Evaluation of CNS and peripheral anti-tumor activity of ANG1005 in patients with brain metastases from breast tumors and other advanced solid tumors

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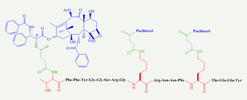
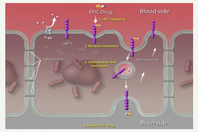
Background

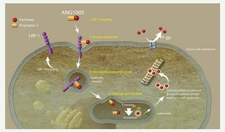
- ANG1005 is a novel, targeted taxane derivative leveraging the LRP-1 pathway to cross the BBB
- Unlike paclitaxel, ANG1005 is not a P-gp substrate and bypasses MDR efflux pump
- Gains entry into tumor cells through LRP-1 expressed on cancer cells
- In the cancer cells, paclitaxel molecules are released by intracellular esterases
- Free paclitaxel binds to tubulin, which leads to mitotic spindle dysfunction, followed by cell cycle arrest in G2/M, and eventual tumor cell death



ANG1005



ANG1005 leverages the LRP-1 pathway to cross the BBB



ANG1005 gains entry into the tumor cells through the LRP-1

Methods

Phase I: Solid tumor with progressive brain metastases (ANG1005-CLN-02)

- Multi-center, open-label, single arm study with escalating doses (30 to 700 mg/m^2)
- ANG1005 IV once every 21 days
- **56 patients dosed (39 patients at ≥ 420 mg/m^2)**

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

SECONDARY OBJECTIVES
- Pharmacokinetics
- Obtain preliminary anti-tumor activity (RECIST v1.0 and uni-dimensional measurements)

Baseline Characteristics (patients at ≥ 420 mg/m^2, n=39)

	420 mg/m^2 (N=6)	500 mg/m^2 (N=4)	550 mg/m^2 (N=3)	650 mg/m^2 (N=20)	700 mg/m^2 (N=6)
AGE, MEDIAN (RANGE)	55.4 (41-68)	50.2 (23-62)	56.9 (38-76)	55.3 (36-73)	49.6 (28-81)
PRIMARY CANCER, N (%)					
Breast	1 (16.7%)	0	0	6 (30.0%)	3 (50.0%)
Melanoma	2 (33.3%)	2 (50.0%)	2 (66.7%)	2 (10.0%)	0
NSCLC	1 (16.7%)	1 (25.0%)	0	4 (20.0%)	1 (16.7%)
SCLC	1 (16.7%)	0	0	5 (25.0%)	1 (16.7%)
Head/Neck	0	1 (25.0%)	1 (33.3%)	1 (5.0%)	1 (16.7%)
Colon	1 (16.7%)	0	0	1 (5.0%)	0
Ovarian	0	0	0	1 (5.0%)	0
PRIOR RADIOTHERAPY, N (%)	0	0	0	1 (5.0%)	2 (33.3%)
PRIOR TAXANE, N (%)	4 (66.7%)	1 (25.0%)	1 (33.3%)	14 (70.0%)	5 (83.3%)
PRIOR CHEMOTHERAPY, N (%)	6 (100.0%)	4 (100.0%)	3 (100.0%)	18 (90.0%)	6 (100.0%)

Phase II: HER2 +/- breast cancer patients with brain metastases (CP1005B016)

- Multi-center, open-label, single arm study with two cohorts (HER2+ and HER2-)
- ANG1005 IV once every 21 days
- **80 patients dosed (67 patients at 550 mg/m^2 and 13 patients at 650 mg/m^2)**

PRIMARY OBJECTIVES
- Intracranial tumor response (CNS RECIST v1.1)

SECONDARY OBJECTIVES
- Extracranial tumor response (RECIST v1.1)
- Duration of intracranial and extracranial tumor response
- Safety and tolerability

Baseline Characteristics (n=80)

	550 mg/m^2 HER2- (N=39)	550 mg/m^2 HER2+ (N=28)	650 mg/m^2 HER2- (N=5)	650 mg/m^2 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%)	
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%)

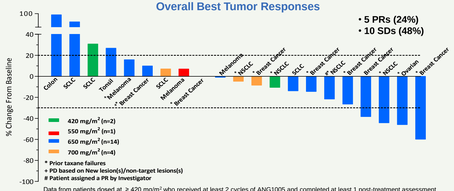
Interim futility analysis by Geron Corporation (Cancer Res 2012; 72: Abstract P3-12-04)
- Futility endpoint is met if 0/30 evaluable patients at 550 mg/m^2 achieve a PR or CR by IRF.
- Futility decision was made based on scans from 12 HER2- and 8 HER2+ patients. Data was not available for 10/30 patients due to missing (8) or un-interpretable scans (2).
- As no PR or CR was observed in these 20 patients, Geron concluded that futility endpoint was met. Further recruitment was halted but 80 patients were already enrolled.
- Some patients were withdrawn from study; however, several investigators continued treatment due to patient benefit.
- **Complete Intent-To-Treat (ITT) data analysis on the 80 patients was performed by Angiochem Inc. (AACR-NCI-EORTC 2013; Abstract B76/989)**

Anti-Tumor Activity

Study	Ph I: Solid tumors with brain metastases (ANG1005-CLN-02)		Ph II: Breast cancer with brain metastases (CP1005B016)			
Dose Level	≥ 420 mg/m^2		550 mg/m^2		650 mg/m^2	
Best Response	CNS (n=18)	Peripheral (n=16)	CNS (n=51)	Peripheral (n=28)	CNS (n=10)	Peripheral (n=4)
CR	0	0	0	1 (4%)	0	0
PR	4 (22%)	4 (25%)	11 (22%)	7 (25%)	4 (40%)	1 (25%)
SD	10 (56%)	7 (44%)	30 (59%)	14 (50%)	4 (40%)	2 (50%)
PD	4 (22%)	5 (31%)	10 (20%)	6 (21%)	2 (20%)	1 (25%)

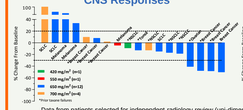
Phase I: Solid tumor with progressive brain metastases (ANG1005-CLN-02)

Overall Best Tumor Responses

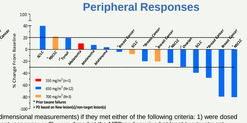


Data from patients dosed at ≥ 420 mg/m^2 who received at least 2 cycles of ANG1005 and completed at least 1 post-treatment assessment at ≥ 6 weeks from 1st treatment; assessed by investigator per RECIST v1.0.

CNS Responses

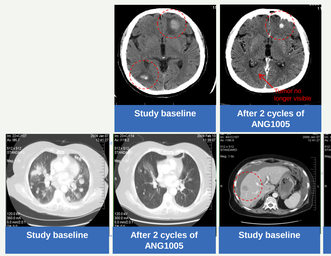


Peripheral Responses



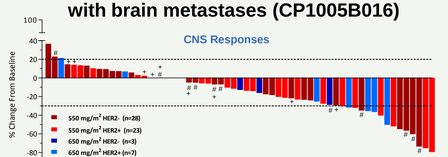
Data from patients selected for independent radiology review (uni-dimensional measurements) if they met either of the following criteria: 1) were dosed with ANG1005 at ≥ 420 mg/m^2 and demonstrated an overall treatment response; or 2) were dosed at the MTD and received at least two treatment cycles, independent of response.

Case study #1: 73 y.o. female with metastases originating from taxane-resistant ovarian cancer



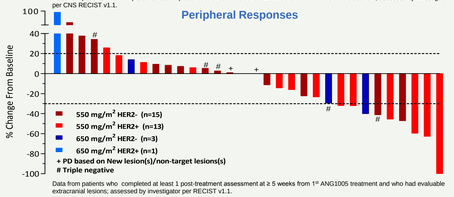
Phase II: HER2 +/- breast cancer patients with brain metastases (CP1005B016)

CNS Responses



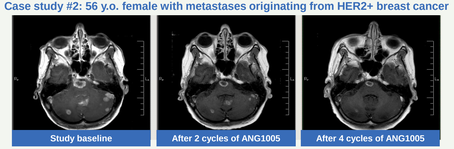
Data from patients who completed at least 1 post-treatment assessment at ≥ 5 weeks from 1st ANG1005 treatment; assessed by investigator per CNS RECIST v1.1.

Peripheral Responses

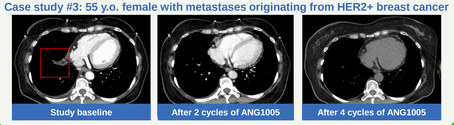


Data from patients who completed at least 1 post-treatment assessment at ≥ 5 weeks from 1st ANG1005 treatment and who had evaluable extracranial lesions; assessed by investigator per RECIST v1.1.

Case study #2: 56 y.o. female with metastases originating from HER2+ breast cancer



Case study #3: 55 y.o. female with metastases originating from HER2+ breast cancer



Safety Results

- Safety and tolerability of ANG1005 consistent with a taxane profile
- ANG1005 did not elicit any antibody production
- There was no evidence of cognitive impairment post-ANG1005 treatment
- Withdrawals due to AEs:
  - 8/39 (20.5%) patients in Ph I and 12/80 (15%) patients in Ph II
  - Most common AEs leading to withdrawal: peripheral neuropathy and fatigue

Key AEs associated with ANG1005

Adverse Events Associated with ANG1005	Ph I: Solid tumors with brain metastases (ANG1005-CLN-02)		Ph II: Breast cancer with brain metastases (CP1005B016)			
	≥ 420 mg/m^2 (n=39)		550 mg/m^2 (n=67)		650 mg/m^2 (n=13)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Hematological						
Neutropenia	24 (61.5%)	19 (48.7%)	19 (28.4%)	18 (26.9%)	11 (84.6%)	9 (69.2%)
Leukopenia	11 (28.2%)	5 (12.8%)	4 (6.0%)	4 (6.0%)	7 (53.9%)	1 (7.7%)
Anemia	19 (48.7%)	6 (15.4%)	12 (17.9%)	4 (6.0%)	4 (30.8%)	0
Thrombocytopenia	10 (25.6%)	5 (12.8%)	5 (7.5%)	1 (1.5%)	3 (23.1%)	0
Neurologic						
Peripheral neuropathy	11 (28.2%)	2 (5.1%)	21 (31.3%)	3 (4.5%)	7 (53.8%)	1 (7.7%)
Gastrointestinal						
Vomiting	6 (15.4%)	2 (5.1%)	10 (14.9%)	1 (1.5%)	3 (23.1%)	0
Nausea	9 (23.1%)	2 (5.1%)	24 (35.8%)	1 (1.5%)	1 (7.7%)	0
Diarrhea	11 (28.2%)	1 (2.6%)	14 (20.9%)	1 (1.5%)	6 (46.2%)	0
General/Others						
Arthralgia	7 (17.9%)	0	5 (7.5%)	0	4 (30.8%)	3 (23.1%)
Mucosal inflammation	8 (20.5%)	1 (2.6%)	11 (16.4%)	1 (1.5%)	5 (38.5%)	1 (7.7%)
Fatigue	13 (33.3%)	4 (10.3%)	34 (50.7%)	3 (4.5%)	9 (69.2%)	4 (30.1%)

Conclusions

- **ANG1005 demonstrated CNS anti-tumor activity**
- **ANG1005 also demonstrated peripheral anti-tumor activity, providing additional patient benefit**

Acknowledgements

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