Cobomarsen, an emerging potential treatment for patients with miR-155 elevated cancers

T-cell Lymphoma Forum
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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
miR-155 is a Master Regulator of Inflammation and Oncology
Cobomarsen (MRG-106), a miR-155-5p Inhibitor, Regulates Genes Implicated in T Cell Regulation, Cell Cycle and Apoptosis

- Cobomarsen is a chemically synthesized, chimeric phosphorothioate oligonucleotide, 14 nucleotides in length
- Genome-wide expression analysis demonstrates that cobomarsen regulates numerous genes implicated in T cell regulation and cell cycle and apoptosis.
- A subset of these genes has been identified monitor cobomarsen activity in clinical samples.

Table 1. Gene regulation by cobomarsen in activated, primary CD4+ T cells isolated from healthy donors.

<table>
<thead>
<tr>
<th>DOWN regulated gene clusters</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Activation of immune response</td>
<td>CXCR5, ICAM3, CD44, LCK, IL17A, IL17RA, IL10, IL6R, IL1R</td>
</tr>
<tr>
<td>2 Inflammatory response</td>
<td>IL1R</td>
</tr>
<tr>
<td>3 T cell receptor signaling pathway</td>
<td>SMAD3, TGFBR2, PIK3R5, LCK, VAV1, IL10</td>
</tr>
<tr>
<td>4 Coagulation, response to wounding, hemostasis</td>
<td>CD28, IL17A, PI3R5, ICOS, IL6R, IL10, CXCR5, VAV1</td>
</tr>
<tr>
<td>5 Adaptive immune response</td>
<td>CD28, IL17A, PI3R5, ICOS, IL6R, IL10, CXCR5, VAV1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>UP regulated gene clusters</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Ribonucleotide binding, ATP binding, RNA binding, nucleic acid binding</td>
<td>RPF2, CDK7, NARS, ALKBH5</td>
</tr>
<tr>
<td>2 Apoptotic process, Programmed cell death</td>
<td>CASP3, TNFRSF9, BNI3L, PPP3CC, MAP3K7</td>
</tr>
<tr>
<td>3 Apoptotic signaling pathway</td>
<td>CASP3, TNFRSF9, BNI3L, PPP3CC, MAP3K7</td>
</tr>
<tr>
<td>4 Immune response</td>
<td>IL5, IL4, IL13, GATA3, CCR7, VEGFA, SMAD7</td>
</tr>
<tr>
<td>5 Cytokine-mediated signaling pathway</td>
<td>STAT2, TICAM2, IL12Rb2, CXCR5, MAP3K5, IL1R, CD44, IL17A</td>
</tr>
</tbody>
</table>

Figure 1. Gene regulation by cobomarsen in activated, primary CD4+ T cells isolated from healthy donors.
Link Between miR-155 and Cancer

- The host gene for miR-155 (BIC) was identified along with myc as a proto-oncogene for virally-induced B-cell lymphomas
- miR-155 and its precursor BIC are highly expressed in hematologic malignancies and solid tumors
- Elevated miR-155 expression correlates with poor prognosis
- miR-155 is regulated by NF-κB, PI3K/AKT, and JAK/STAT, and functions in a feedback loop with these survival pathways
- miR-155 promotes chemoresistance in cancer cell lines
- Expression of miR-155 is sufficient to drive B cell expansion and formation of B cell lymphoma
- Therapeutic inhibition of miR-155 reduces proliferation and increases apoptosis in hematologic and non-hematologic cancer cell lines
Increased miR-155 is Implicated in Multiple Oncology Indications

Hematologic
- Cutaneous T-cell lymphoma (CTCL)
- Acute myelogenous leukemia (AML)
- B-cell lymphoma (DLBCL)
- Chronic lymphocytic leukemia (CLL)
- Adult T-cell leukemia/lymphoma (ATLL)
- Peripheral T-cell lymphoma (PTCL)
- Burkitt’s lymphoma
- Waldenstrom macroglobulinemia (WM)

Non-Hematologic
- Non-small cell lung cancer
- Glioblastoma
- Triple negative breast cancer
- Melanoma
- Colorectal cancer
- Gastric cancer
- Pancreatic cancer
- Gall bladder cancer
- Head and neck squamous cell carcinoma
- Neurofibromatosis
miR-155 is Up-regulated in Multiple Hematological Cancer Cell Lines

![Graph showing absolute miR-155 expression](attachment:miR_155_expression.png)

- **Hodgkin lymphoma**
- **Burkitt lymphoma**
- **ABC-DLBCL**
- **ATLL**
- **MF**

Legend:
- **norm CD19+ B cell**
- **norm CD4+ T cell**
- **KM-H2**
- **L1236**
- **Oci-Ly 3**
- **Jijo Ye**
- **My-La**
- **HH**
- **MJ**
- **HuT102**
miR-155 is Upregulated in Malignant T-cell lines and Inhibition Affects Cell Growth and Apoptosis

- Effects on cell proliferation similar to bexarotene
- Unlike bexarotene, cobomarsen mechanism enhances apoptosis in cell lines
- Different mechanisms suggests potential for additivity/synergy with other therapeutics for CTCL
Cobomarsen PK and Preclinical Safety

- Cobomarsen displays linear kinetics, with dose proportional increases in $C_{\text{max}}$ and AUC across dose groups.
- Cobomarsen is well tolerated in non-human primates up to 30 mg/kg administered by IV 2hr-infusion or as a SC or IV bolus injection.
- No toxicity related to TLR activation, Liver Function, Complement, Platelet function.
- Mild reversible decrease in renal function in rodents with good margin of safety.
Cobomarsen Clinical Program in Hematological Malignancies

CTCL
Mycosis Fungoides

miR-155-high Non-Hodgkins Lymphoma (NHL)/Leukemia

Dose, Schedule Optimization and Response Durability in CTCL

Ph 1 CTCL
mPoC
Ph 2 CTCL
Futility Analysis

Parallel Indication Expansion in Ph1

ATLL
DLBCL
CLL

Ph 2 in NHL / Leukemia
Cobomarsen in CTCL
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)

Figure 3. miR-155-5p copy number in lesion biopsies taken before and after cobomarsen treatment from CTCL subjects enrolled in Parts A and B compared to normal skin biopsies from healthy donors
Thirty-three of Thirty-six Subjects (92%) Treated Systemically with Cobomarsen Have Shown mSWAT Score Improvement

- 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.
Five of Eight (63%) Subjects Treated with Cobomarsen Administered as a 300 mg IV-infusion Achieved a PR. 50% of these reached ORR4

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.
Cobomarsen SOLAR Phase 2 Clinical Trial Initiated in 4Q18
A Randomized, Parallel, Open Label, Active Control, Global Trial in Patients with Stage Ib-III Mycosis Fungoides

Primary Endpoint
• Overall Response Rate of four months (ORR4) using Global Response Criteria

Key Secondary Endpoint
• Progression-free survival

Additional Secondary Endpoint
• Patient reported outcomes
  • Skindex-29, pruritus, pain

Key Inclusion Criteria
- Stage Ib-III
- Must have received at least one prior therapy for CTCL (per NCCN guidelines for generalized skin involvement)
- mSWAT score ≥ 10

Open Label; Randomize to: cobomarsen IV Infusion vs. vorinostat
Randomize

Cobomarsen (300mg IV Infusion anticipated) n=~65 subjects
Follow until progression

Futility Analysis

vorinostat n=~65 subjects
Follow until progression

PRISM (Open label extension)
CTCL: Adverse Events

- 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 to study drug
  One subject (101-003) had tumor flare followed by erythema, rash, leukopenia, lymphopenia and hyperuricemia (all within 2 weeks, reported as 6 separate AEs)
  In 5 subjects, the following were reported:
  - 102-008: Flare-erythema and Tumor pain
  - 105-004: Tumor Flare, Neutropenia, Leukopenia
  - 3 other subjects (each in 1 subject): Intermittent ANC Decreased, hypokalemia, Intermittent Neutropenia
Cobomarsen in ATLL
### Patient Characteristics and Disposition

Subject baseline disease characteristics, duration of cobomarsen treatment, and disposition. Data cut off date 13DEC2018

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Presentation at Screening</th>
<th>Blood Involvement (% tumor cells of WBC)¹</th>
<th># of Prior Therapies</th>
<th>Days Since Last Tx and Start of Cobomarsen</th>
<th>Cobomarsen Treatment Duration (days)</th>
<th>Disposition (reason for discontinuation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>101-008</td>
<td>Acute – in remission</td>
<td>9%</td>
<td>4</td>
<td>21 108</td>
<td>401 days 87 days</td>
<td>Discontinued (progression)</td>
</tr>
<tr>
<td>101-012</td>
<td>Acute – in remission</td>
<td>10%</td>
<td>1</td>
<td>108</td>
<td>87 days</td>
<td>Ongoing</td>
</tr>
<tr>
<td>102-012 / 102-015²</td>
<td>Relapsing – primarily skin disease</td>
<td>9%</td>
<td>10</td>
<td>21 / 30</td>
<td>91 / 42 days²</td>
<td>Ongoing Discontinued (progression)</td>
</tr>
<tr>
<td>101-010</td>
<td>Lymphomatous – in remission</td>
<td>14% (7/9/18)</td>
<td>2</td>
<td>28</td>
<td>366 days</td>
<td>Ongoing</td>
</tr>
<tr>
<td>101-014</td>
<td>Lymphomatous – in remission</td>
<td>Data not collected</td>
<td>7</td>
<td>219</td>
<td>9 days</td>
<td>Ongoing Discontinued (progression)</td>
</tr>
<tr>
<td>101-011</td>
<td>Lymphomatous – relapsing</td>
<td>Data not collected</td>
<td>46</td>
<td>46</td>
<td>366 days</td>
<td>Ongoing Discontinued (progression)</td>
</tr>
<tr>
<td>119-001³</td>
<td>Lymphomatous – stable disease</td>
<td>No abnormal cells</td>
<td>10</td>
<td>NA⁴</td>
<td>161 days</td>
<td>Ongoing Discontinued (progression)</td>
</tr>
<tr>
<td>118-001</td>
<td>Relapsing – primarily skin disease</td>
<td>Data not collected</td>
<td>5</td>
<td>31</td>
<td>23 days</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

¹ The percentage ATL 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⁻

² Patient 102-012 was re-enrolled on study as 102-015

³ Patient 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

⁴ Patient continued to receive AZT/VPA as antiviral therapy while on cobomarsen. Last dose of alemtuzimab was 15 months (450 days) prior to initiation of cobomarsen
Patients all feel well without typical ATLL signs and symptoms

Response ranges from 3 months to one year after cobomarsen initiation as of data cut off

Bone marrows restored

No drug related Grade 3, 4 AEs or SAEs

No new opportunistic infections reported
Cobomarsen Decreases Activation and Proliferation Status of Circulating Tumor Cells in ATLL Subjects

Representative patient with Acute ATLL (101-008)

Average (SD) change in biomarkers in 7 ATLL subjects

Biomarker Expression on ATL Tumor Cells

- % CD69+
- % HLA-DR+
- % Ki-67+

Average (SD) change of % Cells Positive from Baseline

n=7 n=7 n=3 n=3 n=2 n=2 n=2 n=2
Cobomarsen Did Not Inhibit Normal Bone Marrow Recovery of Leukemic ATLL Patient When Administered Starting 21 Days After Last EPOCH Chemotherapy Dose

Immature B cells from bone marrow populate periphery and mature normally during cobomarsen therapy.
Cobomarsen in DLBCL
One of Three Relapsing Patients with DLBCL, ABC Subtype has Demonstrated Beneficial Response

- mir-155 is documented to be elevated in the ABC subtype
- Three patients with ABC have been treated with cobomarsen
  - All three had relapsed after multiple therapies prior to trial initiation
  - Two of three progressed while on therapy and cobomarsen discontinued after one cycle or less
- One patient demonstrated response in measurable lesions after seven weeks of therapy*
  - 60 year old female with four year history of DLBCL
  - Relapsed after multiple regimens
  - Responded to experimental Pi3K +BTK inhibitor – sponsor discontinued trial and patient relapsed
  - Disease at initiation and following cobomarsen below:

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Screening Measurement</th>
<th>C1D3</th>
<th>C1D10</th>
<th>C1D17</th>
<th>C2D1</th>
<th>C2D15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Neck</td>
<td></td>
<td>9</td>
<td>11</td>
<td>20</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Inguinal Node</td>
<td>Not done</td>
<td>9</td>
<td>5</td>
<td>5</td>
<td>23</td>
<td>5</td>
</tr>
</tbody>
</table>

*Patient data courtesy of Dr. L. Pinter-Brown
Conclusions

- miR-155 associated with multiple hematologic and non-hematologic malignancies
- miR-155 regulated genes are essential for malignant processes
- Cobomarsen, and antimiR to miR-155 has shown evidence of activity and clinical benefit in early studies of three hematologic cancers
  - CTCL
  - ATLL
  - DLBCL
- Cobomarsen has demonstrated good safety and tolerability to date
- Continued study of cobomarsen in these and other miR-155 upregulated malignancies is clearly warranted.