Poster #1167

The Pan-CLK/DYRK Inhibitor SM09419 Prolongs Animal Survival Times in a Subset of Pediatric Medulloblastoma Patient-Derived Orthotopic Xenograft Mouse Models

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Introduction

Aberrant RNA splicing contributes to oncogenic transcriptional dysregulation in pediatric brain tumors. SM09419 is a potent pan-CLK/DYRK inhibitor that modulates alternative splicing and Wnt-related signaling pathways. SM09419 is a closely structurally related analog of Cirtuvivint (SM08502), another CLK/DYRK inhibitor from Biosplice Therapeutics, TenaRx, Inc., which has been studied in two completed Phase I clinical trials for treatment in adult solid tumors (NCT03355066 and NCT05084859), and is currently being studied in adults with AML or MDS (NCT06484062), Soft tissue sarcomas (NCT07032285), Ovarian cancer (NCT06856499) and Small cell lung cancer (NCT07155200). The objective of this study is to evaluate antitumor efficacy as a single CLK/DYRK targeting agent in different molecular subtypes of medulloblastoma (MB) in a panel of patient-derived orthotopic xenograft (PDOX) models.

STUDY METHODS

Eleven MB PDOX models including G3 (ICb-1572MB, ICb-1595MB, ICb-2555MB, ICb-5301MB), SHH (ICb-5610MB, ICb-3854MB, ICb-984MB, ICb-4989MB) and WNT (ICb-1192MB, ICb-1140MB, ICb-S1218MB) were treated with SM09419 (25 mg/kg, oral, once daily for 21 days) as listed in Table 1. Changes of animal survival times were assessed by Gehan-Breslow-Wilcoxon tests. Cell proliferation (Ki-67) and (apoptosis cleaved-PARP1, cleaved-Caspase-3) was quantitatively evaluated by Visiopharm-aided immunohistochemistry.

RESULTS

Significant extension of survival times were generated by SM09419 in three MB models, increasing median survival times from 27 days (control) to 36 days (treated) (33.3%) (P = 0.0143) in ICb-1572MB (G3); from 38.0 to 46.0 days (21.1%) (P = 0.0029) in ICb-5610MB (SHH) and from 154.0 days to 219.0 Days (42.2%) (P = 0.0359) in ICb-3854MB (SHH), accompanied by a significant reduction of Ki-67 (P < 0.05) and increased trends in cleaved-PARP1 and cleaved-Caspase-3 levels (P > 0.05) in ICb-1572MB and ICb-5610MB. No significant changes of animal survival times were detected in 7 models (P > 0.05), while the last model exhibited decreased survival times (P < 0.05) following drug treatment.

RESULTS

Table 1. Clinicopathologic and Molecular Characteristics of the 11 Medulloblastoma (MB) PDOX Models

Model No.	Model ID	Race	Age/Sex	Final Diagnosis	Mol Subgroup	Treatment Status	Collected tumor type	Mutations
1	ICb-1572MB	White	15 y/M	MB (Large cell)	G3	Treatment Naïve	Primary	FOXR2
2	ICb-1595MB	-	15 mo/M	MB (Anaplastic)	G3	Treatment Naïve	Primary	-
3	ICb-2555MB	White	5 y/M	MB (Anaplastic)	G3	Treatment Naïve	Primary	TP53, C-MYC
4	Icb-5301MB	White	4 y/M	MB(Surgery-sourced)	G3	-	-	-
5	ICb-5610MB	White	13 y/F	MB(Large cell, anaplastic)	SHH	Treatment Naïve	Primary	TP53, N-MYC
6	ICb-3854MB	White	7 y/M	MB (Anaplastic)	SHH	Treatment Naïve	Primary	
7	ICb-984MB	-	8 y/F	MB (Anaplastic)	SHH	Treatment Naïve	Primary	TP53
8	ICb-4989MB	White	11 y/F	MB	SHH	No treatment Naïve	Local relapse	-
9	ICb-1192MB	Black or African American	13 y/M	MB (Classic)	WNT	Treatment Naïve	Primary	TP53
10	ICb-1140MB	White	6 y/M	MB (classic with anaplastic/large cell component)	WNT	Treatment Naïve	Primary	TP53
11	ICb-S1218MB	-	14/M	MB (autopsy-sourced)	WNT	No treatment Naïve	Local relapse	-

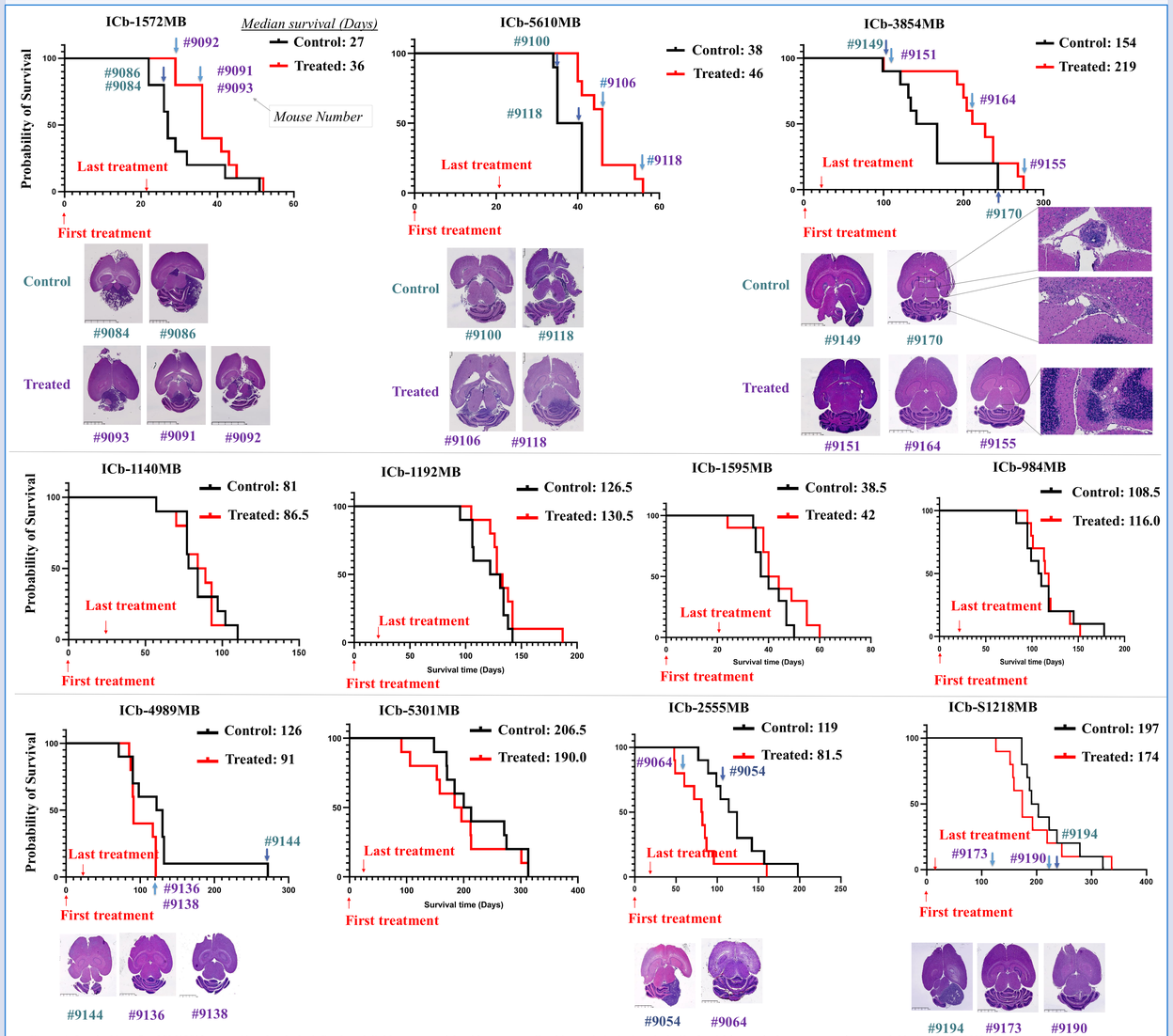
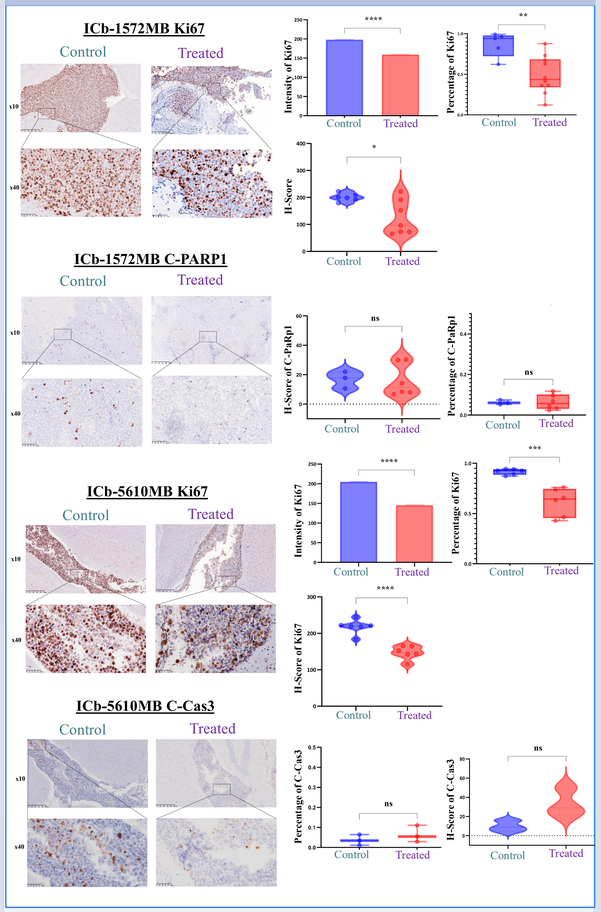


Figure 1. Survival benefit of SM08502 across 11 molecularly defined medulloblastoma models with corresponding histopathological analysis. Kaplan–Meier survival curves comparing control (blue) and SM08502-treated groups (purple) are shown across 11 independent medulloblastoma models, including Group 3 (G3: ICb-1572MB, ICb-1595MB, ICb-2555MB, ICb-5301MB), SHH (ICb-5610MB, ICb-3854MB, ICb-984MB, ICb-4989MB), and WNT (ICb-1192MB, ICb-1140MB, ICb-S1218MB). Representative hematoxylin and eosin (H&E) staining images demonstrate tumor morphology. Scale bars: 2.5 mm (10× magnification) and 50 μm (40× magnification). Statistical significance was determined using the log-rank (Mantel–Cox) test.

RESULTS



CONCLUSION

SM09419 produced significant therapeutic efficacy a subset of MB PDOX models characterized by decreased proliferative activity. Our findings highlight the biological heterogeneity among MB subtypes and support continued investigation of splicing-modulatory CLK/DYRK inhibitors as potential targeted therapies for pediatric brain tumors.

MORE INFORMATION

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