COBOMARSEN (miR155 INHIBITOR) IN MYCOSIS FUNGOIDES

Christiane Querfeld, MD, PhD

2015... 2018  T-Cell Lymphomas: we are close to the finalization

Bologna, IT May 9, 2018
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 a high accuracy

miR-155 is overexpressed in CTCL skin

JAK/STAT, NFkB and PI3K pathways are activated in CTCL and regulated by miR-155 that lead to uncontrolled clonal cell expansion

MIR-155 IS UPREGULATED IN MF LESIONS AND INHIBITION AFFECTS CELL GROWTH & APOPTOSIS

Lesion Type vs miR-155 Copy-Number

Cell Proliferation of HuT102 Cells

Apoptosis Pathway Activation in HuT102 Cells

Archived tissue provided by Madeleine Duvic (MD Anderson)
PHASE 1 COBOMARSEN OPEN LABEL STUDY IN CTCL DESIGN AND INTERIM RESULTS

Safety and efficacy
COBOMARSEN: FIRST-IN-HUMAN PHASE 1 STUDY OF MRG-106 IN PATIENTS WITH MYCOSIS FUNGOIDES TWO-PART PHASE 1 CTCL STUDY

Objectives:

- **Primary**: Investigate safety & tolerability of multiple injections
- **Secondary**: Characterize the pharmacokinetic profile
- **Exploratory**:
  - Pharmacodynamic profile
  - Gene expression alterations
  - Histopathology of lesion biopsy
  - Imaging of tumor morphology

**Part A**
Intra-tumoral delivery of cobomarsen.

- **75 mg dose**

**Part B**
Systemic SC or IV delivery to determine optimal potential dose.

- **300, 600 and 900 mg dose**
### BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Part A n = 6</th>
<th>Part B n = 30</th>
<th>Total n = 36</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>5 (83%)</td>
<td>20 (67%)</td>
<td>25 (69%)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median years (range)</td>
<td>61 (50-64)</td>
<td>63 (21-85)</td>
<td>63 (21-85)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>4 (67%)</td>
<td>24 (80%)</td>
<td>28 (78%)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (17%)</td>
<td>3 (10%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0%)</td>
<td>2 (7%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Not reported</td>
<td>1 (17%)</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td><strong>Disease Stage at Screening</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IA</td>
<td>0 (0%)</td>
<td>6 (20%)</td>
<td>6 (17%)</td>
</tr>
<tr>
<td>Stage IB</td>
<td>1 (17%)</td>
<td>8 (27%)</td>
<td>9 (25%)</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>2 (33%)</td>
<td>3 (10%)</td>
<td>5 (14%)</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>3 (50%)</td>
<td>9 (30%)</td>
<td>12 (33%)</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>0 (0%)</td>
<td>3 (10%)</td>
<td>3 (8%)</td>
</tr>
<tr>
<td><strong>Prior Systemic Therapies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Patients Reporting</td>
<td>6</td>
<td>25</td>
<td>31</td>
</tr>
<tr>
<td>Median # (range)</td>
<td>4 (1-6)</td>
<td>3 (1-13)</td>
<td>4 (1-13)</td>
</tr>
<tr>
<td><strong>Prior Skin Directed Therapies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Patients Reporting</td>
<td>6</td>
<td>26</td>
<td>32</td>
</tr>
<tr>
<td>Median # (range)</td>
<td>4 (1-6)</td>
<td>3 (1-8)</td>
<td>3 (1-8)</td>
</tr>
<tr>
<td><strong>Baseline mSWAT per Subject</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>3</td>
<td>30</td>
<td>33</td>
</tr>
<tr>
<td>Median (range)</td>
<td>23 (3-96)</td>
<td>45 (2-180)</td>
<td>43 (2-180)</td>
</tr>
</tbody>
</table>

- Balanced across stages
- Patient population failed many prior therapies
- miR-155 elevated in most enrolled patient’s lesions

**miR-155 Copy Number in MF Lesion Biopsies**

- [Graph showing miR-155 copy number distribution](#)
COBOMARSEN IMPROVED CAILS WITH INTRALESIONAL INJECTION (PART A)

MRG-106 injected lesions

Early termination

○ = last injection day
GENE EXPRESSION CHANGES WITH INTRALESIONAL INJECTION OF COBOMARSEN CORRELATE TO DRUG LEVELS IN MF LESION BIOPSIES (PART A)

Cobomarsen Decreases Key CTCL Pathways:
- STAT
- PI3K/AKT
- NFkB

Up-regulated vs. untreated
Down-regulated vs. untreated
COBOMARSEN SHOWS FAVORABLE SAFETY AND TOLERABILITY

- Cobomarsen has been safe and generally well tolerated at all doses tested
  - Multiple patients receiving more than a year of therapy (up to 39 grams cumulative dose) with no serious adverse events attributed to cobomarsen
- No significant abnormalities found in liver or kidney function, no abnormalities in platelet counts
- No acute inflammatory toxicities
- No SAEs attributed to cobomarsen
- Two Dose-Limiting Toxicities:
  - Grade 3 worsening pruritus, possible tumor flare, occurred twice in one patient at 900 mg SC and 300 mg IV infusion
  - Grade 3 tumor flare (300 mg IV bolus)
- Novel oligonucleotide drug class
  - Elimination of “gap” reduces chemical class based toxicity
  - Short length minimizes heparin mimetic activity
**COBOMARSEN HAS BEEN WELL TOLERATED**

All Related AEs (grade 1-4): 133 (62.2% subjects)

**Hematology**
- Neutropenia: 9 (20.5%)
- Lymphopenia: 6 (13.6%)
- Anemia: 1 (2.3%)
- Thrombocytopenia: 5 (9.1%)
- Other: 4 (9.1%)
- Hematological: 27 (34.1%)

**Other Non-Hem**
- GI: 12 (15.9%)
- Musculoskeletal: 5 (4.5%)
- Skin: 17 (20.5%)
- Renal: 10 (11.4%)
- Other/Investigations: 22 (29.5%)
- Other Non-Hem: 80 (50%)

**Constitutional/Drug Administration**
- Neurological: 5 (9.1%)
- Infection: 1 (2.3%)
- Cardiac: 3 (4.5%)
- Psychiatric: 2 (2.3%)
- Vascular: 3 (4.5%)
- Constitutional/Drug Administration: 26 (27.3%)

**Other**
- Infusion reaction: 16 (15.9%)
- Injuries: 1 (2.3%)
- Constitutional: 9 (15.9%)

Database April 30 2018
COBOMARSEN HAS BEEN WELL TOLERATED

All Related AEs in > 10% of subjects (grade 1-4)

Hematology
27 (34.1%)

- Neutropenia
  9 (20.5%)

- Lymphopenia
  6 (13.6%)

Other Non-Hem
80 (50%)

- GI
  12 (15.9%)

- Renal
  10 (11.4%)

- Skin
  17 (20.5%)

- Other/Investigations
  22 (29.5%)

Constitutional/Drug Administration
26 (27.3%)

- Infusion reaction
  16 (15.9%)

- Constitutional
  9 (15.9%)

Database April 30 2018
COBOMARSEN- A FAVORABLE SAFETY PROFILE
13 GRADE 3 AND 4 EVENTS WERE POSSIBLY RELATED TO COBOMARSEN ACROSS 45 SUBJECTS

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Part B SQ</th>
<th>Part B (IV, 2 hr infusion)</th>
<th>Part B (IV Bolus)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred Term</td>
<td>n=45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>1</td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>1</td>
<td>1</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricaemia</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Neoplasms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumour flare</td>
<td>1</td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Database April 30 2018
26 OF 29 SUBJECTS TREATED SYSTEMICALLY WITH COBOMARSEN SHOWED mSWAT SCORE IMPROVEMENT

![Graph showing mSWAT score improvement with different treatment types and doses.](image)

- Baseline mSWAT scores: 6, 103, 43, 20, 2, 47, 17, 22, 18, 58, 6, 11, 178, 43, 82, 27, 180, 6, 5, 86, 85, 18, 54, 46, 59, 71, 66, 132
- Doses received: 9, 3, 6, 6, 6, 6, 6, 57, 55, 6, 6, 6, 7, 8, 44, 29, 25, 43, 26, 21, 5, 10, 3, 6, 8, 25, 10, 21, 9

Database January 25 2018

IV infusions showed the most consistent response
6 OF 8 (75%) PATIENTS ELIGIBLE FOR MORE THAN 1 MONTH OF 300MG AND 600MG IV DOSING OF COBOMARSEN ACHIEVED ≥50% mSWAT REDUCTION

Baseline mSWAT: 58 11 178 43 82 27 180 6
# doses rec’d: 6 7 8 44 29 25 43 26

300mg Dose Selected for Phase 2 in MF

Response and durability observed independent of concomitant medication

* Treatment is ongoing

Database January 25 2018
BEST mSWAT IMPROVEMENT WITH COBOMARSEN INDEPENDENT OF ADMINISTRATION AS MONOTHERAPY OR COMBINATION WITH ANOTHER CTCL THERAPY

Greatest mSWAT score improvement of systemically-treated subjects with ≥ 6 doses (N=26)

<table>
<thead>
<tr>
<th>Concomitant med</th>
<th>N</th>
<th>Median time (min, max) on therapy prior to study day 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>bexarotene</td>
<td>7</td>
<td>16 months (2, 26)</td>
</tr>
<tr>
<td>interferon-alfa</td>
<td>2</td>
<td>26 months (17, 34)</td>
</tr>
<tr>
<td>methotrexate</td>
<td>1</td>
<td>22 months</td>
</tr>
<tr>
<td>vorinostat</td>
<td>1</td>
<td>4 months</td>
</tr>
<tr>
<td>other</td>
<td>2</td>
<td>21 months (3, 45)</td>
</tr>
</tbody>
</table>

Database January 25, 2018
PART B: CASE STUDY IMPROVEMENT IN TOTAL SKIN DISEASE SCORE CORRELATES WITH COBOMARSEN TREATMENT

Day 1
CAILS: 13
Day 19
CAILS: 10
Day 27
CAILS: 8
Day 57
CAILS: 5

Day 103
CAILS: 10
Day 131
CAILS: 8
Day 159
CAILS: 7
Day 186
CAILS: 6

Note: Grey shading = drug administration period, White Shading = pause in drug administration
- There is continued improvement that extended beyond discontinuation of the first 4 weeks of dosing that eventually dissipated during the drug holiday
- Patient responded with re-initiation of therapy

Study Day

Day 1
CAILS: 13
Day 19
CAILS: 10
Day 27
CAILS: 8
Day 57
CAILS: 5

Day 103
CAILS: 10
Day 131
CAILS: 8
Day 159
CAILS: 7
Day 186
CAILS: 6
CASE EXAMPLE (102-007): 300 MG IV INFUSION COHORT

- Age: 51; Sex: Male
- Date of diagnosis: 2013
- CTCL stage at screening: IB
- Baseline mSWAT: 180
- Concomitant systemic therapy: Methotrexate (started June 2015)
- Has skin (mSWAT) PR lasting > 4 months

Day 1
mSWAT: 180

Day 93
mSWAT: 68
(62% reduction)

Database Dec. 4, 2017
DISEASE IMPROVEMENT RESULTS IN IMPROVED QUALITY OF LIFE
SKINDEX 29 TOTAL SCORE SHOWS IMPROVEMENT OR STABILIZATION IN MOST PATIENTS

- 13 of 18 subjects show a significant improvement over the first 100 days on study drug.

- Improvement and stabilization seem durable, in 4 subjects for up to one year and one subject is stable after 400+ days on study drug.

- Subject 112-001 (300 mg IV infusion) worsen Skindex 29 and mSWAT response after switched to monthly dosing on day 285.

Database 30 April 2018
QOL CORRELATES WITH DISEASE SEVERITY AT EACH POINT OF THE STUDY
SKINDEX 29 TOTAL SCORE HIGHLY CORRELATES WITH mSWAT SCORE THROUGHOUT THE STUDY DURATION

Mean Skindex 29 Total Score

Cohort

- Part B (Subcutaneous) 600 mg
- Part B (Subcutaneous) 900 mg
- Part B (IV, 2 hr infusion) 600 mg
- Part B (IV, 2 hr infusion) 900 mg
- Part B (IV Bolus) 300 mg
- Part B (IV Bolus) 300 mg

Database 30 April 2018
DOSE SELECTION FOR PHASE II STUDY

- Durable partial responses have been achieved at all dose levels
  - 300-900 mg appear to represent the top of the dose response curve
- 300 and 600 mg IV-infusions had similar efficacy and tolerability, offering the most consistent response rate based on skin mSWAT scores
- 6 of 8 (75%) patients (initially assigned to 300 or 600 mg dose level) achieved skin PR
SUMMARY

- Cobomarsen is generally well-tolerated to date
  - No SAEs deemed related to study drug
  - Two Dose-Limiting Toxicities:
    - Grade 3 worsening pruritus, possible tumor flare, occurred twice in one patient (900 mg SC cohort, 300 mg IV-infusion)
    - Grade 3 tumor flare in 300 mg IV bolus patient
- 6 of 8 (75%) patients treated for > 1 month with 300 or 600 mg systemically had ≥ 50% mSWAT score reduction
- Best improvement in mSWAT score appeared to be seen after 1 or more months of dosing
- Cobomarsen treatment resulted in durable improved quality of life, as measured by the Skindex 29 Total Score
- This improvement parallels improvements in disease, as measured by the mSWAT score, in most subjects, even if the patients achieve less than a defined PR
- Study in CTCL is on-going (enrollment closed)
- Study has expanded to include patients with CLL, DLBCL, and ATLL, diseases in which miR-155 expression is increased
**SOLAR** PHASE 2 CLINICAL TRIAL ANTICIPATED TO INITIATE IN 2H18
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

**Key Secondary endpoints:**
- Progression-free survival
- Patient reported outcomes
  - Pain, itching

**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
- No concurrent systemic therapy

**Stratification factors**
- Stage (Ib-IIa vs IIb-III)
- Prior Therapies (1-2 vs. 3 or more)

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

Randomize

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

Vorinostat n=~65 subjects
Follow until progression or death

Open label extension
SOLAR STUDY LOCATIONS
INVESTIGATORS

Jennifer DeSimone (Inova)
Herbert Eradat (UCLA)
Francine Foss (Yale)
Joan Guitart (Northwestern)
Ahmad Halwani (Huntsman)
Auris Huen (MD Anderson)

Youn Kim (Stanford)
Theresa Pacheco (University of Colorado)
Lauren Pinter-Brown (UC Irvine)
Pierluigi Porcu (Thomas Jefferson)
Christiane Querfeld (City of Hope)
Basem William (The Ohio State University)