ABSTRACT # B76/989

A Phase II study of ANG1005, a novel, brain-penetrant taxane derivative, in breast cancer patients with brain metastases

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Abstract

Background:
Treatment for brain metastases is an unmet medical need. ANG1005 consists of 3 paclitaxels covalently linked to a proprietary 19-AA peptide that targets LRP1, a receptor highly expressed on the surface of the BBB and on tumor cells. Preclinically, ANG1005 achieves significantly higher concentrations in the brain relative to free paclitaxel. Preliminary evidence of efficacy in humans was observed in the Phase I studies.

Methods:
ANG1005 was evaluated for activity to treat brain metastases from breast cancer patients (pts) with HER2- and HER2+ disease. The primary objective was to determine intracranial response. Secondary objectives included safety and tolerability, progression-free survival (PFS), duration of PFS and overall survival (OS). A Phase II, multi-center, open label, single-arm study with ANG1005 IV once every 3 weeks. The initial starting dose was 650 mg/m^2 (13 pts) but decreased to 550 mg/m^2 (67 pts) due to poor tolerance. An interim analysis on 30 pts by Geron Corp. (sponsor at that time) concluded that the futility point was reached. Recruitment was halted and ANG1005 returned to Angiochem Inc. (Cancer Res 2012; 72: Abstract P3-12-04). As a consequence, some pts were withdrawn from study. Nevertheless, several investigators continued treatment due to patient benefit. Here, we present the results from the complete intent-to-treat (ITT) data analyses including pts withdrawn prematurely.

Results:
At both dose levels, side effects were consistent with a taxane profile. At 650 mg/m^2, the most common adverse events (AEs) included neutropenia (69%), fatigue (31%), peripheral (sensory) neuropathy (15%), mucosal inflammation (8%), and leucopenia (8%). At 550 mg/m^2, the most common AEs included neutropenia (27%) with 2 (3%) cases of febrile neutropenia, peripheral (sensory) neuropathy (9%), anemia (6%), leucopenia (6%) and fatigue (5%). Percentages are given for incidences of AEs grade≥3.
At 650 mg/m^2, none of the pts with HER2- disease had intracranial partial response (PR). However, 3/5 (60%) pts had stable disease (SD). PFS rate at three months (PFS3) was 75%, median PFS was 7.9 months and OS at 6 months was 75% for this cohort. Clinical activity in the 650 mg/m^2 HER2+ cohort included 4/8 (50%) pts with PRs, 1/8 (13%) pt with SD, PFS3 of 71%, median PFS of 5.6 months and OS at 6 months of 86%.
At 550 mg/m^2, in the HER2- cohort, 5/39 (13%) pts had PRs and 14/39 (36%) pts had SD. PFS3 was 35%, median PFS was 2.8 and OS at 6 months was 60% in this cohort. Results for HER2+ cohort at 550 mg/m^2 included 5/28 (18%) pts with PRs, 17/28 (61%) pts with SD, PFS3 of 71%, median PFS of 4.2 months and OS at 6 months of 82%. One patient with HER2+ disease has received 14 cycles of ANG1005 at 550 mg/m^2 and is still on treatment.

Conclusion:
ANG1005 has shown evidence of clinical activity for the treatment of brain metastases in breast cancer patients and warrants further development.

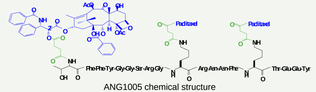
Background

Brain Metastases from Breast Cancer

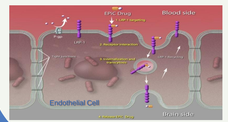
- Brain metastases are the most common tumors that appear in the brain in adults (~98,000 to 170,000 yearly in the US) (NCI Brain Tumor PDQ®)
- Brain metastases occur in 10-15% of advanced breast cancer patients overall, but in 30-50% of patients with HER-2-positive or triple-negative breast cancer (Lin and Winer, 2007)
- Treatment options are limited, especially once brain metastases recur:
  - Currently, no approved systemic treatments for brain metastases
  - The blood-brain barrier (BBB) represents a major obstacle for chemotherapeutic agents
  - Current standard of treatment for newly diagnosed brain metastases consists of WBRT and/or SRS

ANG1005

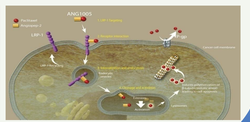
- First oncology product to use the LRP-1 (low density lipoprotein receptor-related protein-1) mediated pathway
- Crosses the BBB by targeting LRP-1, one of the most highly expressed receptors on the surface of the BBB
- Is not a substrate for the P-gp transporter and is therefore not effluxed out of the brain
- Gains entry into tumor cells through LRP-1, which is upregulated in various cancer cells, wherein the paclitaxel molecules are cleaved by intracellular esterases, rendering them active
- Free paclitaxel binds to tubulin, which leads to mitotic spindle dysfunction, followed by cell cycle arrest in G2/M, and eventual tumor cell death
- Cremophor-free formulation



ANG1005 chemical structure



Receptor-mediated transcytosis of ANG1005 across the endothelial cells at the BBB



Receptor-mediated endocytosis of ANG1005 into the tumor cells

Study Design

Multi-center, open label, single-arm study with 2 cohorts (HER2+ and HER2-)

Metastatic Breast Cancer with Brain Metastases

(N = 80 patients)

HER2-negative → ANG1005 IV q3w (N = 5 @ 650 mg/m^2) (N = 39 @ 550 mg/m^2)

HER2-positive → ANG1005 IV q3w + trastuzumab (N = 8 @ 650 mg/m^2) (N = 28 @ 550 mg/m^2)

- Primary Objective:
  - Intracranial response
- Secondary Objectives:
  - Safety and tolerability
  - Progression-free survival (PFS)
  - Duration of PFS
  - Overall survival (OS)
- ANG1005 Treatment
  - Intravenous infusion (~1 hour) every 3 weeks
  - Starting dose 650 mg/m^2 (13 pts) and 550 mg/m^2 (67 pts)
- Study Population
  - Adult breast cancer patients with measurable (≥ 1 cm) brain metastases, with or without prior surgical resection, WBRT, or SRS, and KPS ≥ 70

Interim Futility Analysis by Geron Corp. (Cancer Res 2012; 72: Abstract P3-12-04)

- Futility endpoint is met if none of the first 30 evaluable patients at the starting dose of 550 mg/m^2 achieve an intracranial objective response by Independent Radiology Facility.
- Cut-off date was 30 November 2012, intracranial objective response was defined as PR or CR (CNS RECIST Criteria).
- Evaluable patients were defined as having completed 2 post-baseline scans or having discontinued treatment for any reason prior to completing 2 post-baseline scans (not ITT).
- Futility decision was made based on scans collected from 12 HER2- and 8 HER2+ patients. Data was not available for the remaining 10/30 patients due to missing scans (8) or un-interpretable scans (2).
- As no PR or CR was observed in these 20 patients, Geron concluded that futility endpoint was met. Recruitment was halted and ANG1005 was returned to Angiochem Inc.
- Some patients were withdrawn from study; several investigators continued treatment due to patient benefit.

Complete Intent-To-Treat (ITT) Data Analysis by Angiochem Inc.

- Analysis using all data entered into eCRF at 650 mg/m^2 and 550 mg/m^2 (cut-off date 14 May 2013).
- All patients with post-baseline tumor assessments that have received ANG1005 (51 pts at 550 mg/m^2 and 10 pts at 650 mg/m^2).

Baseline Characteristics (N = 80)

	550 mg/m² HER2- (N=39)	550 mg/m² HER2+ (N=28)	650 mg/m² HER2- (N=5)	650 mg/m² HER2+ (N=8)
Age, Median (range)	53.1 (30-74)	50.0 (30-63)	56.4 (43-68)	49.1 (34-61)
Years since initial diagnosis of breast cancer, Median (range)	6.3 (0-19)	4.2 (1-13)	7.1 (1-14)	5.0 (1-8)
Years since initial diagnosis of brain mets, Median (range)	0.9 (0-4)	1.2 (0-3)	0.5 (0-2)	2.4 (0-4)
Triple negative, N (%)	16 (41%)	---	1 (20%)	---
Number of prior systemic therapies, median (range)[a]	6.0 (2-17)	6.0 (1-21)	4.0 (3-11)	5.5 (3-12)
Prior radiotherapy, N (%)	34 (87.2%)	26 (92.9%)	4 (80%)	8 (100%)
Prior taxane, N (%)	39 (100%)	24 (85.7%)	3 (60%)	8 (100%)
Prior anti-HER2 therapy, N (%)	1 (2.6%)	26 (92.9%)	0	8 (100%)
Prior peripheral neuropathy, N (%)	7 (17.9%)	3 (10.7%)	2 (40%)	3 (37.5%)

[a] Systemic therapy is defined as any chemotherapy (combination or single agent), hormonal therapy, biological therapy, myeloablative therapy (stem cell transplant or bone marrow), or other non-surgical therapy that is not solely radiation therapy.

Safety

- Toxicities were related to paclitaxel (neutropenia, peripheral neuropathy, fatigue, and mucosal inflammation) and were similar in frequency and severity to paclitaxel
- Neutropenia was the most frequent hematological event
- Peripheral (sensory) neuropathy was the most frequent neurological event

Key AEs Associated to ANG1005

Adverse Events Related to ANG1005	550 mg/m² HER2- (N=39)		550 mg/m² HER2+ (N=28)		650 mg/m² HER2- (N=5)		650 mg/m² HER2+ (N=8)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hematological								
Neutropenia	9 (23.1%)	9 (23.1%)	10 (35.7%)	9 (32.1%)	3 (60.0%)	2 (40%	8 (100.0%)	7 (87.5%)
Leukopenia	1 (2.6%)	1 (2.6%)	3 (10.7%)	3 (10.7%)	1 (20.0%)	0	6 (7.5%)	1 (12.5)
Anemia	6 (15.4%)	1 (2.6%	6 (21.4%)	3 (10.7%)	1 (20.0%)	0	3 (37.5%)	0
Febrile Neutropenia	0	0	2 (7.1%)	2 (7.1%)	0	0	0	0
Thrombocytopenia	1 (2.6%)	0	4 (14.3%)	1 (3.6%)	0	0	3 (37.5%)	0
Neurologic								
Headache	4 (10.3%)	0	1 (3.6%)	0	1 (20%)	1 (20%)	1 (12.5%)	0
Peripheral (sensory) neuropathy	20 (51.3%)	3 (7.7)	13 (46.4%)	3 (10.7%)	3 (60%)	1 (20%)	6 (75%)	1 (12.5%)
General/Others								
Nausea	13 (33.3%)	1 (2.6%)	11 (39.3%)	0	0	0	1 (12.5%)	0
Arthralgia	2 (5.1%)	0	3 (10.7%)	0	1 (20%)	1 (20%)	3 (37.5%)	2 (25%)
Mucosal inflammation	7 (17.9%)	0	4 (14.3%)	1 (3.6%)	1 (20%)	0	4 (50%)	1 (12.5%)
Rash	4 (10.3%)	1 (2.6%)	9 (32.1%)	1 (3.6%)	0	0	2 (25%)	0
Fatigue	18 (46.2%)	2 (5.1%)	16 (57.1%)	1 (3.6%)	2 (40%)	2 (40%)	7 (87.5%)	2 (25%)
Myalgia	5 (12.8%)	0	3 (10.7%)	0	2 (40%)	0	2 (25%)	0

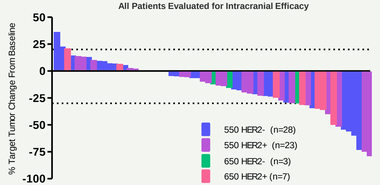
Efficacy

Best Intracranial Response
Investigator's Measurements (ITT)

Outcome by CNS RECIST	550 mg/m² HER2- (n=39)	550 mg/m² HER2+ (n=28)	650 mg/m² HER2- (n=5)	650 mg/m² HER2+ (n=8)
PR / Confirmed	5 (12.8%) 3 (7.7%)	5 (17.9%) 2 (7.1%)	0	4 (50%) 3 (37.5%)
SD	14 (35.9%)	17 (60.7%)	3 (60%)	1 (12.5%)
PD	9 (23.1%)	1 (3.6%)	0	2 (25%)
Missing*	11 (28.2%)	5 (17.9%)	2 (40%)	1 (12.5%)
PFS rate at 3 mos	35.0%	71.3%	75.0%	71.4%
Median PFS	84 days	128 days	240 days	171 days
OS rate at 6 mos	59.6%	81.8%	75.0%	85.7%

* Patients without tumor assessments ≥5 weeks from 1st treatment

All Patients Evaluated for Intracranial Efficacy

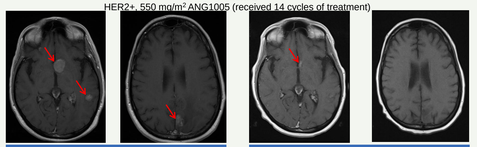


Best Extracranial Response*
Investigator's Measurements (ITT)

Outcome by RECIST	550mg/m² HER2- (n=16)	550 mg/m² HER2+ (n=12)	650 mg/m² HER2- (n=3)	650 mg/m² HER2+ (n=1)
PR	3 (19%)	3 (25%)	1 (33%)	0
SD	7 (44%)	9 (75%)	2 (67%)	0
PD	6 (37%)	0	0	1 (100%)

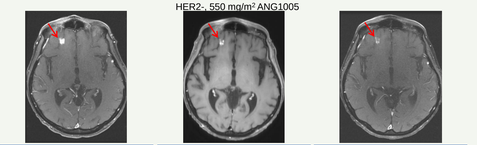
* Includes only patients with measureable extracranial disease

Patient 1
HER2+, 550 mg/m^2 ANG1005 (received 14 cycles of treatment)


Baseline
3 lesions: left caudate, left temporal lobe & left subinsaler cortex

Week 24
79% ↓ in tumor size
After 8 cycles of ANG1005
Out of the 3 lesions, only 1 lesion seen (left caudate)

Patient 2
HER2-, 550 mg/m^2 ANG1005

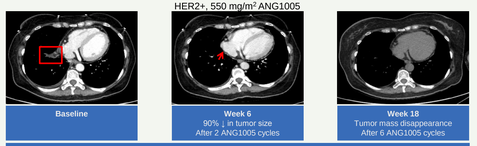

Baseline

Week 6
44% ↓ in tumor size
After 2 ANG1005 cycles

Week 12
56% ↓ in tumor size
After 4 ANG1005 cycles

PR for extracranial disease (32% ↓ in the sum of 3 lymph node lesions)

Patient 3
HER2+, 550 mg/m^2 ANG1005


Baseline

Week 6
90% ↓ in tumor size
After 2 ANG1005 cycles

Week 18
Tumor mass disappearance
After 6 ANG1005 cycles

SD for intracranial disease

Conclusions

- ANG1005 had a measurable anti-cancer effect against brain metastases in heavily pre-treated populations of metastatic breast cancer patients, including those treated with prior taxane therapies.
- ANG1005 also demonstrated efficacy on extracranial tumors.
- Further studies on the potential of ANG1005 as a therapy for metastatic brain tumors arising from breast and other cancers are warranted.

Acknowledgements

All of the patients, caregivers and staff who have participated in this study.

Nancy Lin – Dana-Farber Cancer Institute
Susan Minton - Moffitt Cancer Center
Kathy Miller – Indiana University
Ding Wang – Henry Ford Hospital
Jeff Raizer – Northwestern University
Denise Yardley - Tennessee Oncology
Paula Silverman - University Hospitals of Cleveland
Mark Kozloff - Ingalls Memorial Hospital
Sunil Verma - Sunnybrook Research Institute
Alberto Montero - University of Miami
Nuhad Ibrahim - MD Anderson Cancer Center
Claudine Isaacs - Georgetown University
Debasish Tripathy - University of Southern California
Larry Panasci - McGill University
Steve Weiss - Northwest Oncology & Hematology Associates
Anthony Elias - University of Colorado at Denver
Pia Herbolsheimer - Washington Cancer Institute
Carey Anders - University of North Carolina
Lee Schwartzberg - The West Clinic
Susan Bates - National Cancer Institute
Shaker Dakhil - Cancer Center of Kansas
Petros Nikolinakos - Northeast Georgia Cancer Care
Santosh Kesari – University of California in San Diego
Kurt Jaeckle - Mayo Clinic
William Read - Emory University
George Somlo - City of Hope
Ted Vandenberg - London Regional Cancer Center
Timothy Moynihan - Mayo Clinic
Bichlien Nguyen - Memorial Care Todd Cancer Institute
Jan Drappatz – University of Pittsburg
Andrew Brenner - University of Texas Health Science Center
J. Paul Duic - Neurological Surgery P.C.
Peter Rubin - Cone Health Cancer Center
Mary Helen Hackney – Virginia Commonwealth University

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October 2013