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ANG1005: Results of a phase I study in patients with recurrent malignant glioma

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Background: ANG1005, created from Angiochem's Engineered Peptide Compound (EPiC) platform, has a novel mode of action targeting the low-density lipoprotein receptor-related protein (LRP-1) which is highly expressed on the surface of the blood-brain barrier (BBB) and upregulated on malignant glioma cells to gain access to the brain compartment and entry into tumor cells.
Methods: Patients with recurrent malignant glioma, adequate organ function, ECOG ≤2 received ANG1005 by IV infusion q21d *without premedication*. Doses were escalated using a modified Fibonacci scheme in sequential cohorts of 1-6 patients each. Study objectives included characterizing safety, tolerability, PK, identifying the maximum tolerated dose (MTD) and obtaining preliminary evidence of efficacy. Tumor tissue extracted from patients undergoing debulking surgery following 1 dose of ANG1005 was analyzed to determine if measurable quantities of ANG1005 were present (Surgical Sub-study).
Results: 63 patients received ANG1005 at doses of 30-700 mg/m²; 18 at 650 mg/m², the identified MTD and recommended highest Phase II dose. Median age: 50, male: 57%, ≥3 prior therapies: 54%, WHO Grade 4: 68%, WHO Grade 3: 29%. The most common adverse events (≥Gr. 2, CTCAE v.3.0) were neutropenia (51%), leucopenia (46%) and fatigue (21%); events were transient and manageable with standard treatments. The dose-limiting toxicity was Gr. 3 mucositis. No evidence of CNS toxicity (measured by neurological and neurocognitive testing) or antibody production was found. PK data indicate linear ANG1005 bioavailability. and no accumulation after repeat dosing. Therapeutic concentrations of ANG1005 were found in tumor tissue extracted from patients (n=7) who had received ANG1005 prior to surgery. Additional analysis revealed that samples did *not* grow when placed in neurosphere culture conditions. Disease control (≥ SD by Macdonald criteria) was achieved in 17 out of 28 patients (61%) dosed ≥300 mg/m² including 1 patient who was progressing on bevacizumab therapy at the time of study entry, 2 complete responses and 2 partial responses. Median time to progression was 24 weeks in responders (≥ SD) and 6 weeks in all treated patients.
Conclusion: ANG1005 is safe and well tolerated and demonstrates encouraging activity in recurrent malignant glioma, a disease whose prognosis is currently dismal.

KEY FINDINGS:

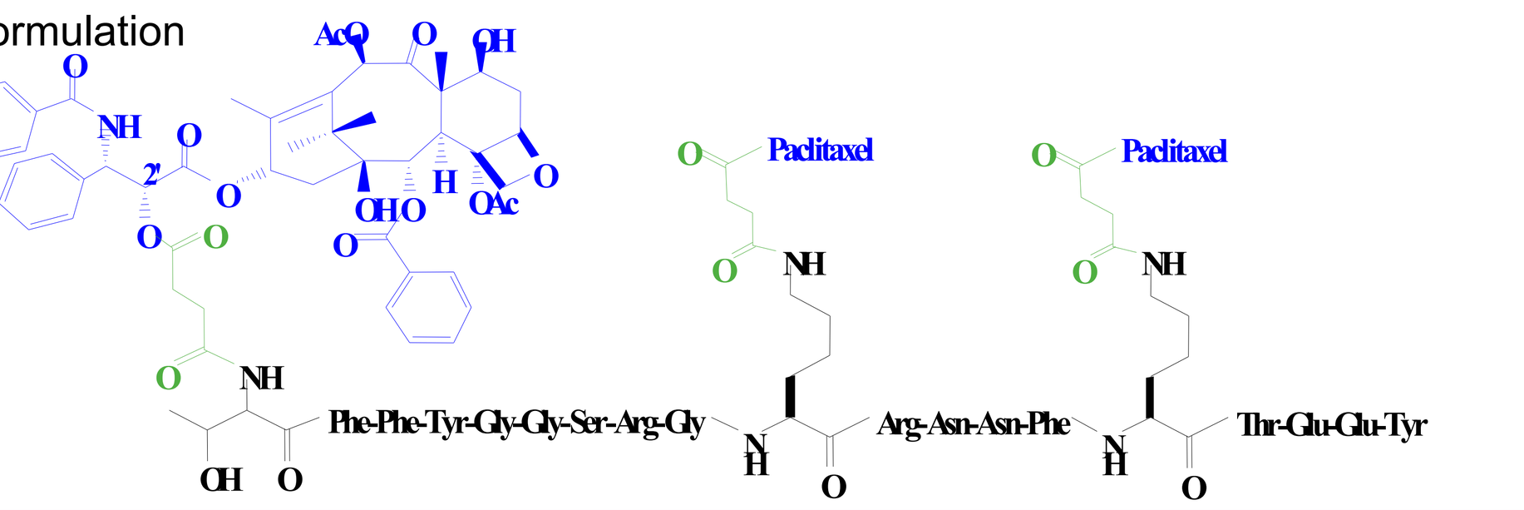
- **ANG1005 is safe and well tolerated; no evidence of CNS toxicity and/or immunogenicity**
- **Minimal systemic toxicity ; main side effect was bone marrow suppression which was transient and easily managed with standard hematopoietic support**
- **ANG1005 has a linear bioavailability; no evidence of accumulation after repeat dosing**
- **Therapeutic doses of ANG1005 were measured in GBM tumor tissue 4-6 hours after IV administration**
- **ANG1005 has a favorable prognostic effect on GBM tumors as demonstrated by a lack of growth when placed in neurosphere culture conditions**
- **Evidence of efficacy; disease control (≥SD) rate of 61% with 2 CR and 2 PR**
- **Several cases of marked increase in PFS, including 15+ months in a bevacizumab refractory patient**
- **At doses ≥ 300 mg/m², estimated median TTP in patients that achieved SD or better was 32 weeks (25 weeks longer than the median TTP in all patients)**
- **Final Phase I results support further development of ANG1005 and lend complementary clinical evidence to the EPiC platform**

INTRODUCTION

MALIGNANT GLIOMAS:
- ~18,000 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:
- First oncology product to use the LRP-1 (low-density lipoprotein receptor-related protein) mediated pathway
- Created using the Engineered Peptide Compound (EPiC) platform
- CROSSES THE BBB by targeting LRP-1, one of the most highly expressed receptors on the surface of the BBB
- Enters tumor cells through LRP-1 which is upregulated in various cancer cells including malignant glioma cells
- Cremophor-free formulation

ANG1005 (MW=5109)



METHODS

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

SECONDARY OBJECTIVES:
- Pharmacokinetics (PK)
- Immunogenicity
- Preliminary antitumor activity
- Measure ANG1005 in malignant glioma tumors (Surgical Sub-study)

STUDY DESIGN:
- Multi-center, 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 2 to 4) after standard first-line therapy and for which no other standard effective therapy is available

PATIENT CHARACTERISTICS (N=63)

Age (years)	
Median (Range)	50 (22-78)
Sex, n (%)	
Male	36 (57%)
WHO Tumor Grade, n (%)*	
Grade 2 (Astrocytoma)	1 (2%)
Grade 3 (Anaplastic Gliomas)	18 (29%)
Grade 4 (GBM)	43 (68%)
No. of Prior Therapies, n (%)	
≤ 2	29 (46%)
3 – 5	24 (38%)
≥ 6	10 (16%)
Prior Radiotherapy, n (%)	
Yes	62 (98%)
ECOG Performance Status Score, n (%)	
0	20 (32%)
1	29 (46%)
2	14 (22%)

* Pathology post-enrolment revealed that 1 patient had a Primitive Neural Ectodermal Tumor (PNET)

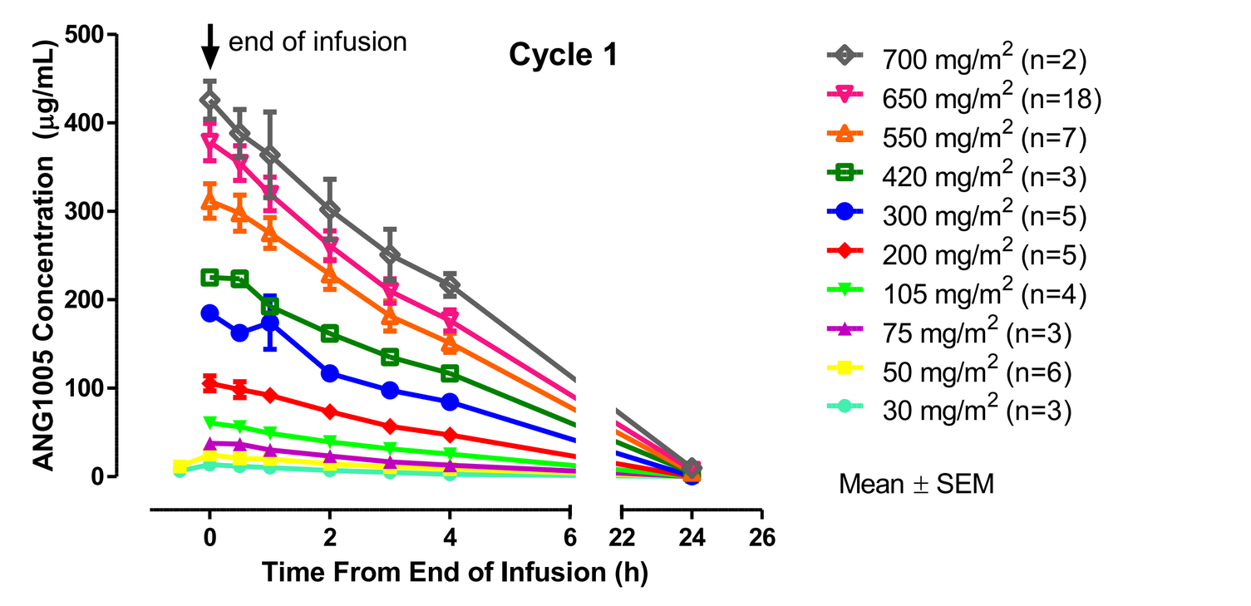
SAFETY RESULTS

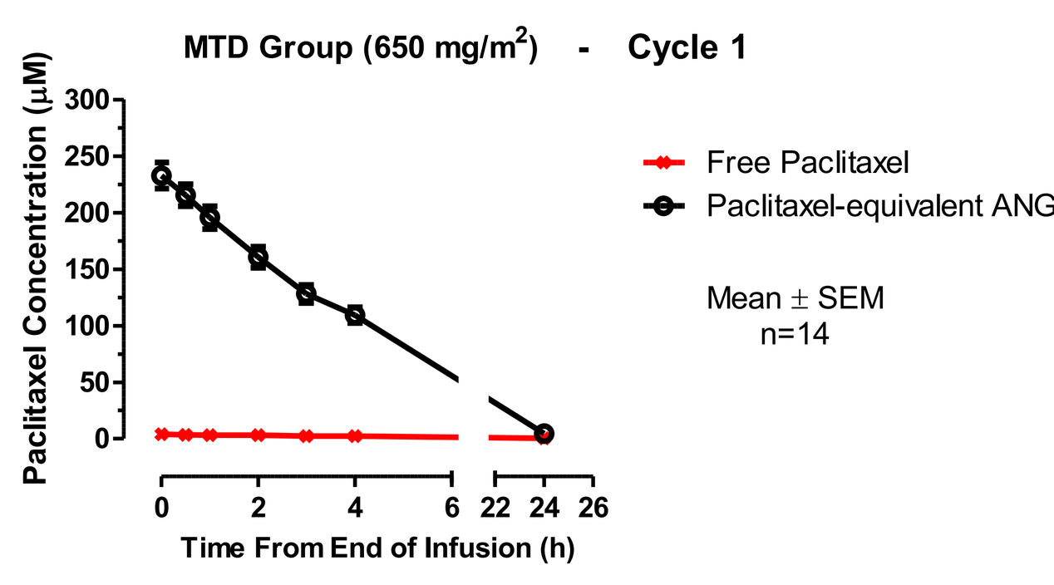
Summary of bone marrow and most commonly reported Grades 2-4 adverse events ≥ possibly related to ANG1005 regardless of baseline severity. The table lists the number of patients who experienced the event by most severe grade. Blank cells denote no observation.

Dose (mg/m²)	< 300			300			420			550			650 (MTD)			700		
n	22			7			4			9			18			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	10		1	2
Leucopenia	1			1	2			2			4	2	1	7	6		2	1
Anemia							2			2	1		7					
Thrombocytopenia										1			3	5	1			
Fatigue	2	1		1	1					2			6					
Peripheral Neuropathy							1	1		2	2		2	2		2		
Infusion Reaction	2			2			1			1				2		1		
Alopecia							1						4					
Mucositis										1			3				1	
Rash				1	1					1			2					

- **NO CNS TOXICITY** as assessed by neurocognitive testing and neurological examination
- **Stable to improved cognitive function** after 6 wks of therapy was observed in a patient with ANAPLASTIC OLIGOASTROCYTOMA
- **Marked improvement in verbal learning and memory** at 24 wks was observed in a patient with GBM
- **Dramatic improvement in left sided weakness and ambulation** 6-12 wks post-treatment in a patient with ANAPLASTIC OLIGOASTROCYTOMA
- **Improvement in aphasia** post-treatment in a patient with GBM
- **NO ANTIBODY PRODUCTION** even in patients who received multiple treatments and/or experienced infusion reactions and/or rashes

PHARMACOKINETIC RESULTS





PK Data at the MTD (650 mg/m²)

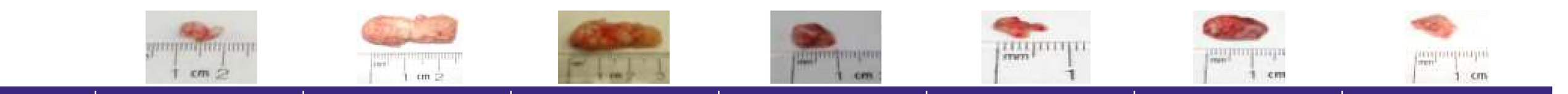
PARAMETER	C_{max} (ug/mL)	T_{max} (h)	AUC_{inf} (ug·h/mL)	half-life (h)	CL (mL/m²·h)	Vd (mL/m²)
Cycle 1 (n=18)	378	0.03	3198	4.12	230	1355

Summary:
- Linear bioavailability
- No accumulation
- Most plasma paclitaxel is associated with ANG1005 (≥92%)

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	#7
Dose Level	200 mg/m²	300 mg/m²	420 mg/m²	550 mg/m²	550 mg/m²	550 mg/m²	550 mg/m²
Extraction Time	~4.0h	~5.0h	~4.0h	~4.5h	~6.0h	~4.5h	~5.5h
Plasma ANG1005	34.3 µM	34.4 µM	53.5 µM	100.1 µM	56.5 µM	63.0 µM	81.0 µM
Tumor ANG1005	2.8 µM	9.4 µM	7.0 µM	23.0 µM	98.0 µM	238.2 µM	31.5 µM
[Tumor]:[Plasma]	**8.2%**	**27.3%**	**13.3%**	**23.0%**	**173%**	**379%**	**38.9%**

GBM TUMOR GROWTH
- **NO GROWTH** was observed after extracted tumor samples were placed in neurosphere culture conditions.

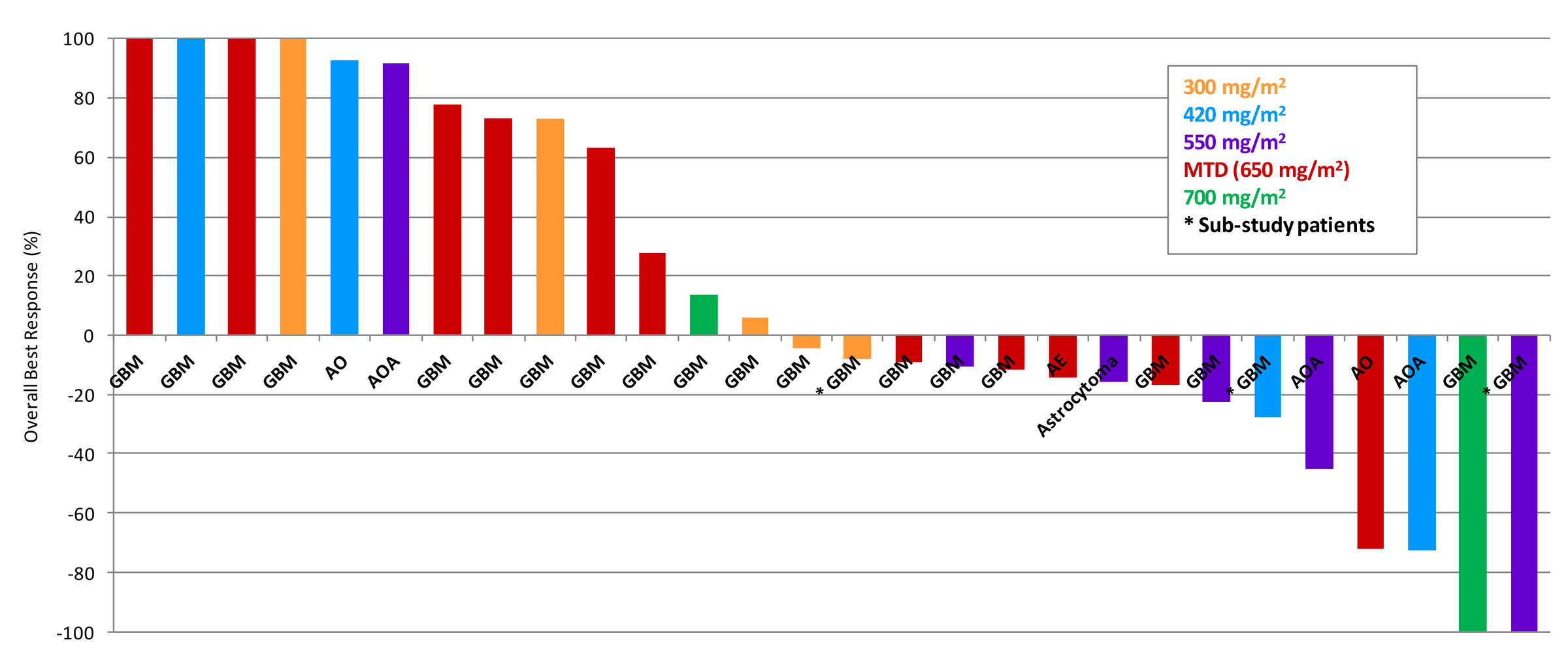
EFFICACY RESULTS

OVERALL BEST RESPONSE

Dose	≤ 200 mg/m²	≥ 300 mg/m²	Surgical Sub-study Patients[1]
Sample Size	n=18	n=25	n=3
Overall Best Response[2]			
CR		1	1
PR		2	
MR	2	9	2
SD	3	2	
PD	13	11	
% ≥ SD	**28%**	**56%**	**100%**
		61%	

[1] Surgical patients that had residual disease post-surgery, continued to receive ANG1005 and were evaluated for treatment response
[2] Assessed by Macdonald criteria

OVERALL BEST RESPONSE, DOSES ≥ 300 mg/m²



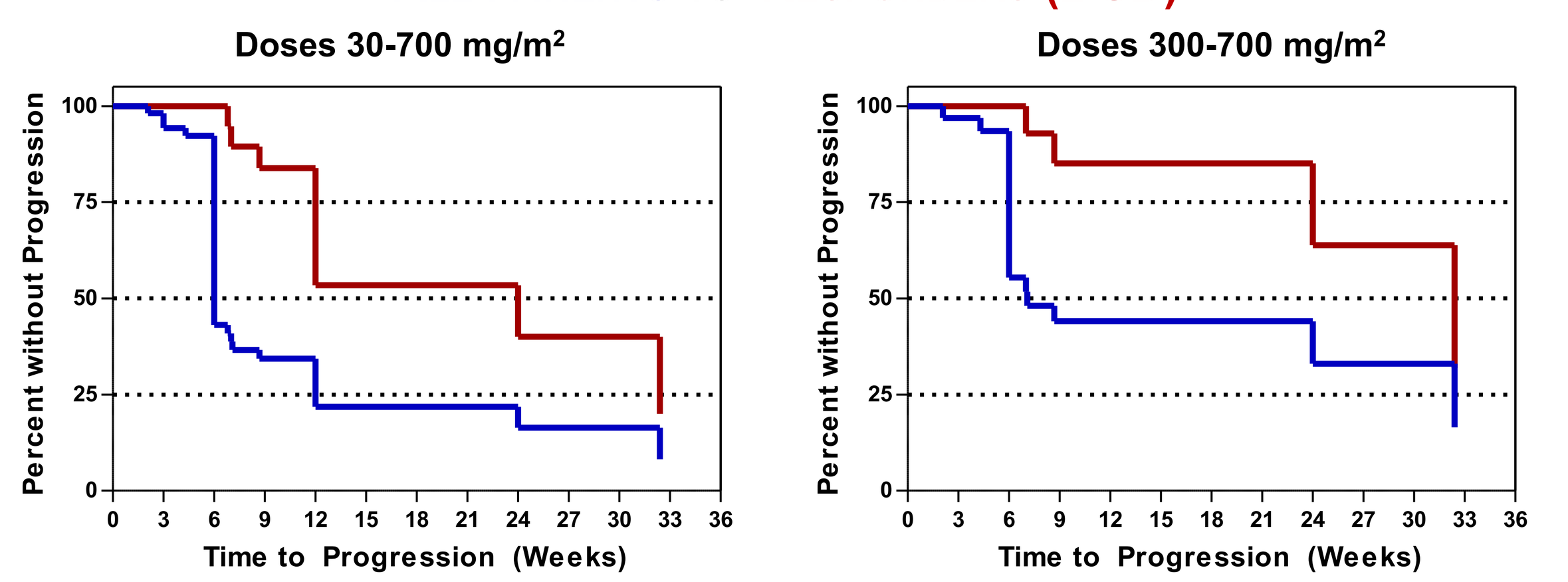
MEDIAN TIME TO PROGRESSION (TTP)

	Sample Size	Median TTP (Weeks)	95% CI (Lower)	95% CI (Upper)
All Patients, 30-700 mg/m²	54	6.0[1]	6.0	8.7
All Patients, 300-700 mg/m²	33	7.1[1]	6.0	32.4
All Responders[2], 30-700 mg/m²	19	24.0[1]	12.0	---
All Responders[2], 300-700 mg/m²	14	32.4[1]	24.0	---

95% CI = 95% Confidence Interval
[1] TTP was underestimated because the largest observation was censored and the estimation was restricted to the largest event time
[2] Patients that experienced stable disease or better on MRI

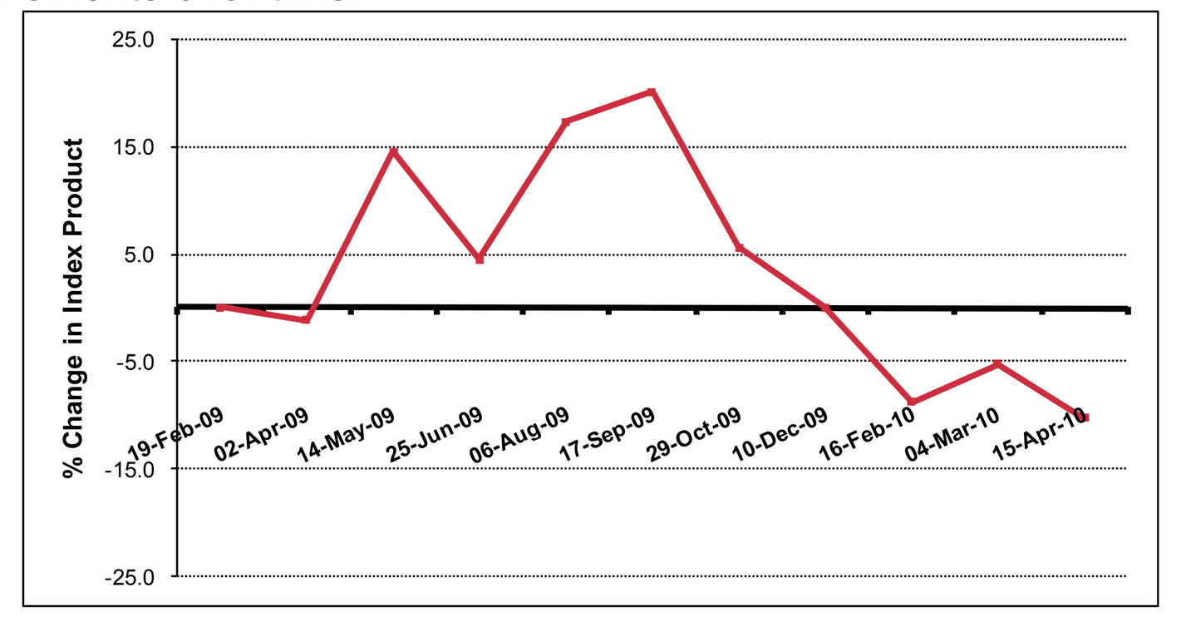
KAPLAN-MEIER CURVES OF TTP

ALL PATIENTS VS. RESPONDERS (≥ SD)

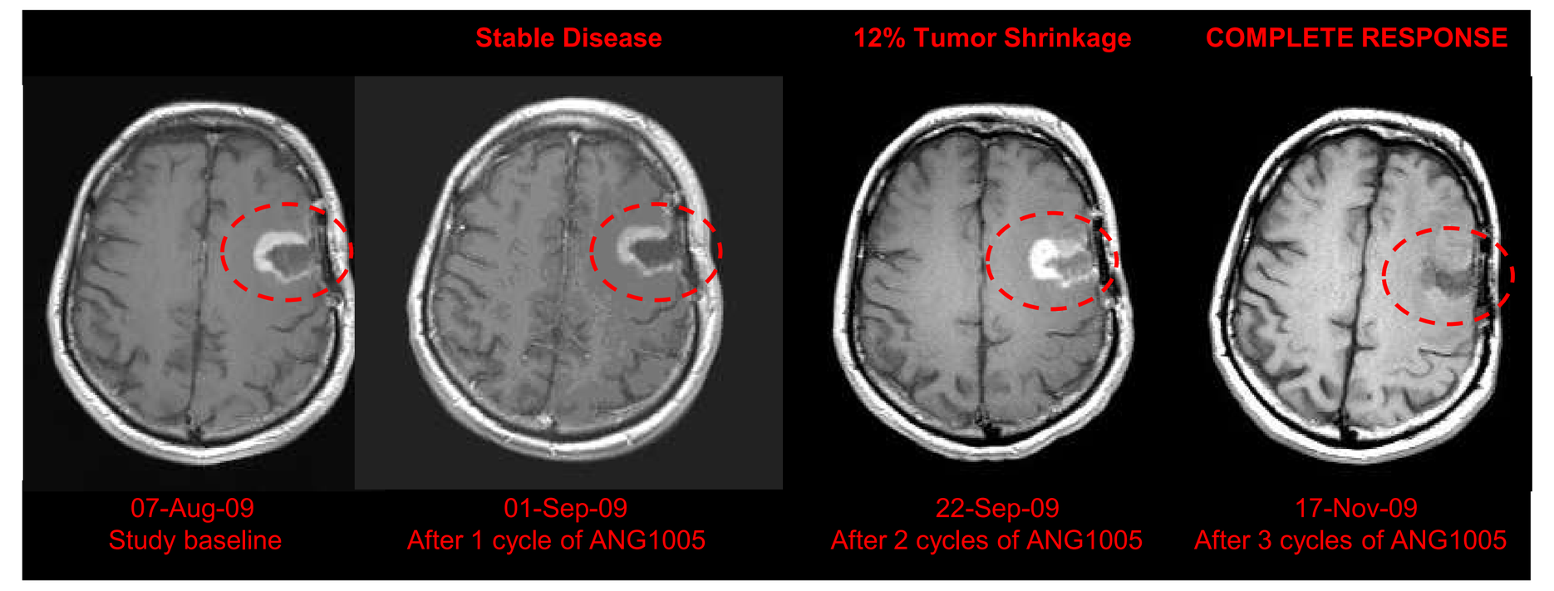


CASE STUDIES

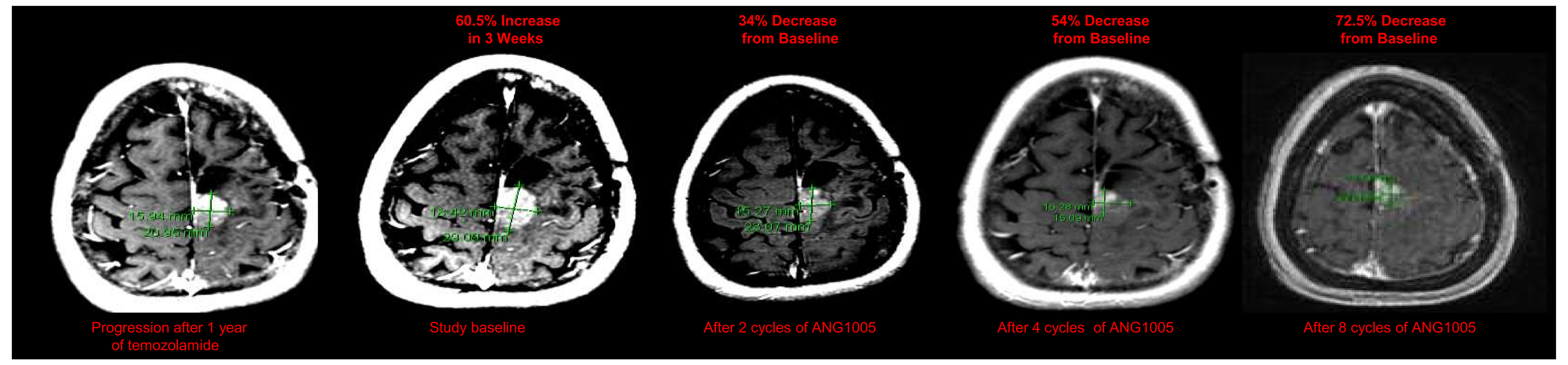
Bevacizumab Refractory Patient
- 51 y.o. male patient with GLIOBLASTOMA MULTIFORME
- 1 lesion in the body and genu of the corpus callosum
- Standard first-line therapy (May-07 – Jun-08), bevacizumab + CPT-11 (Jun-08 – 23-Dec-08)
- Received 6 cycles of ANG1005 at 300 mg/m² starting on 26-Feb-09 followed by 16 cycles at 550 mg/m²
- Currently ongoing in the study; PFS = 15+ months
- Tumor measurements over time:



Complete Response
- 65 y.o. male patient with GLIOBLASTOMA MULTIFORME
- Standard first-line therapy (27-Feb-09 – 01-May-09) with a second debulking surgery (16-Jul-09)
- Received 1 cycle of ANG1005 at 700 mg/m² on 11-Aug-09, 1 cycle at 650 mg/m² on 08-Sep-09 (↓ due to Gr. 4 neutropenia and leucopenia), 1 cycle at 550 mg/m² on 29-Sep-09 (↓ due to Gr. 4 neutropenia)



Partial Response
- 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/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



Complete Response (Surgical Sub-study Patient)
- 54 y.o. female patient with GLIOBLASTOMA MULTIFORME
- Standard first-line therapy (14-Oct-08 – 13-Apr-09), CDX-110 vaccine (08-Jan-09 – 30-Apr-09)
- First dose of ANG1005 at 550 mg/m² on 27-May-09 ~4.5 h prior to a second debulking surgery for recurrent disease
- Presence of residual disease post-surgery; continued to receive ANG1005
- Complete response after 10 post-surgical doses of ANG1005