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Farnesyltransferase Inhibitor (FTI) KO-2806 in Combination With Cabozantinib (Cabo) in Renal Cell Carcinoma (RCC): Preliminary Results From FIT-001 Phase 1 Trial

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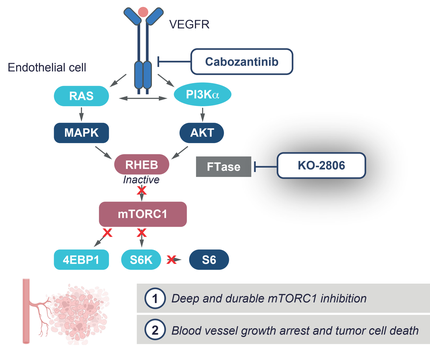
BACKGROUND

- Hyperactivation of the mTOR signaling pathway is a common feature of renal cell carcinoma (RCC)[1–3]
- Overactive mTOR pathway signaling drives cell growth, proliferation, and survival and is associated with poor prognosis[2], making it a critical therapeutic target in RCC
- Rapalogs, such as everolimus and temsirolimus, are FDA approved in RCC but have limited use due to tolerability issues[4-6]
- Cabozantinib, a VEGFR-targeted tyrosine kinase inhibitor (TKI), is a standard RCC treatment, offering clinical benefit (second-line [2L]: objective response rate [ORR] 28%, stable disease [SD] 60%)[7]; however, reduced activity with subsequent VEGFR-targeted TKIs underscores the need to optimize VEGF-targeted therapies[8,9]
- **KO-2806 (darlifarnib)**, a next-generation FTI, inhibits hyperactivated mTORC1 signaling by inhibiting RHEB farnesylation essential to mTORC1 activation, while sparing mTORC2 inhibition and its associated toxicities in preclinical models (**Figure 1**)[10,11]
- KO-2806 enhances cabozantinib's antiangiogenic activity by blocking mTOR reactivation in endothelial cells[12]

Figure 1. KO-2806 + cabozantinib mechanism of action in RCC



AKT, protein kinase B; FTase, farnesyltransferase; MAPK, mitogen-activated protein kinase; mTORC1; mammalian target of rapamycin complex 1; PI3K, phosphatidylinositol 3-kinase; RCC, renal cell carcinoma; RHEB, Ras homolog enriched in brain; VEGFR, vascular endothelial growth factor receptor.

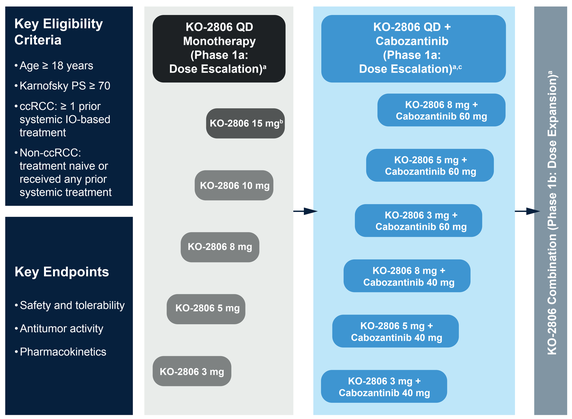
AIM

- We assessed safety, tolerability, and preliminary antitumor activity of KO-2806 in combination with cabozantinib in patients with RCC 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 (**Figure 2**), including:
  - **KO-2806 + cabozantinib combination for patients with clear cell (cc)RCC or non-ccRCC**
  - KO-2806 monotherapy for patients with *RAS*-altered solid tumors
- KO-2806 3, 5, or 8 mg was administered once daily (QD) orally Days 1–7 and 15–21 plus continuous cabozantinib 40 mg or 60 mg QD in 28-day cycles

Figure 2. FIT-001 study design



[a]Each individual patient will receive one of the planned DLs of KO-2806. [b]Non-tolerated DL. [c]KO-2806 + adagrasib combination for patients with *KRAS* G12C-mutated NSCLC, CRC, or PDAC is also being assessed.
cc, clear cell; CRC, colorectal cancer; DL, dose level; IO, immune checkpoint inhibition; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; PS, performance status; QD, once daily; RCC, renal cell carcinoma.

RESULTS

Patients and treatment

- From Oct 18, 2023 to Aug 15, 2025, 56 patients with RCC were enrolled across 9 sites in the US (**Table 1**)
- As of the data cutoff date (Aug 15, 2025; median time on study drug: 6.7 months [range 0.4–18.8]), 56 patients with RCC received KO-2806 + cabozantinib, and 21 had discontinued; reasons included progressive disease (n = 9), symptomatic deterioration (n = 5), patient withdrawal (n = 4[a]), and adverse events (AEs; n = 3)

[a]Including 1 patient who withdrew consent due to AE.

Table 1. Demographics and baseline characteristics

	Cabozantinib 40 mg		
	KO-2806 3 mg (n = 9)	KO-2806 5 mg (n = 12)	KO-2806 8 mg (n = 12)
Median age, years (range)	58 (47–83)	67 (50–80)	59 (39–80)
Male, n (%)	5 (56)	10 (83)	9 (75)
Race, n (%)			
White	7 (78)	6 (50)	6 (50)
Non-White[a]	2 (22)	6 (50)	6 (50)
RCC type, n (%)			
Clear cell	7 (78)	8 (67)	9 (75)
Non-clear cell[b]	2 (22)	4 (33)	3 (25)
Karnofsky PS, n (%)[c]			
50–70	0	1 (8)	0
80–100	9 (100)	11 (92)	11 (92)
Prior therapy lines, n (%)			
1	4 (44)	3 (25)	4 (33)
2	2 (22)	4 (33)	2 (17)
≥3	3 (33)	5 (42)	4 (33)
Prior therapy type(s), n (%)[d]			
IO	4 (44)	7 (58)	6 (50)
IO + TKI combination[e]	7 (78)	7 (58)	6 (50)
Cabozantinib	7 (78)	8 (67)	5 (42)
Other[f]	0	7 (58)	4 (33)

	Cabozantinib 60 mg		
	KO-2806 3 mg (n = 2)	KO-2806 5 mg (n = 12)	KO-2806 8 mg (n = 9)
Median age, years (range)	76 (73–79)	68 (42–76)	72 (61–78)
Male, n (%)	1 (50)	10 (83)	9 (100)
Race, n (%)			
White	1 (50)	9 (75)	9 (100)
Non-White[a]	1 (50)	3 (25)	0
RCC type, n (%)			
Clear cell	1 (50)	11 (92)	9 (100)
Non-clear cell[b]	1 (50)	1 (8)	0
Karnofsky PS, n (%)[c]			
50–70	0	0	0
80–100	1 (50)	12 (100)	9 (100)
Prior therapy lines, n (%)			
1	0	9 (75)	7 (78)
2	1 (50)	2 (17)	2 (22)
≥3	1 (50)	1 (8)	0 (0)
Prior therapy type(s), n (%)[d]			
IO	0	10 (83)	5 (55.5)
IO + TKI combination[e]	2 (100)	3 (25)	3 (33)
Cabozantinib	1 (50)	0	0
Other[f]	0	2 (17)	0

[a]Includes Black or African American, Asian, American Indian or Alaska Native, Other, and Multiple. [b]Including papillary (n = 4), chromophobe (n = 3), sarcomatoid (n = 2), and unknown tumor type (n = 2) across dose levels. [c]Karnofsky PS was missing for 2 patients. [d]Patients may have received multiple prior therapies. [e]Including cabozantinib. [f]Patients received HIF2α inhibitors or experimental therapies.
IO, immune checkpoint inhibition; PS, performance status; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor.

Table 2. Treatment-emergent adverse events (TEAEs)

	Cabozantinib 40 mg		
n (%)	KO-2806 3 mg (n = 9)	KO-2806 5 mg (n = 12)	KO-2806 8 mg (n = 12)
Any-Grade TEAEs (≥ 25% of all patients)	**9 (100)**	**12 (100)**	**11 (92)**
Diarrhea	5 (56)	5 (42)	4 (33)
Neutropenia	1 (11)	5 (42)	6 (50)
Fatigue	2 (22)	2 (17)	7 (58)
Stomatitis	3 (33)	4 (33)	4 (33)
Nausea	3 (33)	4 (33)	3 (25)
Decreased appetite	3 (33)	4 (33)	3 (25)
Grade ≥ 3 TEAEs (≥ 5% of all patients)	**6 (67)**	**11 (92)**	**6 (50)**
Neutropenia	0	5 (42)	6 (50)
Anemia	2 (22)	1 (8)	3 (25)
Fatigue	0	1 (8)	1 (8)
Thrombocytopenia	0	1 (8)	2 (17)
Diarrhea	0	1 (8)	1 (8)
Embolism	0	1 (8)	0

	Cabozantinib 60 mg		
	KO-2806 3 mg (n = 2)	KO-2806 5 mg (n = 12)	KO-2806 8 mg (n = 9)
Any-Grade TEAEs (≥ 25% of all patients)	**1 (50)**	**12 (100)**	**8 (89)**
Diarrhea	1 (50)	9 (75)	2 (22)
Neutropenia	0	6 (50)	5 (56)
Fatigue	0	6 (50)	3 (33)
Stomatitis	1 (50)	4 (33)	3 (33)
Nausea	0	6 (50)	2 (22)
Decreased appetite	0	5 (42)	2 (22)
Grade ≥ 3 TEAEs (≥ 5% of all patients)	**0**	**7 (58)**	**5 (56)**
Neutropenia	0	2 (17)	3 (33)
Anemia	0	0	1 (11)
Fatigue	0	1 (8)	1 (11)
Thrombocytopenia	0	0	0
Diarrhea	0	1 (8)	0
Embolism	0	2 (17)	0

Safety and tolerability

- Most common (≥ 25% of patients) any-grade TEAEs were diarrhea (46%), neutropenia (41%), fatigue (36%), stomatitis (34%), nausea (32%), and decreased appetite (30%) (**Table 2**)
- Most common (≥ 25% of patients) any-grade treatment-related AEs:
  - KO-2806: Neutropenia (36%), fatigue (25%)
  - Cabozantinib: Diarrhea (41%), stomatitis (34%), fatigue (29%), nausea (27%)
- There were 3 dose-limiting toxicities:
  - KO-2806 5 mg + cabozantinib 40 mg: Grade 3 neutropenia
  - KO-2806 8 mg + cabozantinib 40 mg: Grade 4 neutropenia
  - KO-2806 5 mg + cabozantinib 60 mg: Grade 3 neutropenia
- Seven patients had treatment-related serious AEs:
  - KO-2806-related (n = 1 each):
    - Grade 3 anemia; KO-2806 5 mg + cabozantinib 40 mg
    - Grade 3 metabolic encephalopathy; KO-2806 8 mg + cabozantinib 40 mg
    - Grade 4 neutropenia; KO-2806 8 mg + cabozantinib 60 mg
  - Cabozantinib-related (n = 1 each):
    - Grade 2 confusional state, grade 3 anemia, grade 3 acute cardiac failure, and grade 3 embolism; 1 patient treated with KO-2806 5 mg + cabozantinib 40 mg
    - Grade 3 metabolic encephalopathy; KO-2806 8 mg + cabozantinib 40 mg
    - Grade 4 hypokalemia; KO-2806 5 mg + cabozantinib 60 mg
    - Grade 4 nephrotic syndrome; KO-2806 8 mg + cabozantinib 60 mg

Table 3. Response in response-evaluable[a] patients with ccRCC

	Cabozantinib 40 mg			Cabozantinib 60 mg[b]
n (%)	KO-2806 3 mg (n = 6)	KO-2806 5 mg (n = 6)	KO-2806 8 mg (n = 6)	KO-2806 5 mg (n = 10)
ORR (CR + PR)				
ccRCC	2 (33)	2 (33)	2 (33)[c]	5 (50)[d]
95% CI	4.3–77.7	4.3–77.7	4.3–77.7	18.7–81.3
ccRCC with prior cabozantinib, n/N (%)	2/6 (33)	1/6 (17)	1/2 (50)[e]	NA
95% CI	4.3–77.7	0.4–64.1	1.3–98.7	NA
PR	2 (33)	2 (33)	2 (33)[c]	5 (50)[d]
SD	3 (50)	4 (67)	4 (67)	3 (30)
DCR (CR + PR + SD)	5 (83)	6 (100)	6 (100)[c]	8 (80)[d]
95% CI	35.9–99.6	54.1–100	54.1–100	44.4–97.5

[a]Response-evaluable patients had ≥ 1 post-baseline scan. [b]As of the Aug 15, 2025 data cutoff, enrollment in KO-2806 3 mg + cabozantinib 60 mg is ongoing, and response data for KO-2806 8 mg + cabozantinib 60 mg are not yet mature. [c]Including n = 1 confirmed PR, n = 1 unconfirmed PR. [d]Including n = 4 confirmed PR, n = 1 unconfirmed PR. [e]n = 1 unconfirmed PR.
ccRCC, clear cell renal cell carcinoma; CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, objective response rate; PR, partial response; NA, not applicable; SD, stable disease.

Antitumor activity

Among ccRCC patients

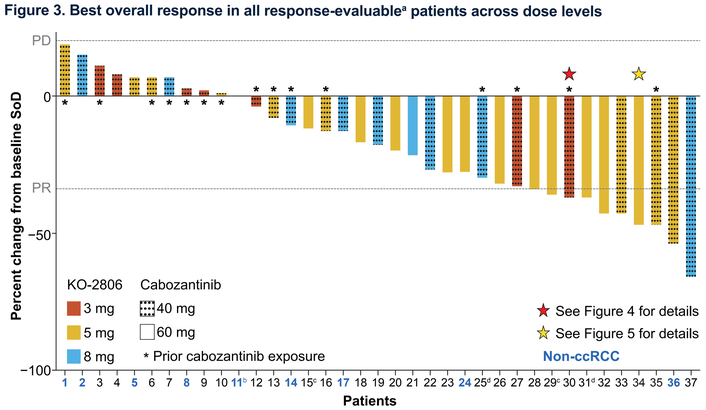
- Among response-evaluable[a] ccRCC patients, clinical activity was observed with all dose levels of KO-2806 in combination with cabozantinib 40 mg: ORR of 33%[b] (2/6 patients; 95% CI 43.3–77.7) at each dose level (**Table 3**)
- In cabozantinib-naive patients[a] at **KO-2806 5 mg and cabozantinib 60 mg**, ORR was 50% (5/10 patients [4 confirmed; 1 unconfirmed]; 95% CI 18.7–81.3); disease control rate (DCR; complete response + partial response [PR] + SD) was 80% (8/10 patients; 95% CI 44.4–97.5)
- In prior cabozantinib-treated patients[a], ORRs (95% CI) were 33% (4.3–77.7), 17% (0.4–64.1), and 50%[c] (1.3–98.7) for KO-2806 3, 5, or 8 mg + cabozantinib 40 mg, respectively; 4[d] of 12 patients who had PR on the combination had best prior response of SD with prior cabozantinib

Among non-ccRCC patients

- One of 3 non-ccRCC patients[a] had a PR with KO-2806 5 mg + 40 mg
- 37.5% (3/8) of non-ccRCC patients treated with KO-2806 + cabozantinib 40 mg and 100% (1/1) with KO-2806 + cabozantinib 60 mg experienced tumor shrinkage (**Figure 3**)
- DCRs were 100% (2/2 patients; 95% CI 15.8–100), 67% (2/3 patients; 95% CI 9.4–99.2), and 67% (2/3 patients; 95% CI 9.4–99.2) with KO-2806 3, 5, or 8 mg + cabozantinib 40 mg, respectively

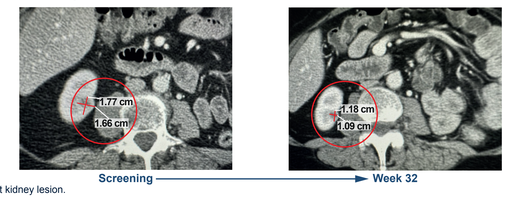
[a]Response-evaluable patients had ≥ 1 post-baseline scan. [b]At KO-2806 8 mg + cabozantinib 40 mg, n = 1 confirmed PR, n = 1 unconfirmed PR. [c]n = 1 unconfirmed PR. [d]Including n = 3 confirmed PR, n = 1 unconfirmed PR.

Figure 3. Best overall response in all response-evaluable[a] patients across dose levels



[a]Response-evaluable patients had ≥ 1 post-baseline scan. [b]Patient received KO-2806 3 mg + cabozantinib 40 mg. [c]Patient had BOR of PD due to new lesion. [d]Unconfirmed PR.
BOR, best overall response; ccRCC, clear cell renal cell carcinoma; PD, progressive disease; PR, partial response; SoD, sum of diameters.

Figure 4. Scans[a] from a responder treated with KO-2806 3 mg + cabozantinib 40 mg who received prior cabozantinib



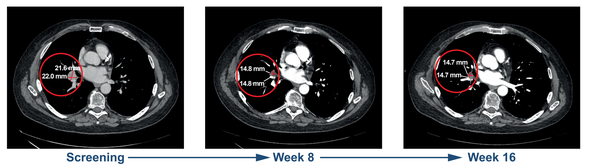
[a]Right kidney lesion.

- 53-year-old female patient with ccRCC diagnosed in 2021 (**Figure 4**)
- Prior therapy:
  - 1L: Ipilimumab + nivolumab (best overall response [BOR]: SD)
  - 2L: Nivolumab + **cabozantinib** (BOR: SD)
- At study start:
  - Stage IV
  - Initiated study treatment Oct 2024
- Response:
  - Confirmed PR, which was durable through week 40 (33% reduction at week 8; 37% reduction at weeks 16 and 24; 32% reduction at week 32; 30% reduction at week 40)
- As of data cutoff, patient remained on treatment

Key consideration

- Clinical activity of the combination in a patient with immediate prior cabozantinib exposure

Figure 5. Scans[a] from a responder treated with KO-2806 5 mg + cabozantinib 60 mg



[a]Right hilar lymph node.

- 61-year-old male patient with ccRCC diagnosed in 2021 (**Figure 5**)
- Prior therapy:
  - Pembrolizumab as adjuvant therapy (nodal metastasis after two months of treatment)
- At study start:
  - Stage IV (right hilar lymph node)
  - Initiated study treatment Feb 2025
- Response:
  - Confirmed PR (38% reduction at week 8; 44% reduction at week 16)
- As of data cutoff, patient remained on treatment

Key consideration

- PR and tumor shrinkage achieved at week 8 were maintained at week 16

CONCLUSIONS

- **In the ongoing FIT-001 study, KO-2806 (darlifarnib) + cabozantinib demonstrated a manageable safety profile in patients with RCC at all dose levels assessed**
- **Antitumor activity of KO-2806 + cabozantinib combination was observed across all doses in RCC (potentially exceeding the activity of cabozantinib alone), including among patients with prior cabozantinib exposure**
  - ORR: 33%–50% in ccRCC (with prior cabozantinib: 17%–50%)
  - DCR: 80%–100% in ccRCC
- **The data support continued dose optimization of KO-2806 + cabozantinib and further investigation of combinations of KO-2806 in VEGFR-targeted TKIs in RCC**

References

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Disclosures

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AA: Consulting or Advisory Role – AVEO, Pfizer/Astellas.

Abbreviations

1L, first-line; 2L, second-line; AE, adverse event; AKT, protein kinase B; BOR, best overall response; cabo, cabozantinib; cc, clear cell; CI, confidence interval; CR, complete response; CRC, colorectal cancer; DCR, disease control rate; DL, dose level; FTase, farnesyltransferase; IO, immune checkpoint inhibition; MAPK, mitogen-activated protein kinase; mo, months; mTORC1; mammalian target of rapamycin complex 1; NE, not evaluable; NSCLC, non-small cell lung cancer; ORR, objective response rate; PDAC, pancreatic ductal adenocarcinoma; PD, progressive disease; PI3K, phosphatidylinositol 3-kinase; PR, partial response; PS, performance status; QD, once daily; RCC, renal cell carcinoma; RHEB, Ras homolog enriched in brain; SD, stable disease; SoD, sum of diameters; TEAE, treatment-emergent adverse event; u, unconfirmed; VEGFR, vascular endothelial growth factor receptor.

For FIT-001 monotherapy data, see Hanna et al., ESMO poster #981P

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