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ANG1005: Development of a new Engineered Peptide Compound (EPiC) for the treatment of malignant glioma

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Introduction: Malignant glioma is an aggressive and fatal cancer whose treatment is limited by the inability of drugs to cross the BBB. Angiochem is developing a deep and broad product pipeline of new breakthrough drugs that are uniquely capable of crossing the BBB to treat brain diseases. ANG1005, the first product created from the Engineered Peptide Compound (EPiC) platform, is a novel, next-generation taxane. Studies show that ANG1005 enters the brain by targeting low-density lipoprotein receptor-related protein (LRP), one of the most highly expressed receptors on the BBB, and also enters tumor cells via LRP, which is upregulated in various cancer cells including malignant glioma cells.
Methods: As of 30-Sep-2009, 55 patients with recurrent/progressive WHO Grades II-IV malignant glioma have received ANG1005 by IV infusion at doses of 30-700 mg/m^2 once every 21 days *without premedication*. Study objectives include characterizing safety/tolerability, identifying the MTD and obtaining preliminary PK, immunogenicity and antitumor information. Drug penetration into extracted tumors was measured in a sub-group of patients undergoing debulking surgery following administration of one dose of ANG1005.
Results: 650 mg/m^2 is currently being expanded as the MTD. Data indicate that ANG1005 is safe and well tolerated. The most commonly occurring events observed to date have been neutropenia, leucopenia, peripheral neuropathy and infusion reactions; these events have been transient and easily 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 experienced infusion reactions. Pharmacokinetic data show a linear relationship between dose and bioavailability. Tumor stabilization and in several cases significant reduction in tumor size and reversal of neurological deficits have been observed including in one patient who was progressing on bevacizumab therapy at the time of study entry. Data from extracted tumors (n=6) show concentrations of ANG1005 in tumors relative to plasma of up to 379%.
Conclusion: Data to date indicate that ANG1005 has an excellent safety/tolerability profile, penetrates into tumors and shows promise as a potential treatment option for patients with recurrent/progressive malignant glioma.

KEY FINDINGS:

- **ANG1005 has a superior side effect profile versus other taxanes:**
  - **Few cases of hematologic toxicity;**
  - **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 in patients who experienced infusion reactions and rashes.**
- **Treatment with ANG1005 shows evidence of efficacy with tumor stabilization and several cases of significant reductions in tumor size and reversal of neurological deficits including in one patient who was progressing on bevacizumab therapy at the time of study entry.**
- **Therapeutic concentrations of ANG1005 found in brain tumors removed from patients; proof-of-concept validation of platform technology.**

INTRODUCTION

MALIGNANT GLIOMAS:
- 10,000 new cases per year in the US alone
- Treatment options are limited, in part due to the difficulties associated with accessing the tumors across the BLOOD-BRAIN BARRIER (BBB)
- Despite available treatment, the median survival is only 12-15 months for patients with GBM and 2-5 years for patients with anaplastic gliomas

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 including malignant glioma cells
- Cremophor-free formulation

METHODS

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

SECONDARY OBJECTIVES
- Pharmacokinetics (PK)
- Immunogenicity of ANG1005
- Obtain preliminary antitumor activity
- Measure ANG1005 in malignant glioma tumors

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 an ECOG status ≤ 2 and measureable recurrent or progressive malignant glioma (WHO Grades II to IV) after standard surgical, radiation, and/or chemotherapy treatment

PATIENT CHARACTERISTICS as of 30-Sep-2009 N=55

Age (years)	
Median (Range)	51 (22-78)
Sex, n (%)	
Male	32 (58%)
WHO Tumor Grade, n (%)	
Grade II (Astrocytoma, Ependymoma)	2 (4%)
Grade III (Anaplastic Gliomas)	16 (29%)
Grade IV (GBM)	37 (67%)
No. of prior therapies, n (%)	
≤ 2	25 (45.5%)
3 – 5	21 (38%)
≥ 6	9 (16.5%)
Prior radiotherapy, n (%)	
Yes	53 (96%)
ECOG performance status score, n (%)	
0	19 (34.5%)
1	27 (49%)
2	9 (16.5%)

SAFETY RESULTS as of 30-Sep-2009

Dose (mg/m²)	< 300			300			420			550			650 MTD			700		
n	22			7			4			8			10			3		
CTCAE Grade	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4
Neutropenia				1	1	1	1	2		1		6	2	2	1		1	2
Febrile Neutropenia														1				
Leucopenia	1			1	2			2			4	2		3			2	1
Thrombocytopenia										1			1		1			
Anemia							2			3			1					
Peripheral Neuropathy	2	1			1		1			2	2		1	2				
Alopecia													1	1				
Myalgia/Arthralgia	1																	
Mucositis										1							1	
Infusion Reactions	2			2			1			1			1	1		1		
Fatigue	3	1			1					2			1					
Nausea	1																	
Rash				1	1					2			1	1				

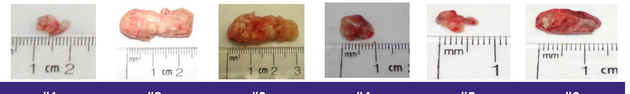
NB: Blank cells denote no observation

- **NO CNS TOXICITY** as assessed by neurocognitive testing and neurological examination
- **Stable to improved cognitive function** after 6 weeks of therapy was observed in a patient with ANAPLASTIC OLIGOASTROCYTOMA
- **Marked improvement in verbal learning and memory** at 24 weeks was observed in a patient with GBM
- **NO ANTIBODY PRODUCTION** even in patients who received multiple treatments or experienced infusion reactions and/or rashes

PRELIMINARY TUMOR EXTRACTION RESULTS

Excised tumor tissue was collected for analysis of ANG1005 by LC/MS/MS from patients undergoing tumor debulking who had received one dose of ANG1005 prior to surgery.

ANG1005 PENETRATION INTO GBM TUMORS



Patient	#1	#2	#3	#4	#5	#6
Dose Level	200 mg/m²	300 mg/m²	420 mg/m²	550 mg/m²	550 mg/m²	550 mg/m²
Extraction Time	~4h	~5h	~4h	~4.5h	~6h	~4.5h
Plasma ANG1005	34.3 µM	34.4 µM	53.5 µM	100.1 µM	56.5 µM	63.0 µM
Tumor ANG1005	2.8 µM	9.4 µM	7.1 µM	23.0 µM	98.0 µM	238.5 µM
[Tumor]:[Plasma]	**8.2%**	**27.3%**	**13.3%**	**23.0%**	**173%**	**379%**

GBM TUMOR GROWTH

- **NO GROWTH** was observed after extracted tumor samples were cultured in neurospheres

PRELIMINARY EFFICACY RESULTS

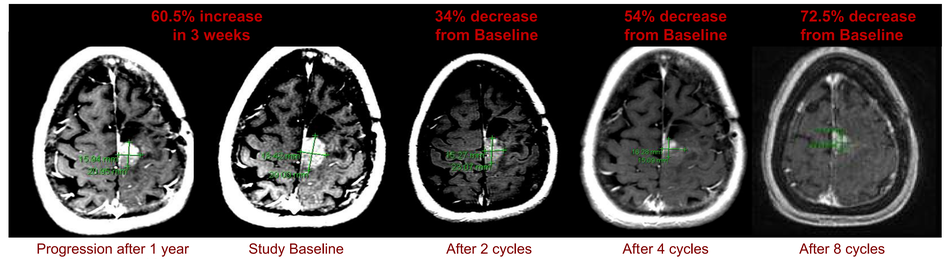
Dose	<300 mg/m²	≥300 mg/m²
Overall Best Response	n=18	n=17
CR		
PR*		1
MR**	2	6
SD	3	4[1]
PD	13	6
% ≥SD	**28%**	**65%**

[1] One of these patients was progressing on bevacizumab therapy at the time of study entry

*Tumor regression = 420 mg/m²: -72.5%
**Tumor regressions = 30 mg/m²: -9.6%
105 mg/m²: -9.7%
300 mg/m²: -4.3%
550 mg/m²: -15.9%
550 mg/m²: -22.3%
550 mg/m²: -45.2%
650 mg/m²: -17.0%
700 mg/m²: -12.2%

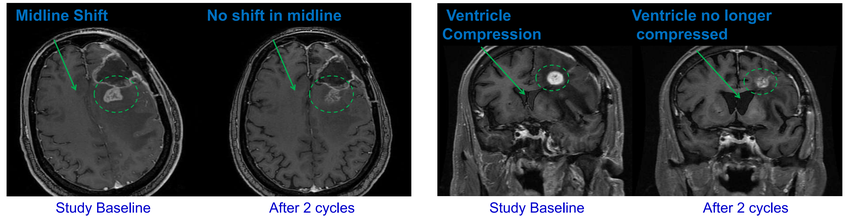
CASE STUDIES

- 49 y.o. female patient with ANAPLASTIC OLIGOASTROCYTOMA
- Heavily pretreated
- At study entry the patient had rapidly progressing symptoms including left hemiparesis; she was using a cane/wheelchair
- After 2 cycles of ANG1005 at 420 mg/m^2 the patient showed marked clinical improvement and had only very mild residual leg weakness; she was no longer using her cane
- After 4 cycles of ANG1005 the patient was walking unaided



Progression after 1 year of temozolamide | Study Baseline | After 2 cycles | After 4 cycles | After 8 cycles

- 59 y.o. male patient with GLIOBLASTOMA MULTIFORME
- Standard prior therapy
- After 2 cycles of ANG1005 at 550 mg/m^2, tumor response on MRI showed a **MINOR RESPONSE (21.5% tumor shrinkage)** and the patient, aphasic upon study entry, demonstrated clinical symptom improvement
- After 4 cycles of ANG1005, tumor response was sustained **(22.3% tumor shrinkage)**



Study Baseline | After 2 cycles | Study Baseline | After 2 cycles