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The B7-H3 Targeting Antibody-Drug Conjugate (ADC) Vobramitamab Duocarmazine (Vobra Duo) Is Potently Effective Against a Broad Panel of Pediatric Solid Tumor Xenograft Models: A Study from the Pediatric Preclinical In Vivo Testing (PIVOT) Consortium

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ABSTRACT

Vobra duo, a duocarmycin-based humanized ADC (drug-to-antibody ratio is ~2.7) targeting B7-H3, shows robust *in vivo* activity against a range of adult cancer models, and a favorable pharmacokinetic and safety profile in cynomolgus monkeys. Initial results from the single agent phase 1 clinical trial of vobra duo (NCT03729596) showed manageable side effects and promising objective response rates in metastatic castration-resistant prostate cancer. B7-H3 is highly expressed in pediatric solid tumors, and it is emerging as a key target for pediatric oncology. Here we report the antitumor activity of vobra duo against preclinical xenograft models of pediatric solid tumors.

STUDY METHODS

Ewing sarcoma (ES), rhabdomyosarcoma (RMS), and neuroblastoma (NB) xenograft models were tested previously with n=1 or n=2 designs. Osteosarcoma (OS) models, due to their slower growth kinetics and lower rates of tumor regression, were tested with n=10 mice per arm. We report here an extension of previous work reported at ASCO 2021 that includes **malignant rhabdoid tumor (MRT), hepatoblastoma (HB), and Wilms tumor (WT) models** using n=5 mice per treatment group. Vobra duo and control ADC (SYD988 anti-CD20 ADC with the same linker and payload as vobra duo) were provided by MacroGenics, Inc., and were administered at **6 mg/kg** as a single administration IP. Time-to-event was defined as 4-fold increase in tumor xenograft volume from the day of treatment. The Kaplan-Meier method was used to compare event-free survival (EFS) between treated and control groups. Objective response categories were determined as described previously (Ped Blood Cancer 2007;49:928-940), with objective responses including partial, complete, and maintained complete responses (PR, CR, and MCR).

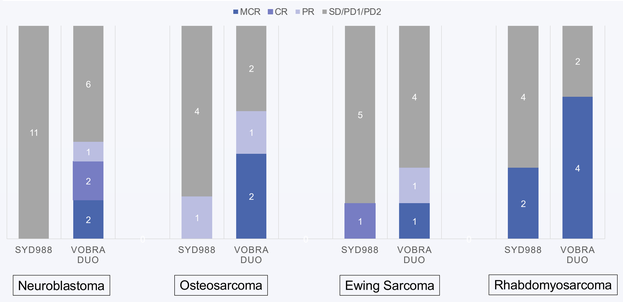
ORM	ORM Code	Criteria
Progressive Disease	PD	**< 50%** tumor regression **throughout** study **> 25%** tumor growth at **end of study**
Progressive Disease 1	PD1	**PD** the mouse's **time-to-event ≤ 200%** the **median time-to-event in control group**
Progressive Disease 2	PD2	**PD** the mouse's **time-to-event 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

Results of previous study testing efficacy of vobra duo in preclinical pediatric models



Vobra duo, as previously reported (ASCO 2021) induced objective responses in multiple pediatric solid tumors, including:

- 5 of 11 neuroblastoma (1PR, 2 CR, and 2 MCR)
- 3 of 5 osteosarcoma (1 PR, 2 MCR)
- 2 of 6 Ewing sarcoma (1 PR, 1 MCR)
- 4 of 6 rhabdomyosarcoma (4 MCR)

The control ADC (SYD988) showed less activity than vobra duo for all tumor types tested.

New study results from testing vobra duo in additional preclinical pediatric models

Hepatoblastoma (HB) (n=7)

Model	Grp	N	KM med	EFST-C	EFST/C	Gehan-Wilcoxon p-value	minRTV mean+/-SD	minRTV p-value	ORM
UTH-0494	A	4	19.39				1.98+/-0.48		PD
	B	5	47.19	27.8	2.43	0.0047	0.4+/-0.34	0.02	PD2
	C	5	98.49	79.11	5.08	0.0047	0.21+/-0.35	0.0179	MCR
COG891760	A	5	16.39				1.53+/-0.19		PD
	B	5	25.28	8.89	1.54	0.0593	1.47+/-0.4	0.5309	PD1
	C	5	98	81.61	5.98	0.0039	0+/-0	0.0075	MCR
COG922822	A	5	16.93				2.36+/-0.33		PD
	B	5	23.06	6.13	1.36	0.1037	2.19+/-0.62	0.5309	PD1
	C	5	98	81.07	5.79	0.0039	0.09+/-0.2	0.0097	MCR
UHS-0648-000	A	5	12.15				3+/-0.12		PD
	B	5	19.04	6.89	1.57	0.0039	1.76+/-0.41	0.0122	PD1
	C	5	65.01	52.86	5.35	0.0039	0.66+/-0.58	0.0122	SD
0498.FT0921	A	5	21.9				1.83+/-0.22		PD
	B	5	46.02	24.12	2.1	0.0098	1.19+/-0.09	0.02	PD1
	C	5	71.21	49.31	3.25	0.0039	0.79+/-0.19	0.0122	PD2
UTSW-2237.FT2342	A	5	35				1.42+/-0.09		PD
	B	5	60.01	25.01	1.71	0.1182	1.03+/-0.16	0.0119	PD1
	C	5	61	26	1.74	0.022	0.66+/-0.23	0.0119	PD1
0674.FT1373	A	5	25.58				1.57+/-0.31		PD
	B	5	28.94	3.36	1.13	0.0382	1.17+/-0.21	0.0601	PD1
	C	5	48.38	22.8	1.89	0.0382	0.71+/-0.22	0.0122	PD1

Malignant Rhabdoid Tumors (MRT) (n=5)

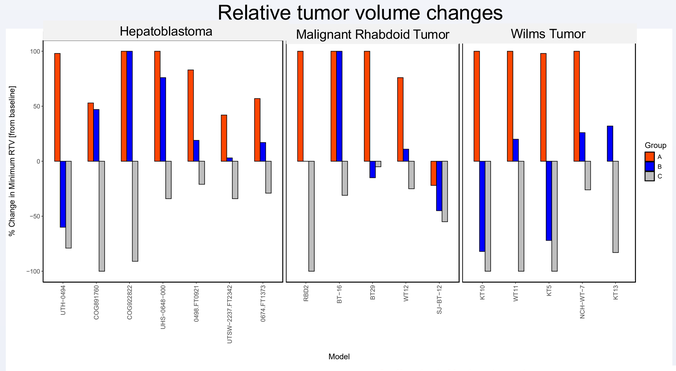
Model	Grp	N	KM med	EFST-C	EFST/C	Gehan-Wilcoxon p-value	minRTV mean+/-SD	minRTV p-value	ORM
RBD2	A	3	15.1				2.12+/-0.09		PD
	B	5	34.35	19.25	2.27	0.0062	1+/-0.26	0.0358	PD2
	C	5	>98	82.9	6.49	0.0062	0.17+/-0.1	0.0358	MCR
BT-16	A	5	10.33				3.57+/-0.49		PD
	B	5	13.46	3.13	1.3	0.0039	2.5+/-0.39	0.0122	PD1
	C	5	84	73.67	8.13	0.0382	0.69+/-1.55	0.0311	MCR
BT29	A	5	13.19				2.02+/-0.68		PD
	B	5	51.07	37.88	3.87	0.0039	0.85+/-0.76	0.0947	PR
	C	4	39.87	26.68	3.02	0.0098	0.95+/-0.32	0.02	PD2
WT12	A	5	18.43				1.76+/-0.23		PD
	B	5	33.13	14.7	1.8	0.3454	1.11+/-0.55	0.0947	PD1
	C	5	71.52	53.09	3.88	0.0039	0.75+/-0.48	0.0122	PD2
SJ-BT-12	A	5	49				0.78+/-0.32		PD
	B	5	56	7	1.14	0.7009	0.55+/-0.36	0.3457	SD
	C	5	62.64	13.64	1.28	0.8815	0.45+/-0.35	0.1412	SD

Wilms tumor (WT) (n=5)

Model	Grp	N	KM med	EFST-C	EFST/C	Gehan-Wilcoxon p-value	minRTV mean+/-SD	minRTV p-value	ORM
KT10	A	5	15.18				2.12+/-0.38		PD
	B	5	85.69	70.51	5.64	0.0039	0.18+/-0.24	0.0119	PR
	C	5	>105	89.82	6.92	0.0039	0+/-0	0.0075	MCR
WT11	A	5	10.98				2.25+/-0.42		PD
	B	5	21.86	10.88	1.99	0.0039	1.2+/-0.26	0.0122	PD1
	C	5	>105	94.02	9.56	0.0039	0+/-0	0.0075	MCR
KT5	A	5	16.59				1.98+/-0.64		PD
	B	5	55.4	38.81	3.34	0.0098	0.28+/-0.42	0.0195	PR
	C	5	>107	90.41	6.45	0.0039	0+/-0	0.0073	MCR
NCH-W	A	5	12.11				2.36+/-0.39		PD
	B	5	23.08	10.97	1.91	0.0204	1.26+/-0.64	0.0216	PD1
	C	5	105	92.89	8.67	0.0652	0.74+/-1.22	0.1388	MCR
KT13	B	1	>29						PD
	C	1	>88	59	3.03	1	0.17	1	PR

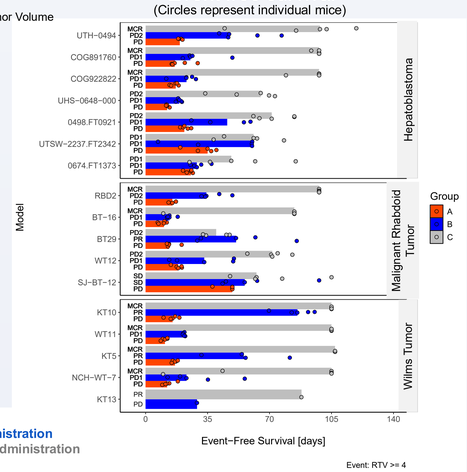
EFS=Event Free Survival; T=treated; C=control
KM med = Median days EFS; RTV=Relative Tumor Volume
ORM= Objective Response Measure

Relative tumor volume changes



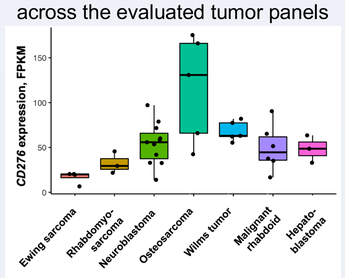
Event free survival

(Circles represent individual mice)

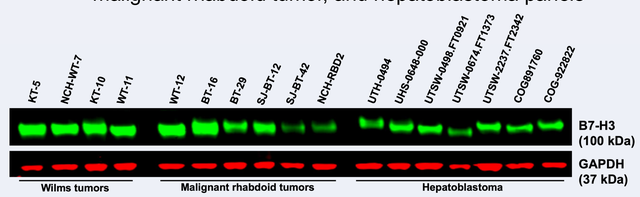


A: Control, No treatment
B: 1816 Control SYD988: 6 mg/kg, IP, Single Administration
C: 1816 MGC018 (vobra duo): 6 mg/kg, IP, Single Administration

CD276 mRNA expression (FPKM) across the evaluated tumor panels



Western blot analysis of B7-H3 protein expression across Wilms tumor, malignant rhabdoid tumor, and hepatoblastoma panels



SUMMARY

Hepatoblastoma (HB):

- All HB models showed some level of tumor regression to vobra duo, but most did not show reduction in tumor volume to compared to the control ADC.
- 3 of 7 HB had MCR responses to vobra duo compared to 0 of 7 with objective responses to control ADC.
- 5 of 7 HB models had time to event extended > 3-fold to vobra duo versus 0 of 7 to control ADC.

Malignant Rhabdoid Tumors (MRT):

- 2 of 5 MRT showed MCR responses to vobra duo with another model showing stable disease. A single model showed PR response to control ADC and another model showed stable disease.
- Median time to event was extended by 3-fold or greater in 4 of 5 models to vobra duo, but in only 1 of 5 models for control ADC.

Wilms tumor (WT):

- All 5 WT models had objective responses to vobra duo and 4 of 5 had MCR responses. No WT models had MCR responses to control ADC, and only 2 of 5 had PR responses.
- Vobra duo extended median time to event by > 6-fold in 4 WT models evaluable for this measure.

WT had higher *CD276* gene expression than MRT and HB, though most models showed some expression comparable to that of rhabdomyosarcoma and neuroblastoma models. B7-H3 protein expression was detectable in all models studied, with highest protein expression levels for Wilms tumor.

CONCLUSION

Vobra duo is highly efficacious across a broad panel of pediatric solid tumor xenograft models. This supports duocarmycin-based payloads as being effective against pediatric solid tumors, and it confirms B7-H3 as a high priority target for multiple solid tumors, including osteosarcoma, rhabdomyosarcoma, neuroblastoma, Wilms tumor, malignant rhabdoid tumor, and hepatoblastoma.

REFERENCES

Houghton et al., Pediatric Blood Cancer 2007; 49:928-940

MORE INFORMATION

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Visit the PIVOT Website

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