A PHASE 1B/2A STUDY OF GNS561 IN COMBINATION WITH TRAMETINIB IN ADVANCED KRAS-MUTATED CHOLANGIOCARCINOMA (CCA)

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BACKGROUND & OBJECTIVES

- Activating Mitogen-Activated Protein Kinase (MAPK) signaling pathway alterations, including KRAS mutations, are found in cholangiocarcinoma (CCA). Inhibiting MAPK and autophagy may result in synergistic effects to treat KRAS mutated CCA.
- GNS561 (ezurpimtrostat) is an autophagy inhibitor that inhibits the enzyme target palmitoyl-protein thioesterase 1 (PPT1). Trametinib (T) is a selective MEK1/MEK2 inhibitor. This study aims to determine the recommended Phase 2 dose of the combination (RP2DC) and to assess preliminary efficacy/safety of GNS561+T in patients with advanced KRAS-mutated CCA.

METHODS

- Open label, multi-center, Phase 1b/2a study (NCT05874414)
- Evaluation of the safety, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy of GNS561+T in adult patients with advanced histologically confirmed KRAS-mutated CCA not amenable to local treatment with surgery or radiotherapy, or with metastatic disease not responding to Standard of Care.
- Patients are treated in 21-day cycles.
- Phase 1b (P1b) is conducted in to determine the maximum tolerated doses of GNS561+T.
- The RP2DC in Phase 2a (P2a) will be based on safety, PK, and PD data

MAIN ELIGIBILITY CRITERIA

Inclusion

- Histologically confirmed CCA with a documented KRAS mutation.
- ≥ 18 years of age.
- Disease progression that is not amenable to potentially curative treatment.
- Must have received at least one line of chemotherapy.
- Must have at least one measurable disease by RECIST v1.1.
- Performance status (ECOG) 0-1.

Exclusion

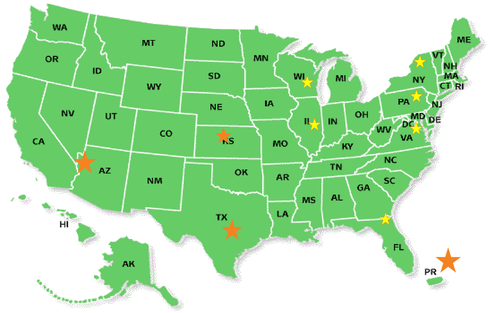
- Previous treatment with a MEK inhibitor or autophagy inhibitor.
- Uncontrolled, significant intercurrent illness
- Clinically significant liver disease
- Allergic reaction to quinoline derivatives (e.g., quinine, chloroquine, mefloquine) and/or hypersensitivity to study drugs.
- Female patients who are pregnant or lactating at the time of enrollment.

FEASIBILITY & ENROLLMENT STATUS

4 Sites Actively Recruiting (★) in CA, PR, TX and VA,

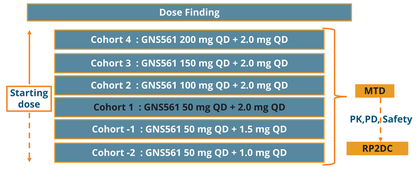
and

6 other Sites soon to be Activated (★) in the US



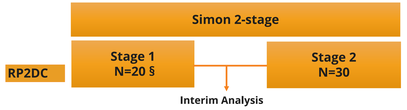
PHASE 1b DOSE FINDING

- Standard 3+3 dose (de-)escalation design
- Based on the number of Dose limit toxicity (DLT) and Safety Monitoring Committee (SMC) review: a cohort of 3 patients are assigned to a dose level, if 0/3 DLTs, dose escalated if 1/3 DLTs, assign additional 3 patients at this dose level. If 1/6 DLTs , dose escalated. If 2 or more DLTs and at least cohort 2 is reached, an intermediate lower dose of trametinib could be evaluated as per SMC decision. if cohort 2 is not achieved, de-escalation to cohort level -1 and -2 .
- The Maximum Tolerated Dose (MTD) is the highest dose level with ≤1/6 DLT
- Up to 24 patients (i.e., 6 patients in up to 4 cohorts) will be enrolled



PHASE 2a PROOF of CONCEPT (POC) SINGLE ARM

- A Simon two-stage design divided in two parts (Stage 1 and stage 2) with interim analysis for assessment of futility.
- Safety assessed at regular intervals by Data Safety Monitoring Board (DSMB)
- Primary endpoint: objective response rate (ORR) [proportion of patients with a best overall response of complete response or partial response using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1] of GNS561+Trametinib.
- Futility not declared if at least 4 responses (CRs and PRs) are observed at the end of stage 1.



§ Efficacy data from patients treated at RP2DC in Phase 1b will be pooled with data of patients in Stage 1 RP2DC=Recommended Phase 2 Dose for the Combination

PATIENT-FRIENDLY LAY SUMMARY

BACKGROUND & OBJECTIVES

- GNS561 is an inhibitor of autophagy, a protective mechanism that allows tumor cells to be resistant to cancer treatments.
- Trametinib ("T") is a drug that blocks the action of proteins that help cancer cells to grow. KRAS mutation in cancer cells may lead to the production of proteins helping cancer cells to grow. "T" might block those proteins, but cancer cells might find another way to grow (autophagy). Adding an inhibitor of autophagy, like GNS561, to "T", may help to treat patients with CCA with a KRAS mutation.
- This study [(https://www.clinicaltrials.gov), NCT05874414)] aims to determine the recommended dose of the combination for Phase 2 (RP2DC) and to assess preliminary efficacy/safety of GNS561+"T" in patients with advanced KRAS-mutated CCA.

METHODS

- Study includes 2 parts (Phase 1b and Phase 2a). The Phase 1b (P1b) is evaluating the safety/tolerability of GNS561+"T" and is aimed to determine the RP2DC for Phase 2a (P2a).
- In P1b, patients will be treated in 21-day treatment cycles with GNS561 (50mg-200mg QD) and "T" (2mg-1.5mg QD; or 1mg QD).
- Three (3) patients will be enrolled into the 1st dose cohort. If there is no dose-limiting toxicity (DLT) in any of these participants, the trial will proceed to enroll additional participants into the next higher dose cohort. If 1 patient shows a DLT, an additional 3 individuals are accrued into that same dose cohort. If 2 or more patients in a dosing cohort (up to 6 patients) show DLT, an intermediate lower dose of "T" may be evaluated or a lower dose of GNS561.
- In P2a, patients will receive GNS561+"T" at the RP2DC based on results from P1b.
- Primary endpoints include the incidence of GNS561+"T" DLT (P1b) and objective response rate (ORR) [proportion of patients with a best overall response of complete response or partial response using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1] of GNS561+"T" (P2a).
- Up to 24 patients in P1b (i.e., 6 patients in up to 4 cohorts) and up to 52 patients in P2a are expected to be enrolled.

RESULTS & CONCLUSION

- The study is recruiting and was approved by ethics committees/institutional review boards at several centers in the USA. Approximately 20 centers are expected to participate, including those in the USA and potentially outside the USA.

CONCLUSION

↳ No currently approved targeted therapies for patients with unresectable or metastatic KRAS-mutated cholangiocarcinoma.

↳ Inhibiting both MAPK and autophagy may result in synergistic effects and offer a potentially novel treatment for KRAS-mutated cholangiocarcinoma.

↳ A Phase 1b/2a study (NCT05874414) is ongoing to evaluate the combination of the autophagy inhibitor, GNS561, and trametinib, a selective MEK1/MEK2 inhibitor, in patients with KRAS-mutated cholangiocarcinoma who have failed previous standard of care therapy.

↳ Phase 1b of the study is currently enrolling patients in the United States, with the possibility of enrolling patients in other countries in the future.

DISCLAIMER

- GNS561 and trametinib are considered as investigational drugs and have not been approved by any regulatory authority for the treatment of cholangiocarcinoma.
- Additional studies are required prior to making any definitive conclusions regarding efficacy, safety, and potential approval for marketing in cholangiocarcinoma by any regulatory authority.

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