ARO-HIF2 Evaluated in Clear Cell Renal Cell Carcinoma, a Ph1b Clinical Trial

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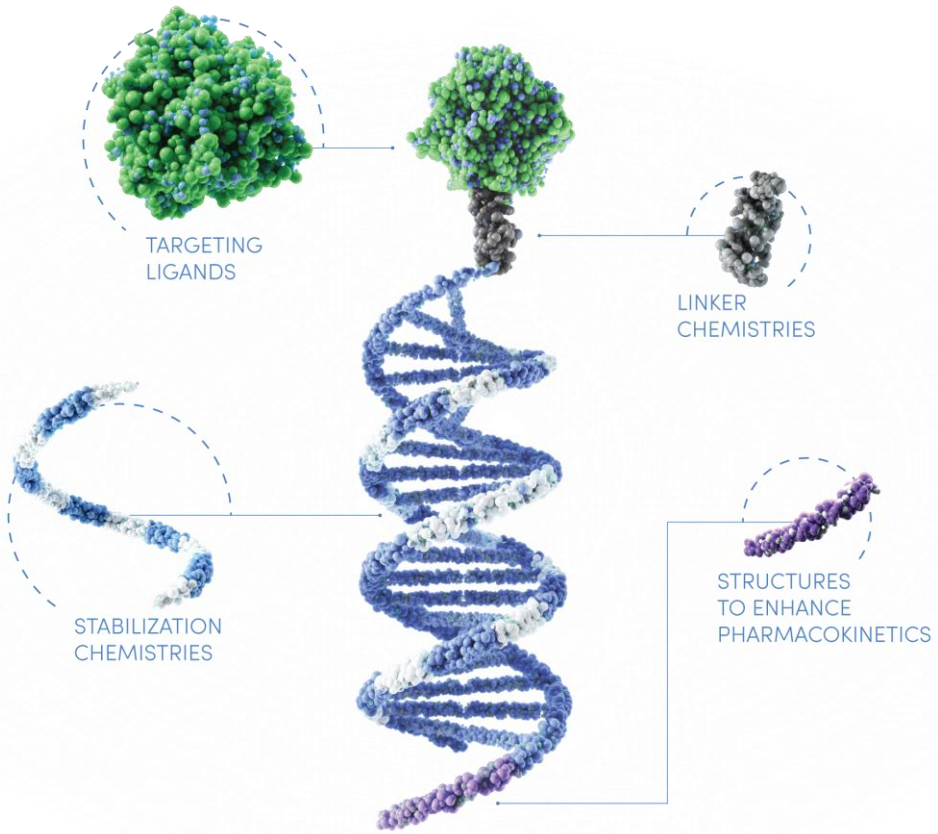
Arrowhead Pharmaceuticals: Focused on RNAi

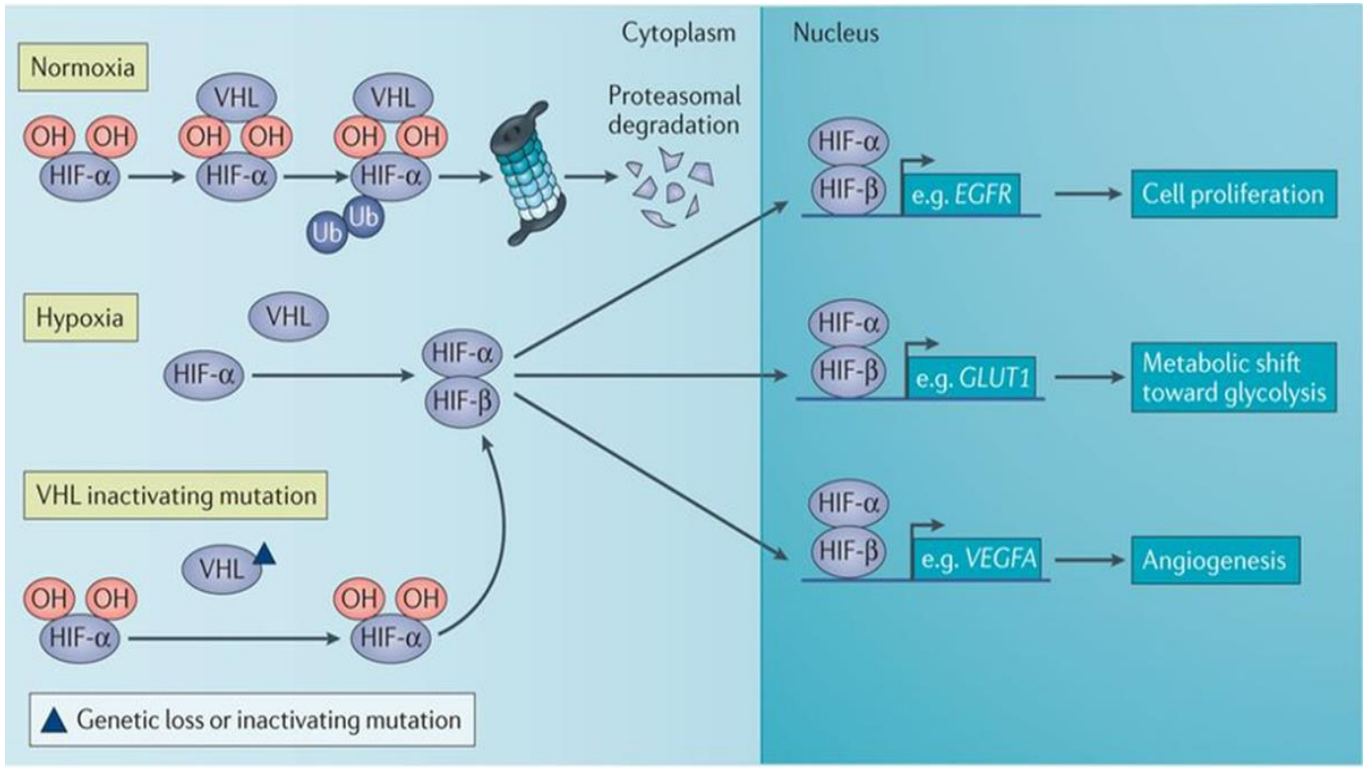


TRiM™ has rules and algorithms to optimize trigger sequence

- Limit cross reactivity with off target genes while disallowing miRNA homology
- Maximize trigger activity, stability and on target gene silencing

Pipeline: Focus on ARO-HIF2

HIF2-alpha as a target for ccRCC

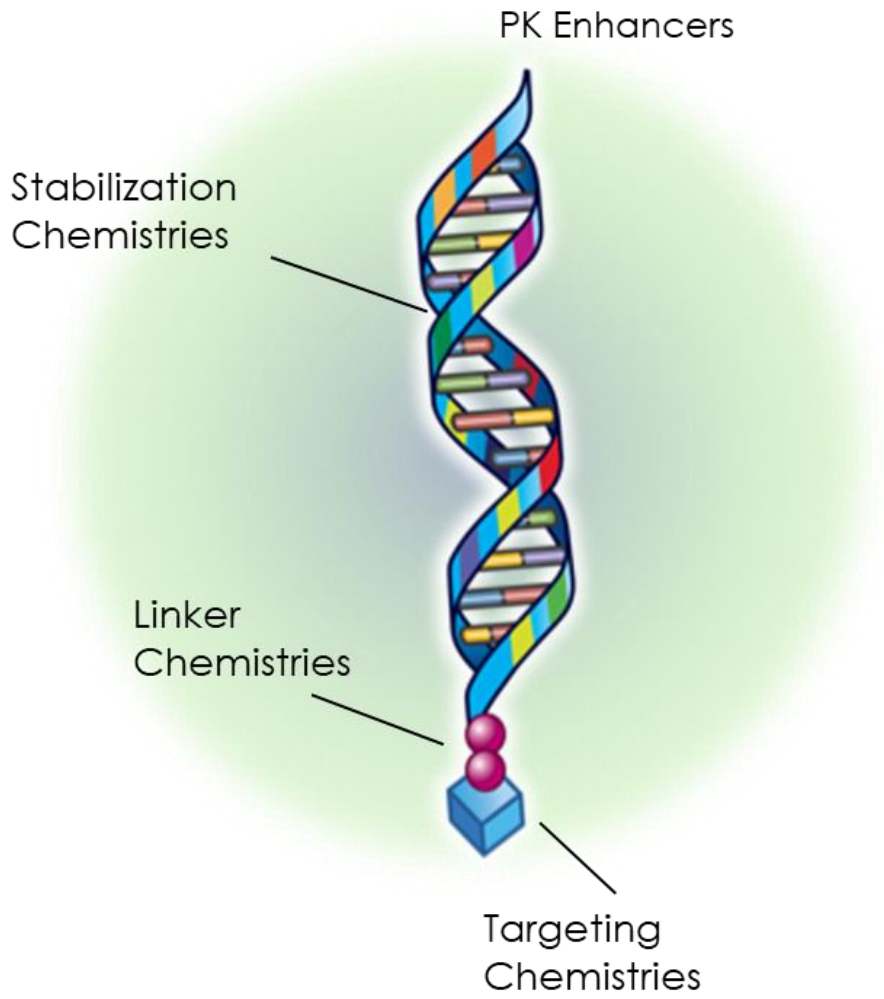


Riazalhosseini and Lathrop, Nature Reviews Nephrology, 2016

Nature Reviews | Nephrology

- Hypoxia inducible factor-2 alpha (HIF2a) is a transcription factor and key tumorigenic driver of ccRCC
- Normally, HIF2a is expressed at low levels and targeted for degradation by the von Hippel-Lindau (VHL) tumor suppressor protein.
- With VHL inactivation, (often the causative event of ccRCC), accumulation of HIF2a leads to overexpression of downstream target genes *(EGFR, VEGF, GLUT1)* implicated in cell survival, cell proliferation and angiogenesis.
- Over expression of HIF2a represents a “gain-of-function” scenario ideal for RNAi

ARO-HIF2



- ARO-HIF2 siRNA sequence specifically targets HIF2-alpha mRNA
- Uses small molecule ligand targeting αvβ3/5 integrin receptor on ccRCC
- Uses lipid moiety to prolong circulation time

αvβ3 integrin receptor rationale: ccRCC expression analysis

Table. ITGB3 Expression in Human ccRCC TMA

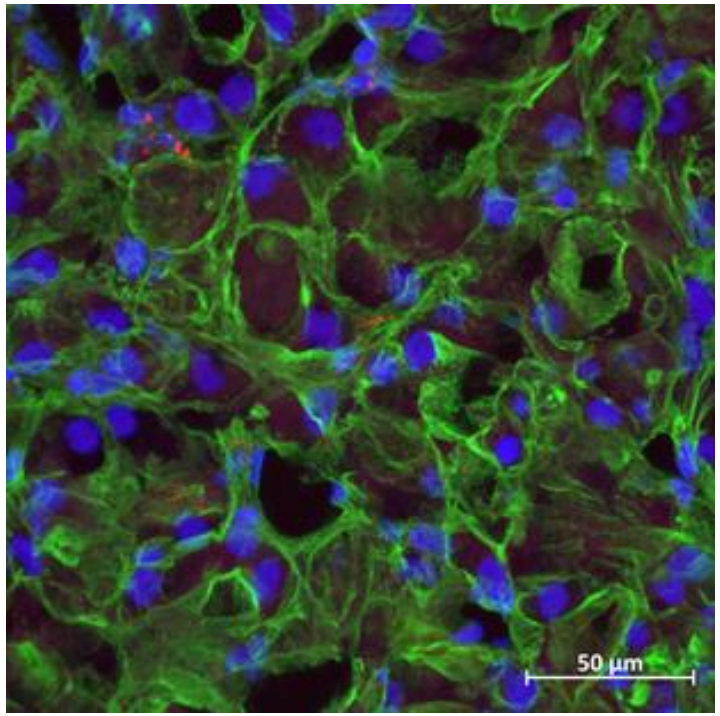
TMA	Total ccRCC case #	% integrin β3-Positive					
		Overall	Tumor Grade				Metastatic
			1	2	3	4	
Vendor 1	77	31.2 (24/77)	29.5 (13/44)	29.6 (8/27)	50 (3/6)	n.a.	50 (1/2)
Vendor 2	20	50 (10/20)	n.a.	37.5 (3/8)	71.4 (5/7)	33.3 (1/3)	50 (2/4)
Vendor 3	34	64.7 (22/34)			n.a.		
Vendor 4	146	68.5 (100/146)	66.7 (30/45)	62.7 (32/51)	62.5 (10/16)	61.1 (11/18)	80 (12/15)

Many, but not all human ccRCC samples express αvβ3 integrin.

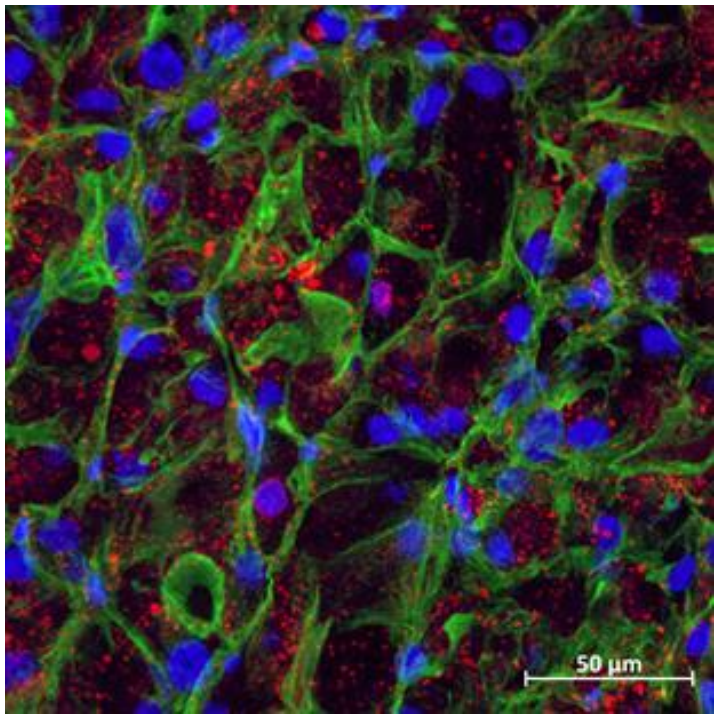
αvβ3/5 integrin receptor rationale

ARO-HIF2 tumor delivery

No Ligand



With Ligand



A498 ccRCC orthotopic tumor mouse model

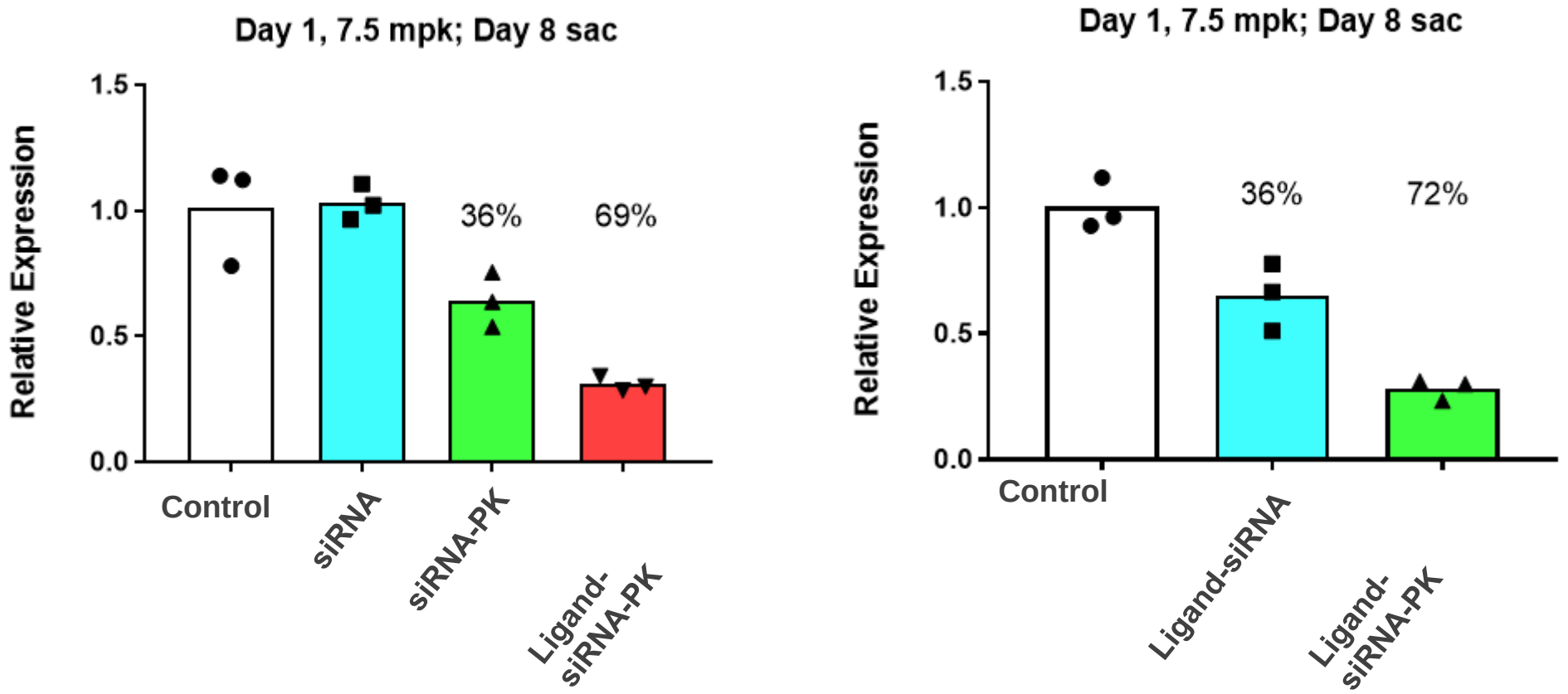
2 mg/kg Cy3-labeled ARO-HIF
4 h after injection

Red = ARO-HIF2
Blue = nuclei
Green = actin (cytoskeleton)

- Overexpressed in many tumors
  (ccRCC expression confirmed by tumor tissue microarray)
- Minimal delivery to tumor cells without ligand
- HIF2a knockdown improved with ligand

Additive Effect of Ligand and PK Extension

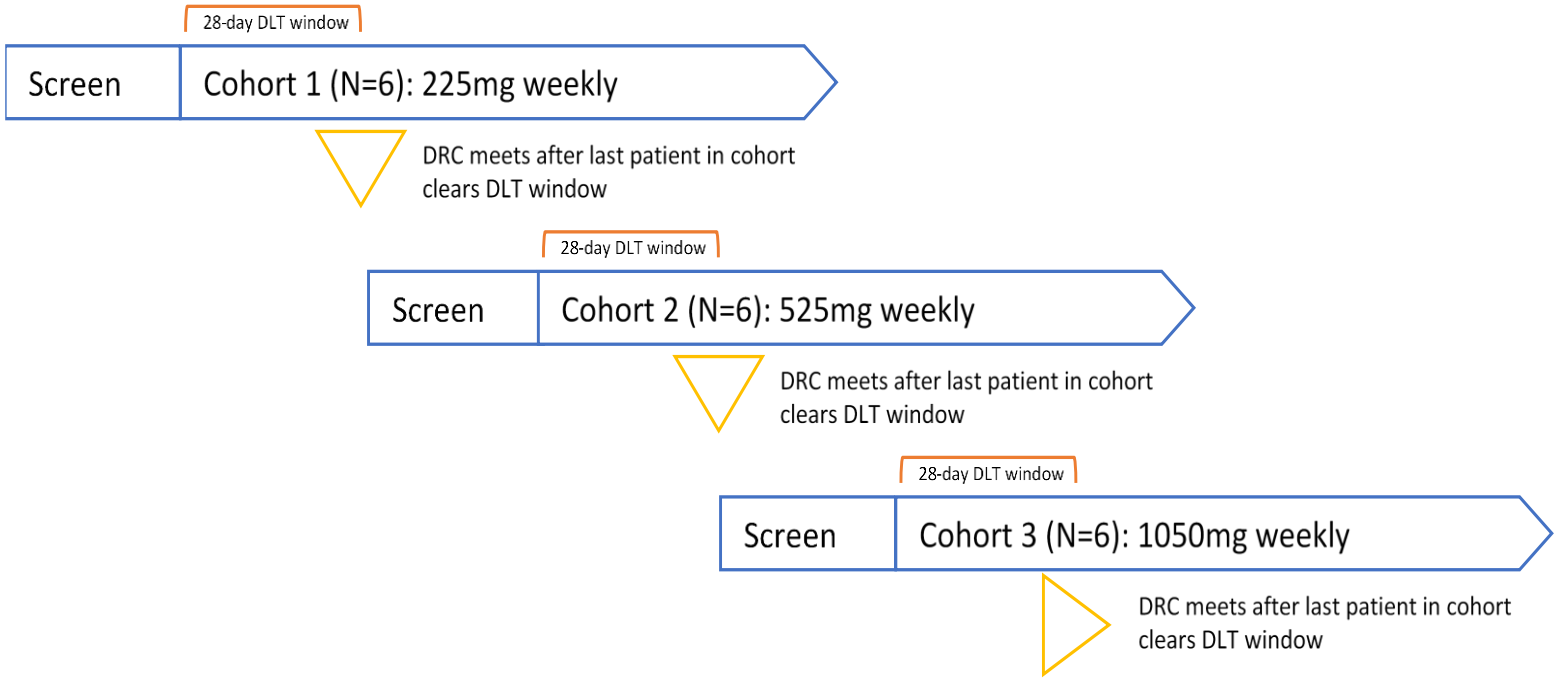
A498 Tumor Model: Hif2a Expression



- Effects of Ligand and PK mod are additive

AROHIF2-1001 Phase 1b Clinical Trial

Objective: evaluate the safety, tolerability, and recommended phase 2 dose based on preliminary efficacy and pharmacodynamic effects



Trial Design:

- Advanced metastatic ccRCC
- Prior failure of TKI and ICI
- Tumor biopsy predose and ~2 weeks post-dose
- Minimum of 6, up to 10 per cohort with at least 4 paired biopsies sufficient for analysis
  - Analysis required tumor cell content of 40% and 5% for qPCR and IHC respectively
- Dose escalate after 28-day DLT period
- Subjects dosed Q1wk at each dose level and continued on drug until toxicity or progression

Baseline Demographics

Mean (min, max)	ARO-HIF2 225 mg (N=7)	ARO-HIF2 525 mg (N=10)	ARO-HIF2 1050 mg (N=9)	Total (N=26)
Age (years)	68.4 (55, 75)	69.5 (63, 87)	57.7 (44, 74)	65.1 (44, 87)
Male (%)	6 (86)	7 (70)	7 (78)	20 (77)
Weight (kg)	81 (67, 104)	82 (49, 113)	86 (57, 124)	83 (49, 124)
BMI (kg/cm2)	26 (21, 32)	26 (17, 33)	28 (20, 37)	27 (17, 37)
IMDC Criteria, n (%)				
Good Risk	1 (14.3)	4 (40.0)	1 (11.1)	6 (23.1)
Intermediate Risk	5 (71.4)	5 (50.0)	4 (44.4)	14 (53.8)
Poor Risk	1 (14.3)	1 (10.0)	2 (22.2)	4 (15.4)
ECOG, n (%)				
0	4 (57.1)	4 (40.0)	3 (33.3)	11 (42.3)
1	3 (42.9)	6 (60.0)	6 (66.7)	15 (57.7)
>1	--	--	--	--
Prior lines of therapy, n (%)				
1	--	--	--	--
2	2 (28.6)	3 (30.0)	3 (33.3)	8 (30.8)
3	2 (28.6)	4 (40.0)	2 (22.2)	8 (30.8)
4	1 (14.3)	1 (10.0)	1 (11.1)	3 (11.5)
≥5	2 (28.6)	2 (20.0)	3 (33.3)	7 (26.9)
Prior Therapy, n (%)				
Anti-VEGF	7 (100)	10 (100)	9 (100)	26 (100)
Checkpoint Inhibitor	7 (100)	10 (100)	9 (100)	26 (100)
VHL mutation status, n (%)			**	**
Frame shift	2 (28.6)	1 (10.0)		3 (17.6)
Missense	1 (14.3)	4 (40.0)*		5 (29.4)
In frame deletion	--	1 (10.0)		1 (5.9)
No variant	2 (28.6)	--		2 (11.8)
Not available	2 (28.6)	4 (40.0)		6 (35.3)

- 26 total patients enrolled
- ECOG of 0 or 1
- 69% of patients had been on 3 or more prior therapies
- All patients received both anti-PD1 and anti-VEGF therapies
- No VHL LOF mutation required for enrollment. Not all patients had VHL variant.

December 1st data cut:

** not all cohort 3 VHL mutation data are available

Safety

Subject Incidence, n (%)	ARO-HIF2 225 mg (N=7)	ARO-HIF2 525 mg (N=10)	ARO-HIF2 1050 mg (N=9)	Total (N=26)
Treatment-emergent AEs* (TEAEs)	7 (100)	10 (100)	8 (88.9)	25 (96.2)
TEAEs by severity				
Grade 1 or 2	5 (71.4)	6 (60.0)	4 (44.4)	15 (57.7)
Grade 3	1 (14.3)	3 (30.0)	4 (44.4)	8 (30.8)
Grade 4	--	1 (10.0)	--	1 (3.8)
Grade 5	1 (14.3)	--	--	1 (3.8)
Treatment-related TEAEs	5 (71.4)	7 (70.0)	5 (55.6)	17 (65.4)
Treatment-emergent SAE	2 (28.6)	4 (40.0)	3 (33.3)	9 (34.6)
TEAEs leading to treatment discontinuation	1 (14.3)	--	--	1 (3.8)
TEAEs in >4 subjects by descending Frequency of PT				
Fatigue	5 (71.4)	5 (50.0)	3 (33.3)	13 (50.0)
Dizziness	1 (14.3)	4 (40.0)	2 (22.2)	7 (26.9)
Dyspnea	1 (14.3)	2 (20.0)	4 (44.4)	7 (26.9)
Nausea	1 (14.3)	3 (30.0)	2 (22.2)	6 (23.1)
Abdominal pain (abdominal pain lower, abdominal discomfort, abdominal distention, abdominal pain, abdominal pain upper)	1 (14.3)	2 (20.0)	3 (33.3)	6 (23.1)
Neuropathy (Peripheral sensory neuropathy, neuropathy peripheral, demyelinating neuropathy)	--	4 (40.0)	1 (11.1)	5 (19.2)
Constipation	--	2 (20.0)	3 (33.3)	5 (19.2)

- Anemia and hypoxia, (frequently reported on-target AEs with small molecule HIF2a inhibitors), were reported in only 12% of patients.
- Peripheral neuropathy reported in several patients
- Five SAEs reported
  - Myocarditis (Hx of TKI induced cardiomyopathy)
  - Demyelinating neuropathy
  - Demyelinating polyradiculoneuropathy
  - Hypoxia (in a patient with lung infiltrate/pneumonia)
  - Acute hypoxemic respiratory failure (in a patient with progressive lung metastasis)

December 1st data cut

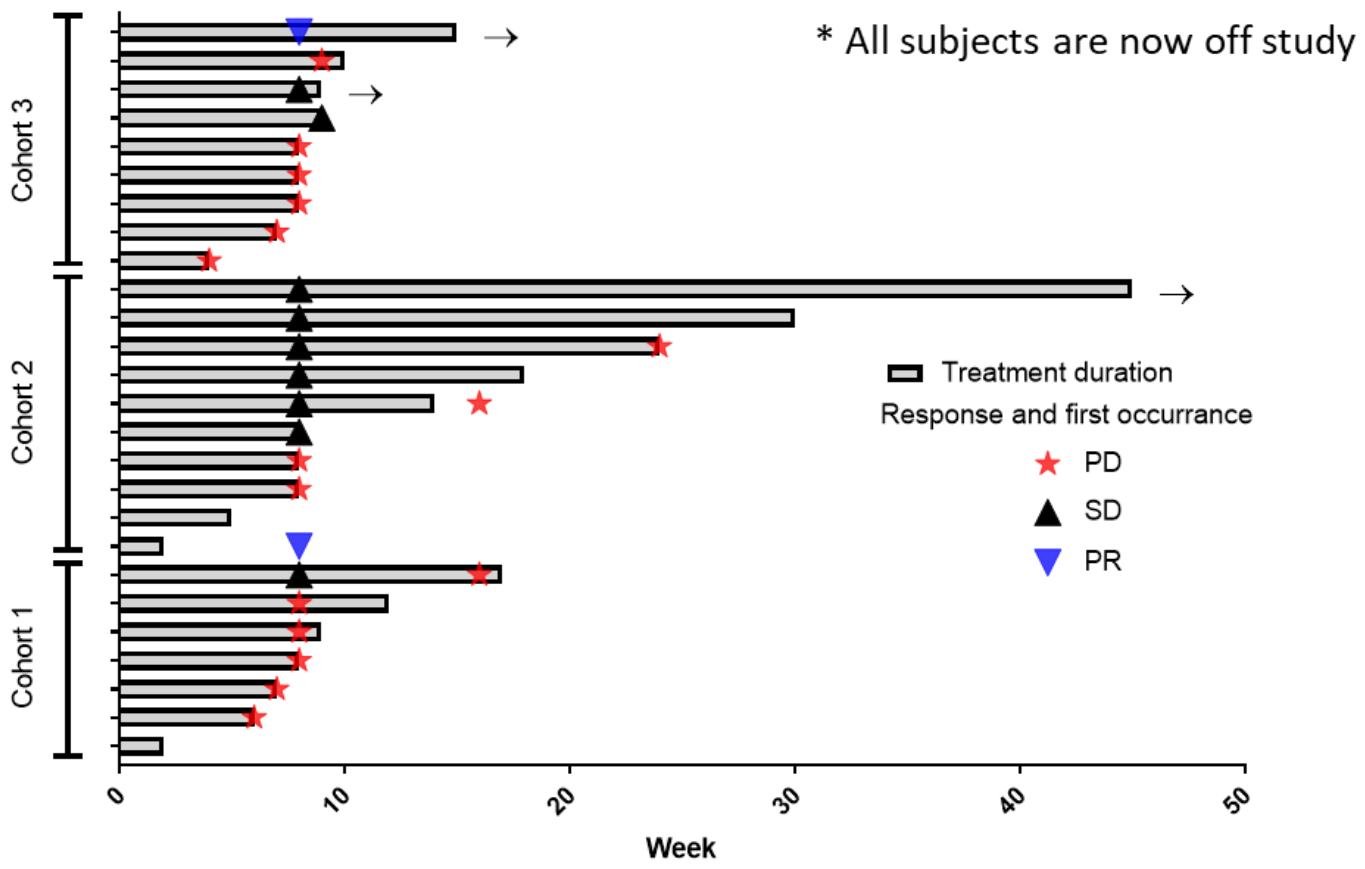
Pharmacodynamics & Efficacy

Median / Mean change (min, max, n)	ARO-HIF2 225 mg (N=7)	ARO-HIF2 525 mg (N=10)	ARO-HIF2 1050 mg (N=9)	Total (N=26)
Hif2a mRNA by qPCR				
All evaluable (median)	-46% (-22, -47, 3)	-27% (-19, -39, 4)	-44% (-28, -59, 2)	-30% (-19, -59, 9)
All reductions (mean)	-38% (-22, -47, 3)	-28% (-19, -39, 4)	-44% (-28, -59, 2)	-35% (-19, -59, 9)
HIF2a protein by IHC				
All evaluable (median)	-26% (500*, -82, 4)	-47% (0, -90, 5)	0% (1700**, -98, 5)	-26% (1700**, -98, 14)
All reductions (mean)	-45% (-26, -82, 3)	-57% (-9, -90, 4)	-80% (-63, -98, 2)	-58% (-9, -98, 9)
Best Response by RECIST, n (%)				
Complete response (CR)	--	--	--	--
Partial response (PR)	--	1 (10.0)	1 (11.1)	2 (7.7)
Stable disease (SD)	1 (14.3)	6 (60.0)	1 (11.1)	8 (30.8)
Progressive disease (PD)	5 (71.4)	2 (20.0)	6 (66.7)	13 (50.0)
Not evaluable (NE)	--	--	1 (11.1)	1 (3.8)
Missing	1 (14.3)	1 (10.0)	--	2 (7.7)
Objective Response (CR+PR), n (%)	0 (0)	1 (10.0)	1 (11.1)	2 (7.7)
Disease control rate (CR+PR+SD***), n (%)	1 (14.3)	7 (70.0)	2 (22.2)	10 (38.5)

* One patient with no VHL variant detected had a very low baseline H score of 1 that increased to 5 at week 2 (+500%). ** One pt had a very low baseline H score of 5 that increased to 85 at week 2 (+1700%, genotyping not available). IHC H score represents overall staining with a maximum score of 300 (100% of cells at intensity 3, 0% at intensity 0, 1, and 2).

- Not all subjects had tumor VHL mutations.
  - PD response impacted by presence of VHL loss-of-function mutation
- Amongst those with PD response (n = 9), mean reductions:
  - In HIF2a mRNA by qPCR of up to **44%**
  - In HIF2a protein by IHC of up to **80%** with a dose response
- Objective Response of **7.7%** driven by one PR in each of 525 mg and 1050 mg cohort.
- Additional analyses (e.g. correlating integrin receptor density and PD response with RECIST response is ongoing)

Duration of Treatment

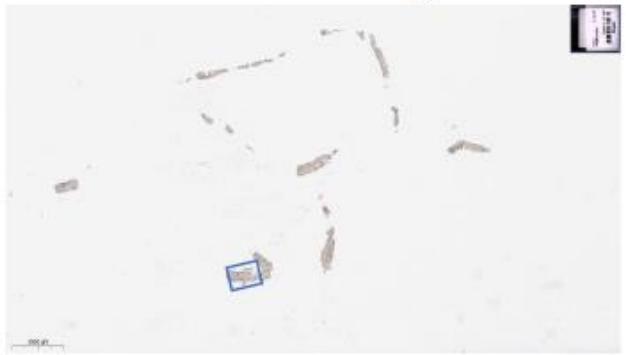


- Three patients were treated with ARO-HIF2 for 5 months or more
- 1 patient remained on therapy with stable disease beyond 10 months
- 1 PR on Week 8 CT scan was confirmed at Week 16 visit
- Other patient with a PR stopped study drug due to an SAE

Histological Example: 98% reduction in HIF2a protein (cohort 3)

Screening

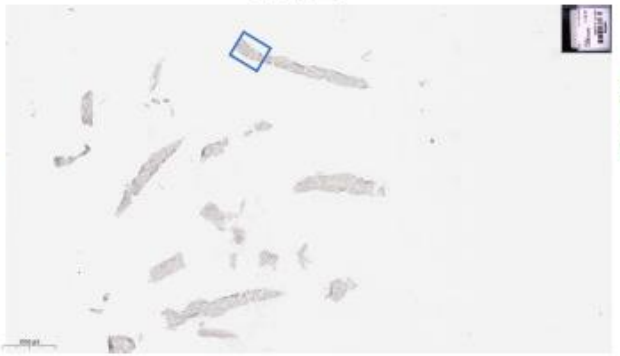
0.7X



Tumor contents
80% screening
60% wk2

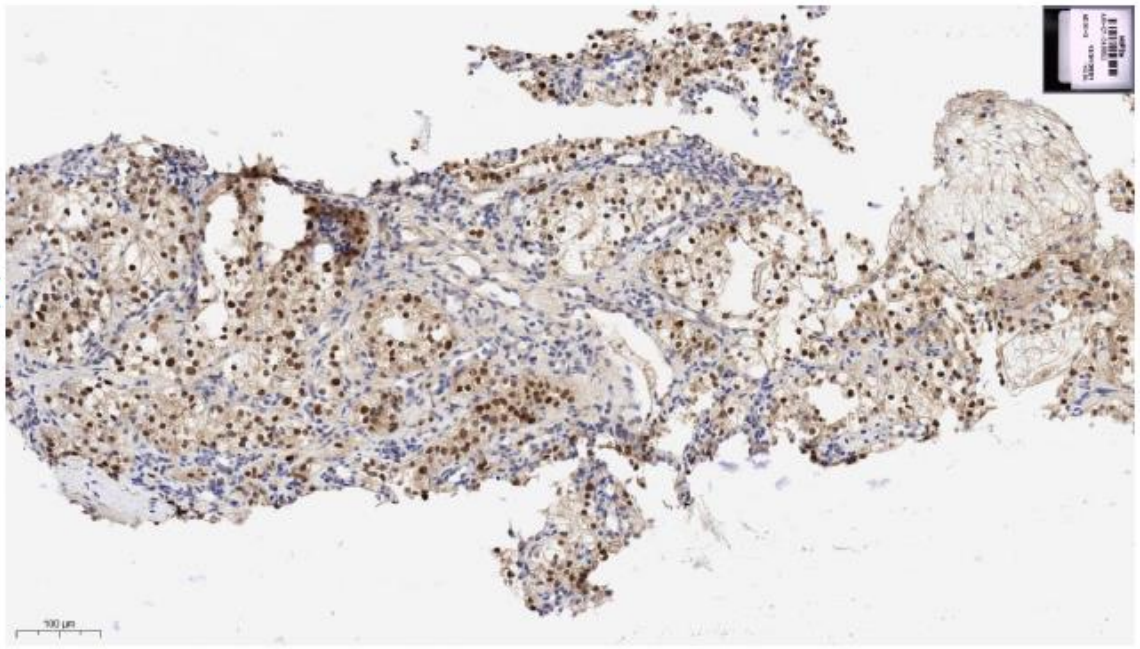
Wk2

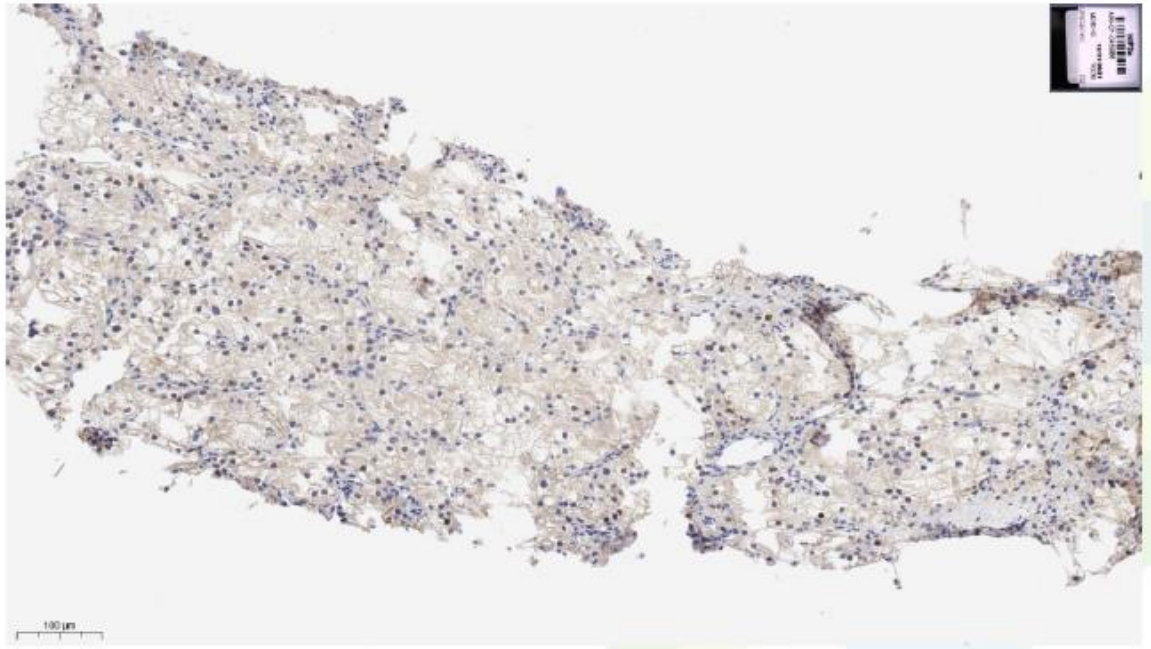
0.7X



98 % ↓(IHC H-Score)
59.01 % ↓ (qPCR)

12.5X





Conclusion

- HIF2a is a clinically validated driver of ccRCC which can be targeted with a RNAi therapeutic
- This phase 1b study provides initial proof of target engagement based on reductions in HIF2a mRNA and protein
- Clinical proof-of-concept was also established based on partial responses in two patients

Thank you to all the patients, investigators and site staff who participated in this study

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