Farnesyl transferase inhibitor (FTI) darlifarnib combined with cabozantinib in renal cell carcinoma (RCC): Updated phase 1a results from FIT-001

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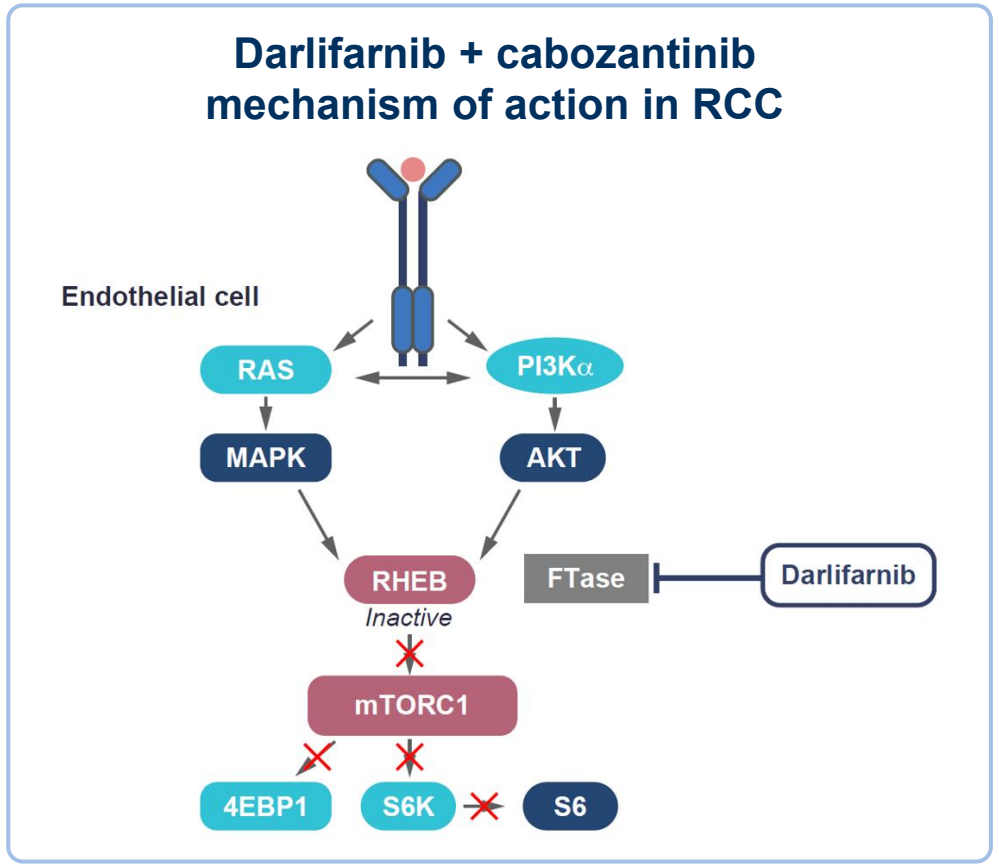
Darlifarnib Has Potential to Enhance Activity of VEGFR-TKIs in RCC



- VEGFR-TKIs are active for advanced RCC but are limited by **persistent mTORC1 signaling that promotes tumor growth, angiogenesis, and disease progression**[1–4]
  - Outcomes with **existing and emerging TKI or HIF-2α monotherapies** in 2L+ are modest (**ORRs 18%–40%,** mPFS 6–11 months)[5–9]
- **Darlifarnib**, a potent next-generation FTI, blocks RHEB farnesylation, resulting in **selective mTORC1 inhibition while sparing mTORC2**[4]
  - A previous report for darlifarnib plus cabozantinib in patients with prior cabozantinib treatment demonstrated ORR of 44% and DCR of 94%[10]

2L+, second-line plus; 4EBP1, 4E binding protein 1; AKT, protein kinase B; DCR, disease control rate; FTase, farnesyl transferase; FTI, farnesyl transferase inhibitor; HIF-2α, hypoxia-inducible factor 2 alpha; MAPK, mitogen-activated protein kinase; mPFS, median progression-free survival; mTORC, mammalian target of rapamycin complex; ORR, objective response rate; PI3K, phosphoinositide 3-kinase; RAS, rat sarcoma virus; RCC, renal cell carcinoma; RHEB, Ras homolog enriched in brain; S6, protein S6; S6K, protein S6 kinase; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

1. Sharma R et al. *J Exp Clin Cancer Res*. 2021;40:186. **2**. Yakes FM et al. *Mol Cancer Ther*. 2011;10:2298-2308. **3**. Cancer Genome Atlas Research Network. *Nature* 2013;499:43-49. **4**. Gasendo JG et al. *Mol Cancer Ther*. 2026; doi: 10.1158/1535-7163.MCT-25-0449. **5**. Rini BI et al. *Lancet Oncol*. 2020;21:95-104. **6**. Choueiri TK et al. *N Engl J Med*. 2024;391:710-721. **7**. Albiges L et al. *The Oncologist*. 2024;29(Suppl 1):42. **8**. Choueiri TK et al. *N Engl J Med*. 2015;373:1814-1823. **9**. Motzer RJ et al. ASCO GU 2026. Oral Abstract LBA417. **10**. Zakharia Y et al. IKCS Europe 2026. Poster C8.

FIT-001: Phase 1a Trial of Darlifarnib and Cabozantinib in Locally Advanced or Metastatic RCC

Key Eligibility Criteria

- Age ≥18 years
- Histologically or cytologically confirmed RCC
- ccRCC: ≥1 prior systemic therapy with IO-based treatment
- Non-ccRCC: Treatment naive or received any prior systemic therapy
- Karnofsky PS ≥70
- No active CNS metastases

Key Endpoints

- Safety and tolerability
- Antitumor activity
- Pharmacokinetics

Phase 1a Dose Escalation[a,b]

Darlifarnib administered orally QD on Days 1–7 and 15–21 plus cabozantinib administered orally QD in 28-day cycles

Cabozantinib-naive ccRCC

- Darlifarnib 8 mg[c] + Cabozantinib 60 mg
- Darlifarnib 5 mg[c] + Cabozantinib 60 mg
- Darlifarnib 3 mg + Cabozantinib 60 mg

- Darlifarnib 8 mg + Cabozantinib 40 mg
- Darlifarnib 5 mg + Cabozantinib 40 mg
- Darlifarnib 3 mg + Cabozantinib 40 mg

Phase 1b Expansion and Dose Optimization in ccRCC

NCT06026410

[a]Each individual patient will receive one of the planned dose levels of darlifarnib and cabozantinib. [b]Darlifarnib + adagrasib combination for patients with *KRAS* G12C-mutated NSCLC, CRC, or PDAC is also being assessed. [c]Darlifarnib 5 and 8 mg + cabozantinib 60 mg cohorts enrolled cabozantinib-naive ccRCC patients only.
cc, clear cell; CNS, central nervous system; CRC, colorectal cancer; IO, immuno-oncology; *KRAS*, Kirsten rat sarcoma virus oncogene homolog; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; PS, performance status; QD, once daily; RCC, renal cell carcinoma.

Baseline Characteristics

All RCC Patients

n (%)	Total (N=72)
Median age, years (range)	67 (24–83)
Male	55 (76)
Race	
White	54 (75)
Non-White[a]	18 (25)
RCC type	
Clear cell	58 (81)
Non-clear cell	13 (18)
Karnofsky PS	
80–100	71 (99)
50–70	1 (1)
Prior therapy lines, median (range)[b]	2 (1–7)
IO only[c]	22 (31)
IO + TKI combination	48 (67)
Cabozantinib (any line)[d]	27 (38)
HIF-2α inhibitor	12 (17)

- As of May 8, 2026, **72 RCC patients** were treated with the combination across dose escalation cohorts
  - 27 patients remained on treatment
  - Median follow-up time was 8.8 months (range 0.9–20.6)
- Patients were **heavily pretreated** with >50% having ≥2 prior lines of therapy
- Most patients had prior IO and/or TKI exposure

[a]Includes Black or African American, Asian, American Indian or Alaska Native, Other, and Multiple. [b]Patients may have received multiple prior therapies. [c]Includes IO as monotherapy or doublet. [d]Darlifarnib 5 and 8 mg + cabozantinib 60 mg cohorts enrolled cabozantinib-naive patients only.
HIF-2α, hypoxia-inducible factor 2 alpha; IO, immuno-oncology; PS, performance status; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor.
Data cutoff: May 8, 2026.

Safety and Tolerability of Darlifarnib + Cabozantinib

All RCC Patients

n (%)	Total (N=72)	
	Any-Grade	Grade ≥3
TEAEs (≥30% of all patients)		
Diarrhea	46 (64)	6 (8)
Fatigue	36 (50)	7 (10)
Neutropenia	34 (47)	27 (38)
Nausea	32 (44)	0
Decreased appetite	26 (36)	0
Stomatitis	24 (33)	1 (1)
Palmar-plantar erythrodysesthesia syndrome	22 (31)	1 (1)

n (%)	Related to darlifarnib	Related to cabozantinib	Total (N=72)
TEAEs, any grade	65 (90)	69 (96)	71 (99)
Grade ≥3	**42 (58)**	**41 (57)**	**55 (76)**
Serious TEAEs, any grade	11 (15)	13 (18)	29 (40)
Death	1 (1)[a]	1 (1)[b]	4 (6)[c]
DLTs[d]	-	-	4 (6)

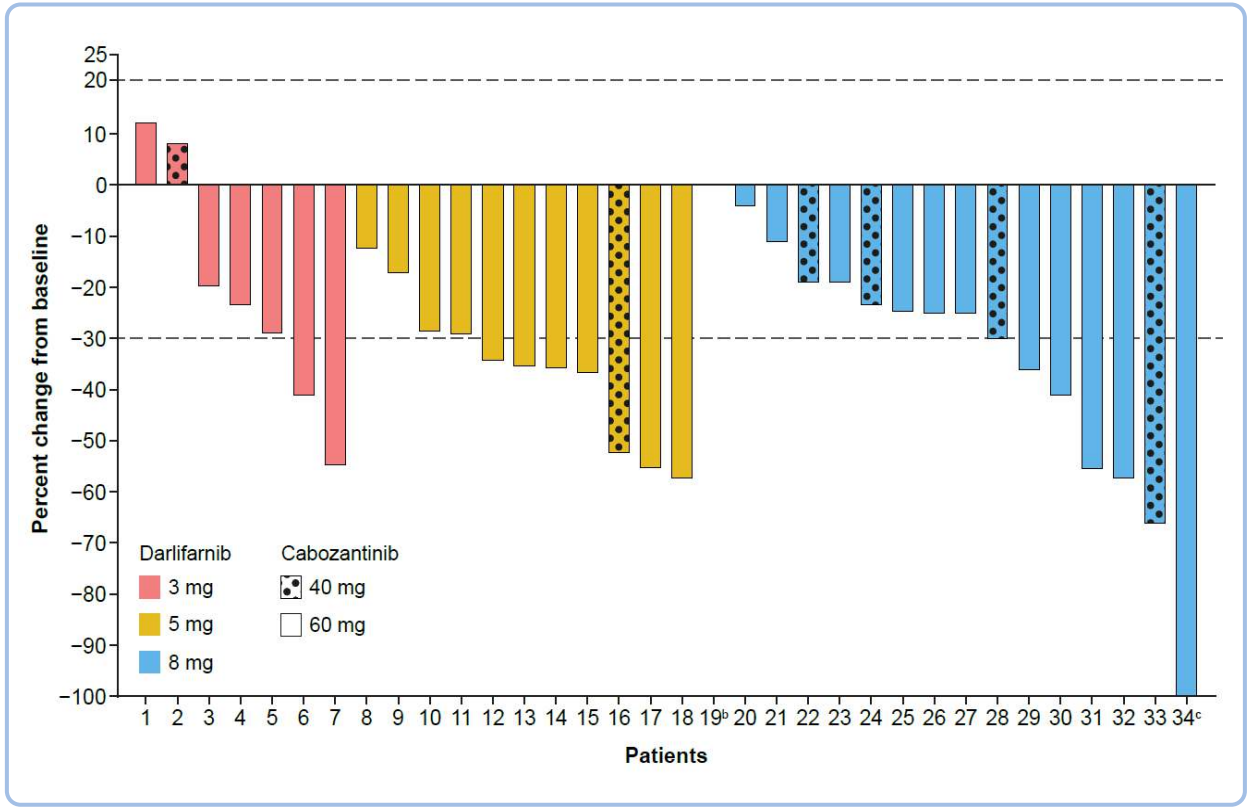
- The safety and tolerability profile was broadly consistent with reported safety profiles of each study drug[1–3]
- Supportive care, including for neutropenia, was not allowed during the DLT period[e]

[a]Due to pneumonia. [b]Due to cardiac arrest. [c]Due to cardiac arrest (n=2), pneumonia (n=1), septic shock (n=1). [d]DLTs were neutropenia (2 grade 3, 1 grade 4) and aspartate aminotransferase increased (1 grade 3). [e]DLT period was the first 28 days of cycle 1.
DLT, dose-limiting toxicity; RCC, renal cell carcinoma; TEAE, treatment-emergent adverse event.
Data cutoff: May 8, 2026.

1. Lacy S et al. *Cancer Chemother Pharmacol.* 2018;81:1061-1070. **2.** Ayanambakkam A et al. ESMO 2025. Poster 2604P. **3.** Hanna GJ et al. ESMO 2025. Poster 981P.

ORR and DCR

Cabozantinib-Naive ccRCC[a]



n (%) [95% CI]	Darlifarnib + Cabozantinib 40 mg (N=6)	Cabozantinib 60 mg[d]		
		Darlifarnib 3 mg (n=6)	Darlifarnib 5 mg (n=10)	Darlifarnib 8 mg (n=12)
ORR (CR+PR)	2 (33) [4.3–77.7]	2 (33) [4.3–77.7]	5 (**50**)[e] [18.7–81.3]	4 (**33**) [9.9–65.1]
DCR (CR+PR+SD)	5 (83) [35.9–99.6]	6 (100) [54.1–100]	8 (80) [44.4–97.5]	12 (100) [73.5–100]
CBR[f]	5 (83) [35.9–99.6]	2 (33) [4.3–77.7]	7 (70) [34.8–93.3]	7 (58) [27.7–84.8]

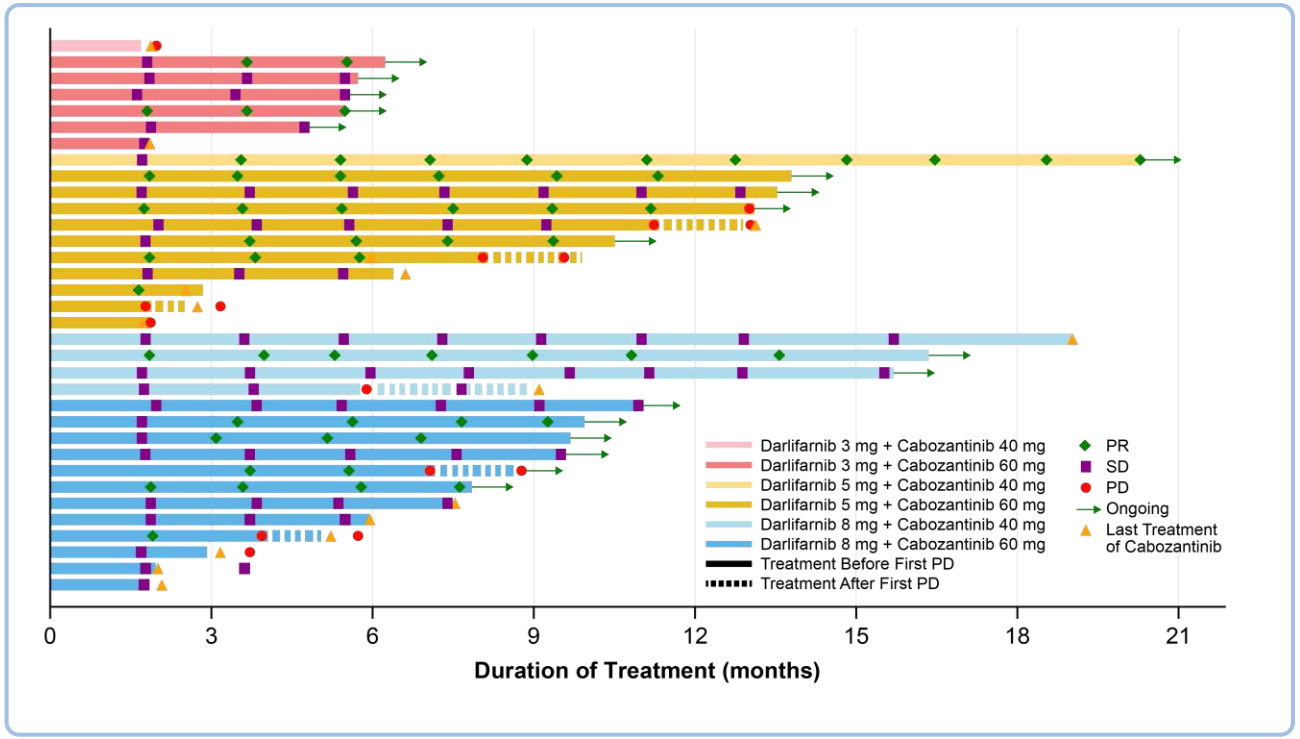
- Encouraging antitumor activity was observed in this pretreated population
  - ORRs 33%–50%, and median DOR was not estimable
  - 47% of cabozantinib-naive patients had prior TKI
- ccRCC patients with prior cabozantinib exposure have also had encouraging responses to the combination[1]

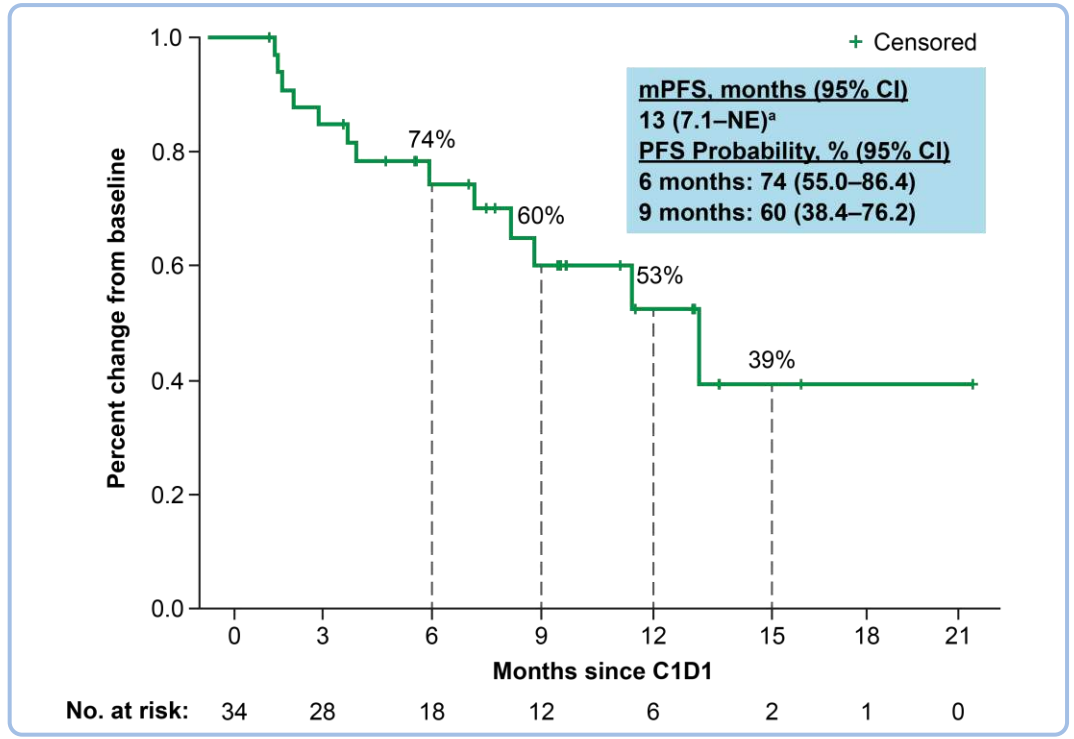
[a]Response-evaluable patients had ≥1 post-baseline scan. [b]Patient received darlifarnib 8 mg + cabozantinib 60 mg. [c]Response was considered PR because 100% tumor reduction was observed in target lesion but not in non-target lesions. [d]Cabozantinib 40 mg cohorts were enrolled before cabozantinib 60 mg cohorts. [e]One PR was unconfirmed; patient withdrew consent for non-study-related reason. [f]CBR defined as confirmed CR, confirmed PR, or SD duration ≥24 weeks. CBR, clinical benefit rate; cc, clear cell; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; ORR, objective response rate; PR, partial response; RCC, renal cell carcinoma; SD, stable disease; TKI, tyrosine kinase inhibitor.
Data cutoff: May 8, 2026. **1**. Zakharia Y et al. IKCS Europe 2026. Poster C8.

Duration of Treatment and Clinical Outcomes

Cabozantinib-Naive ccRCC

- Durable clinical benefit was observed across all evaluated combination dose levels, with more than half of patients remaining on treatment





[a]Median follow-up was 9.4 months (95% CI 6.9–12.8); PFS is aggregated across dose levels and follow-up varied by dose level.
C, cycle; cc, clear cell; CI, confidence interval; D, day; m, median; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; PR, partial response; RCC, renal cell carcinoma; SD, stable disease.
Data cutoff: May 8, 2026.

Conclusions

CLINICAL ACTIVITY	• With long-term follow-up, the combination has demonstrated **durable and encouraging antitumor activity** in cabozantinib-naive and -exposed patients[1], with **ORRs of 33%–50% and mPFS of 13 months** in cabozantinib-naive patients from the FIT-001 phase 1a study
SAFETY	• The combination was **well tolerated with a safety profile that was manageable** with dose modifications and consistent with reported component adverse events[2–4] • Neutropenia was successfully managed with dose interruption/reduction and supportive care after the initial DLT period
NEXT STEPS	• Together, these data support continued development of darlifarnib in combination with cabozantinib and other VEGFR-TKIs to further evaluate its potential to **enhance antiangiogenic and antitumor activity in patients with ccRCC** • FIT-001 phase 1b is currently enrolling cabozantinib-naive ccRCC patients (NCT06026410)

cc, clear cell; DLT, dose-limiting toxicity; mPFS, median progression-free survival; ORR, objective response rate; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

1. Zakharia Y et al. IKCS Europe 2026. Poster C8. **2**. Lacy S et al. *Cancer Chemother Pharmacol.* 2018;81:1061-1070. **3**. Ayanambakkam A et al. ESMO 2025. Poster 2604P. **4**. Hanna GJ et al. ESMO 2025. Poster 981P.

FIT-001: Phase 1b Combination Trial in Cabozantinib-Naive Locally Advanced or Metastatic ccRCC

Dose Optimization to Establish Recommended Phase 3 Dose is Ongoing in Phase 1b

Key Eligibility Criteria

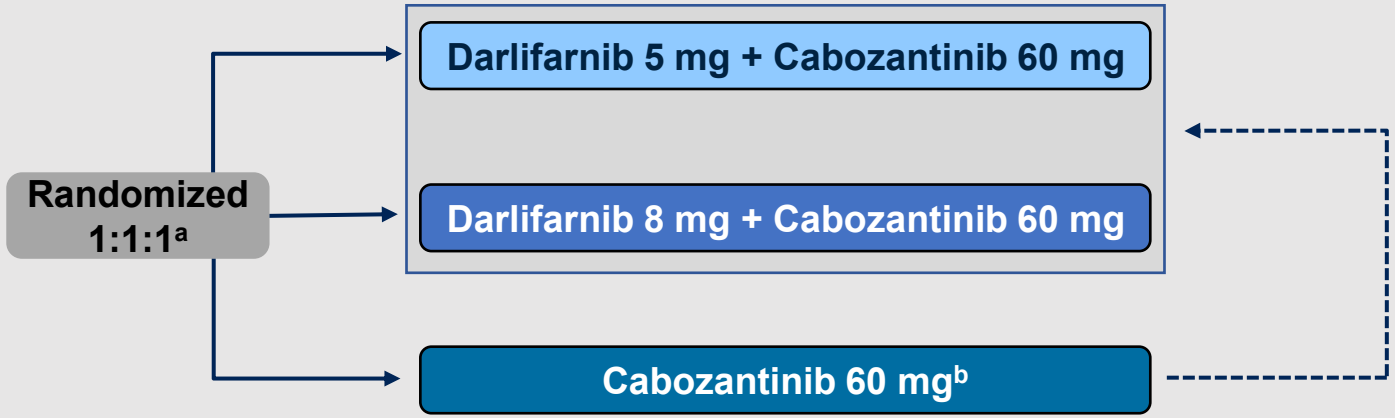
- ≥1 prior systemic therapy with IO-based treatment
- Cabozantinib-naive ccRCC

Key Endpoints

- Safety and tolerability
- Antitumor activity
- Pharmacokinetics

Phase 1b: Expansion and Dose Optimization in ccRCC

Darlifarnib administered orally QD on Days 1–7 and 15–21 plus cabozantinib administered orally QD in 28-day cycles



Phase 1b study is open and enrolling (NCT06026410)

[a]Patients will be stratified based on prior non-cabozantinib TKI exposure (naive or exposed). [b]Crossover to combination cohort allowed upon progression on cabozantinib monotherapy.
cc, clear cell; IO, immuno-oncology; QD, once daily; RCC, renal cell carcinoma.

Acknowledgments

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Slides can be accessed through this Quick Response (QR) code.

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