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Casdatifan in Patients With Previously Treated Clear Cell Renal Cell Carcinoma and Other Solid Tumors: Preliminary Results From ARC-20, a Phase 1, Open-Label, Dose Escalation and Expansion Study

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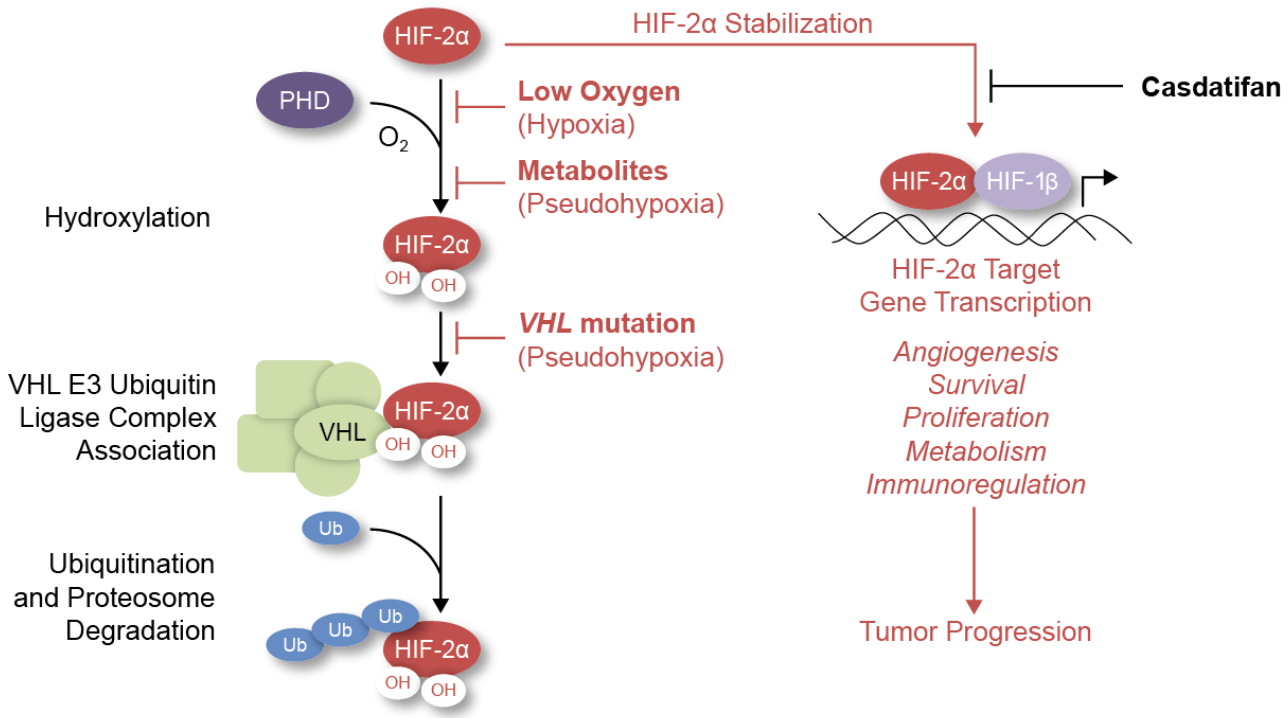
Casdatifan Inhibits Transcription of HIF-2α–Dependent Genes



- HIF-2α is a key driver in the development and progression of ccRCC[1]
  - Mutation of the *VHL* gene is the earliest genetic event in most patients with ccRCC[2]
  - *VHL* inactivation leads to the accumulation of hypoxia-inducible factor (HIF) subunits, especially HIF-2α[3]
- Casdatifan is an orally bioavailable small-molecule inhibitor of HIF-2α with high potency and a favorable human PD/PK profile

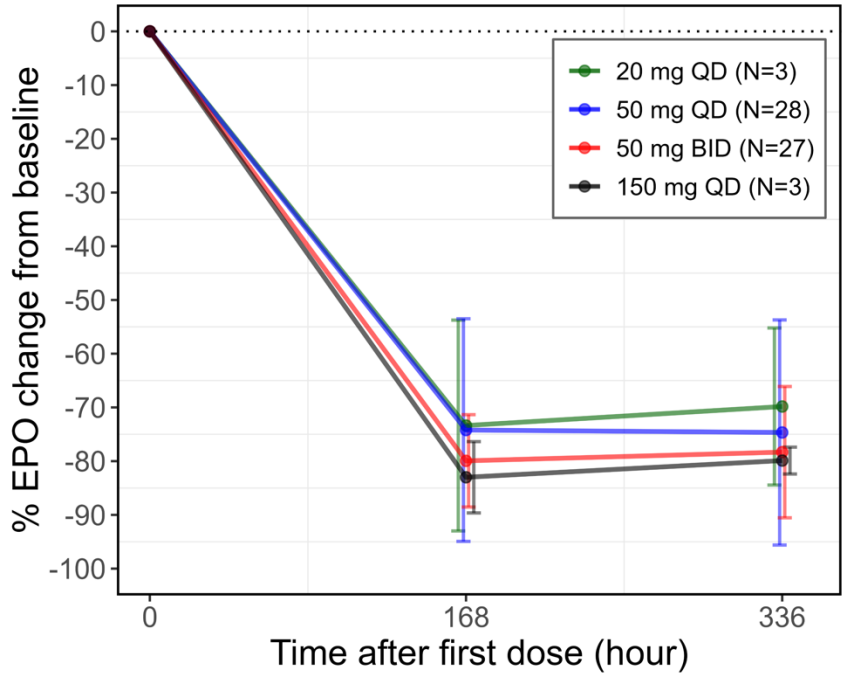
ccRCC, clear cell renal cell carcinoma; HIF, hypoxia-inducible factor; PD, pharmacodynamic; PHD, prolyl hydroxylase domain; PK, pharmacokinetic; Ub, ubiquitin; VHL, von Hippel-Lindau.

1. Culliver O. *Transl Androl Urol.* 2017;6:131-3. 2. Choi WSW et al. *J Kidney Cancer VHL.* 2021;8:1-7. 3. Choueiri TK, et al. *Nat Med.* 2020;26:1519-30.

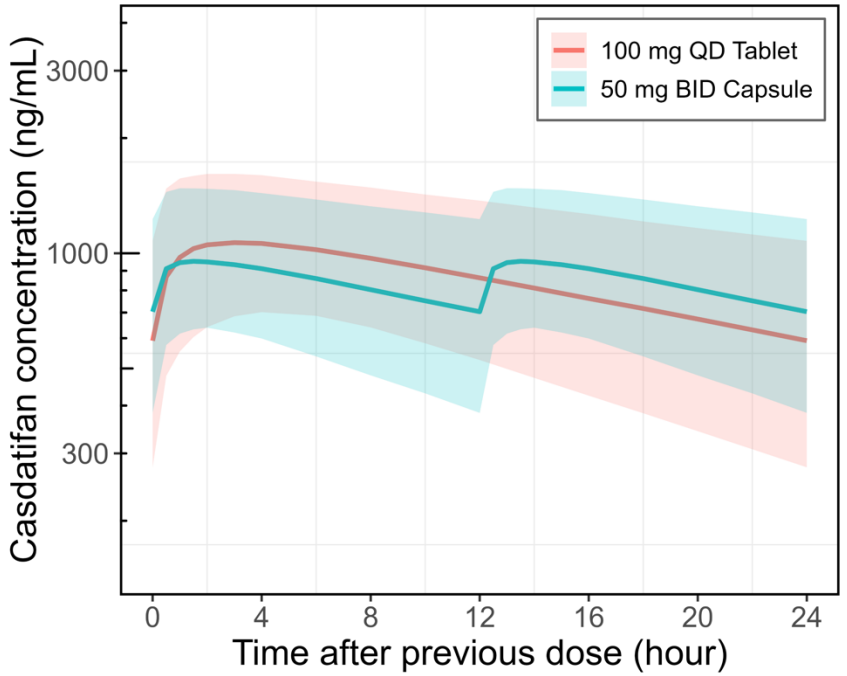
Casdatifan's Pharmacokinetic/Pharmacodynamic Profile

- The PK/PD profile of casdatifan shows dose-proportional exposure increase with a mean terminal half-life of ~18 to 24 hours, supporting QD dosing[1]
- Based on a healthy volunteer study, the 50 mg BID regimen provides drug exposure comparable to the 100 mg QD regimen currently being evaluated for Phase 3

ARC-20 Change in EPO (Mean ± SD) vs Time in Patients With ccRCC and Other Solid Tumors[2]



PopPK Simulations of Casdatifan Steady-State PK Profile After 50 mg BID Capsule and 100 mg QD Tablet*[2]



*Solid line: Median of simulated concentrations. Shaded area: 5th and 95th percentiles of simulated concentrations.
ccRCC, clear cell renal cell carcinoma; BID, twice daily; EPO, erythropoietin; PD, pharmacodynamic; PK, pharmacodynamic; QD, once daily.
1. Ghasemi M et al. Oncologist, 2024;29: Abstract 56. 2. Ghasemi M et al. Presented at the Kidney Cancer Research Summit, Boston, Massachusetts, 11–12 July 2024.

ARC-20 Is a Phase 1 Dose-Escalation and Dose-Expansion Study of Casdatifan Monotherapy

Dose Escalation[a]

3+3 design with 21-day DLT window

Patients with advanced solid tumors

KEY INCLUSION CRITERIA

- At least 1 measurable lesion per RECIST v1.1
- Adequate organ and marrow function

Casdatifan monotherapy

- 200 mg QD
- 150 mg QD
- 50 mg BID
- 50 mg QD
- 20 mg QD

Dose Expansion

Patients with 2L+ ccRCC

N = ~30 per cohort

Casdatifan monotherapy

- 50 mg BID
- 50 mg QD
- 150 mg QD
- 100 mg QD (enrolling)

Casdatifan 100 mg QD + cabozantinib (enrolling)

Primary Outcomes:

AEs

DLTs

Secondary Outcomes:

ORR[b]

PK/PD

2L+, second-line treatment setting or greater; AE, adverse event; BID, twice daily; ccRCC, clear cell renal cell carcinoma; ECOG, Eastern Cooperative Oncology Group; DLT, dose-limiting toxicity; HIF, hypoxia-inducible factor; ORR, objective response rate; PD, pharmacodynamics; PK, pharmacokinetics; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.

[a]Dose escalation enrolled 22 patients at the 20 mg QD, 50 mg QD, 50 mg BID, 150 mg QD, and 200 mg QD doses, 11 of whom had ccRCC (across all 5 doses) (30 August 2024). [b]Assessed by the investigator according to RECIST v1.1.

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Baseline Characteristics

Characteristic	Dose Escalation Advanced Solid Tumors[a]	Dose Expansion 2L+ ccRCC	
	20 mg – 200 mg (n = 22)	50 mg BID (n = 33)	50 mg QD (n = 31)
Age, years, median (range)	66 (49–78)	62 (41–79)	65 (43–82)
Sex, female/male, n (%)	12 (55) / 10 (45)	8 (24) / 25 (76)	10 (32) / 21 (68)
ECOG PS 0/1, n (%)	5 (23) / 17 (77)	16 (48) / 17 (52)	18 (58) / 13 (42)
IMDC risk score, n (%) Favorable Intermediate Poor Unknown	NA	 9 (27) 20 (61) 2 (6) 2 (6)	 8 (26) 16 (52) 5 (16) 2 (6)
Number of regimens, all settings, n (%) **1/2/3/4 or more**	**4 (18) / 2 (9) / 6 (27) / 10 (45)**	**2 (6) / 14 (42) / 8 (24) / 9 (27)**	**5 (16) / 9 (29) / 8 (26) / 9 (29)**
Patients with both VEGFR-TKI and PD-1/PD-L1 inh, n (%)	12 (55)	33 (100)	31 (100)
Number of regimens with any VEGFR-TKI, n (%) 1/2/3/4 or more	3 (14) / 5 (23) / 3 (14) / 2 (9)	13 (39) / 12 (36) / 3 (9) / 5 (15)	15 (48) / 8 (26) / 5 (16) / 3 (10)
Number of patients with prior mTOR treatment, n (%)	NA	5 (15)	7 (23)

BID, twice daily; ccRCC, clear cell renal cell carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; IMDC, international metastatic renal cell carcinoma database consortium; inh, inhibitor; mTOR, mammalian target of rapamycin; NA, not applicable; PD-1, programmed cell death protein-1, PDL1, programmed cell death ligand-1 QD, once daily, RCC, renal cell carcinoma; VEGFR-TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor.
Date cutoff date: 30 August 2024.
Baseline was defined as the last non-missing assessment prior to the first dosing of treatment.
[a]Primary cancer type: 14 RCC (11 ccRCC; 3 non-ccRCC), 2 breast cancer, 1 each of ovarian, colon, ductal, gallbladder, and unknown cancer, and 1 of squamous cell carcinoma.

Dose Escalation: No Dose-Limiting Toxicities Were Reported and the Maximum Tolerated Dose Has Not Been Reached

Safety-Evaluable Population[a]	20 mg QD (n = 3)	50 mg QD (n = 6)	50 mg BID (n = 6)	150 mg QD (n = 5)	200 mg QD (n = 2)	Total (n = 22)
Median treatment duration, months (range)	3 (<1–19)	1 (1–17)	2 (1–13)	5 (<1–5)	<1 (<1–<1+)	1 (<1–19)
Any TEAEs, n (%)	3 (100)	5 (83)	6 (100)	5 (100)	2 (100)	21 (95)
Related to casdatifan	2 (67)	4 (67)	5 (83)	4 (80)	2 (100)	17 (77)
Related to casdatifan leading to discontinuation	0	1 (17)[b]	0	0	1 (50)[b]	2 (9)
TEAEs of interest related to casdatifan, n (%)						
Anemia	1 (33)	3 (50)	5 (83)	4 (80)	0	13 (59)
Fatigue	0	0	3 (50)	4 (80)	0	7 (32)
Hypoxia	0	1 (17)	0	0	1 (50)	2 (9)
Serious TEAEs,[c] n (%)	0	1 (17)	3 (50)	0	1 (50)	5 (23)
TEAEs ≥ grade 4, n (%)	0	0	0	0	0	0

BID, twice daily; QD, once daily; TEAE, treatment-emergent adverse event.
Date cutoff date: 30 August 2024.
[a]All patients who enrolled and received any amount of study treatment. [b]Grade 3 TEAE of hypoxia. [c]1 dyspnea (50 mg QD), 2 pathological fracture (50 mg BID), 1 asthma (200 mg QD), and 1 pyrexia (50 mg BID); all unrelated to casdatifan except the 1 event of dyspnea.

Dose Expansion: No Grade 4 or 5 TEAEs

Safety-Evaluable Population	Dose Expansion	
	50 mg BID (n = 33)	50 mg QD (n = 31)
Any TEAEs, n (%)	32 (97)	30 (97)
Related to casdatifan	31 (94)	28 (90)
Any Grade 3 TEAEs, n (%)	15 (45)	16 (52)
Related to casdatifan	14 (42)	11 (35)
Any Serious TEAEs, n (%)	4 (12)	7 (23)
Related to casdatifan	1 (3)	2 (6)
Anemia, n (%)		
All grades	28 (85)	28 (90)
Grade 3 related	12 (36)	11 (35)
Leading to interruptions	11 (33)	8 (26)
Leading to dose reductions	2 (6)	4 (13)
Leading to discontinuation	**0 (0)**	**0 (0)**
Hypoxia, n (%)		
All grades	5 (15)	3 (10)
Grade 3 related	3 (9)	2 (6)
Leading to interruptions	4 (12)	3 (10)
Leading to dose reductions	1 (3)	0 (0)
Leading to discontinuation	**0 (0)**	**1 (3)**

BID, twice daily; QD, once daily; TEAE, treatment-emergent adverse event.
Date cutoff date: 30 August 2024.
The safety-evaluable population included all dose expansion enrolled patients who received any amount of any study treatment.

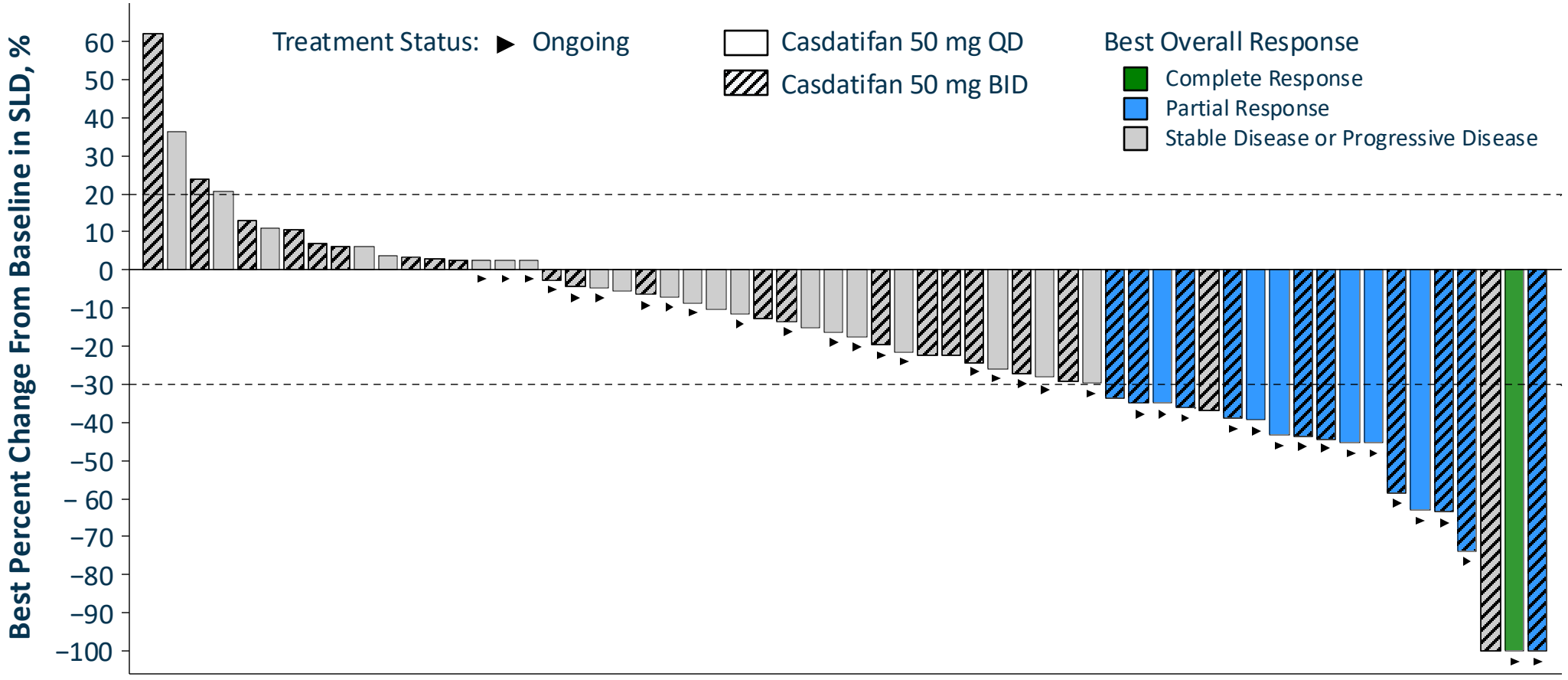
Treatment With Casdatifan Shows Clinical Activity

Efficacy Evaluable Population	Dose Expansion	
	50 mg BID (n = 32)	50 mg QD (n = 28)
Median follow-up [ongoing], months (range)	**11 (3–15+)**	**8 (4–10+)**
ORR, %, n (90% CI)	**31.3%, 10[a] (16.1, 50.0)**	**25.0%, 7 (10.7, 44.9)**
Responses pending confirmation, n	1	1
Confirmed ORR, %, n (90% CI)	**25.0%, 8 (11.5, 43.4)**	**21.4%, 6 (8.3, 41.0)**
Time to response, months, median (range)	2.8 (1.2–5.5)	4 (1.3–4.1)
Patients with progressive disease, %, n	**18.8%, 6**	**14.3%, 4**
Disease control rate (90% CI)	81.3% (63.6, 92.8)	85.7% (67.3, 96.0)
Median progression-free survival	Not reached	Not reached

[a]One patient in 50 mg BID cohort had a new response (also pending confirmation) after data cutoff date; updated ORR, 34.4%

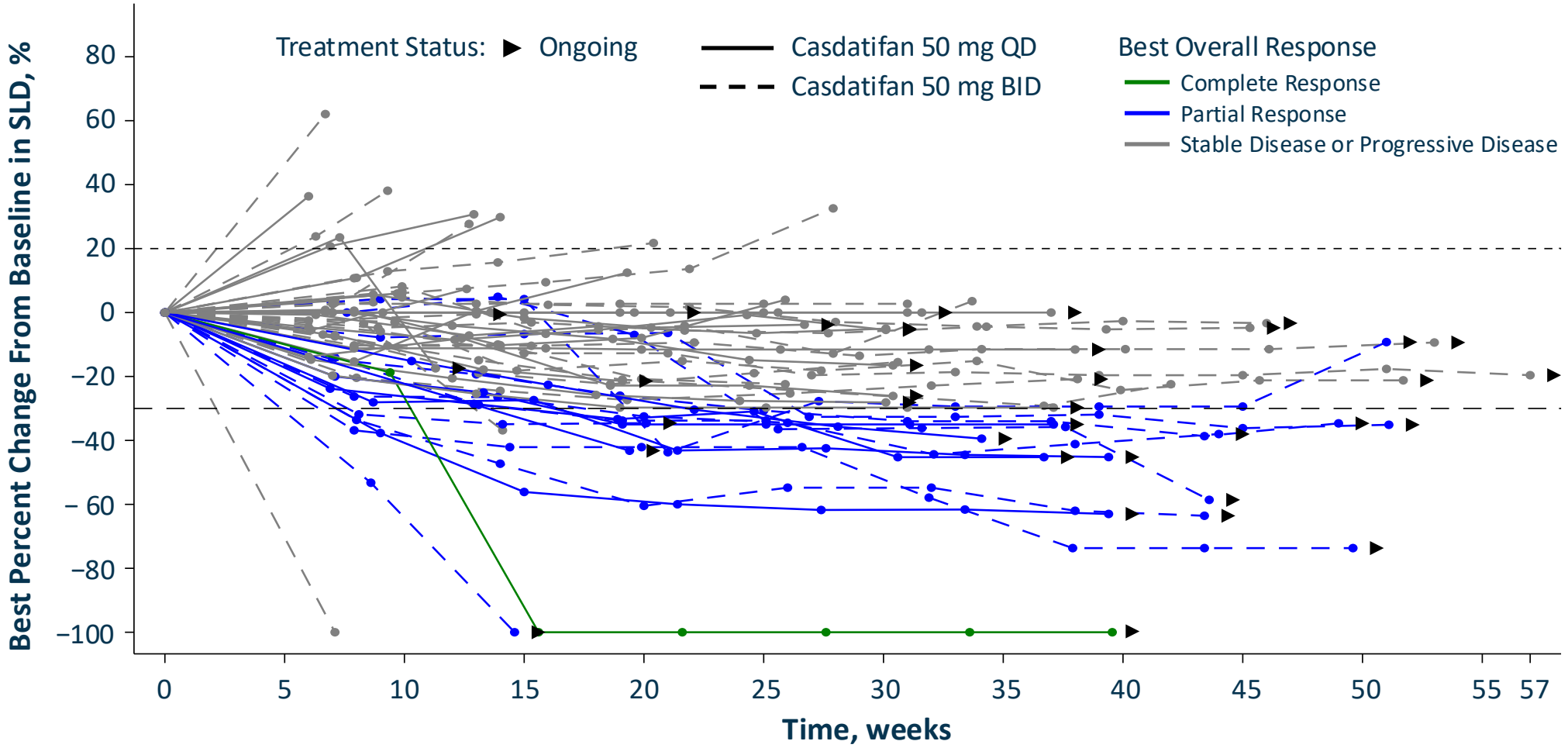
Date cutoff date: 30 August 2024.
ORR is defined as the percentage of patients with a best overall response of CR or PR including confirmed and unconfirmed responders.
Confirmed ORR is defined as the percentage of patients with a confirmed best overall response of CR or PR.
DCR is defined as the percentage of patients with a confirmed best overall response of CR, PR, or SD.
BID, twice daily; CR, complete response; DCR, disease control rate; ORR, objective response rate; PR, partial response; QD, once daily; SD, stable disease.

Treatment With Casdatifan Shows Meaningful Clinical Activity



BID, twice daily; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; SLD, sum of longest diameter.
Data cutoff date: 30 August 2024.

In the Dose Expansion, Treatment With Casdatifan Showed Trend of Decreasing Sum of Target Lesion Diameters



BID, twice daily; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; SLD, sum of longest diameter.
Data cutoff date: 30 August 2024.

Conclusions

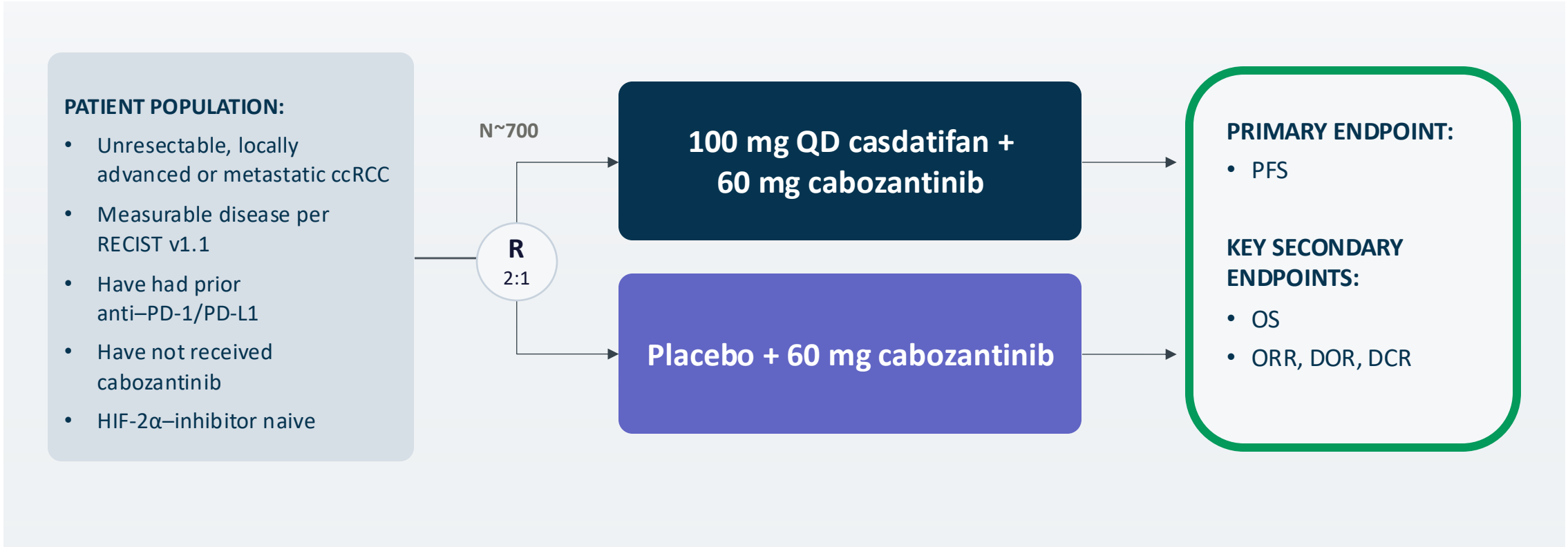
- In heavily pretreated patients, casdatifan was well tolerated, with no DLTs observed, and MTD was not reached
- Casdatifan demonstrated promising durable clinical activity, ORR, and DCR with a similar safety profile
  - 50 mg BID (median f/u 11mo): 34.4% ORR; 25.0% cORR
  - 50 mg QD (median f/u 8mo): 25.0% ORR; 21.4% cORR
- These data demonstrate the therapeutic potential of casdatifan as a potential best-in-class HIF-2α inhibitor and support further development of casdatifan in ccRCC

BID, twice daily; cORR, confirmed objective response rate; ccRCC, clear cell renal cell carcinoma; DLT, dose limiting toxicity; f/u, follow-up; HIF, hypoxia-inducible factor; Mo, month; MTD, maximum tolerated dose; ORR, objective response rate; QD, once daily.

Phase 3 Study Evaluating Cas + Cabo in Advanced or Metastatic ccRCC, Following Prior PD-1 Therapy

PEAK-1

Anticipated in the first half of 2025



DCR, disease control rate; DOR, duration of response; HIF, hypoxia-inducible factor; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; QD, once daily; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors.

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