Clinical Pharmacokinetic/Pharmacodynamic (PK/PD) Relationship for Casdatifan (AB521), a Small Molecule Inhibitor of HIF-2α, Confirms Best-in-class Potential in Treatment of Renal Cell Carcinoma

ENA
Annual Meeting
Oct 23-25th, 2024
Abstract #51

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BACKGROUND

- Hypoxia-inducible factor (HIF)-2α is a transcription factor that is an oncogenic driver in clear cell renal cell carcinoma (ccRCC)
- HIF-2α inhibition has been clinically shown to mitigate tumor growth in patients with ccRCC, a cancer type with a high frequency of genetic anomalies in the von Hippel-Lindau (VHL) tumor suppressor gene
- Casdatifan (AB521), an orally bioavailable small-molecule inhibitor of HIF-2α, potently inhibits transcription of HIF-2α-dependent genes in cell lines and preclinical species

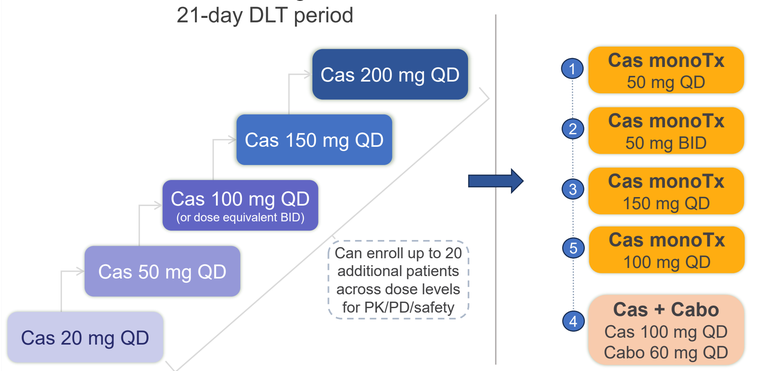
OBJECTIVES

- To characterize the relationship between casdatifan dose, PK, and changes in erythropoietin (EPO), an on-target PD biomarker for HIF-2α inhibition
- To use this understanding to guide dose selection in future clinical trials

METHODS: Clinical Study Design

- Casdatifan plasma concentrations, serum EPO concentration, and hemoglobin data were obtained from
  - 79 healthy participants in two Phase 1 studies, ARC-14 (NCT05117554) and ARC-28 (NCT05999513), and
  - 112 patients with ccRCC and other solid tumors in an ongoing Phase 1 study, ARC-20 (NCT05536141)
- A population PK/PD model was developed to correlate casdatifan dose, PK and changes in EPO and Hb

ARC-20: Clinical Study Design

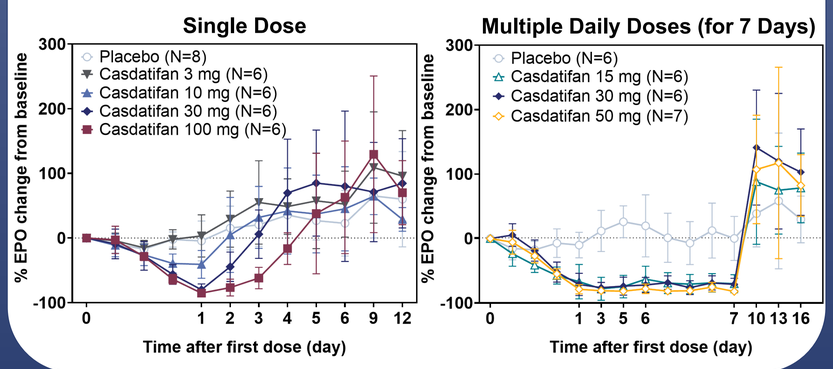


ARC-20 (NCT05536141) is a Phase 1, multicenter, open-label, first-in-patient study that is currently open for enrollment in the United States, South Korea, and Australia. BID: twice daily; Cabo: cabozantinib; Cas: casdatifan; DLT: dose-limiting toxicity; SOC: standard of care; QD: once-daily; Tx: therapy.

RESULTS: Pharmacodynamic Profiles

- Potent HIF-2α inhibition was demonstrated by dose-dependent reductions in serum EPO:
  - In healthy participants (Study ARC-14), EPO reduction was observed following single (10-100 mg) and multiple doses (15, 30, or 50 mg QD for 7 days), with mean maximum reduction from baseline of 85%
  - Rebound in EPO to above baseline levels was seen after end of dosing
  - All patients in the Study ARC-20 cohorts (20 mg to 150 mg QD) showed significant EPO decline, with mean maximum reduction from baseline up to around 80%

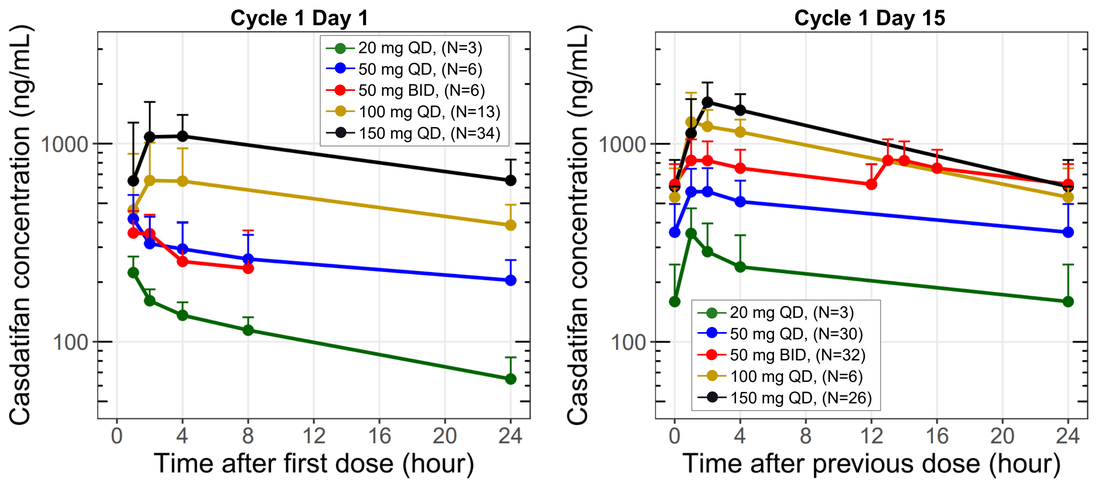
Mean (±SD) Serum EPO Reduction-Time Profiles Following Single or Multiple Oral Dose(s) of Casdatifan or Placebo in Healthy Participants (Study ARC-14)



RESULTS: Pharmacokinetic Profiles

- Following single or multiple oral dosing of casdatifan, median time to reach peak concentration (T_{max}) at Day 1 was 1.0 to 4.0 hours and at steady-state was 1.0 to 2.0 hours, followed by biphasic decline in plasma concentrations
- Mean terminal half-life was approximately 24 hours, supporting QD dosing
- Casdatifan showed dose-proportional exposure increase over the dose range tested (3 to 150 mg)
- After multiple daily dosing, casdatifan reached steady state around Day 4 with ~2.0-fold accumulation, indicating lack of time-dependent PK
- Casdatifan PK exposures at steady state are comparable between 50 mg BID capsule and 100 mg QD tablet regimens

Mean (+SD) Casdatifan Plasma Concentration vs Time Profiles Following Single or Multiple Oral Dose(s) of Casdatifan in Patients with Cancer (Study ARC-20)



Casdatifan Exposure Increases ~5X from 20 to 100 mg Daily Dose

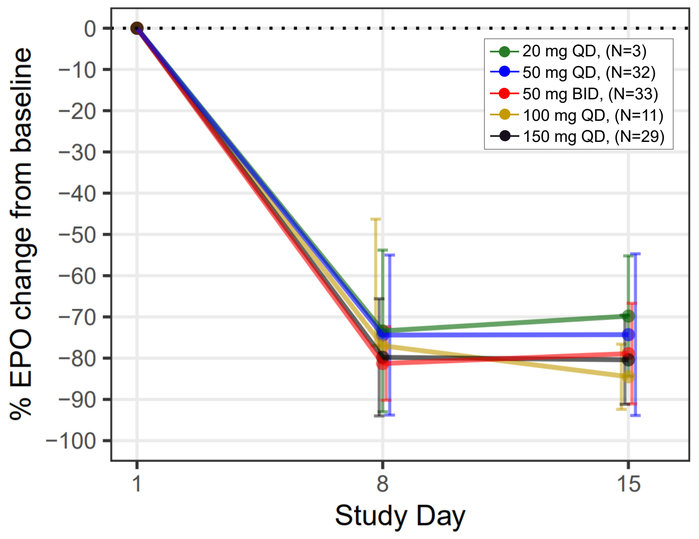
Casdatifan Daily Dose	20 mg	100 mg
Steady-state Daily AUC (h*µg/mL)	4.08	5X → 20.3

AUC values estimated from the population PK model

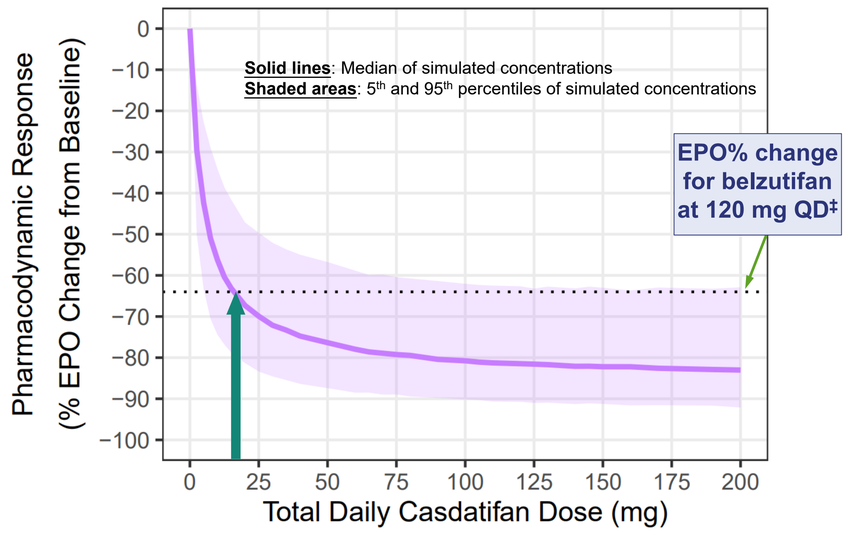
In Cycle 1 Day 15 profiles, timepoints at the end of dosing interval (12h in BID or 24h in QD) are based on pre-dose timepoints, as steady-state was established

RESULTS: PK/PD Relationship

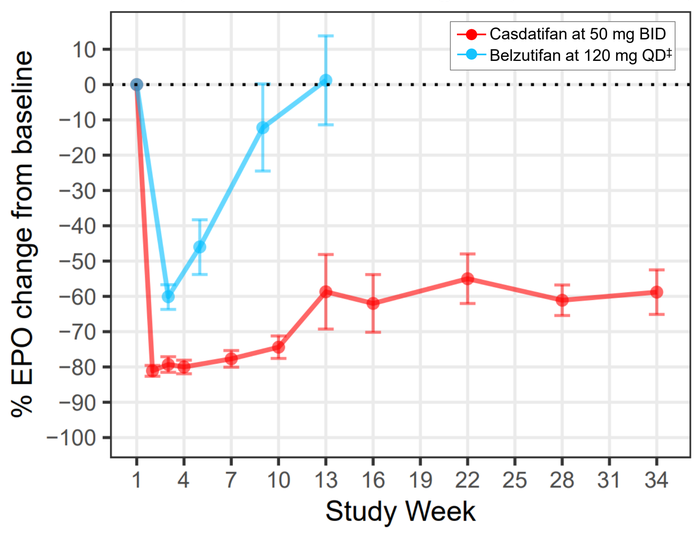
ARC-20 Change in EPO (Mean ± SD) vs Time in Patients with ccRCC and other Solid Tumors



PK/PD Model-derived Relationship of EPO Change on Day 15 vs Casdatifan Dose



Change in EPO vs Time: Casdatifan 50 mg BID (Mean ± SEM) vs Belzutifan 120 mg QD (Mean ± 90%CI)



- A 20 mg daily dose of casdatifan is predicted to provide similar PD effect as 120 mg belzutifan
- The selected casdatifan dose of 100 mg daily provides ~5X higher exposure than 20 mg daily casdatifan, resulting in ~5X higher exposure than that associated with the benchmark peripheral PD
- Casdatifan at a daily dose of 100 mg appears to result in greater and more sustained suppression of EPO level compared to 120 mg belzutifan

‡Belzutifan data from: Marathe DD, J Clin Pharm 2024, Table S3 and Fig S20
SEM = standard error of the mean; CI = confidence interval

CONCLUSION

- Casdatifan showed potential best-in-class PK/PD profile with dose-proportional exposure over the tested range (3 to 150 mg)
- Casdatifan 20 mg QD provided a similar level of EPO suppression in ccRCC patients as belzutifan 120 mg QD (benchmark peripheral PD)
- Casdatifan dose of 100 mg had 5X higher exposure than 20 mg
- Casdatifan at 100 mg daily dose resulted in deeper and more sustained reduction in EPO
- Overall, the casdatifan dose of 100 mg, selected for further development, allows exploration of the full therapeutic potential of HIF-2α inhibition
- Casdatifan is in clinical trials for ccRCC and other solid tumors
  - ARC-20: NCT05536141, STELLAR-009: NCT06191796
  - Upcoming trials in ccRCC: PEAK-1 Phase 3 in combination with cabozantinib, and a Phase 1 study of casdatifan in combination with volrustomig, an investigational PD-1/CTLA-4 bispecific antibody