Angiopep-2/paclitaxel conjugate, ANG1005: A potential treatment option for patients with metastatic brain cancer

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UPATED ABSTRACT

The **BLOOD-BRAIN BARRIER** (BBB) is an obstacle to the clinical treatment of most diseases of the central nervous system (CNS). As a result, treatment options for patients with metastatic brain cancer are limited and often focus on relief of symptoms. Angiopep-2 is a 19 amino acid peptide shown in animal models to cross the BBB using a physiological approach via transcytosis by binding to low-density lipoprotein receptor-related protein (LRP) expressed on the surface of the BBB. ANG1005 is a new chemical entity (NCE) that combines one molecule of Angiopep-2 with three molecules of paclitaxel. Preclinical studies demonstrate the brain uptake of ANG1005 to be 100-1000 times greater than paclitaxel and ~10x greater than temozolomide. Because LRP is upregulated on various cancer cells including metastatic brain cancer cells, ANG1005, once in the brain compartment, is able to enter tumor cells using the same receptor-mediated mechanism described above. ANG1005 is then cleared releasing paclitaxel to perform its antitumor functions. A Phase I multicenter, open-label, dose escalation study of ANG1005 was initiated in Oct 2007 to explore the maximum tolerated dose and brain tumor data on safety, tolerability and progression-free survival of efficacy in patients with advanced solid tumors and/or brain metastases. The dose escalation scheme includes sequential dose cohorts ranging from 30-550 mg/m². ANG1005 is administered IV every 21 days. Study participants are adult patients with measurable disease and an ECOG performance status ≤2 who are ineligible for standard treatment options. As of Nov 3, 2008 30 patients (median age: 54 years; 47% female) with advanced solid tumors (melanoma, n=11; breast cancer, n=5; lung cancer, n=5; hepatic carcinoma, n=2; other, n=7) and/or brain metastases (n=21) have been demonstrated ANG1005. Safety and tolerability have been demonstrated thus far. Anemia, neutropenia and leukopenia, all established paclitaxel-related effects, were observed in the study from the time. To date, ANG1005 was observed to have a good safety and tolerability profile in patients with advanced solid tumors and/or brain metastases. Angiopep conjugates may provide a potentially safe and effective way to treat currently unmanageable CNS diseases. Results of this study will determine future compounds, doses, and/or indications to be explored in further clinical trials.

INTRODUCTION

The physical and physiological characteristics that together form the **BLOOD-BRAIN BARRIER** (BBB) prohibit more than 95% of drugs from reaching the brain, limiting treatment options for patients with diseases including metastatic brain cancer. It is vital that approaches be found that allow therapies access to the brain compartment. The scientific community recognizes that the best approaches are ones that use a physiological mechanism. The research presented herein is based on a physiological approach and the observation that most molecules that reach the brain must interact with specific receptors on the BBB via active transport.

Angiopep-2, a 19-aa amino acid peptid, was designed to target the low-density lipoprotein receptor-related protein (LRP), one of a family of receptors expressed on the BBB and upregulated on the surface of metastatic brain cancer cells. This vector technology is based on chemical linking different molecules to Angiopep-2 in order to access the brain via transcytosis. ANG1005 is a NCE combining Angiopep-2 with 3 molecules of paclitaxel using a water-soluble ester bond.

Paclitaxel and other chemotherapeutics have limited use in brain cancers due to their inability to penetrate the BBB in sufficient quantities. Preclinical studies show that brain uptake of ANG1005 is ~100 times greater than paclitaxel and that once in the brain compartment, ANG1005 favorably targets tumor cells which it enters by endocytosis using the same receptor mechanism. Inside tumor cells, the ester linkages that bind paclitaxel to Angiopep-2 are cleaved by esterase, found in high concentration in the lysosomes of the cells. Furthermore, the therapeutic properties of paclitaxel have been shown to be recovered once it dissociates from Angiopep-2.

Because of strong preclinical data, ANG1005 entered the clinical phase of development late last year. The present Phase I dose-finding study represents the first time ANG1005 is being administered to patients with advanced solid tumors and/or metastatic brain cancer.

MATERIALS AND METHODS

Patients with advanced solid tumors and/or brain metastases are being recruited into this ongoing, sequential cohort, open-label, dose escalation study from 3 sites located in the US (listed alphabetically).

<table>
<thead>
<tr>
<th>Institution Name</th>
<th>Location</th>
<th>Principle Investigator</th>
<th>Study Coordinator</th>
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<tbody>
<tr>
<td>Cancer Therapy and Research Center</td>
<td>San Antonio, Texas</td>
<td>John Gaynor, MD</td>
<td>Cancer Therapy and Research Center</td>
</tr>
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<td>MD Anderson Cancer Center</td>
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<td>MD Anderson Cancer Center</td>
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<tr>
<td>Mita &amp; Guo</td>
<td>Canton, Ohio</td>
<td>Carrie Smith, RN</td>
<td>Mita &amp; Guo</td>
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OBJECTIVES

**Primary**

- To characterize the safety and tolerability of IV administered ANG1005 in pts with advanced solid tumors and metastatic brain cancer
- To identify the maximum tolerated dose (MTD) of ANG1005 in pts with advanced solid tumors and metastatic brain cancer
- To examine the pharmacokinetics (PK) of ANG1005
- To confirm the safety and tolerability of ANG1005 at the MTD

**Secondary**

- To obtain preliminary information about the antitumor activity of ANG1005 in pts with advanced solid tumors and metastatic brain cancer
- To examine the pharmacodynamics (PD) of ANG1005
- To examine the PK/ PD profile and clinical activity of ANG1005

EXCLUSION

- Male or female adults ≥ 18 y.o.
- Metastatic / advanced-stage solid tumor that has progressed following standard therapy
- Measurable disease according to RECIST criteria
- Ineligible for current standard treatment options
- ECOG performance status ≤ 2
- Expected survival of at least 3 months

TREATMENT AND EVALUATIONS:

ANG1005 is currently administered as an IV infusion at a concentration of 1.5 mg/mL, and a rate of 8.0-8.5 mL/h, without *premedication*. Treatment is given once a 3-wk schedule. Baseline blood testing is performed to determine baseline pre-treatment values. Patients are closely monitored during the infusion and for up to 24 h after the end of infusion with weekly safety visits between treatments. AEs are collected from the time of the start of the first infusion until 3 wk after the last infusion. The severity of events is assessed according to the NCI CTCAE, v3.0.

In order to measure disease status, imaging is being performed at 6-wk intervals during therapy. Response is assessed using modified RECIST response evaluation criteria.

DOSE ESCALATION SCHEME:

- **Starting dose:** 30 mg/m²
- **Dose doubling:** 60 mg/m² (n=2)
- **Modified Fibonacci Scheme:**
  - 30 mg/m² (n=2)
  - 60 mg/m² (n=2)
  - 120 mg/m² (n=3)
  - 180 mg/m² (n=2)
  - 220 mg/m² (n=2)
  - 260 mg/m² (n=1)

**PD criteria**

- 1-patient experiences an emergent ANG1005-related toxicity
- 2-patients develop an emergent ANG1005-related toxicity

CONCLUSIONS

- PK data indicate a linear bioavailability of ANG1005
- ANG1005 is well tolerated:
  1. Most of the side effects observed to date with ANG1005 are related to the active drug component – paclitaxel
  2. No adverse events attributable to the conjugate have been reported to date (e.g., central neurotoxicity, immunogenicity, liver toxicity)
  3. Side effects experienced to date have been milder than expected relative to other chemotherapy agents used in humans
- Preliminary response data may suggest prolongation in time to progression compared to current standard treatment

RESULTS

Results presented here include data up to and including November 3, 2008. 30 patients with advanced solid tumors (11 with melanoma, 5 with breast cancer, 5 with lung cancer, 2 with hepatocellular carcinoma and 7 ‘other’ cancers), 21 of which have brain metastases, have received ANG1005 at doses ranging from 30 to 550 mg/m²; escalation is ongoing.

PATIENT PROFILE

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value, Range (as applicable)</th>
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<tbody>
<tr>
<td>Dose (mg/m²)</td>
<td>30 60 120 200 300</td>
</tr>
<tr>
<td>Cmax (mg/mL)</td>
<td>1 3 1 2 2</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>37.3 64 128-146 166-224</td>
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<tr>
<td>AUC(0∞ to ∞) (h/mL)</td>
<td>11 11 11 11</td>
</tr>
<tr>
<td>half-life (h)</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>CL (mL/h/L)</td>
<td>886 414-438 428 172-189 265-330</td>
</tr>
<tr>
<td>Vd (mL/L)</td>
<td>1924 1459-1714 1743 864-1004</td>
</tr>
</tbody>
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SADETY DATA:

Safety data are available for all 30 study patients dosed to date.

CONCLUSIONS

- PK data presented here are preliminary results obtained from cycle 1 in 9 patients dosed between 30 and 300 mg/m².

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TUMOR RESPONSE DATA:

Tumor response data are available for 11 patients to date. Of the 11 patients, 5 had stable disease and the remaining 6 had progressive disease at 6 wks. In addition, of the 5 patients with stable disease at 6 wks, 4 patients continued to have stable disease at 12 wks.

CONCLUSIONS

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