ANG1005, AN ANGIOPEP-2/PACLITAXEL CONJUGATE: THE FIRST CLINICAL TRIAL IN PATIENTS WITH ADVANCED CANCER AND BRAIN METASTASES – PRELIMINARY SAFETY AND TOLERABILITY DATA

Razelle Kurzrock[1], Siqing Fu[1], Alain C. Mita[2], Zhong Guo[1], Cynthia Allison[2], Danielle Bouchard[3], Kelly M. Elian[3], Ann Neale[4], Jean-Paul Castaigne[3], and John Sarantopoulos[2]

ABSTRACT

Background: Treatment options for patients with metastatic brain cancer are limited and often focus on relief of symptoms. The main obstacle to treatment is the blood–brain barrier (BBB) which prevents most drugs from reaching tumour cells in the brain. Angiopep-2 is a 19 amino acid peptide shown in animal models to cross the BBB using a physiological approach through transcytosis via low-density lipoprotein receptor-related protein (LRP) expressed on the surface of the BBB. ANG1005 is a new chemical entity that combines 1 molecule of Angiopep-2 with 3 molecules of paclitaxel. Preclinical studies demonstrate the brain's uptake of ANG1005 to be ~100x greater than paclitaxel and ~10x greater than temozolomide. Once in the brain compartment, ANG1005 again uses LRP, which is upregulated on metastatic brain cancer cells, to enter tumour cells where the molecule is cleaved releasing paclitaxel to exert its antimitotic effects. A Phase I clinical trial was initiated in Oct 2007 to explore the maximum tolerated dose and obtain data on safety, tolerability and preliminary evidence of efficacy of ANG1005 in patients with advanced solid tumours and/or brain metastases. **Materials and methods:** A multicenter, open-label, dose escalation study of ANG1005 is being conducted in the US with sequential dose cohorts ranging from 30-558 mg/m^2. ANG1005 is administered IV every 21 days. Study participants include adult patients with measurable disease and an ECOG performance status ≤ 2 who are ineligible for standard treatment options. **Results:** As of 06-Oct-2008, 27 patients with advanced solid tumours (melanoma, n=9; breast cancer, n=5; lung cancer, n=5; hepatocellular carcinoma, n=2; other, n=6) and/or brain metastases (n=18) have received ANG1005. Safety and tolerability have been demonstrated thus far. Anaemia, neutropenia and leucopenia, all established paclitaxel-related effects, were observed in the study to the present time. **Conclusion:** To date, the safety and tolerability profile of ANG1005 has been good in patients with advanced solid tumours and/or brain metastases. Angiopep conjugates may represent a potentially safe and effective way to treat currently unmanageable CNS diseases; ANG1005 is the first of many compounds to be tested as a means of overcoming restrictions to treatments due to the BBB.

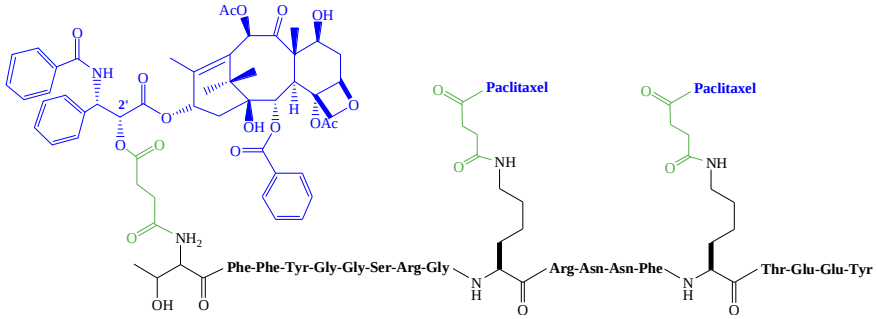
[1]MD Anderson Cancer Center, Houston, Texas; [2]Cancer Therapy and Research Center, San Antonio, Texas; [3]Angiochem Inc., Montreal (Québec), Canada; [4]WinPharm Associates, Danville, California

angiochem

INTRODUCTION

Serving as both a physical and physiological barrier to the passage of most small molecules, including more than 95% of drugs, between the bloodstream and neural tissue, the blood-brain barrier (BBB) presents one of the biggest challenges to the treatment of brain diseases. The observation that most molecules that reach the brain must interact with specific receptors that facilitate active transport across BBB endothelial cells inspired the technology discussed herein.

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 metastatic brain cancers. 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 tumour cells which it enters by endocytosis using the same receptor mechanism. Inside tumour 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 is the first to examine ANG1005 in patients with advanced solid tumours and brain metastases.

MATERIALS & METHODS

Patients with advanced solid tumours and brain metastases are being recruited into this ongoing, sequential cohort, open-label, dose escalation study from 3 sites located in the United States (listed alphabetically).

Institution Name	Location	Principle Investigator	Study Coordinator
Cancer Therapy and Research Center	San Antonio, Texas	John Sarantopoulos, MD	Cynthia Allison, RN
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 tumours and metastatic brain cancer

• To identify the maximum tolerated dose (MTD) of ANG1005 in pts with advanced solid tumours 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 antitumour activity of ANG1005 in pts with advanced solid tumours with brain metastases

Eligibility :

The study includes stable adult patients with:

- Metastatic or advanced-stage solid tumour that has progressed following standard therapy;

- Measurable disease according to RECIST criteria;
- ECOG performance status score ≤ 2;
- Expected survival of at least 3 months;
- Haemoglobin > 9.0 g/dL, ANC > 1.5 x 10^9/L, platelet count > 100 x 10^9/L; and
- Total bilirubin < 1.5 x ULRR, AST or ALT < 2.5 x ULRR, serum calcium < ULRR, estimated Cr. Cl. > 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 tumour progression, general medical deterioration that warrants discontinuation of treatment or withdrawal of consent.

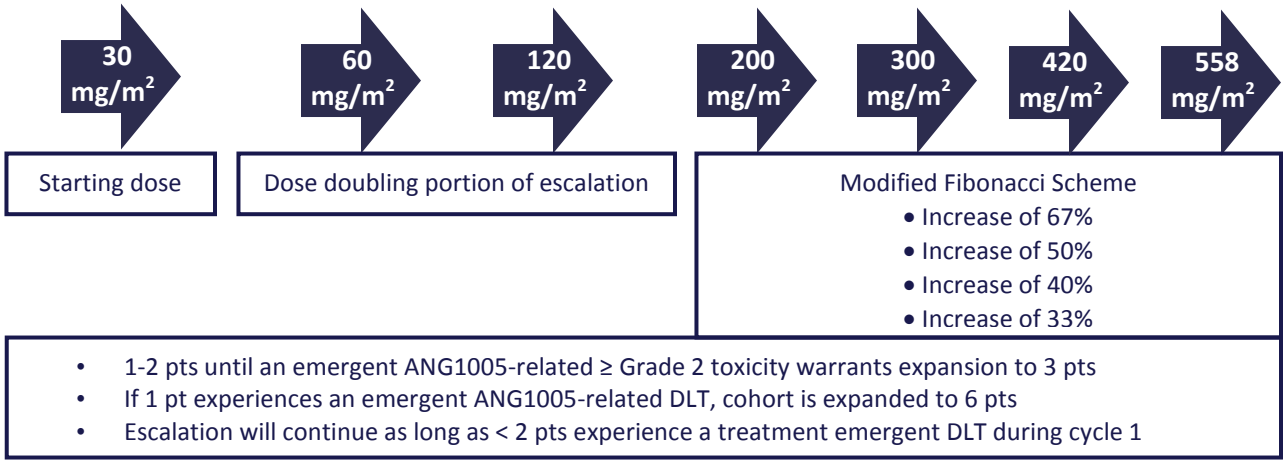
Patients are closely monitored during the infusion and for up to 24 hrs after the end of infusion with weekly safety visits between treatments. AEs are collected from the time of the start of the first infusion until 3 wks after the last infusion. The severity of events is assessed according to the NCI 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 :



RESULTS

Results presented here include data up to and including October 6th, 2008. 27 patients with advanced solid tumours (melanoma, n=9; breast cancer, n=5; lung cancer, n=5; hepatocellular carcinoma, n=2; other, n=6), 18 of which have brain metastases, have received ANG1005 at doses ranging from 30 to 500 mg/m^2.

Patient characteristics at study entry (n = 27)

Age (years)	Median	Range		
	54	23-71		
Sex	Male	Female		
	13 (48%)	14 (52%)		
# Prior Chemotherapies	≤ 3	4	5	> 5
	7	7	1	12
Prior Radiotherapy	Yes	No		
	21	6		
ECOG at Entry	0	1	2	
	3 (11.1%)	19 (70.4%)	5 (18.5%)	

Safety Data :

Safety data are available for all 27 study patients dosed to date.

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.

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		
# Patients :	1 pts			3 pts			3 pts			3 pts			7 pts			6 pts			4 pts		
Total # Cycles/Cohort :	6 cycles			9 cycles			10 cycles			12 cycles			13 cycles			8 cycles			4 cycles		
CTCAE Grade :	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	0	2	1	0	0	1	0
Neutropenia	0	0	0	1	0	0	0	0	0	1	1	0	1	0	1	2	1	0	1	0	0
Thrombocytopenia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1[2]	0	0	0	0	0	0
Anaemia	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Acute Infusion Rxn	0	0	0	0	0	0	0	0	0	0	0	0	0	0	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
Mucositis	0	0	0	0	0	0	0	0	0	0	0	0	0	1	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
Alopecia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0

n = number of patients

[1] Parameter not included in CTCAE; severity assessed *per protocol*: Grade 2=Moderate, Grade 3=Severe, Grade 4=Life-threatening

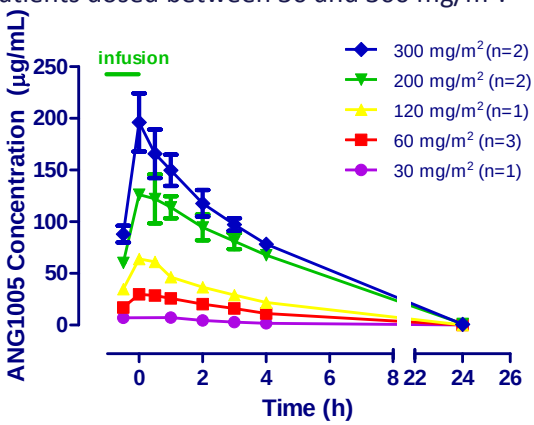
[2] The same pt developed Gr 4 hematoxicity incl. thrombocytopenia. This pt was heavily exposed to radiation and chemotherapy prior to inclusion that resulted in mucositis for which she was hospitalized and treated with several drugs known to cause severe bone marrow suppression; a multifocal infection ensued.

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



Tumour Response Data :

Tumour response data are available for 9 patients to date. Of the 9 patients, 5 had stable disease and the remaining 4 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
SD at 6 wks	1	1	1	2
SD at 12 wks	1	1	1	1
PD at 6 wks	0	1	2	1
PD at 12 wks	0	0	0	1

CONCLUSION

Although it is recognized that at this stage of the study no specific conclusions may be drawn, data to date show that:

- **The observed side effects of ANG1005 are clearly paclitaxel-related *and* ANG1005 is better tolerated at equivalent doses than paclitaxel**
- **No adverse events attributable to the conjugate have been reported to date (e.g., central neurotoxicity, immunogenicity, liver toxicity)**
- **Preliminary response data may suggest prolongation in time to progression compared to current standard treatment**