Preclinical Characterization of CGT6297, a Novel PI3Kα Mutant-Selective Inhibitor

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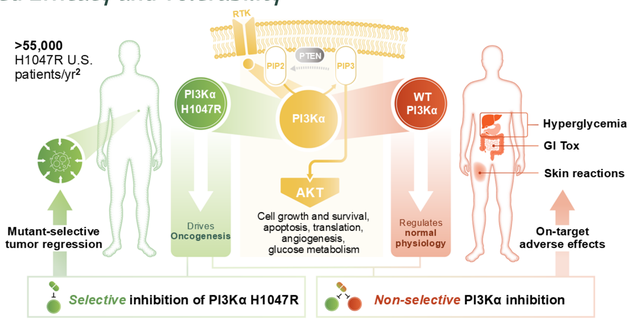
Poster #5
Abstract #3004

BACKGROUND

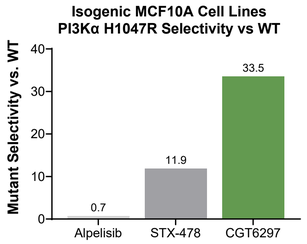
Selective PI3Kα H1047R Inhibition Avoids PI3Kα Wild Type Toxicity for Improved Efficacy and Tolerability

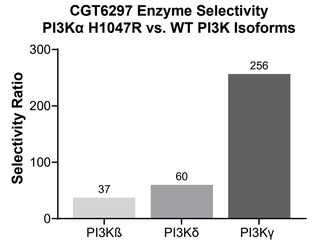


- A mutant-selective inhibitor that avoids on-target, WT-associated toxicities may result in better tolerability, greater target coverage, and improved efficacy compared to approved agents.[1]

RESULTS

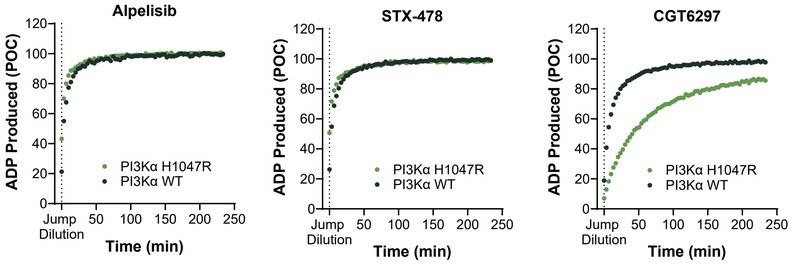
CGT6297 is Selective for PI3Kα H1047R vs PI3Kα WT and Isoforms





- In an engineered MCF10A isogenic model measuring pAKT inhibition, CGT6297 was 34x selective for PI3Kα H1047R compared to the parental (WT) line. In this same experiment, STX-478 was 12x selective.
- CGT6297 spares other PI3K isoforms whose inhibition has been associated with gastrointestinal issues, myelosuppression, and transaminitis.[1]

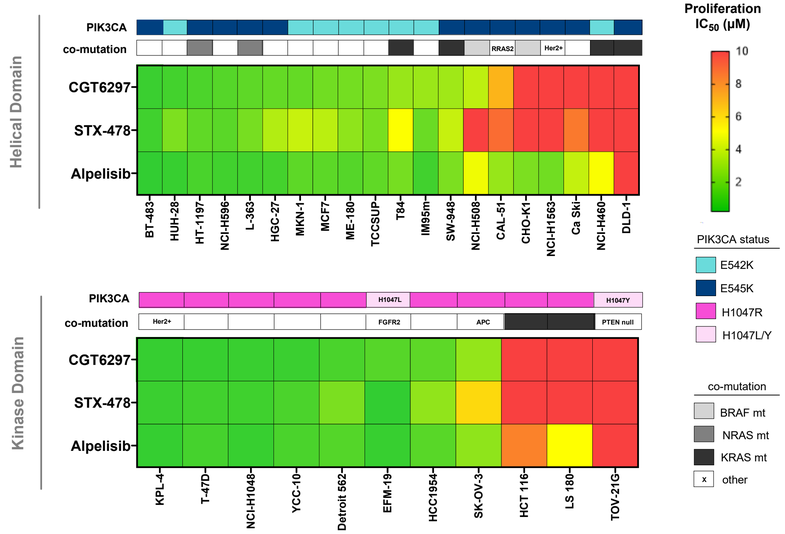
CGT6297 has Residence Time-Based Selectivity for PI3Kα H1047R



- PI3Kα WT and H1047R enzymes were preincubated with compounds (10x IC_{50}), and the resulting complexes were diluted 100-fold into a reaction mixture containing substrate and ATP to mimic compound washout. Reaction progress following dilution was monitored kinetically.
- CGT6297 demonstrated a longer residence time on PI3Kα H1047R compared to alpelisib and STX-478, leading to higher selectivity vs wild type. Long residence time can lead to a sustained pharmacological effect due to the durability of the drug-target complex.[3]

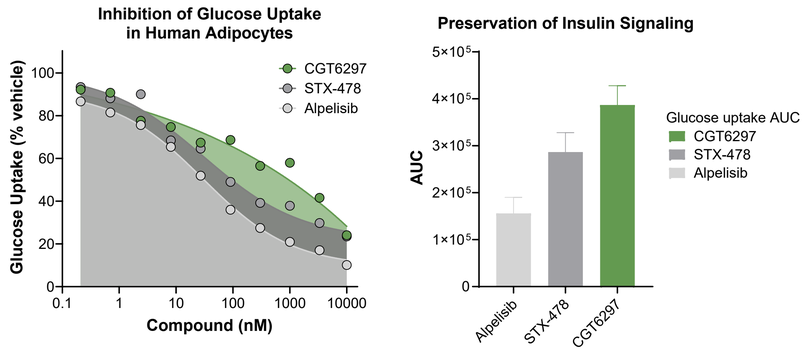
RESULTS, continued

CGT6297 has Potent Antiproliferative Activity in PIK3CA Mutated Cells



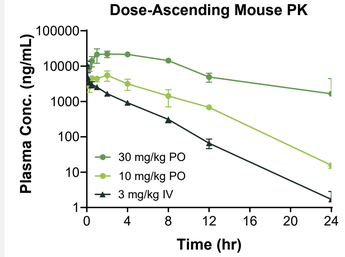
- CGT6297, STX-478, and alpelisib were evaluated in a cell viability panel of 120 cell lines.
- CGT6297 showed potent antiproliferative activity in cell lines containing kinase domain and helical domain mutations, with comparable efficacy to alpelisib and STX-478.

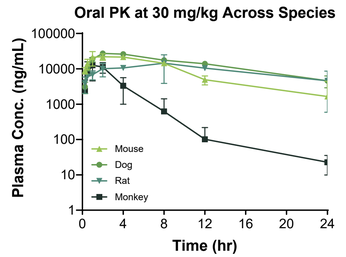
High Selectivity Leads to Preservation of Glucose Uptake and Utilization



- Human adipocytes were differentiated and treated with CGT6297, STX-478, or alpelisib followed by the addition of insulin. The effect on glucose uptake was measured over a range of drug concentrations.
- Glucose dysregulation was improved with CGT6297 compared to STX-478 or alpelisib.
- Improvements in glucose uptake with CGT6297 are consistent with greater wild type selectivity as cellular potency is similar (T-47D pAKT IC_{50} = 38 nM and 36 nM[4] for CGT6297 and STX-478, respectively).
- Alpelisib (T-47D IC_{50} = 58 nM)[5] is less potent and resulted in the highest dysregulation in this assay.

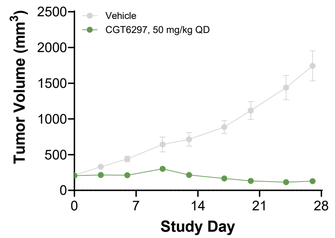
CGT6297 has Dose-Ascending PK With High Bioavailability and Low Clearance

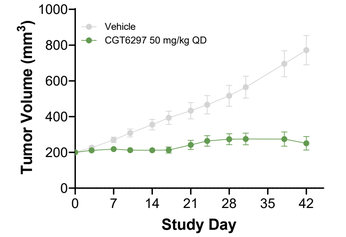




- CGT6297 dose ascends in mouse PK.
- Clearance of 5% extraction ratio dosed at 3 mg/kg IV.
- Oral bioavailability (%F) ranged from 95% to >100%.
- Dose-ascending exposure was observed across preclinical species.
- Oral bioavailability (%F) ranged from 60% to >100% dosed at 30 mg/kg across species.
- CGT6297 showed low clearance ranging from 3% to 19% ER dosed at either 1 or 3 mg/kg IV.

CGT6297 is Efficacious in Mouse Tumor Models





- In a patient derived breast cancer model (ST1056), oral administration of CGT6297 at 50 mg/kg achieved tumor regression after 28 days.
- In an MCF-7 E545K-helical mutation breast cancer TGI experiment, oral administration of CGT6297 at 50 mg/kg dosed for 42 days showed stasis.

CGT6297 KEY FINDINGS AND CONCLUSIONS

- CGT6297 selectively inhibits PI3Kα H1047R and the 542/545 helical mutants.
- It has high oral bioavailability, low clearance, and is efficacious in orally-dosed animal models.
- CGT6297 is >30x selective for PI3Kα H1047R in an isogenic MCF10A cell model and is selective for PI3Kα over other PI3K isoforms in an enzymatic assay.
- CGT6297 binds in the H1047R allosteric pocket and demonstrates a longer residence time on PI3Kα H1047R compared to STX-478 and alpelisib.
- CGT6297 shows potent antiproliferative activity in PI3Kα kinase and helical domain mutant cell lines.
- CGT6297 preserves glucose uptake and utilization in human adipocytes when compared with alpelisib and STX-478 across a range of concentrations.
- Dose-ascending PK observed with high oral bioavailability and low clearance across species.
- CGT6297 exhibited efficacy in both the ST1056 PDX breast cancer model as well as the MCF-7 (E545K mutant) TGI experiment at 50 mg/kg.

Cogent plans to submit an IND application for CGT6297 in 2025.

American Association for Cancer Research (AACR) annual meeting | April 28, 2025 Chicago, Illinois

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