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The potential of amino acid PET imaging for prediction and monitoring of vorasidenib response in *IDH*-mutant gliomas

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Isocitrate dehydrogenase (*IDH*)-mutant gliomas are tumors of the central nervous system (CNS) affecting mainly young adults, which typically progress over years to develop increasing symptoms and ultimately fatal outcomes. For many years, standard treatments for *IDH*-mutant gliomas encompassed surgical resection, radiotherapy, and chemotherapy. Recently, the INDIGO trial has shown that the mutant IDH protein inhibitor vorasidenib significantly improves progression-free survival in patients with *IDH*-mutant grade 2 astrocytoma or oligodendroglioma per World Health Organization 2016 classification without contrast enhancement on MRI and without prior treatment with radiotherapy or chemotherapy.[1] Based on the results of the INDIGO trial, implementation of vorasidenib as a novel treatment option in *IDH*-mutant gliomas may be expected pending regulatory approvals by competent authorities. However, important questions on patient selection, response prediction, and disease monitoring remain. Here, we would like to draw attention to a so far understudied, but in our view highly promising role of molecular positron emission tomography (PET) imaging using amino acid tracers for the evaluation of diffuse gliomas in the context of the emerging treatment option with IDH inhibition.

Imaging of gliomas is usually performed using MRI. However, MRI is limited by ambiguity with regard to the delineation of glioma extent and differentiation of post-therapeutic changes (pseudo-progression, radionecrosis) from actual tumor progression. Modern molecular imaging utilizing PET and specific tracers allows more sophisticated and direct visualization of tumor cell pathophysiology, activity, and metabolism. For gliomas, amino acid or amino acid analogue tracers including ^{11}C-methionine ([^{11}C]MET), ^{18}F-fluoroethyl-L-tyrosine ([^{18}F]FET), ^{18}F-dihydroxyphenylalanine ([^{18}F]F-DOPA), or anti-1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid ([^{18}F]FACBC or Fluciclovine) show increased uptake in tumor cells due to the overexpression of L-amino acid transporters and allow visualization of tumor areas with favorable tumor-to-background contrast in comparison to healthy CNS tissue.[2] Amino acid PET imaging, most commonly utilizing [^{18}F]FET, is therefore increasingly used to aid clinical management of glioma patients, for example, for the planning of neurosurgical procedures, radiotherapy planning, or for differentiation of tumor progression from pseudo-progression, reactive changes, and radionecrosis.[2] Within diffuse gliomas, there is a positive correlation between PET uptake intensity and tumor grade (Figure 1).[3] Overall, the majority of diffuse gliomas shows uptake of amino acid tracers with PET-positivity rates reported to be 70%–80% for grade 2 gliomas and around 90% of grade 3 and 4 gliomas, with oligodendrogliomas showing higher uptake values than astrocytomas.[4] So far, however, no data on amino acid PET imaging in patients exposed to IDH inhibitors are available.

So, how may amino acid PET imaging help to address the open questions regarding the selection and follow-up of patients treated with vorasidenib? In the INDIGO trial, a specific patient population with grade 2 *IDH*-mutant tumors was enrolled. Patients had to have grade 2 *IDH*-mutant glioma with measurable disease lacking contrast enhancement on MRI, at least 1 prior surgery, no other prior anticancer therapy, a Karnofsky performance status of 80 or more, and could be randomized in a time window of between 1 and 5 years after the most recent surgery. Exclusion of patients with contrast media uptake on MRI was based on the previous observation that both, the IDH inhibitor ivosidenib and vorasidenib, showed greater activity against nonenhancing gliomas than against enhancing gliomas.[5,6] This specific patient selection resulted in the proof of activity of vorasidenib in grade 2 tumors, but will restrict it as a treatment option to the patient population mentioned above. Given the fact that tumor grading is prone to inaccuracy due to interrater variability, sampling errors, and ambiguous histological definitions,[7] and that even the

definition of a contrast-enhancing glioma can be equivocal, this has major implications, as a nuance of a single parameter may circumvent individual patients from a potentially effective therapy. A binary classification such as the differentiation between a grade 2 and 3 furthermore does not reflect the biological continuum of tumor aggressiveness. Therefore, additional surrogate markers reflecting tumor aggressiveness could optimize patient selection and warrant further investigation. In our view, amino acid PET imaging is a potential biomarker, as it allows noninvasive in vivo visualization of tumor activity and significantly correlates with tumor malignancy. While low-grade gliomas usually show relatively low amino acid uptake, grade 3 and 4 gliomas are characterized by high uptake intensity (Figure 1). Notably, there is, however, a high overlap of uptake intensity between tumor grades, resulting in the occurrence of patients with a grade 3 diagnosis upon histology but a lack of signs of malignancy on amino acid and vice versa (Figure 2). If the activity of vorasidenib is indeed limited in more aggressive tumors, low amino acid uptake at baseline in grade 3 or contrast-enhancing gliomas may correspond to a less aggressive natural course, similar to that of the INDIGO population. As no information on vorasidenib efficacy is available in patients with a newly diagnosed grade 3 or 4 *IDH*-mutant tumor, in contrast-enhancing tumors, and in recurrent tumors after prior radio- and/or chemotherapy, there is a need to perform additional prospective clinical trials in these patient populations. Given the presumed broader range of biological and clinical behaviors in these patients as compared to that of the selected INDIGO patient group, such trials should incorporate strong translational programs to identify suitable biomarkers such as amino acid PET for response prediction and early response assessment. Concerning follow-up and disease monitoring, metabolic changes on PET images, that is, occurrence of new PET-positive areas or changes of preexisting PET-positive areas, may occur earlier than morphologic changes on MRI and may therefore help to identify responders or nonresponders more timely or more accurately than anatomical imaging alone.[8]

Prospective investigation of amino acid PET for response prediction and response monitoring will help to evaluate and translate the full potential of imaging in this area. It is to be expected that in the upcoming years, many glioma patients worldwide will be treated with vorasidenib within and outside of clinical trials. Given the possibility of more informative visualization of gliomas presented by molecular imaging, we feel that PET applications should be systematically studied and, in particular, should be incorporated into protocols of upcoming clinical trials for patients with *IDH*-mutant gliomas. The recently proposed PET RANO 1.0 criteria provide the framework for the structured implementation of amino acid PET imaging into clinical trials.[9] Furthermore, additional noninvasive methods of metabolic imaging including MR spectroscopy for the measurement of 2-hydroxyglutarate levels may be of value to assess tumor burden, biology, and response to therapy with IDH inhibitors.[10]

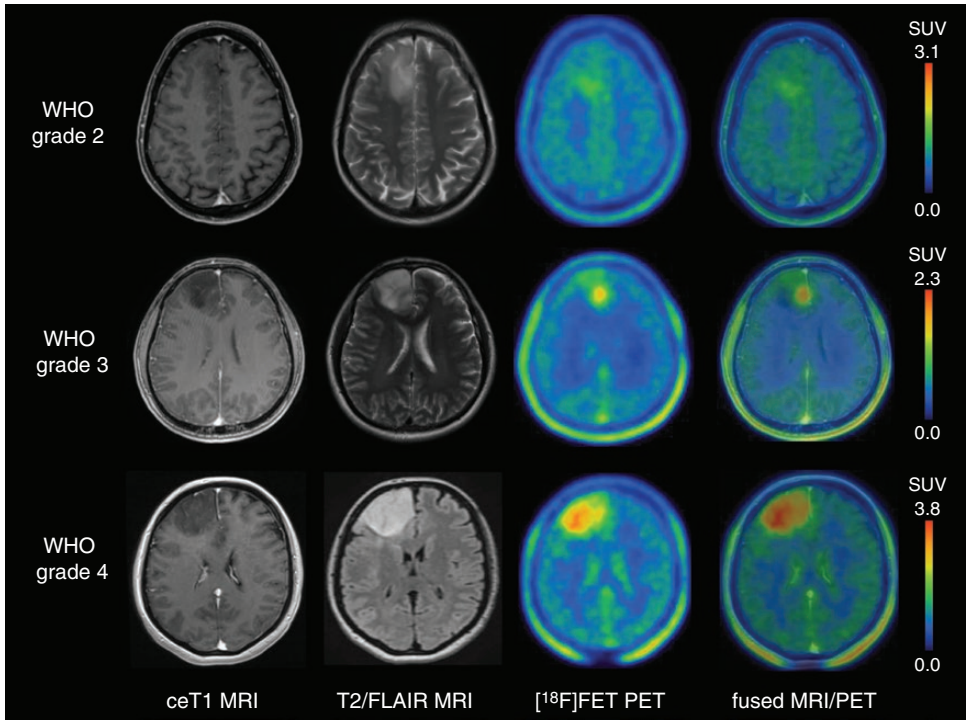

Figure 1. Examples of patients with CNS WHO grade 2, 3, and 4 astrocytoma, *IDH*-mutant, and not 1p/19 codeleted: [^{18}F]FET PET scans show typically a positive correlation between uptake intensity and tumor malignancy, irrespective of the presence of contrast enhancement.

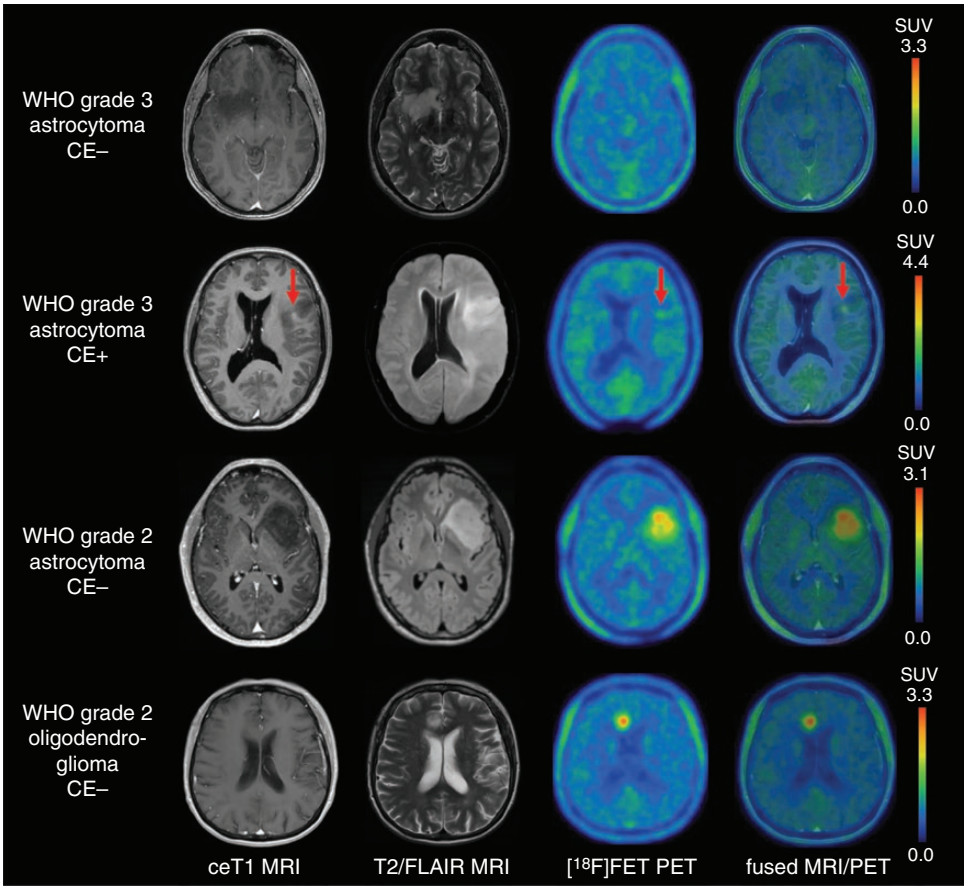

Figure 2. Examples of *IDH*-mutant glioma patients with diverging biomarker characteristics on histology, MRI, and [^{18}F]FET PET: (A) and (B) show WHO grade 3 glioma with low uptake intensity on [^{18}F]FET PET despite the presence of contrast enhancement in (B) (see arrow), suggesting low biological malignancy based on PET characteristics. Contrariwise, (C) and (D) show WHO grade 2 glioma without contrast enhancement on MRI with high uptake intensity on [^{18}F]FET PET, which is usually associated with higher tumor grades.

Conflict of interest statement

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