

From Compassionate Use Toward High-Level Evidence for Radiopharmaceutical Therapy in Recurrent Meningioma: The LUMEN-1 and MOMENTUM-1 Trials

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Theranostics and radiopharmaceutical therapies are rapidly transforming the medical landscape, and the neuro-oncology community is observing these developments with great interest. In a field characterized by a significant unmet clinical need for novel and effective treatment options to slow or ideally halt disease progression, these advances hold considerable promise (1). This is particularly relevant for meningiomas. These tumors typically express somatostatin receptors (SSTRs) (2), which can be targeted by peptide receptor radionuclide therapy (PRRT). The success of PRRT in neuroendocrine tumors, as demonstrated in randomized controlled trials, suggests that a similar therapeutic approach could be effective in meningiomas. In fact, several uncontrolled and controlled retrospective studies have shown promising results for SSTR radiopharmaceutical therapy in recurrent meningiomas. The most recent study to date, involving 32 patients from a single institution, reinforced its potential effectiveness (3). Preliminary results from a prospective phase 2 single-center trial in 14 patients with recurrent meningiomas (grades 1–3) further support the efficacy of [¹⁷⁷Lu]Lu-DOTATATE therapy (NCT03971461). However, robust clinical evidence from randomized prospective clinical trials in this setting is required before widely adopting a “promising” therapy into standard clinical practice. So far, SSTR2 is considered only a hypothetical treatment target in meningiomas with an evidence-based

score of IIIa according to the European Society for Medical Oncology Scale for Clinical Actionability of Molecular Targets.

ADDRESSING THE EVIDENCE GAP

This is precisely where the LUMEN-1 trial (NCT06326190) conducted by the European Organisation for Research and Treatment of Cancer comes into play. Albert et al. initiated the first prospective, randomized trial evaluating [¹⁷⁷Lu]Lu-DOTATATE in recurrent meningioma (4). The study aims to randomize 136 patients with recurrent World Health Organization grade 1, 2, or 3 meningiomas in a 2:1 ratio to receive either [¹⁷⁷Lu]Lu-DOTATATE (up to 4 doses of 7.4 GBq every 4 wk) or a local standard-of-care treatment such as hydroxyurea, bevacizumab, sunitinib, octreotide, everolimus, or surveillance.

In the LUMEN-1 trial, participants must show SSTR expression on baseline PET scans. An absolute SUV_{max} threshold of greater than 2.3 was set as the eligibility criterion, rather than using relative uptake comparisons (e.g., to liver or blood pool), due to the lack of consensus on the best method for defining SSTR uptake. A key inclusion criterion is radiologically confirmed tumor progression, defined as tumor growth exceeding 25% in volume or the development of new lesions within the past 2 y. Another important inclusion criterion is that patients should be treatment-naïve for systemic therapy. Although patients will be treated in the setting of disease recurrence and after surgery or radiation, [¹⁷⁷Lu]Lu-DOTATATE is hereby proposed earlier in the disease course compared with other studies. The primary endpoint in the LUMEN-1 is progression-free survival, as assessed using the Response Assessment in Neuro-Oncology MRI meningioma criteria. An important aspect of the

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LUMEN-1 trial is the inclusion of dosimetry and thereby the possibility of analysis between treatment response and given dose, providing further insights in the effect of PRRT for this patient group.

In parallel with LUMEN-1, a sister study, MOMENTUM-1 (NCT06955169), has emerged as a complementary effort to evaluate [¹⁷⁷Lu]Lu-DOTATATE in a similar patient population but with a U.S.-led multicenter design under the Radiation Therapy Oncology Group Foundation. The LUMEN-1 and MOMENTUM-1 studies share large similarities in their overall design, including patient inclusion criteria such as recurrent meningioma World Health Organization grades 1–3 and a 4-wk cycle treatment regimen in the experimental arm. Some differences distinguish the 2 trials (Table 1). One difference lies in the tumor growth rate requirements: different from LUMEN-1, MOMENTUM-1 permits either more than 15% growth over the past 6 mo or over 25% in the last 12 mo, or development of a new measurable lesion. Additionally, the imaging criteria differ; MOMENTUM-1 mandates the use of [⁶⁸Ga]Ga-DOTATATE PET with a Krenning score of at least 3, making whole-body PET scans obligatory.

The use of a Krenning score of at least 3 in MOMENTUM-1 selects tumors with higher SSTR expression, whereas LUMEN-1, based on a histologically proven SUV threshold, potentially covers the full biologic spectrum of meningiomas. This distinction affects generalizability. As the correlation between SSTR PET signal intensity and tumor grade is still controversially discussed, it is currently unclear how the different inclusion criteria in both trials will influence the patient population and the response to treatment. Exploratory analyses from LUMEN-1 may clarify the predictive role of SSTR intensity and refine patient selection in future trials.

Furthermore, MOMENTUM-1 allows systemic therapy except SSTR-targeting agents before inclusion unlike LUMEN-1. MOMENTUM-1 provides the option for patients to receive 2 additional cycles of [¹⁷⁷Lu]Lu-DOTATATE (4 + 2 optional). Lastly, there is also a difference in sample size between the LUMEN-1 and MOMENTUM-1 trials (136 vs. 153 patients, respectively), reflecting variations in study design and statistical assumptions while both trials use a 2:1 randomization.

TABLE 1
Comparison of LUMEN-1 and MOMENTUM-1 Trials

Characteristic	LUMEN-1	MOMENTUM-1
Trial name, identifier	EORTC-2334-BTG (LUMEN-1), NCT06326190	RTOG Foundation 3523 (MOMENTUM-1), NCT06955169
Design, phase	Prospective, randomized, open-label, multicenter phase 2	Prospective, randomized, open-label, multicenter phase 2
Status (2025)	Activated March 2025; first patient enrolled May 2025	Registered; not yet recruiting
Geographic scope, sponsor	Europe, 35 centers across 10 countries, led by EORTC	U.S.-led, coordinated by RTOG Foundation
Sample size	136 patients	153 patients
Randomization	2:1 ([¹⁷⁷ Lu]Lu-DOTATATE vs. standard of care)	2:1 ([¹⁷⁷ Lu]Lu-DOTATATE vs. standard of care)
Primary endpoint	PFS (according to RANO meningioma criteria)	PFS (according to RANO meningioma criteria)
Secondary endpoints	Radiologic response, overall survival, safety, quality of life, neurologic function	PFS at 6 mo, PFS after cross-over; overall survival, overall survival at 12 mo, safety, radiologic response
Exploratory endpoints	Dosimetry; imaging-based and tissue-based translational analyses	Not specified in detail
Eligible histology	Recurrent WHO grade 1–3 meningioma	Recurrent WHO grade 1–3 meningioma
Progression requirement	Measurable disease (at least 10 × 10 mm contrast enhancing lesion), >25% growth in last 2 y or new lesion	Measurable disease (at least 10 × 10 mm contrast enhancing lesion), ≥15% growth in 6 mo or ≥25% in 12 mo, or new lesion
SSTR PET uptake criteria	SUV _{max} >2.3, SSTR tracer not specified	[⁶⁸ Ga]Ga-DOTATATE PET with Krenning score ≥ 3
Systemic therapy history	Systemic therapy-naïve; prior surgery or radiotherapy allowed	Prior systemic therapy permitted, except prior SSTR-targeted therapy
Experimental treatment	Up to 4 cycles of [¹⁷⁷ Lu]Lu-DOTATATE, 7.4 GBq every 4 wk	4 cycles of [¹⁷⁷ Lu]Lu-DOTATATE, 7.4 GBq every 4 wk, with option for 2 additional cycles (4 + 2)
Control arm	Local standard of care	Local standard of care; cross-over to [¹⁷⁷ Lu]Lu-DOTATATE permitted at progression
Projected timelines	Primary endpoint readout ~2027; study completion ~2029	Timeline not specified

EORTC = European Organisation for Research and Treatment of Cancer; RTOG = Radiation Therapy Oncology Group; PFS = progression-free survival; RANO = Response Assessment in Neuro-Oncology; WHO = World Health Organization.

MOMENTUM-1 has been registered but is not yet accruing. The LUMEN-1 trial was activated for accrual on March 10, 2025, and recruited the first patient in May 2025. It aims to recruit patients from 35 centers across 10 European countries, with primary end-point readout projected after 2 y and study completion after 5 y.

CHALLENGES AND THE NEED FOR ROBUST CLINICAL EVIDENCE

Despite the potential, conducting such large-scale prospective trials comes with inherent challenges. The primary drawback is the long timeline; pending adequate accrual rates, the results on the primary endpoint will mature in 2027 and data on secondary endpoints by 2029, delaying the potential clinical benefits for patients and the neuro-oncology community. Furthermore, compassionate-use programs for PRRT are becoming increasingly common outside of clinical trials, making patient recruitment more difficult, as patients may prefer to access treatment without the risk of being randomized to standard care (i.e., without PRRT). Given the current lack of high-level evidence supporting PRRT in this indication, enrollment of patients with recurrent meningioma in clinical trials should clearly be prioritized over treatment in compassionate-use programs. Overall, it is imperative to acknowledge that only prospective, randomized trials can generate the level of evidence required to support widespread adoption of this therapy. The history of PRRT in neuroendocrine tumors serves as a lesson: although PRRT was used off-label in small cohorts for years, it was only with the NETTER trial (5) that PRRT became widely recognized and adopted. Lessons learned; this should not be repeated with PRRT for meningioma, and rigorous clinical validation is essential.

UNRESOLVED QUESTIONS AND FUTURE DIRECTIONS

While LUMEN-1 (and sister study MOMENTUM-1) represents a major step forward, several questions remain unanswered. Since the study uses a pragmatic threshold for the definition of PET positivity, the prognostic and predictive value of SSTR PET uptake intensity remains undefined and will be investigated as part of the study's exploratory analyses.

Although both trials use experienced centers with quality assurance, PET reconstruction was not standardized. This pragmatic choice enabled rapid initiation but may introduce variability, especially in LUMEN-1, which aims to assess the prognostic value of SSTR PET as an exploratory endpoint.

Although the dosing schedule (every 4 wk) is shorter than that in grade 1 and 2 neuroendocrine tumors (due to the faster tumor growth dynamics in recurrent meningioma), the dose itself is taken over from protocols for neuroendocrine tumors. However, it remains uncertain whether this is optimal for meningiomas. Further research is required to determine whether alternative dosing strategies may enhance treatment efficacy. One example is the LuDO-N study, in which children with neuroblastoma were given 2 high-activity administrations of PRRT, 2 wk apart (6). Up to date, dosimetry analyses in radiopharmaceutical therapies for meningiomas are scarce in the literature, with effective doses significantly lower than those seen in SSTR-expressing neuroendocrine tumors (7). In parallel, reported toxicity of PRRT in meningiomas is infrequent and mostly reversible (8). Dosimetry analyses included in the LUMEN-1 trial should help to address to these questions.

Nuclear medicine community efforts should thus be directed toward increasing the tumoral absorbed doses. In this line, intra-arterial administration, while more technically demanding than

intravenous delivery, could increase tumor uptake and enhance therapeutic efficacy, an important observation that warrants further investigation (9). Using a different radioemitter could increase the tumor dose and potentially improve efficacy. In radiopharmaceutical therapies, sequential use of α and β emitters has been proposed for enhanced treatment effects. Similarly, modifying the radiopharmaceutical could improve outcomes. Instead of using an SSTR agonist, an SSTR antagonist probably enhances tumor accumulation, as observed in the PROMENADE study (10) that compared [^{177}Lu]Lu-DOTA-JR11 with [^{177}Lu]Lu-DOTATOC. Additionally, combining PRRT with radiosensitizers such as the mTOR inhibitor everolimus, which regulates cell proliferation and survival, or immunotherapies could further enhance treatment efficacy (1). This approach is currently being investigated in the single-arm ELUMEN study (NCT06126588).

IMPLICATIONS FOR NUCLEAR MEDICINE AND NEURO-ONCOLOGY

For nuclear medicine specialists, neuro-oncology is still a relatively unfamiliar and emerging field. Aside from meningioma, imaging and therapeutic interventions are challenging because of the infiltrative nature of brain tumors and the presence of a partially intact blood–brain barrier or blood–tumor barrier, which can limit tracer uptake. Despite these challenges, neuro-oncology offers an exciting opportunity for nuclear medicine, with significant unmet clinical needs and promising advances in both technology and therapy on the horizon (1).

As meningiomas are the most common primary intracranial tumors in adults, the increasing popularity of theranostics is likely to increase awareness and exposure to these patients within the nuclear medicine community. The LUMEN-1 and MOMENTUM-1 trial will be key milestones in determining whether [^{177}Lu]Lu-DOTATATE can transition from an experimental therapy to a validated treatment option for recurrent meningioma.

CONCLUSION

Although the results of LUMEN-1 and MOMENTUM-1 will not be available for several years, these studies represent an essential step toward establishing evidence-based nuclear medicine treatments in neuro-oncology. The neuro-oncology and nuclear medicine communities must work together to ensure that the lessons learned from PRRT in neuroendocrine tumors are applied to meningiomas—ultimately improving outcomes for patients with these challenging tumors.

DISCLOSURE

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