#(4543): HIF Family Transcription Factor Expression in a Cohort of 4062 Patients with Renal Cell Carcinoma (RCC)

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BACKGROUND

- The HIF pathway drives RCC pathogenesis operating through transcription factors (TFs).
- TFs function as heterodimers of the oxygen-sensitive α (HIF1α or HIF2α) and constitutively expressed β subunits (HIF1β or HIF2β).
- Loss of VHL leads to HIFα stabilization, nuclear translocation, and formation of transcriptional complexes with β subunits.
- We aimed to characterize the molecular and clinical features associated of HIF TF mRNA expression in RCC:
  - Evaluate HIF TF expression levels across racial/ethnic groups, primary/metastatic tumors and different RCC histology.
  - Investigate the association between HIF TF expression and co-occurring alterations in genes frequently mutated in RCC.
  - Assess the relationship between HIF TF expression and overall survival.
  - Determine the potential of HIF TF expression as a predictive biomarker for benefit to VEGF TKIs.

Methods

- Next generation sequencing of DNA [592-targeted gene panel or whole exome sequencing] and RNA (whole transcriptome sequencing) were performed on RCC specimens (N=4,062) at Caris Life Sciences.
- HIF-High/Low expression was defined as >75th /<25th quartile RNA transcripts per million (TPM).
- Overall survival (OS) was defined as the time of diagnosis to death/last follow-up.
- Time on treatment (TOT) was defined as the time from start of treatment to discontinuation of therapy.
- Descriptive statistics were used to present the baseline tumor characteristics. When appropriate, statistical significance was assessed using Fisher's Exact, Mann-Whitney, or Chi-square tests

Study Population

Category	Sub-category	Patient count (n)
Total	RCC	4,062
Sex	Female	1,163 (28.6%)
	Male	2,899 (71.4%)
Specimen site	Kidney	1,784 (43.9%)
	Lymph node	319 (7.9%)
	Distant metastatic sites	1,959 (48.2%)
Race	Asian or Pacific Islander	972 (2.4%)
	Black or African American	398 (9.8%)
	White	2,492 (61.3%)
	Other	213 (5.2%)
	Unknown	346 (8.5%)
Ethnicity	Not Hispanic or Latino	2,768 (68.1%)
	Hispanic or Latino	453 (11.2%)
	Unknown	325 (8.0%)

Results

- HIF2α (EPAS1) was lower in tumors from Black/AA vs White patients (102.3 vs 157.5 TPM, p<0.0001) and higher in tumors from Hispanic vs non-Hispanic patients (146.1 vs 195.4 TPM, p<0.01).
- Compared to kidney primary (n=1,784, 43.9%, 172.1 TPM), HIF2α (EPAS1) expression was lower in lymph nodes (n=319, 7.9%, 97.9 TPM, p<0.01) but similar to distant metastatic sites (n=1,959, 48.2%, 168.3 TPM).
- Compared to clear cell RCC (n=1198, 29.5%, 224.3 TPM), HIF2α expression was lower in papillary (n=238, 5.9%, 57.5 TPM), chromophobe (n=83, 2.0%, 91.7 TPM), and medullary RCC (n=15, 0.36%, 46.5 TPM) (p<0.01 each).
- Compared to *VHL* wild-type (n=1415, 34.9%), *VHL*-mutated tumors (n=1884, 46.4%) had higher HIF2α (206.6 vs 97.7 TPM), lower HIF1α (184.9 vs 233.9 TPM), lower HIF2β (7.2 vs 10.2 TPM) (p <0.01 each).
- Sarcomatoid RCC (n=119, 2.9%) had lower HIF2α (111.9 vs. 155.0 TPM, p<0.05), lower HIF2β (5.6 vs 8.5 TPM, p<0.01), and higher HIF1α (276.3 vs 197.4 TPM, p<0.01) compared to non-sarcomatoid RCC (n=3947, 97.2%)
- Tumors with high HIF2α were enriched for *VHL*, *PBRM1*, *MTOR*, and *PTEN* alterations and had fewer *TP53*, *BAP1*, *MET*, *SMARCB1*, and *NF2* alterations.
- HIF1α-high tumors had fewer *VHL*, *TSC1*, and *BAP1 alterations*.
- HIF1β -high tumors had decreased *TP53* and *RB1* and increased *CHEK2* and *PALB2* alterations.

HIF 2α (Q4 vs Q1)

	% Prevalence in Q1	% Prevalence IN Q4	q-value
VHL	30.47	75.91	0
PBRM1	17.86	45.45	0
KDM5C	4.33	11	0
PTEN	6.05	9.35	0.0369
TP53	14.22	9.11	0.0067
BAP1	13.07	6.91	0.0004
MTOR	1.46	4.31	0.0038
NF2	10.05	1.59	0
SMARCB1	4.05	1.43	0.0059
NFE2L2	3.18	0.98	0.0184
CDKN2A (p16)	2.13	0.48	0.013
B2M	2.65	0.35	0.002
RB1	2.69	0.19	0.0011
KDM6A	2.64	0.16	0.0003
KRAS	2.27	0.16	0.0009
MET (cMET)	1.62	0	0.0018
LZTR1	1.6	0	0.0035
NF1	1.03	0	0.0185
FLCN	0.81	0	0.0296
PALB2	0.81	0	0.03

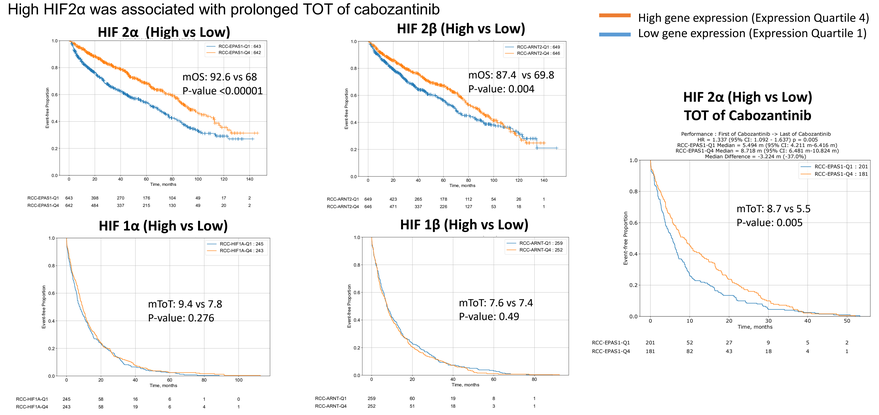
HIF 1α (Q4 vs Q1)

	% Prevalence in Q1	% Prevalence in Q4	q-value
VHL	64.42	43.14	0
BAP1	16.58	6.71	0
TSC1	5.73	3.09	0.0274
STAG2	14.29	2.86	0.0245
FH	1.02	2.62	0.0433
MET (cMET)	0.17	1.54	0.0123
HRAS	0	0.77	0.0384

HIF 1β (Q4 vs Q1)

	% Prevalence in Q1	% Prevalence IN Q4	q-value
TP53	18.23	12.08	0.0034
CHEK2	0.35	2.1	0.0076
RB1	2.87	0.92	0.0243
PALB2	0	0.79	0.036

- High HIF2α was associated with improved OS (92.6 vs 68.1 months, p<0.001)
- High HIF2β was associated with improved OS (87.4 vs 69.8 months, p<0.004)
- HIF1α and HIF1β did not correlate with OS (data not shown).
- HIF1α and HIF1β did not correlate with TOT.
- High HIF2α was associated with prolonged TOT of cabozantinib



Conclusions

- This comprehensive analysis revealed distinct HIF TF expression patterns across RCC subgroups.
- Elevated HIF2α expression was observed in clear cell RCC, VHL-mutated tumors, and was linked to improved OS and prolonged TOT with cabozantinib, suggesting a potential prognostic role for HIF2α in RCC, warranting further clinical investigation.

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