Poster #: 7815

Efficacy of ABBV-706, a novel SEZ6-targeted topoisomerase 1 inhibitor ADC: A report from the Pediatric Preclinical In Vivo Testing (PIVOT) Program

Elizabeth A. Stewart[1], Michael A. Dyer[1], Yael P. Mossé[2], John M. Maris[2], Xiao-Nan Li[3], Stefan Atkinson[1], Chen He[1], David Groff[2], Alvin Farrel[2], Yuchen Du[3], Jinnan Chen[3], Steven Neuhauser[4], Timothy M. Stearns[4], Emily L. Jocoy[4], Jee Young Kwon[4], Jeffrey H. Chuang[4], Emily Faivre[5], Kelly Doyle[5], Kim Ellison[5], Joshua Hernandez[5], Joann Palma[5], Michael Barnes[5], Pooja Hingorani[5], Nandini Rudra-Ganguly[5], Beverly A. Teicher[6], Carol J. Bult[4], Malcolm A. Smith[6]

[1]St. Jude Children's Research Hospital, Memphis, TN, [2]Children's Hospital of Philadelphia, Philadelphia, PA, [3]Ann & Robert H. Lurie Children's Hospital, Chicago, IL, [4]The Jackson Laboratory, [5]AbbVie Inc., North Chicago, IL, [6]National Cancer Institute, Bethesda, MD

https://preclinicalpivot.org

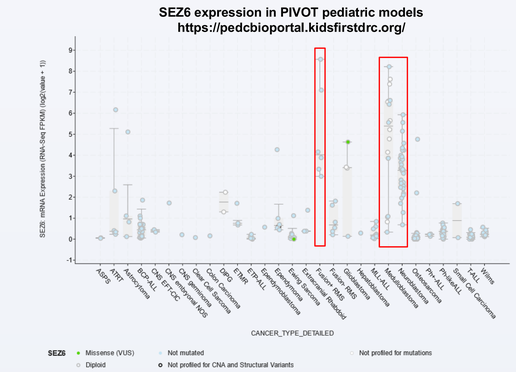
Scan to Download Poster

ABSTRACT

ABBV-706 is an antibody-drug conjugate (ADC) composed of a monoclonal antibody targeting the seizure-related homolog 6 (SEZ6) surface protein linked to topoisomerase 1 inhibitor payload. A Phase 1 trial is underway to determine the safety and efficacy of ABBV-706 in adults with SEZ6 expressing relapsed solid tumors (NCT05599984). ABBV-706 became of interest in childhood cancer as SEZ6 is highly expressed in many pediatric cancers. The goal of this study was to evaluate ABBV-706 anti-tumor activity against xenograft models of childhood cancers with notable SEZ6 expression: neuroblastoma (NB), medulloblastoma (MB), retinoblastoma (RB), and alveolar rhabdomyosarcoma (ARMS) and compare to vehicle and isotype non-target control ADC (IC-ADC).

STUDY METHODS

Pediatric PDX models were screened for SEZ6 expression:



Single agent *in vivo* efficacy studies were completed in NB, MB, RB, and ARMS models with varying SEZ6 expression. MB and ARMS models were implanted orthotopically; NB and RB models were implanted subcutaneously. After engraftment, 2 total doses of ABBV-706 or IC-ADC were given by IP injection 3 weeks apart at 2 dose levels (DL1, DL2). Efficacy was assessed by median event free survival (KM med) and objective response measure (ORM, Ped Blood Cancer 2007;49:928-940). ORM defines an 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).

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

Neuroblastoma (NB) (n=5)

A: Control; B: ABBV-706 DL1; C: ABBV-706 DL2; D: IC-ADC DL1; E: IC-ADC DL2

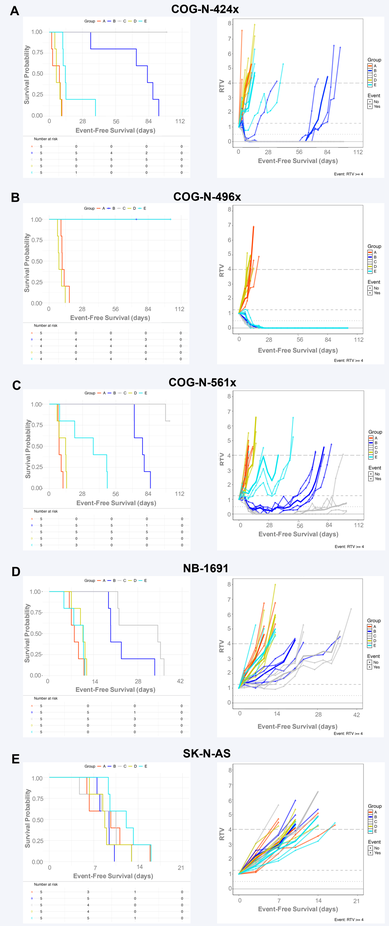


Figure 1 (A-E). Kaplan-Meier survival plots and relative tumor volumes for patient-derived and cell line-derived subcutaneous NB models in mouse flank. Treatment groups: **A** Control; **B** ABBV-706: DL1; **C** ABBV-706: DL2; **D** Non-target ADC: DL1; **E** Non-target ADC DL2.

Table 1. Summary of in vivo efficacy results for pediatric NB models treated with ABBV-706 and a non-target ADC. Treatment groups: **A** Control; **B** ABBV-706: DL1; **C** ABBV-706: DL2; **D** Non-target ADC: DL1; **E** Non-target ADC DL2.

Model	Grp	N	KM med	EFS T/C	Gehan-Wilcoxon p-value	minRTV mean+/-SD	minRTV p-value	ORM	SEZ6 mRNA (FPKM)
COG-N-424x	A	5	9			3.39+/-2.6		PD	
	B	5	83	9.6	0.0039	0.04+/-0.09	0.0097	MCR	46.1
	C	5	>99	11.5	0.0039	0+/-0	0.0075	MCR	
	D	5	6	0.7	0.9174	2.36+/-0.51	0.8345	PD1	
	E	5	14	1.6	0.0039	1.86+/-0.68	0.8345	PD1	
COG-N-496x	A	5	11			2.17+/-0.53		PD	
	B	5	>103	9.3	0.0098	0+/-0	0.0151	MCR	
	C	5	>103	9.3	0.0098	0+/-0	0.0151	MCR	59.89
	D	5	8	0.8	0.1098	2.55+/-0.28	0.2101	PD1	
	E	5	>103	9.3	0.0098	0+/-0	0.0151	MCR	
COG-N-561x	A	5	8			1.7+/-0.25		PD	
	B	5	78	9.5	0.0039	0.15+/-0.15	0.0119	PR	
	C	5	101	12.3	0.0039	0+/-0	0.0075	MCR	12.98
	D	5	14	1.7	0.2463	1.53+/-0.41	0.4633	PD1	
	E	5	37	4.5	0.0204	1.38+/-0.41	0.1437	PD2	
NB-1691	A	5	8			1.84+/-0.26		PD	
	B	5	19	2.5	0.0039	1.3+/-0.19	0.0216	PD2	
	C	5	34	4.3	0.0039	1.17+/-0.28	0.0122	PD2	17.91
	D	5	11	1.3	0.1706	1.52+/-0.17	0.0601	PD1	
	E	5	11	1.4	0.6061	1.85+/-0.35	1	PD1	
SK-N-AS	A	5	10			1.85+/-0.67		PD	
	B	5	9	1.0	0.7545	2.24+/-0.24	0.5309	PD1	
	C	5	11	1.1	0.9183	2.02+/-0.61	0.8345	PD1	0.06
	D	5	9	0.9	0.9174	2.24+/-0.47	0.6761	PD1	
	E	5	12	1.3	0.3507	1.63+/-0.23	0.6761	PD1	

EFS= Event Free Survival, T=Treatment, C=Control, RTV=Relative Tumor Volume, ORM= Objective Response Measure classification.

Medulloblastoma (MB) (n=2)

A: Control; B: ABBV-706 DL1; C: ABBV-706 DL2; D: IC-ADC DL1; E: IC-ADC DL2

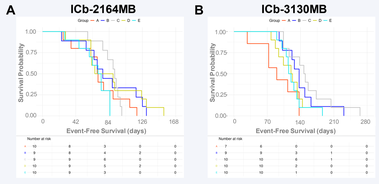


Figure 2 (A,B). Kaplan-Meier survival plots for patient-derived orthotopic MB models in mouse cerebellum (ICb). Treatment groups: A Control; B ABBV-706: DL1; C ABBV-706: DL2; D Non-target ADC: DL1; E Non-target ADC DL2.

Table 2. Summary of in vivo efficacy results pediatric MB models treated with ABBV-706 and a non-target ADC. Treatment groups: **A** Control; **B** ABBV-706: DL1; **C** ABBV-706: DL2; **D** Non-target ADC: DL1; **E** Non-target ADC DL2.

Model	Grp	N	KM med	EFS T/C	Gehan-Wilcoxon p-value	SEZ6 mRNA (FPKM)
ICb-2164MB	A	10	70			
	B	10	76	1.1	0.6268	
	C	10	91	1.3	0.1508	166.4
	D	10	78	1.1	0.5714	
	E	10	72	1.0	0.7922	
ICb-3130MB	A	10	90			
	B	10	137	1.5	0.0286	
	C	10	149	1.7	0.0035	46.1
	D	10	122	1.4	0.1904	
	E	10	118	1.3	0.1378	

EFS= Event Free Survival, T=Treatment, C=Control

Retinoblastoma (RB) (n=2)

A: Control; B: ABBV-706 DL1; C: ABBV-706 DL2; D: IC-ADC DL1; E: IC-ADC DL2; F: CARBO + TOPO (SOC)

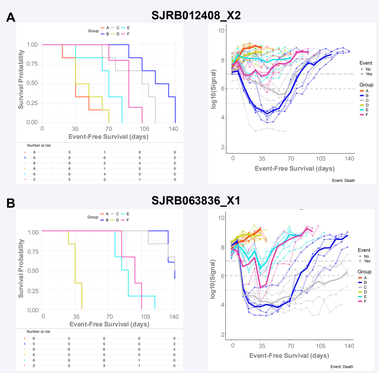


Figure 3 (A,B). Kaplan-Meier survival plots and relative tumor volume for patient-derived subcutaneous RB models in mouse flank. Treatment groups: **A** Control; **B** ABBV-706: DL1; **C** ABBV-706: DL2; **D** Non-target ADC: DL1; **E** Non-target ADC DL2; **F** carboplatin + topotecan (SOC).

Table 3. Summary of in vivo efficacy results for pediatric RB models treated with ABBV-706 and a non-target ADC. Treatment groups: **A** Control; **B** ABBV-706: DL1; **C** ABBV-706: DL2; **D** Non-target ADC: DL1; **E** Non-target ADC DL2; **F** carboplatin + topotecan (SOC).

Model	Grp	N	KM med	EFS T/C	Gehan-Wilcoxon p-value	minSIG mean+/-SD	minSIG p-value	ORM	SEZ6 mRNA (FPKM)
SJRB012408_X2	A	6	35			7.97+/-0.48		PD	
	B	6	126	3.6	0.0013	4.62+/-1.28	0.0051	MCR	
	C	6	109	3.1	0.003	5.32+/-1.41	0.0051	PR	53.77
	D	6	42	1.2	0.4419	8+/-0.42	0.9362	PD1	
	E	6	70	2	0.0353	7.59+/-0.78	0.3785	PD1	
	F	5	91	2.6	0.0049	6.63+/-0.66	0.0137	SD	
SJRB063836_X1	A	6	35			8.2+/-0.15		PD	
	B	5	140	4	0.0034	3.77+/-0.6	0.008	MCR	
	C	6	140	4	0.0015	3.96+/-0.58	0.005	MCR	78.59
	D	6	35	1	1	8.39+/-0.28	0.1727	PD1	
	E	6	88	2.5	0.0015	6.51+/-0.44	0.005	SD	
	F	3	98	2.8	0.0193	5.14+/-0.89	0.0275	PR	

EFS= Event Free Survival, T=Treatment, C=Control, minSIG=relative minimum bioluminescence signal

Abbreviations:

KM med = Median days survival
MCR=Maintained Complete Response
CR=Complete Response
PR=Partial Response
SD=Stable Disease
PD=Progressive Disease
PD1=Progressive Disease w/o tumor growth delay
PD2= Progressive Disease w/tumor growth delay

Alveolar Rhabdomyosarcoma (ARMS) (n=5)

A: Control; B: ABBV-706 DL1; C: ABBV-706 DL2; D: IC-ADC DL1; E: IC-ADC DL2; G: VCR + IRN (SOC)

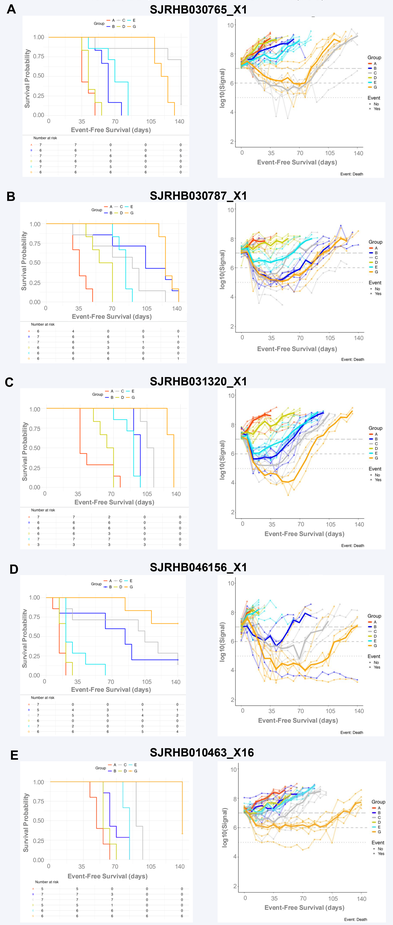


Figure 4 (A-E). Kaplan-Meier survival plots and relative tumor volume for patient-derived orthotopic ARMS models in mouse right biceps femoris muscle. Treatment groups: **A** Control; **B** ABBV-706: DL1; **C** ABBV-706: DL2; **D** Non-target ADC: DL1; **E** Non-target ADC DL2; **G** vincristine + irinotecan (SOC)

Table 4. Summary of in vivo efficacy results for pediatric ARMS models treated with ABBV-706 and a non-target ADC. Treatment groups: **A** Control; **B** ABBV-706: DL1; **C** ABBV-706: DL2; **D** Non-target ADC: DL1; **E** Non-target ADC DL2; **G** vincristine + irinotecan (SOC).

Model	Grp	N	KM med	EFS T/C	Gehan-Wilcoxon p-value	minSIG mean+/-SD	minSIG p-value	ORM	SEZ6 mRNA (FPKM)
SJRHB030765_X1	A	7	35			7.57+/-0.6		PD	
	B	6	63	1.8	0.0021	7.47+/-0.28	0.432	PD1	
	C	7	140	4	0.001	5.02+/-0.98	0.0022	PR	119.78
	D	6	42	1.2	0.2613	7.77+/-0.2	0.8303	PD1	
	E	7	70	2	0.0023	7.32+/-0.12	0.1792	PD1	
	G	6	123	3.5	0.0011	5.47+/-0.84	0.0053	PR	
SJRHB030787_X1	A	6	35			7.59+/-0.19		PD	
	B	7	105	3	0.0129	5.19+/-1.06	0.0184	CR	
	C	7	91	2.6	0.0173	5.31+/-1.57	0.0124	CR	129.25
	D	6	63	1.8	0.0062	7.19+/-0.38	0.3785	PD1	
	E	6	84	2.4	0.0013	6.1+/-0.31	0.0051	SD	
	G	6	126	3.6	0.0013	4.79+/-0.35	0.0051	PR	
SJRHB031320_X1	A	7	35			7.56+/-0.21		PD	
	B	6	98	2.8	0.001	5.3+/-0.62	0.0034	PR	
	C	6	109	3.1	0.001	4.9+/-0.76	0.0034	PR	21.75
	D	6	67	1.9	0.1175	7.2+/-0.37	0.1004	PD1	
	E	7	91	2.6	0.0012	5.92+/-0.41	0.0022	SD	
	G	3	133	3.8	0.0146	3.72+/-0.63	0.0227	MCR	
SJRHB046156_X1	A	7	14			8.01+/-0.4		PD	
	B	5	84	6	0.0214	5.4+/-1.8	0.0348	PR	
	C	7	105	7.5	0.0011	5.18+/-1.26	0.0022	CR	111.68
	D	6	21	1.5	0.1226	7.74+/-0.47	0.6171	PD1	
	E	7	21	1.5	0.0043	7.61+/-0.71	0.3711	PD1	
	G	6	140	10	0.0012	3.66+/-0.52	0.0034	MCR	
SJRHB010463_X16	A	5	49			7.16+/-0.19		PD	
	B	7	63	1.3	0.0086	7.04+/-0.54	0.7453	PD1	
	C	7	91	1.9	0.0007	6.13+/-0.56	0.0058	PD1	
	D	5	56	1.1	0.0976	6.83+/-0.27	0.1437	PD1	2.66
	E	6	84	1.7	0.0016	6.67+/-0.36	0.2353	PD1	
	G	6	140	2.9	0.0016	5.53+/-0.56	0.0081	PR	

EFS= Event Free Survival, T=Treatment, C=Control, minSIG=relative minimum bioluminescence signal

SUMMARY

ABBV-706 showed efficacy in a broad range of SEZ6 expressing non-CNS (NB, RB, ARMS) models:

Neuroblastoma (NB):

- 3 of 5 NB models treated with ABBV-706 (SEZ6 ADC) achieved an objective response at both DL1 and DL2. One model was classified as Progressive Disease with tumor growth delay (PD2) and one was classified as Progressive Disease without tumor growth delay (PD1) at both doses. The model with only PD1 responses (SK-N-AS) has minimal SEZ6 gene expression.

Retinoblastoma (RB):

- 2 of 2 RB models treated with ABBV-706 (SEZ6 ADC) achieved objective responses (MCR and PR) at DL1 and DL2.

Alveolar Rhabdomyosarcoma (ARMS):

- 3 of 5 ARMS models treated with ABBV-706 (SEZ6 ADC) achieved objective responses (CR and PR) at DL1 and DL2. One model (SJRHB030765_X1) achieved an objective response PR at DL2, but not DL1. The model with only PD1 responses (SJRHB010463_X16) has minimal SEZ6 gene expression.

Medulloblastoma (MB):

- 1 of 2 MB models (ICb-3130Mb) achieved statistically significant extension of survival at the DL1 and the DL2 dose of ABBV-706 (SEZ6 ADC). For this model, survival was nominally extended by non-target ADC, but significance was not achieved.

CONCLUSION

We showed high levels of anti-tumor activity for ABBV-706 in several orthotopic and subcutaneous SEZ6 expressing pediatric cancer models and enhanced efficacy versus IC-ADC. Due to high expression of SEZ6 in multiple pediatric histologies, ABBV-706 has potential for clinical activity in pediatric patients with these cancers.

REFERENCES

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

MORE INFORMATION

Corresponding author: Elizabeth A. Stewart, St. Jude Children's Research Hospital, Memphis, TN. Elizabeth.Stewart@stjude.org

Funding: NCI PIVOT. ABBV-706 drug supply by AbbVie Inc.

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

Visit the PIVOT Website