Targeted radionuclide therapy for gliomas: emerging clinical trial landscape

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Key words

Brain, nuclear, radioligand, study, tumor

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Key points

Radionuclide therapy is a type of targeted anti-cancer therapy.

Brain tumors such as meningiomas or gliomas may be targeted by radionuclide therapy.

Several candidate target molecules for radionuclide therapy are explored in clinical trials.

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Conflicts of Interest

MW has received research grants from Novartis, Quercis and Versameb, and honoraria for lectures or advisory board participation or consulting from Anheart, Bayer, Curevac, Medac, Neurosense, Novartis, Novocure, Orbus, Pfizer, Philogen, Roche and Servier.

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Summary

According to the new WHO classification of 2021, gliomas are a heterogeneous group of tumors with very different histology, molecular genetics and prognoses. In addition to glioblastomas, the most common gliomas, there are also numerous less common gliomas, some of which have a very favorable prognosis. Targeted radionuclide therapy is a therapeutic option that can be attractive if a tumor can be targeted based on its molecular characteristics. It is particularly useful when tumors cannot be completely resected or when conventional imaging does not fully capture the extent of the tumor. Numerous approaches to radionuclide therapy for gliomas are in early development. The most advanced approaches for patients with gliomas in the clinic employ L-type amino acid transporter 1 as an uptake mechanism for radiolabeled amino acids or target somatostatin receptor 2 or gastrin-releasing peptide receptor. Here, we discuss the various target structures of radionuclide therapy in gliomas and provide an outlook for which glioma entities radionuclide therapy could most likely provide a therapeutic alternative.

Keywords

atrocytoma; glioblastoma; oligodendroglioma; personnalized medicine; theranostic

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Introduction

Gliomas are the most common brain tumors. The most common types of glioma in adulthood are glioblastoma which is now defined as a tumor lacking mutations in the isocitrate dehdrogenase (IDH) 1 and 2 genes, IDH-mutant astrocytomas, and IDH-mutant and 1p/19q-codeleted oligodendrogliomas. Furthermore, there are several more recently defined rare subtypes of gliomas, mostly affecting children.

Targeted radionuclide therapy (RLT) can be conceptualized as an approach of precision medicine that relies on recognizing and subsequently treating neoplastic disease based on a defined molecular target. In contrast to classical targeted therapy in oncology, radionuclide therapy does not depend on a biological role of the target but merely its presence in the tumor. Radionuclide therapy relies on three components, a radioisotope, a linker and the cell-targeting molecule, the ligand. For each of these components variations exist that influence target engagement and therapeutic potency. The cell-targeting molecule may be a peptide (peptide receptor radionuclide therapy), monoclonal antibody (radioimmunotherapy), or a molecule essential for cell functions (radioactive iodine therapy). Most current available radiopharmaceuticals utilize β-emitting isotopes such as iodine-131 [^{131}I], yttrium-90 [^{90}Y] or lutetium-177 [^{177}Lu], but α-emitting isotopes employing higher energy doses (e.g., actinium-225 [^{225}Ac], radium-223 [^{223}Ra]) or Auger electrons (e.g., iodine-125 [^{125}I], indium-111 [^{111}In]) are under development. Radionuclide therapy is thus intimately linked with the field of theranostics that has only recently received major attention in Neuro-Oncology [1]. A topic of special interest for succesful application of theranostics in Neuro-Oncology concerns restrictions of drug delivery imposed by the blood brain barrier, which needs to be considered for rational design and selection of radionuclide therapies for clinical development in patients with gliomas.

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After the first clear successes of radionuclide therapy in solid tumors, namely neuroendocrine tumors and prostate cancer [2 3 4], there has been growing interest in the development of such therapies for tumors that have previously been relatively refractory to systemic pharmacological treatment approaches, e.g., those tumors for which no specific pharmacological vulnerabilities have been identified. Specifically in the field of neuro-oncology, it should be noted that the neurotoxicity of the therapy must also be monitored in the long-term because most patients who may be eligible for radionuclide therapy have probably been previously exposed to local radiotherapy when used in the recurrent setting, or will probably be exposed to local radiotherapy if used in the newly diagnosed setting. Carefully planned, controlled clinical studies with prior demonstration of target expression with the aim of patient enrichment will be necessary to establish this therapy (Table). The logistical challenges should not be underestimated, especially when it comes to patients in reduced general, neurological and especially cognitive condition.

Generally, in patients with extracranial cancer, e.g., in patients with prostate cancer undergoing PSMA-directed radionuclide therapy (see below), higher standardized uptake values (SUV) at baseline are linked to improved outcome [5 6]. The optimal SUV threshold for radionuclide therapy in patients with primary brain tumors at baseline potentially predicting a favorable outcome remains to be defined and may vary depending on several factors including the type of radionuclide therapy, the tumor type, and specific treatment protocols. With the targeted radionuclide therapy approach even an individual dose optimization in future might also be foreseeable in brain tumor therapy [7 8].

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Cell surface targets

L-type amino acid transporter 1 (LAT1)

One of the oldest approaches of radionuclide therapy makes use of the activity of LAT1 expressed at the surface of glioma cells, relying on the same molecular pathway as amino acid positron emission tomography (PET) and the ability of radiolabeled amino acids to penetrate the blood brain barrier. ^{123}I-L-4-Iodophenylalanine, an analog of the natural amino acid L-phenylalanine, had been explored initially as a diagnostic tool for improved detection of higher grade gliomas using single photon emission computed tomography (SPECT) imaging [9] [10]. Moving from diagnostics to therapeutics by exchanging the isotope to 4-L-[^{131}I]Iodophenylalanine ([^{131}I]IPA), which harbors a β-emitting ^{131}Iodine atom in position 4 of its phenyl ring, [^{131}I]IPA was demonstrated to suppress the growth of experimental gliomas in rodents when administered alone or in combination with external radiotherapy [11] [12]. Proof-of-concept of using [^{131}I]IPA for the treatment of gliomas was reported in two patients already in 2011 [13], but it took several years until this approach was finally explored in clinical trials. The IPAX-1 phase 1 trial (NCT03849105) explored [^{131}I]IPA in combination with external radiotherapy in patients with recurrent glioblastoma and has completed accrual. The IPAX-2 phase 1 trial (NCT05450744) explores [^{131}I]IPA in combination with external radiotherapy and temozolomide in patients with newly diagnosed glioblastoma and is currently enrolling.

Somatostatin receptor (SSTR) type 2

SSTR2 is a receptor for somatostatin and may overall be the most established target for targeted radionuclide therapy. Lutetium oxodotreotide ([^{177}Lu]Lu-DOTA-TATE) has been approved in Europe and the US for the treatment of SSTR2-positive gastroenteropancreatic

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neuroendocrine tumors based on the results of the phase III NETTER-1 trial [2] [3] and is now being investigated for other indications such as meningioma [14] [15].

SSTR2 protein has been described in gliomas by immunohistochemistry two decades ago and attributed mainly to tumor cells [16], but the tumor microenvironment was much less considered an important compartment than today. A follow-up study challenged the role of SSTR2 in glioblastoma and reported overall low expression levels in tumor cells and also myeloid cells, with higher expression on endothelial cells; moreover, immunohistochemical findings did not correlate well with retention of [^{68}Ga]Ga-DOTA-TATE [17]. Another study reported negative SSTR2 staining in the majority of glioblastomas, but strong expression in oligodendrogliomas [18]. Regardless of these studies that challenge the role of SSTR2 as a target in glioblastoma, the first three patients with recurrent glioblastoma treated with [^{90}Y]Y-DOTATOC (edotreotide, another octreotide conjugate similar to DOTA-TATE) were reported to have experienced either complete (n=1) or partial (n=2) responses [19]. A subsequent study explored the efficacy of [^{177}Lu]Lu-DOTATATE in 8 patients each with newly diagnosed or recurrent glioma and reported 2 complete and 3 partial remissions based on RANO MRI criteria [20]. A dose-finding study and evaluation of [^{177}Lu]Lu-DOTATATE in combination with standard of care in newly diagnosed glioblastoma and as a single agent in recurrent glioblastoma is ongoing (NCT05109728) (Figure 1) [21].

Prostate-specific membrane antigen (PSMA)

Prostate-specific membrane antigen (PSMA), a type II transmembrane glycoprotein, was first described as a protein expressed in benign and malignant prostate epithelium, with substantially higher expression in prostate cancer compared with normal prostate tissue. PSMA is also expressed in several non-prostatic tissues such as salivary glands, kidneys, and gastrointestinal mucosa as well as in various other tumors, including brain tumors, allowing the detection by PET imaging [22] [23] [24].

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PSMA protein was almost uniformly detected in glioblastoma samples at diagnosis and in the recurrent setting and expression varied both in the endothelial and non-endothelial cells, but the authors refrained from speculating whether non-endothelial cells were all tumor cells [25].

PSMA has become the second success of radionuclide therapy in general: Lutetium vipivotide tetraxetan ([^{177}Lu]Lu-PSMA-617) has been approved for PSMA-positive metastatic, castration-resistant prostate cancer based on the phase III VISION trial [26]. Accordingly, there is now interest in exploiting PSMA as a target in other PSMA-expressing cancers [27 28]. Proof of concept of targeting PSMA by [^{177}Lu]Lu-PSMA-617 radionuclide therapy was provided in a single case study [29], but the outcome was not reported. Another patient with recurrent glioblastoma was treated with [^{177}Lu]Lu-PSMA-617 and apparently responded to this treatment [30]. Overall, PSMA remains largely a vascular target in glioblastoma. While detection of glioblastoma may therefore be feasible using PSMA labeling (Figure 2), doubts remain whether tracer uptake and exposure would be sufficient for the actual treatment of gliomas.

Gastrin-releasing peptide receptor (GRPR)

GRPR is the receptor for gastrin-releasing peptide and a member of the G protein-coupled receptor family. GRPR has been reported to be highly expressed on various types of gliomas, but data remain inconclusive because of concerns regarding antibody specificity (unpublished observations). A 100% positive staining rate for GRPR in gliomas using the rabbit polyclonal antibody 13339 from Abcam was reported in 2010; both tumor and tumor-associated endothelial cells were GRPR-positive [31]. Similarly, immunostaining using the rabbit anti-human polyclonal antibody PA5–256791 (Thermo Fisher Scientific) yielded positive staining in all of 14 samples [32]. In contrast, we have detected only very low levels of

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GRPR mRNA expression in cultured glioma cells (unpublished). A single cell line study claimed induction of senescence when GRPR expression was reduced siRNA [33].

In an early GRPR PET study from China using a ^{68}Ga-labeled bombesin peptide derivative PET tracer, NOTA-Aca-BBN(7–14) ([^{68}Ga]Ga-bombesin), uptake in normal brain was very low whereas all of 12 examined glioma patients were PET-positive. Furthermore, intensity of immunohistochemical staining was reported to correlate with SUV [32]. A comparative study of [^{18}F]FDG-PET and GRPR-PET using another ^{68}Ga-labeled bombesin analog, [^{68}Ga]Ga-BZH3, in 15 patients with recurrent glioma revealed enhanced [^{68}Ga]Ga-BZH3 uptake in 10 patients and superior tumor delineation compared with [^{18}F]FDG-PET [34].

GRPR is therefore also currently being considered as a target for targeted radionuclide therapy. The most advanced molecule, NeoBOMB1, now referred to as NeoB, is a high-affinity antagonist for GRPR which is radiolabeled with ^{68}Ga for diagnostics and with ^{177}Lu as a therapeutic agent [35 36 37]. A phase 1 study of NeoB in various solid tumors including glioblastoma is ongoing (NCT03872778).

Our failure to detect GRPR mRNA or protein *in vitro* and the lack of contemporary immunohistochemistry studies on GRPR in gliomas *in vivo* suggest that GRPR expression is rapidly lost *in vitro* or that the positive signal on PET imaging stems from non-tumor cells, including endothelial cells, or even recognition by the radioligand of a different molecule or other off target bindings. The success of GRPR-directed therapy will mainly depend on the level of expression of the target. Therefore, regulatory mechanisms determining expression of GRPR on glioma cells are highly relevant, also with a view to interventions that could impact GRPR expression.

Challenges for the future development of GRPR targeting include the uncertainty regarding reliability of assessment of GRPR expression in human gliomas as well the safety of this approach, given the potential expression of GRPR in neurons [31] that remains to be corroborated.

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Other targets

Poly(adenosine diphosphate ribose) polymerase (PARP)

PARP is a DNA damage repair enzyme that has emerged as a therapeutic target for multiple cancers, including glioblastoma. The PARP gene is highly expressed in many types of cancer, but not affected by mutation or amplification, and can therefore not be considered as a tumor-specific target. Radiolabeled PARP-targeting compounds trapped in vicinity to damaged DNA might therefore selectively eliminate tumor cells. [^{123}I]I-CC1, a ^{123}I-labeled analog of the PARP inhibitor olaparib [38] [39], has been explored in various human cancer xenografts, including the U87MG glioma model. Systemic administration at well tolerated doses had variable effects and caused a modest growth delay in the U87MG model [40]. Data on the treatment of human patients with brain tumors have not been publicly reported.

Other

Several other targets for radionuclide therapy are under evaluation, including the hypoxia-associated protein carbonic anhydrase XII which is targeted by a local approach in a phase I trial (NCT05533242) [41], chemokine receptor CXCR4 or NK1R. Potential targets in the microenvironment include fibronectin or tenascin C.

Outlook

As targeted radionuclide therapy comes into the focus of neuro-oncology, the essential task will be to identify the right tumor types for available drugs and the right drug for a specific tumor. At present, it remains an open question whether the right targets for the treatment of

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common gliomas have already been identified. There may be shared targets among the most common types of gliomas, but also targets preferentially expressed by distinct types of gliomas, e.g., IDH-mutant gliomas without (astrocytoma) or with 1p/19q chromosomal codeletion, or histone-mutant gliomas. Further topics to be addressed beyond the search for the target include the limitation of off-target binding as well as penetrating the blood brain barrier which can be achieved either by appropriate design of the molecule or additional technologies such as blood brain barrier disruption, e.g., with focused ultrasound. Also the specific binding and kinetic properties will determine whether the needed dose can be delivered to the tumor without major side effects and radiation toxicity to sensitive organs. Moreover, the type of radioisotype (alpha emitter, beta emitter, Auger electrons) included within the therapeutic molecule may contribute to the efficacy or lack thereof in distinct types of gliomas. Major pharmaceutical development and preclinical modelling efforts will be required to prepare a path forward for targeted radionuclide therapy of gliomas.

Furthermore, the patient population for early clinical trials of radionuclide therapy needs to be defined. In glioblastoma, for example, the maintenance setting may be more appropriate for timing issues than the newly diagnosed or recurrent setting. The amount of tumor volume to be treated might be of critical importance for dosimetry as well. Patients with rapid neurological deterioration are not good candidates for radionuclide therapy because assessment for target expression takes time and a setting of enhanced seizure risk complicates treatment in countries where hospitalization and isolation are required. Accordingly, the introduction of targeted radionuclide therapy for patients with gliomas will require education on the part of neuro-oncologists, patients and caregivers, and the establishment of joint nuclear medicine, radiation oncology, and medical neuro-oncology teams at dedicated sites.

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Figure Legends

Figure 1. A phase Ib dose finding study assessing safety and activity of [^{177}Lu]Lu-DOTA-TATE in newly diagnosed glioblastoma in combination with radiotherapy with or without temozolomide and in recurrent glioblastoma as single agent (NCT05109728)

Figure 2. Patient with recurrent glioblastoma, IDH wildtype, CNS WHO grade 4, with focal uptake (SUV_{max} 4.9) in the PSMA PET at the anterior rim of the resection cavity.

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Table. Clinical trials of targeted radionuclide therapy for gliomas.

NCT number	Target	Title	Indication	Application	Status
NCT03849105	LAT-1	A Multi-centre, Open-label, Single-arm, Dose-finding Phase I/II Study to Evaluate Safety, Tolerability, Dosing Schedule, and Preliminary Efficacy of Carrier-added 4-L-[131I]Iodo-phenylalanine (131I-IPA), Administered as Single or Repetitive Injections in Patients With Recurrent Glioblastoma Multiforme (GBM), Concomitantly to 2nd Line External Radiation Therapy (XRT) -IPAX-1	Recurrent glioblastoma	i.v.	Closed
NCT05450744	LAT-1	A Phase 1 Safety and Dose Finding Study of 131I -TLX101 Plus Standard of Care in Patients With Newly Diagnosed Glioblastoma	Newly diagnosed glioblastoma	i.v.	Open
NCT05109728	SSTR2	A Phase Ib Dose Finding Study Assessing Safety and Activity of [177Lu]Lu-DOTA-TATE in Newly Diagnosed Glioblastoma in Combination With Radiotherapy With or Without Temozolomide and in Recurrent Glioblastoma as Single Agent	Newly diagnosed and recurrent glioblastoma	i.v.	Open
NCT03872778	GRPR	A Phase I/IIa Open-label, Multi-center Study to Evaluate the Safety, Tolerability, Whole-body Distribution, Radiation Dosimetry and Anti-tumor Activity of [177Lu]-NeoB Administered in Patients With Advanced Solid Tumors Known to Overexpress Gastrin-releasing Peptide Receptor (GRPR)	Recurrent glioblastoma	i.v.	Open

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NCT05533242	Carbonic anhydrase XII	A Phase I Trial to Determine the Maximum Tolerated Dose and Patient-specific Dosimetry of Fractionated Intracavitary Radioimmunotherapy With Lu-177 Labeled 6A10 Fab-fragments in Patients With Glioblastoma After Standard Treatment	Newly diagnosed glioblastoma after completion of maintenance temozolomide	Intra-cavitary	Open

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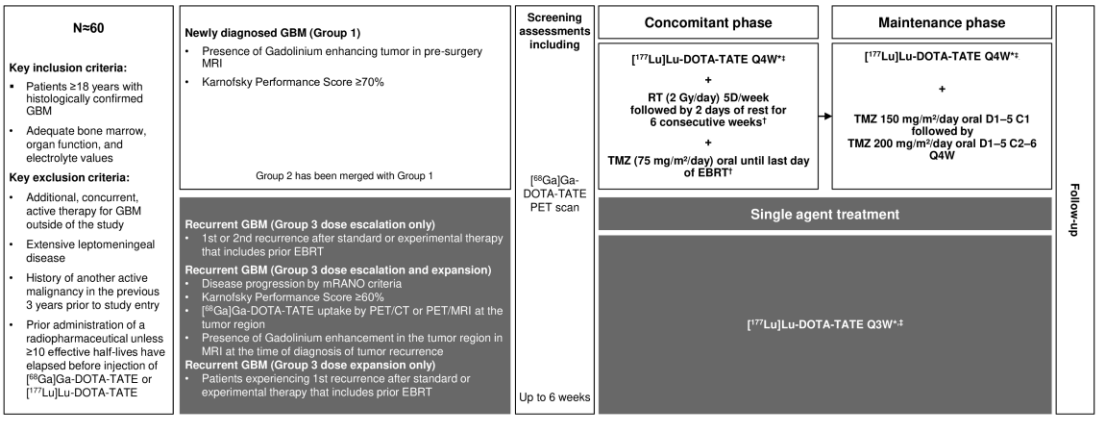
Figure 1. A phase Ib dose finding study assessing safety and activity of [^{177}Lu]Lu-DOTA-TATE in newly diagnosed glioblastoma in combination with radiotherapy with or without temozolomide and in recurrent glioblastoma as single agent (NCT05109728)



- **Primary endpoints:** Frequency of DLTs
- **Secondary endpoints:** AEs, SAEs, Overall Objective Status as per mRANO criteria, PFS, OS, PK and dosimetry of [^{177}Lu]Lu-DOTA-TATE, AEs and SAEs within 48 hours after [^{68}Ga]Ga-DOTA-TATE infusion

*Dose levels (Dose level +2: 250 mCi; Dose level +1: 200 mCi; Dose level 0: 150 mCi; Dose level −1: 100 mCi) will be assessed. †Administered 7–10 days after first administration of [^{177}Lu]Lu-DOTA-TATE treatment. ‡An infusion of sterile 2.5% Lysine - Arginine amino acid solution co-administered with each [^{177}Lu]Lu-DOTA-TATE dose for renal protection.
AE, adverse event; C, cycle; CT, computed tomography; D, day; DLT, dose-limiting toxicity; EBRT, external beam radiation therapy; GBM, glioblastoma; MGMT, O-6-methylguanine-DNA methyltransferase; mRANO, modified Response Assessment in Neuro-Oncology; MRI, magnetic resonance imaging; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PK, pharmacokinetics; QnW, every n weeks; RT, radiotherapy; SAE, serious adverse event; TMZ, temozolomide.
https://clinicaltrials.gov/ct2/show/NCT05109728; Accessed March 2024.

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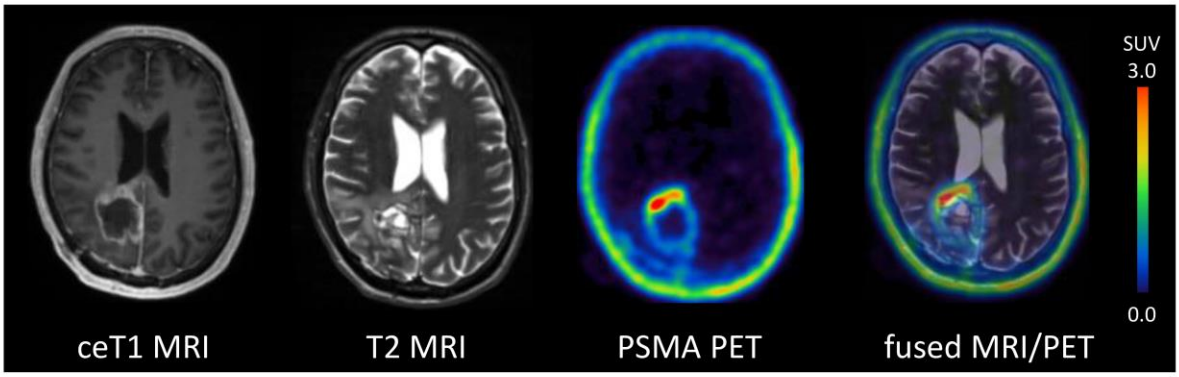

Figure 2. Patient with recurrent glioblastoma, IDH wildtype, CNS WHO grade 4, with focal uptake (SUV_{max} 4.9) in the PSMA PET at the anterior rim of the resection cavity.

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