Poster #: 7041

The CLK/DYRK inhibitor SM09419 shows potent efficacy across a broad panel of pediatric preclinical xenograft models: A report from the Pediatric Preclinical In Vivo Testing Consortium (PIVOT)

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ABSTRACT

SM09419 is an experimental small-molecule pan-inhibitor targeting CDC-like (CLK) and dual-specificity tyrosine phosphorylation-regulated (DYRK) kinases, which play a key role in RNA splicing and other cancer associated processes. SM09419 exhibited promising activity in preclinical models of *TP53*- and *FLT3*-mutated acute myeloid leukemia (AML), and the related compound cirtuvivint (SM08502) has previously been tested as monotherapy and in combination with other anti-cancer agents in patients with advanced solid tumors (NCT03355066 and NCT05084859) and is in clinical testing for adults with AML (NCT06484062). To evaluate the role of CLK and DYRK kinase inhibition in pediatric cancers, SM09419 was tested against panels of pediatric solid tumor and leukemia patient-derived xenografts (PDXs).

STUDY METHODS

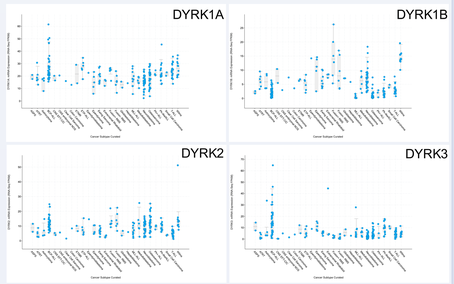
Dosing: SM09419 was provided by Biosplice Therapeutics, Inc. and administered orally (PO) at 25 mg/kg daily for 5 days per week x 3 weeks followed by up to 12-weeks of post treatment observation for the acute lymphoblastic leukemia, neuroblastoma, sarcoma, hepatoblastoma, and osteosarcoma models.

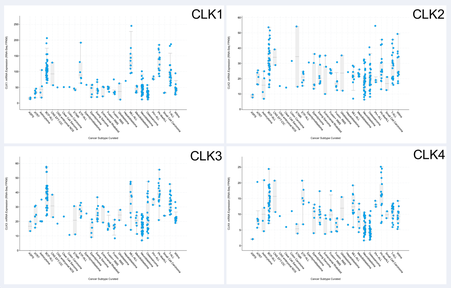
Tolerability: Tolerability was assessed in groups of 3 non-tumor bearing immune-deficient mice (NSG, CB17 SCID) at 100%, 75% and 50% of the recommended dose of 25 mg/kg.

Efficacy Testing: For efficacy testing, a single mouse trial (SMT) design (one vehicle control, one drug treated mouse per PDX) was used for ALL (n=30 PDXs), NB (n=14), HB (n=7), Ewing sarcoma (ES, n=8), rhabdomyosarcoma (RMS, n=5), Wilms tumor (WT, n=2) and malignant rhabdoid tumors (MRT, n=3). For the osteosarcoma (OS, n=6) models a conventional study design of 10 mice per treatment group (vehicle or drug) was employed.

Treatment Response: Standard PIVOT methods were used to assess event-free survival (EFS T/C = ratio of median EFS for treated versus control animals). Stringent objective response measures (ORMs) modeled after the clinical setting were also used to evaluate activity (Houghton et al., Pediatr Blood Cancer, 2007).

DYRK gene expression in pediatric PDX models (from PPTC 2019 data in cBioPortal)



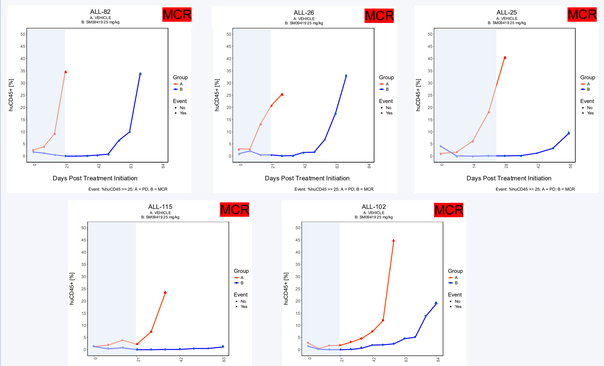


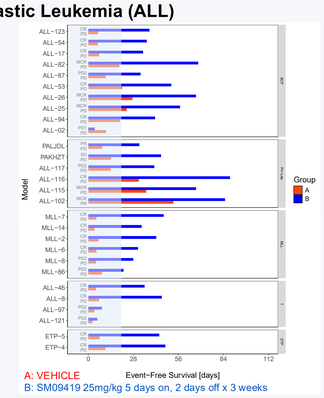
CLK expression in pediatric PDX models (from PPTC 2019 data in cBioPortal)

RESULTS

Acute Lymphoblastic Leukemia (ALL)

Best responders (ALL)

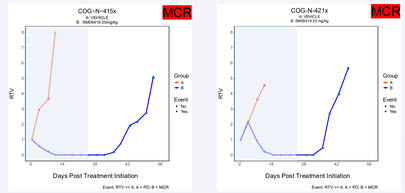


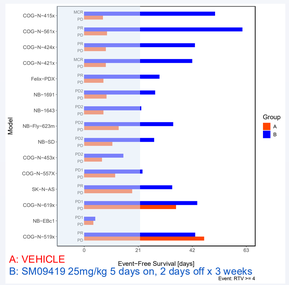


Model	Subtype	KM med	EFS T-C	EFS T/C	ORM
ALL-123	BCP	38	32	6.33	CR
ALL-54	BCP	36.34	30.53	6.25	CR
ALL-17	BCP	34.03	27.22	5	CR
ALL-82	BCP	68.28	49	3.54	MCR
ALL-87	BCP	32.49	21.73	3.02	PD2
ALL-53	BCP	51.64	30.69	2.46	CR
ALL-26	BCP	66.95	39.49	2.44	MCR
ALL-25	BCP	57	33.16	2.39	MCR
ALL-94	BCP	41.5	21.75	2.1	CR
ALL-02	BCP	4	-6.96	0.37	PD1
PALIDL	Ph-Like	31.74	22.98	3.62	PR
PAKH2T	Ph-Like	45.21	31.1	3.2	SD
ALL-117	Ph-Like	41.04	27.13	2.95	PD2
ALL-116	Ph-Like	88.09	56.72	2.81	CR
ALL-115	Ph-Like	67	31	1.86	MCR
ALL-102	Ph-Like	85	32.1	1.61	MCR
MLL-7	MLL	46.85	41.8	9.28	CR
MLL-14	MLL	33.15	29.33	8.68	CR
MLL-2	MLL	42.2	35.72	6.51	CR
MLL-6	MLL	30.87	25.91	6.22	CR
MLL-8	MLL	27.95	23.06	5.72	PD2
MLL-86	MLL	21.74	13.38	2.6	PD2
ALL-46	T	35	30.21	7.31	CR
ALL-8	T	45.69	39.01	6.84	CR
ALL-97	T	8.37	4.57	2.2	PD2
ALL-121	T	5.55	2.98	2.16	PD2
ETP-5	ETP	44.1	36.97	6.19	CR
ETP-4	ETP	47.9	37.25	4.5	CR

Neuroblastoma

Best responders (Neuroblastoma)





Model	KM med	EFS T-C	EFS T/C	ORM
COG-N-415x	50.84	43.57	6.99	MCR
COG-N-561x	61.51	52.66	6.95	PR
COG-N-424x	43.04	34.61	5.11	PR
COG-N-421x	42	33.62	5.01	MCR
Felix-PDX	29.3	21.82	3.92	PR
NB-1691	27.62	18.97	3.19	PD2
NB-1643	22.23	14.72	2.96	PD2
NB-Fly-623m	34.6	21.19	2.58	PD2
NB-SD	27.19	16.23	2.48	PD2
COG-N-453x	15.24	8.32	2.2	PD2
COG-N-557X	22.62	10.59	1.88	PD1
SK-N-AS	34.21	15.59	1.84	PR
COG-N-619x	43.94	8.29	1.23	PD1
NB-EBc1	4.28	0.71	1.2	PD1
COG-N-519x	43.14	-3.48	0.93	PR

Plots and Tables:

Relative Tumor Volume (RTV) plots show tumor growth over days post treatment. An event is defined as when tumor volume is greater than >4X the initial volume.

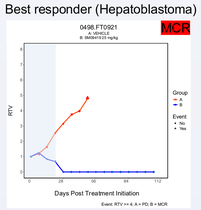
Swimmer plots show Event Free Survival (EFS) in days.

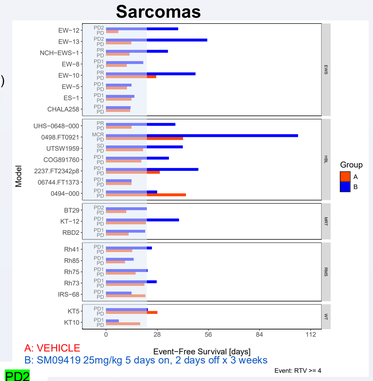
Shaded areas on the plots indicate the treatment period.

Tables show detailed EFS and RTV data and the calculated ORM.

Sarcomas

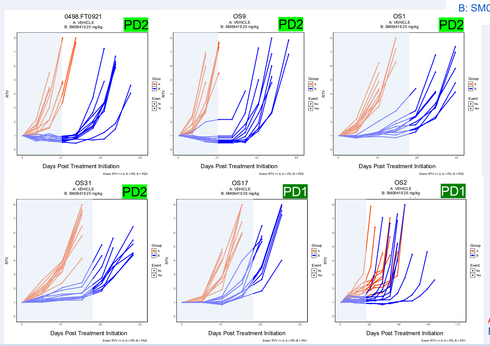
Best responder (Hepatoblastoma)





Model	Subtype	KM med	EFS T-C	EFS T/C	ORM
EW-12	Ewing sarcoma	39.44	32.76	5.9	PD2
EW-13	Ewing sarcoma	55.34	41.58	4.02	PD2
NCH-EWS-1	Ewing sarcoma	33.88	21.03	2.64	PR
EW-8	Ewing sarcoma	20.29	8.91	1.78	PD1
EW-10	Ewing sarcoma	>49	21.51	1.78	PR
EW-5	Ewing sarcoma	>14	2.57	1.22	PD1
ES-1	Ewing sarcoma	15.54	1.54	1.11	PD1
CHLA258	Ewing sarcoma	13.48	0.37	1.03	PD1
UHS-0648-000	Hepatoblastoma	37.94	24	2.72	PR
0498.FT0921	Hepatoblastoma	>105	62.81	2.49	MCR
UTSW 1959	Hepatoblastoma	>42	21.74	2.07	SD
COG891760	Hepatoblastoma	34.43	15.14	1.78	PD1
2237.FT2342p8	Hepatoblastoma	50.51	21.11	1.72	PD1
06744.FT1373	Hepatoblastoma	>14	0	1	PD1
0494-000	Hepatoblastoma	>28	-15.73	0.64	PD1
BT29	Rhabdoid tumor	22.38	11.29	2.02	PD2
KT12	Rhabdoid tumor	39.84	18.05	1.83	PD1
RBD2	Rhabdoid tumor	21.41	9.02	1.73	PD1
Rh41	Alveolar rhabdomyosarcoma	25.08	10.74	1.75	PD1
Rh85	Embryonal rhabdomyosarcoma	15.17	4.8	1.46	PD1
Rh75	Embryonal rhabdomyosarcoma	22.78	6.65	1.41	PD1
Rh73	Embryonal rhabdomyosarcoma	27.76	6.67	1.32	PD1
IRS-68	Embryonal rhabdomyosarcoma	13.95	-7.58	0.65	PD1
KT5	Wilms tumor	22.91	-5.2	0.81	PD1
KT10	Wilms tumor	6.96	-11.73	0.37	PD1

Osteosarcoma



Model	Grp	N	KM med	EFS T-C	EFS T/C	Gehan-Wilcoxon p-value	minRTV mean+/-SD	minRTV p-value	ORM
OS33	A	10	14.94				1.5+/-0.33		PD
	B	10	44.94	30	3.01	< 0.0001	0.69+/-0.15	0.0002	PD2
OS9	A	10	15.84				1.64+/-0.44		PD
	B	10	45.18	29.34	2.85	< 0.0001	0.69+/-0.25	0.0003	PD2
OS1	A	10	13.96				1.61+/-0.29		PD
	B	10	34.89	20.93	2.5	< 0.0001	0.91+/-0.06	0.0002	PD2
OS31	A	10	15.34				1.94+/-0.32		PD
	B	10	32.84	17.5	2.14	< 0.0001	1.2+/-0.14	0.0002	PD2
OS17	A	10	15.89				1.25+/-0.13		PD
	B	10	28.87	12.98	1.82	< 0.0001	0.95+/-0.07	0.0002	PD1
OS2	A	10	42.12				1.32+/-0.2		PD
	B	10	52.09	9.97	1.24	0.0374	1.14+/-0.18	0.0695	PD1

A: VEHICLE
B: SM09419 25mg/kg 5 days on, 2 days off x 3 weeks

Abbreviations:

KM med = Median days survival
EFS=Event Free Survival
T=treated (blue), C=control (orange/red)
RTV=Relative Tumor Volume
minRTV=minimum Relative Tumor Volume
ORM= Objective Response Measure
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

SUMMARY

SM09419 was well tolerated at all dose levels with <20% weight loss observed, irrespective of the mouse strain used.

SM09419 showed objective responses (e.g., PR, CR, or MCR) in:

- 20 of 28 evaluable ALL models
- 7 of 14 Neuroblastoma (NB) models
- 2 of 7 Hepatoblastoma (HB) models
- 2 of 8 Ewing sarcoma (ES) models
- 0 of 2 Wilms tumor (WT) models
- 0 of 5 Rhabdomyosarcoma (RMS) models
- 0 of 3 Malignant Rhabdoid tumor (MRT) models
- 0 of 6 Osteosarcoma (OS) models

EFS T/C values ranged from:

- 0.37-9.28 in ALL models
- 0.93-6.99 in Neuroblastoma models
- 1.0-2.72 in Hepatoblastoma models
- 1.03-5.9 in Ewing sarcoma models
- 0.37-0.81 in Wilms tumor models
- 0.65-1.83 in Rhabdomyosarcoma models
- 1.73-2.02 in Malignant rhabdoid tumor models
- 1.24–3.01 Osteosarcoma models

CONCLUSION

SM09419 exhibited broad antitumor activity across several pediatric cancers (e.g., ALL and NB), with activity also observed for ES and HB. Lower activity was seen in the RMS and OS models which may require longer treatment. The promising results for selected cancer types support further evaluation of CLK/DYRK as therapeutic targets for these cancers. Future research directions for these cancers include identifying biomarkers that predict sensitivity to CLK/DYRK inhibition as well as efforts to identify effective combinations with targeted and/or standard-of-care drugs.

REFERENCES

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MORE INFORMATION

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Visit the PIVOT Website

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