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ANG1005: Results of a Phase I study in patients with advanced solid tumors and metastatic brain cancer

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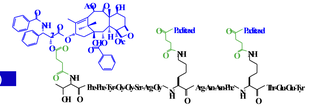
UPDATED ABSTRACT:

ANG1005 is a novel, next-generation taxane created using Angiochem's Engineered Peptide Compound (EPiC) platform. 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 brain cancer cells. Metastatic brain cancer is the most common intracranial neoplasm in adults with an estimated incidence of 200, 000 cases each year in the US alone. There is currently no approved chemotherapy and prognosis is dismal. A multi-center, phase I, open-label, sequential cohort, dose escalation study of ANG1005 in patients with advanced solid tumors and brain metastases is ongoing in the US. Study objectives include characterization of safety and tolerability and identification of maximum tolerated dose (MTD). ANG1005 is administered by IV infusion once every 21 days (1 treatment cycle) *without premedication*. After evaluating doses of 30-700 mg/m^2, 650 mg/m^2 was identified as MTD. Data including adverse events and hematological parameters indicate that ANG1005 is safe and well tolerated. The most common events occurring at a severity ≥ Grade 2 according to CTCAE, version 3.0 at MTD (n=20) were leucopenia (100% of patients; Grade 4 in 40%), neutropenia (95%; Grade 4 in 75%), anemia (55%; no cases of Grade 4), thrombocytopenia and fatigue (40% each; no cases of Grade 4); these events have been transient and manageable with standard treatments. There has been no evidence of CNS toxicity as assessed by neurocognitive testing and neurological examination. Biological data show that ANG1005 does not elicit an immune response even in patients who have received more that 6 treatment cycles. Pharmacokinetic data indicate linear ANG1005 bioavailability. Disease control (≥ stable disease) assessed by CT/MRI in this heavily pre-treated group of patients was achieved in 71% at doses > 300 mg/m^2 including 7 prior taxane failure patients. Partial response was observed in 33% of patients dosed > 300 mg/m^2. Tumor types that showed the best improvements were breast, non-small cell lung and ovarian cancers. Furthermore, partial and complete responses were achieved in metastatic locations including the brain (67% disease control), liver (63% disease control), lung (80% disease control) and lymph nodes (73% disease control). Clinical data gathered to date indicate that ANG1005 shows promise as a potential treatment option for patients with advanced solid tumors and brain metastases.

INTRODUCTION

Brain metastases:
- Up to 200,000 cases per year in the US alone
- Incidence continues to rise as improved therapies for systemic cancers extend survival and provide more time for brain metastases to develop
- Most commonly arise from cancers of the lung and breast
- NO APPROVED CHEMOTHERAPY in the US
- Prognosis is dismal
- BLOOD-BRAIN BARRIER (BBB) represents a major treatment obstacle

ANG1005:
- A novel, next-generation taxane created using the Engineered Peptide Compound (EPiC) platform
- CROSSES THE BBB by targeting LRP (low-density lipoprotein receptor-related protein), one of the most highly expressed receptors on the surface of the BBB
- Enters tumor cells through LRP which is upregulated in various cancer cells
- Cremophor-free formulation



ANG1005 (MW=5109)

METHODS

PRIMARY OBJECTIVES
- Characterize safety and tolerability
- Identify maximum tolerated dose (MTD)

SECONDARY OBJECTIVES
- Pharmacokinetics (PK)
- Immunogenicity of ANG1005
- Obtain preliminary antitumor activity

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

TREATMENT
- ANG1005 by intravenous infusion (~1 hour) once every 21 days ***without premedication***

STUDY POPULATION
- Adult patients with progressing advance-stage solid tumors and brain metastases, an ECOG status ≤ 2 and measureable disease

PATIENT CHARACTERISTICS (N=56)

Age (years)	
Median (Range)	54 (23-81)
Sex, n (%)	
Male	24 (43%)
Primary tumor site, n (%)	
Breast	14 (25%)
Skin (Melanoma)	13 (23%)
Lung (NSCLC)	8 (14.5%)
Lung (SCLC)	8 (14.5%)
Head and Neck	7 (12.5%)
Other	6 (10.5%)
No. of prior therapies, n (%)	
≤ 2	15 (27%)
3 – 5	23 (41%)
≥ 6	18 (32%)
Prior radiotherapy, n (%)	
Yes	44 (79%)
ECOG performance status score, n (%)	
0	12 (21.5%)
1	35 (62.5%)
2	9 (16%)

SAFETY RESULTS as of 29-Oct-2009

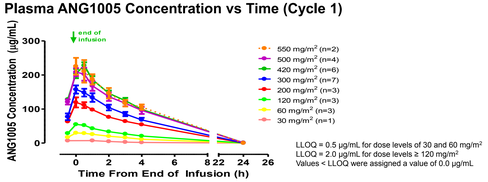
Dose (mg/m^2)	≤300			420			500			550			650 MTD			700		
n	17*			6			4*			3			20			6		
CTCAE Grade	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4
Neutropenia	4		1	3	1		1			1		1	1	3	15	1		5
Febrile Neutropenia													1		1			
Leucopenia	4	2	1	2	2			1		2		1	1	11	8	1		5
Thrombocytopenia			1			1*					1		3	5		1	1	2
Anemia	4	1		1			4			2			8	3		2	1	1
Peripheral Neuropathy				1									4	1				
Alopecia				1			1						4					
Myalgia/Arthralgia																		
Mucositis		1											4	2			1	1
Infusion Reactions				1		1							1	1				
Fatigue	1	1		1			1			2			5	3		1	1	
Nausea	1	1								1						1	2	
Rash													2	1				

NB: Blank cells denote no observation
* One patient in each of 60, 200, 300 and 500 mg/m^2 cohorts experienced all indicated hematoxicities; the patient had extensive metastatic disease and was heavily treated prior to entering the study
* Patient had Grade 3 thrombocytopenia at screening; patient experienced leucopenia, neutropenia and thrombocytopenia during the study

- **NO CNS TOXICITY** as assessed by neurocognitive testing and neurological examination
- **Marked improvement in memory, processing speed and executive function** at 6, 12, 18 and 24 weeks was observed in a patient with NSCLC and brain metastases
- **NO ANTIBODY PRODUCTION** even in patients who received more than 6 treatment cycles

PRELIMINARY PHARMACOKINETIC RESULTS

Plasma ANG1005 Concentration vs Time (Cycle 1)



LLOQ = 0.5 µg/mL for dose levels of 30 and 60 mg/m^2
LLOQ = 2.0 µg/mL for dose levels ≥ 120 mg/m^2
Values < LLOQ were assigned a value of 0.0 µg/mL

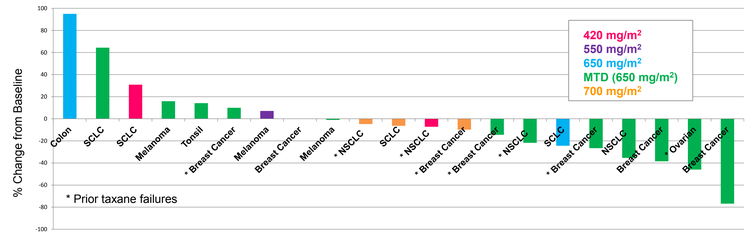
Parameter	Value / Mean (as applicable)							
Dose (mg/m^2)	30	60	120	200	300	420	500	550
n	1	3	3	3	7	6	4	2
C_{max} (µg/mL)	7.24	30.0	55.2	119	160	225	190	225
T_{max} (h)	1.0	0.167	0.167	0.167	0.071	0.33	0.375	0.00
AUC_{inf} (µg·h/mL)	28	140.3	261	664	818	1352	1332	1613
half-life (h)	1.50	2.57	2.94	3.52	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

CYCLE 3: Data from Cycle 3 show that there is no accumulation of ANG1005

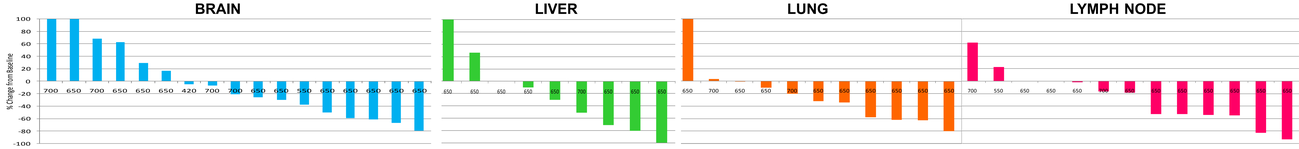
PRELIMINARY EFFICACY RESULTS

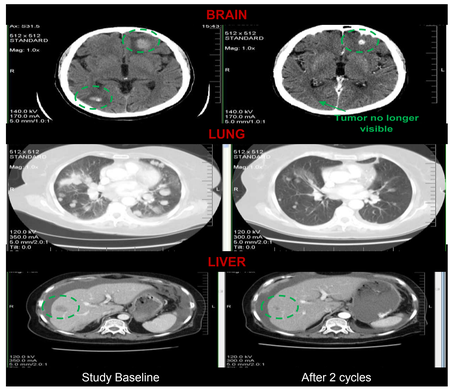
Dose	≤300 mg/m^2	>300 mg/m^2	Prior Taxane Failures**
Overall Best Response*	**n=12**	**n=21**	**n=9**
CR			
PR		7	3
MR		4	4
SD	5	4	
PD	7	6	2
% ≥SD	**42%**	**71%**	**78%**

* Assessed using RECIST criteria
**9 of 21 patients dosed >300 mg/m^2 had failed on prior taxane therapy



RESPONSES IN METASTATIC DISEASE LOCATIONS

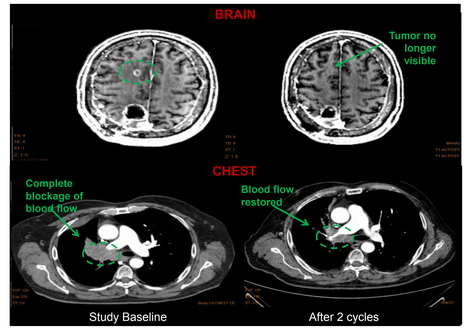




CASE STUDIES

- 73 y.o. female patient with OVARIAN CANCER and BRAIN, LIVER, LUNG AND LYMPH METASTASES
- Taxane-resistant
- After 2 cycles of ANG1005 at 650 mg/m^2 the OVERALL tumor response on CT showed 46% tumor shrinkage

- 61 y.o. male patient with SCLC and BRAIN, LIVER AND LUNG METASTASES
- Heavily pretreated
- After 2 cycles of ANG1005 at 650/550 mg/m^2 the OVERALL tumor response on CT showed 24% tumor shrinkage



KEY FINDINGS:

- **ANG1005 has a superior side effect profile versus other taxanes:**
  - **Hematologic tolerability – effects are transient and easily manageable with standard treatments;**
  - **Few reports of AEs such as peripheral neuropathy, infusion reactions, fatigue and rashes (CTCAE ≥ Grade 2); and**
  - **No CNS toxicity as assessed by neurocognitive testing and neurological examination.**
- **No immunogenicity; no antibody production even after repeat dosing.**
- **Treatment with ANG1005 shows evidence of efficacy with drastic reductions in tumor sizes in the brain, liver, lung, lymph nodes and other organs including in patients who have failed prior taxane therapy.**
- **ANG1005: An active taxane derivative with a unique mechanism of action.**