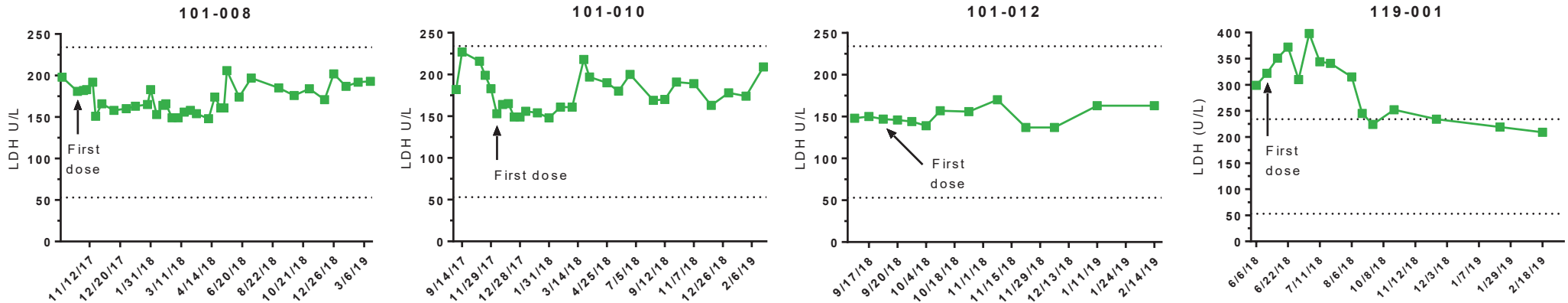


C) B cell maturation is shown as %mature B cell (CD10-CD27-IgD+) and %transitional B cells (CD10+CD38++) of CD19+ cells over the course of treatment

- Subject 101-008 underwent EPOCH chemotherapy 21 days prior to cobomarsen treatment
- Over the first cycle of cobomarsen treatment, immature B cells populate the periphery as transitional B cells and undergo maturation into mature naïve B cells over the next few cycles of cobomarsen treatment
- Evidence of B cell maturation in 3 other subjects

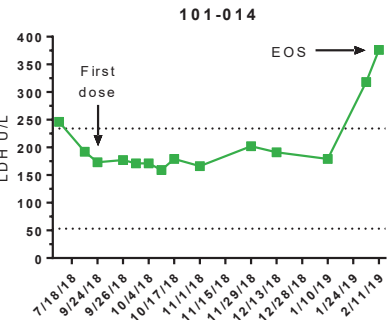
LDH Values in ATLL Subjects in Partial Remission and in Relapsing Subjects

Subjects in Partial Remission Still on Study

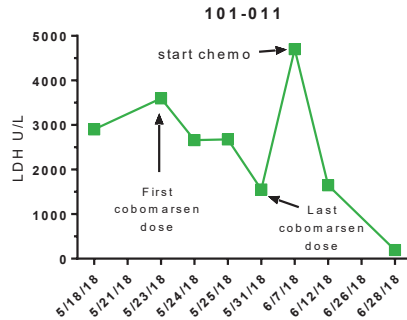
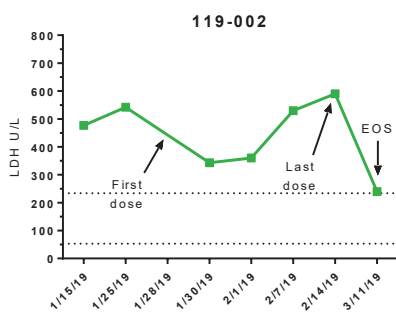


Subjects Off Study

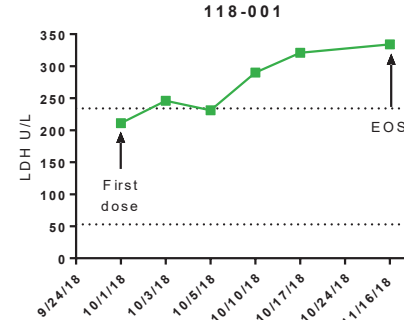
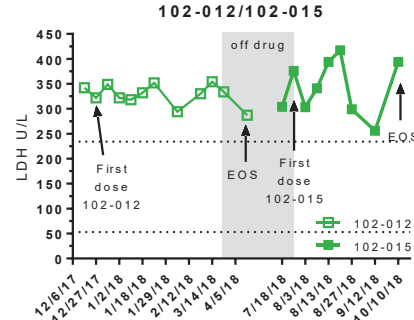
Subject in Partial Remission



Relapsing Subjects

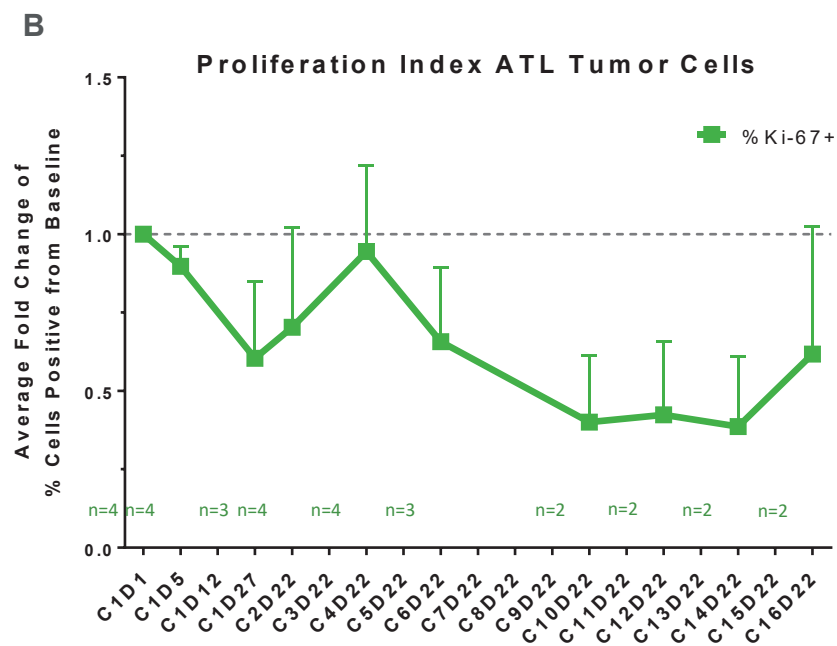
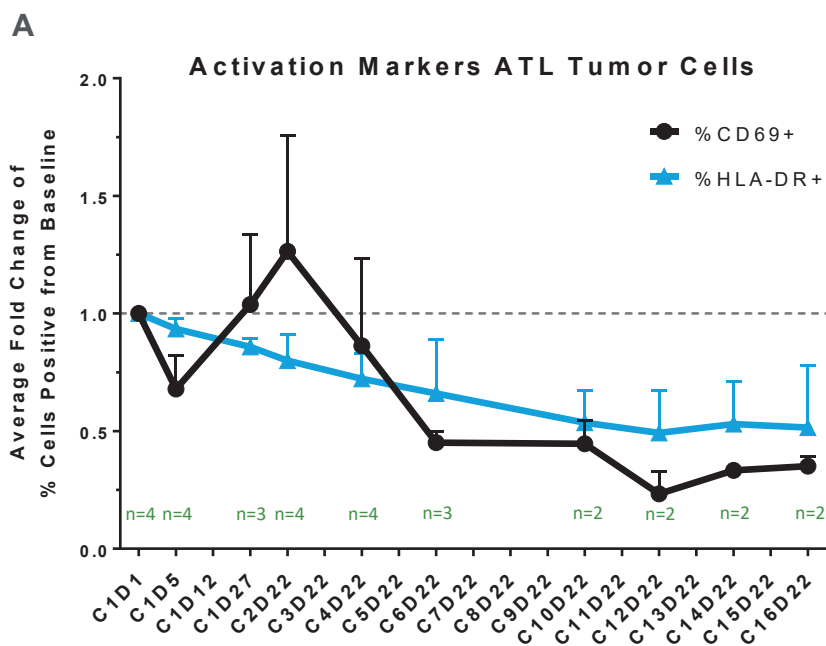


Relapsing Subjects with Primarily Skin Disease



Cobomarsen Decreases the Activation and Proliferation Status of Circulating Tumor Cells for ATLL Subjects in Partial Remission Who Remain on Study

Average Fold Change in Biomarkers for 4 ATLL Subjects in Partial Remission



Subjects in Remission

- 101-008
- 101-010
- 101-012
- 101-014 – off study
- 119-001

Average fold change (±SEM) from the pretreatment time point (C1D1) in the percentage of ATL tumor cells expressing A) HLA-DR and CD69 activation and B) Ki-67 proliferation markers from all evaluable ATLL subjects over multiple cycles of cobomarsen treatment. The number of subjects assessed is indicated as n on the x axis. Fold change for subject 119-001 could not be assessed due to a missing baseline (C1D1) sample.

Conclusions

Cobomarsen treatment resulted in durable clinical stabilization of all subjects with acute, lymphomatous and unfavorable chronic ATLL after partial remission for up to 16 months (median= 9 months); Four of 5 subjects continue dosing on study

Biomarkers of cell activation and proliferation decrease with cobomarsen treatment underscoring the biological effect of the drug in supporting the clinical stabilization in subjects in partial remission

Safety and tolerability profile appears benign, with no deaths, DLTs, related SAEs, related Grade 3 or Grade 4 AEs, hematological events, or discontinuation from trial due to related AEs

The preliminary results are encouraging and supports trial continuation to explore cobomarsen for the treatment of ATLL subjects

Phase I Investigators (USA)

- **Francine Foss, MD** – *Smilow Cancer Hospital at Yale-New Haven*
- **Juan Carlos Ramos, MD** – *University of Miami Sylvester Comprehensive Cancer Center*
- **Christiane Querfeld, MD** – *City of Hope*
- **Jasmine Zain, MD** – *City of Hope*
- **Alison Moskowitz, MD** – *Memorial Sloan Kettering Cancer Center*
- **Adrienne A. Phillips, MD** – *Weill Cornell Medicine*

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miRagen Therapeutics, Inc