Poster #: 1528

AZD5851, a TGF-β-Resistant GPC3 CAR-T Cell Product, Prolongs Animal Survival Times in Patient-Derived Orthotopic Xenograft Models of Medulloblastoma and Atypical Teratoid Rhabdoid Tumor

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ABSTRACT

- Pediatric brain tumors are the leading cause of cancer-related death in children.
- Glypican-3 (GPC3) is a cell-surface proteoglycan involved in embryonic development of the liver and kidney and has been associated with several pediatric embryonal tumors, making it a potential target for CAR-T cell therapy.
- In solid tumors, transforming growth factor-β (TGF-β) within the tumor microenvironment suppresses T-cell activation and can limit the efficacy of CAR-T therapies.
- AZD5851 is an autologous GPC3-targeted CAR-T therapy engineered with a dominant- negative TGF-β receptor II (dnTGFβRII) to overcome TGF-β–mediated immunosuppression.
- This study evaluates the antitumor activity of AZD5851 in pediatric orthotopic patient-derived xenograft (PDOX) brain tumor models.

STUDY METHODS

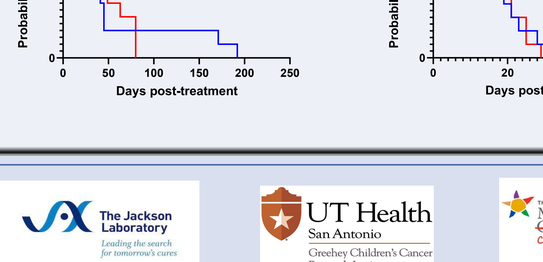
- Five established patient-derived orthotopic xenograft (PDOX) models of pediatric medulloblastoma (ICb-2123MB, ICb-1299MB, ICb-S1129MB), atypical teratoid rhabdoid tumor (IC-L1115ATRT), and high-grade glioma (IC-2664HGG) were evaluated.
- GPC3 and TGF-β expression were confirmed by AstraZeneca using immunohistochemistry (IHC) prior to efficacy studies.
- 20 eight-week-old SCID mice received intracerebral (IC) or intracerebellar (ICb) tumor cell implantation and were divided into 2 treatment groups (n=10 per group): Untransduced T cells [dosed at $12x10^6$ cells/mouse, intravenously (IV) once] or GPC3 CAR-T cells (dosed at $5x10^6$ cells/mouse; 12x10^6 total cells infused based on transduction efficiency, IV once).
- Animal survival was analyzed using the Gehan–Breslow–Wilcoxon test

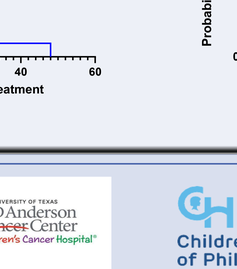
RESULTS

Table 1 . Summary of clinical information of 5 PDOX models

No.	Model ID	Age/Sex	Race/Ethnicity	Tumor Type	Diagnosis	Molecular subgroup	WHO Grade	Molecular Alterations	Timing of Collection
1	ICb-1299MB	2y 9m / F	Hispanic	Primary	Medulloblastoma	Group 3	IV	MYC amplification	At Diagnosis
2	IC-2664HGG	14y / F	–	Primary	Diffuse pediatric-type high-grade glioma	MYCN	IV	–	At Diagnosis
3	IC-L1115ATRT	3m / M	–	Recurrent	Atypical teratoid/rhabdoid tumor	SHH	IV	SMARCB1 mutation	Post-mortem
4	ICb-2123MB	6m / F	Hispanic	Primary	Medulloblastoma	SHH	IV	TP53 mutation	At Diagnosis
5	ICb-S1129MB	17m / F	–	Recurrent	Medulloblastoma	–	IV	–	Post-mortem

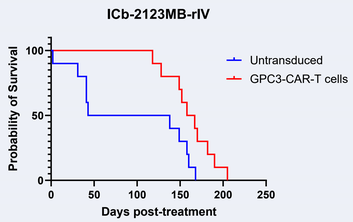
Figure 1 . GPC3 expression in pediatric brain tumors and PDOX models

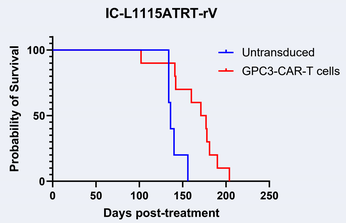




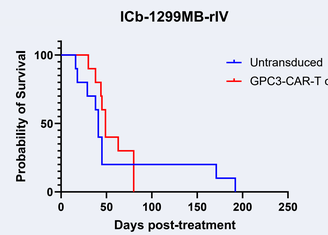
Model ID	GPC3 H-Score
ICb-2123MB	182.5
ICb-1299MB	47.5
ICb-S1129MB	95
IC-L1115ATRT	120
IC-2664PNET	160

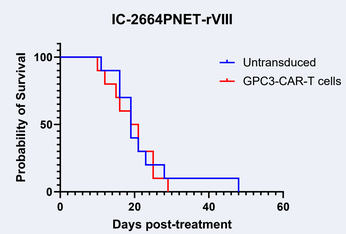
Figure 2 . Kaplan-Meier survival plots for 5 PDOX models treated with GPC3 CAR-T cells

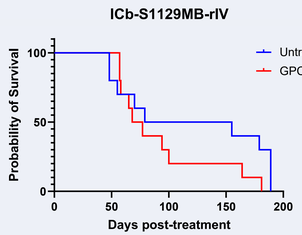




Model ID	Treatment Group	Median Survival Time (days)	Gehan-Wilcoxon p-value
IC-2664HGG	Untransduced T cells	19	0.7912
	GPC3 CAR-T cells	21	
IC-L1115ATRT	Untransduced T cells	136	0.0184
	GPC3 CAR-T cells	174	
ICb-1299MB	Untransduced T cells	41	0.1805
	GPC3 CAR-T cells	49	
ICb-2123MB	Untransduced T cells	90.5	0.02
	GPC3 CAR-T cells	163	
ICb-S1129MB	Untransduced T cells	117	0.5444
	GPC3 CAR-T cells	72.5	







CONCLUSION

- GPC3 CAR-T therapy prolonged survival in 2 of 5 pediatric PDOX models:
  - 1 medulloblastoma model (ICb-2123MB)
  - 1 atypical teratoid rhabdoid tumor (IC-L1115ATRT)
- No significant survival benefit was observed in the remaining models: ICb-1299MB, ICb-S1199MB, IC-2664HGG.
- Median survival times varied across models, highlighting heterogeneous responses to GPC3 CAR-T therapy.
- These findings demonstrate single-agent antitumor activity of GPC3 CAR-T cells in selected pediatric brain tumor models.
- Results support further clinical translational efforts involving the use of AZD5851 alone or in combination with other therapies for the treatment of these tumors.

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MORE INFORMATION

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We gratefully acknowledge AstraZeneca for performing the immunohistochemistry (IHC) analyses and providing the GPC3 CAR-T cell product, AZD5851, used in this study.

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