A phase 1 clinical trial of the novel farnesyl transferase inhibitor KO-2806 (FIT-001) 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.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).³,⁴
- Clinical trials (NCT03532927, NCT03719690) of the FTI tipifarnib in patients with NRAS-mutant (∼25%) and non-small squamous cell carcinoma (NSQCC) with high-voltage allele frequency mutations (20% or higher) had an objective response rate (ORR) of 52.8% or 30%, and favorable long-term outcome.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 farnesyl transferase inhibitors by inhibiting farnesylnation of farnesyltransferase inhibitor-resistant prostate cancer cell lines.
- KRAS inhibitors in KRAS-m CDX and PDX models, including adagrasib in non-small cell lung cancer (NSQCC) and colorectal cancer (CRC) and pancreatic ductal adenocarcinoma (PDAC).⁶

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.

OUTCOME MEASURES

- Monotherapya
  - Objective: Phase 1a (dose escalation) consists of three arms with specific eligibility criteria shown in the table below.
  - Objective: Phase 1b (dose expansion) will enroll up to 20 patients; patients will be randomized to each of the three monotherapy arms in a 1:1:1 ratio.
- Combination therapy
  - Objective: Phase 1a (dose escalation) consists of three arms with specific eligibility criteria shown in the table below.
  - Objective: Phase 1b (dose expansion) will enroll up to 20 patients; patients will be randomized to each of the three combination arms in a 1:1:1 ratio.

STUDY POPULATION

- FIT-001 is a first-in-human, multicenter, open-label, phase 1a/b dose escalation/expansion clinical trial (NCT06694110) (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 shown in the table below.
- Based on emerging data from phase 1a, up to two PD cohorts may be explored for each of the monotherapy, cCRC combination and NSQCC combination.
- In each cohort, 6–12 patients may be enrolled; taking paired fresh tumor biopsies at screening and on day 21 will be mandatory.

STUDY TOOLS

- ClinicalTrials.gov.
- Safety and Efficacy of Tipifarnib in Head and Neck Cancer With HRAS Mutations and/or Overexpression (NCT02383927, NCT03719690).

KEY ELIGIBILITY CRITERIA

<table>
<thead>
<tr>
<th>Key eligibility criteria</th>
<th>Arm 1 monotherapy</th>
<th>Arm 2 cCRCC combination (KO-2806 and cabozantinib)</th>
<th>Arm 3 NSQCC combination (KO-2806 and adagrasib)</th>
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<tr>
<td>Age</td>
<td>≥18 years</td>
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<td>Diagnosis of advanced solid tumor</td>
<td>Histologically or cytologically confirmed advanced solid tumor</td>
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<td>Disease severity</td>
<td>Measurable disease per RECIST (version 1.1)</td>
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<td>Arm-specific criteria</td>
<td>KRAS mutation and/or amplification (any solid tumor type), HRAS overexpression (NSQCC only), KRAS, HRAS and/or PIK3CA mutation and/or amplification (PDAC)</td>
<td>Have received at least one prior systemic therapy with an immunotherapy for locally advanced or metastatic CRC</td>
<td>Have received at least one prior systemic therapy for KRAS-G12C-m locally advanced or metastatic NSQCC</td>
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<td>Prior or ongoing treatment conditions</td>
<td>Prior treatment with an FTI or HRAS inhibitor</td>
<td>Major surgery in the previous 25 days or still recovering from surgery</td>
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<td>Spinal cord compression, leptomeningeal disease or clinically active CNS metastases</td>
<td>Active or documented autoimmune or inflammatory disorders in the previous 5 years (with exceptions)</td>
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<td>Inability to swallow, impairment of GI function or GI disease that may significantly alter the absorption of the trial drugs</td>
<td>Inadequate cardiac, pulmonary, 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</td>
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<td>Other invasive malignancy in the previous 2 years</td>
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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 NSQCC, and other potential combinations.

References


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