Abstract: LB402

In vivo efficacy of B7-H3 (CD276)-directed antibody-drug conjugate (ADC) ifinatamab deruxtecan (I-DXd; DS-7300a): an update from the Pediatric Preclinical In Vivo Testing (PIVOT) Program

Richard Gorlick[1], Jonathan Gill[1], Wendong Zhang[1], Peter J Houghton[2], Raushan Kurmasheva[2], Yael P Mossé[3], John M Maris[3], David Groff[3], Jun Hasegawa[4], Xiaozhong Qian[4], Steve Neuhauser[5], Tim Stearns[5], Emily L. Jocoy[5], Jeff Chuang[5], Carol J Bult[5], Beverly Teicher[6], Malcolm A. Smith[6]

[1]MD Anderson Cancer Center, [2]University of Texas Health Sciences Center, San Antonio; Greehey Children's Cancer Research Institute, [3]Children's Hospital of Philadelphia, [4]Daiichi Sankyo, Inc., [5]The Jackson Laboratory, [6]National Cancer Institute

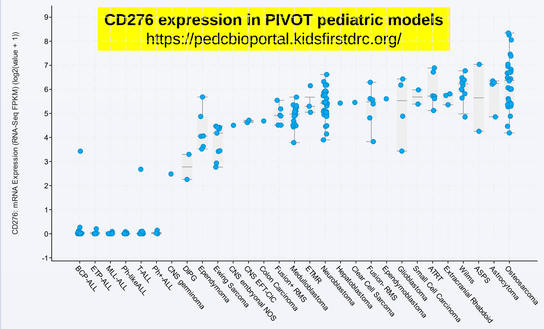
https://preclinicalpivot.org

ABSTRACT

I-DXd is a B7-H3-directed ADC with a topoisomerase 1 inhibitor payload (an exatecan derivative, DXd). I-DXd has demonstrated clinical efficacy in adults with heavily pretreated solid tumors (Patel et al., ESMO 2023) and is in clinical testing for adults with small cell lung cancer (NCT05280470 and NCT06203210). We previously reported that I-DXd induced objective responses in PDX models for multiple B7-H3 (*CD276*) expressing pediatric histologies, including rhabdomyosarcoma, osteosarcoma, neuroblastoma, and Wilms tumor. We extend these results with dose-response testing and include an isotype control ADC (IC-ADC) to evaluate whether B7-H3 expression is required for optimal response.

STUDY METHODS

Patient derived *in vivo* models for several pediatric cancer types were selected for preclinical testing of DS-7300a based on the high rates of B7-H3 (*CD276*) expression.



PDX models were dosed with vehicle, I-DXd, or IC-ADC, the latter two at 1, 3, and 10 mg/kg intravenously on days 1 and 15. Testing was performed using 5 animals per treatment group. Activity was assessed by the PIVOT objective response measure (ORM) (Ped Blood Cancer 2007;49:928-940) that defines objective response as partial, complete, or maintained complete response (PR, CR, and MCR) compared to stable disease (SD) or progressive disease, with or without growth delay (PD2 and PD1, respectively).

To evaluate treatment efficacy for osteosarcoma, neuroblastoma, rhabdomyosarcoma, Ewing sarcoma and Wilms (kidney) tumor, **objective response measures (ORM)** based on changes in **relative tumor volume** (**RTV**) were used (Houghton, Pediatric 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. For orthotopic CNS models, survival was the study endpoint. 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]

RESULTS

Treatment Arms

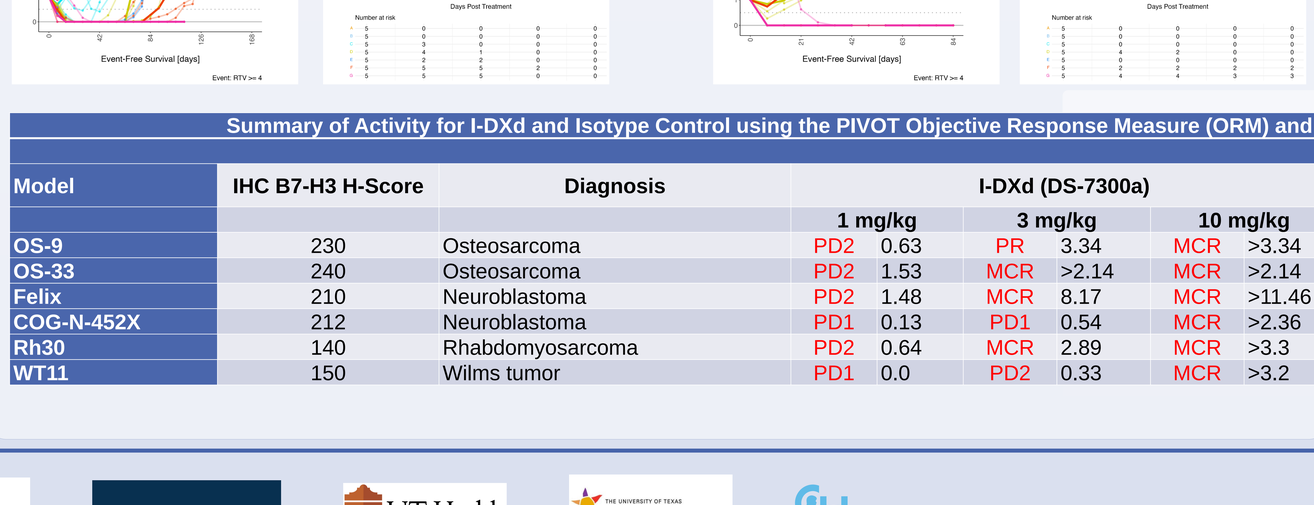
A: Control (IV) vehicle, day1 and day15
B: Isotype control ADC (IV) 1mg/kg, day1 and day15
C: Isotype control ADC (IV) 3mg/kg, day1 and day15
D: Isotype control ADC (IV) 10mg/kg, day1 and day15
E: I-DXd (IV) 1mg/kg, day1 and day15
F: I-DXd (IV) 3mg/kg, day1 and day15
G: I-DXd (IV) 10mg/kg, day1 and day15

N=5 per treatment arm

Limit of detection for tumor volume = 0.04 cm³

Bold lines in Relative Tumor Volume (RTV) plots reflects median response for the treatment group.

Osteosarcoma



Neuroblastoma

Rhabdomyosarcoma, Wilms tumor

Summary of Activity for I-DXd and Isotype Control using the PIVOT Objective Response Measure (ORM) and Net Log Cell Kill in Preclinical Models

Model	IHC B7-H3 H-Score	Diagnosis	I-DXd (DS-7300a)						Isotype Control (IC-ADC)					
			1 mg/kg		3 mg/kg		10 mg/kg		1 mg/kg		3 mg/kg		10 mg/kg	
OS-9	230	Osteosarcoma	PD2	0.63	PR	3.34	MCR	>3.34	PD1	0.03	PD1	0.06	PD1	0.03
OS-33	240	Osteosarcoma	PD2	1.53	MCR	>2.14	MCR	>2.14	PD1	0.04	PD2	0.81	SD	>2.14
Felix	210	Neuroblastoma	PD2	1.48	MCR	8.17	MCR	>11.46	PD1	-0.21	PD1	-0.18	PD2	3.03
COG-N-452X	212	Neuroblastoma	PD1	0.13	PD1	0.54	MCR	>2.36	PD1	-0.08	PD1	0.08	PD1	0.53
Rh30	140	Rhabdomyosarcoma	PD2	0.64	MCR	2.89	MCR	>3.3	PD1	0.06	PR	1.05	MCR	2.05
WT11	150	Wilms tumor	PD1	0.0	PD2	0.33	MCR	>3.2	PD1	-0.07	PD1	-0.02	PD2	1.18

DISCUSSION

- ❑ I-DXd showed dose-dependent activity with maintained complete responses (MCR) for all preclinical models at 10 mg/kg.
- ❑ Partial response (PR) or MCR were observed in 4 of 6 models to I-DXd at 3 mg/kg, with no objective responses to I-DXd at 1 mg/kg.
- ❑ Activity was lower for IC-ADC compared to I-DXd for all models at all doses tested. Only the rhabdomyosarcoma model showed objective response to IC-ADC.
- ❑ Multiple log cell kill was observed with two 10 mg/kg I-DXd doses, and tumor regrowth was not observed at 80-100 days following treatment initiation.

CONCLUSIONS

- ❑ We confirm significant anti-tumor activity for I-DXd in preclinical models of multiple pediatric solid tumors with B7-H3 expression.
- ❑ Study results provide evidence of a dose response effect for I-DXd and for enhanced efficacy for I-DXd versus IC-ADC.
- ❑ Testing in additional preclinical models of glioblastoma is underway.
- ❑ Due to the high expression of B7-H3 in multiple pediatric histologies of preclinical models, I-DXd is a high priority for clinical evaluation for multiple B7-H3 expressing pediatric solid tumors.

REFERENCES

Clark, Breast Cancer Research and Treatment 1997; 46:255-278
Houghton, Pediatric Blood Cancer 2007; 49:928-940
Johnson, Annals of Oncology 2021; 32:S583-S585
Patel, J Clinical Oncology 2022; 40:87

MORE INFORMATION

Corresponding author: Richard Gorlick, MD, MD Anderson Cancer Center

Presented at: AACR Annual Meeting, 2024 (San Diego)

Funding: 3U01CA199221, 3U01CA199287, 3U01CA199297, 3U01CA199288, U24CA263963