ANG1005: Results of a Phase I study with advanced solid tumors and metastatic breast cancer

Razelle Kurzrock1, Nash Gabrail1, Stacy Moulder1, Cherie Noles4, Carrie L Smith2, Zhong Guo5, Danielle Bouchard5, Wendy Churchill1, Paula Bento1, Ann Neale2, Jean-Paul Castaigne1, John Sarantopoulos1

1 MD Anderson Cancer Center, Houston, Texas; 2 Gabriel Cancer Center, Canton, Ohio; 3 Cancer Therapy and Research Center, San Antonio, Texas; 4Angiochem Inc., Montreal, Quebec, Canada; 5WinPharm Associates, Danville, California.

UPDATED ABSTRACT:
ANG1005 is a novel generation tumor necrosis factor-alpha (TNF-α) inhibitor that acts through two distinct mechanisms: it is directly cytotoxic for TNF-α-expressing tumor cells as well as TNF-α-dependent tumor microvascular endothelial cells (TECs). Tumor necrosis factor-alpha (TNF-α) is a pro-inflammatory cytokine that is overexpressed in most solid tumors, including breast, non-small cell lung, and ovarian cancers. Resistance to TNF-α may be due to elevated levels of TEC-derived TNF-α (cytoplasmic shuttling) or decreased endothelial cell death in response to TNF-α signaling. Hence, ANG1005, an angiogenesis and tumor necrosis factor-alpha inhibitor, is expected to be effective for patients with TNF-α-positive tumors even in patients who received more than 6 treatment cycles. ANG1005 is currently being evaluated in patients with advanced solid tumors and brain metastases. (as using blood flow blockage of tumor vessels,...)

INTRODUCTION
ANG1005, a novel generation tumor necrosis factor-alpha (TNF-α) inhibitor that acts through two distinct mechanisms: it is directly cytotoxic for TNF-α-expressing tumor cells as well as TNF-α-dependent tumor microvascular endothelial cells (TECs). Tumor necrosis factor-alpha (TNF-α) is a pro-inflammatory cytokine that is overexpressed in most solid tumors, including breast, non-small cell lung, and ovarian cancers. Resistance to TNF-α may be due to elevated levels of TEC-derived TNF-α (cytoplasmic shuttling) or decreased endothelial cell death in response to TNF-α signaling. Hence, ANG1005, an angiogenesis and tumor necrosis factor-alpha inhibitor, is expected to be effective for patients with advanced solid tumors and brain metastases. (as using blood flow blockage of tumor vessels,...)

METHODS
ANG1005 is a novel generation tumor necrosis factor-alpha (TNF-α) inhibitor that acts through two distinct mechanisms: it is directly cytotoxic for TNF-α-expressing tumor cells as well as TNF-α-dependent tumor microvascular endothelial cells (TECs). Tumor necrosis factor-alpha (TNF-α) is a pro-inflammatory cytokine that is overexpressed in most solid tumors, including breast, non-small cell lung, and ovarian cancers. Resistance to TNF-α may be due to elevated levels of TEC-derived TNF-α (cytoplasmic shuttling) or decreased endothelial cell death in response to TNF-α signaling. Hence, ANG1005, an angiogenesis and tumor necrosis factor-alpha inhibitor, is expected to be effective for patients with advanced solid tumors and brain metastases. (as using blood flow blockage of tumor vessels,...)

RESPONSES IN METASTATIC DISEASE LOCATIONS

LIVER
LUNG
LYMPH NODE

CASE STUDIES

• 73 y.o. female patient with OVARIAN CANCER and BRONCHUS, LUNG, AND LIVER METASTASIS
   - Taxane-resistant
   - After 2 cycles of ANG1005 at 600 mg/m² the objective tumor response on CT showed 46% tumor shrinkage

• 61 y.o. male patient with SCLC and BRAIN, LUNG, AND LUNG METASTASIS
   - Previously pretreated
   - After 2 cycles of ANG1005 at 600/1500 mg² the objective tumor response on CT showed 24% tumor shrinkage

PRELIMINARY PHARMACOKINETIC RESULTS

Plasma ANG1005 Concentration vs Time (Cycle 1)

PRELIMINARY PHARMACOKINETIC RESULTS

Plasma ANG1005 Concentration vs Time (Cycle 1)

KEY FINDINGS:
• ANG1005 has a superior side effect profile versus other taxanes:
  - Hematologic tolerability – effects are transient and easily manageable with standard treatments.
  - Steady-state pharmacology in peripheral neuropathy, infusion reactions, and other toxicities (CTCAE 2 Grade 3);
  - No CNS toxicity as assessed by neurocognitive testing and neurological examination.
  - No immunogenicity; no antibody production even after repeat dosing.

  Treatment with ANG1005 shows evidence of efficacy with drastic reductions in tumor sizes in the brain, lung, liver, and other organs including in patients who have failed prior taxane therapy.

  ANG1005: An active taxane derivative with a unique mechanism of action.