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ANG1005: Development of a new chemical entity for the treatment of advanced solid tumors and brain metastases

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It is estimated that in the US, over 150 000 patients with systemic tumors develop brain metastases each year and this incidence is expected to rise. The challenge in treating brain tumors stems from the inability of most drugs to cross the blood-brain barrier (BBB) to reach the site of disease in sufficient concentrations to act effectively without the limitation of systemic toxicity. Exciting preclinical data has been gathered on a deep and broad product pipeline of new breakthrough drugs uniquely capable of crossing the BBB to treat brain diseases including metastatic 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 metastatic cancer 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 advanced solid tumors / brain metastases. Secondary objectives include obtaining preliminary antitumor information in humans. As of April 1, 2009, a total of 42 patients with advanced solid tumors / brain metastases, have received ANG1005 by IV infusion at doses of 30-700 mg/m^2, inclusive, q 21 days without premedication. Severity of adverse events is assessed using CTCAE, version 3. At present, although some patients have developed the chemotherapeutic-associated hematologic toxicities of neutropenia, leucopenia, thrombocytopenia and anemia, these cases have been both less common and less severe than expected based on clinical observation with paclitaxel therapy. Furthermore, neurocognitive data gathered to date show no evidence of central nervous toxicity and in fact data from one patient with a minor tumor response to therapy even showed significant improvement on memory, processing speed and executive function after 6 and 12 weeks of therapy. Immunogenicity data show that ANG1005 does not elicit an immune response, including in patients who have received up to 6 treatment cycles. Moreover, pharmacokinetic data obtained so far on study patients show a linear relationship between dose and bioavailability. MRI data indicate potential efficacy in tumor regression and slowing tumor progression. Together the data presented offer encouragement to patients suffering from brain metastases.

KEY RESULTS:

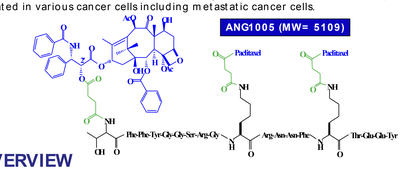
- **ANG1005 has an excellent safety and tolerability profile to date:**
  - **Changes in hematologic parameters are consistent with / milder than observed with known chemotherapeutics and manageable with standard treatments**
  - **Few reports of adverse events such as infusion reactions, mucositis, peripheral neuropathy**
  - **No evidence of central nervous system toxicity**
- **ANG1005 shows no evidence of invoking an immune response even in patients who have received 6 treatment cycles**
- **PK data show a linear relationship between dose and bioavailability**
- **Early MRI data indicate that ANG1005 may cause tumor regression and/or slow the progression of disease in patients with advanced solid tumors and brain metastases**

Brain metastases are the most common intracranial tumors in adults. Their incidence continues to increase as improved therapies for systemic cancers extend survival and provide more time for brain metastases to develop. Although most cancers can metastasize to the brain, melanoma and carcinomas of the lung, breast, kidney, and thyroid have a particular propensity to do so. Treatment options are limited due to the difficulties associated with drug delivery across the BLOOD-BRAIN BARRIER (BBB).

Median survival after surgical resection of brain metastases is poorest for melanoma (7 mo.) and better for lung and breast cancers (12 mo.)

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 vesicles. 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 metastatic cancer cells.



STUDY OVERVIEW

PRIMARY OBJECTIVES

•To characterize the safety and tolerability of IV administered ANG1005
•To identify the maximum tolerated dose (MTD) of ANG1005
… in patients with advanced solid tumors and metastatic brain cancer

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 advanced solid tumors and metastatic brain cancer

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 metastatic and/or advance-stage solid tumors, an ECOG status ≤ 2 and measureable disease after surgical, radiation, and/or chemotherapy treatment

INVESTIGATIONAL SITES

•Cancer Therapy and Research Center, San Antonio, TX •MD Anderson Cancer Center, Houston, TX
•Gabrail Cancer Center, Canton, OH

PATIENT CHARACTERISTICS

Data presented here are current up to April 1, 2009, except where indicated.
42 patients with advanced solid tumors / brain metastases (melanoma, n= 12; lung cancer, n= 10; breast cancer, n= 9; hepatocellular carcinoma, n= 2; other, n= 9) have received ANG1005 at doses ranging from 30 to 700 mg/m^2.

Age (years)	Median	Range	
	53.5	23-81	
Sex	Male	Female	
	20 (48%)	22 (52%)	
# Prior Chemotherapies	≤ 3	4	≥ 5
	18	8	16
Prior Radiotherapy	Yes	No	
	29	13	
ECOG at Entry	0	1	2
	6 (14%)	29 (69%)	7 (17%)

SAFETY DATA

Dose (mg/m^2)	30			60			120			200			300			420			500			550			650			700		
n	1			3*			3			3*			7			5			4*			3			6			6		
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	2	3	4	2	3	4
Neutropenia	0	0	0	1	0	0	0	0	0	2	0	0	1	0	1	3	1	0	1	0	0	1	0	1	0	1	5	1	0	5
Leucopenia	0	0	0	0	1	0	0	0	0	2	0	0	2	1	1	2	2	0	0	1	0	2	0	1	0	4	2	1	1	4
Thrombopenia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1§	0	0	0	0	1	0	1	2	0	1	0	2
Anemia	0	0	0	1	0	0	0	0	0	1	0	0	3	1	0	1	0	0	4	0	0	2	0	0	2	2	0	1	1	0
Infusion Reactions	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	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	0	0	0	0	0	1
Peripheral Neuropathy	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0

* One patient in cohort experienced all indicated hematoxicities; the patient has extensive metastatic disease and was heavily treated prior to entering the study
§ Patient had Grade 3 thrombopenia at screening; pt experienced leucopenia, neutropenia and thrombopenia during the study

Preliminary **NEUROCOGNITIVE DATA** show that ANG1005 does not affect cognitive performance at these doses in this population. Moreover, data from 1 patient dosed at 420 mg/m^2 who had a minor tumor response showed significant improvement on memory, processing speed and executive function after 6, 12 and 24 weeks of therapy.

IMMUNOGENICITY DATA to date indicate that ANG1005 does not elicit an immune response, even in patients who have received 6 treatment cycles.

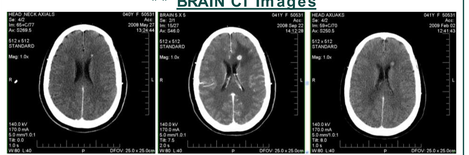
RADIOLOGY DATA

Tumor response at 6 weeks

Dose	≤ 300 mg/m^2	> 300 mg/m^2
Response	n= 12	n= 7
PR		1*
MR		2**
SD	5	2
PD	7	2

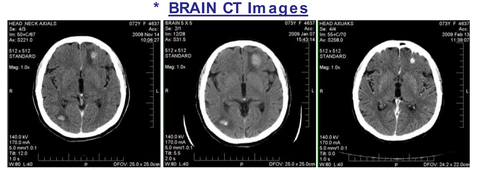
** One of the 2 pts who had MR at 6 wks is a 41 y.o F with NSCL (Aug-2007) with multiple brain mets (Sep-2008) who received 6 cycles at 420 mg/m^2 followed by 3 cycles at 550 mg/m^2; pt ongoing. Tumor evaluation at 24 weeks shows SD = PFS6
BRAIN CT IMAGES SHOWN (BELOW)

** BRAIN CT Images

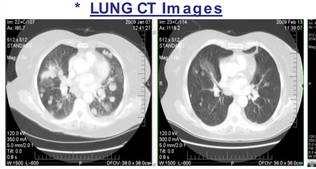


* 73 y.o. F with Ovarian Ca (Nov-2006) with Lung, Lymph, Liver and Brain mets who received 4 cycles at 650 mg/m^2.
RADIOLOGY IMAGES OF BRAIN, LUNG AND LIVER SHOWN (BELOW)

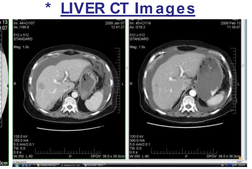
* BRAIN CT Images



* LUNG CT Images



* LIVER CT Images



PK DATA

PK data presented here are *preliminary* results obtained from cycle 1 in **29** patients dosed between 30 and 550 mg/m^2; data obtained so far show linear bioavailability of ANG1005.

Parameter	Value / Mean (as applicable)							
Dose (mg/m^2)	30	60	120	200	300	420	500	550
n	1	3	3	3	7	6	4	2
C_{max} (ug/mL)	7.24	30.0	55.2	119	160	225	190	225
T_{max} (h)	1.0	0.167	0.167	0.167	0.071	0.33	0.375	0.00
AUC_{inf} (ug·h/mL)	28	140.3	261	664	818	1352	1332	1613
half-life (h)	1.50	2.57	2.94	3.52	3.19	3.73	3.86	3.47
CL (mL/m^2·h)	1055	428	470	302	381	325	401	364
Vd (mL/m^2)	2285	1588	1947	1537	1769	1698	2212	1834

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