ANG1005: Development of a new chemical entity for the treatment of advanced solid tumors and brain metastases


MD Anderson Cancer Center, Houston, Texas; 2 Gbabral Cancer Center, Gompo, Ohio; 3 Cancer Therapy and Research Center, San Antonio, Texas; 4Angiochem Inc., Montreal (Quebec), Canada; 5Intrinsik Health Sciences Inc., Mississauga (Ontario), Canada.

It is estimated that in the US over 150,000 patients with systemic tumors develop brain metastases each year and this incidence is expected to rise. The challenge in treating brain tumors stems from the inability of most drugs to cross the blood-brain barrier (BBB) to reach the site of disease in sufficient concentrations to act effectively without the limitation of systemic toxicity. Preliminary preclinical data have been gathered on a deep brain-implanted system utilizing the continuous delivery of crossing the BBB to treat brain diseases including metastatic cancer. ANG1005 is the first of these new Engineered Peptide Compounds (ePRCs) to reach the clinical stage of development. Studies 900d to toxicit y obtained from patients stable show of the 0.167 using EPiC the low are surface patients of disease breast, the pumps receptors BBB excellent neuropathy At LRP of same 5 of cells 30-70%m, inclusive, q 21 days without premedication. Severity of adverse events is assessed using CTCAE, version 3.0. At present, although some patients have developed the chemotherapeutic and hematologic toxicities of neurotoxicity, leucopenia, and thrombocytopenia, toxicity has not been observed at doses beyond what is expected from clinical observation with palmital therapy. Furthermore, neurocognitive data gathered to date show no evidence of central nervous toxicity and in fact in data from one patient with a minor tumor response to therapy even showed significant improvement on memory, processing speed and executive function after 6 weeks of therapy. Immunosuppression data show that ANG1005 does not elicit an immune response, including in patients who have received up to 6 treatment cycles. Moreover, pharmacodynamic data obtained so far show patients benefit from a linear relationship between dose and bioavailability.

Early MRI data indicate that ANG1005 may cause tumor regression and slow the progression of disease in patients with advanced solid tumors and brain metastases.

**Study Overview**

- **Primary objectives:** To examine the pharmacokinetics (PK) of ANG1005 and to identify the maximum tolerated dose (MTD) of ANG1005.
- **Secondary objectives:** To evaluate the pharmacodynamics and efficacy of ANG1005, and to assess on treatment changes in cognition, memory, and quality of life.

**Patient Characteristics**

Data presented here are current up to April 1, 2009, where indicated. 42 patients with advanced solid tumors and brain metastases (median age: 54, long survival: 6 months to 10 years) have received ANG1005 at doses ranging from 30 to 700 mg/m2.

**Safety Data**

- **CTCAE Grade:**
  - Neutropenia: 0.01%
  - Leukopenia: 0.01%
  - Thrombocytopenia: 0.01%
  - Anemia: 0.01%
  - Infusion reactions: 0.01%
  - Mucositis: 0.01%
  - Peripheral Neuropathy: 0.01%
  - oth : 0.01%

- **Drug Administration:**
  - Median dose: 125 mg/m2
  - Median cycle: 6
  - Median therapy: 24 weeks

- **PK Data:**
  - PK data presented here are preliminary results obtained from cycle 1 in 29 patients dosed between 30 and 550 mg/m2, obtained so far show linear bioavailability of ANG1005.

**Radionuclide Data**

- **Tumor response:**
  - Tumors at 6 weeks: 3/3 (100%)
  - Tumors at 12 weeks: 10/12 (83.3%)
  - Tumors at 24 weeks: 10/12 (83.3%)

- **Brain CT Images:**
  - Pre-treatment: Baseline
  - At 6 weeks

- **LUNG CT Images:**
  - Baseline
  - At 6 weeks

**Key Results:**

- ANG1005 has an excellent safety and tolerability profile to date: Changes in hematologic parameters are consistent with mild or lesser observed with known chemotherapeutics and manageable with standard treatments.
- Few reports of adverse events with reactions, mucositis, peripheral neuropathy.
- No evidence of central nervous system toxicity.
- ANG1005 shows no evidence of invoking an immune response even in patients who have received 6 treatment cycles.
- PK data show a linear relationship between dose and bioavailability.
- Early MRI data indicate that ANG1005 may cause tumor regression and slow the progression of disease in patients with advanced solid tumors and brain metastases.