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ANG1005 as a promising new drug therapy for patients with malignant glioma

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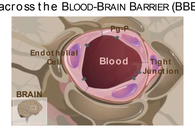
Malignant glioma (MG) is an aggressive and fatal cancer. Limited efficacy is achieved with existing therapies due to the inability of drugs to cross the blood-brain barrier (BBB). In fact, the BBB prohibits > 95% of drugs from entering the brain. Angiochem Inc. is developing a deep and broad product pipeline of new breakthrough drugs that are uniquely capable of crossing the BBB to treat brain diseases including brain cancer. ANG1005 is the first of these new Engineered Peptide Compounds (EPiC) to reach the clinical stage of development. Studies have shown that ANG1005 enters the brain compartment by targeting the low-density lipoprotein receptor-related protein (LRP) which is one of the most highly expressed receptors on the surface of the BBB. Once inside the brain, ANG1005 enters tumor cells using the same receptor-mediated pathway through LRP, which is upregulated in various cancer cells including MG cells. The main objectives of the present study are to characterize the safety and tolerability and identify the maximum tolerated dose of ANG1005 in patients with MG. Secondary objectives include obtaining preliminary antitumor information and preliminary information about whether or not ANG1005 crosses the BBB into MG tumors in humans. As of April 1, 2009, a total of 32 patients with recurrent or progressive WHO Grades III or IV MG have received ANG1005 by IV infusion at doses of 30-420mg/m², inclusive, once every 21 days without premedication. Dose escalation is ongoing. Severity of adverse events is assessed using CTCAE, version 3. At present, very few, if any, patients have experienced the common chemotherapeutic-associated hematologic toxicities of neutropenia, leucopenia, thrombocytopenia or anemia, infusion reactions, mucositis or peripheral neuropathy at a severity ≥Grade 2. Furthermore, preliminary neurocognitive data show that ANG1005 does not affect cognitive performance at these doses in this population and immunogenicity data show that ANG1005 does not elicit an immune response, including in patients who have received multiple treatment cycles. MRI data indicate potential efficacy in tumor regression and slowing tumor progression. Moreover, the total amount of paclitaxel equivalents in the tumor parenchyma of a tumor sample that was collected from one patient after receipt of a single 200mg/m² dose of ANG1005 was approx. 20 x higher than the corrected concentration reported in tumor following paclitaxel administration. Data to date demonstrate that ANG1005 has an excellent safety and tolerability profile in humans and shows promise as a potential treatment option for patients with MG.

KEY RESULTS:

- **ANG1005 has an excellent safety and tolerability profile to date:**
  - **Very few, if any, cases of hematologic toxicity**
  - **Few reports of AEs such as infusion reactions / no reports of mucositis, peripheral neuropathy (≥ Gr 2)**
  - **No evidence of central nervous system toxicity**
- **ANG1005 shows no evidence of invoking an immune response even in patients who have received multiple treatment cycles**
- **Early MRI data indicate that ANG1005 may cause tumor regression and/or slow the progression of disease in patients with recurrent Grades III and IV malignant glioma**
- **Preliminary data show that ANG1005 crosses the BBB and enters malignant glioma tumors in humans more efficiently than after administration of paclitaxel**

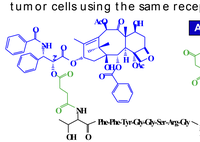
MALIGNANT GLIOMAS (MG) are histologically heterogeneous and invasive tumors that are derived from glial cells. They are classified by the World Health Organization (WHO) as Grades III (anaplastic gliomas) and IV (glioblastoma multiforme, GBM) tumors on the basis of their pathologic features. Treatment options for patients with MG are limited, in part due to the difficulties associated with drug delivery across the BLOOD-BRAIN BARRIER (BBB). In fact, despite optimal treatment, the median survival is only 12-15 months for patients with GBM and 2-5 years for patients with anaplastic gliomas.



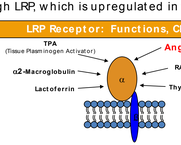
The **BBB** serves to provide an insulated environment for stable neuronal function. Endothelial cells that line cerebral capillaries are tightly packed and they lack fenestra, transendothelial channels and pinocytic vescicles. Together, these characteristics, along with expression of high levels of active efflux pumps (e.g., P-gp) allow the BBB to act as a unique, selective barrier and hinder the delivery of many potentially important therapeutic agents to the brain.

ANG1005 is a novel taxane engineered peptide compound (EPiC) that is designed to cross the BBB. Studies have shown that ANG1005 gains entry into the brain compartment by targeting the low-density lipoprotein receptor-related protein (LRP) which is one of the most highly expressed receptors on the surface of the BBB. Once inside the brain, ANG1005 enters tumor cells using the same receptor-mediated pathway through LRP, which is upregulated in various cancer cells including MG cells.

ANG1005 (MW= 5109)



LRP Receptor: Functions, Characteristics and Major Ligands



- LRP transports small and large molecules
- LRP is robust and difficult to saturate

STUDY OVERVIEW

PRIMARY OBJECTIVES

- To characterize the safety and tolerability of IV administered ANG1005 in patients with recurrent MG
- To identify the maximum tolerated dose (MTD) of ANG1005 in patients with recurrent MG

SECONDARY OBJECTIVES

- To examine the pharmacokinetics (PK) of ANG1005
- To confirm the safety and tolerability of ANG1005 at the MTD
- To assess the immunogenicity of ANG1005
- To obtain preliminary information about the antitumor activity of ANG1005 in patients with recurrent MG
- To obtain preliminary information about whether or not ANG1005 crosses the BBB into MG tumors (Sub-study)

STUDY DESIGN

- Multi-centre, sequential cohort, open-label study using a modified rapid dose-escalation design

INTERVENTION

- ANG1005 by intravenous infusion once every 21 days at a concentration of 1.5 mg/mL and a set rate of 8.0-8.5 mL/min, ***without premedication***

STUDY POPULATION

- Adult patients with an ECOG status ≤ 2 and measureable recurrent or progressive malignant glioma (WHO Grades II and IV) after standard surgical, radiation, and/or chemotherapy treatment

INVESTIGATIONAL SITES

- Cancer Therapy and Research Center, San Antonio, TX
- Columbia University Medical Center , New York, NY
- Dana Farber Cancer Institute, Boston, MA
- Henry Ford Health System, Detroit, MI
- MD Anderson Cancer Center, Houston, TX
- University of Virginia Health System, Charlottesville, VA

PATIENT CHARACTERISTICS

Data presented here are current up to April 1, 2009.

32 patients with recurrent malignant glioma (21 with GLIOBLASTOMA MULTIFORME, 1 with ANAPLASTIC ASTROCYTOMA, 8 with ANAPLASTIC OLIGODENDROGLIOMA, 2 with ANAPLASTIC OLIGOASTROCYTOMA) have received ANG1005 at doses ranging from 30 to 420 mg/m²; escalation is ongoing.

Age (years)	Median	Range	
	53	26-78	
Sex	Male	Female	
	17 (53%)	15 (47%)	
# Prior Chemotherapies	≤ 2	3	≥ 4
	16	6	10
Prior Radiotherapy	Yes	No	
	31	1	
ECOG at Entry	0	1	2
	12 (38%)	17 (53%)	3 (9%)

SAFETY DATA

Dose (mg/m²)	30			50			75			105			200			300			420		
n	3			6			3			6			4			7					
CTCAE Grade	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4
Neutropenia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0
Leucopenia	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	2	0	0	0	0
Thrombopenia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Anemia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Infusion Reactions	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	2	0	0	0	0	0
Mucositis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Peripheral Neuropathy	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Preliminary NEUROCOGNITIVE DATA show that ANG1005 does not affect cognitive performance at these doses in this population. Moreover, data from 1 patient dosed at 105 mg/m² who had a minor tumor response showed stable to improved cognitive function after 6 weeks of therapy.

IMMUNOGENICITY DATA to date indicate that ANG1005 does not elicit an immune response, even in patients who have received multiple treatment cycles.

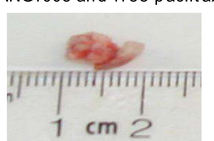
MRI DATA

Tumor response at 6 weeks by dose level

Dose	30 mg/m²	50 mg/m²	75 mg/m²	105 mg/m²	200 mg/m²	300 mg/m²
Response	n= 2	n= 5	n= 3	n= 5	n= 3	n= 4
PR						
MR	1			1		
SD			1	1	1	2
PD	1	5	2	3	2	2

ANG1005 MEASUREMENT IN TUMOR

A single tumor sample (~100 mg) was taken approx. 4 hours following infusion of 200 mg/m² ANG1005; a simultaneous PK sample was taken. The sample was extracted and analyzed for ANG1005 and free paclitaxel by LC/MS/MS.



RESULTS:

	ANG1005	Free Paclitaxel	% Free Paclitaxel
TUMOR PARENCHYMA	3.43 µg/g	0.695 µg/g	28.7 %
PLASMA	57 µg/mL	0.597 µg/mL	2.0 %

The total amount of paclitaxel equivalents in the tumor parenchyma was ~20x higher than the corrected concentration reported in tumor following paclitaxel administration; however *it is expected that this number will be* ***significantly higher at MTD****. This* ***trend has already been confirmed in a second sample*** *taken from a patient dosed at 300 mg/m².*

Moreover, the higher ratio of free paclitaxel in tumor relative to plasma suggests accumulation in the tumor.

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