To inform the clinical translation of ependymoma dependencies, we prioritized targets for which small molecules were available by integrating our analysis of tumour-specific super-enhancer-regulated genes with the Washington University Drug Gene interaction database[17] (Fig. 4a, Supplementary Table 21). *HDAC7*, *EPHA2*, *FGFR1* and *CACNA1H* were identified as candidate genes on which ependymomas depend that could be responsive to small-molecule inhibitors (Fig. 4a). Numerous subtype-restricted lead compounds were also identified (Supplementary Table 22). Active super enhancers marking molecular dependencies for ependymomas suggested that ependymoma cells would be responsive to inhibition of the BET bromodomain family of proteins by JQ1, which blocks protein 'readers' of H3K27 acetylation. JQ1 inhibited the proliferation of ependymoma cells at clinically achievable nanomolar concentrations and showed limited efficacy against normal brain cell proliferation (Fig. 4b). Our super enhancer analysis identified FGFR1 small-molecule inhibitors as possible pan-ependymoma therapies, whereas inhibitors of another super-enhancer-associated gene product, WEE1, are likely to be active for subsets of ependymoma. AZD4547 (FGFR1 inhibitor) and AZD1775 (WEE1 inhibitor) exhibited potent and clinically achievable anti-tumour activity (Fig. 4c, d). Treatment of immunodeficient mice bearing posterior fossa ependymoma intracranial xenografts (H.612) with AZD4547 extended survival (Fig. 4e), suggesting that chromatin landscapes can inform therapeutic paradigms.

Our study of active chromatin landscapes within ependymomas identified tumour- and subgroup-specific super-enhancer-driven genes in ependymoma as potential leads for further testing. By integrating our data with drug interaction databases, we identified and validated novel cancer dependencies of ependymoma that are responsive to pharmacologic inhibition. Our study further demonstrates that knowledge of enhancer landscapes can be used to dissect the molecular differences between histologically similar tumour entities and to provide unique information that may inform precision therapies. These differences are captured by the characterization of variant enhancer and super enhancer loci, in addition to the reverse engineering of core transcriptional regulatory circuitries in tumours. Finally, as shown in ependymomas and other tumours, knowledge of core and subgroup-specific transcription factors reveals a molecular basis for the oncogenic transcriptional programs of cancer, and provides insight into lineage programs that persist in the neoplastic state[8].

**Online Content** Methods, along with any additional Extended Data display items and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

**Received 19 December 2016; accepted 22 November 2017.**
**Published online 20 December 2017.**

1. Pajtler, K. W. *et al.* Molecular classification of ependymal tumors across all CNS compartments, histopathological grades, and age groups. *Cancer Cell* **27,** 728–743 (2015).
2. Mack, S. C. *et al.* Epigenomic alterations define lethal CIMP-positive ependymomas of infancy. *Nature* **506,** 445–450 (2014).
3. Witt, H. *et al.* Delineation of two clinically and molecularly distinct subgroups of posterior fossa ependymoma. *Cancer Cell* **20,** 143–157 (2011).
4. Parker, M. *et al. C11orf95-RELA* fusions drive oncogenic NF-κB signalling in ependymoma. *Nature* **506,** 451–455 (2014).
5. Kundaje, A. *et al.* Integrative analysis of 111 reference human epigenomes. *Nature* **518,** 317–330 (2015).
6. Hnisz, D. *et al.* Super-enhancers in the control of cell identity and disease. *Cell* **155,** 934–947 (2013).
7. Hnisz, D. *et al.* Convergence of developmental and oncogenic signaling pathways at transcriptional super-enhancers. *Mol. Cell* **58,** 362–370 (2015).
8. Lin, C. Y. *et al.* Active medulloblastoma enhancers reveal subgroup-specific cellular origins. *Nature* **530,** 57–62 (2016).
9. Lovén, J. *et al.* Selective inhibition of tumor oncogenes by disruption of super-enhancers. *Cell* **153,** 320–334 (2013).
10. Taylor, M. D. *et al.* Radial glia cells are candidate stem cells of ependymoma. *Cancer Cell* **8,** 323–335 (2005).
11. Johnson, R. A. *et al.* Cross-species genomics matches driver mutations and cell compartments to model ependymoma. *Nature* **466,** 632–636 (2010).
12. Mohankumar, K. M. *et al.* An *in vivo* screen identifies ependymoma oncogenes and tumor-suppressor genes. *Nat. Genet.* **47,** 878–887 (2015).
13. Ramsey, S. A. *et al.* Genome-wide histone acetylation data improve prediction of mammalian transcription factor binding sites. *Bioinformatics* **26,** 2071–2075 (2010).
14. Saint-André, V. *et al.* Models of human core transcriptional regulatory circuitries. *Genome Res.* **26,** 385–396 (2016).
15. Pope, B. D. *et al.* Topologically associating domains are stable units of replication-timing regulation. *Nature* **515,** 402–405 (2014).
16. Abedalthagafi, M. S. *et al.* Decreased FOXJ1 expression and its ciliogenesis programme in aggressive ependymoma and choroid plexus tumours. *J. Pathol.* **238,** 584–597 (2016).
17. Griffith, M. *et al.* DGIdb: mining the druggable genome. *Nat. Methods* **10,** 1209–1210 (2013).

**Supplementary Information** is available in the online version of the paper.

**Acknowledgements** This work was supported by an Alex's Lemonade Stand Young Investigator Award (S.C.M.), The CIHR Banting Fellowship (S.C.M.), The Cancer Prevention Research Institute of Texas (S.C.M., RR170023), Sibylle Assmus Award for Neurooncology (K.W.P.), the DKFZ-MOST (Ministry of Science, Technology & Space, Israel) program in cancer research (H.W.), James S. McDonnell Foundation (J.N.R.) and NIH grants: CA154130 (J.N.R.), R01 CA169117 (J.N.R.), R01 CA171652 (J.N.R.), R01 NS087913 (J.N.R.) and R01 NS089272 (J.N.R.). R.C.G. is supported by NIH grants T32GM00725 and F30CA217065. M.D.T. is supported by The Garron Family Chair in Childhood Cancer Research, and grants from the Pediatric Brain Tumour Foundation, Grand Challenge Award from CureSearch for Children's Cancer, the National Institutes of Health (R01CA148699, R01CA159859), The Terry Fox Research Institute and Brainchild. M.D.T. is also supported by a Stand Up To Cancer St. Baldrick's Pediatric Dream Team Translational Research Grant (SU2C-AACR-DT1113). Stand Up To Cancer is a program of the Entertainment Industry Foundation administered by the American Association for Cancer Research. We thank S. Archer for technical writing and editing expertise. In addition, we thank the High-Throughput Sequencing Unit of the DKFZ Genomics and Proteomics Core Facility for technical support and acknowledge technical assistance by M. Mauermann, T. Wedig, A. Wittmann and L. Siebert. Additional support came from the ICGC DE-Mining grant (#01KU1505). We thank The Children's Hospital at Westmead (CHW) Tumour Bank for support of tumour samples (H.W.). We thank D. Schumick (Cleveland Clinic Art Department) and G. Hsu (https://www.hsubiomedicalvisual.com) for their assistance with creative artwork.

**Author Contributions** S.C.M., K.W.P. and L.C. designed, performed and analysed the majority of the experiments in this study. Q.W. performed genetic knockdown experiments along with *in vivo* drug studies. K.C.B. performed all of the ChIP QC including library preparations and pre- and post-qPCR for the entire cohort. A.F., K.O. and S.E. performed the transcription factor network mapping of the super enhancer data. J.J.M. and T.E.M. assisted with super enhancer analysis and overall interpretation of data and analysis. Xin W., L.M., A.F.M. and I.S. led all of the zebrafish experiments in terms of establishment, interpretation and analysis. L.G., A.M., Y.T. and B.L.H. performed timed mating and tissue isolation in developing mouse embryos. J.R. assisted with pathway analysis of super enhancers. J.J.Y.L. assisted with ChIP experiments and library preparations. A.S. guided analysis of super-enhancer-subgroup stratification. D.C.F. performed RNA-seq pre-processing and analysis. B.L. helped with tissue isolation, preparation and submission for ChIP sequencing and DNA methylation analysis. Xia.W. and L.G. directed breeding and establishment of meis1–GFP mice. C.L.L.V., R.C.G. K.A.M. and A.T. performed data integration and mining of drug databases and identification of lead therapeutic compounds. A.M. performed super-enhancer-saturation analysis. P.C.S. assisted with study design, data analysis interpretation and manuscript review. S.Q.K., J.Z., V.M. and S.L., assisted with qPCR of numerous targets in genetic knockdown and differentiation experiments. P.J.H., T.M., A.M.C., S.K.S. and S.T.K. provided ependymoma models, controls and helped design the study. Xiu.W., L.D., S.D., L.K. and B.C.P. assisted with normal NSC drug treatments with drug inhibitors used in this study. C.L., C.-J.L., X.-W.B., C.G.H., M.R., S.D., S.V., S.N.G., H.W., D.T.W.J., P.A.N., P.L., A.K., N.J., J.T.R., E.B., A.H., K.D.A., P.B.D., Y.L., M.L., Z.H., M.Z., V.R., J.E.B, S.M.P., P.S.-C. and P.C.S., assisted with data interpretation, manuscript preparation and review. M.D.T., J.N.R. and M.K. conceived, designed, interpreted and funded the study.

**Author Information** Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of the paper. Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations. Correspondence and requests for materials should be addressed to J.N.R. (drjeremyrich@gmail.com), M.D.T. (mdtaylor@sickkids.ca) or M.K. (m.kool@dkfz-heidelberg.de).

**Reviewer Information** *Nature* thanks S. Pomeroy, W. Weiss and the other anonymous reviewer(s) for their contribution to the peer review of this work.