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# A Phase 1 Study of the Next-Generation Farnesyltransferase Inhibitor (FTI) KO-2806 as Monotherapy in Advanced Solid Tumors


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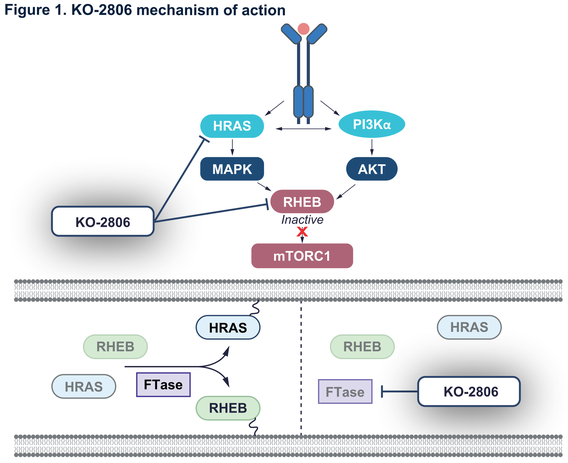
## BACKGROUND

- **Farnesylation**, a post-translational modification, attaches a farnesyl group to proteins, anchoring them to cell membranes to facilitate signaling complexes critical for cellular function[1]
- **Key signaling proteins**, including NRAS, KRAS, HRAS, and RHEB, require farnesylation for localization and activity in oncogenic pathways[2–4]
- **HRAS** and **RHEB** depend solely on farnesylation for function, whereas NRAS and KRAS can use alternative prenylation (eg, geranylgeranylation) when farnesylation is inhibited[2–4]
- ***HRAS*-mutant** (-m) tumors, which are highly reliant on farnesylation, are sensitive to farnesyltransferase inhibitors (FTIs), with the FTI tipifarnib demonstrating encouraging clinical activity in patients with *HRAS*-m tumors[5,6]
- **KO-2806 (darlifarnib)**, a next-generation FTI (**Figure 1**), offers enhanced potency[7–9] and optimized pharmacokinetic (PK) properties that support **once daily dosing**

**Figure 1. KO-2806 mechanism of action**




AKT, protein kinase B; FTase, farnesyltransferase; MAPK, mitogen-activated protein kinase; mTORC1; mammalian target of rapamycin complex 1; PI3K, phosphatidylinositol 3-kinase; RHEB, Ras homolog enriched in brain.

## AIM

- We evaluated safety, tolerability, PK, and preliminary antitumor activity of KO-2806 monotherapy in patients with *RAS*-altered advanced solid tumors in the FIT-001 study (NCT06026410)

## METHODS

- FIT-001 is an ongoing first-in-human, multicenter, open-label, phase 1a/b dose-escalation/-expansion study of KO-2806 alone and in combination in patients with advanced solid tumors:
  - **KO-2806 monotherapy for patients with *RAS*-altered solid tumors (Figure 2)**
- KO-2806 3, 5, 8, 10, or 15 mg was orally administered once daily (QD) on Days 1–7 and 15–21 in 28-day cycles

**Figure 2. FIT-001 study design**

**Key Eligibility Criteria**

- Age ≥ 18 years
- Karnofsky PS ≥ 70
- Advanced solid tumors
  - Any solid tumor: *HRAS*-m/-amp
  - HNSCC: *HRAS* overexpression
  - NSCLC/CRC: *KRAS*/*NRAS*/*HRAS*-m/-amp

**Key Endpoints**

- Safety and tolerability
- Antitumor activity
- Pharmacokinetics

**KO-2806 QD Monotherapy (Phase 1a: Dose Escalation)[a]**

- KO-2806 15 mg
- KO-2806 10 mg
- KO-2806 8 mg
- KO-2806 5 mg
- KO-2806 3 mg

[a]Each individual patient will receive one of the planned dose levels of KO-2806.
amp, amplified; CRC, colorectal cancer; HNSCC, head and neck squamous cell carcinoma; m, mutant; NSCLC, non-small cell lung cancer; PS, performance status; QD, once daily.

## RESULTS

### Patients and treatment

- From Oct 18, 2023 to Aug 15, 2025, 31 patients with advanced, *RAS*-altered solid tumors were enrolled across 9 sites in the US (**Table 1**)
- As of the data cutoff date (Aug 15, 2025), 31 patients received KO-2806 monotherapy; 24 had discontinued due to progressive disease (n = 20), adverse events (AEs; n = 2), or other reason (n = 2; including symptomatic deterioration, use of prednisone > 12 mg during palliative radiation; n = 1 each)

**Table 1. Demographics and baseline characteristics**

| | KO-2806 3 mg (n = 3) | KO-2806 5 mg (n = 5) | KO-2806 8 mg (n = 12) | KO-2806 10 mg (n = 10) | KO-2806 15 mg (n = 1) |
|---|---|---|---|---|---|
| **Median age, years (range)** | 63 (61–74) | 61 (53–75) | 57 (36–70) | 54 (47–76) | 77 (77–77) |
| **Male, n (%)** | 1 (33) | 3 (60) | 8 (67) | 9 (90) | 1 (100) |
| **Race, n (%)** | | | | | |
| White | 3 (100) | 5 (100) | 8 (67) | 8 (80) | 1 (100) |
| Other | 0 | 0 | 2 (17) | 1 (10) | 0 |
| Asian | 0 | 0 | 2 (17) | 0 | 0 |
| Black or African American | 0 | 0 | 0 | 1 (10) | 0 |
| **Ethnicity, n (%)** | | | | | |
| Hispanic or Latino | 0 | 0 | 2 (17) | 1 (10) | 0 |
| Not Hispanic or Latino | 3 (100) | 5 (100) | 10 (83) | 8 (80) | 1 (100) |
| NR | 0 | 0 | 0 | 1 (10) | 0 |
| **Primary tumor type, n (%)** | | | | | |
| Pancreas | 1 (33) | 3 (60) | 1 (8) | 3 (30) | 0 |
| Rectum | 1 (33) | 1 (20) | 2 (17) | 2 (20) | 0 |
| Colon | 0 | 0 | 1 (8) | 4 (40) | 0 |
| Head and neck[a] | 1 (33) | 1 (20) | 2 (17) | 0 | 1 (100) |
| Other | 0 | 0 | 4 (33) | 0 | 0 |
| Salivary gland[a] | 0 | 0 | 1 (8) | 1 (10) | 0 |
| Thyroid gland[a] | 0 | 0 | 1 (8) | 0 | 0 |
| **Karnofsky PS, n (%)** | | | | | |
| 50–70 | 0 | 0 | 1 (8) | 0 | 0 |
| 80–100 | 3 (100) | 5 (100) | 11 (92) | 10 (100) | 1 (100) |
| **Prior therapy lines[b], n (%)** | | | | | |
| 0 | 0 | 1 (20) | 0 | 0 | 0 |
| 1 | 0 | 2 (40) | 3 (25) | 0 | 0 |
| 2 | 2 (67) | 0 | 2 (17) | 5 (50) | 1 (100) |
| ≥ 3 | 1 (33) | 2 (40) | 7 (58) | 5 (50) | 0 |
| ***HRAS* alteration, n (%)** | 1 (33) | 2 (40) | 8 (67) | 1 (10) | 1 (100) |

[a]*HRAS*-m-driven tumors. [b]Prior therapy lines in the advanced/metastatic setting.
NR, not reported; PS, performance status.

### Safety and tolerability

- Treatment-emergent AEs were consistent with the mechanism of action of FTIs (**Table 2**)
- Five patients had dose-limiting toxicities: 1 patient at 8 mg (lipase increased), 3 patients at 10 mg (platelet count decreased, anemia, and neutropenia, n = 1 each), and 1 patient at 15 mg (platelet count decreased)
- Treatment-related serious AEs occurred in 1 patient (8 mg): myalgia (grade 2), platelet count decreased (grade 2), and neutrophil count decreased (grade 4)
- Three patients discontinued per investigator decision for KO-2806-related toxicity (n = 1, grade 3 malignant ascites and grade 3 acute kidney injury at 5 mg; n = 1, grade 3 tumor pain at 8 mg; n = 1, grade 1 nausea and grade 2 anemia at 10 mg)
- **The maximum tolerated dose was determined to be 10 mg**

**Table 2. Treatment-emergent adverse events (TEAEs)**

| n (%) | KO-2806 3 mg (n = 3) | KO-2806 5 mg (n = 5) | KO-2806 8 mg (n = 12) | KO-2806 10 mg (n = 10) | KO-2806 15 mg (n = 1) |
|---|---|---|---|---|---|
| **Any-Grade TEAEs (≥ 25% of all patients)** | **3 (100)** | **5 (100)** | **11 (92)** | **9 (90)** | **1 (100)** |
| Neutropenia | 2 (67) | 2 (40) | 5 (42) | 7 (70) | 1 (100) |
| Anemia | 3 (100) | 3 (60) | 7 (58) | 1 (10) | 1 (100) |
| Nausea | 1 (33) | 1 (20) | 5 (42) | 4 (40) | 0 |
| Thrombocytopenia | 0 | 0 | 5 (42) | 4 (40) | 1 (100) |
| Fatigue | 0 | 3 (60) | 1 (8) | 3 (30) | 1 (100) |
| **Grade ≥ 3 TEAEs (≥ 5% of all patients)** | **3 (100)** | **1 (20)** | **8 (67)** | **6 (60)** | **1 (100)** |
| Neutropenia | 0 | 0 | 4 (33) | 6 (60) | 1 (100) |
| Anemia | 1 (33) | 0 | 3 (25) | 1 (10) | 1 (100) |
| Thrombocytopenia | 0 | 0 | 1 (8) | 2 (20) | 1 (100) |
| Leukopenia | 0 | 0 | 1 (8) | 1 (10) | 1 (100) |
| Ascites | 1 (33) | 1 (20) | 0 | 0 | 0 |
| Hypokalemia | 0 | 0 | 2 (17) | 0 | 0 |

### Antitumor activity

- Of 25 response-evaluable patients with ≥ 1 post baseline scan, 3 (12%) receiving KO-2806 monotherapy achieved a partial response (PR) (**Table 3**)

**Table 3. Response in all response-evaluable[a] patients**

| n (%) | KO-2806 3 mg (n = 3) | KO-2806 5 mg (n = 5) | KO-2806 8 mg (n = 8) | KO-2806 10 mg (n = 8) | KO-2806 15 mg (n = 1) |
|---|---|---|---|---|---|
| **ORR (CR + PR)** | 0 | 1 (20) | 2 (25)[b] | 0 | 0 |
| 95% CI | 0.0–70.8 | 0.5–71.6 | 3.1–65.1 | 0.0–36.9 | 0.0–97.5 |
| *HRAS*-m patients, n/N (%) | 0/1 (0) | 1/2 (50) | 2/4 (50) | 0/1 (0) | 0/1 (0) |
| 95% CI | 0.0–97.5 | 1.3–98.7 | 6.8–93.2 | 0.0–97.5 | 0.0–97.5 |
| **PR** | 0 | 1 (20) | 2 (25)[b] | 0 | 0 |
| **SD** | 1 (33) | 2 (40) | 3 (38) | 2 (25) | 0 |
| **DCR (CR + PR + SD)** | 1 (33) | 3 (60) | 5 (63)[b] | 2 (25) | 0 |
| 95% CI | 0.8–90.6 | 14.7–94.7 | 24.5–91.5 | 3.2–65.1 | 0.0–97.5 |

[a]Response-evaluable patients had ≥ 1 post-baseline scan. [b]Including n = 1 confirmed PR; n = 1 unconfirmed PR.
CI, confidence interval; CR, complete response; DCR, disease control rate; m, mutant; ORR, objective response rate; PR, partial response; SD, stable disease.

### Antitumor activity (continued)

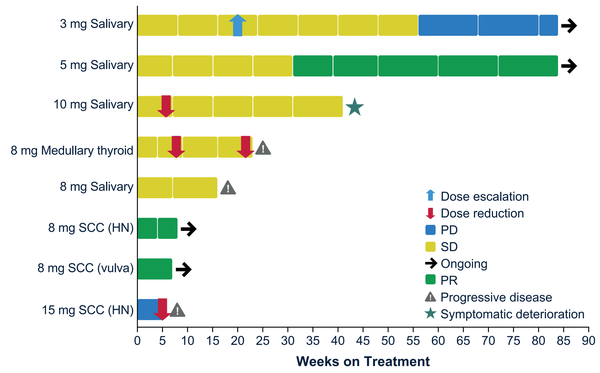
- In a subset of patients with advanced *HRAS*-m tumors who had clinical benefit, KO-2806 monotherapy demonstrated encouraging clinical activity with responses and/or durable disease control across 4 dose levels (**Table 4**)
  - PRs were achieved in patients across tumor types: salivary, squamous cell carcinoma (head and neck), and squamous cell carcinoma (vulva)
- Durability of response and time on treatment are presented in **Figure 3**

**Table 4. Subset of response-evaluable[a] patients with *HRAS*-m tumors with clinical benefit[b]**

| Dose | Indication | *HRAS*-m | BOR | Max. Tumor Shrinkage, % | Time on Treatment, mo |
|---|---|---|---|---|---|
| **3 mg**[c] | Salivary[d] | Q61R | SD | 0 | 21[e] |
| **5 mg** | Salivary[d] | Q61R | PR | 63 | 20[f] |
| **8 mg** | Salivary | Q61R | SD | 18 | 4 |
| | SCC (HN)[d] | G13V | PR | 61 | 3 |
| | SCC (vulva)[d] | K117N | PR[g] | 56 | 2 |
| | Medullary thyroid | G13R | SD | 0 | 6 |
| **10 mg** | Salivary | Q61R | SD | 25 | 11 |

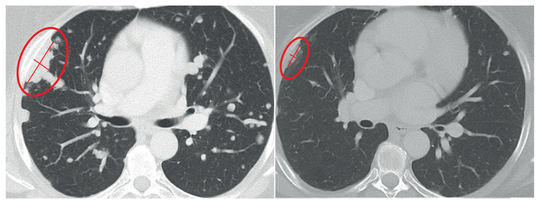
[a]Response-evaluable patients had ≥ 1 post-baseline scan. [b]8 of 13 patients with *HRAS*-m tumors were response-evaluable; 1 patient did not have clinical benefit with KO-2806 monotherapy. [c]Dose was increased to KO-2806 5 mg at week 20. [d]On study treatment as of Aug 15, 2025. [e]Patient progressed 13.9 mo after treatment initiation; as of Jun 18, 2025, patient remained on study treatment (time from cycle 1 day 1 to most recent scan: 19.4 mo). [f]Durable response. [g]Unconfirmed PR as of data cutoff.
BOR, best overall response; HN, head and neck; m, mutant; max, maximum; mo, months; PR, partial response; SCC, squamous cell carcinoma; SD, stable disease.

**Figure 3. Time on treatment and durability of response in response-evaluable[a] patients[b] with *HRAS*-m tumors**




[a]Response-evaluable patients had ≥ 1 post-baseline scan. [b]8 of 13 patients with *HRAS*-m tumors were response-evaluable.
HN, head and neck; m, mutant; PD, progressive disease; PR, partial response; SCC, squamous cell carcinoma; SD, stable disease.

**Figure 4. Scans from a responder treated with KO-2806 5 mg**




cPR, confirmed partial response; SoD, sum of diameters; TL, target lesion.

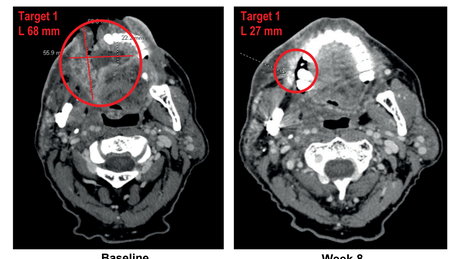
- 60-year-old female patient with stage IVc salivary gland carcinoma (**Figure 4**)
  - *HRAS* Q61R, variant allele frequency (VAF): 16%[a]
  - PD-L1 tumor proportion score: 1%[a]
- Prior therapies:
  - Left total parotidectomy (Aug 2014), radiotherapy (Nov 2014), right lung video-assisted thoracic surgery, and wedge resection (Feb 2021)
- Initiated KO-2806 5 mg treatment in Dec 2023
- Response:
  - PR (62.8% tumor shrinkage vs baseline)
- As of data cutoff, patient remained on treatment

[a]Sample collected in Feb 2021; no intervening systemic anticancer therapy prior to patient initiating KO-2806 treatment in Dec 2023.

**Key considerations**

- Deep and durable response in a patient with *HRAS*-m salivary gland carcinoma
- Supports monotherapy clinical activity

**Figure 5. Scans from a responder treated with KO-2806 8 mg**




cPR, confirmed partial response; SoD, sum of diameters; TL, target lesion.

- 70-year-old male patient with stage IVa head and neck squamous cell carcinoma (HNSCC) (**Figure 5**)
  - *HRAS* G13V, VAF: 61%[a]
  - PD-L1 combined positive score: 60%[a]
- Prior therapies:
  - Marginal mandibulectomy + modified radical neck dissection (Oct 2022)
  - Adjuvant radiotherapy (Jan to Feb 2023)
  - 1L carboplatin + paclitaxel (CP) + pembrolizumab (P) then P (Sep 2023 to Jul 2024)
  - 2L CP + P (Sep to Dec 2024)
  - 3L cetuximab + ficlatuzumab (Feb 2025 to Apr 2025)
- Initiated KO-2806 8 mg treatment in May 2025
- Response:
  - PR (60% tumor shrinkage at week 8 vs baseline)
- As of data cutoff, patient remained on treatment

[a]Sample collected in Jan 2024; patient received 3 treatment lines from time of biopsy to KO-2806 treatment initiation.

**Key considerations**

- Deep, early response in a 4L patient with advanced *HRAS*-m HNSCC
- Indicates monotherapy clinical activity

### Pharmacokinetics

- KO-2806 demonstrated a linear, dose-proportional increase in exposure with doses up to 10 mg

## CONCLUSIONS

- **KO-2806 (darlifarnib) demonstrates a manageable safety and tolerability profile with preliminary PK data supporting QD dosing**
- **Encouraging monotherapy antitumor activity was observed at multiple doses (KO-2806 3–10 mg) in advanced *HRAS*-m solid tumors, evidencing a broad therapeutic window**
- **KO-2806 is currently being evaluated in combination with cabozantinib (in renal cell carcinoma) and adagrasib (in *KRAS*-G12C-m non-small cell lung cancer, colorectal cancer, or pancreatic duct adenocarcinoma) in the phase 1 FIT-001 study (NCT06026410)[10]**


### References

**1.** Mijimolle N et al. *Cancer Cell* 2005;7:313-24; **2.** Whyte DB et al. *J Biol Chem* 1997;272:14459-64; **3.** McGeady P et al. *J Biol Chem* 1995;270:26347-51; **4.** Castro AF et al. *J Biol Chem* 2003;278:32493-6; **5.** Ho AL et al. *J Clin Oncol* 2021;39:1856-64; **6.** Ho AL et al. *Ann Oncol* 2023;34(suppl_2):S1286-7; **7.** Gatchalian J et al. Poster (abstract #34634) presented at the 36th EORTC-NCI-AACR Symposium, October 11–15, 2023, Boston, MA, USA; **8.** Patel HV et al. Poster (abstract #34968) presented at the 36th EORTC-NCI-AACR Symposium, October 11–15, 2023, Boston MA, USA; **9.** Smith A et al. Poster (abstract #34971) presented at the 36th EORTC-NCI-AACR Symposium, October 11–15, 2023, Boston MA, USA; **10.** Ayanambakkam A et al. Poster (abstract #70) presented at the Kidney Cancer Research Summit (KCRS), July 17–18, 2025, Boston MA, USA.



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### Abbreviations

AE, adverse event; AKT, protein kinase B; amp, amplified; BOR, best overall response; CI, confidence interval; CP, carboplatin + paclitaxel; cPR, confirmed partial response; CR, complete response; CRC, colorectal cancer; DCR, disease control rate; FTase, farnesyltransferase; FTI, farnesyltransferase inhibitor; HN, head and neck; m, mutant; MAPK, mitogen-activated protein kinase; max, maximum; mo, months; mTORC1; mammalian target of rapamycin complex 1; NR, not reported; NSCLC, non-small cell lung cancer; ORR, objective response rate; P, pembrolizumab; PD, progressive disease; PI3K, phosphatidylinositol 3-kinase; PK, pharmacokinetic; PR, partial response; PS, performance status; QD, once daily; RCC, renal cell carcinoma; RHEB, Ras homolog enriched in brain; SCC, squamous cell carcinoma; SD, stable disease; SoD, sum of diameters; TL, target lesion; VAF, variant allele frequency.

**For FIT-001 combination in RCC data, see Ayanambakkam et al., ESMO poster #2604P**

Poster PDF can be accessed through this Quick Response (QR) code. Copies obtained are for personal use only.

Additional information on the FIT-001 study can be accessed here.

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