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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 mutation positive solid tumors

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On behalf of Study KN-8701 Investigators

Disclosures

Dr Meredith McKean

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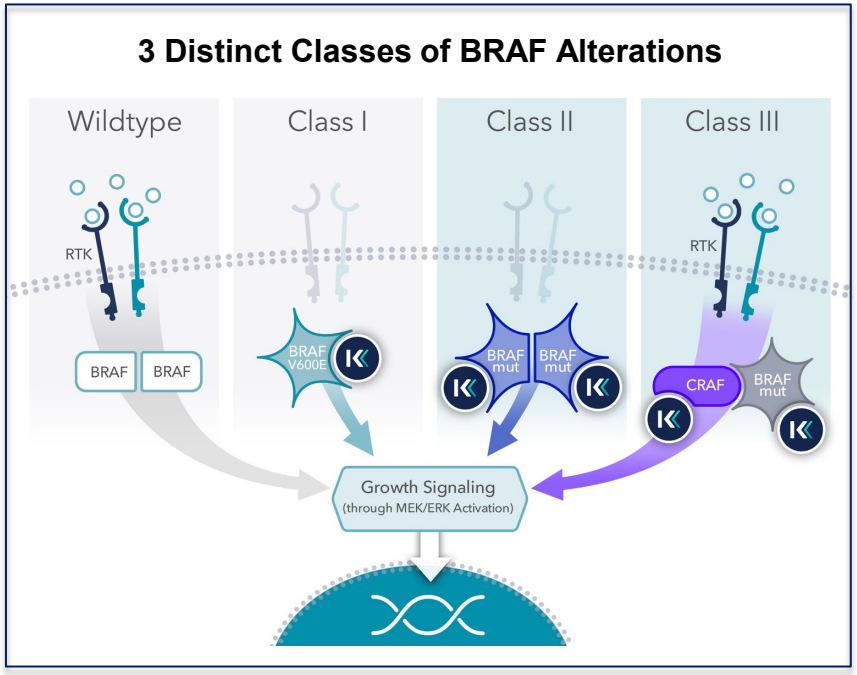
BRAF ALTERATIONS in CANCER

BRAF Class I Alterations

- Represented by the archetypical $BRAF^{V600E/K}$ mutations
- Function as activated monomers to drive MAPK signaling
- 3 BRAF kinase inhibitors approved for cancers driven by Class I mutations



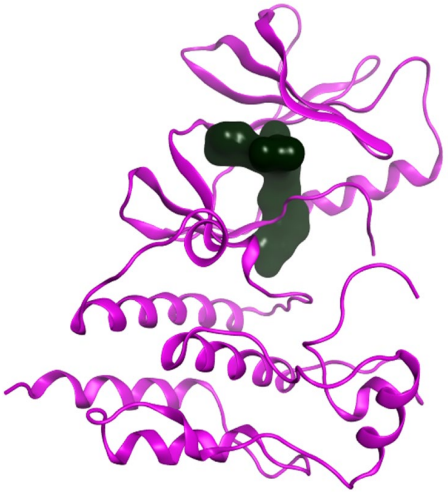
BRAF Class II & Class III Alterations

- Include diverse alterations of SNVs, Indels & gene fusions
- Activate MAPK signaling by BRAF homodimer (Class II) or BRAF/CRAF heterodimer (Class III) formation
- Occur across a wide spectrum of solid tumors, including ~10% of melanoma and ~3% of NSCLC cases
- No BRAF kinase inhibitors are approved for cancers driven by these alterations

KIN-2787 INTRODUCTION

KIN-2787 is a potent & highly selective Type II pan-RAF kinase inhibitor that targets BRAF monomer and dimer-dependent signaling

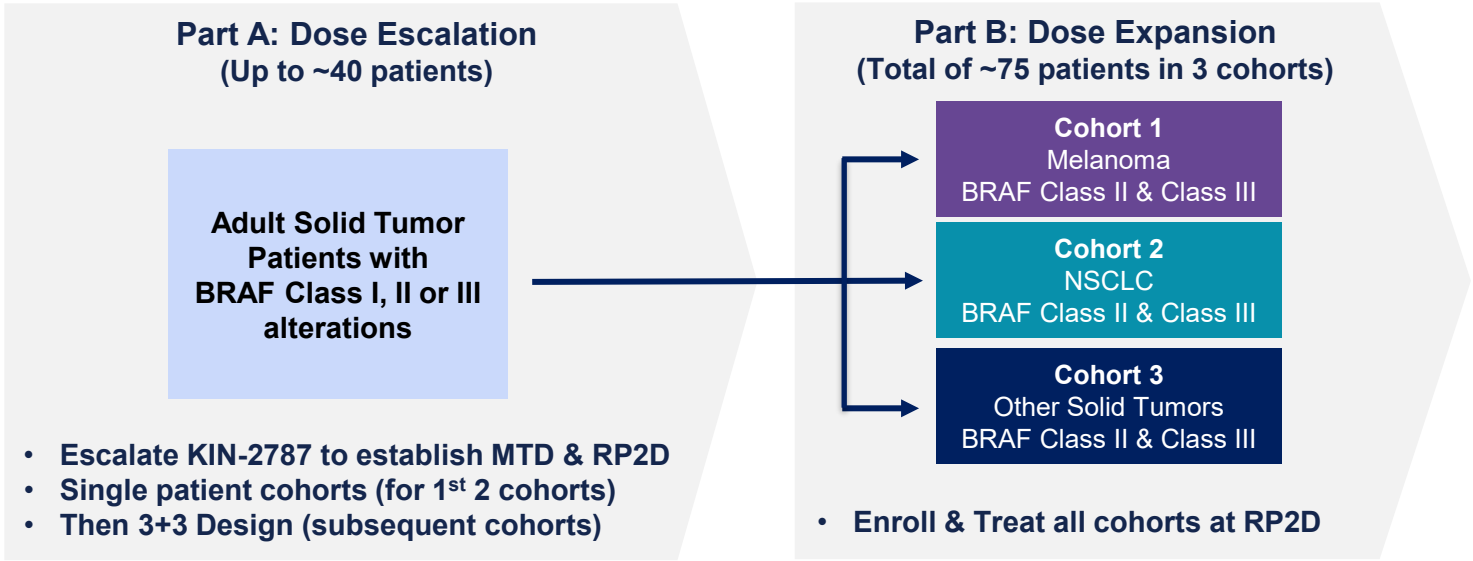
KIN-2787 co-crystal structure in BRAF



KIN-2787 Properties

- Demonstrates high kinome selectivity & exhibits long on-target residence time
- Favorable pharmaceutical properties enhance drug exposure leading to sustained target coverage *in vivo*
- Paradoxical activation, a liability of other RAF inhibitors, was selectively engineered out
- Robust tumor regressions were observed in pre-clinical human xenograft models driven by BRAF Class I, II or III driver alterations

DESIGN of TWO-PART PHASE 1 STUDY KN-8701



Initiate Dose Escalation at 50 mg/day (25 mg BID) in Dose Level 1

Part A is actively recruiting, and study is listed on ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT04913285

STUDY KN-8701 KEY ELIGIBILITY CRITERIA

Key Inclusion Criteria

- Adult Solid Tumor patients with advanced & unresectable or metastatic disease
- BRAF alteration previously detected in tumor tissue or blood-based (e.g., ctDNA) genomic testing in a CLIA-certified lab:
  - Part A: BRAF Class I, II or III alteration or
  - Part B: BRAF Class II or III alteration
- Patients previously received standard cancer therapy
- In Part A only: Previous BRAF inhibitor treatment is required for Class I mutation-positive cases with 'on label' indications (NSCLC, melanoma, CRC, ATC)
- Measurable or evaluable disease by RECIST v1.1
- ECOG PS 0, 1 or 2, and adequate organ function

Key Exclusion Criteria

- Known clinically active CNS metastatic disease (prior CNS-directed therapy is permissible)
- Prior treatment with BRAF-, MEK-, MAPK-directed therapy is excluded for all patients - except for cases in which a BRAFi and/or a MEKi is FDA-approved
- Concomitant anti-cancer therapy is not permitted – except for endocrine therapy for breast & prostate cancer
- Women who are pregnant, breastfeeding or lactating

STUDY KN-8701 TREATMENTS and PROCEDURES

Study Treatment

- KIN-2787 is administered orally twice daily (bid) in 28 day cycles
- KIN-2787 treatment continues until radiological evidence of disease progression or drug intolerance
- DLT evaluation period is 28 days
- KIN-2787 interruptions & dose reductions are permitted per protocol
- Part A: Backfill enrollment of additional patients at 'cleared' doses is encouraged
- Part A: Intra-subject dose escalation is permitted

Study Procedures

- Regular clinical, laboratory & ECG assessments
- PK assessments during Cycle 1 & later cycles
- Food Effect Assessment on the PK of KIN-2787
- Tumor tissue & blood specimens will be collected in screening & during treatment for PD assessments
- Tumor response assessment per RECIST v 1.1 based upon CT imaging every 2 cycles (8 weeks)
- All patients are followed for up to 2 years after last dose of KIN-2787

STUDY KN-8701 ENDPOINTS

Safety Endpoints

- Incidence of dose limiting toxicity (DLTs)
- Incidence of Adverse Events (AEs), including treatment-emergent AEs, treatment-related AEs, serious AEs
- Clinically significant changes in vital signs, physical examinations, ECGs & clinical laboratory tests

Efficacy Measures

- Objective response rate (ORR) defined as the rate of partial responses (PR) plus complete responses (CR) according to RECIST v1.1
- Disease control rate (DCR)
- Duration of overall response (DOR)
- Duration of stable disease

Secondary Endpoints

- PK parameters of KIN-2787 including maximum observed plasma concentration (C_{max}), time to achieve C_{max} (t_{max}), and area under the plasma concentration-time curve (AUC), including in a fed and fasted state

Exploratory Endpoints

- KIN-2787 exposure/safety & exposure/efficacy relationships
- Characterization of potential metabolites of KIN-2787 in plasma & urine
- Progression-free survival (PFS) & Overall survival (OS)
- Quantification of biomarker expression at protein, RNA and DNA levels

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- **Richard Williams MBBS PhD**, Kinnate Biopharma Inc, San Diego, CA

Referrals of potentially eligible patients to recruiting study centers is welcome !

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See ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT04913285 and www.kinnate.com/patients