What is a glioblastoma?

Andrew B. Lassman: Division of Neuro-Oncology, Department of Neurology, Herbert Irving Comprehensive Cancer Center and Irving Institute for Clinical and Translational Research, Columbia University Vagelos College of Physicians and Surgeons and New York-Presbyterian Hospital, New York, NY, USA

Martin J van den Bent: Department of Neurology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

Correspondence: Andrew B. Lassman, Columbia University Irving Medical Center/New York-Presbyterian Hospital, 710 West 168th Street, 9th Floor, New York, NY, USA

Phone: +1-212-342-0871

Fax: +1-212-342-1246

E-mail: ABL7@cumc.columbia.edu

Disclosure: The text is the sole product of the authors and that no third party had input or gave support to its writing. The authors report no manuscript-specific conflicts of interest.

Funding: There was no manuscript-targeted external funding. Outside of the submitted work, ABL was supported in part by The William Rhodes and Louise Tilzer-Rhodes Center for Glioblastoma at New York-Presbyterian Hospital, the Hearst Foundations, and by NIH/NCI/NCATS grants P30CA013696 and UL1TR001873. Publication costs were paid by The Michael Weiner Glioblastoma Research Into Treatment Fund.

The 2021 revised World Health Organization (WHO) classification of central nervous system (CNS) tumors was a herculean effort.[1] Building on preparatory work by the "Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy-Not Official WHO (cIMPACT-NOW)", the updated classification incorporates observations that some *IDH* wild-type (*IDH*wt) lower grade gliomas behave as aggressively as histologically defined glioblastomas (i.e., "h-GBMs"), and should carry the highest CNS WHO grade. Such IDHwt histologically grade 2-3 tumors exhibiting specific alterations (*Telomerase Reverse Transcriptase* (*TERT*) gene promoter mutation and/or *Epidermal Growth Factor Receptor* (*EGFR*) gene amplification and/or combined chromosome 7 gain/10 loss), initially labelled "molecular glioblastomas" (m-GBMs) by cIMPACT-NOW, are now fully comingled by the WHO with h-GBMs as the singular entity "Glioblastoma, *IDH*wt; CNS WHO grade 4".[1]

We agree that nomenclature should be informed by new knowledge. We note as precedence the evolving definition of "glioblastoma" since it was first used more than 100 years ago, reflecting scientific and clinical advancements, differences among schools of thought (e.g., histologic vs. clinical malignancy), concepts related to cell(s) of origin, and other considerations (**supplemental file)** as reviewed elsewhere.[2] For example, the definition widened in 2007 with the reclassification as glioblastomas (and as grade IV) of high grade tumors with mixed astrocytic and oligodendroglial components (formerly "anaplastic oligo-astrocytomas"[3], then considered as "glioblastoma with oligodendroglioma component…as a compromise term"[4]) that harbored necrosis. [5] This change resulted from observations that necrosis portended a bad outcome and that such tumors typically lacked chromosome 1p19q codeletion which was emerging as a biomarker linked to the more favorable diagnosis of oligodendroglioma.[5] The 2016 WHO classification defined with precision, "what is an oligodendroglioma?"[6] by **restriction** to *IDH*-mutant and 1p19q codeleted tumors,[7]; by contrast the 2021 edition **expanded** the definition of glioblastoma by labelling the m-GBMs of cIMPACT-NOW as simply "GBM".[1]

However, we believe the prognostic and therapeutic implications of this broadened glioblastoma definition are not yet fully elucidated. Expanding on the incorporation of molecular testing into diagnostic nomenclature of CNS tumors that began robustly with the 2016 classification system,[7] we applaud the efforts by the WHO and cIMPACT-NOW teams to systematize biomarker-informed prognostic grading, recognizing that some *IDH*wt tumors should carry the highest WHO grade of 4 despite an absence of classic glioblastoma histology. Yet, there is evidence that m-GBMs and h-GBMs may behave differently, and series reporting on comparative outcomes are still limited.

For example, *IDH*wt tumors that are histologically lower grade (yet would be now considered glioblastoma on molecular grounds, i.e., m-GBMs) are associated with a higher incidence of pre-diagnosis epilepsy (and longer time to diagnosis) than h-GBMs.[8] Most concerning for comingling m-GBMs with h-GBMs in clinical trials designed to test the impact of therapeutic interventions on survival, a retrospective study[9] reported median survival of 42 months in patients with m-GBMs that were histologically low grade (WHO grade II per 2016 criteria[7]) tumors (**supplemental file**). Although the study was small (n=29), the reported outcomes were substantially better than survival typically associated with h-GBM, ***particularly* for cases with isolated *TERT* promoter mutation (n=23, median survival 88 months for histologically grade 2 disease).**[9] Further suggesting biologic differences between h- and m-GBMs, there was no evidence of benefit from temozolomide in the CATNON trial (NCT00626990) in the subset of cases that would now be classified as m-GBMs, regardless of *MGMT* promoter methylation.[10] Conversely, and supporting the new WHO schema, the CATNON trial (for patients with tumors exhibiting grade 3 histology) also demonstrated that isolated *TERT* promoter mutation was associated with poor survival.[10]

Without stratification or other guards against imbalance between/among arms, the pooling m-GBMs with h-GBMs in time to event analyses could result in falsely declaring a trial as positive if the median survival is lengthened by only 4 months through inclusion of m-GBMs that may have a better natural history than h-GBMs. The risk of such overinterpretation is even higher in single arm studies if a substantial subset of patients accrued has m-GBM rather than h-GBM. Some trials (e.g., NRG Oncology-BN010, NCT04729959) have already taken the expansive approach, which may allow more rapid accrual (and trial completion), and broaden the population of patients for whom favorable (or unfavorable) results would apply, but at the risk of misattributing a resulting survival advantage in the trial to study therapy rather than natural history. Further investigation of the incidence and natural history of patients with m-GBM is still needed, especially in light of the conflicting literature[9,10] noted above. Furthermore, some new drugs may penetrate a non-enhancing m-GBM less well than the enhancing h-GBM, with resulting differences in anti-tumor effects. Penetration of the blood-brain barrier is already a challenge in the treatment of non-enhancing tumor (or even non-visible microscopic disease) in h-GBM. Therefore, we urge caution on including patients with non-enhancing histologically low grade tumors that are m-GBMs in clinical trials that would previously have been limited to h-GBMs.

We suggest consideration be given to approaches that, at present, defer fully comingling m- and h-GBMs in clinical trials with survival endpoints to collect more prospective data first. Options include formalized stratification in randomized studies, or, better in our view, allowing enrollment of patients with m-GBMs as separately analyzed exploratory cohorts to collect evidence. At a minimum, each case should be coded as “m-GBM” or “h-GBM”, so that a subsequent set of analyses can be performed to understand the impact, if any, of comingling. We see at least two favorable implications of such approaches: 1) patients with m-GBMs would have increased clinical trial options; 2) our field could learn more about the natural history of m-GBMs and their responsiveness

to novel therapies. We (ABL) have already observed that some institutions are no longer distinguishing m- from h-GBM in diagnostic reports; therefore, implementing a distinction, or at least a labeling, in clinical trials may depend on central review.

Of note, sampling error needs, however, also to be considered. For example, histologically low grade tumors typically present with lesions that do not contrast-enhance on brain imaging, often with an appearance of the now antiquated term "gliomatosis cerebri." Therefore, despite our above reasoning, patients with tumors that are clearly glioblastomas based on imaging (e.g., heterogeneous ring-enhancement with a necrotic center; **supplemental file, Figure S1**) should not be excluded from trials (such as through mechanisms analogous to those suggested for m-GBMs above) if a biopsy yields only low grade histology and molecular analysis demonstrates m-GBM – in that situation most likely the biopsy was taken from an area that was not representative for the true nature of the lesion.

REFERENCES

1. Louis DN, Giannini C, Perry A, et al. Glioblastoma, IDH-wildtype. In: WHO_Classification_of_Tumours_Editorial_Board, ed. *Central nervous system tumours [internet].* Vol 6. 5th ed. Lyon, France: International Agency for Research on Cancer (IARC); 2021:Available from: https://tumourclassification.iarc.who.int/chapters/45.

2. Mclendon RE, Kleihues P. Classification of tumors of the central nervous system: an historical annotation. In: McLendon RE, Rosenblum MK, Bigner DD, eds. *Russell & Rubinstein's Pathology of Tumors of the Nervous System*. 7th ed. London: Hodder Aronold; 2006:26-29.

3. Kleihues P, Cavenee WK. *Pathology and genetics of tumours of the nervous system*. 2nd ed. Lyon, France: International Agency for Research on Cancer (IARC) Press; 1997.

4. Kleihues P, Cavenee WK. *World Health Organisation classification of tumours: Pathology and genetics of tumours of the nervous system*. 3rd ed. Lyon, France: International Agency for Research on Cancer (IARC) Press; 2000.

5. Louis DN, Ohgaki H, Wiestler OD, Cavanee WK. *WHO Classification of Tumours of the Central Nervous System*. 4th ed. Lyon, France: International Agency for Research on Cancer (IARC); 2007.

6. Burger PC. What is an oligodendroglioma? *Brain Pathol.* 2002; 12(2):257-259.

7. Louis DN, Ohgaki H, Wiestler OD, Cavanee WK. *WHO Classification of Tumours of the Central Nervous System*. Revised 4th ed. Lyon, France: International Agency for Research on Cancer (IARC); 2016.

8. van Opijnen MP, Tesileanu CMS, Dirven L, et al. IDH1/2 wildtype gliomas grade 2 and 3 with molecular glioblastoma-like profile have a distinct course of epilepsy compared to IDH1/2 wildtype glioblastomas. *Neuro Oncol.* 2022:Aug 15;noac197. doi: 110.1093/neuonc/noac1197. Online ahead of print.

9. Berzero G, Di Stefano AL, Ronchi S, et al. IDH-wildtype lower-grade diffuse gliomas: the importance of histological grade and molecular assessment for prognostic stratification. *Neuro Oncol.* 2021; 23(6):955-966.

10. Tesileanu CMS, Sanson M, Wick W, et al. Temozolomide and Radiotherapy versus Radiotherapy Alone in Patients with Glioblastoma, IDH-wildtype: Post Hoc Analysis of the EORTC Randomized Phase III CATNON Trial. *Clin Cancer Res.* 2022; 28(12):2527-2535.