First-in-Human Phase 1/1b Study Evaluating KIN-3248, a Next-Generation, Irreversible Pan-FGFR Inhibitor, in Patients With Advanced Cholangiocarcinoma and Other Solid Tumors Harboring *FGFR2* and/or *FGFR3* Gene Alterations

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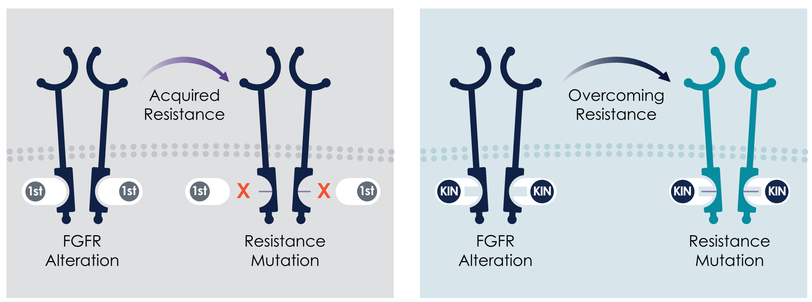
SUMMARY

- **KN-4802 is a phase 1 study designed to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and anti-tumor activity of KIN-3248 in patients with advanced tumors harboring *FGFR2* and/or *FGFR3* gene alterations**
- **The objective of this study is to identify the MTD and/or RP2D of KIN-3248 for further clinical development and assess the objective response to KIN-3248 therapy in participants with advanced tumors harboring pertinent *FGFR2* and/or *FGFR3* gene alterations**

Background: FGFR2/3 Inhibition

- Acquired resistance limits clinical benefit of approved and other fibroblast growth factor receptor (FGFR) inhibitors in development
- KIN-3248 is a next-generation, irreversible, small molecule pan-FGFR inhibitor
- KIN-3248 is a potent and highly selective, covalent FGFR inhibitor targeting:
  - *FGFR2* and *FGFR3* driver alterations in solid tumors, including intrahepatic cholangiocarcinoma (ICC) and urothelial cancers (UC)
  - Known and predicted "on target" *FGFR2* and *FGFR3* kinase domain mutations that confer clinical resistance (eg, gatekeeper and molecular brake)
  - *FGFR1*, *R2*, and *R3* isoforms, thereby reducing opportunities to bypass resistance



1st First-generation *FGFR* inhibitors

KIN KIN-3248 *FGFR* inhibitor

Methods

Study design

- KN-4802 is a first-in-human, multicenter, non-randomized phase 1 study of KIN-3248 in patients with advanced and metastatic solid tumors (AMST) harboring *FGFR2* and/or *FGFR3* gene alterations
- Planned sample size is approximately 120 patients:
  - **Part A** is a dose-escalation to maximum tolerated dose (MTD) of single-agent KIN-3248 for patients with AMST having either *FGFR2* and/or *FGFR3* alterations
  - **Part B** will evaluate a selected dose of KIN-3248 in three cohorts of patients:
    - Cohort 1: ICC with *FGFR2* alterations
    - Cohort 2: UC with *FGFR2* and/or *FGFR3* alterations
    - Cohort 3: Other AMST with *FGFR2* and/or *FGFR3* alterations

Study treatment

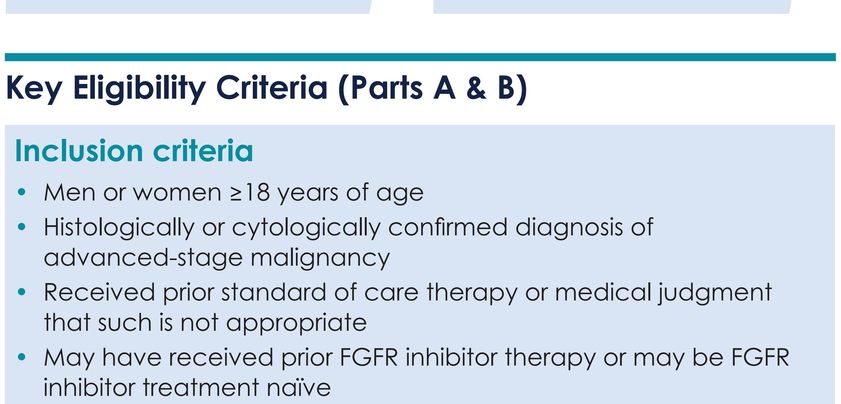
- KIN-3248 is given orally once daily in 28-day cycles until drug intolerance or disease progression
- **Part A:** Backfill enrollment of additional patients at "cleared" doses and intrapatient dose escalation allowed

Study procedures

- Regular clinical, laboratory & electrocardiogram (ECG) assessment; including pharmacokinetics (PK) assessment and screening for FGFR-associated adverse events (AEs)
- Tumor biopsy taken at baseline and in-treatment; including blood-based biomarker collections
- Tumor response assessment per RECIST v1.1

KN-4802: Phase 1 First-In-Human Study Schema

Population: Adult patients with advanced or metastatic solid tumors. *FGFR2* & *FGFR3* gene alterations previously detected by tissue-based or blood-based genomic testing



Key Eligibility Criteria (Parts A & B)

Inclusion criteria

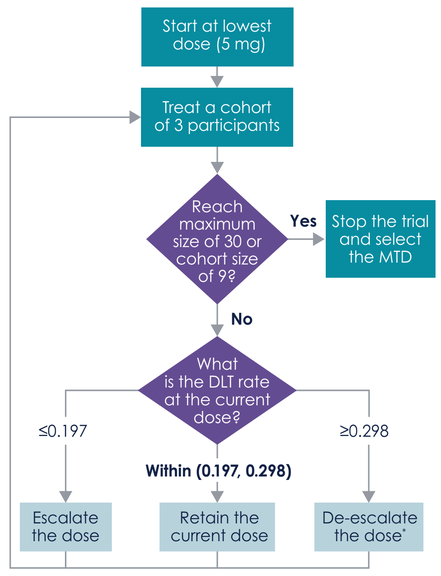
- Men or women ≥18 years of age
- Histologically or cytologically confirmed diagnosis of advanced-stage malignancy
- Received prior standard of care therapy or medical judgment that such is not appropriate
- May have received prior FGFR inhibitor therapy or may be FGFR inhibitor treatment naïve
- Have measurable or evaluable disease
- Advanced tumors harboring *FGFR2* and/or *FGFR3* gene alterations (central testing not required)
- Willing to provide archived tumor tissue samples (FFPE) <5 years old, if available, and/or undergo pretreatment tumor biopsy if medically feasible
- ECOG PS 0–1
- Normal organ function
- Estimated life expectancy of at least 3 months
- Adequate hematological, renal, liver, and chemistry laboratory assessments

Exclusion criteria

- Known clinically active or clinically progressive brain metastases from non-brain tumors
- History and/or current evidence of medical conditions that might synergize with or predispose to FGFRi-related metabolic or retinal toxicity
- Significant cardiac or GI disease
- Active infectious disease, recent anti-tumor therapy, or unresolved toxicity from prior anti-tumor treatment

Part A: Dose Escalation

Modified BOIN Design[1]



Tentative KIN-3248 dose levels for Part A

Dose level	Target daily dose
1	5 mg
2	10 mg
3	20 mg
4	30 mg
5	40 mg
6	50 mg

KIN-3248 presented as 2.5 mg, 5 mg, and 20 mg tablets.

*Exception: if there is one DLT in the first 3 participants, the dose will be maintained.
[1]*Modified from:* Yuan Y, et al. *Clin Cancer Res.* 2016;22:4291–4301.

Study Objectives

Primary objectives

- **Part A:** Determine the safety and tolerability of KIN-3248, including dose-limiting toxicities (DLTs), in patients with advanced tumors harboring *FGFR2* and/or *FGFR3* gene alterations, and to identify the MTD and/or the recommended phase 2 dose (RP2D) of KIN-3248 for further clinical development
- **Part B:** Assess preliminary evidence of the anti-tumor activity of KIN-3248 in patients with advanced tumors harboring *FGFR2* and/or *FGFR3* gene alterations

Secondary objective

- **Parts A & B:** Characterize the PK of KIN-3248

Exploratory objectives

- **Parts A & B:** Confirm on-target pharmacodynamic (PD) modulation by KIN-3248; assess potential correlates of response to KIN-3248 treatment; evaluate potential biomarkers of response/resistance to KIN-3248 in blood samples and/or tumor biopsies

Study Endpoints

Primary endpoints

- Safety: Incidence of DLTs, AEs, treatment-emergent AEs, and treatment-related AEs. Clinically significant changes in vital signs, physical examinations, ECGs, and clinical laboratory tests
- Efficacy: Objective response rate, disease-control rate, duration of overall response, and progression-free survival

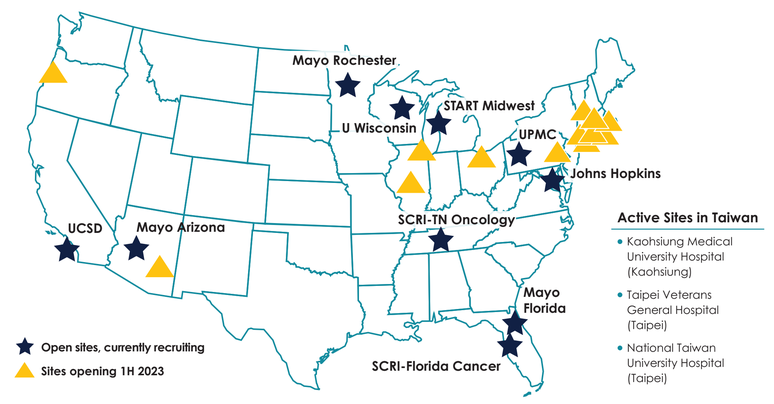
Secondary endpoints

- PK parameters of KIN-3248 including, but not limited to, C_{max}, t_{max}, and AUC

Exploratory endpoints

- KIN-3248 exposure-safety and exposure-efficacy relationships
- Overall survival
- Duration of stable disease
- Evaluation of PD relationships and correlative biomarkers

KN-4802 Study Sites



- KN-4802 is a global study with planned sites in multiple countries (US, China, Taiwan, South Korea, France, Italy, Spain, and Denmark)
- Patient perspectives have been incorporated into the design of the study from the informed consent form to providing complimentary travel services (eg, car services, flights, hotels, etc.) to a study site

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Additional Information and Supplementary Materials

More information about this trial can be found at the www.ClinicalTrials.gov listed under this number: NCT05242822. For additional information, please email ClinicalTrials@Kinnate.com.

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