Abstract: 1088

AN EVALUATION OF PATRITUMAB DERUXTECAN (HER3-DXD, U3-1402) AGAINST PEDIATRIC PDX MODELS FOR HEPATOBLASTOMA AND RHABDOMYOSARCOMA – A REPORT FROM THE NCI PIVOT PROGRAM

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Pediatric Preclinical In Vivo Testing

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ABSTRACT

HER3-DXd is an ADC consisting of a fully human monoclonal antibody to HER3 attached to a topoisomerase 1 (topo-1) inhibitor payload (DXd, an exatecan derivative) that has demonstrated clinically meaningful efficacy with durable responses in adults with non-small cell lung cancer and advanced breast cancer. The goal of this work was to evaluate the activity of HER3-DXd against PDX models for two childhood cancers with HER3 expression [rhabdomyosarcoma (RMS) and hepatoblastoma (HB)] and to compare the activity of HER3-DXd with isotype control ADC (IC-ADC).

STUDY METHODS

Response Assessment: To evaluate treatment efficacy **objective response measures (ORM)** based on changes in **relative tumor volume** (**RTV**) were used (Houghton, Pediatr Blood Cancer 2007;49:928-940).

To calculate **event free survival** for these models a relative tumor volume greater than or equal to 4 was used as the event. A statistical comparison of survival days was computed using two approaches: Gehan-Wilcoxon and exact rank tests. The Gehan-Wilcoxon test gives more weight to deaths at earlier time points and is most sensitive to early differences between survival. The null hypothesis of no differences between the curves is rejected at a p-value threshold of < 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

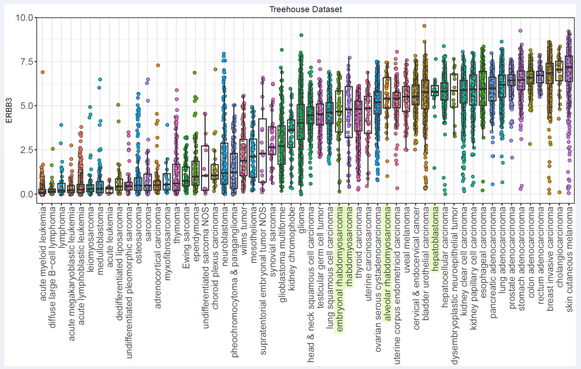
Each mouse was assigned a score from 0 to 10 based on their ORM. PD1 = 0, PD2 = 2, SD = 4, PR = 6, CR = 8, and MCR = 10, and the median for the group determines the overall response.

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

Log cell kill (LCK) per dose (Clark, 1997) was estimated from: LCK/dose =(T-C)/(3.32)(T_D)(n), where T_D = tumor doubling time and n = number of treatments. The equation simplifies to LCK/dose = 0.301 x [T/C -1]

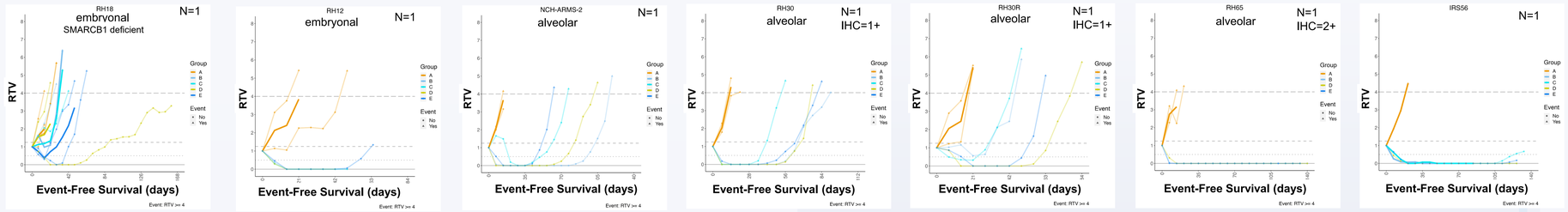
ERBB3 Expression

***ERBB3* Expression:** The figure below is from the Treehouse Childhood Cancer Initiative (UCSC) and shows *ERBB3* expression [$\log_2$(TPM+1)] for a range of adult and pediatric cancers. Among pediatric cancers, hepatoblastoma had the highest ERBB3 gene expression followed by rhabdomyosarcoma. Other childhood cancers such as neuroblastoma, Ewing sarcoma, Wilms tumor, and osteosarcoma show much lower *ERBB3* expression.



RESULTS

Rhabdomyosarcoma (RMS) Testing Results



A: Control, No treatment B: HER3-DXd, 3 mg/kg, IV, Once a week x 3 wks C: IC-ADC, 3 mg/kg, IV, Once a week x 3 wks D: HER3-DXd, 10 mg/kg, IV, Once a week x 3 wks E: IC-ADC, 10 mg/kg, IV, Once a week x 3 wks

Bold lines on the RTV plots reflects median response for the treatment group

RMS HER3 Expression by IHC:

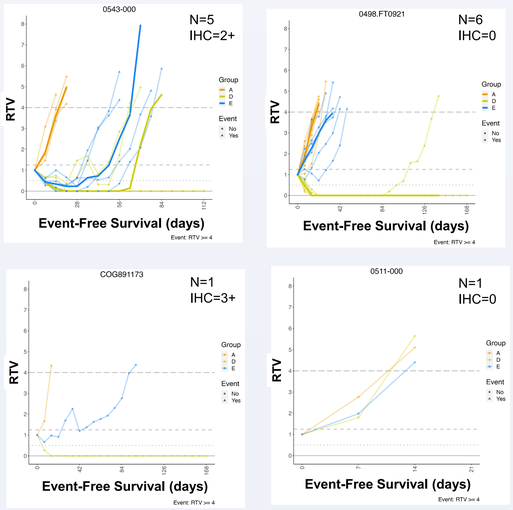
Among 9 rhabdomyosarcoma models tested for IHC expression using tissue microarray specimens (most with 11-12 cores per model), 2 had a median IHC score of 0 (Rh18 and Rh36), while 7 other models had a median IHC score of either 1+ (Rh10, Rh28, Rh30, Rh30R, and Rh41) or 2+ (Rh65 and Rh66).

Objective Response Measure and Log Cell Kill (red font) for RMS Models Treated with HER3-DXd or with IC-DXd

Model	HER3 IHC Score	HER3-DXd				IC-DXd			
		3 mg/kg		10 mg/kg		3 mg/kg		10 mg/kg	
Rh18	-	0.4	PD1	2.31	SD	0.44	PD1	1.07	PR
Rh12	-	>0.38	MCR	>0.24	MCR	>0.38	MCR	>0.68	MCR
NCH-ARMS-2	-	4.5	MCR	3.84	MCR	2.72	CR	2.11	CR
Rh30	+1	2.79	MCR	2.25	MCR	1.39	CR	2.42	CR
Rh30R	+1	0.96	PD2	2.05	MCR	0.86	PR	1.5	MCR
Rh65	+2	>4.37	MCR	>4.37	MCR	-	-	>4.12	MCR
IRS-56	-	>2.59	MCR	>3.36	MCR	>2.81	MCR	>3.36	MCR

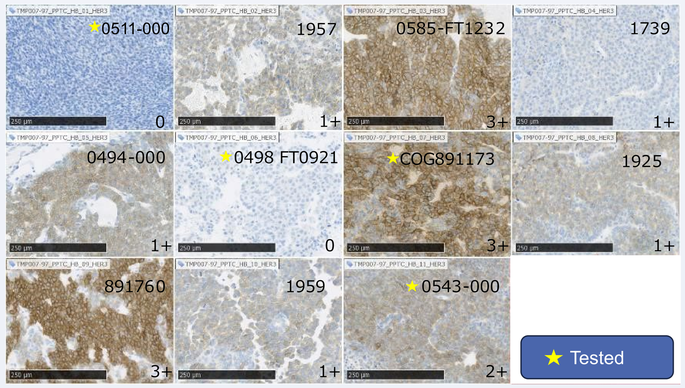
Hepatoblastoma (HB) Testing Results

A: Control, No treatment
D: HER3-DXd, 10 mg/kg, IV, Once a week x 3 wks
E: IC-ADC, 10 mg/kg, IV, Once a week x 3 wks



Hepatoblastoma PDX HER3 Expression

HER3(ERBB3) Expression: IHC testing was conducted on FFPE tissue (slides or TMA) using HER3/ErbB3 (D22C5) XP rabbit mAB. The IHC score was determined from membrane expression of HER3 stained in ≥10% of tumor cells using a microscope: 0 for negative; 1+ for weak; 2+ for moderate; and 3+ for strong intensity. Expression for HB PDX models, including those tested with HER3-DXd, is shown below to illustrate the range of staining observed. For the 11 HB models, HER3 expression was 0 (n=2), 1+ (n=5), 2+ (n=1), and 3+ (n=3).



EFS, Objective Response Measure, and Log Cell Kill (LCK) for Hepatoblastoma Models Treated with HER3-DXd or with IC-DXd

		Control			HER3-DXd			IC-ADC		
MODEL	HER3 IHC	EFS (days)	LCK	ORM	EFS (days)	LCK	ORM	EFS (days)	LCK	ORM
0498.FT0921	0	19	-	PD	>140	>3.88	MCR	34	0.5	PD1
0511-000	0	11	-	PD	12	0.04	PD1	13	0.1	PD1
0543-000	2+	16	-	PD	78	2.25	MCR	64	1.74	PR
COG891173	3+	13	-	PD	>168	>6.93	MCR	92	3.51	PR

DISCUSSION

- ❑ The majority of RMS and HB models evaluated showed HER3 expression by IHC.
- ❑ HER3-DXd was highly active against RMS models at 3 and 10 mg/kg with most models achieving MCR.
- ❑ IC-ADC was also highly active against RMS models at both dose levels, suggesting that the RMS models are highly responsive to the DXd payload.
- ❑ Three of 4 HB models treated with HER3-DXd showed MCR, including one model with no HER3 expression by IHC. One other HB model with no HER3 expression showed progressive disease to HER3-DXd.
- ❑ The 3 HB models with MCR responses to HER3-DXd showed lesser responses and lower LCK to IC-ADC, supporting a role for HER3 expression in HER3-DXd activity for HB.
- ❑ At 10 mg/kg HER3-DXd, 2 of 4 HB models and 3 of 6 evaluable RMS models had time to event > 100 days.

CONCLUSIONS

- ❑ HER3-DXd is highly active against both HB and RMS models.
- ❑ The high activity of IC-ADC for RMS models suggests exquisite sensitivity of RMS models to the DXd payload, which is supported by prior in vivo testing of RMS models with topo-1 inhibitors (Houghton, et al. 1995).
- ❑ Based on the high level of activity observed for HER3-DXd against RMS and HB PDX models, this ADC has potential for clinical activity in pediatric patients with these cancers.

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MORE INFORMATION

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