Clinical and Biological Evaluation of the Novel CD30/CD16A Tetravalent Bispecific Antibody (AFM13) in Relapsed or Refractory CD30-Positive Lymphoma with Cutaneous Presentation: A Biomarker Phase Ib/IIa Study (NCT03192202).

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BACKGROUND

- AFM13 is a CD30/CD16A targeting high affinity bispecific tetravalent antibody that engages and activates NK cells and macrophages.

METHODS

- Population: subjects with relapsed or refractory CD30 expressing lymphoma with cutaneous involvement

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose regimen</th>
<th>Total exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5 mg/kg</td>
<td>weeks 1-8</td>
</tr>
<tr>
<td>2</td>
<td>7.0 mg/kg</td>
<td>weeks 1-8</td>
</tr>
<tr>
<td>3</td>
<td>7.0 mg/kg</td>
<td>weeks 1-8</td>
</tr>
<tr>
<td>4</td>
<td>200 mg/kg</td>
<td>weeks 1-8</td>
</tr>
</tbody>
</table>

*1 mg/kg loading 6 mg/kg as continuous infusion for 5 days per week

- Response assessment performed by mSWAT, photography, PET imaging and peripheral blood flow cytometry.
- A second cycle was administered if there was no progression of disease.
- Skin biopsies, whole blood and plasma were collected: pretreatment, day 5 post first dose, week 4 and week 8 of therapy.
- Tumor biopsies were analyzed and evaluated by a pathologist and IHC image analyzer to characterize immune cell subpopulations.
- Peripheral blood samples were analyzed by flow cytometry.

RESULTS

Patient Demographics Table

<table>
<thead>
<tr>
<th>Patient Demographics Table</th>
<th>N=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, (range)</td>
<td>65 (37-79)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>Race (% white/ non-white)</td>
<td>30%/70%</td>
</tr>
<tr>
<td>Median number of prior therapy, (range)</td>
<td>4 (1-11)</td>
</tr>
<tr>
<td>Patients progressed on brentuximab vedotin</td>
<td>2</td>
</tr>
<tr>
<td>Total Skin Electron Beam Radiotherapy</td>
<td>5</td>
</tr>
</tbody>
</table>

Disease Histologies

- Transformed Mycosis Fungoides (T-MF) | 5 |
- Mycosis Fungoides, non-transformed (MF) | 2 |
- Systemic Anaplastic Large Cell Lymphoma-ALK negative (S-ALCL, ALK -) | 2 |
- Cutaneous Anaplastic Large Cell Lymphoma (C-ALCL) | 1 |

Skin Response in T-MF Patient

- Pre Study
- Cycle 1 Week 11
- Post Cycle 2

Rapid and Durable Response in T-MF

- Response in a T-MF subject then consolidated with an Allogenic stem cell transplant.
- Responses were seen in:
  - Nodes
  - Skin
  - Peripheral blood

Peripheral Blood Biomarker Correlatives

- % CD69 expressing NK cells over time in responders
- % CD69 expressing NK cells over time in non-responders
  - Δ +98%
  - Δ -31%

- Increased CD69 expression (activation marker) on circulating NK cells from responders vs. non-responders.
- Decreased in circulating NK cells during therapy with post therapy recovery, by following cells CD56+ CD3-, CD56+ CD16+ and NKP46+.
- Circulating CD4+ CD25+ T cells (Tregs) decrease in responders vs. non-responders.

Tumor Biopsies Biomarker Correlatives

- Tumor biopsies showed increased infiltration of CD56+ NK cells pre therapy and during therapy in responders (red) vs. non-responders (blue).
- Tumor CD30 expressing cells decrease significantly in response to therapy in responders (red) vs. non-responders (blue).
- NK cell (green) cytotoxicity through the expression of Granzyme B (red) was seen in responders vs. non-responders by comparing pre therapy tumor biopsy (top panel) to W4 tumor biopsy (bottom panel).
- No change in CD68 expressing cells (not shown).

CONCLUSION

- AFM13 was well tolerated.
- AFM13 demonstrated a high ORR of 50% and showed activity post-brentuximab vedotin failure.
- Tumor biopsies in patients who were responding to AFM13 showed increased NK cells both before and during treatment.
- A phase II multicenter international study of AFM13 in PTCL and T-MF is planned.