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

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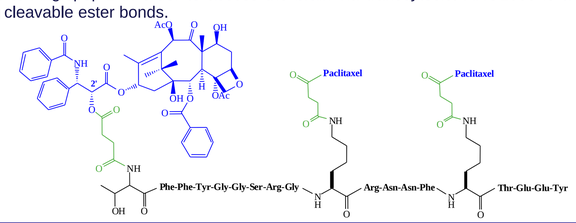
UPDATED ABSTRACT

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's uptake of ANG1005 to be ~100x 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 cleaved releasing paclitaxel to perform its antimitotic functions. A Phase I multicenter, open-label, dose escalation study of ANG1005 was initiated in Oct 2007 to explore the maximum tolerated dose and obtain data on safety, tolerability and preliminary evidence 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/m^2. 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; hepatocellular carcinoma, n=2; other, n=7) and/or brain metastases (n=21) have received ANG1005. Safety and tolerability have been demonstrated thus far. Anemia, neutropenia and leucopoenia, all established paclitaxel-related effects, were observed in the study to the present 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 possible 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 brain 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 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 metastatic brain cancer cells. 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 advanced solid tumors and/or metastatic brain cancer.

MATERIALS and METHODS

Patients with advanced solid tumors and/or brain metastasis are being recruited into this ongoing, sequential cohort, open-label, dose escalation study from 3 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
Gabrail Cancer Center	Canton, Ohio	Nashat Y. Gabrail, MD	Carrie Smith, RN
MD Anderson Cancer Center	Houston, Texas	Razelle Kurzrock, MD	Zhong Guo, MS

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

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 pts with advanced solid tumors and metastatic brain cancer

ELIGIBILITY :

⊕ INCLUSION

- Male and 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 score ≤ 2
- Expected survival of at least 3 months

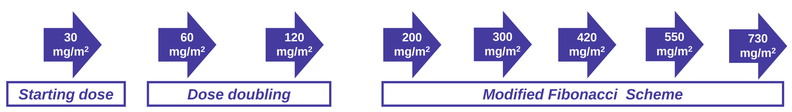
⊗ EXCLUSION

- 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, imaging is being performed at 6-wk intervals during therapy. Response is assessed using modified RECIST response evaluation criteria.

DOSE ESCALATION SCHEME :



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

∗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

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. **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/m^2; escalation is ongoing.

Patient characteristics at study entry (n = 30)

Age (years)	**Median**	**Range**		
	54	23-76		
Sex	**Male**	**Female**		
	16 (53%)	14 (47%)		
# Prior Chemotherapies	**≤ 3**	**4**	**5**	**> 5**
	9	7	1	13
Prior Radiotherapy	**Yes**	**No**		
	22	8		
ECOG at Entry	**0**	**1**	**2**	
	3 (10%)	22 (73%)	5 (17%)	

SAFETY DATA :

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

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

Dose Level :	30 mg/m^2			60 mg/m^2			120 mg/m^2			200 mg/m^2			300 mg/m^2			420 mg/m^2			500 mg/m^2			550 mg/m^2		
# Patients :	1 pt			3 pts			3 pts			3 pts			7 pts			6 pts			4 pts			3 pts		
Total # Cycles/Cohort :	6 cycles			9 cycles			10 cycles			12 cycles			13 cycles			11 cycles			4 cycles			3 cycles		
CTCAE Grade :	2	3	4	2	3	4	2	3	4	2	3	4	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	2	1[2]	0	2	2	0	0	1	0	2	0	1
Neutropenia	0	0	0	1	0	0	0	0	0	2	0	0	1	0	1[2]	3	1	0	1	0	0	1	0	1
Thrombocytopenia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1[2]	1	0	0	0	0	0	0	1	0
Anemia	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0
Infusion–Type Reactions	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0
Peripheral Neuropathy[1]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mucositis	0	0	0	0	0	0	0	0	0	0	0	0	0	1	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	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	1	0	0	0	0	0	1	0	0	0	0	0

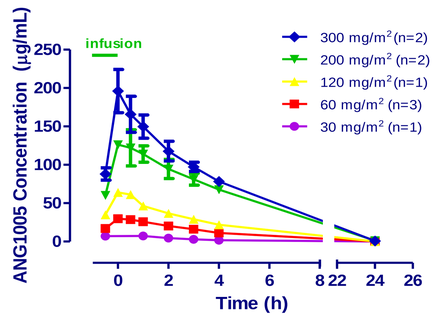
n = number of patients who experienced a treatment-emergent event
[1] Parameter not included in CTCAE; severity assessed *per protocol*: Grade 2=Moderate, Grade 3=Severe, Grade 4=Life-threatening
[2] The same patient developed grade 4 hematoxicity including thrombocytopenia; this patient was heavily exposed to radiation prior to inclusion

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.

PK DATA :

PK data presented here are *preliminary* results obtained from cycle 1 in **9** patients dosed between 30 and 300 mg/m^2.

Parameter	Value / Range (as applicable)				
Dose (mg/m^2)	30	60	120	200	300
n	1	3	1	2	2
C_{max} (ug/mL)	13	27-32	64	128-146	168-224
T_{max} (h)	1	1.0-1.5	1	1.0-1.5	1
AUC_{inf} (ug·h/mL)	34	137-145	281	1061-1163	909-1459
half-life (h)	1.5	2.4-2.7	2.8	3.5-3.7	3.1-3.6
CL (mL/m^2·h)	888	414-438	428	172-189	206-330
Vd (mL/m^2)	1924	1459-1714	1743	864-1004	918-1694



Note that all values < the lower limit of quantification (0.5 µg/mL) have been reported as 0.0

PK data obtained so far show linear bioavailability of ANG1005.

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.

	30 mg/m^2 n = 1	60 mg/m^2 n = 2	120 mg/m^2 n = 3	200 mg/m^2 n = 3	300 mg/m^2 n = 2
SD at 6 wks	1	1	1	2	0
SD at 12 wks	1	1	1	1	0
PD at 6 wks	0	1	2	1	2
PD at 12 wks	0	0	0	1	0

CONCLUSIONS

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