**Supplemental Data**

**MENINGIOMAS**

*Studies in progress*

Several studies are currently in progress to prospectively evaluate in a single arm, open-label, multicenter phase II design the efficiency of $^{177}$Lu-DOTATATE peptide receptor radionuclide therapy (PRRT) in patients with progressive meningiomas including young adults (NCT03971461, NCT04082520, NCT05278208) or to compare safety and preliminary efficacy of a newly developed radiolabelled somatostatin antagonists, namely $^{177}$Lu-DOTA-JR11, as compared to those of $^{177}$Lu-DOTATOC PRRT in a phase 1 study (NCT04997317). Other ongoing studies focus on the dosimetry aspect of PRRT in meningiomas, with a phase II dosimetry-guided $^{90}$Y-DOTATOC PRRT study to limit the kidney radiation exposure monitored by somatostatin receptor (SSTR)-positron emission tomography (PET) imaging (NCT03273712), and a study employing semi-automated segmentation methods to analyze pre-therapeutic SSTR PET scans for improved dosimetry estimation (NCT05537675).

**GLIOMAS**

*Studies in progress*

**Tenascin**

Tenascin, an extracellular matrix protein, is highly expressed on the majority of high grade gliomas (80-90%) and is the most frequently investigated radioimmunotherapy target for gliomas (1,2). In the mid 90s and the beginning of the new century, locally administered $^{90}$Y- and $^{131}$I-labelled murine monoclonal antibodies (mABs) against tenascin were used in a small series of patients with newly diagnosed or recurrent glioma, showing up to 40% overall responses (3). Another study used similar mABs against tenascin, labelled with the alpha emitter $^{211}$At (4). It is important to note that these studies included only selected patients with low residual tumour volume and immediately after surgery. The main weakness in all studies is the lack of correction for residual tumour volume.
As with other radiopharmaceutical therapies, a sufficient expression of tenascin on the tumour cells is crucial for success. Therefore, pretherapeutic imaging of tenascin is essential. In this context, Jacobson et al. presented a tenascin-C aptamer as a potential PET tracer to determine tenascin expression \textit{in vivo} (5). However, no human studies have been performed so far with this tracer candidate. In particular, there is no knowledge about tracer penetration through the human blood-brain-barrier (BBB). Future studies are needed to determine whether the preliminary results can be repeated with statistical correction of residual tumour volume and less selective patient inclusion.

\textbf{Epidermal growth factor receptor (EGFR)}

An $^{125}$I-labelled murine antibody against the EGFR known as mAb425 has been used for the treatment of gliomas through multiple intravenous injections, either alone or in combination with temozolomide. This phase II study suggested a survival benefit of several months of temozolomide combined with radioimmunotherapy over radioimmunotherapy alone (6). A similar study of post-surgery radiotherapy versus post-surgery radiotherapy combined with anti EGFR radionuclide therapy was performed by Wygoda et al. (7) and showed no effect. These studies illustrate that the EGFR is of limited use as target in glioma.

\textbf{Neurokinin type 1 receptor (NK1R)}

The NK1R which is expressed in almost all gliomas, has been therapeutically targeted using $^{213}$Bi- and $^{90}$Y-DOTA-substance P. Only small patient numbers have been included (9–11). Due to the wide expression NK1R could be a potential target for radionuclide therapy. In line with the meningioma radionuclide therapy, NK1R-targeted $^{68}$Ga/$^{177}$Lu-radioconjugates have been developed (12) and research into this target is constantly evolving (13). Future studies are necessary to address the potential of NK1R.
Somatostatin receptor

There is histological evidence of SSTR expression in gliomas (14), mainly in grade 2 gliomas, but not in glioblastomas. The latter might explain why the research community is focusing its efforts on other, more ubiquitously expressed, theranostic targets across all higher-grade glioma types. Findings from a small case series indicate that local injection of $^{90}$Y-DOTATOC can provide lasting responses in progressive recurrent gliomas (15). Also, Nemati et al. showed preliminary results in a phase 1 prospective trial (16). Other studies showed mixed results (17,18). Recently, a prospective trial has been initiated to assess the safety and activity of $^{177}$Lu-DOTATATE in newly diagnosed glioblastoma patients in combination with radiotherapy, with or without temozolomide and in recurrent glioblastoma as single agent (NCT05109728). The major weakness of the application of $^{177}$Lu-DOTATE in glioma is the need for extensive BBB disruption as demonstrated by Nemati et al. (16) Therefore, general application is unlikely.

Gastrin-releasing peptide receptor (GRPR)

GRPRs are expressed in nearly all gliomas, and in 45% of medulloblastomas (see pediatric brain tumours). An ongoing first-in-human study tests the use of the GRPR-binding $^{177}$Lu-NeoB in patients with glioblastoma. Before treatment, sufficient target expression is verified by $^{68}$Ga-NeoB PET imaging. In this study, the safety, tolerability, pharmacokinetics as well as the distribution, radiation dosimetry and anti-tumoural activity of $^{177}$Lu-NeoB will be determined (NCT03872778 and NCT05739942). Currently, no efficacy results are available.

L-type amino-acid transporter 1 (LAT-1)

An ongoing study is the IPAX-1 trial (19). As known from amino acid PET imaging, many primary tumours including glioblastomas overexpress the LAT-1. $^{123}$I-iodo-phenylalanine (I-IPA) is a small-molecule amino acid derivative transported into primary brain tumour cells via the LAT-1. The above-mentioned trial is currently evaluating the
safety, tolerability and the anti-neoplastic effects of $^{131}$I-IPA combined with radiotherapy versus standard of care in the refractory setting and in newly diagnosed patients with glioblastoma. A new trial evaluating the combination with post-surgical standard of care comprised of external beam radiation therapy and temozolomide in newly diagnosed glioblastoma patients is on its way (NCT03849105 and NCT05450744). Glioma is a systemic brain disease (20) so focal disruption of the BBB is insufficient to treat all tumour cells. Therefore, LAT-1 targets can allow treatment of all tumoural cells, however at the expense of radiation exposure of the healthy brain and low residence time.

**Carbonic anhydrase XII**

6A10 Fab binds specifically to human CA XII (21). CA XII is overexpressed on primary and metastatic brain tumours, with the intensity of expression increasing with the grade of malignancy (22,23). In Germany, a study using $^{177}$Lu-6A10 Fab fragments has started in glioblastoma patients as a potential add-on after standard treatment (NCT05533242). No study results are available to date.

**Others**

Other potential theranostic targets in gliomas such as the prostate specific membrane antigen (PSMA) (24,25), matrix metalloproteinase (26), DNA Histone H1 complex (27), integrins (28), Poly ADP ribose polymerase 1 (29), chemokine receptor-4 (30,31), disialoganglioside GD2 (see brain metastases) (32) and fibroblast activation protein (33) have been investigated or are under investigation.

Boron neutron capture therapy is an alternative treatment option to increase the therapeutic ratio and has also been used in meningioma. $^{18}$F-boron phenylalanine can be applied as a surrogate marker to test the uptake of boron phenylalanine in tumours (34,35).
BRAIN METASTASES

Studies in progress

In breast cancer, glucose metabolism in the intracranial lesions as determined by $^{18}$F-FDG PET decreased as a sign of response to therapy 6 months after the administration of $^{131}$I-L19SIP which targets the extracellular matrix component fibronectin (39). Also, human epidermal growth factor receptor 2 (HER2) as target yielded encouraging results to further explore their theranostic potential with a good uptake of some radiolabeled anti-HER2 antibodies, namely $^{64}$Cu-DOTA-trastuzumab, $^{89}$Zr-trastuzumab and $^{89}$Zr-pertuzumab in brain metastases (40–42). A recent phase 1 trial identified $^{131}$I-GMIB-Anti-HER2-VHH1 as new candidate. Currently, a phase 1-2 trial using the latter is ongoing in HER2-positive metastases of breast, gastric and gastro-esophageal junction cancer (NCT04467515).

In prostate cancer brain metastases, both $^{177}$Lu-PSMA617 and $^{225}$Ac-PSMA617 were examined. The selectivity and accessibility of the target have been determined using $^{89}$Zr-IAB2M, an anti-PSMA minibody. After treatment with $^{177}$Lu-PSMA617 and $^{225}$Ac-PSMA617, a significant reduction of brain metastatic volume was observed, illustrating the therapeutic potential (43–45). However, $^{225}$Ac-PSMA617 showed significant toxicity to the salivary glands causing xerostomia as salivary glands also have high PSMA-expression (44).

Several other theranostic studies in brain metastases using a multitude of targets were carried out:

Using $^{131}$I-Me1-14 F(ab’)2, an antibody against proteoglycan chondroitin sulfate-associated protein expressed for instance by gliomas and melanomas, in patients with tumours metastasic to the central nervous system (CNS) a signal for prolonged survival has been observed in several cases (46).

A phase 1 trial evaluating $^{131}$I-TM-601, a target for matrix metalloproteinase, in patients with recurrent or refractory somatic and/or cerebral metastases of solid tumours was terminated in 2009 (NCT 00379132). No study results have been published.
Breast and bladder cancer, sarcomas, melanomas, or small cell lung carcinomas express the GD2 that recognizes IgG3 antibody (3F8). GD2 is a tumour antigen homogeneously distributed on the cell membrane of solid tumours, mainly, of neuroectodermal origin (47). Currently, the sides effect and efficiency in patients with leptomeningeal metastases from GD2-expressing solid tumours are investigated in a phase 2 trial (NCT00445965).

PEDIATRIC BRAIN TUMOURS

Studies in progress

SSTR

A recent study evaluating membranous SSTR type 2A expression with immunohistochemistry found high expression in medulloblastoma, meningioma, and some rarer embryonal tumours (48).

To date only sparse clinical data is available on the potential of PRRT targeting the SSTR in pediatric brain tumours: Menda et al. demonstrated the safety and efficacy of intravenously administered $^{90}$Y-DOTATOC therapy in pediatric patients with refractory solid tumours that were SSTR positive on pretreatment $^{111}$In-DTPA-D-Phe1-octreotide scan (49). Amongst the included patients were 1 patient with a medulloblastoma, 1 with anaplastic astrocytoma, pineoblastoma, and choroid plexus carcinoma. Beutler et al. reported a case of a patient with a complete remission of a conal medulloblastoma with consolidation using intrathecal treatment with $^{90}$Y-DOTATOC after conventional chemotherapy and resection (50). More recently, intra-therapy images in a 7-year-old girl with relapsed medulloblastoma after administration of 7.4 GBq $^{177}$Lu-PRRT for palliative purpose were reported showing intense uptake at the tumour site (51).

In line with these findings, an ongoing study is the study on $^{177}$Lu-DOTATATE for treatment of recurrent or progressive high-grade CNS tumours or meningiomas expressing SST2A (NCT05278208). Among the potentially included tumours are meningioma, medulloblastoma, anaplastic ependymoma, and refractory diffuse midline glioma. Another studies uses $^{90}$Y-DOTATOC in SSTR positive tumours such as medulloblastoma (NCT03273712). These studies will evaluate the safety and efficacy.
B7-H3

B7-H3, also known as CD276 and peripheral membrane protein on activated antigen presenting cells, is expressed on a range of solid tumours with a restricted expression on normal tissue (52). The overwhelming majority of medulloblastoma express B7-H3 (96%) (53) The use of intraventricular $^{131}$I-8H9, binding to the tumour antigen B7-H3, was explored in pediatric patients with the rare embryonal tumour with multilayered rosettes (54). A recent successful phase I study also demonstrated the safety of intraventricular radioimmunotherapy with $^{131}$I bound B7-H3 with increased survival compared to historical data (55). Tringale et al. performed a prospective study in patients with recurrent ependymoma and medulloblastoma. They demonstrated $^{131}$I B7-H3 can be safely administrated after external beam radiation therapy and no evidence of disease prior to $^{131}$I B7-H3 was associated with improved survival in medulloblastoma (56). Similar results were observed by Kramer et al (57). A phase 1 study in $^{131}$I-omburtamab delivered by CED in patients with diffuse midline gliomas H3-K27-altered is underway (NCT05063357).

Other targets

A recent and unique phase II study (58) of radioimmunotherapy with intraventricular $^{131}$I-3F8, targeting GD2, revealed the technique to be safe and having potential therapeutic benefit as adjuvant treatment. For instance, in medulloblastoma, it could be potentially useful in maintaining remission.

GRPR which is ectopically expressed/overexpressed in 100% in glioma cells, is also present in 45% of medulloblastoma and can therefore be a promising target in the latter (59). For optic pathway glioma GRPR-targeted therapy might have potential (60) Also, CXCR4 is known to be expressed on medulloblastoma (61)

Other targets such as CuCl$_2$ (62) have been examined for their potential for theranostics in pediatric brain tumours, however further studies are needed to determine their clinical value.


