ANG1005, the first clinical trial in patients with malignant glioma: Preliminary safety and tolerability data

Danielle Bouchard[1], Kelly Elian[1], Ann Neale[2], Steven Rosenfeld[3], Jan Drappatz[4], Morris Groves[5], Patrick Wen[4], Paula Bento[1], Betty Lawrence[1], Jean-Paul Castaigne[1]

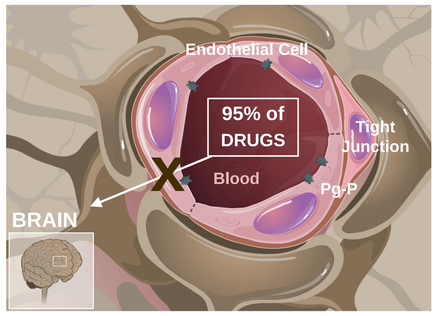
[1]Angiochem Inc., Montreal (Québec), Canada; [2]WinPharm Associates, Danville, California; [3]Columbia University Medical Center, New York, New York; [4]Dana Farber Cancer Institute, Boston, Massachusetts; [5]MD Anderson Cancer Center, Houston, Texas

UPDATED ABSTRACT

Treatment options for recurrent malignant gliomas are limited and prognosis is dismal mostly due to the presence of the **BLOOD-BRAIN BARRIER** (BBB) which prevents most cancer drugs from reaching tumor cells in the brain. 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's uptake of ANG1005 to be approximately 100x greater than paclitaxel alone and approximately 10x greater than temozolomide. Once inside the brain, ANG1005 enters tumor cells using the same receptor-mediated pathway described above, through LRP, which is upregulated in various cancer cells including malignant glioma cells. The cleavable ester linkage between paclitaxel and Angiopep-2 is broken by esterase in the lysosomes of the cells releasing paclitaxel which has been shown to retain its antimitotic abilities. A multicenter, open-label, dose escalation study of ANG1005 was initiated in October 2007 to explore the maximum tolerated dose and obtain data on safety, tolerability and preliminary evidence of efficacy in patients with recurrent malignant glioma. The dose escalation scheme includes sequential dose cohorts ranging from 30-550 mg/m^2. ANG1005 is administered IV every 21 days with weekly safety visits. Study participants are adult patients with measureable disease and an ECOG performance status less than or equal to 2 who are ineligible for standard treatment options. As of Nov 3, 2008 **17** patients with recurrent malignant glioma have received ANG1005 (10 patients with glioblastoma multiforme, 1 with anaplastic astrocytoma, 5 with anaplastic oligodendroglioma and 1 with oligoastrocytoma). No patient has discontinued from the study due to study drug-related adverse events. The currently enrolling dose is 105 mg/m^2 and escalation is ongoing. Angiopep conjugates may represent a potentially safe and effective way to treat presently unmanageable CNS disorders. ANG1005 is the first of a list of compounds to be tested in this regard.

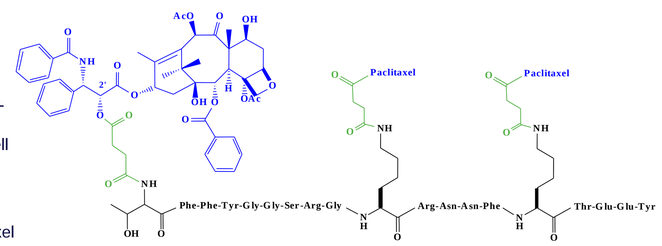
INTRODUCTION

The **BLOOD-BRAIN BARRIER** prohibits more than 95% of drugs from reaching the site of diseases located in the brain, such as brain cancer.



- It is vital that approaches be found that allow therapies access to the brain compartment.
- The scientific community recognizes distinct advantages of physiological approaches.
- 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 to cross the BBB via active transport.

- Angiopep-2, a 19-amino acid peptide, was designed to target the low-density lipoprotein receptor-related protein (LRP), one of a family of receptors expressed at the BBB and upregulated on the surfaces of cell lines from primary brain tumors.
- This vector technology is based on chemically attaching 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 cleavable ester bonds.



ANG1005 (MW=5107) : Angiopep-2 (black) conjugated with 3 paclitaxel molecules (blue); succinyl linkers (green)

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 ~100x 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 recurrent malignant gliomas, the most common and aggressive primary brain cancers.

MATERIALS and METHODS

Patients with recurrent or progressive malignant glioma (MG) are being recruited into this ongoing, sequential cohort, open-label, dose escalation study from 6 sites located in the US (listed alphabetically).

Institution Name	Location	Principle Investigator	Study Coordinator
Cancer Therapy and Research Center	San Antonio, Texas	John Sarantopoulos, MD	Cynthia Allison, RN / Cherie Noles
Columbia University Medical Center	New York, New York	Steven Rosenfeld, MD	Mahogany Ayele, RN
Dana Farber Cancer Institute	Boston, Massachusetts	Jan Drappatz, MD	Margaret Brenna McNamara, RN
Henry Ford Health System	Detroit, Michigan	Tom Mikkelsen, MD	Amy Williamson, RN
MD Anderson Cancer Center	Houston, Texas	Morris Groves, MD	Kathy Hunter, RN
University of Virginia Health System	Charlottesville, Virginia	David Schiff, MD	Yuliya Havaleshko, MD

OBJECTIVES :

Primary

- 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

- 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

ELIGIBILITY :

⊕ INCLUSION

- Male and female adults ≥ 18 y.o.
- WHO grades III and IV MG which progressed following resection, first-line treatment or current standard of care
- Measurable disease according to Macdonald
- Ineligible for current standard treatment options
- ECOG performance status score ≤ 2
- Expected survival of at least 3 months

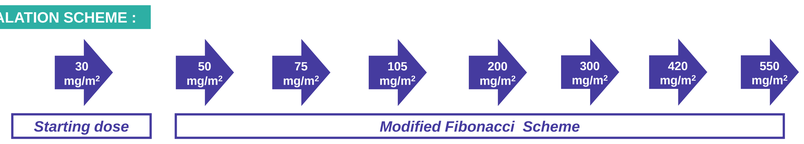
⊗ EXCLUSION

- Hemoglobin < 9.0 g/dL
- ANC < 1.5 x 10^9/L
- Platelet count < 100 x 10^9/L
- Total bilirubin > 1.5 x ULRR
- AST or ALT > 2.5 x ULRR
- Serum calcium > ULRR
- Estimated creatinine clearance < 60 mL/min

TREATMENT AND EVALUATIONS :

ANG1005 is currently administered as an IV infusion at a concentration of 1.5 mg/mL and a set rate of 8.0-8.5 mL/min, ***without premedication***. Treatment is given once q 3 wks until progression, general medical deterioration that warrants discontinuation of treatment or withdrawal of consent.
Patients are closely monitored during the infusion and for up to 24 hrs 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 wks after the last infusion. The severity of events is assessed according to the NCI CTCAE, v. 3.0, when possible and per protocol otherwise.
Potential neurocognitive changes are being explored through the use of a brief, simple and standardized battery of cognitive performance tests administered before, every 6 wks during, and following treatment.
Blood sampling is being done to look at the PK profile and immunogenicity of ANG1005.
In order to measure disease status, magnetic resonance imaging (MRI) is being performed at 6-wk intervals during therapy. Response is assessed using WHO response evaluation criteria modified to include consideration of corticosteroid dose.

DOSE ESCALATION SCHEME :



∗1-2 pts until an emergent ANG1005-related ≥ Grade 2 toxicity (except alopecia) warrants expansion to 3 pts
∗If 1 pt experiences an emergent ANG1005-related DLT, cohort is expanded to 6 pts
∗Escalation will continue as long as < 2 pts experience a treatment emergent DLT during cycle 1

MTD = dose level at which ≤ 1 of 6 patients develops an emergent ANG1005-related DLT

Dose Limiting Toxicity (DLT):
- Any Grade 3 or 4 nonhematologic toxicity
- Febrile neutropenia
- Grade 4 neutropenia of ≥ 7 d duration
- Any Grade 4 thrombocytopenia
- Grade 2 peripheral neuropathy > 7 d *OR* a ≥ Grade 3 peripheral neuropathy of any duration

RESULTS

PATIENT PROFILE :

Results presented here include data up to and including November 3, 2008. **17** patients with recurrent malignant glioma (10 with GLIOBLASTOMA MULTIFORME, 1 with ANAPLASTIC ASTROCYTOMA, 5 with ANAPLASTIC OLIGODENDROGLIOMA, 1 with OLIGOASTROCYTOMA) have received ANG1005 at doses ranging from 30 to 105 mg/m^2; escalation is ongoing.

Patient characteristics at study entry (n = 17)

Age (years)	**Median**	**Range**	
	49	26-64	
Sex	**Male**	**Female**	
	10 (59%)	7 (41%)	
# Prior Chemotherapies	**≤ 2**	**3**	**≥ 4**
	8	3	6
Prior Radiotherapy	**Yes**	**No**	
	17	0	
ECOG at Entry	**0**	**1**	**2**
	9 (53%)	7 (41%)	1 (6%)

SAFETY DATA :

Safety data are available for all **17** study patients dosed to date.

Summary of common chemotherapeutic adverse events reported by dose level and CTCAE grade

Dose Level :	30 mg/m^2			50 mg/m^2			75 mg/m^2			105 mg/m^2		
# Patients :	3 pts			6 pts			3 pts			5 pts		
Total # Cycles/Cohort :	7 cycles			10 cycles			8 cycles			8 cycles		
CTCAE Grade :	2	3	4	2	3	4	2	3	4	2	3	4
Leucopenia	0	0	0	0	0	0	0	0	0	0	0	0
Neutropenia	0	0	0	0	0	0	0	0	0	0	0	0
Thrombocytopenia	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
Infusion Related Reaction	1	0	0	0	0	0	1	0	0	0	0	0
Peripheral Neuropathy[1]	0	0	0	0	0	0	0	0	0	0	1[2]	0
Mucositis	0	0	0	0	0	0	0	0	0	0	0	0
Myalgia / Arthralgia[1]	0	0	0	0	0	0	0	0	0	0	0	0
Alopecia	0	0	0	0	0	0	0	0	0	0	0	0

n = number of patients that experienced a treatment-emergent event
[1] Parameter not included in CTCAE; severity assessed *per protocol*: Grade 2=Moderate, Grade 3=Severe, Grade 4=Life-threatening
[2] Verbatim term = Stiffness of extremities

Three infusion reactions (2 Grade 2, listed above, and 1 Grade 1) have been observed; all occurred within the first few minutes of the infusion – in 2 cases the reactions were seen during cycle 1 while in the other case the reaction occurred during the 2nd cycle of treatment . Due to the reactions, the infusions were interrupted and the patients were treated with success allowing the infusions to be completed.

No patient has discontinued from the study due to study drug-related AEs.

Preliminary neurocognitive data show that ANG1005 does not affect cognitive performance at these doses in this population. Furthermore, immunogenicity data to date indicate that ANG1005 does not elicit an immune response.

TUMOR RESPONSE DATA :

6-week tumor response data is available for 10 patients. Although efficacy is not expected at the low doses used thus far, 6-week data reveal 1 minor response (~10% decrease) in a GBM patient dosed at 30 mg/m^2 and 2 stable diseases – one in a GBM patient dosed at 75 mg/m^2 and one in a patient with anaplastic oligodendroglioma dosed at 105 mg/m^2.

	30 mg/m^2 n = 2	50 mg/m^2 n = 4	75 mg/m^2 n = 3	105 mg/m^2 n = 1
SD at 6 wks	1*	0	1	1
SD at 12 wks	0	0	n/a	n/a
PD at 6 wks	1	4	2	0
PD at 12 wks	1	0	n/a	n/a

* Decrease in tumor size of ~ 10%
n/a = not applicable or not yet assessed

CONCLUSIONS

- **Existing drug candidates (mostly biologic) available to address conditions localized in the brain have limited to no therapeutic value *in vivo* due to the fact that they do not permeate the BBB to reach the site of disease.**
- **In an effort to overcome this obstacle, Angiochem has developed a new vector technology based on chemically attaching small molecules, peptides, monoclonal antibodies, siRNA, etc. to a vector that shuttles them into the brain using LRP receptors that are naturally expressed at the BBB.**
- **ANG1005, a conjugate of Angiopep-2 and paclitaxel, is the first new chemical entity to use this technology and the first drug candidate to be tested in humans to use a physiological approach to cross the BBB.**
- **Promising preclinical studies and preliminary clinical safety and tolerability data provide new hope to those dealing with brain cancers and, in future, possibly other brain diseases.**