^{177}Lu-DOTATATE in Combination with PARP Inhibitor Olaparib Is Feasible in Patients with Somatostatin-Positive Tumors: Results from the LuPARP Phase I Trial

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This phase I trial aimed to assess the feasibility and toxicity of combining the poly(adenosine diphosphate–ribose) polymerase inhibitor olaparib with ^{177}Lu-DOTATATE in patients with somatostatin receptor–positive tumors, with the goal of enhancing treatment efficacy through the inhibition of tumor cell DNA repair mechanisms. **Methods:** Eighteen patients were enrolled, mostly with pancreatic or small intestinal neuroendocrine tumors or atypical lung carcinoids. Patients received a standard dose of ^{177}Lu-DOTATATE (7,400 MBq) for up to 4 cycles, combined with escalating doses of olaparib (50–300 mg twice a day [BID]). The primary objective was to evaluate toxicity using National Cancer Institute Common Toxicity Criteria version 5.0. Secondary objectives included time to progression, overall survival, response rate, and dosimetry variables. **Results:** The combination of olaparib and ^{177}Lu-DOTATATE was generally well tolerated. Five patients did not complete the 4 cycles because of progression, noncompliance, and carcinoid crisis after the first ^{177}Lu-DOTATATE infusion. Among the remaining patients, thrombocytopenia was the primary dose-limiting toxicity, observed in 3 patients at the 300-mg dose level. Other toxicities were mild, predominantly low-grade bone marrow suppression, nausea, and fatigue. **Conclusion:** This study demonstrates that combining olaparib with ^{177}Lu-DOTATATE is feasible, with toxicity primarily related to thrombocytopenia. On the basis of the findings, we recommend a starting dose of 200 mg BID for future studies, with the potential to escalate to 300 mg BID depending on patient tolerance. Further investigation in larger, randomized trials is warranted to assess the clinical efficacy of this combination and optimize dosing strategies.

Key Words: peptide receptor radionuclide therapy; PRRT; ^{177}Lu-DOTATATE; somatostatin receptors; PARP inhibitor; neuroendocrine tumors

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Peptide receptor radionuclide therapy (PRRT) with ^{177}Lu linked to a somatostatin analog is a mainstay strategy for patients with low- to intermediate-grade metastatic tumors expressing somatostatin receptors. ^{177}Lu-DOTATATE was formally approved for gastroenteropancreatic neuroendocrine tumors (GEPNETs) after the NETTER-1 trial, which demonstrated increased progression-free survival compared with somatostatin analogs (*1*) but no survival advantage with longer follow-up (*2*). This targeted radiation therapy may provide a prolonged treatment effect, sometimes lasting for several years, but some patients experience suboptimal responses or early relapse, and ultimately all patients will progress, highlighting the need for improved treatment strategies.

Strategies to optimize treatment efficacy include modifying the number of treatment cycles or adjusting the administered activity based on the absorbed doses to critical organs, such as the kidneys (*3–5*). In addition, because ^{177}Lu-DOTATATE is generally well tolerated, there is potential to explore combination therapies. Feasibility studies have been performed with ^{177}Lu-DOTATATE combined with chemotherapy agents such as capecitabine and temozolomide (*6–8*) but indicated increased toxicity with the combination (*9*), as well as with the mTOR inhibitor everolimus (*10*).

One limitation of ^{177}Lu-DOTATATE is the tumor cells' ability to repair DNA damage. ^{177}Lu decays primarily by emitting β-particles, which penetrate up to 1.5 mm in tissue, predominantly causing single-strand breaks in the DNA. However, the primary cell-killing effect of ionizing radiation is due to double-strand breaks, because these are more challenging to repair than single-strand breaks. Poly(adenosine diphosphate–ribose) polymerase 1 (PARP-1) inhibitors are pharmaceuticals that inhibit the repair of DNA damage (*11*). Combining a PARP inhibitor with ^{177}Lu-DOTATATE could sensitize tumor cells to β-irradiation and increase the likelihood of tumor cell death by preventing effective repair of radiation-induced damage (*12*,*13*).

This combination strategy is theoretically appealing and has been preclinically investigated by Nonnekens et al. (*13*), who demonstrated that cells expressing somatostatin receptors could be synergistically sensitized to PRRT when combined with the PARP inhibitor olaparib. This combination resulted in increased cell death and reduced cellular proliferation compared with PRRT alone, primarily because of a greater number of double-strand breaks, leading to genomic instability (*13*).

To optimize the sequence of this combination, biokinetic modeling was conducted (*14*). The published results suggest that to maximize the tumor–to–normal tissue absorbed dose ratio, olaparib should be administered approximately 24 h after the start of the ^{177}Lu-DOTATATE infusion, thereby minimizing the risk of bone marrow toxicity. Olaparib administration should continue for up to 4 wk, after which the irradiation dose to the tumor becomes

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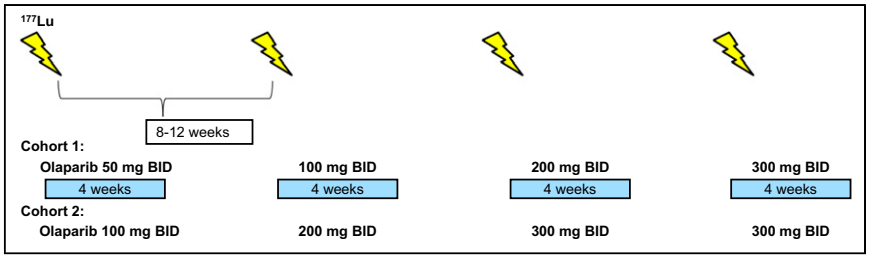

FIGURE 1. Schematic overview of study design.

minimal and no additional effect from PARP inhibition is expected. This approach also allows normal tissue time to recover from nonspecific systemic side effects associated with olaparib.

These findings informed the design of a phase I clinical trial aimed at assessing the toxicity and feasibility of combining ^{177}Lu-DOTATATE with olaparib (^{177}Lu-DOTATATE and olaparib in somatostatin receptor positive tumors, NCT04375267). Here, we report the primary objective of the study, which focuses on the assessment of toxicity.

MATERIALS AND METHODS

This prospective phase I trial evaluated the combination of a standard dose of ^{177}Lu-DOTATATE (7,400 MBq for up to 4 infusions) with individual dose escalation of olaparib (Fig. 1). The study was approved by the Swedish Ethical Review Authority, and all patients provided informed consent before study-specific procedures. The primary objective was to assess the toxicity and feasibility of the combination, measured by Common Terminology Criteria for Adverse Events version 5.0 (National Cancer Institute). Secondary objectives included time to progression, overall survival, time to death from any cause, response rate, and dosimetry variables.

Eligible patients had NETs or other tumors expressing somatostatin receptors, as confirmed by ^{68}Ga-DOTATATE PET, including grade 2–3 GEPNETs, other NETs after standard therapy, or inoperable meningiomas not suitable for external radiotherapy. Patients were required to have documented disease progression within the past 14 mo and to have regional or distant metastases, or unresectable localized disease. Tumors had to be measurable according to RECIST 1.1, and patients needed a performance status of 0–1 with a life expectancy greater than 6 mo. Patients were required to be more than 18 y old (no upper age limit) and have adequate organ function, including a glomerular filtration rate greater than 50 mL/min. Key exclusion criteria included grade 1 GEPNETs, previous treatment with ^{177}Lu-DOTATATE, antitumoral treatment (chemotherapy, tyrosine kinase inhibitors, and interferon) within 4 wk, or persisting toxicity from prior treatment. Patients with significant heart disease (New York Heart Association class III–IV) or extensive liver metastases with impaired liver function (>grade 1 of the Common Terminology Criteria for Adverse Events) were also excluded.

Pretreatment work-up included a CT scan of the thorax and abdomen, ^{18}F-FDG PET/CT, ^{68}Ga-DOTATATE or ^{68}Ga-DOTATOC PET within 6 wk, iohexol clearance testing, and comprehensive blood sampling. The ^{177}Lu-DOTATATE infusion was administered according to clinical practice with amino acid support (Vamin; Fresenius Kabi), with 1,500 mL given intravenously over 6–8 h starting 30 min before the radiopharmaceutical. Antiemetics, such as corticosteroids and 5-hydroxytryptamine type 3 inhibitors, were given, and 7,400 MBq of ^{177}Lu-DOTATATE was infused intravenously over 30 min. Starting on day 2 (24 h after infusion), patients received 4 wk of oral olaparib twice a day (BID).

The study planned to include 18 patients. Cohort 1 started with olaparib at 50 mg BID for the first cycle, with dose escalation in subsequent cycles to 100, 200, and 300 mg BID if no dose-limiting toxicities (DLTs) occurred (Fig. 1). ^{177}Lu-DOTATATE infusions were repeated every 8–12 wk for 4 cycles. A DLT was defined as any treatment-related reaction of grade 3 or higher of the Common Terminology Criteria for Adverse Events deemed attributable to olaparib and affecting treatment continuation (excluding short-term grade 3 nausea because of the ^{177}Lu-DOTATATE infusion). If a DLT occurred at the 50-mg dose level, olaparib was discontinued, and the patient continued with ^{177}Lu-DOTATATE alone. If a DLT occurred at higher doses (100, 200, or 300 mg), the subsequent cycle was deescalated by 1 dose level. Depending on cohort 1 outcomes, the starting dose in subsequent cohorts could be increased to 100 mg BID.

TABLE 1
Patient Characteristics

Variable	*n*
Sex	
Male	11
Female	7
Performance status	
0	8
1	10
Age (y)	65.5 (42–84)
Ki-67	15
<3%	0
3%–20%	10
>20%	5
Tumor type	
Pancreatic NETs	7
Small intestinal NETs	4
AC lung NETs	4
Other*	3
Metastatic disease	17
Previous lines of systemic therapy	
0–1	8
2–3	9
>3	1
Previous therapies	
Somatostatin analogs	14
Chemotherapy	11†
Surgery	8
mTOR inhibitor or tyrosine kinase inhibitor	7
Other‡	6

*Meningioma, medullary thyroid cancer, and unknown NET.
†One patient received systemic chemotherapy because of different malignancy after NET diagnosis.
‡External radiation, liver embolization, or liver radioembolization.
AC = atypical carcinoid.
Age is median followed by range in parentheses.

SPECT imaging for dosimetry was performed after each cycle. Patients were monitored with weekly blood tests and follow-up visits at 2 and 4 wk after infusion. CT scans of the thorax and abdomen was performed after 2 and 4 cycles and every 3 mo thereafter. ^{68}Ga-DOTATATE or ^{68}Ga-DOTATOC PET was performed at 3 and 12 mo after the last ^{177}Lu-DOTATATE infusion and then annually. If the ^{18}F-FDG PET/CT scan was positive at baseline, it was repeated at the same intervals.

RESULTS

In total, 18 patients were included in the study. Most patients had pancreatic NETs (n = 7), small intestinal NETs (n = 4), or atypical lung carcinoids (n = 4). All patients had a performance status of 0–1, with a median age of 65 y (range, 42–84 y) and a Ki-67 index between 7% and 50%. Detailed patient characteristics are presented in Table 1.

All patients in the first cohort were escalated to 200 mg or more of olaparib, and the starting dose was increased to 100 mg BID for the second cohort. Subsequent cycles were dosed at 200 and 300 mg BID. Three patients had progressive disease after the first 2 cycles and were removed from the study. Three patients did not escalate to the maximum dose despite no DLT: 1 because of grade 1 abdominal pain, 1 because of prolonged grade 2 thrombocytopenia, and 1 because of grade 2 nausea and fatigue. One patient was noncompliant, and another experienced a carcinoid crisis after the first ^{177}Lu-DOTATATE infusion, leading to study discontinuation. Consequently, 10 patients completed escalation of olaparib: all reached 200 mg BID without a DLT, and 7 reached 300 mg BID. Three patients developed grade 3 thrombocytopenia at the 300-mg dose level (Table 2), which resolved to grade 0–1 within 6 mo. Two of these patients had bone metastases.

Reported adverse events occurring in at least 3 patients are listed in Table 3, and additional rare events in fewer than 3 patients are listed in Supplemental Table 1 (supplemental materials are available at http://jnm.snmjournals.org). The most common adverse events, aside from bone marrow toxicity, were low-grade nausea and fatigue. Lymphocytopenia rated at least grade 3 was common but not classified as a DLT, because it is typically associated with PRRT. Four severe adverse events were reported, all requiring hospitalization or extended hospital stay, but nonattributable were to olaparib; these adverse events were infection, traumatic fall, congestive heart failure, and carcinoid crisis. The carcinoid crisis occurred after the first infusion of ^{177}Lu-DOTATATE; this patient did not receive olaparib, and no further study-related treatment was administered.

Longer follow-up is needed to determine efficacy and other secondary endpoints, but RECIST assessment at 6 mo follow-up demonstrated a disease control rate of 69% (11/16, excluding the 2

TABLE 2
Cycles, Escalated Dose of Olaparib, and DLT

Patient	Cycles (*n*)	Reached dose of olaparib	DLT	Other reason for hampered escalation
Cohort 1				
1	2	100 mg BID		Progressive disease after 2 cycles*
2	4	300 mg BID		
4	4	200 mg BID		Abdominal pain G1†
5	2	100 mg BID		Progressive disease after 2 cycles*
6	4	300 mg BID		
7	2	50 mg BID		Noncompliant*
8	4	100 mg BID		Fatigue G2, nausea G2, loss of appetite G2
9	4	300 mg BID		
10	4	300 mg BID		
11	4	300 mg BID‡	Thrombocytopenia G3	
12	4	300 mg BID		
Cohort 2				
13	4	300 mg BID‡	Thrombocytopenia G3	
14	3	100 mg BID		Thrombocytopenia G2
15	4	300 mg BID		
16	4	300 mg BID‡		Thrombocytopenia G2
17	1	0 mg		Carcinoid reaction on first ^{177}Lu infusion*
19	2	200 mg BID		Progressive disease after 2 cycles*
20	4	300 mg BID‡	Thrombocytopenia G3	

*Premature study discontinuation.
†Not escalated at cycle 1 because of abdominal pain G1, so did not reach 300 mg.
‡Discontinued last cycle of olaparib.
G1 = grade 1; G2 = grade 2; G3 = grade 3.
Patients 3 and 18 were excluded from the study.

TABLE 3
Adverse Events in at Least 3 Patients

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	11 (61)	5 (28)		
Thrombocytopenia	6 (33)	3 (17)	5 (28)	
Leucopenia	4 (22)	6 (33)	3 (17)	
Lymphocytopenia	1 (6)	5 (28)	10 (56)	1 (6)
Neutropenia	1 (6)	5 (28)	3 (17)	
Nausea	11 (61)	3 (17)		
Fatigue	9 (50)	4 (22)	1 (6)	
AST increased	8 (44)			
Hyponatremia	5 (28)	1 (6)		
Hypochloremia	5 (28)			
Diarrhea	5 (28)			
Hypokalemia	5 (28)			
ALT increased	4 (22)	2 (11)		
ALP increased	4 (22)	1 (6)		
Weight loss	4 (22)	1 (6)		
Bicarbonate increased	4 (22)			
Alopecia	4 (22)			
Abdominal pain	3 (17)	1 (6)	1 (6)	
Creatinine increased	3 (17)	1 (6)		
Dizziness	3 (17)	1 (6)		
Dyspnea	3 (17)			
Bilirubin increased	2 (11)	1 (6)	1 (6)	
Hypotension	2 (11)	2 (11)		
Constipation	2 (11)	1 (6)		
Pain	1 (6)	2 (11)	1 (6)	

AST = aspartate transaminase; ALT = alanine transaminase; ALP = alkaline phosphatase.
Data are number followed by percentage in parentheses.

patients who were removed from study because of noncompliance and carcinoid reaction). Three patients with pancreatic NETs (2 patients with grade 3 and 1 patient with a high grade 2) had progressive disease after just 2 cycles, 1 patient had progressive disease after 4 cycles, and 1 patient had progressive disease at 6 mo follow-up. Twelve patients were still participating in the study at 6 mo follow-up and had partial remission (3 patients), stable disease (8 patients), and progressive disease (1 patient).

DISCUSSION

This phase I trial demonstrates the feasibility of combining the PARP inhibitor olaparib with ^{177}Lu-DOTATATE. On the basis of our findings, we recommend that future studies begin with a dose of olaparib at 200 mg BID, escalating to 300 mg in subsequent cycles if bone marrow function permits.

PARP inhibition is a promising strategy for enhancing PRRT efficacy. As monotherapy, PARP inhibitors generally do not harm normal cells but are effective against DNA repair–deficient cancer cells, such as BRCA-mutated breast cancer cells (*15*). When combined with β-emitters, the ability of PARP inhibitors to impair DNA repair may increase the frequency of tumoricidal double-strand breaks. Preclinical data suggest a class effect across different PARP inhibitors, with several studies reporting synergistic effects. In addition to the synergy observed with olaparib plus ^{177}Lu-DOTATATE mentioned earlier (*13*), similar effects have been observed with olaparib and ^{131}I-meta-iodobenzylguanidine (*16*), ^{177}Lu-DOTATATE and talazoparib (*17*), and other PARP inhibitors (*18*).

To our knowledge, no clinical data have been published on PARP inhibitors in combination with PRRT, but several studies are ongoing (Table 4). A preliminary report has been presented as a conference abstract from a phase I–II dose-escalation trial of olaparib (50, 100, 200, and 300 mg). This trial uses a classic 3 + 3 phase I design, rather than individual dose escalation, and olaparib was administrated for approximately 4 wk, starting 2 d before ^{177}Lu-DOTATATE infusion (*19*). In addition, 4 other trials are recruiting for a Dutch phase I trial (NCT05870423) in locally advanced or metastatic NETs, using a 3 + 3 design with olaparib escalation from 100 to 300 mg that starts 3 d before ^{177}Lu-DOTATATE and continues for 2 wk after infusion, and an Australian phase I trial (NCT05053854) in grade 2 GEPNETs, evaluating escalated doses of talazoparib administrated on days 2–6 after ^{177}Lu-DOTATATE infusion. In addition, an ongoing phase I–II trial with an initial escalation phase of olaparib for 4 wk per cycle (NCT04086485) is in progress, and a recently launched phase II trial of ^{177}Lu-DOTATATE and olaparib in children and adolescents (NCT06607692) is also under way (Table 4).

In some of these trials with olaparib, the PARP inhibitor is administrated before ^{177}Lu-DOTATATE infusion. In contrast, we delayed olaparib administration (similar to the Australian trial with talazoparib) based on biokinetic modeling, which suggested that early administration might increase bone marrow toxicity. Thrombocytopenia, a known side effect of olaparib, was observed in 3 of 10 fully evaluable patients at the 300-mg dose level, although it was transient. Two of these patients had bone metastases. Other toxicities were generally mild, predominantly grade 1–2 bone marrow suppression, with some more severe lymphocytopenia as expected with PRRT. Because thrombocytopenia was the only DLT observed, further research on bone marrow dosimetry is warranted.

PARP inhibition is just one of many possibilities to intensify treatment with ^{177}Lu-DOTATATE or ^{177}Lu-DOTATOC. Given the excellent tolerability of ^{177}Lu-DOTATATE as monotherapy, there are numerous avenues for combination therapy or treatment customization. Individualized approaches might adjust the number of cycles or the activity per cycle based on the radiation dose to the kidneys, a strategy supported by promising prospective data, although no randomized trials have been conducted yet (*3–5*). Another option is linking ^{177}Lu to a somatostatin antagonist (*20*,*21*), but there is some concern with regard to bone marrow toxicity. Alternatively, replacing ^{177}Lu with α-emitters such as ^{231}Bi, ^{225}Ac, or ^{212}Pb offers a potential advantage; a phase I trial showed ^{212}Pb-DOTAMTATE to be well tolerated and effective (*22*). β-emitters such as ^{161}Tb, which also emit Auger electrons, represent another promising option (*23–26*).

Combination trials integrating chemotherapy (e.g., temozolomide and capecitabine) and everolimus with PRRT have been performed (*6–8*,*10*), although no published studies have shown superiority over PRRT alone. The START-NET trial (NCT05387603) is a 3-armed randomized trial that compares standard PRRT with 4 cycles of ^{177}Lu-DOTATOC and an individualized approach based on kidney dosimetry; the third arm adds capecitabine for ^{18}F-FDG–positive tumors. In addition, at least 4 other trials are under way for PRRT

TABLE 4
Ongoing Studies with ^{177}Lu-PRRT and PARP Inhibitors

Study	Phase	*n*	Reference
^{177}Lu-DOTATATE in combination with olaparib in metastatic or inoperable gastrointestinal NETs	I–II	33	(*16*)
^{177}Lu-DOTATATE in combination with olaparib in recurrent or relapsed solid tumor expressing somatostatin receptor (children and adolescents)	II	25	NCT06607692
^{177}Lu-DOTATATE in combination with olaparib in locally advanced or metastatic NETs	I	24	NCT05870423
^{177}Lu-DOTATATE in combination with talazoparib in NETs	I	24	NCT05053854
^{177}Lu-DOTATATE in combination with olaparib in inoperable GEPNETs	I–II	42	NCT04086485

with ^{177}Lu and a comparator in a randomized setting. The COMPETE trial (NCT03049189) compares ^{177}Lu-edotreotide with standard-dose everolimus in GEPNETs, and a phase II trial compares ^{177}Lu-DOTATOC with everolimus in bronchial NETs (NCT04665739). Another phase II trial compares ^{177}Lu-DOTATOC with capecitabine plus temozolomide in pancreatic NETs (NCT05247905), whereas the COMPOSE trial (NCT04919226) compares ^{177}Lu-edotreotide with the standard of care (capecitabine plus temozolomide; folinic acid, fluorouracil, and oxaliplatin; or everolimus) in grade 2–3 GEP-NETs. Efficacy in this latter group has been demonstrated with ^{177}Lu-DOTATATE in the NETTER-2 trial (*27*), although the comparator was a somatostatin analog, a treatment rarely used alone in highly proliferative grade 2–3 tumors.

Although this phase I trial establishes the feasibility of combining the PARP inhibitor olaparib with ^{177}Lu-DOTATATE, several limitations must be acknowledged. There are so far inadequate efficacy data, and the small sample size, inherent to early-phase trials, limits the ability to detect rare adverse events. In addition, the trial's design, with individual dose escalation, might not fully represent the tolerability and safety profile across broader patient populations. The short follow-up period restricts the assessment of long-term efficacy and toxicity, especially bone marrow function and potential delayed adverse effects. In particular, myelodysplastic syndrome and acute myeloid leukemia, which have been associated with both PARP inhibitors and PRRT, need to be monitored closely with long-term follow-up.

CONCLUSION

This phase I trial demonstrates the feasibility and tolerability of combining the PARP inhibitor olaparib with ^{177}Lu-DOTATATE in patients with somatostatin receptor–positive tumors. The findings suggest that starting olaparib at 200 mg BID, with potential escalation to 300 mg BID, is a viable strategy that warrants further exploration. The observed bone marrow toxicity, particularly thrombocytopenia, underscores the need for careful patient selection and monitoring, as well as further research into optimizing bone marrow dosimetry. Although this combination approach holds promise for enhancing the efficacy of PRRT, larger randomized trials are necessary to determine its clinical benefit over monotherapy and to refine the optimal dosing schedule.

DISCLOSURE

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KEY POINTS

QUESTION: Can the combination of olaparib and ^{177}Lu-DOTATATE enhance treatment efficacy in patients with somatostatin receptor–positive tumors while maintaining manageable toxicity?

PERTINENT FINDINGS: The combination was generally well tolerated, with thrombocytopenia being the primary DLT at a dose level of 300 mg BID of olaparib. The study recommends starting at 200 mg BID, with potential escalation depending on patient tolerance.

IMPLICATIONS FOR PATIENT CARE: This combination therapy offers a promising approach for enhancing treatment in patients with somatostatin receptor–positive tumors. However, careful monitoring of bone marrow function is essential, and further research is needed to optimize dosing and confirm clinical efficacy in larger trials.

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