GRN1005 PHASE I STUDIES
FINAL RESULTS

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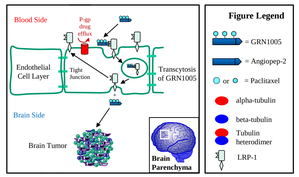
Introduction

- GRN1005 (formerly ANG1005) is a peptide-drug conjugate (PDC) that is being developed for the targeted treatment of metastatic and primary brain cancers.
- GRN1005 consists of 3 molecules of paclitaxel covalently linked to a proprietary 19-amino acid peptide (Angiopep-2) that targets the low-density lipoprotein receptor-related protein 1 (LRP-1), which is highly expressed on the blood-brain barrier (BBB) [1] and on the cells of various tumor types [2-3]. LRP-1 is a transporter [4] as well as a cancer cell signaling protein [5].
- Paclitaxel has proven efficacy against various tumors; however, its use to treat brain tumors has been hampered by its inability to cross the BBB and to reach the tumor cells at therapeutic levels [6,7].

Mechanism of Action of GRN1005

- GRN1005 has been shown to cross the BBB via LRP-1 mediated transcytosis (Figure 1-A).
- GRN1005 is not a substrate for the P-gp efflux transporter and is therefore not effluxed out of the brain like free paclitaxel.
- Once in the brain, GRN1005 gains entry into tumor cells via LRP-1 mediated endocytosis (Figure 1-B).
- GRN1005 is a prodrug that becomes activated in the tumor cell after the conjugated paclitaxel is cleaved by esterases from the Angiopep-2 backbone, to release active paclitaxel leading to a G2/M arrest and eventual tumor cell death.



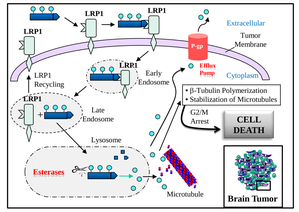


Figure 1. (A) Transcytosis through the blood brain barrier; (B) Uptake into a tumor cell via endocytosis

Methods

ANG1005-CLN-01 Study [8] (Malignant Glioma)

Purpose	Investigate GRN1005 as therapy for patients with malignant glioma
Patients	Adult patients with recurrent or progressive malignant glioma (WHO Grades II to IV) after standard surgical, radiation, and/or chemotherapy treatment; ECOG PS ≤2

ANG1005-CLN-02 Study [9] (Solid Tumor and Brain Metastases)

Purpose	Investigate GRN1005 as therapy for patients with brain metastases
Patients	Adult patients with progressing advance-stage solid tumors and brain metastases; ECOG PS ≤ 2

Both Studies

Design	Multi-center, sequential cohort, open-label study using a dose-escalation design
Treatment	GRN1005: IV infusion once every 21 days (1 cycle) Dose-Escalation (30-700mg/m²)
Endpoints	Primary- Safety, tolerability, and Maximum tolerated Dose (MTD) Secondary - Pharmacokinetics (PK), Immunogenicity, preliminary antitumor activity

ANG1005-CLN-01 [8] (Malignant Glioma Sub-Study)

Purpose	To gather clinical evidence that GRN1005 crosses the BBB and enters tumor
Design	Prospectively collect tumor samples from patients scheduled for debulking surgery 4-6 hours following receipt of GRN1005
Endpoint	GRN1005 concentration in glioma tumor tissue

Baseline Characteristics

Table 1. Patient Characteristics

ANG1005-CLN-02 (Solid Tumor and Brain Metastases)

Age, Years	
Median (Range)	54 (23-81)
Sex, n (%)	
Male	24 (42.9)
Primary Tumor Site, n (%)	
Breast	15 (26.8)[1]
Skin (Melanoma)	13 (23.2)
Lung (NSCLC)	8 (14.3)
Lung (SCLC)	8 (14.3)
Head and Neck	7 (12.5)
Other	6 (10.7)
With Brain Metastases, n(%)	
Yes	40 (71)
No. of Prior Onco-Drug Therapies, n (%)	
≤ 2	15 (26.8)
3	9 (16.1)
4	10 (17.9)
5	4 (7.1)
≥ 6	18 (32.1)
Prior Taxane (Paclitaxel, Docetaxel, Nab-Paclitaxel), n (%)	
Yes	34 (60.7)
Prior Radiotherapy, n (%)	
Prior WBRT	23 (41.1)
Prior SRS	20 (35.7)
Prior WBRT & SRS	12 (21.4)
ECOG Performance Status Score, n (%)	
0	12 (21.4)
1	35 (62.5)
2	9 (16.1)

[1] one patient had both Breast and Colon cancer

Table 2. Number of Patients in Each Dose Cohort (420 mg/m² or above) in Each Study

ANG1005-CLN-01

Dose (mg/m²)	420	550	650	700
n	4	9	18	3

ANG1005-CLN-02

Dose (mg/m²)	420	500	550	650	700
n	6	4	3	20	6

ANG1005-CLN-01 (Malignant Glioma)

Age, Years	
Median (Range)	50 (22-78)
Sex (%)	
Male	36 (57)
WHO Tumor Grade, n (%)	
Grade 2 (astrocytoma, ependymoma)	2 (3)
Grade 3 (anaplastic gliomas)	18 (29)
Grade 4 (GBM)	43 (68)
No. of Prior Onco-Drug 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)

Pharmacokinetics

Table 4. Free Paclitaxel vs. GRN1005 Pharmacokinetic Parameters at Cycle 1 and 650 mg/m²

	ANG1005-CLN-01: Malignant Glioma		ANG1005-CLN-02: Solid Tumor & Brain Metastases	
Parameter (units)	**Free Paclitaxel from GRN1005**	**GRN1005[1]**	**Free Paclitaxel from GRN1005**	**GRN1005[1]**
n	12 to 14[2]	12 to 14[2]	15 or 16[3]	16
C_{max} (μM)	4.20	233	13.0	187
AUC_{last} (μM·h)	41.6	1876	101	1447
half-life (h)	6.47	4.13	6.87	3.97

[1] parameters converted to paclitaxel equivalents in molar units
[2] n = 12 for AUC_{last}; n = 13 for half-life; n = 14 for all other parameters.
[3] n = 15 for T_{max} and half-life; n = 16 for all other parameters

AUC_{last} = area under the curve from time 0 to time of the last quantifiable concentration; C_{max} = maximum concentration; n = number of patients

- The PK profile of GRN1005 was similar in both Phase I studies and appeared to be linear over the range of doses studied.
- There was no evidence of accumulation after repeated 21-day treatment cycles.
- Free paclitaxel levels in plasma from patients who received 650 mg/m² (MTD) of GRN1005 suggested that only a small fraction of the total plasma exposure is accounted for by free paclitaxel.

Malignant Glioma Sub-Study

Table 5. GRN1005 Concentration in Malignant Glioma

Patient tumor type		GBM	GBM	GBM	GBM	GBM	GBM	GBM	GBM	PNET	AA
GRN1005 Dose level (mg/m²)		200	300	420	550	550	550	550	550	650	650
Extraction time (h)		~ 4	~ 5	~ 4	~ 4.5	~ 4.5	~ 5.5	~ 6	~ 6	~ 3.5	
Plasma (μM)	**GRN1005***	33.6	34.1	52.6	98.2	62.5	79.5	55.0	69.7	123.4	
	Paclitaxel	0.7	0.3	0.9	1.8	0.4	1.5	1.5	1.6	2.3	
Tumor (μM)**	**GRN1005***	2.0	8.6	5.8	22.4	237.9	28.3	95.3	19.6	18.4	
	Paclitaxel	0.8	0.9	1.2	0.6	0.6	3.2	2.8	8.6	0.9	

AA=anaplastic astrocytoma; GBM=glioblastoma multiforme; PNET= primitive neural ectodermal tumor
* Paclitaxel equivalents ** Corrected for vascular content.

- Plasma GRN1005 concentrations were greater than plasma paclitaxel concentrations consistent with the prodrug property of GRN1005 being systemically available for LRP-1 receptor-mediated transcytosis across the BBB and into tumor cells.
- GRN1005-associated paclitaxel concentrations in the excised tumor samples were greater than those reported for naked paclitaxel administration and well above those required for cytotoxicity.[10]

Tumor Response in 1 Dimension (1-D): ANG1005-CLN-02

Table 6. Summary of Best Overall Response

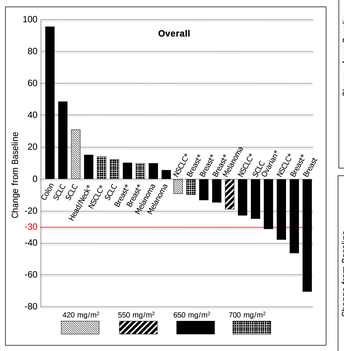
Tumor assessment criteria: patients who received ≥2 cycles

Dose	30 – 300 mg/m²	420 – 700 mg/m²	650 mg/m² (MTD)	Prior Taxane Failures *
n	17	39	20	21
PR		4 (10%)	4 (20%)	3 (14%)
SD	5 (29%)	12 (31%)	5 (25%)	8 (38%)
PD	9 (53%)	9 (23%)	6 (30%)	3 (14%)
UE/Missing	3 (17%)	14 (36%)	5 (25%)	7 (33%)

* Patients dosed 420-700 mg/m² that had failed prior taxane therapy.
CR = Complete Response; MRI = Magnetic Resonance Imaging; PD = Progressive Disease; PR = Partial Response (1-D assessment: ≥ 30% reduction in sum of diameters,); SD = Stable Disease; UE = Unable to Evaluate, n = number of patients

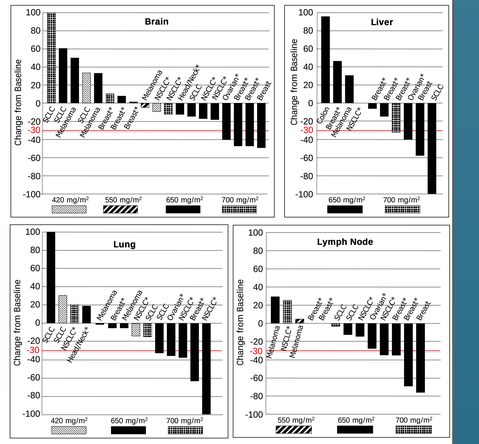
Figure 2. Best Overall Response Assessment (1-D) by Primary Tumor Type and Dose.

Included patients dosed ≥ 420 mg/m², received ≥ 2 cycles, and had at least 1 post-treatment response assessment ≥ 6 weeks after the 1st dose.



Each bar in Figure 2 represents one patient, depicting the best percentage change from baseline. Independent radiologist assessments were used whenever available.
SCLC = Small cell lung cancer; NSCLC = non-small cell lung cancer; * = prior taxane failure

Figure 3. Percent Change from Baseline to Best Response (1-D) by Primary Tumor Type



Each bar in Figure 3 represents one patient, depicting the best percentage change from baseline. Independent radiologist assessments were used whenever available.
SCLC = Small cell lung cancer; NSCLC = non-small cell lung cancer; * = prior taxane failure

Table 7. Summary of the Four Responding Patients

Primary Tumor	Prior SRS	Prior WBRT	Other Prior Treatment	Best OR	% Change[1]			Doses[2]
					Overall	Brain	Lung	
Breast[3]			none	PR	-70.5	-50.0	NA	7
Breast	√		surgery, CTX, DOX, paclitaxel, pamidronate, zoledronate, fulvestrant; extra-cranial RT	PR	-46.25	-47.62	-63.64	7
NSCLC[3]	√ (x3)	√	carboplatin, paclitaxel, extra-cranial RT	PR	-37.65	-18.18	-100	7
Ovarian			carboplatin; docetaxel, DOX, gemcitabine, topotecan	PR	-30.89	-40.59	-36.67	4

[1]Best %change from baseline in tumor burden (1-D) [2]No. of doses received by database lock
[3]still on GRN1005 treatment by database lock
PR = Partial Response (1-D assessment: ≥ 30% reduction in sum of diameters)
CTX = cyclophosphamide; DOX = doxorubicin; RT = radiotherapy; OR = overall response
WBRT = whole brain radiotherapy ; SRS=stereotactic radiosurgery; PR=partial response

Safety

Table 3. Adverse Events (AE) of Interest occurring at ≥ 15% in either study at the MTD Dose of 650 mg/m²

System Organ Class Preferred Term	ANG1005-CLN-01 (n=18) Grade 3	Grade 4	All Grades*	ANG1005-CLN-02 (n=20) Grade 3	Grade 4	All Grades*
Blood and lymphatic system disorders						
Neutropenia[1]	3 (16.7%)	5 (27.8%)	8 (44.4%)	3 (15.0%)	9 (45.0%)	13 (65.0%)
Leukopenia[2]	0	3 (16.7%)	3 (16.7%)	1 (5.0%)	0	2 (10.0%)
Thrombocytopenia[3]	1 (5.6%)	1 (5.6%)	2 (11.1%)	2 (10.0%)	0	4 (20.0%)
Anaemia[4]	0	0	1 (5.6%)	3 (15.0%)	0	8 (40.0%)
Gastrointestinal disorders						
Constipation	0	0	5 (27.8%)	0	0	3 (15.0%)
Nausea	0	0	5 (27.8%)	0	0	7 (35.0%)
Dyspepsia	0	0	3 (16.7%)	0	0	1 (5.0%)
Diarrhoea	0	0	2 (11.1%)	1 (5.0%)	0	9 (45.0%)
Stomatitis	0	0	2 (11.1%)	1 (5.0%)	0	8 (40.0%)
Vomiting	0	0	1 (5.6%)	0	0	7 (35.0%)
General disorders and administration site conditions						
Infusion related reaction	2 (11.1%)	0	2 (11.1%)	2 (10.0%)	0	3 (15.0%)
Infections and infestations						
Urinary tract infection	1 (5.6%)	0	3 (16.7%)	0	0	1 (5.0%)
Oral candidiasis	0	0	2 (11.1%)	0	0	3 (15.0%)
Pneumonia bacterial	0	0	2 (11.1%)	3 (15.0%)	0	5 (25.0%)
Candidiasis	0	0	1 (5.6%)	0	0	3 (15.0%)
Nervous system disorders						
Headache	0	0	4 (22.2%)	0	0	2 (10.0%)
Neuropathy peripheral[5]	2 (11.1%)	0	5 (27.8%)	1 (5.0%)	0	7 (35.0%)
Somnolence	2 (11.1%)	0	4 (22.2%)	0	0	0
Ataxia	1 (5.6%)	0	3 (16.7%)	0	0	0
Convulsion	0	1 (5.6%)	3 (16.7%)	1 (5.0%)	0	1 (5.0%)
Hemiparesis	2 (11.1%)	0	3 (16.7%)	0	0	1 (5.0%)
Dizziness	0	0	2 (11.1%)	0	0	3 (15.0%)

* includes AEs of all Grades (1-5); there was 1 Grade 5 event of bacterial meningitis at the MTD in the ANG1005-CLN-01 study , and no Grade 5 events for the ANG1005-CLN-02 study at MTD
The information in Table 3 is based on reported AE. For reported AE and hematology laboratory data:
[1] **Neutropenia** for ANG1005-CLN-01: 1 (5.6%) Grade 1, 1 (5.6%) Grade 2, 2 (11%) Grade 3, 10 (56%) Grade 4, and 14 (78%) for Grade 1-5. For ANG1005-CLN-02: 0 Grade 1, 2 (10%) Grade 2, 3 (15%) Grade 3, 14 (70%) Grade 4, and 19 (95%) for Grade 1-5.
[2] **Leukopenia** for ANG1005-CLN-01 : 2 Grade 1 (11%), 1 (5.6%) Grade 2, 5 (28%) Grade 3, 8 (44%) Grade 4, and 16 (89%) for Grade 1-5. For ANG1005-CLN-02: 0 Grade 1, 1 (5%) Grade 2, 11 (55%) Grade 3, 8 (40%), Grade 4, and 20 (100%) for Grade 1-5
[3] **Thrombocytopenia** for ANG1005-CLN-01: 6 Grade 1 (33%), 2 (11%) Grade 2, 6 (33%) Grade 3, 1 (6%) Grade 4, and 15 (83%) for Grade 1-5. For ANG1005-CLN-02: 5 (25%) Grade 1, 3 (15%) Grade 2, 3 (15%) Grade 3, no Grade 4, and 11 (55%) for Grade 1-5.
[4] **Anaemia** for ANG1005-CLN-01 : 8 Grade 1 (44%), 6 Grade 2 (33%), 0 Grade 3, 0 Grade 4, and 14 (78%) for Grade 1-5. For ANG1005-CLN-02: 7 (35%) Grade 1, 8 (40%) Grade 2, 4 (20%) Grade 3, no Grade 4, and 19 (95%) for Grade 1-5
[5] including peripheral sensory neuropathy

GRN1005 Safety Summary for Phase I Studies

Overall

- GRN1005 was generally well tolerated
- Most frequently reported adverse events were related to bone marrow suppression
- The overall incidence of infusion reactions of any grade with any dose was 13% (15/119)
- No evidence of GRN1005 CNS toxicity, as measured by neurocognitive testing and neurological examination
- Liver toxicity was not observed in these studies
- No anti-drug antibody production was observed

Safety Summary at MTD

- The MTD was determined to be 650 mg/m² by IV infusion q3wk
- Neutropenia was the DLT
  - It was of short duration and manageable by cytokine growth factors
  - Overall incidence of neutropenia of any grade was 87% (33/38) and of Grade 4 neutropenia was 63% (24/38) with a nadir at approximately 1 week after dosing
  - Febrile neutropenia occurred in three patients (8%)
- Other Adverse Events at MTD
  - Peripheral neuropathy 31.6% all grades. (5/38 [13%] Grade 2 and 3/38 [8%] Grade 3, no Grade 4
  - Thrombocytopenia (16/38 [42%] Grades 1-2, 9/38 [23%] Grade 3, and 1/38 [3%] Grade 4)
  - Gastrointestinal events observed: diarrhea, nausea, vomiting, stomatitis

Tumor Response in 2-D: ANG1005-CLN-01

Table 8. Summary of Best Response[3]

Tumor assessment criteria in 2-D: patients who received ≥ 2 cycles

Dose	30 - 300 mg/m²	420 - 700 mg/m²	650 mg/m² (MTD)
n	27	27	17
CR	---	1 (4%)	---
PR	---	2 (7%)	1 (6%)
SD	8 (30%)	8 (30%)	4 (24%)
PD	16 (59%)	9 (33%)	6 (35%)
UE/Missing	3 (11%)	7 (26%)	6 (35%)

PR = Partial Response (in 2-D defined as ≥ 50% reduction in the product of the cross sectional diameters of lesions)
CR = Complete Response (in 2-D defined as 100% reduction in the product of the cross sectional diameters of lesions)

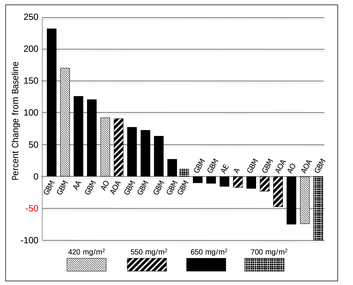
Table 9. Summary for Three Responding Patients[3]

Tumor subtype	Prior Tx	Best Response	%Change[1]	Doses[2]
GBM	TEM, RT, brachytherapy, craniotomy, surgery	CR	-100.00	3
AOA	TEM, RT, lomustine, procarbazine, vincristine, craniotomy, stereotactic biopsy	PR	-72.50	8
AO	TEM, RT, carmustine	PR	-71.90	4

[1] Best % change from baseline in tumor burden (2-D)
[2] No. of doses received by database lock.
Listed patients stopped GRN1005 by database lock.
TEM = temozolomide; RT = radiotherapy

Figure 4. Best Response Assessment (2-D) by Brain Tumor Subtypes and Dose[3]

Included patients dosed at ≥ 420 mg/m² and had at least 1 post-treatment assessment



Each bar represents one patient, depicting the best percentage change from baseline.

[3]Patients (n=9) from surgical debulking sub-study were excluded.
A = Astrocytoma; AA = Anaplastic Astocytoma; AE = Anaplastic Ependymoma; AO = Anaplastic Oligodendroglioma; AOA = Anaplastic Oligoastrocytoma; GBM = Glioblastoma multiforme

Conclusions

- GRN1005, a peptide-drug conjugate (PDC), has an MTD of 650 mg/m² every three weeks in the Phase I studies.
- Single agent GRN1005 clinical activity was observed in patients with malignant gliomas and in patients with solid tumor brain metastases.
- GRN1005 clinical activity was observed in prior taxane failure patients; in addition, extra-cranial and intra-cranial responses were observed in some patients.
- GRN1005's safety profile is consistent with that of paclitaxel chemotherapy treatment; GRN1005 itself is a prodrug.
- Active concentrations of GRN1005 and free paclitaxel were present in resected brain tumor samples, suggesting that GRN1005 successfully crossed the blood brain barrier.
- Given the clinical activity and safety/tolerability observed in Phase I, GRN1005 as therapy for patients with intra-cranial tumors is being further investigated in Phase 2 studies.

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