#CT248

Design and rationale of a first in human (FIH) phase 1/1b study evaluating KIN-2787, a potent and highly selective pan-RAF inhibitor, in adult patients with BRAF- and NRAS-mutation positive solid tumors

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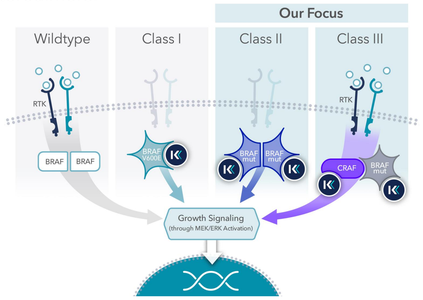
BACKGROUND

Three classes of BRAF alterations:

- **Class I** - kinase active signaling of BRAF mutant monomers
- **Class II** - kinase active signaling of BRAF mutant homodimers
- **Class III** - kinase impaired BRAF that signals through RAS-dependent, BRAF mutant / RAF wild-type heterodimers.



- No RAF-targeted therapies are approved for either Class II/III BRAF or NRAS mutant (NRASm) melanoma.
- Approved BRAF inhibitors are inactive (as monotherapy) against CRAF-dependent, NRASm melanoma.
- NRASm melanoma signaling has shown to be highly CRAF-dependent and recent data validates use of a pan-RAFi+MEKi regimen
  - e.g., 33% PR rate in with patients with NRASm melanoma[1]

KIN-2787 is a novel, orally-available, selective small molecule pan-RAF inhibitor designed to be effective in RAF-dependent cancers, including all classes of BRAF alterations

[1]Kim TW et al. ESMO 2021 Congress, 16-21 September 2021, Poster #529P.
https://clinicaltrials.gov/ct2/show/NCT03284502

METHODS

KN-8701 is a first-in-human, open-label, multicenter, Phase 1/1b study to investigate the safety, tolerability, pharmacokinetics, and antitumor activity of KIN-2787 in participants with BRAF and/or NRAS mutation-positive solid tumors

- Phase 1 dose escalation is 3+3 study design

Study Treatment

- KIN-2787 and binimetinib both administered orally twice daily (bid)
- Part A: Backfill enrollment of additional patients at 'cleared' doses and intra-patient dose escalation allowed (for monotherapy only)

Study Procedures

- Regular clinical, laboratory & ECG assessments; Regular monitoring specific for binimetinib component as indicated
- Food Effect Assessment (for monotherapy only)
- Tumor tissue & blood specimen collection for PD assessments
- Tumor response assessment per RECIST v 1.1

KEY ELIGIBILITY CRITERIA

Key Inclusion Criteria:

- Adult Solid Tumor patients with advanced & unresectable or metastatic disease
- BRAF alteration previously detected in tumor genomic testing[2]:
  - Part A (Monotherapy & Combination Dose Escalation): BRAF Class I,II, III alteration in solid tumors and/or NRASm melanoma
  - Part B: BRAF Class II or III alteration in solid tumors

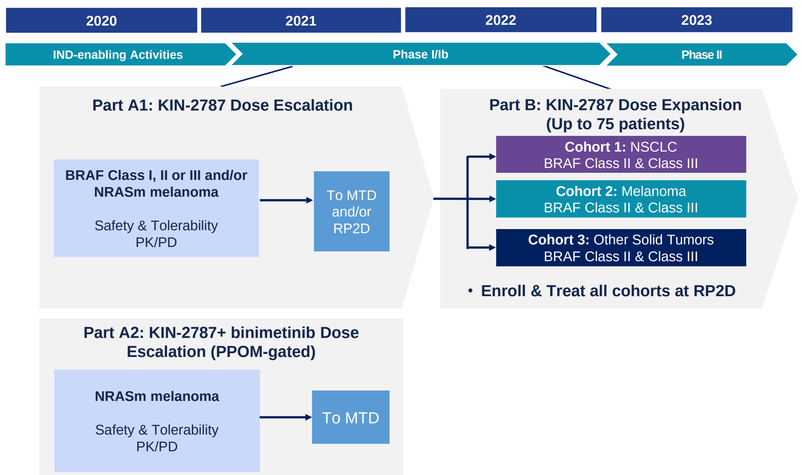
  Prior receipt of standard cancer therapy (or contraindication for such therapy)
- Monotherapy Escalation Only: Prior BRAF inhibitor treatment for patients with Class I mutation-positive cancers with 'on label' indications (non-small cell lung cancer (NSCLC), melanoma, CRC, ATC)
- Measurable or evaluable disease by RECIST v1.1
- ECOG PS 0-2 and adequate organ function

[2] Central testing not required

Key Exclusion Criteria:

- Known clinically active CNS metastatic disease (prior CNS-directed therapy is permissible)
- Prior treatment with BRAF-, MEK-, MAPK-directed therapy (Part B)
- Concomitant anti-cancer therapy is not permitted (continuation of endocrine therapy for breast & prostate cancer is allowed)
- Women who are pregnant, breastfeeding or lactating
- For Combination Dose Escalation Cohorts Only:
  - History or current evidence/risk of RVO
  - History of allogeneic bone marrow or organ transplantation

TRIAL STUDY DESIGN



STUDY ENDPOINTS

Safety Endpoints

- Incidence of dose limiting toxicity (DLTs), MTD and/or RP2D
- Incidence of (Serious) Adverse Events (AEs and SAEs)
- Clinically significant changes in signs, symptoms, and clinical laboratory tests

Efficacy Measures

- Objective Response Rate (ORR) and Disease Control Rate (DCR)[3]
- Duration of Overall Response (DOR) and of Stable Disease

Secondary Endpoint

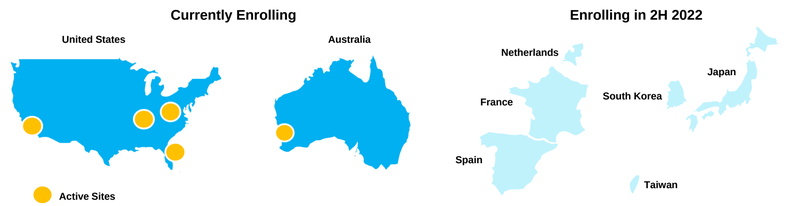
- PK parameters of KIN-2787 and KIN-2787+binimetinib (e.g., Cmax, time to Cmax (tmax), and AUC) in both fed and fasted states

Key Exploratory Endpoints

- KIN-2787 and KIN-2787+binimetinib exposure/safety & exposure/efficacy relationships
- Progression-Free Survival (PFS) & Overall Survival (OS)
- Quantification of biomarker expression at protein, RNA and DNA levels

[3] Defined as the rate of PR plus CR according to RECIST v1.1

STUDY ENROLLMENT INFRASTRUCTURE



- Patient perspective incorporated into the design of the study from the ICF to providing complimentary travel service (e.g., car services, flights, hotels, etc.) to a study site.
- As of April 2022, study centers are in California, Tennessee, Virginia, Florida, and Western Australia. More locations will be available soon.

CONCLUSIONS

- KIN-2787 is a potent & highly selective Type II pan-RAF kinase inhibitor designed to target BRAF monomer and dimer-dependent signaling and to avoid paradoxical activation of the MAPK pathway.
- The KN-8701 trial opened mid-2021 and is currently enrolling globally.
- Patients whose tumors contain mutations of the BRAF (Class I, II, or III) or of the NRAS gene may be able to enroll in this study. These are found with genetic testing and are common in melanoma, NSCLC, and other solid cancer tumors.
- More information about this trial can be found at the www.ClinicalTrials.gov listed under this number: NCT04913285 or consult your oncologist. For additional information, please email ClinicalTrials@Kinnate.com.

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