Immunotherapy approaches for the treatment of relapsed or progressive medulloblastoma

Review | Published: 11 March 2026

Volume 177, article number 39 (2026) Cite this article

Save article View saved research >

Journal of
Neuro-Oncology

Journal of Neuro-Oncology

Aims and scope →

Submit manuscript →

Mohammad H. Abu-Arja, Austin Stuckert, Rahawa T. Ghebrelul, Murali Chintagumpala, Michael D. Taylor & Nabil Ahmed

229 Accesses Explore all metrics →

Abstract

Purpose

Immunotherapy provides a novel and alternative treatment strategy to improve the outcomes in patients with refractory medulloblastoma. Two promising immunotherapies are immune checkpoint inhibitors (ICI) and chimeric antigen receptor (CAR) T-cells. In this review, we aim to summarize the available and investigational opportunities for ICI and CAR T-cell therapies, specifically for patients with refractory or relapsed medulloblastoma, tailored to their tumor molecular subtypes.

Methods

We searched the PubMed database and clinicaltrials.gov from January 2010 through October 2025 for studies evaluating treatments for patients with relapsed medulloblastoma.

Results

A point somatic mutation (r.3A>G) in *U1*, a non-coding snRNA, is found in two-thirds of patients with SHH-α tumors with *TP53* mutations and in over 95% of SHH-δ tumors. The *U1* mutation leads to altered splicing, potentially causing post-translational hypermutation. Accordingly, these tumors may be responsive to ICI. CAR T-cell therapies have shown promising results in patients with brain tumors. CAR T-cell therapies are designed to target universal tumor epitopes to improve their clinical testing feasibility. However, one challenge to achieving durable tumor control is the existence of treatment-resistant populations driven by intratumor heterogeneity. Therefore, we summarized the expression of available targets in specific medulloblastoma molecular groups to guide therapy selection.

Conclusion

We provide a basic understanding of how the medulloblastoma molecular heterogeneity can serve as a window for ICI. Furthermore, we provide a summary of the current and future CAR-T cells being tested for the treatment of different refractory medulloblastoma based on their molecular subtypes.

Clinical trial number

Not applicable. For the clinical trial number NCT05298995: Registration date: 03-28-2022.

This is a preview of subscription content, log in via an institution to check access.

Access this article

Log in via an institution →

Subscribe and save

Springer+ from €37.37 /Month

- Starting from 10 chapters or articles per month
- Access and download chapters and articles from more than 300k books and 2,500 journals
- Cancel anytime

View plans →

Buy Now

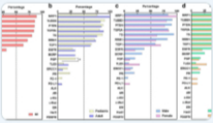
Buy article PDF 39,95 €

Price includes VAT (Italy)

Instant access to the full article PDF.

Institutional subscriptions →

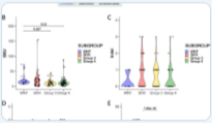
Similar content being viewed by others



Rethinking medulloblastoma from a targeted therapeutics perspective

Article | Open access

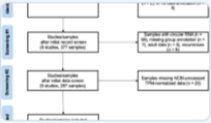
05 June 2018



Identification of tumor rejection antigens and the immunologic landscape of medulloblastoma

Article | Open access

19 August 2024



Profiling T-cell activity and exclusion in pediatric medulloblastoma highlights immunotherapy-responsive…

Article | 21 January 2026

Explore related subjects

Discover the latest articles, books and news in related subjects, suggested using machine learning.

- Brain Cancer
- Cancer Immunotherapy
- CNS cancer
- Gene targeting
- Molecularly targeted therapy
- Targeted therapies
- Immunotherapy Approaches for Pediatric Brain Tumors

Data availability

No new data were generated or analyzed in support of this research.

Abbreviations

CAR:	Chimeric antigen receptor
CNS:	Central nervous system

EGFR: Epidermal growth factor receptor

EphA2: Ephrin type-A receptor 2

EZH2: Enhancer of zeste homolog 2

FAK: Focal adhesion kinase

GPC2: Glypican 2

HER2: Human Epidermal Growth Factor Receptor 2

ICI: Immune checkpoint inhibitors

IgC: Immunoglobulin constant-like

IgV: Immunoglobulin variable-like

IL-13Rα2: Interleukin-13 Receptor Subunit Alpha 2

MAPK: Mitogen-activated protein kinase

MeSH: Medical subject headings

NK: Natural killer

RL: Rhombic lip

PFS: Progression-free survival

PRTG: Protogenin

SHH: Sonic hedgehog

snRNA: Small nuclear RNA

SVZ: Subventricular zone

TAM: Tumor-associated macrophages

TME: Tumor microenvironment

WNT: Wingless-related integration site

VZ: Ventricular zone

References

1. Price M, Ballard C, Benedetti J, Neff C, Cioffi G, Waite KA, Kruchko C, Barnholtz-Sloan JS, Ostrom QT (2024) CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the united States in 2017–2021. Neurooncology 26(Supplement6):vi1–vi85. https://doi.org/10.1093/neuonc/noae145

   Article **Google Scholar**

2. Cavalli FMG, Remke M, Rampasek L, Peacock J, Shih DJH, Luu B, Garzia L, Torchia J, Nor C, Morrissy AS, Agnihotri S, Thompson YY, Kuzan-Fischer CM, Farooq H, Isaev K, Daniels C, Cho BK, Kim SK, Wang KC, Lee JY, Taylor MD (2017) Intertumoral heterogeneity within Medulloblastoma subgroups. Cancer Cell 31(6):737–754e6. https://doi.org/10.1016/j.ccell.2017.05.005

   Article **CAS** **PubMed** **PubMed Central** **Google Scholar**

3. Ramaswamy V, Remke M, Bouffet E, Bailey S, Clifford SC, Doz F, Kool M, Dufour C, Vassal G, Milde T, Witt O, von Hoff K, Pietsch T, Northcott PA, Gajjar A, Robinson GW, Padovani L, André N, Massimino M, Pizer B, Pomeroy SL (2016) Risk stratification of childhood Medulloblastoma in the molecular era: the current consensus. Acta Neuropathol 131(6):821–831. https://doi.org/10.1007/s00401-016-1569-6

   Article **CAS** **PubMed** **PubMed Central** **Google Scholar**

4. Gajjar A, Robinson GW, Smith KS, Lin T, Merchant TE, Chintagumpala M, Mahajan A, Su J, Bouffet E, Bartels U, Schechter T, Hassall T, Robertson T, Nicholls W, Gururangan S, Schroeder K, Sullivan M, Wheeler G, Hansford JR, Kellie SJ, Northcott PA (2021) Outcomes by clinical and molecular features in children with Medulloblastoma treated with Risk-Adapted therapy: results of an international phase III trial (SJMB03). J Clin Oncology: Official J Am Soc Clin Oncol

39(7):822–835. https://doi.org/10.1200/JCO.20.01372

Article CAS Google Scholar

5. Northcott PA, Robinson GW, Kratz CP, Mabbott DJ, Pomeroy SL, Clifford SC, Rutkowski S, Ellison DW, Malkin D, Taylor MD, Gajjar A, Pfister SM (2019) Medulloblastoma Nat Reviews Disease Primers 5(1):11. https://doi.org/10.1038/s41572-019-0063-6

   Article PubMed Google Scholar

6. Tabori U, Sung L, Hukin J, Laperriere N, Crooks B, Carret AS, Silva M, Odame I, Mpofu C, Strother D, Wilson B, Samson Y, Bouffet E, Canadian Pediatric Brain Tumor Consortium (2006) Distinctive clinical course and pattern of relapse in adolescents with Medulloblastoma. Int J Radiat Oncol Biol Phys 64(2):402–407. https://doi.org/10.1016/j.ijrobp.2005.07.962

   Article PubMed Google Scholar

7. Hwang EI, Sayour EJ, Flores CT, Grant G, Wechsler-Reya R, Hoang-Minh LB, Kieran MW, Salcido J, Prins RM, Figg JW, Platten M, Candelario KM, Hale PG, Blatt JE, Governale LS, Okada H, Mitchell DA, Pollack IF (2022) The current landscape of immunotherapy for pediatric brain tumors. Nat Cancer 3(1):11–24. https://doi.org/10.1038/s43018-021-00319-0

   Article PubMed Google Scholar

8. Das A, Tabori U, Nahum S, Collins LC, Deyell NB, Dvir R, Faure-Conter R, Hassall C, Minturn TE, Edwards JE, Brookes M, Bianchi E, Levine V, Stone A, Sudhaman SC, Sanchez Ramirez S, Ercan S, Stengs AB, Chung L, Negm J, Morgenstern L, D. A (2023) Efficacy of nivolumab in pediatric cancers with high mutation burden and mismatch repair deficiency. Clin Cancer Research: Official J Am Association Cancer Res 29(23):4770–4783. https://doi.org/10.1158/1078-0432.CCR-23-0411

   Article CAS Google Scholar

9. Das A, Sudhaman S, Morgenstern D, Coblentz A, Chung J, Stone SC, Alsafwani N, Liu ZA, Karsaneh OAA, Soleimani S, Ladany H, Chen D, Zatzman M, Cabric V, Nobre L, Bianchi V, Edwards M, Nahum S, Ercan LC, Nabbi AB, Tabori A, U (2022) Genomic predictors of response to PD-1 Inhibition in children with germline DNA replication repair deficiency. Nat Med 28(1):125–135. https://doi.org/10.1038/s41591-021-01581-6

   Article CAS PubMed PubMed Central Google Scholar

10. Lin FY, Stuckert A, Tat C, White M, Ruggieri L, Zhang H, Mehta B, Lapteva N, Mei Z, Major A, Thakkar S, Shum T, Parikh K, Wu MF, Lindsay HB, Scherer L, Shekar M, Baxter P, Wang T, Grilley B, Omer B (2024) Phase I trial of GD2.CART cells augmented with constitutive Interleukin-7 receptor for treatment of High-Grade pediatric CNS tumors. J Clin Oncology: Official J Am Soc Clin Oncol 42(23):2769–2779. https://doi.org/10.1200/JCO.23.02019

Article CAS Google Scholar

11. Monje M, Mahdi J, Majzner R, Yeom KW, Schultz LM, Richards RM, Barsan V, Song KW, Kamens J, Baggott C, Kunicki M, Rietberg SP, Lim AS, Reschke A, Mavroukakis S, Egeler E, Moon J, Patel S, Chinnasamy H, Erickson C, Mackall C (2025) Intravenous and intracranial GD2-CAR T cells for H3K27M + diffuse midline gliomas. Nature 637(8046):708–715. https://doi.org/10.1038/s41586-024-08171-9

Article CAS PubMed Google Scholar

12. Vitanza NA, Ronsley R, Choe M, Seidel K, Huang W, Rawlings-Rhea SD, Beam M, Steinmetzer L, Wilson AL, Brown C, Beebe A, Lindgren C, Gustafson JA, Wein A, Holtzclaw S, Hoeppner C, Goldstein HE, Browd SR, Hauptman JS, Lee A, Jensen MC (2025) Intracerebroventricular B7-H3-targeting CAR T cells for diffuse intrinsic Pontine glioma: a phase 1 trial. Nat Med 31(3):861–868. https://doi.org/10.1038/s41591-024-03451-3

Article CAS PubMed PubMed Central Google Scholar

13. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, Hawkins C, Ng HK, Pfister SM, Reifenberger G, Soffietti R, von Deimling A, Ellison DW (2021) The 2021 WHO classification of tumors of the central nervous system: a summary. Neurooncology 23(8):1231–1251. https://doi.org/10.1093/neuonc/noab106

Article CAS Google Scholar

14. Hovestadt V, Ayrault O, Swartling FJ, Robinson GW, Pfister SM, Northcott PA (2020) Medulloblastomics revisited: biological and clinical insights from thousands of patients. Nat Rev Cancer 20(1):42–56. https://doi.org/10.1038/s41568-019-0223-8

Article CAS PubMed Google Scholar

15. Liu Y, Su Z, Tavana O, Gu W (2024) Understanding the complexity of p53 in a new era of tumor

suppression. Cancer Cell 42(6):946–967. https://doi.org/10.1016/j.ccell.2024.04.009

Article CAS PubMed PubMed Central Google Scholar

16. Suzuki H, Kumar SA, Shuai S, Diaz-Navarro A, Gutierrez-Fernandez A, De Antonellis P, Cavalli FMG, Juraschka K, Farooq H, Shibahara I, Vladoiu MC, Zhang J, Abeysundara N, Przelicki D, Skowron P, Gauer N, Luu B, Daniels C, Wu X, Forget A, Taylor MD (2019) Recurrent noncoding U1 SnRNA mutations drive cryptic splicing in SHH Medulloblastoma. Nature 574(7780):707–711. https://doi.org/10.1038/s41586-019-1650-0

    Article CAS PubMed PubMed Central Google Scholar

17. Wu Q, Jiang L, Li SC, He QJ, Yang B, Cao J (2021) Small molecule inhibitors targeting the PD-1/PD-L1 signaling pathway. Acta Pharmacol Sin 42(1):1–9. https://doi.org/10.1038/s41401-020-0366-x

    Article CAS PubMed Google Scholar

18. Dunkel IJ, Doz F, Foreman NK, Hargrave D, Lassaletta A, André N, Hansford JR, Hassall T, Eyrich M, Gururangan S, Bartels U, Gajjar A, Howell L, Warad D, Pacius M, Tam R, Wang Y, Zhu L, Cohen K (2023) Nivolumab with or without ipilimumab in pediatric patients with high-grade CNS malignancies: Safety, efficacy, biomarker, and pharmacokinetics-CheckMate 908. Neurooncology 25(8):1530–1545. https://doi.org/10.1093/neuonc/noad031

    Article CAS Google Scholar

19. Ramaswamy V, Remke M, Bouffet E, Faria CC, Perreault S, Cho YJ, Shih DJ, Luu B, Dubuc AM, Northcott PA, Schüller U, Gururangan S, McLendon R, Bigner D, Fouladi M, Ligon KL, Pomeroy SL, Dunn S, Triscott J, Jabado N, Taylor MD (2013) Recurrence patterns across Medulloblastoma subgroups: an integrated clinical and molecular analysis. Lancet Oncol 14(12):1200–1207. https://doi.org/10.1016/S1470-2045(13)70449-2

    Article CAS PubMed PubMed Central Google Scholar

20. Das A, Fernandez N, Levine A, Smith K, Wang E, Galati M, Aamir Z, Chung J, Negm L, Friedman H, O'Flaherty K, Crump O, Trinh Q, Nunes N, Bianchi V, Stengs L, Edwards M, Stein L, Bouffet E, Taylor M, Northcott P, Ramaswamy V, Hawkins C, Tabori U (2024) IMMU–14. Trans–species analysis of replication–repair deficient (RRD) Medulloblastoma and response to immune checkpoint inhibition: an IRRDC report. Neuro–Oncology 26(Suppl 8):viii154–viii155. https://

doi.org/10.1093/neuonc/noae165.0607

Article PubMed Central Google Scholar

21. Machy P, Mortier E, Birklé S (2023) Biology of GD2 ganglioside: implications for cancer immunotherapy. Front Pharmacol 14:1249929. https://doi.org/10.3389/fphar.2023.1249929

Article CAS PubMed PubMed Central Google Scholar

22. Filbin M, Monje M (2019) Developmental origins and emerging therapeutic opportunities for childhood cancer. Nat Med 25(3):367–376. https://doi.org/10.1038/s41591-019-0383-9

Article CAS PubMed PubMed Central Google Scholar

23. Svennerholm L, Rynmark BM, Vilbergsson G, Fredman P, Gottfries J, Månsson JE, Percy A (1991) Gangliosides in human fetal brain. J Neurochem 56(5):1763–1768. https://doi.org/10.1111/j.1471-4159.1991.tb02078.x

Article CAS PubMed Google Scholar

24. Svennerholm L, Boström K, Fredman P, Jungbjer B, Lekman A, Månsson JE, Rynmark BM (1994) Gangliosides and allied glycosphingolipids in human peripheral nerve and spinal cord. Biochim Biophys Acta 1214(2):115–123. https://doi.org/10.1016/0005-2760(94)90034-5

Article CAS PubMed Google Scholar

25. Ciccone R, Quintarelli C, Camera A, Pezzella M, Caruso S, Manni S, Ottaviani A, Guercio M, Del Bufalo F, Quadraccia MC, Orlando D, Di Cecca S, Sinibaldi M, Aurigemma M, Iaffaldano L, Sarcinelli A, D'Amore ML, Ceccarelli M, Nazio F, Marabitti V, Locatelli F (2024) GD2-Targeting CAR T-cell therapy for patients with GD2 + Medulloblastoma. Clin Cancer Research: Official J Am Association Cancer Res 30(11):2545–2557. https://doi.org/10.1158/1078-0432.CCR-23-1880

Article CAS Google Scholar

26. Probstmeier R, Pesheva P (1999) Tenascin-C inhibits beta1 integrin-dependent cell adhesion and neurite outgrowth on fibronectin by a disialoganglioside-mediated signaling mechanism. Glycobiology 9(2):101–114. https://doi.org/10.1093/glycob/9.2.101

Article CAS PubMed Google Scholar

27. Chuang HH, Zhen YY, Tsai YC, Chuang CH, Hsiao M, Huang MS, Yang CJ (2022) FAK in cancer: from mechanisms to therapeutic strategies. Int J Mol Sci 23(3):1726. https://doi.org/10.3390/ijms23031726

Article CAS PubMed PubMed Central Google Scholar

28. Zhang P, Ohkawa Y, Yamamoto S, Momota H, Kato A, Kaneko K, Natsume A, Farhana Y, Ohmi Y, Okajima T, Bhuiyan RH, Wakabayashi T, Furukawa K, Furukawa K (2021) St8sia1-deficiency in mice alters tumor environments of gliomas, leading to reduced disease severity. Nagoya J Med Sci 83(3):535–549. https://doi.org/10.18999/nagjms.83.3.535

Article CAS PubMed PubMed Central Google Scholar

29. Theruvath J, Menard M, Smith BAH, Linde MH, Coles GL, Dalton GN, Wu W, Kiru L, Delaidelli A, Sotillo E, Silberstein JL, Geraghty AC, Banuelos A, Radosevich MT, Dhingra S, Heitzeneder S, Tousley A, Lattin J, Xu P, Huang J, Majzner RG (2022) Anti-GD2 synergizes with CD47 Blockade to mediate tumor eradication. Nat Med 28(2):333–344. https://doi.org/10.1038/s41591-021-01625-x

Article CAS PubMed PubMed Central Google Scholar

30. Shum T, Omer B, Tashiro H, Kruse RL, Wagner DL, Parikh K, Yi Z, Sauer T, Liu D, Parihar R, Castillo P, Liu H, Brenner MK, Metelitsa LS, Gottschalk S, Rooney CM (2017) Constitutive signaling from an engineered IL7 receptor promotes durable tumor elimination by tumor-Redirected T cells. Cancer Discov 7(11):1238–1247. https://doi.org/10.1158/2159-8290.CD-17-0538

Article CAS PubMed PubMed Central Google Scholar

31. Chapoval AI, Ni J, Lau JS, Wilcox RA, Flies DB, Liu D, Dong H, Sica GL, Zhu G, Tamada K, Chen L (2001) B7-H3: a costimulatory molecule for T cell activation and IFN-gamma production. Nat Immunol 2(3):269–274. https://doi.org/10.1038/85339

Article CAS PubMed Google Scholar

32. Steinberger P, Majdic O, Derdak SV, Pfistershammer K, Kirchberger S, Klauser C, Zlabinger G, Pickl WF, Stöckl J, Knapp W (2004) Molecular characterization of human 4Ig-B7-H3, a member of the B7 family with four Ig-like domains. J Immunol (Baltimore Md: 1950) 172(4):2352–2359.

https://doi.org/10.4049/jimmunol.172.4.2352

Article CAS Google Scholar

33. Prasad DV, Nguyen T, Li Z, Yang Y, Duong J, Wang Y, Dong C (2004) Murine B7-H3 is a negative regulator of T cells. J Immunol (Baltimore, Md.: 1950) 173(4):2500–2506. https://doi.org/10.4049/jimmunol.173.4.2500

34. Kang FB, Wang L, Li D, Zhang YG, Sun DX (2015) Hepatocellular carcinomas promote tumor-associated macrophage M2-polarization via increased B7-H3 expression. Oncol Rep 33(1):274–282. https://doi.org/10.3892/or.2014.3587

Article CAS PubMed Google Scholar

35. Cardoso-Moreira M, Halbert J, Valloton D, Velten B, Chen C, Shao Y et al (2019) Gene expression across mammalian organ development. Nature 571(7766):505–509. https://doi.org/10.1038/s41586-019-1338-5

36. Fontão P, Teixeira GR, Moreno DA, Marques RF, Stavale JN, Malheiros SMF, Júnior CA, Mançano BM, Reis RM (2025) High B7-H3 protein expression in Medulloblastoma is associated with metastasis and unfavorable patient outcomes. Diagn Pathol 20(1):49. https://doi.org/10.1186/s13000-025-01645-y

Article CAS PubMed PubMed Central Google Scholar

37. Li S, Poolen GC, van Vliet LC, Schipper JG, Broekhuizen R, Monnikhof M et al (2022) Pediatric medulloblastoma express immune checkpoint B7-H3. Clin Transl Oncol 24(6):1204–1208. https://doi.org/10.1007/s12094-021-02762-y

38. Majzner RG, Theruvath JL, Nellan A, Heitzeneder S, Cui Y, Mount CW, et al (2019) CAR T cells targeting B7-H3, a pan-cancer antigen, demonstrate potent preclinical activity against pediatric solid tumors and brain tumors. Clin Cancer Res 25(8):2560–2574. https://doi.org/10.1158/1078-0432.CCR-18-0432

39. Nguyen P, Okeke E, Clay M, Haydar D, Justice J, O'Reilly C et al (2020) Route of 41BB/41BBL costimulation determines effector function of B7-H3-CAR.CD28ζ T Cells. Mol Ther Oncolytics 18:202–214. https://doi.org/10.1016/j.omto.2020.06.018

40. Filmus J, Capurro M, Rast J (2008) Glypicans Genome Biology 9(5):224. https://doi.org/10.1186/gb-2008-9-5-224

Article CAS PubMed PubMed Central Google Scholar

41. Chen G, Luo D, Zhong N, Li D, Zheng J, Liao H, Li Z, Lin X, Chen Q, Zhang C, Lu Y, Chan YT, Ren Q, Wang N, Feng Y (2022) GPC2 is a potential Diagnostic, Immunological, and prognostic biomarker in Pan-Cancer. Front Immunol 13:857308. https://doi.org/10.3389/fimmu.2022.857308

Article CAS PubMed PubMed Central Google Scholar

42. Brégère C, Fisch U, Halbeisen FS, Schneider C, Dittmar T, Stricker S, Aghlmandi S, Guzman R (2023) Doublecortin and Glypican-2 concentrations in the cerebrospinal fluid from infants are developmentally downregulated. PLoS ONE 18(2):e0279343. https://doi.org/10.1371/journal.pone.0279343

Article CAS PubMed PubMed Central Google Scholar

43. Foster JB, Griffin C, Rokita JL, Stern A, Brimley C, Rathi K, Lane MV, Buongervino SN, Smith T, Madsen PJ, Martinez D, Delaidelli A, Sorensen PH, Wechsler-Reya RJ, Karikó K, Storm PB, Barrett DM, Resnick AC, Maris JM, Bosse KR (2022) Development of GPC2-directed chimeric antigen receptors using mRNA for pediatric brain tumors. J Immunother Cancer 10(9):e004450. https://doi.org/10.1136/jitc-2021-004450

Article PubMed PubMed Central Google Scholar

44. Barrett DM, Zhao Y, Liu X, Jiang S, Carpenito C, Kalos M, Carroll RG, June CH, Grupp SA (2011) Treatment of advanced leukemia in mice with mRNA engineered T cells. Hum Gene Ther 22(12):1575–1586. https://doi.org/10.1089/hum.2011.070

Article CAS PubMed PubMed Central Google Scholar

45. Singh N, Barrett DM, Grupp SA (2015) Roadblocks to success for RNA cars in solid tumors. Oncoimmunology 3(12):e962974. https://doi.org/10.4161/21624011.2014.962974

Article CAS PubMed PubMed Central Google Scholar

46. Heitzeneder S, Bosse KR, Zhu Z et al (2020) Abstract A09: Glypican-2 targeted CAR T cells designed to effectively eradicate endogenous site density solid tumors in the absence of toxicity. Cancer Res 80(14Suppl):A09. https://doi.org/10.1158/1538-7445.PEDCA19-A09

Article Google Scholar

47. Cheng X (2024) A comprehensive review of HER2 in cancer biology and therapeutics. Genes 15(7):903. https://doi.org/10.3390/genes15070903

Article CAS PubMed PubMed Central Google Scholar

48. Zelinski DP, Zantek ND, Stewart JC, Irizarry AR, Kinch MS (2001) EphA2 overexpression causes tumorigenesis of mammary epithelial cells. Cancer Res 61(5):2301–2306

CAS PubMed Google Scholar

49. Knudson KM, Hwang S, McCann MS, Joshi BH, Husain SR, Puri RK (2022) Recent advances in

IL-13Rα2-Directed cancer immunotherapy. Front Immunol 13:878365. https://doi.org/10.3389/fimmu.2022.878365

Article CAS PubMed PubMed Central Google Scholar

50. Chow KK, Naik S, Kakarla S, Brawley VS, Shaffer DR, Yi Z, Rainusso N, Wu MF, Liu H, Kew Y, Grossman RG, Powell S, Lee D, Ahmed N, Gottschalk S (2013) T cells redirected to EphA2 for the immunotherapy of glioblastoma. Mol Therapy: J Am Soc Gene Therapy 21(3):629–637. https://doi.org/10.1038/mt.2012.210

Article CAS Google Scholar

51. Donovan LK, Delaidelli A, Joseph SK, Bielamowicz K, Fousek K, Holgado BL et al (2020) Locoregional delivery of CAR T cells to the cerebrospinal fluid for treatment of metastatic medulloblastoma and ependymoma. Nat Med 26(5):720–731. https://doi.org/10.1038/s41591-020-0827-2

52. Bielamowicz K, Fousek K, Byrd TT, Samaha H, Mukherjee M, Aware N, Wu MF, Orange JS, Sumazin P, Man TK, Joseph SK, Hegde M, Ahmed N (2018) Trivalent CAR T cells overcome interpatient antigenic variability in glioblastoma. Neurooncology 20(4):506–518. https://doi.org/10.1093/neuonc/nox182

Article CAS Google Scholar

53. Brown CE, Hibbard JC, Alizadeh D, Blanchard MS, Natri HM, Wang D et al (2024) Locoregional delivery of IL-13Rα2-targeting CAR-T cells in recurrent high-grade glioma: a phase 1 trial. Nat Med 30(4):1001–1012. https://doi.org/10.1038/s41591-024-02875-1

54. Ahmed N, Ratnayake M, Savoldo B, Perlaky L, Dotti G, Wels WS, Bhattacharjee MB, Gilbertson RJ, Shine HD, Weiss HL, Rooney CM, Heslop HE, Gottschalk S (2007) Regression of experimental Medulloblastoma following transfer of HER2-specific T cells. Cancer Res 67(12):5957–5964. https://doi.org/10.1158/0008-5472.CAN-06-4309

Article CAS PubMed Google Scholar

55. Vitanza NA, Johnson AJ, Wilson AL, Brown C, Yokoyama JK, Künkele A et al (2021) Locoregional infusion of HER2-specific CAR T cells in children and young adults with recurrent or refractory CNS tumors: an interim analysis. Nat Med 27(9):1544–1552. https://doi.org/10.1038/

s41591-021-01404-8

56. Hegde M, Mukherjee M, Grada Z, Pignata A, Landi D, Navai SA et al (2021) Tandem CAR T cells targeting HER2 and IL13Rα2 mitigate tumor antigen escape. J Clin Invest 131(13):e152477. https://doi.org/10.1172/JCI152477

57. Visvanathan A, Saulnier O, Chen C, Haldipur P, Orisme W, Delaidelli A et al (2024) Early rhombic lip Protogenin + ve stem cells in a human-specific neurovascular niche initiate and maintain group 3 medulloblastoma. Cell 187(17):4733–4750.e26. https://doi.org/10.1016/j.cell.2024.06.011

58. Hendrikse LD, Haldipur P, Saulnier O, Millman J, Sjoboen AH, Erickson AW et al (2022) Failure of human rhombic lip differentiation underlies medulloblastoma formation. Nature 609(7929):1021–1028. https://doi.org/10.1038/s41586-022-05215-w

59. Wong YH, Lu AC, Wang YC, Cheng HC, Chang C, Chen PH, Yu JY, Fann MJ (2010) Protogenin defines a transition stage during embryonic neurogenesis and prevents precocious neuronal differentiation. J Neuroscience: Official J Soc Neurosci 30(12):4428–4439. https://doi.org/10.1523/JNEUROSCI.0473-10.2010

Article **CAS** **Google Scholar**

60. Bunse L, Bunse T, Kilian M, Quintana FJ, Platten M (2025) The immunology of brain tumors. Sci Immunol 10(112):eads0449. https://doi.org/10.1126/sciimmunol.ads0449

Article **CAS** **PubMed** **Google Scholar**

61. Karimi E, Yu MW, Maritan SM, Perus LJM, Rezanejad M, Sorin M et al (2023) Single-cell spatial immune landscapes of primary and metastatic brain tumours. Nature 614(7948):555–563. https://doi.org/10.1038/s41586-022-05680-3

62. Friebel E, Kapolou K, Unger S, Núñez NG, Utz S, Rushing EJ, Regli L, Weller M, Greter M, Tugues S, Neidert MC, Becher B (2020) Single-Cell mapping of human brain cancer reveals Tumor-Specific instruction of Tissue-Invading leukocytes. Cell 181(7):1626–1642e20. https://doi.org/10.1016/j.cell.2020.04.055

Article **CAS** **PubMed** **Google Scholar**

63. Perelroizen R, Philosof B, Budick-Harmelin N, Chernobylsky T, Ron A, Katzir R, Shimon D, Tessler A, Adir O, Gaoni-Yogev A, Meyer T, Krivitsky A, Shidlovsky N, Madi A, Ruppin E, Mayo L (2022) Astrocyte immunometabolic regulation of the tumour microenvironment drives glioblastoma pathogenicity. Brain 145(9):3288–3307. https://doi.org/10.1093/brain/awac222

Article PubMed PubMed Central Google Scholar

64. Nayak D, Roth TL, McGavern DB (2014) Microglia development and function. Annu Rev Immunol 32:367–402. https://doi.org/10.1146/annurev-immunol-032713-120240

Article CAS PubMed PubMed Central Google Scholar

65. Steffin D, Ghatwai N, Montalbano A, Rathi P, Courtney AN, Arnett AB et al (2025) Interleukin-15-armoured GPC3 CAR T cells for patients with solid cancers. Nature 637(8047):940–946. https://doi.org/10.1038/s41586-024-08261-8

66. Woroniecka K, Chongsathidkiet P, Rhodin K, Kemeny H, Dechant C, Farber SH et al (2018). T-cell exhaustion signatures vary with tumor type and are severe in glioblastoma. Clin Cancer Res 24(17):4175–4186. https://doi.org/10.1158/1078-0432.CCR-17-1846

67. El Andaloussi A, Lesniak MS (2006) An increase in CD4 + CD25 + FOXP3 + regulatory T cells in tumor-infiltrating lymphocytes of human glioblastoma multiforme. Neurooncology 8(3):234–243. https://doi.org/10.1215/15228517-2006-006

Article Google Scholar

68. Landi D, Navai SA, Brock RM, Fousek K, Nawas Z, Sanber K et al (2025) A checkpoint reversal receptor mediates bipartite activation and enhances CAR T-cell function. Cancer Res Commun 5(3):527–548. https://doi.org/10.1158/2767-9764.CRC-24-0125

69. Schneider BJ, Naidoo J, Santomasso BD, Lacchetti C, Adkins S, Anadkat M et al (2021). Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. J Clin Oncol 39(36):4073–4126. https://doi.org/10.1200/JCO.21.01440

70. Chan JTN, Henley-Waters J, Kayhanian S (2025) Chimeric antigen receptor (CAR)-T-cell therapy

for glioblastoma: what can we learn from the early clinical trials? A systematic review. Neuro-oncology Adv 7(1):vdaf115. https://doi.org/10.1093/noajnl/vdaf115

Article Google Scholar

71. Morris EC, Neelapu SS, Giavridis T, Sadelain M (2022) Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. Nat Rev Immunol 22(2):85–96. https://doi.org/10.1038/s41577-021-00547-6

Article CAS PubMed Google Scholar

72. Ross AB, Puri K, Johnson TL, Correa LD, John TD, Friend B, Navai SA, Ahmed N, Hegde MG, Omer B, Heczey A, Salem BM, Tcharmtchi H, Rouce RH, Steffin DH, Krance RA, Rainusso NC, Bhar S (2025) Cardiovascular complications of immune effector cell therapies in pediatric hematological and solid tumors. Pediatr Blood Cancer 72(4):e31557. https://doi.org/10.1002/pbc.31557

Article CAS PubMed Google Scholar

73. Jain T, Olson TS, Locke FL (2023) How I treat cytopenias after CAR T-cell therapy. Blood 141(20):2460–2469. https://doi.org/10.1182/blood.2022017415

Article CAS PubMed PubMed Central Google Scholar

74. Mahdi J, Dietrich J, Straathof K, Roddie C, Scott BJ, Davidson TB et al (2023) Tumor inflammation-associated neurotoxicity. Nat Med 29(4):803–810. https://doi.org/10.1038/s41591-023-02276-w

75. Steffin DHM, Muhsen IN, Hill LC, Ramos CA, Ahmed N, Hegde M et al (2022) Long-term follow-up for the development of subsequent malignancies in patients treated with genetically modified IECs. Blood 140(1):16–24. https://doi.org/10.1182/blood.2022015728

76. Berg P, Bakker C, Sander M, Hasselblad Lundstrøm N, Erneholm K, Musuamba Tshinanu F, Kholmanshikh O, Van Nuffel F, Müller S, Ruppert-Seipp G, Maurer GD, Januskiene J, Mantziri M, Mulder B, van Nimwegen FA, Vasilcanu D, Wändel Liminga U (2025) Secondary malignancy of T-cell origin after CAR T-cell therapy: ema's conclusions from the evaluation of 38 suspected cases. Gene Ther. https://doi.org/10.1038/s41434-025-00586-xAdvance online publication

Article PubMed Google Scholar

77. Tix T, Alhomoud M, Shouval R, Cliff ERS, Perales MA, Dos Santos C, D. M., Rejeski K (2024) Second primary malignancies after CAR T-Cell therapy: A systematic review and Meta-analysis of 5,517 lymphoma and myeloma patients. Clin Cancer Research: Official J Am Association Cancer Res 30(20):4690–4700. https://doi.org/10.1158/1078-0432.CCR-24-1798

Article CAS Google Scholar

78. Leary SES, Packer RJ, Li Y, Billups CA, Smith KS, Jaju A, Heier L, Burger P, Walsh K, Han Y, Embry L, Hadley J, Kumar R, Michalski J, Hwang E, Gajjar A, Pollack IF, Fouladi M, Northcott PA, Olson JM (2021) Efficacy of carboplatin and isotretinoin in children with High-risk medulloblastoma: A randomized clinical trial from the children's oncology group. JAMA Oncol 7(9):1313–1321. https://doi.org/10.1001/jamaoncol.2021.2224

Article PubMed PubMed Central Google Scholar

Download references ⤓

Acknowledgements

Mohammad H. Abu-Arja receives salary support from the Rally Foundation and Kids Join The Fight Foundations, the Be Brooks Brave Fund and the St. Baldrick's Foundation, and the National Cancer Institute (NCI).

Funding

No relevant funding was received for this study. The authors declare that no funds, grants, or other support were received specifically for this project. Mohammad H. Abu-Arja receives salary support from the following: The Rally Young Investigator and Kids Join The Fight Young Investigator Grant. Grant No.: 25YIN38. The Be Brooks Brave Fund St. Baldrick's Foundation Fellowship Award. Grant No.: 1-1186766. The National Cancer Institute (NCI) Paul Calabresi Career Development Award for Clinical Oncology (K12). Grant ID: 5K12CA090433-23.

Author information

Authors and Affiliations

Division of Hematology and Oncology, Department of Pediatrics, Baylor College of Medicine, Texas Children's Cancer and Hematology Center, Texas Children's Hospital, 1102 Bates Ave, Houston, TX, 77030, USA

Mohammad H. Abu-Arja, Rahawa T. Ghebrelul, Murali Chintagumpala, Michael D. Taylor & Nabil Ahmed

Center for Cell and Gene Therapy, Baylor College of Medicine, Texas Children's Hospital, Houston Methodist Hospital, Houston, TX, USA

Mohammad H. Abu-Arja, Rahawa T. Ghebrelul & Nabil Ahmed

The Dan L. Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, TX, USA

Mohammad H. Abu-Arja, Murali Chintagumpala, Michael D. Taylor & Nabil Ahmed

Division of Hematology, Oncology, Transplant, and Cellular Therapy, Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Austin Stuckert

Department of Neurosurgery, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA

Michael D. Taylor

Contributions

All authors contributed to the conception and design of the study. Mohammad H. Abu-Arja, Austin Stuckert, and Rahawa T. Ghebrelul completed the data collection, interpretation, and drafted the manuscript. All authors participated in revising the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

Corresponding author

Correspondence to Mohammad H. Abu-Arja.

Ethics declarations

Ethical approval

This article is a review and does not involve any studies with human participants or animals performed by any of the authors.

Competing interests

Mohammad H. Abu-Arja receives salary support from the following:- The Rally Young Investigator

and Kids Join The Fight Young Investigator Grant. Grant No.: 25YIN38. - The Be Brooks Brave Fund St. Baldrick's Foundation Fellowship Award. Grant No.: 1-1186766. - The National Cancer Institute (NCI) Paul Calabresi Career Development Award for Clinical Oncology (K12). Grant ID: 5K12CA090433-23Nabil Ahmed is named inventor on patent applications in the field of CAR T cell therapy owned by Baylor College of Medicine. He also received one-time royalties from Celgene and Cell Medica, consulted in the past for Adaptimmune, and continues to consult for Equillium (pro bono) and The Children's Cancer Hospital, Egypt 57357. None of these relationships conflicts with the published work.All other authors have no relevant financial or non-financial interests to disclose.

Additional information

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Rights and permissions

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.

Reprints and permissions

About this article

Check for updates

Cite this article

Abu-Arja, M.H., Stuckert, A., Ghebrelul, R.T. *et al.* Immunotherapy approaches for the treatment of relapsed or progressive medulloblastoma. *J Neurooncol* **177**, 39 (2026). https://doi.org/10.1007/s11060-026-05437-2

Download citation

Received

26 November 2025

Accepted
19 January 2026

Published
11 March 2026

Version of record
11 March 2026

DOI
https://doi.org/10.1007/s11060-026-05437-2

Keywords

Immunotherapy
Checkpoint inhibitors
Chimeric antigen receptor
Medulloblastoma

Discover content
Journals A-Z
Books A-Z

Publish with us
Journal finder
Publish your research
Language editing
Open access publishing

Products and services
Our products
Librarians
Societies
Partners and advertisers

Our brands
Springer
Nature Portfolio
BMC
Palgrave Macmillan
Apress
Discover

Your privacy choices/Manage cookies
Your US state privacy rights
Accessibility statement
Terms and conditions
Privacy policy
Help and support
Legal notice
Cancel contracts here

2.157.136.20
Not affiliated

SPRINGER NATURE
© 2026 Springer Nature