FLT-PET/CT for the Prediction of Response to ANG-1005 Therapy in Patients with Brain Metastases from Breast Cancer

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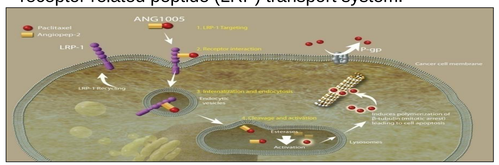
Background

- 18F-FLT (3'-Fluoro-3' deoxythymidine)-PET imaging is a novel imaging study and a tool for measuring in vivo tumor cell proliferation.
- FLT is an analog of thymidine. Retention of FLT by the cells reflects DNA synthesis.

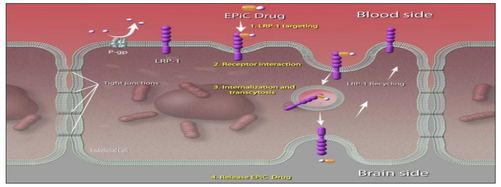
ANG1005

- ANG1005 (formerly called GRN1005) is a peptide-drug conjugate being developed for targeted treatment of brain metastases (Cremophor-free formulation)
- It consists of 3 molecules of paclitaxel covalently linked to Angiopep-2 designed to cross the blood brain barrier via LDL receptor related peptide (LRP) transport system.



Receptor-mediated endocytosis of ANG1005 into the tumor cells

- Gains entry into tumor cells through LRP-1(upregulated in various cancer cells) wherein the paclitaxel molecules are cleaved by intracellular esterases, rendering them active



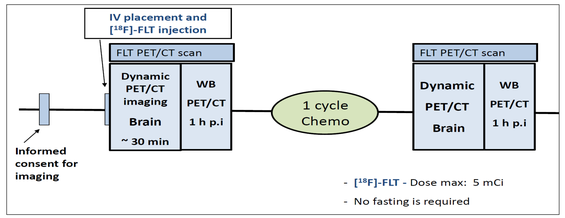
Receptor-mediated transcytosis of ANG1005 across the endothelial cells at the BBB

- This drug was being evaluated in multi-center, open-label single-arm study, with the primary endpoint of intracranial ORR (GRABMB study). Adult patients with measurable brain metastases from breast cancer were eligible with or without history of prior WBRT.

Study Objectives

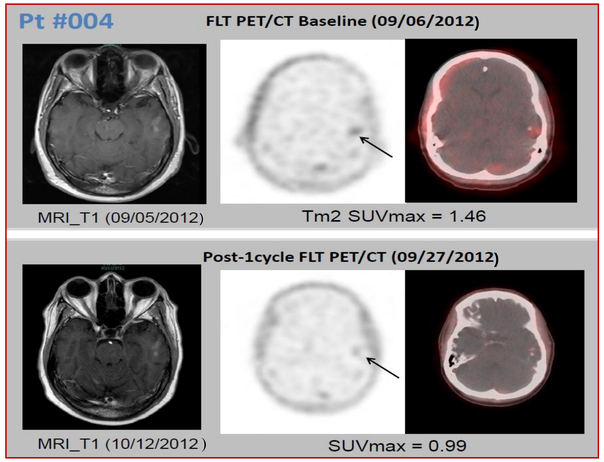
- **Primary Objective:**
  - Determine whether one cycle of therapy ANG1005 is associated with a significant change in FLT-PET uptake.
- **Key Secondary Objectives:**
  - Determine whether change in the FLT-PET/CT uptake after 1 cycle of therapy with ANG1005 is associated with intracranial tumor response
  - Compare brain metastasis detection by standard contrast-enhanced MRI vs. FLT-PET/CT vs. dynamic contrast MRI

Study Design & Methods

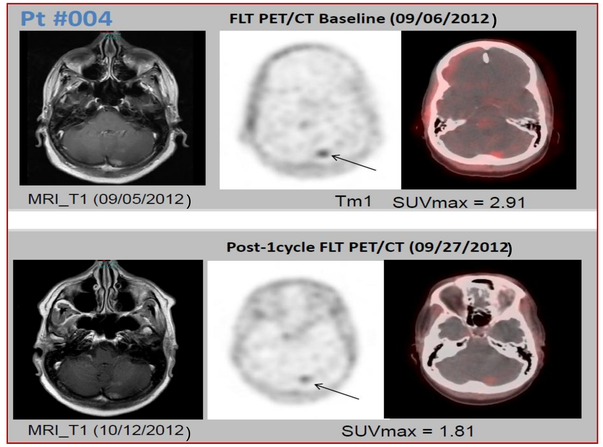


- ANG1005 therapy was administered intravenously at 550 mg/m^2 every 21 days till progression of intra-cranial disease or unacceptable toxicity.
- All patients underwent FLT PET/CT imaging before and after 1 cycle of therapy with ANG1005.
- For [18F]-FLT PET/CT scan: Volumes of Interest were drawn in target brain metastases:
  - SUVmax (80% Threshold : average value of the maximum 20% pixels)
  - SUVmax *Volume
  - Tumor: Normal Ratio (T:N)
  - % of Change pre/post therapy
    - ❖ % of change (using SUVmax)
    - ❖ % of change (using T:Normal ratio)
- Patients underwent dynamic brain imaging over 30 min and then a static whole body PET scan at 1 hour post-injection.
- We calculated the % of change before and after therapy, considering "significant response" if the % of change was larger than 20%.

Results



Results for pt # 4 Target 1 lesion (above) had (-) 32.19% of change and Target 2 lesion (below) had (-) 37.8% of change



FLT–PET/CT & Response

Patient	Best MRI Response	Cycles	% FLT Decrease (using SUVmax)
#1	Stable Disease	2	(-) 44.50
#2	Stable Disease	6	Not seen
#3	Stable Disease	8	(-) 29.25
#4	Partial Response	6	(-) 37.80
#5	Partial Response	6	(-) 66.80

Pt # 1 left the study to receive radiation therapy. Pt # 5 left the study to enroll on a immunotherapy study. Pt # 4 had an unconfirmed PR.

- 6 out of projected 10 patients have been accrued so far.
- Data analysis has been completed for 12 metastatic brain lesions identified in the first 5 patients; analysis of lesions in the 6th patient is ongoing.
- The maximum standardized uptake value (SUVmax) ranged from 0.8 to 4.0 in the baseline scan, with average of 1.8.
- Tumor to Normal ratio ranged from 3.2 to 22.3, average 9.4.
- 7 of the 12 lesions showed significant % of change between pre and post therapy.
- Average % of change was -42.39% (Range: -29.2% to -66.8%) using SUVmax and -38.7% (Range = -20.12% to -57.10 %) using Tumor to Normal background brain.

Conclusion

- FLT-PET/CT imaging seems to be a promising tool for the detection of brain metastases and the assessment of response to therapy.
- The accrual to this study is ongoing.

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