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Board: 3
Section: 48
Abstract: 7898

Clinical Benefit of the HIF-2α Inhibitor Casdatifan (Cas) Across Molecular Subtypes in Clear Cell Renal Cell Carcinoma (ccRCC) Patients From The ARC-20 Clinical Study

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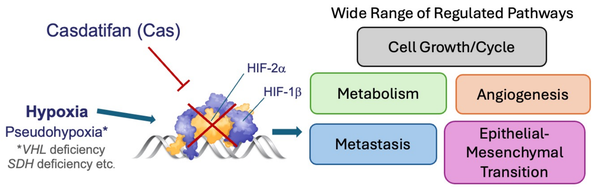
Objective

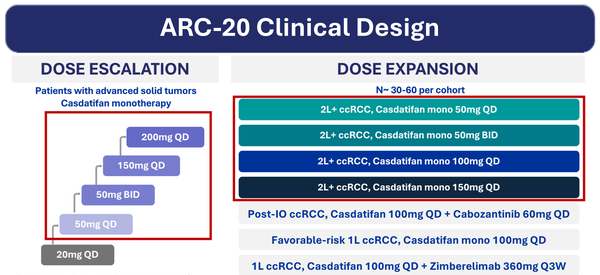
- Assess clinical outcomes for patients treated with cas, a potent and selective HIF-2α inhibitor, across literature-proposed molecular subtypes.
- Better understand transcriptomic markers associated with cas benefit, both within and beyond the proposed subtyping framework

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]
- ccRCC molecular subtypes have been used to characterize patient tumors and shown to associate with response to angiogenic and IO treatments in retrospective studies[3,4].



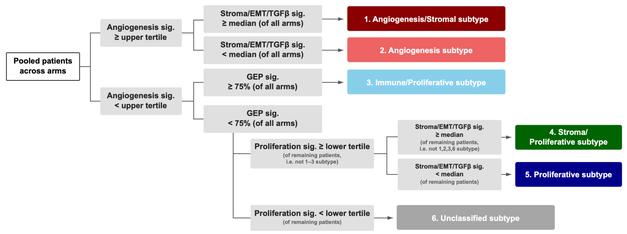
ARC-20 Clinical Design



Red boxes denote cohorts assessed in downstream analysis.

	Baseline RNAseq Available	Paired Biopsies Available
N	67	2

Classification Methodology

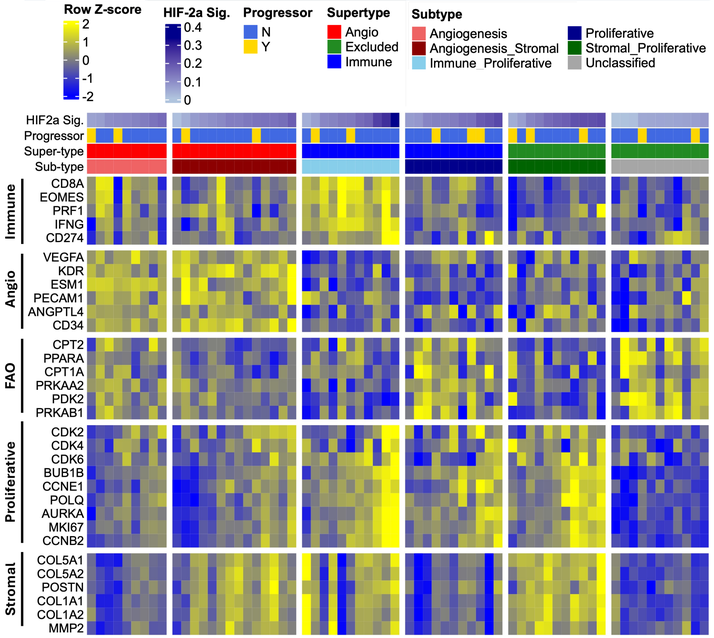


The "Unclassified" subtype was characterized as having a low-angiogenesis signature, a low-TcellinfGEP signature, and low-proliferation.
EMT, epithelial-mesenchymal transition; sig, signature; TcellinfGEP, T-cell inflamed gene expression profile; TGFβ, transforming growth factor β.

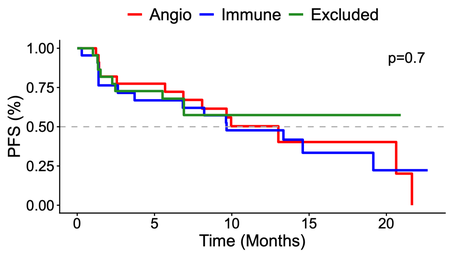
Classification protocol was adapted from biomarker analysis performed on the CLEAR trial (NCT02811861) using quantile normalized RNA expression and gene signature scoring.[3]

Results

Figure 1. Disease Control Rates and PFS Are Comparable Across Literature-Defined Subtypes in ARC-20



	Angiogenic		Immune		Excluded	
	Angio	Angio/ Stromal	Immune/ Proliferative	Proliferative	Stromal/ Proliferative	Unclassified
Dis. Control (% subtype):	7 (78.8 %)	12 (85.7%)	9 81.8 %)	8 (72.7 %)	8 (72.7%)	9 (81.8%)
subtype N (% total):	9 (13.4%)	14 (20.9%)	11 (16.4%)	11 (16.4%)	11 (16.4%)	11 (16.4%)
supertype N (% total):	23 (34.3%)		22 (32.8%)		22 (32.8%)	

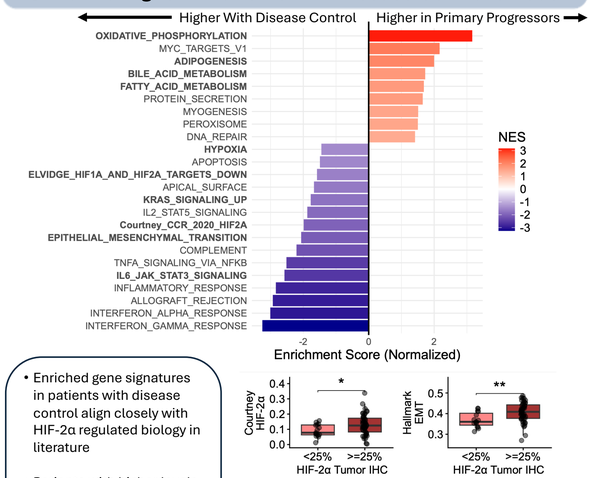


- Classified molecular subtypes in ARC-20 align with published gene expression profiles
- Disease control rates with cas are comparable across molecular subtypes (p = 0.961)
- Progression free survival with cas is not different across molecular-supertypes (p=0.7)

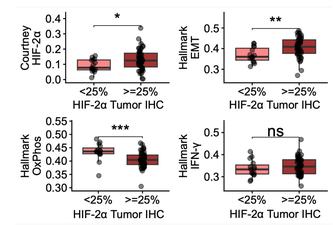
subtypes were defined using the flowchart under "classification methodology", then binned into supertype. Genes denoted in the heatmap are defined based on the relevant modules from the clustering framework initially proposed in Motzer et al. (*Cancer Cell*, 2020)[4]. Genes were row-scaled based on voom-normalized log2 TPM values. Disease control is defined as a confirmed patient best response of stable disease or better. Stable disease rates across subtypes were compared via Chi-square test for proportions. PFS comparisons were based on patients with available outcomes and RNA-seq data as of AUG 15th, 2025 data cut-off and compared via log-rank test.

Results

Figure 2. Expression of Biological Signatures Related to HIF-2α Are Higher in Patients with Disease Control on Cas

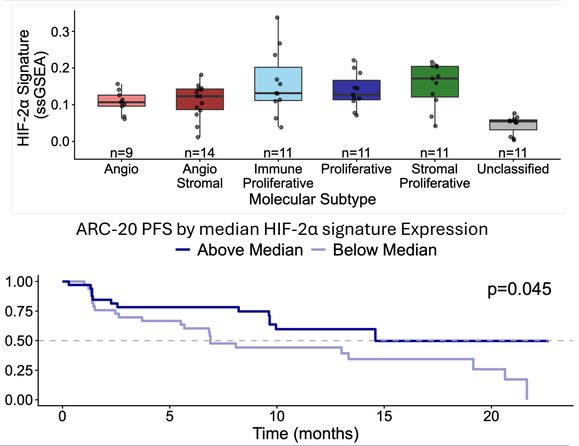


- Enriched gene signatures in patients with disease control align closely with HIF-2α regulated biology in literature
- Patients with higher levels of HIF-2α IHC staining show differences in expression of gene signatures consistent with HIF-2α activity



GSEA was performed using both hallmark signatures and literature defined HIF-2α gene lists. Patients with stable disease or better were compared to those who progressed as best response. HIF-2α IHC categories were based on natural breakpoint of total tumor % staining and compared via Wilcoxon rank-sum test.

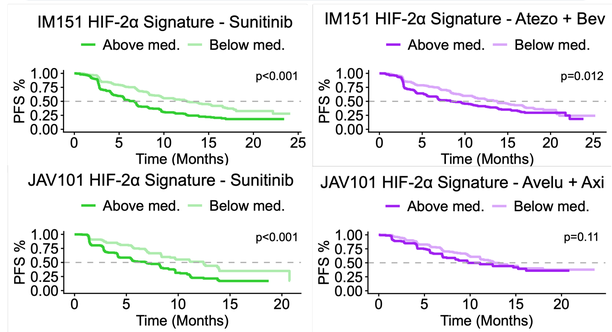
Figure 3. HIF-2α Signature Expression is Comparable Across Subtypes and Associated With Longer PFS on Cas



- HIF-2α related signature expression is comparable across most molecular subtypes
- Patients with higher HIF-2α related signature have significantly longer PFS (by median)

HIF-2α signature references the gene list (n=277) defined in Courtney et al.[5] PFS comparisons based on patients with available outcomes and RNA-seq data as of AUG 2025 data cut-off and assessed via log-rank test.

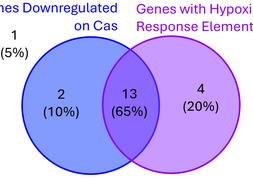
Figure 4. HIF-2α Signature Expression is Associated With Worse PFS In 1L ccRCC Data From Available Ph3 Studies



- In external 1L datasets of patients treated with standard of care modalities, patients with higher HIF-2α signature expression typically experience shorter PFS.

Expression data from IMmotion151 Sunitinib (n=416) and Atezolizumab+Bevacizumab (n=407) arms were generated by Genentech/gRED and used under agreement with Genentech. Expression data from Javelin101 Sunitinib (n=372) and Avelumab+Axitinib (n=354) arms are publicly available. Gene signature scores were calculated via ssGSEA and medians used for thresholding were determined trial-wide. HIF-2α signature references the gene list (n=277) defined in Courtney et al.[5]

Figure 5. Most Top Leading Edge Genes From the HIF-2α Signature Show Evidence of HIF-2α Regulation



- Using GSEA results comparing patients based on stable disease status,19 of the top 20 leading edge HIF-2α signature genes show some indication of HIF-2α or hypoxia dependent regulation
- 65% have overlapping evidence from both binding site analysis and paired on-treatment changes

Leading edge genes from the HIF-2α signature were identified from comparison of stable disease or better vs. progressor defined in Fig. 2. Motif analysis was performed using FIMO, with promoter regions defined as 2000 bases upstream and 500 bases downstream from the gene TSS. Motifs for hypoxia response elements (HIF-1/2 binding sites) were obtained from HOCOMOCO and JASPAR databases.

Conclusions

- **DCR and PFS with cas are not associated with molecular subtype**
- **Gene sets differentially expressed in cas treated patients experiencing disease control aligned closely with expected HIF-2α related pathways and showed increased expression in patients with higher HIF-2α IHC staining**
- **HIF-2α gene signature expression is comparable across most ccRCC subtypes, but associated with longer PFS in ARC-20 and shorter PFS on multiple 1L therapies in external datasets, representing an orthogonal transcriptomic signal**
- **19/20 of the top leading edge genes in the HIF-2α gene signature show evidence of direct regulation by HIF-2α**

References, Acknowledgments & Disclosures

References: 1. Mouayad, ZB, The Distinct Role of HIF-1α and HIF-2α in Hypoxia and Angiogenesis, *Cells* 2025. 2. Choueiri, TK et al., Activity and biomarker analyses with casdatifan (cas), a next-generation HIF-2α inhibitor, in refractory clear cell renal cell carcinoma (ccRCC): Results from ARC-20. *J Clin Oncol* 2026. 3. Motzer, R J et al. Biomarker analyses from the phase III randomized CLEAR trial: lenvatinib plus pembrolizumab versus sunitinib in advanced renal cell carcinoma. *Annals of Oncology* 2025 4. Motzer, R. J. *et al.* Molecular Subsets in Renal Cancer Determine Outcome to Checkpoint and Angiogenesis Blockade. *Cancer Cell* 2020. 5. Courtney, KD et al. HIF-2 Complex Dissociation, Target Inhibition, and Acquired Resistance with PT2385, a First-in-Class HIF-2 Inhibitor, in Patients with Clear Cell Renal Cell Carcinoma. *CCR* 2020.

p-value notations across all figures. ns = not significant; p < 0.05 = *; p < 0.01 = **; p < 0.001 = ***; p < 0.0001 = ****