Novel PET and MRI based markers for predicting response to IDH inhibitors in gliomas

Background and objectives

Diffuse gliomas are the most common malignant primary brain tumors (1). According to the World Health Organization (WHO) classification, gliomas are classified based on histological and molecular characteristics. Isocitrate dehydrogenase 1 or 2 (*IDH1/2*) mutations, found in approximately 30% of diffuse gliomas (2), define two adult-type diffuse gliomas: oligodendrogliomas (grade 2 or 3) which are *IDH1/2*-mutant and exhibit a co-deletion of the 1p and 19q chromosome arms (1p/19q co-deletion), and astrocytomas (grade 2 to 4) which are *IDH1/2*-mutant (3). IDH1/2 enzymes catalyze the convertion isocitrate to alpha-ketoglutarate in the tricarboxylic acid cycle. *IDH1/2* mutations lead to the production of D2-hydroxyglutarate (D-2HG), which drives gliomagenesis through metabolic, epigenetic and microenvironment alterations (4–9). *IDH1/2*-mutant gliomas are associated with distinct clinical features, better outcomes, and improved therapy response compared to *IDH1/2*-wild-type glioblastomas (10).

IDH inhibitors (IDHi) including ivosidenib and vorasidenib recently emerged as effective treatments for patients with *IDH1/2*-mutant glioma (11). Vorasidenib demonstrated efficacy in extending progression-free survival (PFS) *vs* placebo in grade 2 *IDH1/2*-mutant gliomas, leading to its approval by the FDA. However, while some objective responses to IDHi therapy have been observed on MRI, most patients exhibit stable disease or only minor delayed responses (12–14), underscoring the limitation of standard 2D MRI-based response assessment methods (RANO criteria) in capturing the full magnitude of response to effective therapy (15). In addition, this group of patients is usually clinically stable, thus it is difficult to identify clinical correlates to response, highlighting the need for using biological changes as an early and reliable indicator of response to therapy (16). Although advanced imaging markers hold potential for improving the accuracy of response assessments, their use remains underexplored. IDHi treatment was shown to suppress D-2HG levels as detected by MR spectroscopy, (17,18) demonstrating target engagement but not predicting clinical efficacy. Early increase in relative cerebral blood volume (rCBV) post-treatment was correlated with shorter PFS (19). To date, data on the utility of positron emission tomography (PET) imaging in this context remains limited (20).

These limitations underscore the need for complementary approaches to guide clinical decision-making and future trial design. Identifying meaningful surrogate markers for response and long-term outcomes is indeed essential. To address this, our group recently performed longitudinal and multimodal monitoring of one of the largest existing cohorts of glioma patients treated with IDHi (**Figure 1**). **We will leverage this unique cohort to identify novel imaging biomarkers using longitudinal and multimodal PET and MRI assessments to predict response to IDHi. To achieve this, we will:**

- Develop an integrated database to store clinical, histomolecular, and imaging data of IDH1/2-mutant glioma patients treated with IDHi.
- Develop machine learning algorithms to analyze MRI and ^{18}F-DOPA-PET imaging data and identify predictive markers of treatment response.
- Assess the prognostic and predictive value of radiomic signatures in baseline and on-treatment PET/MRI scans.
- Correlate radiological imaging features with histomolecular markers using multi-omic analysis, and find as much as possible causality relations to go further than correlations.
- Validate identified biomarkers using independent control cohorts of glioma patients treated with other therapeutic modalities.

Methods

We conducted a longitudinal and multimodal study on one of the largest existing cohorts of glioma patients treated with IDHi (Mehdi Touat). The dataset includes: MRI scans (3-15 per patient) with 3D pre- and post-contrast T1-weighted images, 3D FLAIR/T2-weighted images, diffusion-weighted imaging (DWI), and dynamic susceptibility contrast (DSC) sequences without gadolinium preload, along with rCBV maps; ^{18}F-DOPA-PET scans (2–4 per patient) with baseline and on-treatment scans; and clinical, histomolecular and treatment response annotation.

The first step will consist of data quality check, harmonization, normalization and pre-processing using available tools such as ComBat to extract features on each modality and to serve the data all along the project and afterwards (21,22). Radiomic feature extraction, data integration and analysis will then be performed using pipelines developed in collaboration with the LIP6 lab (Isabelle Bloch). We will explore the role of novel signatures in predicting treatment outcomes (i.e. tumor radiological response, progression-free survival, overall survival) and apply deep learning algorithms such as XGBoost and LightGBM on radiological data, and develop automated MRI/PET tumor segmentation methods using convolutional neural networks taking into account the complementarity between these modalities. This will allow us to identify predictive markers of long-term benefit in the baseline MRI/PET images. We will explore the prognostic and predictive value of MRI/PET lesions texture analysis. For the subset of patients for which multimodal data is available (methylome, genome, transcriptome, tissue whole-slide histopathology images), correlations of results and signatures with histomolecular markers will be performed, or potential causality relations to go one step further. This will also allow to investigate explainability of the results and outcomes. If needed, control cohorts of patients who received treatment with other modalities will be available to test the specificity of the identify signature (n>200 patients treated with chemotherapy with available scans).

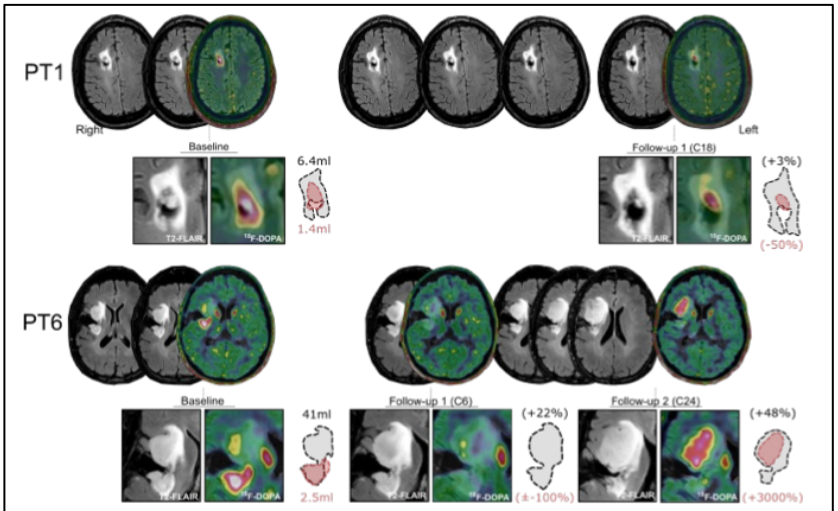

Fig. 6. Example of longitudinal monitoring with MRI and PET in two patients treated with IDH inhibitors. Scans were acquired on the same machines and lesions were segmented using semi-automated methods.

Associated teams and added value

This proposal involves two teams with complementary expertise in the development of precision medicine approaches for glioma patients (**Mehdi Touat, Co-PI**) and biomedical image analysis, artificial intelligence, and deep learning for classification and segmentation (**Isabelle Bloch, Co-PI**). The PhD student will be co-mentored by the two Co-PIs.

ICM team (Mehdi Touat, Sorbonne University, https://parisbraininstitute.org/paris-brain-institute-research-teams/bright-brain-tumor-heterogeneity-immunity-and-therapy**)** leads the RENOCLIP-LOC reference network for rare brain tumors. The team includes several researchers with extensive expertise in translational and clinical research on gliomas, preclinical research, and development of novel MRI and PET markers for primary brain tumors. The team participated to the demonstration that mutant IDH1/2 targeting is safe and provides durable tumor growth control in IDH-mutant gliomas. The project lead (Mehdi Touat) was involved in the development of IDH1/2 inhibitors as one of the main investigators from the first-in man, first-in-class, phase 1 trial of Ivosidenib (*Mellinghoff et al. J Clin Oncol 2020*) to the randomized phase 3 trial of Vorasidenib (*Mellinghoff et al. NEJM 2023*). The team manages a large cohort of *IDH1/2*-mutant glioma patients treated with IDHi (vorasidenib) as well as other standard treatment (chemotherapy, radiotherapy) and has access to clinical, histomolecular and imaging data from the cohort. Patients are consented for research which will support this proposal (protocol ONCONEUROTEK 2.0).

LIP6 team (Isabelle Bloch, Sorbonne University, https://www.lip6.fr/isabelle.bloch**)** with more than 500 members, including 200 permanent members, LIP6 is one of the largest computer science research laboratories in France. Located in the heart of Paris, LIP6 is a Joint Research Unit (UMR 7606) of Sorbonne University (SU) and the National Center for Scientific Research (CNRS). The 21 teams of the laboratory cover a wide field of computer sciences from electronics to artificial intelligence. LIP6 collaborations relate to both fundamental research (modeling and resolution of fundamental problems) and applied research (implementation and validation of solutions in real conditions). The laboratory's activities revolve around four transversal axes: artificial intelligence and data sciences; architecture, systems and networks; safety, security and reliability; theory and mathematical tools for computer science.

References

1. Ostrom QT, Price M, Neff C, Cioffi G, Waite KA, Kruchko C, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2016—2020. Neuro-Oncol 2023;25(Supplement_4):iv1-99.
2. Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, et al. IDH1 and IDH2 Mutations in Gliomas. N Engl J Med 2009;360(8):765-73.
3. Louis DN, Perry A, Reifenberger G, Von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol (Berl) 2016;131(6):803-20.
4. Dang L, White DW, Gross S, Bennett BD, Bittinger MA, Driggers EM, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature 2009;462(7274):739-44.
5. Ruiz-Rodado V, Malta TM, Seki T, Lita A, Dowdy T, Celiku O, et al. Metabolic reprogramming associated with aggressiveness occurs in the G-CIMP-high molecular subtypes of IDH1mut lower grade gliomas. Neuro-Oncol 2020;22(4):480-92.
6. Grassian AR, Parker SJ, Davidson SM, Divakaruni AS, Green CR, Zhang X, et al. IDH1 mutations alter citric acid cycle metabolism and increase dependence on oxidative mitochondrial metabolism. Cancer Res 2014;74(12):3317-31.
7. Wakimoto H, Tanaka S, Curry WT, Loebel F, Zhao D, Tateishi K, et al. Targetable Signaling Pathway Mutations Are Associated with Malignant Phenotype in IDH -Mutant Gliomas. Clin Cancer Res 2014;20(11):2898-910.
8. Turcan S, Rohle D, Goenka A, Walsh LA, Fang F, Yilmaz E, et al. IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. Nature 2012;483(7390):479-83.
9. Xu W, Yang H, Liu Y, Yang Y, Wang P, Kim SH, et al. Oncometabolite 2-Hydroxyglutarate Is a Competitive Inhibitor of α-Ketoglutarate-Dependent Dioxygenases. Cancer Cell 2011;19(1):17-30.
10. Tesileanu CMS, Dirven L, Wijnenga MMJ, Koekkoek JAF, Vincent AJPE, Dubbink HJ, et al. Survival of diffuse astrocytic glioma, IDH1/2 wildtype, with molecular features of glioblastoma, WHO grade IV: a confirmation of the cIMPACT-NOW criteria. Neuro-Oncol 2020;22(4):515-23.
11. Reitman ZJ, Jin G, Karoly ED, Spasojevic I, Yang J, Kinzler KW, et al. Profiling the effects of isocitrate dehydrogenase 1 and 2 mutations on the cellular metabolome. Proc Natl Acad Sci 2011;108(8):3270-5.
12. Mellinghoff IK, Penas-Prado M, Peters KB, Burris HA, Maher EA, Janku F, et al. Vorasidenib, a dual inhibitor of mutant IDH1/2, in recurrent or progressive glioma; Results of a first-in-human phase I trial. Clin Cancer Res 2021;27(16):4491-9.
13. Mellinghoff IK, Lu M, Wen PY, Taylor JW, Maher EA, Arrillaga-Romany I, et al. Vorasidenib and ivosidenib in IDH1-mutant low-grade glioma: a randomized, perioperative phase 1 trial. Nat Med 2023;29(March).
14. Mellinghoff IK, Ellingson BM, Touat M, Maher E, De La Fuente MI, Holdhoff M, et al. Ivosidenib in isocitrate dehydrogenase 1-mutated advanced glioma. J Clin Oncol 2020;38(29):3398-406.
15. Wen PY, van den Bent M, Youssef G, Cloughesy TF, Ellingson BM, Weller M, et al. RANO 2.0: Update to the Response Assessment in Neuro-Oncology Criteria for High- and Low-Grade Gliomas in Adults. J Clin Oncol 2023;41(33):5187-99.
16. Ellingson BM, Kim GHJ, Brown M, Lee J, Salamon N, Steelman L, et al. Volumetric measurements are preferred in the evaluation of mutant IDH inhibition in non-enhancing diffuse gliomas: Evidence from a phase I trial of ivosidenib. Neuro-Oncol 2022;24(5):770-8.
17. Andronesi OC, Kim GS, Gerstner E, Batchelor T, Tzika AA, Fantin VR, et al. Detection of 2-Hydroxyglutarate in IDH -Mutated Glioma Patients by In Vivo Spectral-Editing and 2D Correlation Magnetic Resonance Spectroscopy. Sci Transl Med 2012 ;4(116).
18. Di Stefano AL, Nichelli L, Berzero G, Valabregue R, Touat M, Capelle L, et al. In Vivo 2-Hydroxyglutarate Monitoring With Edited MR Spectroscopy for the Follow-up of IDH-Mutant Diffuse Gliomas: The IDASPE Prospective Study. Neurology 2023;100(1):e94-106.
19. Cho NS, Hagiwara A, Eldred BSC, Raymond C, Wang C, Sanvito F, et al. Early volumetric, perfusion, and diffusion MRI changes after mutant isocitrate dehydrogenase (IDH) inhibitor treatment in IDH1-mutant gliomas. Neuro-Oncol Adv 2022;4(1):vdac124.
20. Galldiks N, Werner JM, Stetter I, Puhr HC, Nakuz TS, Stoffels G, et al. Evaluation of early metabolic changes following vorasidenib using FET PET in patients with IDH -mutant gliomas. Neuro-Oncol Adv 2024;vdae210.
21. Orlhac F, Eertink JJ, Cottereau AS, Zijlstra JM, Thieblemont C, Meignan M, Boellaard R, Buvat I. A Guide to ComBat Harmonization of Imaging Biomarkers in Multicenter Studies. J Nucl Med 2022;63(2):172-179.
22. Beer JC, Tustison NJ, Cook PA, Davatzikos C, Sheline YI, Shinohara RT, Linn KA; Alzheimer's Disease Neuroimaging Initiative. Longitudinal ComBat: A method for harmonizing longitudinal multi-scanner imaging data. Neuroimage 2020;220:117129.