FIT-001: A phase 1 clinical trial of the farnesyl transferase inhibitor KO-2806 alone or as part of combination therapy for advanced solid tumors

Glenn J Hanna1, Douglas R Adkins2, Jacob S Thomas3, Justine Y Bruce4, Manish R Patel5, Guru Sonpavde6, Jason Henry7, Nawal Bendris8, Zijing Zhang8, Amitava Mitra8, Andrew Saunders3, Stephen Dale8

1 Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; 2 Washington University School of Medicine, St Louis, MO, USA; 3 University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, CA, USA; 4 University of Wisconsin Carbone Cancer Center, Madison, WI, USA; 5 Florida Cancer Specialists, Sahara Cancer Research Foundation, Tamarac, FL, USA; 6 AdventHealth Cancer Institute and the University of Central Florida, Orlando, FL, USA; 7 Sarah Cannon Research Institute at HealthONE, Denver, CO, USA; 8 Kura Oncology, Inc., Boston, MA, USA

BACKGROUND

- RAS mutations are found in a wide range of human cancers, including lung, colon and pancreatic cancers; approximately 30% of human tumors express a mutation in a RAS gene.1
- HRAS, unlike NRAS and KRAS, is completely dependent on the post-translational modification farnesylation for downstream activity, making it particularly sensitive to farnesyl transferase inhibitors (FTIs).1,2
- Clinical trials (NCT02383837, NCT03719690) of the FTI tipifarnib in patients with HRAS-mutant (-m) head and neck squamous cell carcinoma (HNSSC) with high-variant allele frequency mutations (20% or higher) had an objective response rate (ORR) of 52.6% or 30%, and favorable long-term outcomes.3–5
- KO-2806 is a next-generation FTI with increased potency and improved pharmacokinetic (PK) properties compared with current FTIs; in preclinical studies, KO-2806 enhanced the antitumor activity of- -tyrosine kinase inhibitors, including cabozantinib, in clear cell renal cell carcinoma (ccRCC) cell line-derived xenograft (CDX) and patient-derived xenograft (PDx) models.6
- KRAS inhibitors in KRAS-m CDX and PDx models, including adagrasib in non-small cell lung cancer (NSCLC), and MITT1313 in colorectal cancer (CRC) and pancreatic ductal adenocarcinoma (PDAC).7,8

OBJECTIVE

- To assess the safety, tolerability, PK, pharmacodynamics (PD) and preliminary antitumor activity of KO-2806, as a monotherapy and in combination, in adult patients with advanced solid tumors.

STUDY POPULATION

- FIT-001 is a first-in-human, multicenter, open-label, phase 1a dose escalation/expansion clinical trial (KO-2806-001; NCT06026410) (Figure 1).
- Approximately 270 patients will be enrolled in phases 1a and 1b across 50 sites globally.
- Phase 1a (dose escalation) consists of three arms with specific eligibility criteria.
- Based on emerging data from phase 1a, up to two PD cohorts may be explored for each of the monotherapy, ccRCC combination and NSCLC combination.
- In each cohort, 6 to 12 patients may be enrolled; taking paired fresh tumor biopsies at screening and on day 21 will be mandatory.
- As of March 9, 2024, arms 1 and 2 are recruiting; the first patient dose for arm 3 is expected by mid-2024.
- In phase 1b (dose expansion), patients will receive the recommended phase 2 dose (RP2D) of KO-2806 with cabozantinib (in ccRCC) or adagrasib (in NSCLC), or will be randomized if two potential RP2Ds are identified for combination therapy.
- Other combination arms may also be considered.

OUTCOME MEASURES

- Objectives
  - Safety
    - Evaluate safety and tolerability of KO-2806 as monotherapy and in combination in patients with advanced solid tumors (phase 1a) and in combination in patients with advanced solid tumors (phase 1b).
    - Determine MTM-PDPD and/or OABD of KO-2806 as monotherapy and in combination (phase 1a).
    - Define RP2D of KO-2806 in combination (phase 1b).
  - Efficacy
    - Evaluate antitumor activity of KO-2806 in combination in patients with advanced solid tumors (phase 1b).
    - ORR per RECIST (version 1.1).
  - Secondary
    - Safety
      - Evaluate safety and tolerability of KO-2806 in combination in patients with advanced solid tumors (phase 1b).
      - Incidence and severity of treatment-emergent AEs, incidence of dose interruptions, reductions and discontinuations due to AEs.
    - Efficacy
      - Evaluate preliminary antitumor activity of KO-2806 as monotherapy or in combination in patients with advanced solid tumors (phase 1a).
      - ORR, DCR, DoR, PFS per RECIST (version 1.1) per Investigator assessment and OS.
      - Further evaluate the antitumor activity of KO-2806 in combination in patients with advanced solid tumors (phase 1b).
      - ORR, DCR, PFS and OS.
      - Characterize PK of KO-2806 as monotherapy and in combination (phase 1a and 1b).
      - Systemic plasma concentration of KO-2806 and the combination agent.
      - PK parameters, including AUC0-24h, Cmax, T1/2, tmax and CL/F.
    - Other objectives
      - Evaluate effect of food on the PK of KO-2806 as monotherapy.
      - Evaluate relationship between plasma concentrations and QTc intervals for KO-2806 and adagrasib as monotherapy and KO-2806 and adagrasib in combination.
      - Characterize urine PK for KO-2806 monotherapy.

CONCLUSIONS

- This study is exploring the safety and preliminary antitumor activity of KO-2806 for patients with advanced solid tumors; the results will inform the design of future trials.
- The data will also allow evaluation of the safety and preliminary antitumor activity of KO-2806 administered in combination with cabozantinib in ccRCC or adagrasib in NSCLC, and other potential combinations.