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# ANG1005: A promising new Engineered Peptide Compound (EPiC) for patients with advanced solid tumors and brain metastases


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Introduction: Up to 200,000 patients with solid tumors develop brain metastases in the US annually and this incidence is expected to rise. Challenges to treatment stem from the inability of most drugs to cross the BBB in sufficient quantities without the limitation of systemic toxicity. Angiochem is developing a broad pipeline of new drugs uniquely capable of crossing the BBB to treat brain diseases. ANG1005, a novel, next-generation taxane, is the first from the Engineered Peptide Compounds (EPiC) platform to be developed clinically. 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 that ANG1005 also enters tumor cells via LRP, which is upregulated in various cancer cells including metastatic cancer cells.
Methods: As of 30-Sep-2009, 56 patients with advanced solid tumors/brain metastases have received ANG1005 by IV infusion at doses of 30-700 mg/m$^2$ every 21 days *without premedication*. Study objectives include characterizing the safety/tolerability of ANG1005, identifying the MTD, and obtaining preliminary PK, immunogenicity and antitumor information. Severity of AEs is assessed using CTCAE, v.3.
Results: 650 mg/m$^2$ has been identified as the MTD. Although neutropenia, leucopenia, thrombocytopenia and anemia have developed, these cases have been both milder than expected based on clinical observation with paclitaxel 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 than 6 treatment cycles. Pharmacokinetic data show a linear relationship between dose and bioavailability. Radiology data show evidence of efficacy in terms of tumor regression / slowing tumor progression, with 15 out of 21 patients evaluated at doses above 300 mg/m$^2$ experiencing stable disease or better after initiation of treatment. Furthermore, a marked improvement in memory, processing speed and executive function after 6, 12 and 24 weeks of therapy was observed in one patient who had a minor tumor response.
Conclusion: Data to date support the continued development of ANG1005 as a safe, tolerable and potentially efficacious treatment option for patients suffering from brain metastases.


## 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 previously progressed on prior taxane therapy.**
- **ANG1005: An active taxane derivative with a unique mechanism of action.**

## 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

## 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 30-Sep-2009

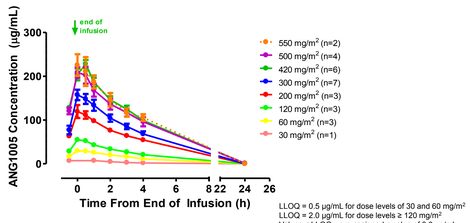
| Dose (mg/m$^2$) | ≤300 | | | 420 | | | 500 | | | 550 | | | 650 MTD | | | 700 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| n | 17* | | | 6 | | | 4* | | | 3 | | | 20 | | | 6 | | |
| CTCAE Grade | 2 | 3 | 4 | 2 | 3 | 4 | 2 | 3 | 4 | 2 | 3 | 4 | 2 | 3 | 4 | 2 | 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 | | | | | | | | 1 | 1 | | 1 | 1 | | | | |
| Alopecia | | | | 1 | | | 1 | | | | | | 4 | | | | | |
| Myalgia/Arthralgia | | | | | | | | | | | | | | | | | | |
| Mucositis | | 1 | | | | | | | | | | | 4 | 1 | | | 2 | 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

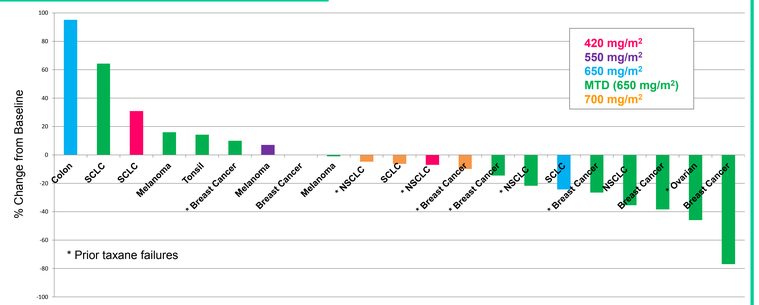
| Parameter | Value / Mean (as applicable) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Dose (mg/m$^2$) | 30 | 60 | 120 | 200 | 300 | 420 | 500 | 550 |
| n | 1 | 3 | 3 | 3 | 7 | 6 | 4 | 2 |
| $C_{max}$ (µg/mL) | 7.24 | 30.0 | 55.2 | 119 | 160 | 225 | 190 | 225 |
| $T_{max}$ (h) | 1.0 | 0.167 | 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**

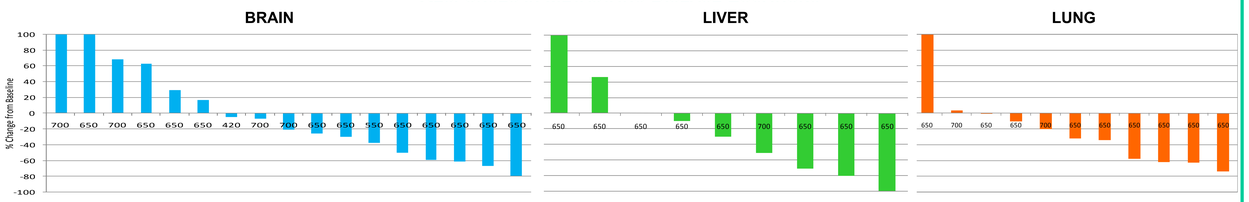
## PRELIMINARY EFFICACY RESULTS

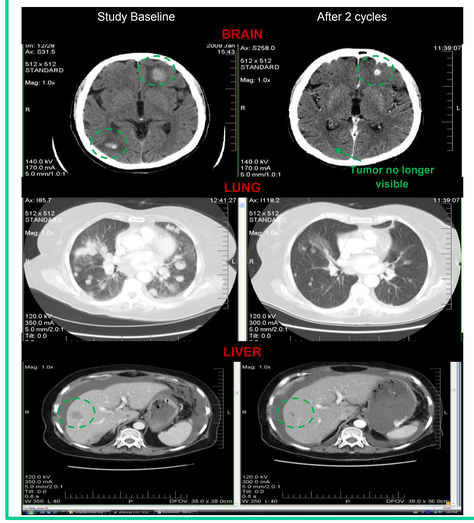
| Dose | ≤300 mg/m$^2$ | >300 mg/m$^2$ | Prior Taxane Failures* |
|---|---|---|---|
| Overall Response | n=12 | n=21 | n=9 |
| CR | | | |
| PR | | 7 | 3 |
| MR | | 4 | 4 |
| SD | 5 | 4 | |
| PD | 7 | 6 | 2 |
| % ≥SD | 42% | 71% | 78% |

*9 of 21 patients dosed >300 mg/m$^2$ had previously progressed on 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