Pre-Radiation Targeted Therapy for Highly Selected Patients with Newly Diagnosed Glioblastoma: New Tricks for an Old Dog?

Macarena I. de la Fuente and Andrew B. Lassman

Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA (MID); Department of Neurology, University of Miami, Miami, FL, USA (MID); Division of Neuro-Oncology, Department of Neurology, and the Herbert Irving Comprehensive Cancer Center, Columbia University Vagelos College of Physicians & Surgeons and New York-Presbyterian New York, NY, USA (ABL)

Corresponding author:

Macarena I. de la Fuente

Neuro-Oncology Division, University of Miami

1120 NW14th St. Miami, FL 33136

Tel: 305-243-4951

Fax: 305-243-4832

mdelafuente@med.miami.edu

© The Author(s) 2025. Published by Oxford University Press on behalf of the Society for Neuro-Oncology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com.

Accepted Manuscript

Downloaded from https://academic.oup.com/neuro-oncology/advance-article/doi/10.1093/neuonc/noaf014/7978613 by guest on 28 January 2025

Despite substantial preclinical research and innumerable clinical trials, very little has translated into improved survival for patients with glioblastoma (GBM) which remains almost always incurable with an unacceptable median survival of less than 2 years. New thinking is needed.

In this issue of *Neuro-Oncology*, Bazer et al.[1] review the extensive use of neoadjuvant and pre-radiation chemotherapy (PRC) in a variety of cancers, contrasting it with the very limited use of this approach in current GBM clinical trials even though several GBM studies have demonstrated its safety and feasibility.[1] Furthermore, the authors rightly lament that most clinical trials for newly diagnosed GBM anchor their design on a backbone of radiotherapy and temozolomide, acknowledging that traditional radiochemotherapy is important yet also reminding us it is neither curative nor toxicity-free. This anchor has become an albatross, evidenced most obviously by the absence of any new drug approvals for newly diagnosed GBM in the United States in nearly 20 years with multiple late phase trials (including several we have led[2-4]) that have not improved survival, and even perhaps shortened it.[2,5] Bazer et al implore considerations of alternative approaches, such as PRC which can assess response as a rapid readout. We agree, particularly in light of recent results of PRC in other gliomas.

For example, in the INDIGO study, vorasidenib, a brain-penetrant small molecule inhibitor of mutant IDH1/2 proteins, significantly and meaningfully lengthened progression-free survival (PFS) and time to next intervention (versus placebo) in patients with *IDH*-mutant WHO grade 2 glioma.[6] Similarly, in the FIREFLY-1 trial, in which >90% of patients were radiotherapy naïve, tovorafenib, a brain-penetrant type II RAF inhibitor, demonstrated an objective response rate of >50% in *BRAF*-altered pediatric low-grade glioma.[7] INDIGO and FIREFLY-

Accepted Manuscript

Downloaded from https://academic.oup.com/neuro-oncology/advance-article/doi/10.1093/neuonc/noaf014/7978613 by guest on 28 January 2025

1 results demonstrate unambiguously and forcefully that pre-radiotherapy targeted therapy is both safe and effective for the right patients treated with the right stuff.

In our view, past failures of PRC trials to improve outcome for patients with GBM should not impugn PRC as an inherently flawed study design; rather, the lack of adequate patient selection and effective drugs were at least partly to blame. As Bazer et al. reviewed in-depth,[1] previous PRC trials for GBM were associated with a range of outcomes, likely reflecting at least in part the heterogenous populations and drugs studied. Although none, perhaps with the exception of surgically implantable carmustine eluting wafers, led to improved survival, perhaps more importantly, none also raised an alarm that deferring radiochemotherapy in a PRC trial clearly worsened survival. Today, advances in comprehensive diagnostic testing technologies demonstrate that approximately 5% of GBMs harbor *BRAF* V600 mutations or fusions, *FGFR* fusions, or *NTRK* fusions.

Accordingly, we believe the time has come to dust off the old PRC-based approach and apply it in a new way: analyzing tumors to identify those harboring unusual but druggable targets, treatment with brain-penetrant therapies that are beneficial and tolerable in recurrent high-grade gliomas and other solid tumors,[8] and agilely using response to test for efficacy in highly selected patients (**Fig.1**). Such an approach is further justified by recent successes with vorasidenib and tovorafenib in lower grade gliomas as detailed above. Close monitoring for resistance to a targeted agent with the ability to initiate radiochemotherapy rapidly may be more important for a trial in high-grade gliomas than was necessary in the INDIGO and FIREFLY-1 studies of low-grade gliomas. Admittedly, such PRC clinical trials may also be logistically complicated and require collaboration at multiple levels, and the effect of deferring radiochemotherapy on survival would need to be assessed. Still, we

Accepted Manuscript

Downloaded from https://academic.oup.com/neuro-oncology/advance-article/doi/10.1093/neuonc/noaf014/7978613 by guest on 28 January 2025

believe that PRC offers an ideal setting for assessing targeted therapies that may benefit patients with GBM and other high-grade gliomas.

Assessing response before rather than after radiochemotherapy also avoids the confusing factors that confound interpretation of efficacy in a trial testing second (or later) line therapy, such as spontaneous resolution of post-treatment pseudo-progression that would falsely increase the response rate. As a corollary, enrollment at diagnosis avoids the potential for invalid assumptions at recurrence about the persistence (and importance) of drug targets identified in radiochemotherapy naïve tissue that has not been surgically resampled since diagnosis. It is well established that intervening radiochemotherapy alters tumor drivers and that radiation is likely to create additional resistance mechanisms to targeted therapy, reducing the likelihood of success.[9-10]

Counterbalancing stringent molecular selectivity with more liberal diagnostic criteria would enhance accrual to a PRC trial for rare biomarker subsets. For example, the same *BRAF* V600E mutant high-grade glioma can be diagnosed as a GBM (typically epithelioid) at one institution and as a high-grade pilocytic astrocytoma at another. There is precedent for similar inter-pathologist variability in neuro-oncology: it previously plagued oligodendroglioma diagnoses until molecular rather than histopathologic criteria came to define the disease.[11] Like oligodendroglioma, the diagnosis of “GBM” has also changed with gains in knowledge since it was first used over a century ago, and it will undoubtedly evolve further as science advances.[12] Therefore, basing patient selection for a targeted therapy on the objective presence of the biomarker of interest rather than relying exclusively on somewhat subjective histopathology makes sense to us. We suggest casting a wide histopathologic net for a trial designed primarily with molecular eligibility criteria in mind, rather than constraining accrual by a formalized diagnostic nomenclature that may change in

Accepted Manuscript

Downloaded from https://academic.oup.com/neuro-oncology/advance-article/doi/10.1093/neuonc/noaf014/7978613 by guest on 28 January 2025

future classifications of brain tumors. Pre-specifying primary and exploratory histopathologic cohorts is one approach to ameliorate concerns about enrolling a diagnostically heterogenous population in a registration trial.

In summary, for highly selected glioma patients with druggable molecular alterations, PRC offers a valuable window of opportunity to evaluate brain-penetrant targeted therapies, enabling quicker assessment of treatments than more traditional trial designs, and hopefully expanding the therapeutic options available to improve survival.

Accepted Manuscript

Downloaded from https://academic.oup.com/neuro-oncology/advance-article/doi/10.1093/neuonc/noaf014/7978613 by guest on 28 January 2025

Conflict of Interest Statement

The text is the sole product of the authors. 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, MID was supported in part by The Sylvester Comprehensive Cancer Center Support Grant 5P30CA240139-04, The Dowskin Family Foundation, and by National Institutes of Health (NIH) grants 2UM1-CA186644-06, 1R37CA262510-01A1 and1R21CA282543. Outside of the submitted work, ABL was supported in part by The William Rhodes and Louise Tilzer-Rhodes Center for Glioblastoma at NewYork-Presbyterian Hospital, the Hearst Foundations, The Michael Weiner Glioblastoma Research into Treatment Fund, and by Herbert Irving Comprehensive Cancer Center Support Grant P30CA013696 and National Center for Advancing Translational Sciences (NCATS), NIH, through Grant Number UL1TR001873. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH, NCI, or NCATS.

Accepted Manuscript

Downloaded from https://academic.oup.com/neuro-oncology/advance-article/doi/10.1093/neuonc/noaf014/7978613 by guest on 28 January 2025

Figure 1: Potential schema for pre-radiation chemotherapy trial for patients with glioblastoma or other high-grade gliomas harboring biomarkers that predict deep and durable responses to brain-penetrant targeted therapy such as in recurrent gliomas or other solid tumors. Patients with post-operative measurable disease (per RANO) are evaluable for response (minor, partial, complete). All patients are evaluable for time to event (e.g., progression-free survival, overall survival, time to next intervention) and toxicity. Frequent brain MRI/CT scans may be needed to guard against early failure of targeted therapy. Radiotherapy is deferred but can be planned and simulated to allow rapid initiation for progressive disease.

Accepted Manuscript

Downloaded from https://academic.oup.com/neuro-oncology/advance-article/doi/10.1093/neuonc/noaf014/7978613 by guest on 28 January 2025

References

1. Bazer DA, Wolff AC, Grossman SA. Using a Pre-Radiation Window to Identify Potentially Active Cytotoxic Agents in Adults with Newly Diagnosed Glioblastoma. *Neuro Oncol.* 2024.

2. Lassman AB, Polley MC, Iwamoto FM, et al. NRG Oncology study BN007: randomzied phase II/III trial of ipillimumab plus nivolumab vs. temozolomide in MGMT-unmethylated newly diagnosed glioblastoma. *Neuro-Oncology.* 2023; 25(Supplement_5 (Proceedings of the 29th Annual Meeting of the Society for Neuro-Oncology)):v65-v65 (Abstract CTIM-18).

3. Lassman AB, Alexander B, Berry DA, et al. GBM AGILE platform trial for newly diagnosed and recurrent GBM: results of the first experimental arm, regorafenib. *Neuro-Oncology.* 2024; 26(Supplement_5 (Proceedings of the 19th Meeting of the European Association of Neuro-Oncology)):v26-v27 (Abstract OS09.27.A).

4. Lassman AB, Pugh SL, Wang TJC, et al. Depatuxizumab mafodotin in EGFR-amplified newly diagnosed glioblastoma: A phase III randomized clinical trial. *Neuro Oncol.* 2023; 25(2):339-350.

5. Omuro A, Brandes AA, Carpentier AF, et al. Radiotherapy combined with nivolumab or temozolomide for newly diagnosed glioblastoma with unmethylated MGMT promoter: An international randomized phase III trial. *Neuro Oncol.* 2023; 25(1):123-134.

6. Mellinghoff IK, van den Bent MJ, Blumenthal DT, et al. Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma. *N Engl J Med.* 2023; 389(7):589-601.

Accepted Manuscript

Downloaded from https://academic.oup.com/neuro-oncology/advance-article/doi/10.1093/neuonc/noaf014/7978613 by guest on 28 January 2025

7. Kilburn LB, Khuong-Quang DA, Hansford JR, et al. The type II RAF inhibitor tovorafenib in relapsed/refractory pediatric low-grade glioma: the phase 2 FIREFLY-1 trial. *Nat Med.* 2024; 30(1):207-217.

8. de la Fuente M, Butowski N, Taylor J, et al. Abstract CTNI-76: Efficacy of BRAF inhibitor plixorafenib (FORE8394) in recurrent, primary central nervous system tumors. *Neuro Oncol.* 2023; 25(Supplement_5):v95-v95.

9. Ceccarelli M, Barthel FP, Malta TM, et al. Molecular Profiling Reveals Biologically Discrete Subsets and Pathways of Progression in Diffuse Glioma. *Cell.* 2016; 164(3):550-563.

10. Eke I, Aryankalayil MJ, Bylicky MA, et al. Radiotherapy alters expression of molecular targets in prostate cancer in a fractionation- and time-dependent manner. *Sci Rep.* 12, 3500 (2022). https://doi.org/10.1038/s41598-022-07394-y.

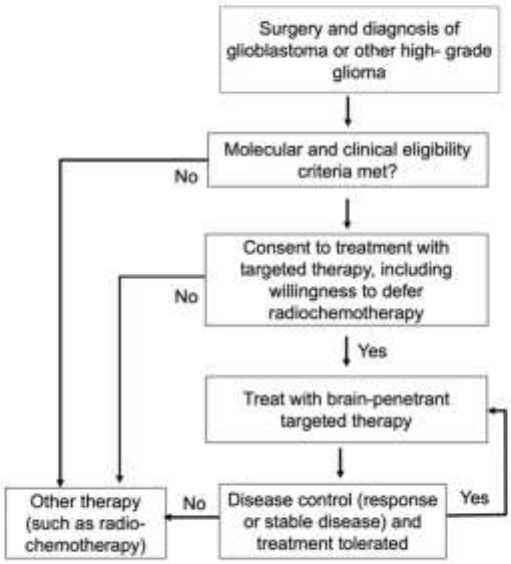
11. Burger PC. What is an oligodendroglioma? *Brain Pathol.* 2002; 12(2):257-259.

12. Lassman AB, van den Bent MJ. What is a glioblastoma? *Neuro Oncol.* 2023; 25(6):1015-1016.

Accepted Manuscript

Downloaded from https://academic.oup.com/neuro-oncology/advance-article/doi/10.1093/neuonc/noaf014/7978613 by guest on 28 January 2025

Figure 1



Accepted Manu

Downloaded from https://academic.oup.com/neuro-oncology/advance-article/doi/10.1093/neuonc/noaf014/7978613 by guest on 28 January 2025