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ANG1005: New EPiC compound for the treatment of recurrent malignant glioma

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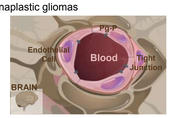
UPDATED ABSTRACT:

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 malignant glioma cells. Approximately 10, 000 new cases of malignant glioma are diagnosed in adults in the United States every year with poor prognosis. A multi-center, phase I, open-label, sequential cohort, dose escalation study of ANG1005 in patients with recurrent malignant glioma is ongoing in the US. Study objectives include characterization of safety and tolerability and identification of maximum tolerated dose (MTD). To examine whether or not ANG1005 could be measured in malignant glioma tumors in humans, fresh, excised tumor samples from patients undergoing debulking surgery following administration of one dose of ANG1005 were collected and analyzed. ANG1005 is administered by IV infusion once every 21 days (1 treatment cycle) *without premedication*. After evaluating doses of 30-700 mg/m², 650 mg/m² 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 in patients dosed at MTD (n=17) were neutropenia (71% of patients; Grade 4 in 35%), leucopenia (59%; Grade 4 in 18%), thrombocytopenia (24%; 1 case of Grade 4) and rash (24%; mostly Grade 2 – 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 had reported infusion reactions and/or rashes. Pharmacokinetic data indicate linear ANG1005 bioavailability. Analysis of tumor samples from patients who had received doses of ANG1005 of 200-550 mg/m² 4-6 hours prior to debulking shows a concentration of ANG1005 in tumors relative to plasma of 8 to 379%. Differences between samples are attributed to the different dose levels tested, the range of timing between dosing and tumor extraction and differences in tumor consistencies. Additional analysis revealed that the tumor samples did *not* grow when placed in neurosphere culture conditions. Disease control (≥ stable disease) assessed by MRI was achieved in 65% of patients dosed ≥ 300 mg/m² including one patient who was progressing on bevacizumab therapy at the time of study entry. Tumor stabilization and in some cases significant reduction in tumor size and reversal of neurological deficits were observed in patients with high grade gliomas. Clinical data gathered to date indicate a promising future for the development of ANG1005 for the treatment of patients with malignant glioma.

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



BLOOD-BRAIN BARRIER; PROTECTS THE BRAIN AND REGULATES HOMEOSTASIS:

- Acts as a unique, selective barrier and hinders the delivery of many potentially important therapeutic agents to the brain
- Comprised of tightly packed endothelial cells, absence of fenestra, transendothelial channels and pinocytic vesicles
- Expression of high levels of active efflux pumps (e.g., P-gp)
- Provides an insulated environment for stable neuronal function
- Presence of active transport systems for essential molecules

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 29-Oct-2009 (N=61)

Age (years)	
Median (Range)	51 (22-78)
Sex, n (%)	
Male	34 (56%)
WHO Tumor Grade, n (%)	
Grade II (Astrocytoma, Ependymoma)	2 (3%)
Grade III (Anaplastic Gliomas)	17 (28%)
Grade IV (GBM)	42 (69%)
No. of prior therapies, n (%)	
≤ 2	27 (44%)
3 – 5	24 (39.5%)
≥ 6	10 (16.5%)
Prior radiotherapy, n (%)	
Yes	59 (97%)
ECOG performance status score, n (%)	
0	20 (33%)
1	28 (46%)
2	13 (21%)

SAFETY RESULTS as of 29-Oct-2009

Dose (mg/m²)	< 300			300			420			550			650 MTD			700		
n	22			7			4			8			17			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	4	6		1	2
Febrile Neutropenia														1				
Leucopenia	1			1	2			2			4	2		7	3		2	1
Thrombocytopenia										1			2	1	1			
Anemia							2			2	1		3					
Peripheral Neuropathy	2						1			1	3		2	1		2		
Alopecia							1						3					
Myalgia/Arthralgia	1												2					
Mucositis										1			2	1			1	
Infusion Reactions	2			2			1			1			1	1		1		
Fatigue	3	1			1					2			2					
Nausea	1																	
Rash				1	1					1			3	1				

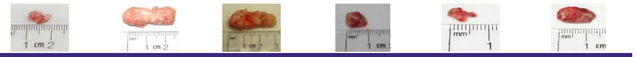
NB: Blank cells denote no observation

- **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	7.0 µM	23.0 µM	98.0 µM	238.2 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 placed in neurosphere culture conditions

PRELIMINARY EFFICACY RESULTS

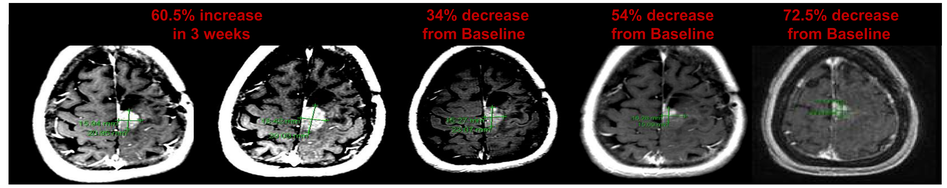
Dose	<300 mg/m²	≥300 mg/m²
Overall Best Response[1]	n=18	n=17
CR		
PR*		1
MR**	2	7
SD	3	3[2]
PD	13	6
% ≥SD	**28%**	**65%**

[1] Assessed using MacDonald criteria
[2] 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: -8.8%
650 mg/m²: -17.0%
700 mg/m²: -12.2%

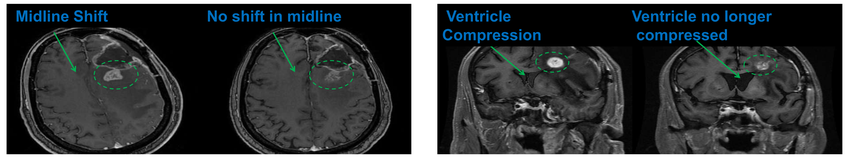
CASE STUDIES

- 49 y.o. female patient with ANAPLASTIC OLIGOASTROCYTOMA
- Standard prior therapy with progression after 1 year of temozolamide
- 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/m² 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
- Progression after standard prior therapy
- After 2 cycles of ANG1005 at 550 mg/m², 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

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.**