AACR-NCI-EORTC 2025

Abstract #:

Oct 22nd-26th

Erythropoietin (EPO) is a Pharmacodynamic Biomarker for Systemic HIF-2α Inhibition that Correlates with the Clinical Activity of Casdatifan

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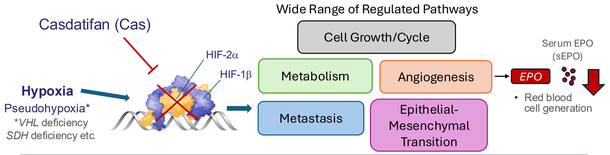
Objective

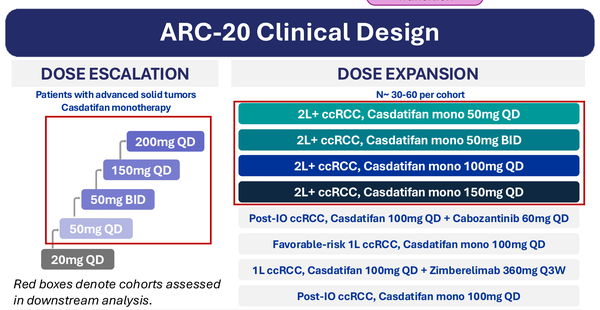
To evaluate EPO levels both in circulation and in tumor samples as a potential pharmacodynamic and predictive biomarker for systemic HIF-2α inhibition on Casdatifan in clear cell RCC (ccRCC) Patients.

Background

- **Dysregulation of hypoxia-inducible factor 2-alpha (HIF-2α) in patients with ccRCC contributes to increased angiogenesis, proliferation, and cancer cell survival.[1]**
- **Casdatifan (Cas) is an orally bioavailable small-molecule HIF-2α inhibitor that has shown promising efficacy in metastatic ccRCC in the ARC-20 clinical trial (NCT05536141).[2]**
- **Erythropoietin (EPO) is a known HIF-2α transcription target, and serum EPO (sEPO) levels decrease after treatment with HIF-2α inhibitors.[3]**



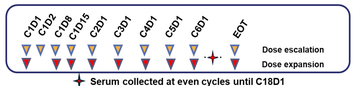
ARC-20 Clinical Design



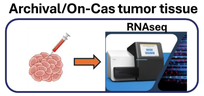
Red boxes denote cohorts assessed in downstream analysis.

Methods and Biomarker Population

Serum EPO collection timepoints in ARC-20



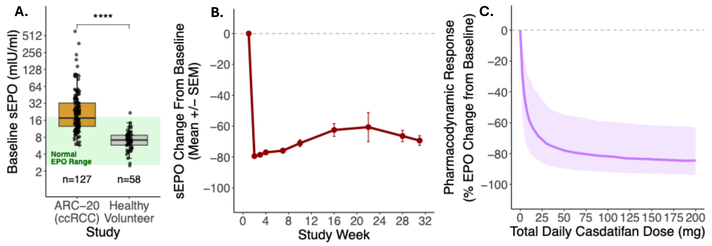
Archival/On-Cas tumor tissue



Biomarker Evaluable Population (BEP)	Total with serum EPO	Total with tumor RNA sequencing	Total with paired on-treatment biopsies
ccRCC treated with 50mg-200mg Casdatifan	127	53	2

Results

Figure 1. Cas Treatment Results in Deep and Sustained Suppression of sEPO



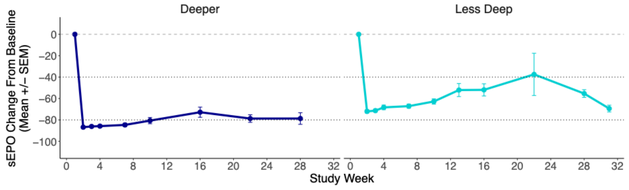
EPO data collected as of March 14th, 2025. Baseline data for healthy volunteers collected as part of ARC-14 Study. Normal serum EPO range 2.59-18.5 mIU/ml. Statistical comparisons performed using Wilcoxon ranked-sum test. Longitudinal EPO data shown for pooled Cohorts. sEPO changes from baseline exclude values measured within 28 days of an erythropoietin stimulating agent (ESA) or during Casdatifan dose-hold. Pharmacodynamic (PD) responses per dose were calculated at day 15. Shaded band represents the 95% confidence interval of simulated concentrations.

Pharmacodynamic (PD) analysis of EPO

- **49% of ccRCC patients in ARC-20 have elevated sEPO levels at baseline (Figure 1A)**
- **Patients experienced a median maximum reduction in sEPO of -84.8% (mean= -82.9%; SD=12.4%) compared to baseline sEPO levels (Fig 1B)**
- **Deep suppression of EPO seen with 50mg-200mg daily Cas at day 15 (Figure 1C)**

Figure 2. Higher ORR is Observed in Patients With Deeper Than Median sEPO Suppression

cBOR	Deeper sEPO Reduction (n=64)		Less Deep sEPO Reduction (n=63)	
	% (95% CI)	n	% (95% CI)	n
CR/PR	37.5% (25.7, 50.5)	24	17.5% (9.1, 29.1)	11
PD	7.5% (2.6, 17.3)	5	23.8% (14.0,36.2)	15

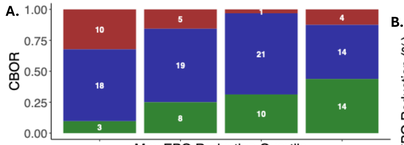


EPO data and efficacy data collected as of March 14th, 2025. 95% CI calculated with Clopper Pearson test; CR: complete response; PR: partial response; PD: progressive disease

Assessment of Response Rates by EPO Stratified Suppression Levels

- **Response rate is higher and PD rate is lower in patients with deeper than median EPO suppression (Figure 2)**
- **Even patients with sEPO reduction less than median experience sustained sEPO suppression on treatment (Figure 2)**

Figure 3. Better Overall Responses on Cas Coincide with Deeper Levels of Maximal sEPO Suppression



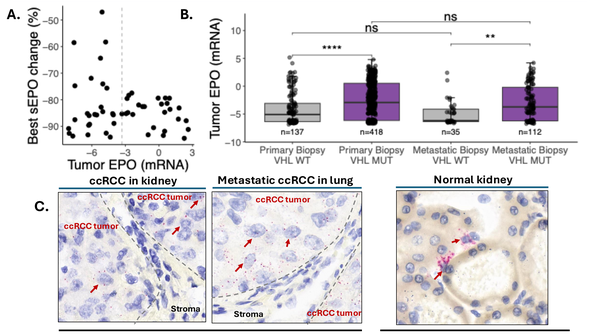
cBOR	<25th %-ile	25th -50th	50th-75th	≥75th %-ile
	N = 31	N = 32	N = 32	N = 32
PR/CR	9.7%	25%	31.3%	48.3%
PD	32.3%	15.6%	3.1%	12.5%

EPO data and efficacy data collected as of March 14th, 2025. cBOR: Confirmed best overall response; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease. Statistical comparisons performed using Wilcoxon R-S test.

Assessment of sEPO Suppression and Best Overall Responses

- **Response rate rises steadily across best EPO change quartiles (Figure 3A)**
- **There is a significant and continuous trend showing better responses with stronger levels of EPO reduction (Figure 3B)**

Figure 4. Malignant Epithelial Cells Are a Source of EPO

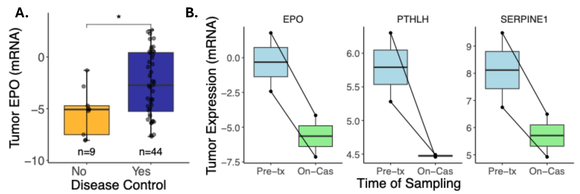


Dashed line represents median tumor EPO expression. IMmotion151 data for VHL WT and mutant biopsies obtained from EGA through data agreement with Genentech (EGAS00001004353).[4] Statistical comparisons performed using Wilcoxon ranked-sum.

Cancer Cells are a Direct Source of EPO

- **ARC-20 Patients with high tumor EPO mRNA experience strong suppression of sEPO (Fig 4A).**
- **VHL mutant ccRCC tumors express higher levels of tumor EPO mRNA than wildtype tumors regardless of biopsy site in data from IMmotion151[4] (Fig 4B).**
- **Cancer cells, not adjacent stroma, of primary and metastatic ccRCC express EPO. EPO observed only in interstitial kidney fibroblasts of normal kidney (Fig 4C, ISH).**

Figure 5. Tumor EPO mRNA is Associated With Disease Control and Shows On-Target Inhibition of HIF-2α by Cas



Disease control defined by BOR of stable disease or better. Statistical comparisons performed using Wilcoxon ranked-sum test. Paired biopsies are from patients receiving 100mg QD Cas monotherapy. Pre-tx biopsies were taken from archival tissue, while treatment biopsies were taken 14-20 days after treatment initiation.

ARC-20 Tumor mRNA analysis

- **Higher tumor EPO mRNA expression at baseline is associated with disease control (Figure 5A)**
- **In on-treatment tumor biopsies, mRNA expression of EPO and two other canonical HIF-2α targets, PTHLH (PTHrP) and SERPINE1 (PAI-1), are reduced dramatically compared to baseline measures (Figure 5B)**

Conclusions

- **Cas treatment results in deep and sustained suppression of sEPO**
- **Deeper maximal reduction in sEPO is associated with better clinical benefit on Cas monotherapy**
- **Cancer cells express EPO in ccRCC, which may be linked to sEPO levels and depth of change on treatment.**
- **Higher tumor EPO mRNA expression is also associated with disease control and EPO decreases dramatically on-treatment in a way that parallels peripheral changes.**

References, Acknowledgments & Disclosures

References: 1. Mouayad, ZB, The Distinct Role of HIF-1α and HIF-2α in Hypoxia and Angiogenesis, *Cells* 2025. 2. Ghasemi, M. *et al.* Pharmacokinetics, pharmacodynamics and safety of casdatifan, a novel hypoxia-inducible factor-2α inhibitor, in healthy participants. *British Journal of Clinical Pharmacology*. 3. Chen W. Targeting Renal Cell Carcinoma with a HIF-2 antagonist, *Nature* 2016 4. Motzer, R. J. *et al.* Molecular Subsets in Renal Cancer Determine Outcome to Checkpoint and Angiogenesis Blockade. *Cancer Cell* **38**, 803-817.e4 (2020).

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