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

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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.[1,2]
- 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).[2,3]
- Clinical trials (NCT02383927, NCT03719690) of the FTI tipifarnib in patients with *HRAS*-mutant (-m) head and neck squamous cell carcinoma (HNSCC) 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 MRTX1133 in colorectal cancer (CRC) and pancreatic ductal adenocarcinoma (PDAC).[7,8]

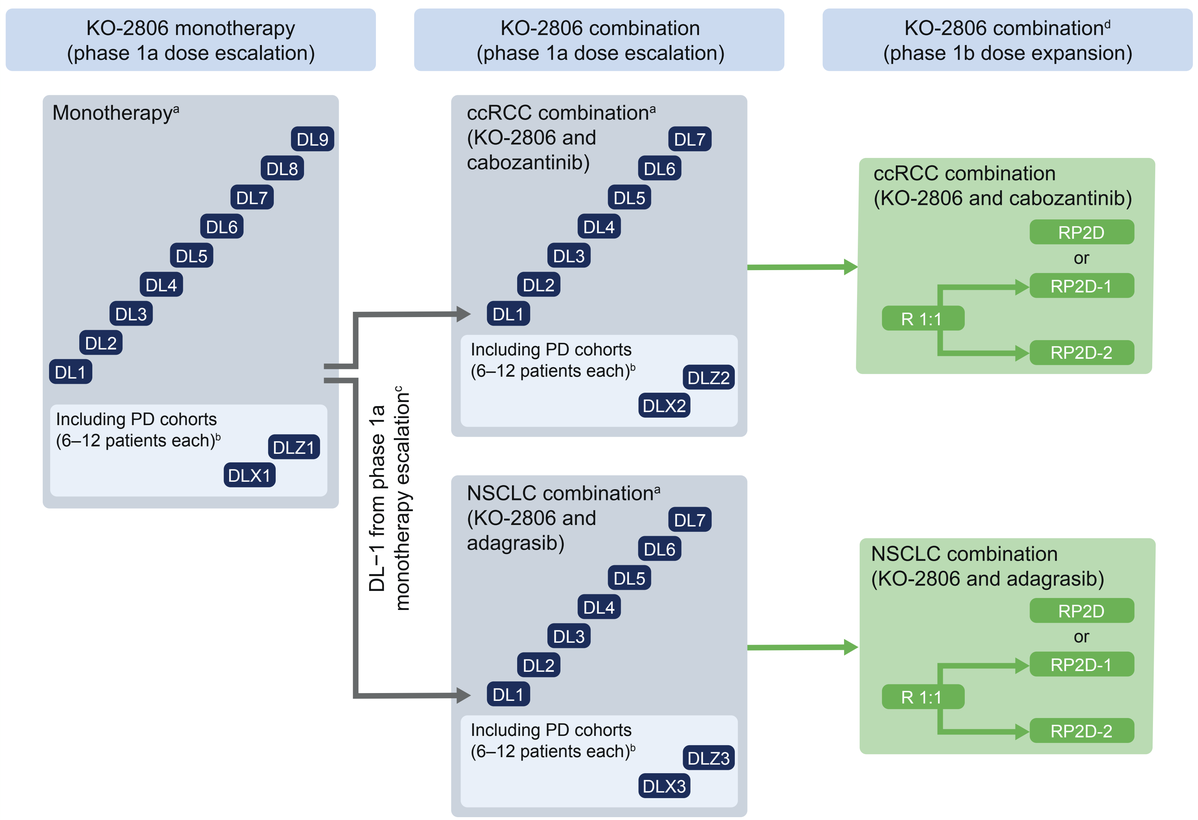
OBJECTIVE

- 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/b 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.

FIGURE 1. OVERALL STUDY DESIGN



[a]Each individual patient will receive one of the planned dose levels of KO-2806.
[b]Mandatory pretreatment and on-treatment fresh tumor biopsies.
[c]KO-2806 combination dose level will start one level lower than the recommended monotherapy dose.
[d]Patients will receive the RP2D of KO-2806 or will be randomized if two potential RP2Ds are identified.

KEY ELIGIBILITY CRITERIA

	Arm 1 monotherapy	Arm 2 ccRCC combination (KO-2806 and cabozantinib)	Arm 3 NSCLC combination (KO-2806 and adagrasib)
Key inclusion criteria			
Age	≥ 18 years		
Diagnosis of advanced solid tumor	Histologically or cytologically confirmed advanced solid tumor		
Disease severity	• Measurable disease per RECIST (version 1.1) • Karnofsky Performance Status Scale score of ≥ 70 with no clinically significant deterioration in the previous 2 weeks • Acceptable endocrine, hematologic, liver and renal functions		
Arm-specific criteria	*HRAS* mutation and/or amplification (any solid tumor type); *HRAS* overexpression (HNSCC only); *KRAS*, *NRAS* and/or *HRAS* mutation and/or amplification (NSCLC or CRC); *KRAS* mutation and/or amplification (PDAC)	Must have received at least one prior systemic therapy with an immunotherapy for locally advanced or metastatic ccRCC	Must have received at least one prior systemic therapy for *KRAS-G12C*-m locally advanced or metastatic NSCLC
Key exclusion criteria			
Prior or ongoing treatment/conditions	• Prior treatment with an FTI or HRAS inhibitor • Major surgery in the previous 28 days or still recovering from prior surgery • Spinal cord compression, leptomeningeal disease or clinically active CNS metastases • Active or prior documented autoimmune or inflammatory disorders in the previous 5 years (with exceptions) • Inability to swallow, impairment of GI function or GI disease that may significantly alter the absorption of the trial drugs • Inadequate cardiac and/or vascular function, including mean QTcF ≥ 470 ms, presence of acute coronary syndrome in the past 6 months or class II or greater congestive heart failure • Other invasive malignancy in the previous 2 years		

OUTCOME MEASURES

Objectives	Endpoints
Primary	
Safety	
• Evaluate safety and tolerability of KO-2806 as monotherapy and in combination in patients with advanced solid tumors (phase 1a) • Determine MTD/HPDD and/or OBAD of KO-2806 as monotherapy and in combination (phase 1a) • Define RP2D of KO-2806 in combination (phase 1b)	• Incidence and severity of treatment-emergent AEs, incidence of SAEs, dose-limiting toxicities, abnormal laboratory parameters, abnormal vital signs and abnormal ECG results • Incidence of dose interruptions, reductions and discontinuations due to AEs
Efficacy	
• Evaluate antitumor activity of KO-2806 in combination in patients with advanced solid tumors (phase 1b)	• ORR per RECIST (version 1.1)
Secondary[a]	
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 SAEs, dose-limiting toxicities, abnormal laboratory parameters, abnormal vital signs and abnormal ECG results • 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)	• DCR, DoR, PFS per RECIST (version 1.1) per Investigator assessment and OS
PK	
• 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 AUC_{last}, C_{max}, T_{max}, $t_{½}$ 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	

[a]Not a comprehensive list.

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.**

Disclosures

Disclosure information is available with the online abstract.

References

1. Cox AD, Der CJ. *Small GTPases* 2010;1:2–27.
2. Kessler L *et al. Cancers (Basel)* 2021;13:5310.
3. Ho AL *et al. J Clin Oncol* 2021;39:1856–64.
4. ClinicalTrials.gov. Safety and Efficacy of Tipifarnib in Head and Neck Cancer With HRAS Mutations and Impact of HRAS on Response to Therapy (AIM-HN/SEQ-HN). Available from: https://www.clinicaltrials.gov/study/NCT03719690 (Accessed February 27, 2024).
5. Ho AL *et al.* Poster (abstract #LBA47) presented at the European Society for Medical Oncology Congress, October 20–24, 2023, Madrid, Spain.
6. Gatchalian J *et al.* Poster (abstract #34634) presented at the 36th EORTC-NCI-AACR Symposium, October 11–15, 2023, Boston, MA, USA.
7. Patel HV *et al.* Poster (abstract #34968) presented at the 36th EORTC-NCI-AACR Symposium, October 11–15, 2023, Boston, MA, USA.
8. Smith A *et al.* Poster (abstract #34971) presented at the 36th EORTC-NCI-AACR Symposium, October 11–15, 2023, Boston, MA, USA.

Abbreviations

-m, mutant; AE, adverse event; AUC_{last}, AUC from time 0 to last measurable concentration; ccRCC, clear cell renal cell carcinoma; CDX, cell line-derived xenograft; CL/F, total apparent clearance; C_{max}, maximum plasma concentration; CNS, central nervous system; CRC, colorectal cancer; DCR, disease control rate; DL, dose level; DLX, dose for the first PD cohort; DLZ, dose for the second PD cohort; DoR, duration of response; ECG, electrocardiogram; FTI, farnesyl transferase inhibitor; GI, gastrointestinal; HNSCC, head and neck squamous cell carcinoma; HPDD, highest protocol-defined dose; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; OBAD, optimal biologically active dose; ORR, objective response rate; OS, overall survival; PD, pharmacodynamic(s); PDAC, pancreatic ductal adenocarcinoma; PDX, patient-derived xenograft; PFS, progression-free survival; PK, pharmacokinetic(s); QTc, corrected QT interval; QTcF, QT interval corrected for heart rate by Fridericia's cube-root formula; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; SAE, serious adverse event; $t_{½}$, half-life; T_{max}, time to maximum observed plasma concentration.

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Author contributions

All authors contributed to study conception/design or data collection/analysis/interpretation, development of this poster or critical review of the content; and gave their approval for the final poster.

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