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ANG1005: Results of a phase I study in patients with advanced solid tumors and brain metastases

John Sarantopoulos[1], Nashat Gabrail[2], Stacy Moulder[3], Andrew Brenner[1], Carrie Smith[2], Danielle Bouchard[4], Kelly Elian[4], Betty Lawrence[4], Wendy Churchill[4], Paula Bento[4], Dimitri Fitsialos[5], Ann Neale[6], Jean-Paul Castaigne[4], Razelle Kurzrock[3]

[1]Cancer Therapy and Research Center, San Antonio, Texas; [2]Gabrail Cancer Center, Canton, Ohio; [3]MD Anderson Cancer Center, Houston, Texas; [4]Angiochem Inc., Montreal, Québec, Canada; [5]Intrinsik Health Sciences Inc., Mississauga, Ontario, Canada; [6]WinPharm Associates, Danville, California.

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 various tumor cells to gain access to the brain compartment and entry into tumor cells.
Methods: Patients with advanced solid tumors, adequate organ function, ECOG ≤2 received ANG1005 by IV infusion q21d *without premedication*. Brain metastases were required at the maximum tolerated dose (MTD). 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 MTD and obtaining preliminary evidence of efficacy.
Results: 56 patients received ANG1005 at doses of 30-700 mg/m^2; 20 at 650 mg/m^2, the identified MTD and recommended highest Phase II dose. Median age: 54, male: 43%, ≥3 prior therapies: 73%. Most common adverse events (≥Gr. 2, CTCAE v.3.0) were leucopenia (73%), neutropenia (66%), anemia (48%), thrombocytopenia (27%) and fatigue (18%); events were transient and manageable. The dose-limiting toxicity was Grade 4 thrombocytopenia. No evidence of CNS toxicity or antibody production even in patients who received multiple doses. Only 4 patients experienced infusion related reactions and there was no significant peripheral neuropathy (5 Gr.2, 2 Gr.3). PK data indicate linear ANG1005 bioavailability and no accumulation after repeat dosing. At 650 mg/m^2, Cycle 1: C_{max} 306 ug/mL, AUC_{inf} 2571 ug·h/mL, $T_{1/2}$ 4.0 h, CL 285 mL/m^2·h. Plasma concentrations of free paclitaxel measured at MTD revealed that it accounted for only a small fraction (<8%) of total plasma exposure. Overall disease control (≥ SD by RECIST) was achieved in 71% of patients dosed ≥ 420mg/m^2 including 10 patients who failed prior taxane therapy. PR in 5 patients at MTD: 2 Breast, 2 NSCL, 1 Ovarian. Important reductions were also achieved in metastases located in organs including the brain, liver, lung and lymph nodes. Median time to progression was 18 weeks in responders (≥ SD) and 8 weeks in all patients.
Conclusion: ANG1005 is safe and well tolerated and demonstrates activity in advanced solid tumors and brain metastases, a disease for which there is currently no approved chemotherapy drug.

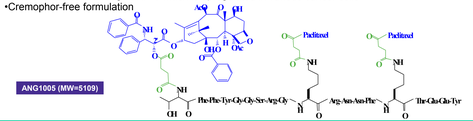
KEY FINDINGS:

- **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**
- **Evidence of efficacy; disease control (≥SD) rate of 71% with 5 overall PRs in this heavily pre-treated patient population**
- **Disease control in 83% of patients who failed prior taxane therapy**
- **Marked tumor reductions in metastatic disease locations including the brain, liver, lung and lymph nodes**
- **Estimated median TTP in patients that achieved SD or better was 18 weeks (10 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

Brain metastases:
- ~ 180,000 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:
- 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
- Cremophor-free formulation



METHODS

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

SECONDARY OBJECTIVES:
- Pharmacokinetics (PK)
- Immunogenicity
- Preliminary antitumor activity

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 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%)

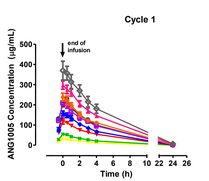
SAFETY RESULTS

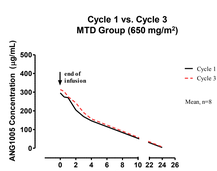
Summary of bone marrow and most commonly reported Grades 2-4 adverse events ≥ possibly related to ANG1005 regardless of baseline severity.
The table lists the number of patients who experienced the event by most severe grade.
Blank cells denote no observation.

Dose (mg/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
Leucopenia	4	2	1	2	2			1		2		1	1	11	8	1		5
Neutropenia	4		1	3	1		1			1		1	1	3	15	1		5
Anemia	4	1		1			4			2			8	3		2	1	1
Thrombocytopenia			1			1					1		3	5		1	1	2
Fatigue	1			1			1			1			3	2		1		
Alopecia				1			1						5					
Peripheral Neuropathy				1									4	1			1	
Dehydration		1											3	2				
Hypotension			1	3													1	

- **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 up to 11 treatment cycles

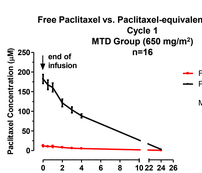
PHARMACOKINETIC RESULTS





PK Data at the MTD (650 mg/m^2)

PARAMETER	Cycle 1 (n=20)
C_{max} (ug/mL)	306
T_{max} (h)	0.33
AUC_{inf} (ug·h/mL)	2571
half-life (h)	4.00
CL (mL/m^2·h)	285
Vd (mL/m^2)	1666



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

EFFICACY RESULTS

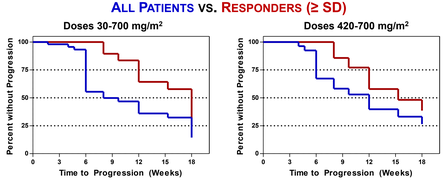
OVERALL BEST RESPONSE

Dose	≤300 mg/m^2	≥420 mg/m^2	Prior Taxane Failures[1]	MTD[2]	Primary Tumor Type: Breast Doses ≥420 mg/m^2	Primary Tumor Type: NSCLC Doses ≥420 mg/m^2
Overall Best Response[3]	n=12	n=21	n=12	n=12	n=7	n=4
CR						
PR		5	4	5	2	2
MR		6	5	2	3	2
SD	5	4	1	1	1	
PD	7	6	2	4	1	
% ≥SD	42%	71%	83%	67%	86%	100%

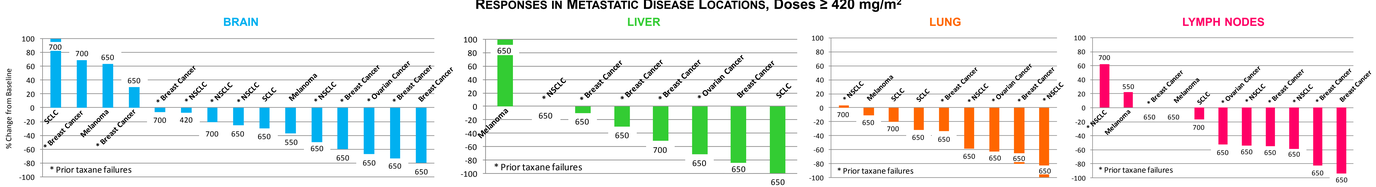
[1]12 of 21 patients dosed ≥420 mg/m^2 had previously progressed on taxane therapy
[2]Patients with brain metastases dosed at 650 mg/m^2
[3]Assessed by RECIST

KAPLAN-MEIER CURVES OF TIME TO PROGRESSION

ALL PATIENTS VS. RESPONDERS (≥ SD)

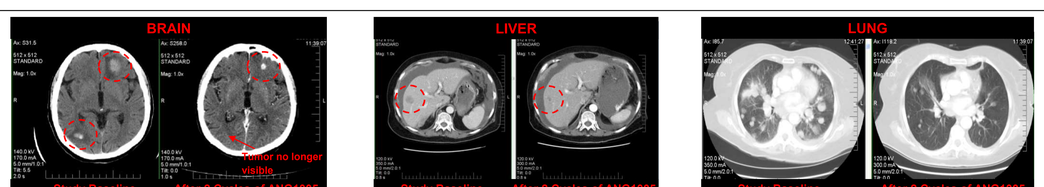


RESPONSES IN METASTATIC DISEASE LOCATIONS, Doses ≥ 420 mg/m^2



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



- 38 y.o. female patient with BREAST CANCER and BRAIN, BONE, LIVER AND LYMPH METASTASES
- Received 3 cycles of ANG1005 at 650 mg/m^2 followed by 5 cycles at 550 mg/m^2
- After 2 cycles of ANG1005, the OVERALL tumor response on CT showed 25% tumor shrinkage (45% reduction in the brain alone)
- After 4 cycles of ANG1005, the OVERALL tumor response on CT showed 38% tumor shrinkage (55% reduction in the brain alone)