CREATING BREAKTHROUGH DRUGS
TO TREAT BRAIN DISEASES AND FIGHT CANCER

~ ANG1005 ~
Targeting LRP-1 in Brain Cancer

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Brain Cancers

Treatment options are limited, in part due to the difficulties associated with drug delivery across the BLOOD-BRAIN BARRIER (BBB)

- **Brain Metastases**: Up to 180,000 cases per year in the US, mostly from lung and breast cancers
  - Standard of care includes surgery and radiotherapy
  - No standard of care at the time of recurrence
  - Median survival is very poor

- **Malignant Gliomas**: 18,000 new cases per year in the US alone
  - Despite standard treatment, median survival is only 12-15 months for patients with GBM, and 2-5 years for patients with anaplastic gliomas
ANG1005: Clinical Program
Two Phase I Studies

- **Solid tumor with Progressive Brain Metastases**: 56 patients
- **Recurrent Glioma**: 63 patients

**PRIMARY OBJECTIVES**
- Characterize safety and tolerability
- Identify maximum tolerated dose (MTD)

**SECONDARY OBJECTIVES**
- Pharmacokinetics
- Immunogenicity of ANG1005
- To determine preliminary efficacy
119 Patients Treated from US Sites

**Brain Metastases Study Sites**
- MD Anderson Cancer Center, Houston, TX
  ~ Dr. Razelle Kurzrock
- Cancer Therapy Research Center, San Antonio, TX
  ~ Dr. John Sarantopoulos
- Gabrail Cancer Center, Canton, OH
  ~ Dr. Nashat Gabrail

**Recurrent Glioma Study Sites**
- Dana Farber Cancer Institute,
  Beth Israel Deaconess Medical Center,
  Massachusetts General Hospital, Boston, MA
  ~ Dr. Jan Drappatz
- Cancer Therapy Research Center, San Antonio, TX
  ~ Dr. Andrew Brenner
- Columbia University Medical Center, New York, NY
  ~ Dr. Steven Rosenfeld
- MD Anderson Cancer Center, Houston, TX
  ~ Dr. Morris Groves
- Henry Ford Health System, Detroit, MI
  ~ Dr. Tom Mikkelsen
- University of Virginia Health System,
  Charlottesville, VA
  ~ Dr. David Schiff
Key Safety Findings

• **Dose levels from 30 to 700 mg/m\(^2\)**
  – MTD is 650 mg/m\(^2\), IV infusion once every 21 days

• **No toxicity related to the EPiC platform**
  – No evidence of CNS toxicity
  – No antibody production (dosing up to 18 cycles)

• **Favourable tolerability profile**
  – AEs of highest frequencies are of hematological origin:
    • neutropenia (58% <1.5x10\(^9\)/L), leucopenia (59% <3.0x10\(^9\)/L), anemia (33% Hg <10.0 g/dL)
  – The most common non-hematological AEs (all severities) are:
    • fatigue (31%), peripheral neuropathy (23%), alopecia (22%), nausea (20%), mucositis (14%), diarrhea (13%), rash (13%), infusion reactions (12%).
## Brain Metastases Study

### Summary of Overall Best Response

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>420-700 mg/m²</th>
<th>Prior Taxane Failures*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size (n=33)</td>
<td>n=21</td>
<td>n=12</td>
</tr>
<tr>
<td>CR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>MR</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>SD</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>PD</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>% ≥ SD</td>
<td>71%</td>
<td>83%</td>
</tr>
</tbody>
</table>

*Patients treated at 420-700mg/m² group

CR=Complete Response; PR=Partial Response; MR=Minor Response; SD=Stable Disease; PD=Progressive Disease
KAPLAN-MEIER CURVES OF MEDIAN TTP

ALL PATIENTS VS. RESPONDERS (≥ SD)

Doses 30-700 mg/m²
Response - Liver Metastases
Responders# Dosed ≥420 mg/m²

* Prior taxane failures

# Patients that had an OVERALL best response of stable disease or better
Response - Lung Metastases Responders\# Dosed ≥420 mg/m²

* Patients that had an OVERALL best response of stable disease or better
Case Study #1
BRAIN IMAGES

73 y.o. female with metastases originating from taxane-resistant ovarian cancer

Progression on doxorubicin

Study baseline

After 2 cycles of ANG1005

Tumor no longer visible
Case Study #1
LUNG IMAGES

Study baseline
After 2 cycles of ANG1005
**Recurrent Glioma Study ~ Summary of Best Response**

<table>
<thead>
<tr>
<th>Dose</th>
<th>300-700 mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size (n=46)</td>
<td>n=28</td>
</tr>
<tr>
<td>CR</td>
<td>2</td>
</tr>
<tr>
<td>PR</td>
<td>2</td>
</tr>
<tr>
<td>MR</td>
<td>11</td>
</tr>
<tr>
<td>SD</td>
<td>2</td>
</tr>
<tr>
<td>PD</td>
<td>11</td>
</tr>
<tr>
<td>% ≥ SD</td>
<td>61%</td>
</tr>
</tbody>
</table>

CR=Complete Response; PR=Partial Response; MR=Minor Response; SD=Stable Disease; PD=Progressive Disease
KAPLAN-MEIER CURVES OF MEDIAN TTP

ALL PATIENTS VS. RESPONDERS (≥ SD)

Doses 300-700 mg/m²
## Tumor Extraction Results

<table>
<thead>
<tr>
<th>Sample</th>
<th>#1</th>
<th>#2</th>
<th>#3</th>
<th>#4</th>
<th>#5</th>
<th>#6</th>
<th>#7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose Level (mg/m²)</td>
<td>200</td>
<td>300</td>
<td>420</td>
<td>550</td>
<td>550</td>
<td>550</td>
<td>550</td>
</tr>
<tr>
<td>Extraction Time (h)</td>
<td>~4.0</td>
<td>~5.0</td>
<td>~4.0</td>
<td>~4.5</td>
<td>~6.0</td>
<td>~4.5</td>
<td>~5.5</td>
</tr>
<tr>
<td>Plasma ANG1005 (μM)</td>
<td>34.3</td>
<td>34.4</td>
<td>53.5</td>
<td>100.1</td>
<td>56.5</td>
<td>63.0</td>
<td>81.0</td>
</tr>
<tr>
<td>Tumor ANG1005 (μM)</td>
<td>2.8</td>
<td>9.4</td>
<td>7.0</td>
<td>23.0</td>
<td>98.0</td>
<td>238.2</td>
<td>31.5</td>
</tr>
<tr>
<td>[Tumor]:[Plasma]</td>
<td>8.2%</td>
<td>27.3%</td>
<td>13.3%</td>
<td>23.0%</td>
<td>173%</td>
<td>379%</td>
<td>38.9%</td>
</tr>
</tbody>
</table>
Case Study #2

Bevacizumab Refractory Patient:
• 51 y.o M with GBM
• Treated with TMZ/RT upfront followed by Bev/CPT-11 for 1\textsuperscript{st} recurrence
• Received 22 cycles of ANG1005 for 2\textsuperscript{nd} relapse
• Patient remains progression free, PFS = 15+ months
• Tumor measurements over time:
Case Study

49 y.o. female patient with anaplastic oligoastrocytoma

Progression after 1 yr of temozolomide. Prior treatments include radiation, surgery.

Study baseline
Rapidly progressive symptoms including left hemiparesis and was using a cane and wheelchair

After 8 cycles of ANG1005
Walking unaided
Key Findings To Date

- Well tolerated with no CNS toxicity and no antibody induction
- Encouraging responses in primary and secondary brain tumors
- Reversal of neurological deficits observed in several cases
- Significant tumor reductions also in liver, lung and other organs
- Encouraging response rate in taxane-failure cancers
- Therapeutic concentrations of ANG1005 in brain tumors = Proof-of-concept validation of the platform technology
- Results warrant further development