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Harnessing the power of biomarkers for diffuse intrinsic pontine gliomas

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The BIOMEDE trial, although negative for its primary endpoint, illustrates the utility of adaptive trial designs and biopsy-informed tumor profiling in guiding treatment decisions and patient counseling — and provides mechanistic evidence that can inform future therapeutic strategies.

Diffuse intrinsic pontine gliomas (DIPGs) in which H3K27 is altered ('H3K27-altered' DIPGs) are aggressive, high-grade central nervous system tumors associated with a dismal median overall survival of 11 months and limited therapeutic options beyond palliative radiation[1]. As more information has been uncovered about the distinct molecular and genetic profiles of these tumors[2], targeted therapies have increasingly been studied for the treatment of DIPG. The BIOMEDE trial — reported by Debily et al. in this issue of *Nature Medicine* — was an international, randomized, phase 2 clinical trial that assessed the efficacy of combining radiotherapy with molecularly targeted therapies in children, adolescents and young adults with biopsy-proven H3K27-altered DIPG[3]. Although the trial did not reach its primary endpoint of improved overall survival compared with that of a historical control group, the results provide novel evidence and insights into the molecular profiles and tumor biomarkers that could influence response to treatment and patient outcomes in this setting. This work underscores the potential advantage of adaptive clinical trial designs with extensive tumor genetic and molecular testing, providing a framework with which to better understand the mechanisms underlying therapeutic responses of H3K27-altered DIPG tumors.

The findings of the BIOMEDE trial highlight how biopsies can serve as critical diagnostic tools that can identify specific prognostic molecular biomarkers to guide clinical decision-making (Fig. 1). DIPGs were historically diagnosed on the basis of imaging and clinical characteristics, because of the risks associated with performing a biopsy within the neuroanatomically delicate brainstem. However, in recent years, neurosurgeons have been performing biopsies more frequently for patients with DIPG[4] — and as this trial confirmed, biopsies can now be safely performed with the appropriate training. There were no deaths secondary to biopsy on the trial, and the median duration of the hospital stay following biopsy was only 2 days. Correspondingly, the molecular and genetic data gleaned from these biopsies proved to be indispensable for patients, directly impacting treatment decisions and even serving as prognostic markers in a subset of patients.

All the patients on trial underwent biopsy and subsequent whole-exome and RNA sequencing, with tumor samples assessed centrally for immunohistochemical biomarkers. This allowed personalized precision-based medical treatment, as patients could not be randomly assigned to a treatment arm if the corresponding tumor biomarker was absent. On the basis of biomarker analysis, patients were assigned to receive EGFR inhibition (with erlotinib), mTOR inhibition (with everolimus), or multitargeted tyrosine kinase inhibition (with dasatinib) — all in addition to standard radiotherapy. There was no statistically significant difference between any of the treatment arms and the control cohort in overall survival, clinical response or imaging response, but each treatment was well tolerated with no severe adverse events or deaths. This favorable safety profile, together with

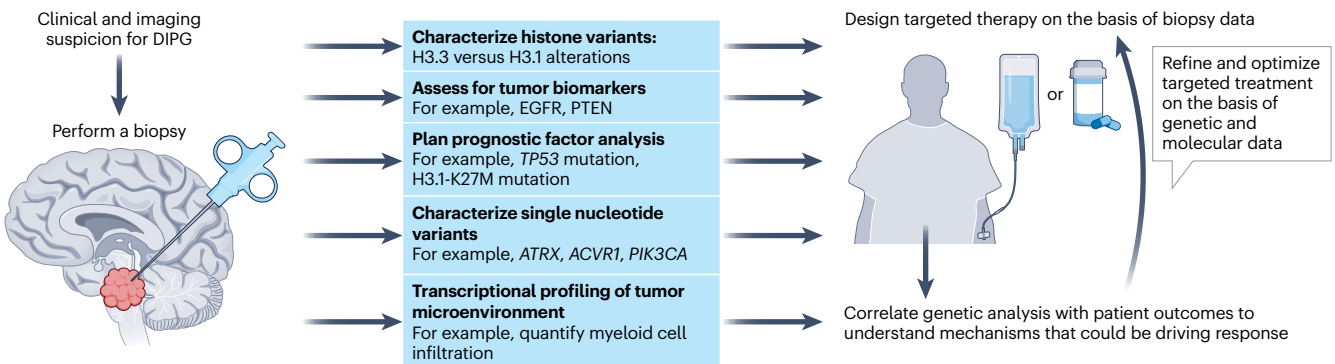

Fig. 1 | Framework for targeted therapy selection in H3K27-altered DIPGs. The BIOMEDE clinical trial design and analysis provides a framework that clinicians can universally apply when selecting targeted treatment in H3K27-altered DIPG. Patients with suspected DIPG should undergo biopsy, if it is deemed safe by a neurosurgeon. The tissue from the patient's biopsy should then be thoroughly analyzed to assess histone variants, tumor biomarkers, and potential mutations that could hold prognostic importance. Deeper analysis of the genomic landscape with single-nucleotide variant and transcriptional profiling of the tumor microenvironment should also be performed. These data can directly help inform the selection of which targeted agents could be most effective for a particular patient and can help elucidate the mechanisms that could be driving anti-tumoral responses.

molecular profiling and biomarker analysis, provides the basis for a treatment model that clinicians can employ in their decision-making and counseling of patients with H3K27-altered DIPG.

In the BIOMEDE trial, there was a correlation between a patient's tumor biomarkers and response to treatment and overall prognosis. In patients treated with everolimus, mutations in genes encoding components of the PI3K–AKT–mTOR pathway correlated with better progression-free survival ($P = 0.02$) and overall survival ($P = 0.08$) and, consistent with previously published literature[5], H3.1-K27M was a favorable biomarker for survival, relative to H3.3-K27M. The authors also found that *TP53* mutation was the main negative prognostic factor for overall survival, which validates what prior studies have shown about this mutation in DIPG[6,7].

Although immunotherapies were not included in this biomarker-driven trial, the tumor-profiling results provide information on how patients with H3K27-altered DIPG may potentially respond to immunotherapy. For example, transcriptional profiling demonstrated a more immunosuppressive phenotype in p53-mutant tumors, which could limit tumor response to immunotherapy. Conversely, these data suggest that if the tumor microenvironment could be pushed from an immunosuppressive state to a pro-inflammatory state, patients may have a survival advantage — and immunotherapies that specifically target the relevant immunological effectors could be harnessed to achieve this[8]. Interestingly, long-term survivors in the trial had distinct, pro-inflammatory tumor microenvironments with immunoproficient myeloid cell populations that could, in theory, confer improved response to immunotherapies. This warrants further investigation, as recent studies using immunotherapies — such as peptide vaccines[9] and chimeric antigen receptor T cell therapy[10] — for the treatment of H3K27-altered DIPG have shown early signs of benefit for some patients, and there is a growing interest in using immunotherapies in combination with targeted therapies to optimize anti-tumor responses[11].

These combinatorial approaches are currently being assessed in both the preclinical setting and the clinical setting for H3K27-altered DIPGs. One such example is PNOC022 (NCT05009992), a phase 2 clinical trial that is testing combination therapy via an adoptive platform design similar to that of BIOMEDE. This trial is assessing the efficacy of ONC201 (a dopamine receptor D2 antagonist recently approved by the US Food and Drug Administration)[12] in combination with radiation and paxalisib (a targeted inhibitor of the PI3K–AKT–mTOR pathway), other molecularly targeted therapies (based on BRAFV600E, PDGFRA, FGFR1 and NF1 status), or intratumoral injection of DNX-2401, an oncolytic adenovirus immunotherapy. More such trials are needed to design molecularly driven and durable therapeutic combinatorial regimens for patients with H3K27-altered DIPG.

Overall, the prospective validation of prognostic biomarkers for all patients on the BIOMEDE trial — and the comprehensive molecular and gene expression profiling of long-term survivors — reaffirms the heterogeneity of H3K27-altered DIPGs and the influence of specific mutations and the tumor microenvironment on patient outcomes. Such testing is currently being performed mainly in the clinical trial setting, given the costs and resources required. It is important to note that the financial burden associated with testing may limit the feasibility of performing these analyses for all patients. The oncology field must work to mitigate this potential barrier to care and improve access to molecular and/or genetic testing across clinical centers, given its potential to directly improve clinical care.

Thus, the BIOMEDE trial findings provide a platform for determining how tumor biomarkers and genetic profiling can be utilized to stratify targeted treatments for H3K27-altered DIPG on future clinical trials. They also demonstrate how these targeted therapies could potentially be combined with other treatments, such as immunotherapy, to improve the lives of patients with this otherwise fatal tumor.

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References

1. Cooney, T. et al. *Neuro. Oncol.* **19**, 1279–1280 (2017).
2. Louis, D. N. et al. *Neuro. Oncol.* **23**, 1231–1251 (2021).
3. Debily, M.-A. et al. *Nat. Med.* https://doi.org/10.1038/s41591-026-04354-1 (2026).
4. Sheikh, S. R. et al. *Front. Oncol.* **14**, 1504440 (2024).
5. Castel, D. et al. *Acta Neuropathol.* **130**, 815–827 (2015).
6. Vuong, H. G. et al. *J. Neurooncol.* **55**, 225–234 (2021).
7. Kline, C. et al. *Clin. Cancer Res.* **28**, 3965–3978 (2022).
8. Andrade, A. F. et al. *Nat. Commun.* **15**, 7769 (2024).
9. Grassl, N. et al. *Nat. Med.* **29**, 2586–2592 (2023).
10. Monje, M. et al. *Nature* **637**, 708–715 (2025).
11. Myers, D. R., Wheeler, B. & Roose, J. P. *Immunol. Rev.* **291**, 134–153 (2019).
12. Venneti, S. et al. *Cancer Discov.* **13**, 2370–2393 (2023).

Competing interests

The author declares no competing interests.