Translating the theranostic concept to neuro-oncology: disrupting barriers

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Theranostics integrate molecular imaging and targeted radionuclide therapy for personalised cancer therapy. Theranostic treatments have shown meaningful efficacy in randomised clinical trials and are approved for clinical use in prostate cancer and neuroendocrine tumours. Brain tumours represent an unmet clinical need and theranostics might offer effective treatment options, although specific issues need to be considered for clinical development. In this Policy Review, we discuss opportunities and challenges of developing targeted radionuclide therapies for the treatment of brain tumours including glioma, meningioma, and brain metastasis. The rational choice of molecular treatment targets is highlighted, including the potential relevance of different types of targeted radionuclide therapeutics, and the role of the blood–brain barrier and blood–tumour barrier. Furthermore, we discuss considerations for effective clinical trial design and conduct, as well as logistical and regulatory challenges for implementation of radionuclide therapies into neuro-oncological practice. Rational development will foster successful translation of the theranostic concept to brain tumours.

Introduction

Primary and secondary brain tumours encompass a large collection of tumour types with a high diversity of clinical presentations, histopathological and molecular genetic features, imaging characteristics, management strategies, and prognosis. In adults, the most common neuro-oncological diagnoses are meningioma, glioma, pituitary tumours, and brain metastasis of lung cancer, breast cancer, or melanoma. Although some tumour types might generally be cured by surgical resection alone, the majority of brain tumours are life-limiting despite multimodal therapies including surgery, radiotherapy and pharmacotherapy.[1–3] In the past decade, some therapeutic advances with novel pharmacotherapies have emerged for specific subpopulations of patients with primary or secondary brain tumours. For example, immune checkpoint inhibitors or targeted therapies were developed for patients with brain metastasis of melanoma and lung cancer, antibody–drug conjugates for patients with brain metastasis of HER2-positive breast cancer, or specific inhibitors for *BRAF* or *IDH* mutant gliomas.[1,3–5] However, a large number of clinical trials investigating novel treatments did not improve patient outcomes, and for many patients with a brain tumour, treatment options remain scarce. Thus, there is an urgent need to develop novel treatment approaches for patients with a brain tumour.

Theranostics is an evolving concept of precision medicine, which integrates targeted therapy based on diagnostic biomarker assessment with the use of molecular imaging. This concept has been present in nuclear medicine since the early 1940s, when the production of the β-emitter and γ-emitter Iodine-131 enabled both imaging and therapy of benign thyroid diseases and differentiated thyroid cancer.[6,7] However, the potential of theranostics has only gained a widespread recognition within the medical community in the past decade, thanks to the development of targeted therapies and imaging modalities based on more sophisticated radiolabelled macromolecules. In targeted radionuclide therapy, a ligand (ie, a peptide or an antibody) binding to a specific molecular target can be used not only for diagnostic visualisation, for example using PET, but also for therapeutic delivery of ionising radiation to target structures, such as tumour cells or components of the tumour microenvironment (commonly referred to as the treat what you see concept), independently of the role of the target in the pathophysiology of the disease (figure 1). Typically, positron-emitting or γ-emitting isotopes are used for diagnostic purposes and α-emitting or β-emitting isotopes are used for therapy. Radionuclide therapies are mostly applied intravenously, but intra-arterial, intratumoural, and intrathecal delivery are also being investigated. Utilisation of the theranostic concept offers several advantages for effective application of precision medicine in patients with cancer including: non-invasive biomarker-driven patient selection; assessment of biomarker heterogeneity across tumour manifestations in individual patients; dosimetry-adapted individualised adjustment of the administered activity; and imaging-based disease monitoring of response to therapy over time.

In several non-brain tumour types, targeted radionuclide therapies have shown clinically relevant efficacy and favourable tolerability and have been approved by regulatory authorities. In the USA and Europe, lutetium oxodotreotide ([^{177}Lu]Lu-DOTATATE) is approved and routinely used for the treatment of SSTR2-positive gastroenteropancreatic neuroendocrine tumours (GEP-NET) based on the results of the phase 3 NETTER-1 trial.[8,9] Lutetium vipivotide tetraxetan ([^{177}Lu]Lu-prostate specific membrane antigen (PSMA)-617) is approved for PSMA-positive metastatic castration-resistant prostate cancer based on the phase 3 VISION trial.[10] Furthermore,

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See Online for appendix

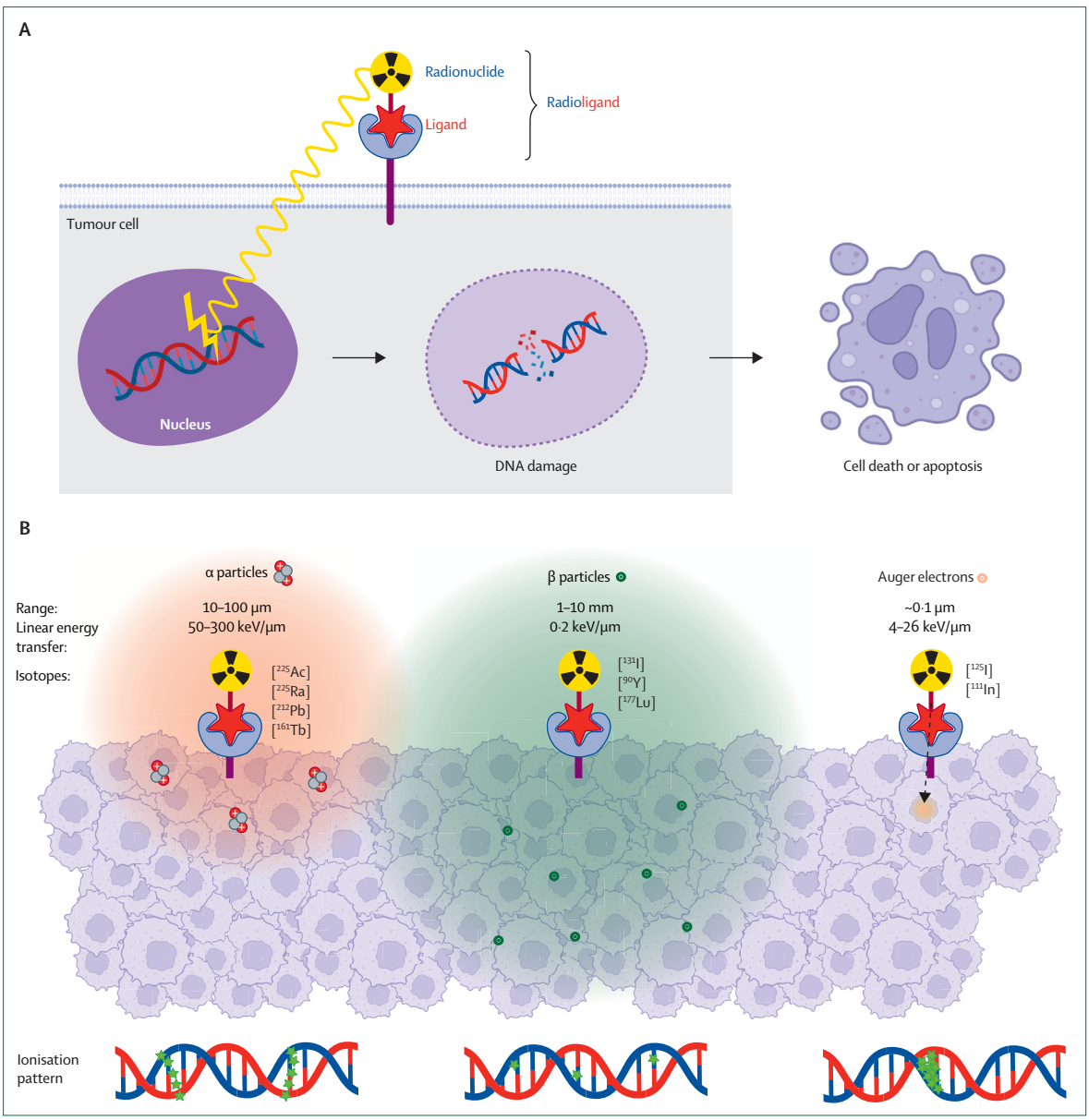

Figure 1: **Overview on the principle of radioligand treatments and used radionuclides**
(A) Mode of action of theranostic approaches. (B) Distinct types of emitters (α, β, Auger electrons) including typical ranges and linear energy transfer.

in the past few years, clinical trials have reported positive outcomes in early lines of therapy and additional tumour subtypes. The phase 3 NETTER-2 trial met the primary endpoint of significant improvement in progression-free survival and the secondary endpoint of objective response rate in patients with grade 2 and 3 advanced SSTR2-positive GEP-NET who received first-line treatment with [177Lu]Lu-DOTATATE in combination with long-acting octreotide compared with patients who received high-dose long-acting octreotide alone.[11] The randomised phase 2 OCLURANDOM trial showed a higher progression-free survival rate at 12 months in patients with progressive, SSTR2-positive, unresectable advanced pancreatic neuroendocrine tumours treated with [177Lu]Lu-DOTATATE compared with sunitinib.[12] Clinical trials evaluating various radionuclide therapies are ongoing in multiple non-CNS oncological indications including lung, breast, pancreatic, and colon cancers. Overall, targeted radionuclide therapy is a treatment option with proven efficacy in several extracranial tumour types.[7]

Theranostic treatments, and in particular targeted radionuclide therapies, might also present an opportunity for patients with primary and secondary brain tumours. External beam radiotherapy (EBRT) is an established and effective treatment for most brain tumour types, such as gliomas, subgroups of meningiomas, or brain

metastases, in addition to surgical resection and pharmacotherapy.[1–3] However, despite the availability of modern technologies (eg, volumetric modulated arc therapy, stereotactic radiosurgery) and advanced radiation types (eg, particle therapy) that allow highly conformal treatments, use of EBRT is restricted due to neurological side-effects. The delivery of high focal doses within short time periods might be associated with possibly severe adverse events, such as radiation necrosis, and, most importantly, irradiation of large volumes might be associated with leukoencephalopathy and vascular changes associated notably with neurocognitive decline.[13] Furthermore, many brain tumours grow diffusely, with tumour cells invading the CNS parenchyma distant from the main tumour bulk and are not fully covered by the radiotherapy target volume. Targeted radionuclide therapies might be suitable to overcome some of these limitations due to their pharmacokinetic, pharmacodynamic, and radiobiological properties that differ from conventional irradiation.[14] Indeed, primary and secondary brain tumours are biologically well characterised and display a multitude of possibly suitable molecular targets for specific binding of peptide or antibody ligands. However, the biology and localisation of brain tumours also present specific challenges associated with their epidemiology, clinical presentation, natural history, and pathobiology, including limitations imposed by the blood–brain barrier and blood–tumour barrier. In this Policy Review, the members of the European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumor Group Nuclear Medicine Committee discuss considerations for effective clinical trial design and conduct, as well as logistical and regulatory challenges for implementation of radionuclide therapies into neuro-oncological practice and patient care.

Process of position paper development

EORTC is an independent, non-governmental, non-profit cancer research organisation based in Brussels, Belgium. The aim of the EORTC is to coordinate and conduct international translational and clinical research to improve the standard of cancer treatment for patients. The Brain Tumor Group (BTG) is one of several disease-oriented groups of the EORTC and focuses on clinically oriented research in primary and secondary brain tumours. Given the emerging role of theranostic applications, the BTG Steering Committee implemented a dedicated Nuclear Medicine Committee (NMC) and presented this project on March 17, 2023 at the EORTC BTG General Assembly in Brussels, Belgium. The NMC has developed this position paper through a dedicated strategic survey, and literature review and consensus finding among its multidisciplinary and international expert members. The positions provided in this manuscript were elaborated in consensus-finding meetings and communications among the coauthors between Sept 20 and Nov 30, 2023. NLA and MP drafted the Policy Review in several subsequent virtual consensus-finding meetings, which were then reviewed and adapted by the expert coauthor panel until unequivocal agreement was achieved.

NMC survey on targeted radionuclide therapy trials for brain tumours

To evaluate the level of interest and the accrual capacity for clinical trials exploring targeted radionuclide therapies in brain tumours, a survey was done among the EORTC BTG membership. On April 21, 2023, a link to an online questionnaire developed by the NMC was sent out via email to a total of 552 investigators in 277 cancer centres in 26 countries and responses were collected until June 14, 2023. The survey questions are shown in table 1. The results were analysed by NLA and MP.

Opportunities and challenges for theranostics in neuro-oncology

Strategic alignment and accrual capacity

The focus of the EORTC Brain Tumor Group is the conduct of practice-changing clinical trials in the field of neuro-oncology. Over the past decades the group has defined treatment standards for patients with a brain tumour through large randomised clinical trials, partly done in collaboration with other international cooperative groups, with a focus on EBRT and systemic pharmacotherapy.[1,15–20] The results of the strategic NMC survey show the widespread availability of nuclear medicine departments among EORTC BTG sites and experience with the application of radionuclide therapies in non-CNS cancers at the BTG investigator sites, as well as the high interest in accruing patients with glioma, meningioma, or brain metastasis into clinical trials investigating targeted radionuclide therapies (table 1). Thus, the NMC survey results support the strategic development of a clinical trial portfolio investigating targeted radionuclide therapies for patients with a brain tumour.

For more on **EORTC** see https://www.eortc.org

Considerations for clinical trial planning

Several factors need to be considered to decide which clinical trial initiatives to prioritise to maximise the chance for successful translation of the theranostic concept to neuro-oncology.

Brain tumours represent a large diversity of tumour types and subtypes, and specific tumour-related characteristics might influence the probability of therapeutic efficacy of radiopharmaceuticals. A main parameter for selection of a tumour type for targeted radionuclide therapy is the expression of a suitable molecular target. Ideally, a molecular target should be expressed homogeneously throughout the tumour tissue or on key components of the tumour to maximise the therapeutic efficacy; should be expressed exclusively or mainly on tumour cells or in the tumour microenvironment to limit off-target effects and toxicity; must

	Answers
Is there a nuclear medicine department at your site? (n=119)	
Yes	114 (96%)
No	5 (4%)
No answer	0
Is your site treating patients with cancer with radionuclide therapy? (n=118)	
Yes	104 (88%)
No	12 (10%)
No answer	2 (2%)
Do patients have to stay overnight after radionuclide therapy at your site? (n=121)	
Yes	76 (63%)
No	31 (26%)
No answer	14 (12%)
Is your site treating patients with gliomas using radionuclide therapy? (n=118)	
Yes	18 (15%)
No	98 (83%)
No answer	2 (2%)
Is your site treating patients with meningiomas using radionuclide therapy? (n=118)	
Yes	32 (27%)
No	82 (69%)
No answer	4 (3%)
Is your site treating patients with CNS metastases using radionuclide therapy? (n=118)	
Yes	4 (3%)
No	106 (90%)
No answer	8 (7%)
Is your site interested in enrolling patients with gliomas into trials testing radionuclide therapies? (n=118)	
Yes	102 (86%)
No	16 (14%)
No answer	0
Is your site interested in enrolling patients with meningiomas into trials testing radionuclide therapies? (n=120)	
Yes	106 (88%)
No	14 (12%)
No answer	0
Is your site interested in enrolling patients with CNS metastases into trials testing radionuclide therapies? (n=119)	
Yes	98 (82%)
No	21 (18%)
No answer	0

Table 1: **Results of the European Organisation for Research and Treatment of Cancer–Brain Tumour Group–Nuclear Medicine Committee survey on radioligand therapy trials for patients with a brain tumour**

be accessible from the circulation at least for systemic delivery; and should be expressed consistently over time to avoid waning of therapy effects. Potential molecular targets of interest for targeted radionuclide therapies in gliomas, meningiomas, and brain metastases, SSTR2, LAT-1, EGFRvIII, carbonic anhydrase, NK1R, FAP, and others are shown in figure 2.

Targeted radionuclide therapies might show differential efficacy in relation to tumour-related characteristics, such as malignancy, growth dynamics, and radio-resistance (primary or secondary to prior therapies). So far, regulatory approvals for targeted radionuclide therapies and positive results of randomised phase 3 trials have been achieved in extracranial malignant tumour types with relatively slow growth dynamics (ie, thyroid cancer, metastatic prostate cancer, and metastatic neuroendocrine tumours). Median progression-free survival in the radioligand therapy arm of the NETTER-1 trial was not reached, in the VISION trial was 8·7 months, and in the OCLURANDOM trial was 20·7 months.[8,10–12] Among brain tumours, a large range of progression-free survival and overall survival times can be observed, even within diagnostic categories as defined by the current WHO classification.[21] Pending the outcome of ongoing clinical trials in a variety of tumour types, the potential efficacy of currently available radiopharmaceuticals in highly aggressive tumour types remains to be defined. Currently available radiopharmaceuticals mostly use β-emitting isotopes, such as iodine-131 [^{131}I], yttrium-90 [^{90}Y], or lutetium-177 [^{177}Lu] (figure 1). Next-generation radiopharmaceuticals engaging α-emitting isotopes (eg, actinium-225 [^{225}Ac], radium-223 [^{223}Ra]), or Auger electrons (eg, iodine-125 [^{125}I], indium-111 [^{111}In]) with higher energy and different irradiation range might be more suitable for tumour types with particularly high growth rates and radio-resistance, but these therapies are not available for large-scale use in humans yet due to logistical reasons.[22–24] Especially for α-emitters and Auger emitters, which have characteristic short spatial radiation ranges, strategies for tumour cell internalisation, intracellular trapping, and adequate retention time of the radionuclide (eg, by ligation to suitable carrier molecules) need to be considered to maximise therapeutic efficacy.[25,26] Combination therapies of targeted radionuclides with EBRT, radiosensitisers, or immunotherapies should also be explored to generate synergistic anti-tumour activity. In this respect, emerging preclinical data indicate immunostimulatory effects of radionuclide therapies as a potential way to address resistance to immunotherapies by immunologically cold tumors.[27]

A topic that needs special consideration for systemically applied therapies for patients with a brain tumour is the blood–brain barrier and blood–tumour barrier, which limits the ingress of substances into the brain from the circulation.[28] Radiopharmaceuticals are complex molecules consisting of ligands, linkers, chelators, and radioactive isotopes. The optimal structure of targeted radionuclides for optimal penetration into brain tumours after intravenous application remains to be determined. Lipophilicity, molecular weight, and affinity for transport mechanisms influence blood–brain barrier penetration and should be considered for selection of candidate radiopharmaceuticals for treatment of brain tumours. Tumour-related alterations might be associated with

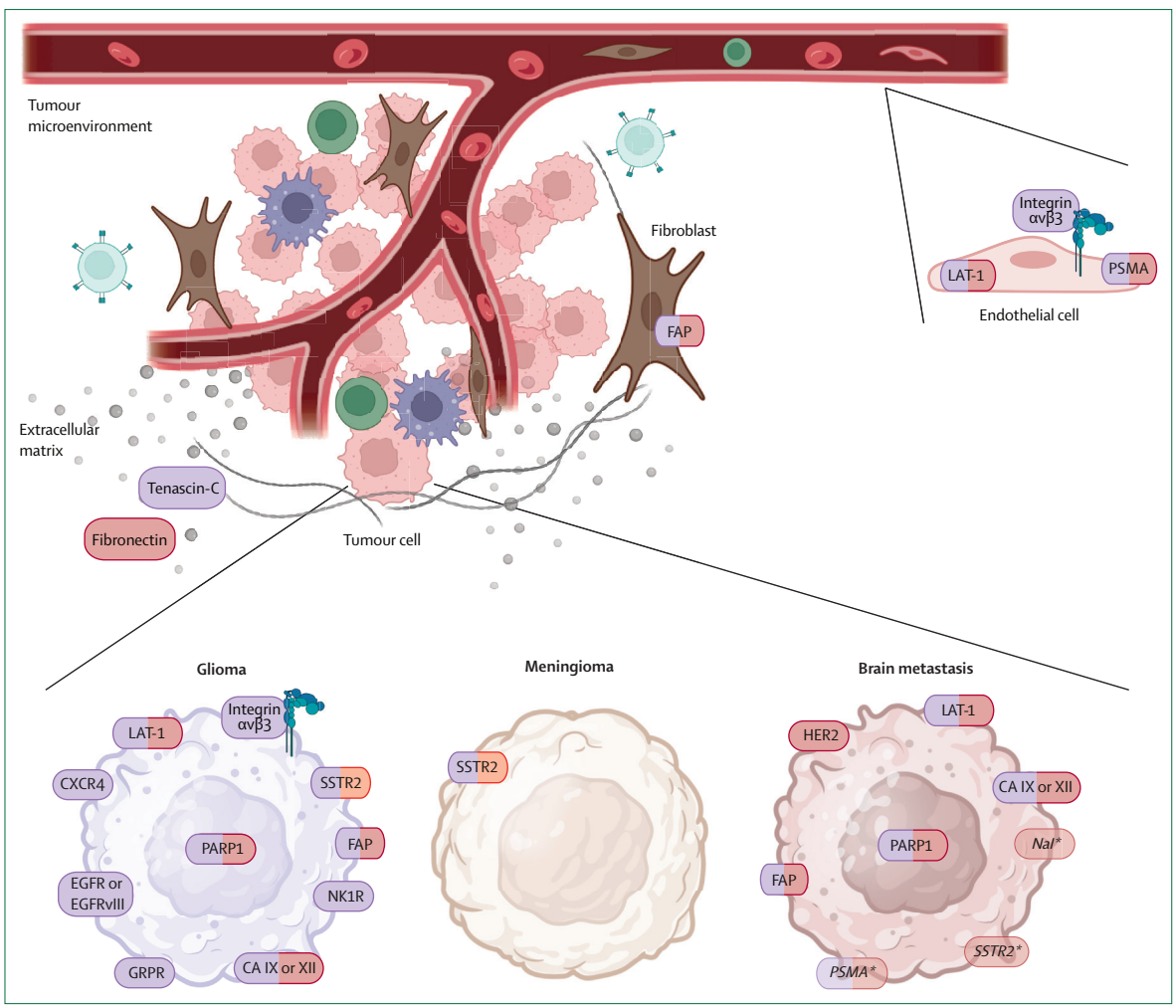

Figure 2: **Localisation of potential targets for radionuclide therapies on tumour cells and in the tumour microenvironment of glioma, meningioma, or brain metastasis**

Targets in glioma, meningioma, and brain metastases are given in purple, orange, and red, respectively. CA IX/XII=carbonic anhydrase IX/XII. NaI=sodium–iodide co-transporter. PARP=poly (ADP-ribose) polymerase. PSMA=prostate-specific membrane antigen. *Targets in brain metastasis are approved for metastatic disease irrespective of metastatic site.

disturbed blood–brain barrier and blood–tumour barrier function (except for meningiomas that do not have a relevant blood–brain barrier) that favours intratumoral accumulation of therapeutically relevant radionuclide concentrations, at least in areas with contrast-enhancement. However, development of radiopharmaceuticals with high blood–brain barrier and blood–tumour barrier penetration, such as TLX101 (4-L-[^{131}I]iodo-phenylalanine, or [^{131}I]iodo-phenylalanine) targeting LAT-1 should be prioritised to effectively target diffusely infiltrating brain tumours. Several strategies, including alternative modes of application of targeted radionuclides, such as intra-arterial injection into tumour-feeding arteries, intracavitary application, convection-enhanced delivery, intrathecal application, or methods for opening of the blood–brain barrier and blood–tumour barrier, such as focused ultrasound, are currently under investigation and

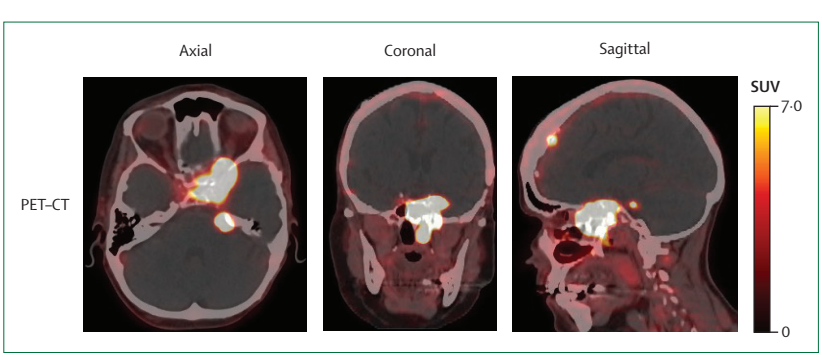

Figure 3: **SSTR2 PET–CT scan of a patient with multifocal recurrence of a sphenoid wing meningioma, CNS WHO grade 2, after surgical resection and irradiation**

SUV=standardised uptake value.

	Molecular target	Targeted radionuclide	Study sponsor	Mode of application	Tumour type	Stage of disease	Study phase	Study design	Sample size or current enrolment	Primary endpoint	Study status	Planned completion date
NCT03849105 (IPAX-1)	LAT-1	4-L-[^{131}I]iodo-phenylalanine	Telix International	IV injection (concomitantly with re-radiation)	Glioblastoma	First recurrence	1–2	Open-label, single-arm	10	Safety and tolerability	Completed	October, 2022
NCT05450744 (IPAX-2)	LAT-1	4-L-[^{131}I]iodo-phenylalanine	Telix International	IV injection (concomitantly with chemoradiotherapy)	Glioblastoma	Newly diagnosed	1	Open-label, single-arm, parallel group	12	Safety and tolerability, maximum tolerated dose	Recruiting	June, 2025
NCT05109728	SSTR2	[^{177}Lu]Lu-DOTATATE	Novartis	IV injection (concomitantly with chemoradiotherapy in newly diagnosed glioblastoma, single agent treatment in recurrence)	Glioblastoma	Newly diagnosed and recurrent	1	Open-label, non-randomised, parallel group	60	Safety and tolerability	Recruiting	July, 2026
NCT01906385 (ReSPECT)	NA	[^{186}Re]rhenium nanoliposomes	Plus Therapeutics	Convection-enhanced delivery catheter	Glioma	Any recurrence	1–2	Open-label, single-arm	55	Safety and tolerability, maximum tolerated dose (phase 1), and overall survival (phase 2)	Recruiting	January, 2025
NCT05533242	CA XII	[^{177}Lu]Lu-labelled 6A10-Fab-fragment	University Hospital Muenster	Intracavitary application	Glioblastoma	Newly diagnosed after chemoradiotherapy	1	Open-label, single-arm	15	Safety and tolerability, maximum tolerated dose	Recruiting	June, 2025
NCT05034497 (ReSPECT-LM)	NA	[^{186}Re]rhenium nanoliposomes	Plus Therapeutics	Intraventricular administration	Leptomeningeal disease of any primary tumour	Not applicable	1	Open-label, single-arm	18	Safety and tolerability, maximum tolerated dose	Recruiting	June, 2026
NCT05739942	GRPR	[^{177}Lu]Lu-NeoB	Novartis	IV injection	Glioblastoma	Newly diagnosed and recurrent	1b	Open-label, parallel group	48	Safety and tolerability	Not yet recruiting	November, 2025
NCT05977322	αvβ3 and αvβ5 integrins	[^{177}Lu]Lu-FF58	Novartis	IV injection	Advanced solid tumours (pancreatic ductal adenocarcinoma, gastroesophageal adenocarcinoma, and glioblastoma)	Glioblastoma: recurrent; other tumours: locally advanced unresectable or metastatic	1	Open-label, single-arm	116	Safety and tolerability, dose intensity	Recruiting	July, 2026

(Table 2 continues on next page)

might be helpful to maximise intratumoral concentrations of therapeutic radionuclides.[29–32] Yttrium-90 trans-arterial radioembolisation, an established treatment of liver tumours, has been investigated in a canine brain tumour model, but further studies on safety and potential efficacy are required for translation of this concept to the human setting.[33]

Currently available radionuclide therapies are in general well tolerated. However, of relevance for patients with brain tumours might be the necessity for radioprotection measures after exposure to radiopharmaceuticals, as these measures might limit caregiver support with activities of daily living and neurological and neurocognitive symptom control for some time. Clinical trial inclusion criteria and procedures need to take local regulations and guidelines into account.

Based on these considerations, the EORTC BTG has initiated the development of a prospective clinical trial on β-emitting targeted radionuclide therapy for recurrent meningioma. Meningioma was chosen as the indication as there is a high unmet clinical need, a highly expressed molecular target (SSTR2) with proven efficacy of a theranostic treatment ([^{177}Lu]Lu-DOTATATE) in another tumour type (neuroendocrine tumours),[34] and no relevant blood–brain barrier or blood–tumour barrier.[2,35] Furthermore, retrospective series and an interim analysis of a prospective, single-arm study suggest encouraging efficacy signals for SSTR2-targeted radionuclide therapy in meningioma.[36–39] EORTC-BTG-2334 (LUMEN-1; NCT06326190) is a randomised, phase 2 trial that will compare the efficacy of intravenously applied [^{177}Lu]Lu-DOTATATE with the standard of care in patients with CNS WHO grade 1, 2, or 3 recurrent meningioma expressing SSTR2 confirmed by PET imaging after surgery and radiotherapy (figure 3). The primary endpoint will be progression-free survival and secondary endpoints include overall survival, tolerability, and quality of life. An accompanying translational research programme will aim to investigate tissue and imaging biomarkers and explore dosimetry measures for outcome prediction. Further clinical trials will be developed based on preclinical investigations, radiobiological considerations, and the results of ongoing early-phase clinical trials (table 2).

Clinical trial design and conduct

Outside of a few prospective and randomised clinical trials, targeted radionuclide therapies are occasionally prescribed in off-label or compassionate use circumstances that do not allow conclusions to be drawn on their true therapeutic efficacy due to patient selection, heterogeneous patient populations, ill-defined endpoints, and underpowered statistical analyses inherent to retrospective analyses. To generate the appropriate evidence for effective translation of theranostics to neuro-oncology, the EORTC BTG prioritises the conduct of prospective, controlled clinical trials with robust designs and endpoints. To generate

	Molecular target	Targeted radionuclide	Study sponsor	Mode of application	Tumour type	Stage of disease	Study phase	Study design	Sample size or current enrolment	Primary endpoint	Study status	Planned completion date
(Continued from previous page)												
NCT03971461	SSTR2	[^{177}Lu]Lu-DOTATATE	New York University Langone Health	IV injection	Meningioma	Grade I: progressive disease after resection and radiotherapy or progressive residual tumour after maximum safe resection near regions at high risk for radiation injury; grade II/III: progressive disease after surgical resection and radiotherapy, or residual disease after surgery	2	Open-label, single-arm	32	Progression-free survival rate at 6 months	Recruiting	June, 2025
NCT06126588	SSTR2	[^{177}Lu]Lu-DOTATATE (in association with everolimus)	University Hospital Nancy	IV injection	Meningioma	Grade II/III: not amenable to surgery or radiotherapy, with clinical or radiological progression	2b	Open-label, single-arm	28	Progression-free survival rate at 6 months	Not yet recruiting	March, 2026
NCT06326190 (LUMEN-1)	SSTR2	[^{177}Lu]Lu-DOTATATE	EORTC	Intravenous injection	Meningioma	Grade I–III with radiologically documented progression of any existing tumour (growth >25% in the last 2 years) or appearance of new lesions after at least one previous surgery and one line of external beam radiotherapy	2	Open-label, randomised (vs local standard-of-care)	135	Progression-free survival	Not yet recruiting	December, 2028

All clinical trials listed are multicentric. CA XII=carboanhydrase XII. IV=intravenous. NA=not applicable.

Table 2: **Clinical trials on theranostics approaches in brain tumours**

high-level evidence that is suitable to inform clinical practice, we commit to performing randomised clinical trials, including for the evaluation of targeted radionuclide therapies whenever feasible. Alternative clinical trial designs, such as single-arm enrolment and the utilisation of external control data, will only be considered when randomisation is not practicable and renders accrual goals unrealistic.[40] The preferred primary endpoint for evaluation of treatment efficacy is overall survival, although other outcome measures might be considered depending on the study rationale and feasibility considerations. For imaging-based readouts, such as response rates and progression-free survival times, international consensus recommendation guidelines, such as the MRI-based RANO 2.0 or the PET-based PET RANO 1.0 response criteria, should be included in clinical trial protocols for gliomas.[41–43] Radionuclide therapy trials need to collect information on specific toxicities and adverse events of special interest in a standardised way. Indeed, short-term, mid-term, and long-term toxicities must be monitored by collecting clinical and imaging data until loss to follow-up. To this end, collection of post-treatment brain tissue (from clinically indicated resections) or autoptic tissue (even long after study treatment) should be considered to investigate on-target and off-target effects of radionuclide therapies.

Patient-reported outcomes, including quality of life and neurocognitive function, as well as neurological function, should be assessed with standardised tools, (eg, the EORTC quality of life questionnaire QLQ-C30, brain tumour specific questionnaire QLQ-BN20, or the Neurologic Assessment in Neuro-Oncology scale).[44–46] Similar to other EORTC BTG clinical trials testing other treatments, radionuclide therapy study protocols should include collection of imaging data and biomaterials (eg, tumour tissue samples and liquid biopsies) to facilitate translational research and secondary investigations.

Panel: **Priorities for effective translation of theranostics to neuro-oncology**

- Provide public funding opportunities and support public–private partnerships aimed at supporting translational research for identification of suitable molecular targets for radionuclide therapies and increasing understanding of radiobiology in glioma, meningioma, and brain metastasis
- Prioritise prospective and controlled phase 2 or 3 trials with robust designs and established endpoints over compassionate use, retrospective series, and single-arm studies
- Harmonise regulatory and legal policies to facilitate efficient and effective clinical trial conduct and routine clinical application in the field of theranostics
- Develop educational activities and knowledge transfer on regulatory, operational, and legal aspects of clinical trial conduct with theranostic agents

Performing internal dosimetry in theranostic procedures using radiopharmaceuticals, either for treatment planning or verification, is required by current EU regulations.[47] In the past few years, scientific societies, such as the European Association of Nuclear Medicine (EANM), have made tremendous efforts to increase the recognition of the importance of internal dosimetry and to ensure widespread application and standardisation of this procedure.[48] However, the EORTC BTG NMC recognises that internal dosimetry has a heterogeneous acceptance across institutions, has scarce resources, and that it is not universally available to investigators.[49] Nevertheless, collection of internal dosimetry data is strongly encouraged, as these data might be used to elucidate radiobiological aspects typical of molecular radiotherapy, explain dose-effect relationships, and inform future trials towards personalisation and optimisation.

The conduct of informative prospective clinical trials with adequate sample sizes might be challenging, not only due to the relative rarity of some tumour types of interest and the high morbidity and mortality of patients with brain tumours, but also due to the regulatory and logistical complexities associated with the application of radiopharmaceuticals. The delivery of targeted radionuclide therapies needs to respect legal and regulatory frameworks relating to radiation protection, manufacturing authorisation, distribution, handling, waste management, and specific requirements for patient hospitalisation and discharge. There is a high heterogeneity of requirements and guidelines for clinical use of radionuclide therapies across Europe and globally. Examples of regulatory requirements that currently limit or complicate site selection for participation in clinical trials include strict waste management policies (eg, Belgium), the necessity to hospitalise patients for a long time after injection of radionuclide treatments (eg, Germany and Switzerland), or lengthy and complex national regulatory procedures for authorising a new radiopharmaceutical drug for human use (eg, France), among others. There is a strong need to harmonise regulatory and legal policies to facilitate efficient and effective clinical trial conduct in the field of theranostics across Europe.[50,51] In addition, there is a need to build effective distribution networks that take production workflows, transportation times, and storage and destruction of radiopharmaceuticals of different radiation potency and half-life into account. Of relevance for correlative translational research projects conducted within multicentric clinical trials is the collection and biobanking of biological materials, such as tumour tissue samples and liquid biopsies taken after exposure to radionuclide therapies and in compliance with radioprotection policies, together with data acquired from other imaging modalities (in particular MRI). To overcome these challenges, the EORTC BTG NMC is implementing several dedicated measures to ensure a

high level of expertise in all aspects of clinical trial conduct and a strong investigator network for the delivery of clinically relevant theranostic trials. These measures include implementation of practice guidelines and procedure standards, such as those jointly provided by the EANM, the European Association of Neuro-Oncology (EANO), The Response Assessment in Neuro-Oncology (RANO), and the Society of Nuclear Medicine and Molecular Imaging (SNMMI),[34] collaborative knowledge transfer with regulatory authorities and radiopharmaceutical industry, and training and education of investigators and study site staff.

Translation into routine clinical practice

Widespread implementation of targeted radionuclide therapies into routine neuro-oncological practice with regulatory approvals, reimbursement plans, and evidence-based recommendations in clinical practice guidelines requires proof of sufficient and clinically relevant antitumour activity and safety of application. Insufficient evidence is available to recommend approval of any targeted radionuclide therapy for patients with a primary tumour and most patients with a secondary brain tumour, and these approaches should be proposed ideally within prospective clinical trials or in well annotated compassionate use programmes. The development of meaningful prospective and controlled clinical trials based on sound pathobiological and clinical rationale is necessary. Furthermore, the integration of nuclear medicine specialists into interdisciplinary patient care and clinical research is of importance to facilitate patient selection, tumour board quality, and, ultimately, optimal patient access to PET imaging and theranostic treatments.

Conclusions and outlook

Targeted radionuclide therapies have shown clinically relevant activity in some extracranial tumour types. The field of theranostics is rapidly evolving with ongoing research and development efforts, including generation of novel radiopharmaceuticals and ongoing clinical trials in multiple tumour types. For primary and secondary brain tumours, targeted radionuclide therapies are possibly an effective treatment option, and adequately timed, designed, and efficiently executed clinical trials are required for efficient translation into clinical practice. The EORTC BTG prioritises randomised, controlled trials with translational research components for the development of theranostics in neuro-oncology. Generation of effective infrastructure and supply chains is needed, as well as harmonisation of legal and regulatory policies for the optimal conduct of informative clinical trials with targeted radionuclide therapies across Europe. The panel summarises priorities for effective translation of theranostics to neuro-oncology.

Search strategy and selection criteria

References for this Policy Review were identified by all authors through searches of PubMed with the search terms "theranostics", "glioma", "glioblastoma", "brain metastases", "meningioma", "brain tumor", "radioligand therapy", "targeted radionuclide therapy", and combinations thereof from Oct 1, 2023 until Dec 31, 2023 and included full journal articles published between Jan 1, 2003 and Dec 31, 2023. Only papers published in English were reviewed. The final reference list was generated based on originality and relevance to the broad scope of this Policy Review.

Contributors

NLA and MP: conceptualisation, methodology, project administration, visualisation, and writing of the original draft. FC, NG, ASJ, ELR, GM, MN, MS, MJM, NT, MW, and AV: methodology, writing of the Policy Review, and editing. The first manuscript draft was generated by NLA and MP. It was then refined in several review rounds done by all coauthors. All authors approved the final position statements and manuscript version.

Declaration of interests

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