Poster #: 7050

Preclinical evaluation of the AKR1C3-activated alkylator, OBI-3424, in hepatoblastoma – A report from the Pediatric Preclinical In Vivo Testing Consortium (PIVOT)

Filemon S. Dela Cruz[1], Andrew L. Kung[1], Daoqi You[1], Glorife Ibanez Sanchez[1], Raushan Kurmasheva[2], Peter Houghton[2], Yu-Jung Chen[3], Ming-Chen Yang[3], Samantha Brosius[1], Dylan Domenico[1], Jeff Chuang[4], Jee Young Kwon[4], Emily L. Jocoy[4], Steve Neuhauser[4], Tim Stearns[4], Carol J. Bult[4], Beverly Teicher[5], Malcolm A. Smith[5]

[1]Memorial Sloan Kettering Cancer Center, New York, New York, [2]Univ. Texas Health Sciences Center San Antonio, San Antonio, Texas [3]OBI Pharma Inc., Taipei City, Taiwan
[4]The Jackson Laboratory, Bar Harbor, Maine, [5]National Cancer Institute, Bethesda, Maryland

https://preclinicalpivot.org

ABSTRACT

OBI-3424 is a DNA alkylating prodrug activated by aldo-keto reductase family 1 member C3 (AKR1C3). Elevated AKR1C3 expression is observed in a variety of tumors including prostate cancer, T-cell acute lymphoblastic leukemia (T-ALL), hepatocellular carcinoma (HCC) and hepatoblastoma (HBL). Evaluation of AKR1C3 expression across a spectrum of pediatric tumors showed highest expression in T-ALL and hepatoblastoma. Indeed, prior preclinical testing of OBI-3424 in T-ALL patient-derived xenograft (PDX) models showed significant activity with prolonged complete remissions (1). Additionally, promising clinical activity was observed in a Phase 2 clinical trial of patients with advanced HCC (2). Hence, we evaluated the anti-tumor activity of OBI-3424 across a panel of hepatoblastoma PDXs and examined the role of AKR1C3 expression as a response biomarker.

STUDY METHODS

Tumor evaluation: Tumors from 8 hepatoblastoma (HBL) PDX models were assessed for AKR1C3 expression by immunohistochemistry with H-scores assigned after pathology review.

Drug dosing: OBI-3424 (supplied by OBI Pharma) was given at 2.5 mg/kg IV once weekly for 3 weeks.

Tolerability testing: Conducted in 2 mouse strains at 100%, 75%, and 50% of the recommended dose to assess safety (N=3/dose level).

Efficacy studies: 3-6 mice/treatment group (vehicle or OBI-3424) were tested across 8 HBL PDXs, evaluating event-free survival (EFS) and overall objective response measures (ORMs) based on clinical assessment methods (3).

Pharmacodynamic (PD) assessment: For 4 HBL PDXs, 3 mice/treatment group received OBI-3424 or vehicle and tumors harvested for PD assessment 30 minutes after receipt of the 3rd dose. Metabolite analysis was conducted by LC-MS/MS.

AKR1C3 expression and response correlation: A Wilcoxon rank-sum test compared AKR1C3 H-scores between response groups, classifying PR, CR, and MCR as responders and others as non-responders with significance set at 0.05.

ORM	ORM Code	Criteria
Progressive Disease	PD	**< 50%** tumor regression **throughout** study **> 25%** tumor growth at **end of study**
Progressive Disease 1	PD1	**PD** the mouse's **time-to-event ≤ 200%** the **median time-to-event in control group**
Progressive Disease 2	PD2	**PD** the mouse's **time-to-event is > 200%** the **median time-to-event in control group**
Stable Disease	SD	**< 50%** tumor regression **throughout** study **≤ 25%** tumor growth at **end of study**
Partial Response	PR	**≥ 50%** tumor regression at **any point during study** but **measurable tumor** throughout study period
Complete Response	CR	**disappearance** of measurable tumor mass during the study period
Maintained Complete Response	MCR	**no measurable tumor mass** for at **least 3 consecutive weekly** readings at any time after treatment has been completed

Each mouse was assigned a score from 0 to 10 based on their ORM. PD1 = 0, PD2 = 2, SD = 4, PR = 6, CR = 8, and MCR = 10. The median for the group determined the overall response.

If the median score was half-way between an ORM category, the objective response was assigned to the lower response category.

RESULTS

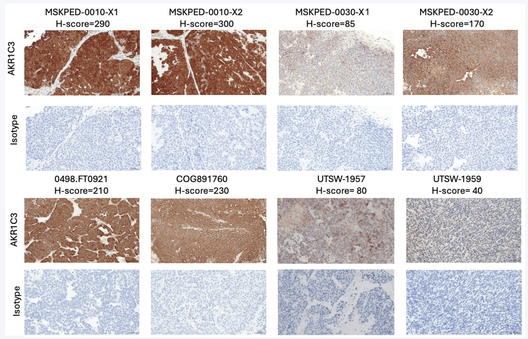

Figure 1. AKR1C3 Immunohistochemistry (IHC) for representative pediatric hepatoblastoma PDX models. IHC performed by OBI Pharma.

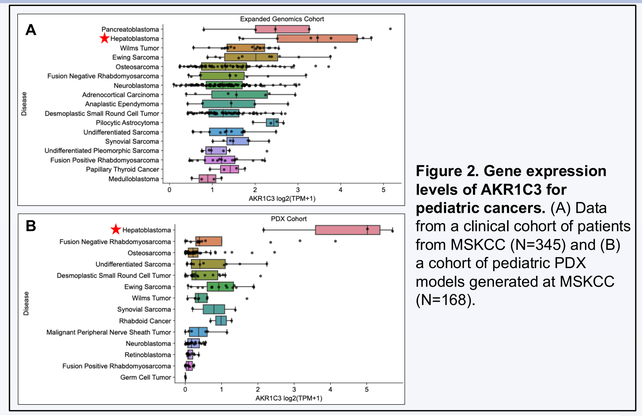

Figure 2. Gene expression levels of AKR1C3 for pediatric cancers. (A) Data from a clinical cohort of patients from MSKCC (N=345) and (B) a cohort of pediatric PDX models generated at MSKCC (N=168).

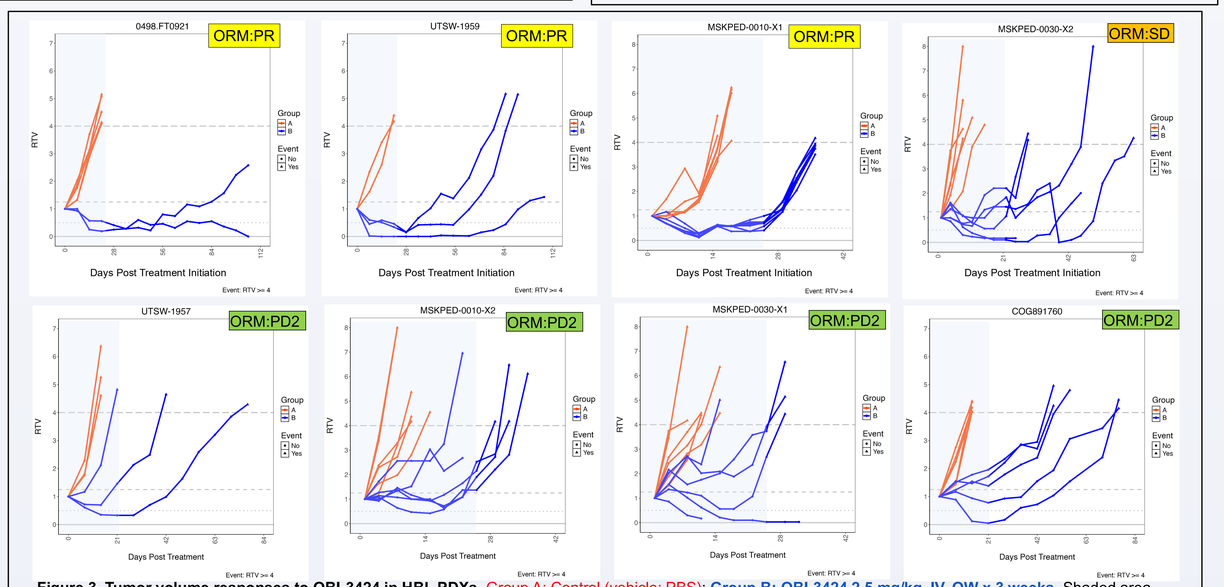

Figure 3. Tumor volume responses to OBI-3424 in HBL PDXs. Group A: Control (vehicle; PBS); **Group B: OBI-3424 2.5 mg/kg, IV, QW x 3 weeks.** Shaded area highlights the treatment period.

Model	Group	N	KM med	EFS T/C	p-value	minRTV mean+/-SD	p-value	ORM	AKR1C3 H-Score
0498.FT0921	A	5	18.67			1.66+/-0.32		PD	210
	B	2	>105	5.62	0.0679	0.2+/-0.2	0.0369	PR	
UTSW-1959	A	2	19.66			1.98+/-0.51		PD	40
	B	3	86.03	4.38	0.0455	0.1+/-0.09	0.1489	PR	
MSKPED-0010-X1	A	6	15.4			1.12+/-0.29		PD	290
	B	6	36	2.34	0.0013	0.24+/-0.08	0.0045	PR	
MSKPED-0030-X2	A	6	7.04			2.54+/-0.92		PD	170
	B	6	37.4	5.31	0.0013	0.42+/-0.42	0.0051	SD	
UTSW-1957	A	3	12.25			1.95+/-0.29		PD	80
	B	3	40.31	3.29	0.0339	0.73+/-0.42	0.0809	PD2	
MSKPED-0010-X2	A	6	9.87			2.42+/-0.92		PD	300
	B	6	29.54	2.99	0.0013	0.9+/-0.45	0.0131	PD2	
MSKPED-0030-X1	A	6	9.85			2.62+/-0.87		PD	85
	B	6	25.4	2.58	0.0015	0.96+/-0.8	0.02	PD2	
COG891760	A	5	13.45			2.05+/-0.59		PD	230
	B	5	49.45	3.68	0.0039	1.01+/-0.61	0.0947	PD2	

Table 1. Summary of efficacy testing of OBI-3424 against a panel of pediatric hepatoblastoma models.

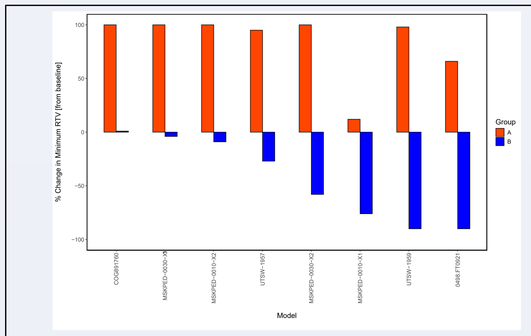

Figure 4. Percent tumor volume change to OBI-3424 in HBL PDXs.
Group A: Control (vehicle; PBS); **Group B:** OBI-3424 2.5 mg/kg, IV, QW x 3 weeks.

SUMMARY

- AKR1C3 expression H-scores ranged from 40 – 300 (median: 190) with 5 of 8 models having H-scores ≥100. AKR1C3 transcript levels correlated with protein levels.
- OBI-3424 was well tolerated at all dose levels with no significant weight loss in 2 different immunodeficient mouse strains.
- Time to event was prolonged > 2-fold for all models with OBI-3424 treatment (EFS T/C range: 2.34 to 5.62).
- Tumor shrinkage to OBI-3424 was observed in 7 of 8 models (range: -58% to -90%). 4 models had > 50% volume reduction.
- For 8 models tested, 3 PRs and 1 SD were observed. Four models were categorized as progressive disease with tumor growth delay (PD2).
- No significant difference in the distribution of AKR1C3 H-scores is detected between responders and non-responder groups (p=0.08 Wilcoxon rank-sum test).
- OBI-3424 induced formation of the active metabolite (OBI-2660; range: 124.2 – 672 ng/g) in 4 HBL PDXs while vehicle controls showed no quantifiable metabolite confirming in vivo activation

CONCLUSION

- AKR1C3, the activating enzyme for OBI-3424, is overexpressed at the RNA and protein level in many cases of hepatoblastoma.
- OBI-3424 shows promising preclinical activity in pediatric hepatoblastoma PDX models.
- The role of AKR1C3 expression as a response biomarker for hepatoblastoma requires further investigation.
- Early trial results in HCC and preclinical activity in HBL support further clinical development of OBI-3424 for patients with HCC and HBL.

REFERENCES

(1) Evans et al., Clin Cancer Res 2019; 25:4493-4503
(2) Qin et al., Oral presentation, Chinese Society of Clinical Oncology Meeting, 2024 Sep 27, Nanjing, China.
(3) Houghton et al., Pediatric Blood Cancer 2007; 49:928-940

MORE INFORMATION

Corresponding author: Filemon Dela Cruz, Memorial Sloan Kettering Cancer Center (Email: delacrf1@mskcc.org)

Funding: 3U01CA199221, 3U01CA199287, 3U01CA199297, 3U01CA199288, U24CA263963, 1U01CA263967-01

Visit thePIVOT website

NCI Pediatric Preclinical Testing Consortium
A program funded by the National Cancer Institute of the National Institutes of Health

The Jackson Laboratory — Leading the search for tomorrow's cures
UT Health San Antonio — Greehey Children's Cancer Research Institute
The University of Texas MD Anderson Cancer Center — Children's Cancer Hospital
Children's Hospital of Philadelphia
Ann & Robert H. Lurie Children's Hospital of Chicago
Children's Cancer Institute
Memorial Sloan Kettering Cancer Center
St. Jude Children's Research Hospital — Finding cures. Saving children.