Theranostics in neuro-oncology: heading towards new horizons

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ABSTRACT

Therapeutic approaches for brain tumours remain a challenge, with considerable limitations regarding delivery of drugs. There has been renewed and increasing interest in translating the popular theranostic approach well known from prostate and neuro-endocrine cancer to neuro-oncology. Although far from perfect, some of these approaches show encouraging preliminary results for instance for meningioma and leptomeningeal spread of certain pediatric brain tumours. In brain metastases and gliomas, clinical results so far fail to impress. Perspectives on these theranostic approaches regarding meningiomas, brain metastases, gliomas and common pediatric brain tumours will be discussed. For each tumour entity, the general context, an overview of the literature available to date and future perspectives will be provided. Ongoing studies will be discussed in the supplementary material.

As most theranostic agents are unlikely to cross the blood-brain barrier, the delivery of these agents will be dependent on the successful development and clinical implementation of techniques enhancing the permeability and retention. Moreover, the international community should strive towards sufficiently large and randomized studies in order to generate high level evidence on theranostic approaches with radioligand therapies in CNS tumours.

INTRODUCTION

In the last decade we have observed a huge step forward in the treatment options for a wide range of tumours both in terms of survival and quality of life. However, therapeutic approaches for brain tumours remain a challenge, with considerable limitations regarding delivery of drugs. Due to the recent success of theranostics in oncology with ^{177}Lu-DOTATATE for neuroendocrine tumours (NET) and ^{177}Lu-prostate specific antigen (PSMA) for prostate cancer resulting in Food and Drug Administration and European Medicines Agency approvals, there has been renewed and increasing interest in translating the theranostic approach to neuro-oncology (1–3). Extra cranially, such approaches are generally well tolerated, delivering high absorbed dose with a low dose rate, specifically to the tumour, even on anatomically complex lesions, with a targeting that preserves the surrounding parenchyma. The latter is of course of high critical importance for brain interventions. Theranostics are also particularly adapted to treat multiple tumoural lesions in the whole body at the same time, e.g. in metastatic disease. An added benefit is the possibility to identify patients with high target availability by using the corresponding imaging ligand, often the 'diagnostic twin', e.g. the positron emitting version suitable for Positron Emission Tomography (PET), of the therapeutic ligand.

In this paper theranostic approaches in brain tumours will be discussed. For each tumour entity, the general context and future perspectives will be provided. In the supplementary material an overview of the literature available to date and ongoing studies is provided. Table 1 gives an overview of potential molecular targets for theranostic applications in neuro-oncology. Moreover, strategies to overcome the blood-brain-barrier (BBB) and blood-tumour-barrier (BTB) will be briefly discussed.

BLOOD-BRAIN AND BLOOD-TUMOUR BARRIER

The main obstacle in neuro-oncology compared to other solid tumours is getting therapeutics over the BBB. Brain tumours are known to alter the physiological BBB integrity, some producing a highly heterogeneous vasculature known as the BTB. This altered physiological BBB and BTB integrity is heterogenous between metastatic lesions and various primary tumour types and shown by contrast enhancement on MRI (4). Several strategies have been developed to bypass the BBB/BTB (4–6): local administration (including intraventricular administration), convection-enhanced delivery (CED), focused ultrasound (FUS), and innovatively designed monoclonal antibodies and neural stemcells. Below we will describe some of these mechanisms in more detail (Figure 1). Most of these techniques are complex and, as such, can only be performed in expert centres.

Therapeutics can be directly administered into the tumour or surgical/anatomical cavities (such as intraventricular administration using a catheter). Compared to systemic therapy, the toxicity to the body is thereby reduced. Nevertheless, a certain grade of hematologic and neurologic toxicities can still be present through dissemination of the compound into the blood, catheter dislocation and leakage in other vital areas (7).

CED represents a well-studied way to bypass BBB in which one or more microcatheters are implanted into and around the tumour. CED, mostly of chemo- and immunotherapeutic drugs, has a long history and has been repeatedly used safely in clinical trials in both adults and pediatric patients (8,9). However, no durable clinical impact despite multiple clinical trials has been seen (10). Due to its complex nature, studies vary with respect to for instance agent, infusion volume and rate and cannula design. CED has specific issues due to slow and

continuous delivery with varying clearance via the interstitial fluid and back into the bloodstream over the BBB. Personalized image-guided drug delivery using PET, pre-, during and post-CED, could increase the potential of this technique. Upfront pharmacokinetic imaging, especially for large-size drugs such as monoclonal antibodies, using imaging ligands with a long half-life could be used for patient selection, treatment planning and dose scheduling. A recent study in murine models of diffuse intrinsic pontine glioma revealed significant variability in post-CED clearance within and across injection cohorts with post-CED PET. This was probably due to heterogeneity of and from inherent technical variance. The use of PET-guided CED dosing schedules did however result in survival prolongation (11). Clinical studies combining CED with labeled drugs have recently been performed. Safety and feasibility were shown in a study evaluating CED of ^{124}I-8H9, a monoclonal antibody targeting the glioma-associated B7-H3 antigen in children with diffuse midline glioma (5). Safety and feasibility were also confirmed in glioblastoma (6). When using ligands with simultaneous diagnostic-theranostic characteristics such as [^{124}I] (12), post-therapy dosimetry can be used to not only validate the principles of CED, but for verification and adjustment of dosing schedule and treatment plan.

An alternative method to enhance radio-isotope-labeled drug delivery to the brain is focused ultrasound mediated blood-brain barrier opening (FUS-BBBO). FUS-BBBO employs low frequency ultrasound waves inducing stable cavitation of intravenously injected microbubbles (MBs), resulting in a BBB opening (BBBO) (13) Mechanical interaction of MBs with the BBB temporarily cause the dislocation of tight junctions between endothelial cells and increased transcytosis, thereby enhancing permeability into the brain parenchyma (13,14).

This technique has so far only been explored in limited clinical trials (15,16) and currently different technical implementations of this technology exist. Technical implementations are diverse which range from implanted ultrasound transducer designs (17) appearing favorable for cost-effective repetitive openings of the supratentorial brain to fully MR-guided transcranial (and thus non-invasive) devices (18) which appear favorable for deep seated brain stem/thalamic lesions. While this technology has clinically not yet been used in combination with a theranostic approach, preclinical studies demonstrating enhanced delivery of monoclonal antibodies to the parenchyma have shown considerable promise (19–21).

Innovative designs of monoclonal antibodies also show promise to pass the physiological BBB such as nanobodies and antibodies modified into a bispecific format (22,23). Additionally, various transporters such as the L-type amino-acid transporter 1 (LAT-1) are present on the physiological BBB. These transporters deliver essential nutrients and energy and can be used in a carrier-mediated manner to cross the BBB. LAT-1 is very promising for carrier-mediated brain drug delivery: it has a rapid BBB exchange, accepts various amino-acids and analogs and a transient disruption in essential amino-acid transport will not cause irreversible brain damage (24). The use of LAT1 targets is further discussed in the glioma section.

MENINGIOMAS

Context

Meningiomas are the brain tumours in which peptide receptor radionuclide therapy (PRRT) has been most performed so far. They represent 30% of primary intracranial tumours. While approximately 80% of these tumours are benign (central nervous system (CNS) world health organization (WHO) grade 1), the remaining cases are classified as high-grade meningiomas (related to CNS WHO grade 2 and 3) (25,26). Treatment options mainly encompass neurosurgical resection and external beam irradiation. PRRT is currently considered in meningiomas when they cannot be treated by surgery or conventional radiation therapy irrespectively of their grade (27,28). PRRT targets the somatostatin receptor (SSTR) type 2, since meningiomas almost invariably express SSTR type 2 (29) which can be monitored with SSTR-targeted PET imaging. Patients with grade 1, well differentiated and thus generally less aggressive meningiomas, exhibit higher levels of SSTR and may have the best responses to PRRT (30). ^{90}Y-SSTR- and ^{177}Lu-SSTR-targeted PRRT similarly combine a molecular vector targeting the SSTR receptor with a β-emitting radioactive label and are used in PRRT of meningiomas.

Perspectives

Most of the available data on PRRT in meningiomas are in patients at a late course of the disease (27,30), a disease stage in which the efficacy of the treatment is potentially limited. Achieving partial response after PRRT (31) or other systemic therapies (32) in meningiomas is rare. It might therefore be advantageous to start PRRT earlier in the disease course (after surgery), i.e. before patients develop treatment-refractory, progressive, and extensive disease. Moreover, identification of potentially dedifferentiated meningiomas with poorer

prognosis (lesions with high ^{18}F-FDG uptake, low SSTR uptake) with multitracer pretherapeutic SSTR-PET and ^{18}F-FDG PET imaging (33) could help to select patients for whom PRRT could provide more benefit. Meningioma are considered as a very heterogenous group and even the pathological benign subtypes (grade 1) can have a high recurrence risk depending on their molecular alterations (34,35). PRRT should be investigated not only in refractory (end-stage) meningioma, but also in surgically inoperable, high-grade and high-recurrence risk meningioma. In high-grade meningioma additional value for dedifferentiated meningioma can be expected, so in this patient group pretherapeutic ^{18}F-FDG PET will be critical (36). Future efforts should include the development of criteria for an appropriate use of PRRT in the specific subtypes (with the current insight in molecular alterations and the risk of recurrence) and determine the efficacy in randomized prospective trials.

Moreover, so far, SSTR-targeted PRRT in meningiomas is based on the standard approach in neuro-endocrine tumours, i.e. a sequential treatment by multiple doses. This paradigm requires re-evaluation in meningiomas, ideally including personal tumoural dosimetry as well as alternative administration modes. For the latter, promising preliminary results were reported for intra-arterial administration boosts of ^{177}Lu-SSTR targeted PRRT in salvage meningioma patients (37). Moreover, as currently all studies used beta-emitters (Lutetium-177 and Yttrium-90), the efficiency of labelling STTRs with alpha-emitters should be investigated.

Lastly, futures studies should also focus on treatment combinations. The combination of external beam radiation therapy and PRRT, for instance, could improve the absorbed dose while limiting the organ at risk irradiation. This is as the radiation fields differ between the two modalities, by that potentially providing better local disease control than PRRT alone (38,39). In the study of Kreissl et al., one cycle PRRT has been administrated in combination with

external radiation therapy which brings us to the point mentioned above. Randomized control trial comparing the effect of one cycle versus 4 cycles PRRT with or without external beam radiation therapy should be investigated in terms of safety and efficacy. Also, radiation exposure increases SSTR type 2 expression, a pre-PRRT external radiation therapy might be able to boost the antitumour effects of PRRT (40). As another example, PRRT and targeted therapies like everolimus, a mammalian target of rapamycine (mTOR) inhibitor, may potentially act synergistically without potentiating adverse effects (41). Phase II trial results with everolimus and non-radiolabeled octreotide combination have been encouraging in terms of progression-free survival (55% after 6 months) in a study population encompassing 90% of WHO grade 2 and 3 meningiomas (42).

GLIOMAS

Context

Gliomas are the most common malignant brain tumours. They include diffuse gliomas such as astrocytomas, oligodendrogliomas and glioblastomas, as well as ependymomas. Around 80% are high grade gliomas. They are classified according to the WHO as CNS WHO grade 2, 3 or 4 glioma (43). Currently a combined approach of maximal safe surgical resection, external beam radiation therapy and chemotherapy represent the standard of care for diffuse gliomas, but new therapeutic approaches are needed (44).

Gliomas are characterized by a high level of treatment resistance, immune escape as well as temporospatial heterogeneity. It does not surprise that although considerable effort has been put in the development of new treatment options, the last decades have only revealed a few significant changes in the outcome of glioma patients. The limited overall survival especially for patients with glioblastoma underlines the need for new therapeutic concepts in the management of glioma patients (45). Many potential theranostic targets have been investigated in gliomas, with variable but mostly discouraging results: tenascin, epidermal growth factor receptor (EGFR), neurokinin type 1 receptor (NK1R), SSTR, gastrin-releasing peptide receptor (GRPR), L-type amino transporter 1 (LAT-1), carbonic anhydrase (CA) XII, PSMA, matrix metalloproteinase, DNA histone H1 complex, poly(ADP-ribose) polymerase 1 (PARP1), integrins, chemokine receptor 4, disialoganglioside (GD2) and fibroblast activation protein (FAP).

Perspectives

Similar to the situation in meningiomas, most of the theranostic studies in gliomas have so far been performed either after incomplete surgery or as a second line in recurrent disease, for the latter most often in combination to chemotherapy or radiation therapy (46). Main weaknesses of the current studies are selection bias in patient inclusion, small patient numbers and / or lack of efficacy data. All planned and performed glioma studies based on systemic administration of a non-BBB penetrant compound has or is likely to fail, and all performed studies with direct tumour administration are discouraging. Therefore, currently the most promising studies are the trials targeting LAT-1 although the low residence time and radiation burden to normal brain parenchyma should be closely investigated. Moreover, future studies should focus on using multi modal approaches combining theranostic agents with techniques enhancing BBB/BTB permeability.

BRAIN METASTASES

Context

Brain metastases are diagnosed in 50% of patients with advanced primary lung cancer and melanoma and 20% of patients with breast cancer (47). The presence of brain metastases is associated with poor prognosis. Currently, therapeutic options consist of a combination of surgery, external radiation therapy, targeted and immune-modulating therapies (48). As primary cancer control is advancing dramatically, brain metastases across many cancer types occur more frequently, illustrating the need for more effective therapies.

Perspectives

Radionuclide therapy for brain metastases has only scarcely been investigated. Like in primary brain tumours, in brain metastases, the physiological BBB is – in most cases - altered with formation of a BTB (49). An advantage of radionuclide therapy over immune therapy is that the effective targeting of all lesions can be visualized using an intra-therapy scanning (1,2). Although studies of radionuclide therapy in brain metastases are scarce and efficacy need to be proven, there is very preliminary data with exemplary cases in breast cancer, prostate cancer and melanoma.

Added value of radionuclide therapy for metastasis is the simultaneous treatment of most tumour localisations in the body, when using intravenous or intra-arterial administration. Moreover, the effective targeting of brain metastases can be non-invasively, i.e. repeatedly monitored by PET imaging. These features might translate into an advantage over the current standard of care in terms of clinical benefit. With regard to the development of theranostic radiopharmaceutical pairs to treat brain metastases, these must focus on specific targets for specific cancer types.

PEDIATRIC BRAIN TUMOURS

Context

Brain tumours are the most frequent solid malignancy in childhood and account for around 20% of all pediatric tumours (the second most frequent after leukemias). They differ in many aspects when compared to the disease in the adults, both in site (pediatric brain tumours are more often infra-tentorial, up to 60% of cases) and histology (50), as it has been recognized in the most recent WHO classification of CNS tumours (WHO CNS5 2021), where specific pediatric variants have been added (eg pediatric-type low-grade and high-grade diffuse gliomas) (51–53). Recent advances in molecular and genetic characterization have detected many peculiarities of pediatric CNS tumours, impacting significantly on spreading, response to treatment and survival (54,55).

Surgery is the mainstay in many pediatric brain tumours. It offers the perspective of a cure in the non-infiltrating forms, but it is often performed also to treat diffuse infiltrating disease, because “debulking” can improve survival and quality of life. Surgery can be combined with adjuvant therapy (external radiation therapy and/or chemotherapy) when complete resection is not achievable or when microscopic persistence of disease is probable (56).

Surgical options are often heavily limited by the anatomical relationships of the lesion(s) with critical structures, as it is often the case for diffuse midline gliomas H3-K27-altered (formerly known as diffuse intrinsic pontine gliomas), where external radiation therapy offers the best chance for palliation. External radiation therapy increases survival in many high-grade tumours, as in medulloblastoma, one of the most frequent CNS neoplasms in childhood, typically located in the posterior fossa. However, it can have devastating long-term effects (neurocognitive, endocrine, etc), particularly in younger patients (0-3 y) (57). Therefore,

external radiation therapy is often avoided when prolonged survival is expected in younger ages, despite its efficacy.

Chemotherapy is used in combination with surgery and/or external radiation therapy, considering the interactions of the drug with the BBB. Intraventricular administration is often used in young children with embryonal tumours (atypical teratoid rhabdoid tumour, medulloblastoma), who cannot receive external radiation, to treat and/or prevent meningeal spread or dissemination through the cerebrospinal fluid circulation. Pediatric CNS tumours remain the leading cause of cancer-related death in childhood, despite many progresses in the comprehension of their molecular bases and are in high need for alternative options of treatment, as in the case of theranostic approach.

Perspectives

Considering the field, a relatively large amount of literature is available on theranostic approaches of radioligands in pediatric neuro-oncology. One of the most well documented and promising approaches is the use of intracranioventricular [^{131}I]Omburtamab via an intrathecal Ommaya reservoir in metastatic neuroblastoma, recurrent medulloblastoma and ependymoma for treatment of leptomeningeal disease (58).

In leptomeningeal disease cancer cells are located in the cerebrospinal fluid space. intracranioventricular administration enables targeted treatment with high regional tracer concentrations and low systemic distribution, confirmed by pretherapeutic [^{131}I]omburtamab scans (58).

Currently it is too early to know which radionuclide therapy shows the greatest potential and like in adults, more research must be done with innovative techniques to resolve the issue of

penetrability of the physiological BBB/ BTB. Several (pre)clinical studies are on their way, and the near future will show whether theranostic approaches will be able to serve as the desperately needed tools to improve patient care in neuro-oncology.

CONCLUSION

Theranostics is an exciting field of nuclear medicine with proven efficacy up to now mainly in thyroid cancer, prostate cancer and neuro-endocrine tumours. The theranostic concept is increasingly also tested in brain tumours, with preliminary encouraging results in meningiomas and leptomeningeal disease of pediatric brain tumours but discouraging results for gliomas. To date, no studies have proven clinical efficacy. Currently existing concepts from extra-cranial malignancies - such as ^{177}Lu-DOTATATE - are translated to the brain tumour setting. In parallel, new theranostic targets are explored. However, unlike extra cranial malignancies, the BBB/BTB forms an significant hurdle in development of effective therapies for primary and secondary brain tumours. Respective therapeutics are desired which can cross the (partially) intact BBB/BTB. While some therapeutics do in fact actively cross this barrier, the success of the majority of agents will be dependent on the successful development and clinical implementation of other principles that increase permeability of the BBB in combination with agents that decrease efflux. These techniques are still under development without proven efficacy and are found in multiple versions. Although here nuclear medicine techniques can aid and potentially speed up development by enabling visualisation and verification of the principle, for instance imaging after FUS with radiolabelled monoclonal antibodies which a large by nature and normally wouldn't cross the BBB (59,60). Besides standalone therapy, synergistic approaches with external beam radiation or immunotherapy could potentially even be more effective and are being evaluated. Additionally, as with all

theranostic approaches, the most optimal positioning in time (e.g. phase of treatment) should be explored. Another major limitation of substantial progress so far is the use of underpowered and uncontrolled clinical trial designs. The international community should strive towards sufficiently large and randomized studies in order to generate high level evidence on radioligand therapies in CNS tumours. More basic and clinical research is certainly necessary.

KEY POINTS

Question: Radionuclide therapy in brain tumours, where do we stand?

Pertinent findings: In this paper we describe the general context, an overview of the literature available to date andfuture perspectives of radionuclide therapy for meningiomas, gliomas, brain metastases, and pediatric brain tumours.

Implications for patient care: Preliminary research of theranostics in meningioma and leptomeningeal of certain pediatric brain tumours disease is encouraging. To date, other entities fail to impress. Ssuccessful development of other principles enabling blood-brain-barrier passage are crucial for the future success of radionuclide therapy in brain tumours.

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TABLES

	Meningioma	Glioma	Brain metastases	Pediatric brain tumours
SSTR	O (phase 1-2) (NCT03971461, NCT04997317, NCT03273712, NCT04082520, NCT05278208)	O (phase 1) (NCT05109728)		O (phase 1-2) (NCT05278208, NCT03273712)
Tenascin		X	O (phase 1-2) (NCT00002752)	
EGFR		X		
NK1R		X		
GRPR		O (phase 1-2) (NCT03872778, NCT05739942)		X
LAT-1		O (phase 1-2) (NCT03849105, NCT05450744)		
Carbonic anhydrase XII		O (phase 1) (NCT05533242)		
Integrins		X		
PARP1		X		
PSMA		X	X	
MMP		X	X	
DNAH1		X		
Chemokine receptor 4		X		
Fibronectin			X	
HER2			O (phase 1-2) (NCT04467515)	
PCSP			X	

Disialoganglioside GD2			O (phase 2) (NCT00445965)	X
B7-H3				O (phase 1) (NCT00089245, NCT05063357)
$CuCl_2$				X
FAP		X		

Table 1: Overview of molecular targets which have been used or are currently in use for radionuclide therapy in meningioma, brain metastases, glioma and pediatric brain tumours. Prostate specific antigen (PSMA), somatostatin receptor (SSTR), epidermal growth factor receptor (EGFR), neurokinin type 1 receptor (NK1R), gastrin-releasing peptide receptor (GRPR), L-type amino transporter 1 (LAT-1), matrix metalloproteinase (MMP), DNA histone H1 complex (DNAH1), human epidermal growth factor receptor 2 (HER2), proteoglycan chondroitin sulfate-associated protein (PCSP), fibroblast activation protein (FAP). O = ongoing studies (NCT number), X = target have been investigated in previous studies

FIGURES

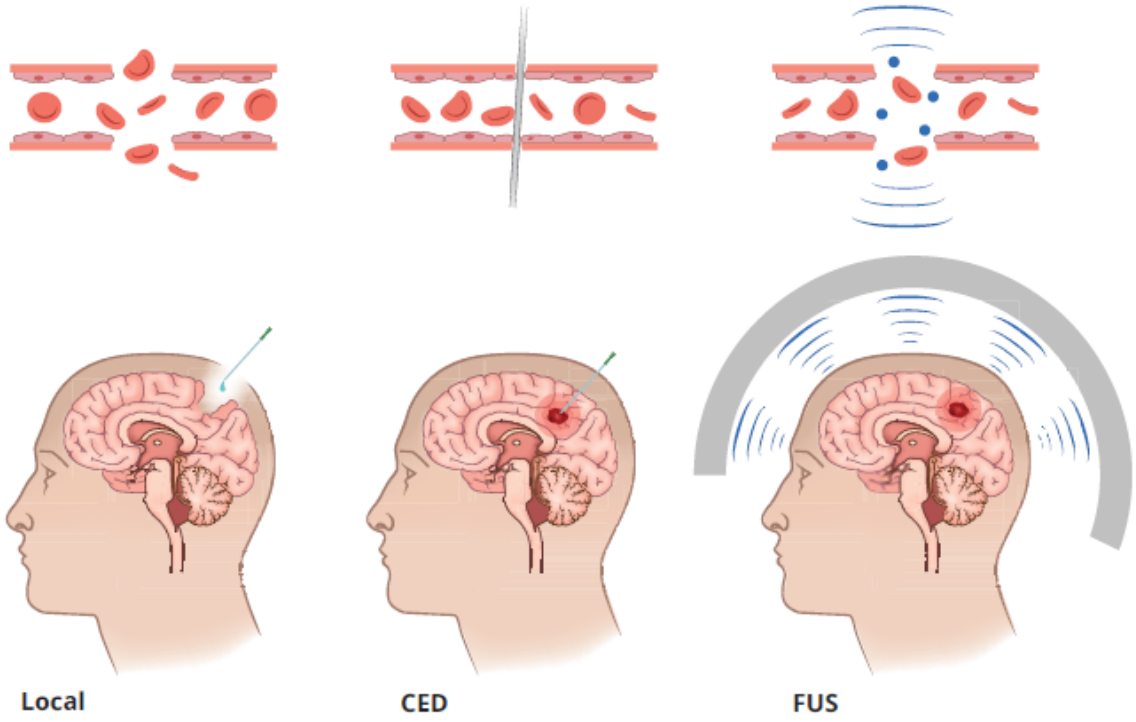
Figure 1

Example of interventional approaches to bypass the physiological blood brain barrier (BBB)/ blood tumour barrier. Normal transport in the BBB is not included.

Left panel: local delivery with administration of radioactivity directly in the resection cavity.

Middle panel: Convection enhanced delivery (CED): a microcatheter is implanted into the tumour and hydraulic pressure is used to distribute the drugs in the brain parenchyma.

Right panel: Focused ultrasound (FUS) reshapes the BBB using a targeted ultrasonic wave. This on its turn causes an interaction between administered microbubbles and the capillary bed resulting in enhanced vessel permeability



DISCLOSURES

MP has received honoraria for lectures, consultation or advisory board participation from the following for-profit companies: Bayer, Bristol-Myers Squibb, Novartis, Gerson Lehrman Group (GLG), CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, BMJ Journals, MedMedia, Astra Zeneca, AbbVie, Lilly, Medahead, Daiichi Sankyo, Sanofi, Merck Sharp & Dome, Tocagen, Adastra, Gan & Lee Pharmaceuticals, Servier. NLA has received honoraria for consultation or advisory board participation from Novartis and Telix and research funding from Novocure.

AV has received honoraria for lectures from General Electrics, Curium and Eisai.

KH reports personal fees from Bayer, personal fees and other from Sofie Biosciences, personal fees from SIRTEX, non-financial support from ABX, personal fees from Adacap, personal fees from Curium, personal fees from Endocyte, grants and personal fees from BTG, personal fees from IPSEN, personal fees from Siemens Healthineers, personal fees from GE Healthcare, personal fees from Amgen, personal fees from Novartis, personal fees from ymabs, personal fees from Aktis Oncology, personal fees from Theragnostics, personal fees from Pharma15, personal fees from Debiopharm, personal fees from AstraZeneca, personal fees from Janssen. MG reports honoraria from Roche, Novartis, UCB, Abbvie, Daiichi Sankyo, Novocure, Bayer, Janssen-Cilag, Medac, Merck, Kyowa Kirin, travel support from Novocure and Medac, research grant from Novocure.

MW has received research grants from Quercis and Versameb and honoraria from Bayer, Curevac, Medac, Novartis, Novocure, Orbus, Philogen, Roche and Sandoz. MW is part of the EORTC board and the president of the Swiss neuro-oncology society. HB received reader honoraria from Life Molecular Imaging, and dosing committee honoraria from Pharmtrace.

IY receives speaker honoraria from Piramal and consultant fees from ABX-CRO and Blue Earth Diagnostics. IY receives research funding from the federal ministry of education and research Germany (grant number 031L0200B, PI, 2020-2022), German research foundation (grant number 491096247, PI, 2021-2024), international brain research organization (meeting support award 2022) and international society for cerebral blood flow and metabolism (satellite symposia sponsorship 2022).

ACKNOWLEDGEMENTS

We would like to thank Dr. Dannis Van Vuurden and Dr. Mario Ries for their valuable contribution.