Survival Outcomes in Metastatic Gastroenteropancreatic Neuroendocrine Tumor Patients Receiving Concomitant $^{225}$Ac-DOTATATE–Targeted $\alpha$-Therapy and Capecitabine: A Real-World-Scenario Management-Based Long-Term Outcome Study

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Although the short-term results of targeted $\alpha$-therapy (TAT) with $^{225}$Ac-DOTATATE in gastroenteropancreatic neuroendocrine tumors (GEP-NETs) have proven the therapy to be effective, to our knowledge no one has assessed the long-term outcome results. In this study, we aimed to evaluate the long-term outcome of $^{225}$Ac-DOTATATE TAT in patients with somatostatin receptor–expressing advanced-stage metastatic GEP-NETs.

**Methods:** Patients with $^{68}$Ga-DOTANOC PET/CT scans showing moderate-to-high somatostatin receptor expression were recruited. Systemic TAT was performed on 91 adults with GEP-NETs (54 men and 37 women; mean age, 54.3 y; range, 25–75 y) using $^{225}$Ac-DOTATATE (100–120 kBq/kg of body weight). All patients were given capecitabine therapy as a radiosensitizer (2 g/d) from days 0 to 14 of every $^{225}$Ac-DOTATATE treatment cycle. Patients were categorized into 3 groups based on the status of prior $^{177}$Lu-peptide receptor radionuclide therapy (PRRT): a prior-$^{177}$Lu-PRRT-naïve group; a prior-$^{177}$Lu-PRRT–refractory group; and a $^{177}$Lu-PRRT–refractory group. Primary endpoints were overall survival (OS), and secondary endpoints included progression-free survival (PFS), objective tumor response, clinical response, and assessment of treatment-related toxicities. **Results:** Among the 91 patients, 57 underwent prior $^{177}$Lu-DOTATATE therapy (24 with controlled disease [partial response/stable disease] and 33 with progressive disease [PD]). In total, 453 $^{225}$Ac-DOTATATE TAT cycles were administered (median, 4 cycles per patient; range, 1–10) in a median follow-up of 24 mo (range, 5–41 mo). Median OS was not attained, with a 24-mo OS probability of 70.8%. In multivariate analysis, prognostic factors associated with a poor OS included the presence bone metastases (hazard ratio [HR], 2.501; 95% CI, 1.826–9.769; $P < 0.001$) and $^{225}$Ac-DOTATATE therapy–refractory disease (HR, 5.791; $P < 0.032$) and $^{225}$Ac-DOTATATE therapy–refractory disease (HR, 2.501; 95% CI, 1.826–9.769; $P < 0.001$) and $^{225}$Ac-DOTATATE therapy–refractory disease (HR, 8.781; 95% CI, 3.843–20.062; $P < 0.0001$). Median PFS was also not reached, with a 24-mo PFS probability of 67.5%. The multivariate analysis revealed only $^{177}$Lu-PRRT–refractory disease to be significantly associated with a reduced PFS (HR, 14.338; 95% CI, 1.853–97.698; $P = 0.011$). Two of 79 patients (2.5%) with assessable disease experienced a complete response, 38 (48%) had a partial response, 23 (29%) had stable disease, and 16 (20.2%) had PD. PD was observed in more patients from the prior-$^{177}$Lu-PRRT–refractory group (11/33, 34%) than in $^{177}$Lu-PRRT-naïve patients (4/24, 11%; $P = 0.056$). Patients from the prior-$^{177}$Lu-PRRT–refractory group had the highest risk of poor PFS (HR, 13.553; 95% CI, 4.343–42.271; $P = 0.0009$). A significant clinical benefit was achieved after $^{225}$Ac-DOTATATE therapy with minimal treatment-related toxicities. **Conclusion:** In long-term results, $^{225}$Ac-DOTATATE TAT showed promise and improved the OS, even in patients refractory to prior $^{177}$Lu-DOTATATE treatment, with transient and acceptable adverse effects.

**Key Words:** $^{225}$Ac-DOTATATE TAT; GEP-NETs; overall survival; progression-free survival; objective response

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Expanded treatment options have recently become available to patients with well-differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NETs) (1). Surgery offers the best chance of curing patients with localized GEP-NETs; however, surgery is not feasible when extensive metastases are present. In such cases, other options include somatostatin analogs (SSAs; e.g., lanreotide and octreotide) (2,3), interferons, tyrosine kinase inhibitors (e.g., sunitinib) (4), mammalian-target-of-rapamycin inhibitors (e.g., everolimus) (5), peptide receptor radionuclide therapy (PRRT) (6), systemic chemotherapy, and liver-targeted therapies, depending on the extent, stage, and location of disease and the tumor grade (7). The phase III NETER-1 trial provided evidence for the efficacy and safety of PRRT using $^{177}$Lu in this setting (8). However, only 18% of patients achieved a partial or complete response, despite treatment with $^{177}$Lu-DOTATATE, a $\beta$- and $\gamma$-emitting radionuclide, and most patients relapsed within 2–3 y of treatment (9,10).

One promising option that has gained interest is using high-linear-energy-transfer $\alpha$-emitting radioisotopes such as $^{225}$Ac and $^{218}$Bi instead of low-linear-energy-transfer $\beta$-emitting radioisotopes such as $^{90}$Y and $^{177}$Lu. The theoretic physical advantages of $\alpha$-radiation over $\beta$-radiation are an endearing option to further improve the efficacy of PRRT by labeling the peptides with $\alpha$-particle emitters (11).

Results from preclinical and clinical studies have suggested that an alternative strategy using PRRT delivering an $\alpha$-emitting radionuclide...
such as $^{213}\text{Bi}$ and $^{225}\text{Ac}$-DOTATOC may have promise in patients with advanced GEP-NETs refractory to $^{177}\text{Lu}$-PRRT ($^{12}$–$^{16}$).

One clinical study used $^{213}\text{Bi}$-DOTATOC in 7 patients with neuroendocrine tumor progression on $\beta$-PRRT ($^{17}$). Although that study demonstrated the therapeutic potential of this approach, $^{213}\text{Bi}$-DOTATOC was administered via intraarterial delivery, limiting the more widespread application of $\alpha$-radionuclide therapy in the real-world setting. $^{213}\text{Bi}$ also has a physical half-life of only 46 min, resulting in logistic challenges for broader adoption.

These studies prompted us to investigate the role of $^{225}\text{Ac}$-DOTATATE as salvage treatment for patients with GEP-NETs ($^{18}$). Initial results from 32 patients who had previously received $^{177}\text{Lu}$-PRRT indicated that $^{225}\text{Ac}$-DOTATATE administered intravenously induced sustained responses. Approximately two thirds of the 24 patients (15/24, 62.5%) who underwent interim morphologic response analysis had a partial response, and the disease control rate of the 24 patients (15/24, 62.5%) who underwent interim morphologic response analysis had a partial response, and the disease control rate was 100% (15 with PR and 9 with stable disease). Furthermore, there was no documented progressive disease (PD), and no deaths occurred during a median follow-up of 8 mo (range, 2–13 mo). We observed minimal and reversible toxicities and no life-threatening adverse events (AEs). These data suggested that multiple cycles of therapy could be safely administered without a significant risk of either acute or delayed radiation toxicity ($^{18}$). Despite the favorable short-term results, as far as we are aware no comprehensive long-term outcome results have been extensively studied to demonstrate the survival benefit of $^{225}\text{Ac}$-DOTATATE therapy in both prior $^{177}\text{Lu}$-PRRT and $^{177}\text{Lu}$-PRRT-naive groups of GEP-NET patients.

In the current study, we extensively studied the long-term follow-up data in an expanded cohort of patients to assess overall survival (OS), progression-free survival (PFS), factors predicting survival, response to treatment, and the patterns of the delayed AE profile in advanced metastatic GEP-NETs.

**MATERIALS AND METHODS**

**Study Design**

The independent institutional review board of All India Institute of Medical Sciences approved the study. All patients provided written informed consent before participating. Ethical clearance was received (reference number IEC-517). The study design and treatment regimen are depicted schematically in Figure 1. The methodology is detailed in the supplemental materials (available at http://jnm.snmjournals.org).

The study was on patients with histologically well-differentiated, inoperable, or metastatic GEP-NETs. Patients were included if they had a history of prior concomitant therapies, such as SSAs and chemotherapy, as well as $^{177}\text{Lu}$-DOTATATE therapy. Essential prerequisites were significant somatostatin receptor expression and at least 1 measurable lesion on the CT component of the baseline $^{68}\text{Ga}$-DOTANOC PET/CT scan (uptake ≥ 2 as compared on maximum-intensity-projection, coronal, and transaxial images). Patients with inadequate laboratory parameters (baseline hemoglobin < 9 g/dL, platelet count < 75,000/μL, serum creatinine > 1.6 mg/dL, or serum bilirubin > 3 mg/dL) or a Karnofsky performance status (KPS) of less than 40 were excluded.

**Treatment Planning and Follow-up**

**Image Acquisition.** All patients underwent a baseline diagnostic $^{68}\text{Ga}$-DOTANOC PET/CT scan as a pretherapeutic work-up. For morphologic assessment, additional $^{68}\text{Ga}$-DOTANOC PET/CT scans were repeated within 6–8 wk after patients completed every 2–3 cycles of $^{225}\text{Ac}$-DOTATATE-targeted $\alpha$-therapy (TAT), when patients presented with clinical disease progression, or at the investigator’s discretion.

$^{68}\text{Ga}$-DOTANOC PET/CT Imaging. The $^{68}\text{Ga}$-DOTANOC PET/CT scans did not require special preparation. A mean activity of 111 MBq (3 mCi) was injected, and PET/CT scans were acquired between 45 and 60 min after injection. For the acquisition, the patient lay supine on the examination table. The protocol constituted of an initial

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**FIGURE 1.** $^{225}\text{Ac}$-DOTATATE TAT treatment regimen and follow-up. CBC = complete blood count; ECOG = Eastern Cooperative Oncology Group; KFT = kidney function testing; LFT = liver function testing; PS = performance status.
scout image to define the field of view from vertex to mid thigh, followed by diagnostic CT and PET scans. The diagnostic whole-body CT scan parameters involved a diagnostic-dose CT scan with 300–380 mAs, 120 kVp, a slice thickness of 3.75 mm, and a pitch of 0.6. Additionally, spot views were acquired if required, with a slice thickness of 1.25 mm on CT at 120 kVp, 300–380 mAs, and a pitch of 0.6.

The administration and route of the contrast medium depended on the site of the tumor and scan indication. Generally, CT scans were acquired with a nonionic, isomolar contrast medium (iodixanol injection, U.S. Pharmacopeia; 1 mL/kg of body weight) containing 320 mg I/mL intravenously or orally and a neutral oral contrast medium (water). Fifty-six patients were injected with nonionic, isomolar contrast medium. Positive oral (iodixanol) and neutral (water) contrast media were administered when indicated. All tumors were visualized on the diagnostic CT scan, but only tumors with measurable dimensions according to RECIST, version 1.1, were included for the assessment of morphologic response.

**Treatment.** Long- and short-acting somatostatin agents were stopped 4–5 wk and 48–72 h, respectively, before $^{225}$Ac-DOTATATE therapy. Premedications, including an antiemetic (ondansetron) or corticosteroid (dexamethasone), were administered and repeated if necessary. For kidney protection, a single-day kidney protection protocol was followed, which consisted of an injection solution containing lysine (23.3 g) and arginine (8 g) in 1 L of water. This cocktail was infused over 4 h, starting 30–60 min before the $^{225}$Ac-DOTATATE infusion.

As previously described, $^{225}$Ac-DOTATATE (100–120 kBq/kg [3–3.2 μCi/kg]) of body weight per cycle diluted in 50 mL of saline) was administered over 30 min (flow rate, 1.6 mL/min) every 8 wk up to a maximum cumulative dose of 111 MBq (3 mCi). All patients received capetebatine as a radiosensitizer (2 g) from days 0 to 14 of every cycle. Patients were monitored for 24 h after $^{225}$Ac-DOTATATE TAT to observe any acute side effects. Patients on supportive care or octreotide continued to receive those treatments at the investigator’s discretion.

Patients were withdrawn from the study in the event of any serious AEs; lack of adherence to the treatment protocol due to unavoidable pandemic conditions; demonstration of disease progression; withdrawal of consent to further treatment cycles; or death.

**Assessments.** Safety was monitored at baseline and at 8-wk intervals thereafter. Assessments included physical examination, vital parameters, laboratory tests (assessed at 2, 4, and 6- to 8-week intervals), and clinical evaluation via KPS and Eastern Cooperative Oncology Group (ECOG) performance status. Patients were given a diary to document any side effects or discomfort. With the exception of blood parameters, all other assessments were conducted at baseline and at 8 wk after each cycle of $^{225}$Ac-DOTATATE TAT or on withdrawal from the study or at treatment completion.

**Patient Groups.** On the basis of $^{177}$Lu-PRTT history, patients were categorized into 2 groups: a prior-$^{177}$Lu-PRTT group and a $^{177}$Lu-PRTT-naïve group (Fig. 2). The prior-$^{177}$Lu-PRTT group was further divided according to cancer status after $^{177}$Lu-PRTT, that is, those who were treatment-refractory and those who were stable or responded to $^{177}$Lu-PRTT (Fig. 2). Patients in the prior-$^{177}$Lu-PRTT-refractory group ($n = 33$) progressed during the $^{177}$Lu-DOTATATE treatment course or within 12 mo of completion of the $^{177}$Lu-DOTATATE treatment regimen. Patients in the prior-$^{177}$Lu-PRTT disease-control group ($n = 24$) completed the $^{177}$Lu-DOTATATE treatment regimen and achieved disease control (partial response or stable disease) but were further treated with $^{225}$Ac-DOTATATE because of the persistent high tumor burden. Patients in the $^{177}$Lu-PRTT-naïve group ($n = 34$) did not receive $^{177}$Lu-DOTATATE therapy at any point in the treatment course.

**Outcomes.** The primary endpoint was OS (defined as the time from initiation of $^{225}$Ac-DOTATATE TAT until death due to any cause or the date of the last contact). Patients who were lost to follow-up were considered alive but were censored (supplemental material). The key secondary endpoint was PFS (defined as the first observation of documented morphologic disease progression on diagnostic CT according to the assessment by RECIST 1.1) or the development of pleural/pericardial effusion/malignant ascites or disease-specific death, whichever occurred first. Other secondary endpoints included objective tumor response by RECIST 1.1, clinical response assessment with KPS and ECOG performance status (20), and evaluation of treatment-related AEs using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) and the Food and Drug Administration document entitled, “Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials” (21,22).

**Statistical Analysis.** Univariate analysis was used to compare characteristics among patient groups. On the basis of the normality of parameters, continuous variables with a normal distribution were represented as mean, SD, range, median, and interquartile range. Parameters of the same population at different time points were compared using a paired t-test (parametric test) or Wilcoxon signed-rank test (nonparametric test). OS and PFS plots were constructed using the Kaplan–Meier methodology; a log-rank test was used to compare survival between groups. The Cox proportional-hazards regression model was performed to determine the predictive and prognostic factors associated with OS and PFS. P values of less than 0.05 were considered to be significant. The analysis was conducted using MedCalc statistical software (version 15.1; MedCalc Software Ltd.).
RESULTS

Baseline Demographic and Clinical Characteristics of Patients

Between April 2018 and February 2022, 91 consecutive GEP-NET patients (54 men and 37 women, mean ±SD age, 54.3 ± 11.6 y; range, 25–75 y) were enrolled. The first 225Ac-DOTATATE TAT treatment was administered in April 2018, and the last patient was recruited in October 2021. The last date for follow-up cutoff was February 20, 2022. The median follow-up duration was 24 mo (range, 5–41 mo) from the start of 225Ac-DOTATATE TAT.

Baseline characteristics are summarized in Table 1. The pancreas (33%) was the most common site of the primary tumor, followed by the duodenum (14.3%) and ileum (13%). GEP-NETs were World Health Organization grade 1 in 33 patients (36.2%), grade 2 in 48 (52.7%), and grade 3 in 7 (7%) (Table 1; Supplemental Table 1). Primary or residual tumor was noted in 55 patients (60.4%), and all patients demonstrated metastases on somatostatin receptor PET/CT, with the most common metastatic sites being the liver (n = 88, 96.7%), lymph nodes (n = 66, 72.5%), and bone (n = 25, 27.5%)

<table>
<thead>
<tr>
<th>Characteristic Value</th>
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<tr>
<td><strong>Patient Characteristics at Baseline (n = 91)</strong></td>
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<tr>
<td>Characteristic</td>
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<td>Age (y)</td>
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<td>Sex</td>
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<td>Tumor location</td>
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<td>WHO = World Health Organization.</td>
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<td>Data are number and percentage, except for age.</td>
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(Observable Table 2). Eighteen patients (20%) had received prior chemotherapy (Supplemental Table 3), most of whom had 1 previous line (n = 12, 66.6%); 4 patients (22.2%) had 2 prior lines, and 2 (11%) had at least 3 prior lines. Ten symptomatic patients were on long-acting SSAs, which were stopped 4 wk before commencing 225Ac-DOTATATE TAT.

Treatment

The mean cumulative radioactivity administered was 35.52 MBq (range, 21.64–59.47 MBq [960 µCi; range, 583.7–1,607.3 µCi]). The median interval between treatment cycles was 8 wk. In total, 453 cycles of 225Ac-DOTATATE TAT were administered: 32 patients received 1–3 cycles, and the remaining 59 patients received 4–10 cycles (Supplemental Table 4). Three patients received a single cycle of 225Ac-DOTATATE TAT: the first patient died after the first cycle, the second was lost to follow-up, and the third withdrew consent.

Efficacy Assessment

OS and PFS. Twenty-six patients (26.5%) died during follow-up. The causes of death are detailed in Supplemental Table 5. In the overall patient population, the median OS was not attained, with a 24-mo survival probability of 70.8% (Fig. 3A). On univariate analysis, whereas 16 (16/33, 48.5%) deaths occurred in the prior-177Lu-PRRT–refractory group, of the 225Ac-DOTATATE patients, 4 (5/24, 12.5%) and 7 deaths (7/34, 20.6%) occurred in the prior-177Lu-PRRT disease-control group and 177Lu-PRRT naïve group, respectively (P = 0.0003) (Fig. 3B). Interestingly, in patients who demonstrated disease control on 177Lu-PRRT, none of the 3 deaths was disease-specific (Supplemental Table 5). The prior-177Lu-PRRT disease-control group showed significantly better OS than the 177Lu-PRRT–native group (Fig. 2). We speculated that these differences might be due to inherent differences in the baseline demographic or clinical characteristics of the patient cohorts. However, univariate comparison between the groups did not reveal any differences in the demographic parameters (Supplemental Table 6).

On univariate analysis, the presence of bone metastases (Fig. 3C), a cumulative 225Ac-DOTATATE TAT dose of less than 37,000 kBq (Fig. 3D), and PD to 225Ac-DOTATATE TAT (Fig. 3E) were associated with significantly poorer OS (Supplemental Table 7). However, on multivariate analysis, the presence of bone metastases (hazard ratio [HR], 2.718; 95% CI, 1.826–7.393; P = 0.028) and 225Ac-DOTATATE therapy–refractory disease (PD) persisted as significant prognostic factors associated with poor OS (HR, 8.781; 95% CI, 3.843–20.062; P < 0.0001) (Fig. 3E).

At the time of this analysis, median PFS had not been attained in the overall patient population. The median PFS was 30 mo in the prior-177Lu-PRRT–refractory group and was not reached in the prior-177Lu-PRRT disease-control group (HR, 13.533; 95% CI, 4.343–42.271; P = 0.0009) (Fig. 4A). Similarly, univariate analysis revealed an association between the presence of bone metastases (Fig. 4B) and a cumulative 225Ac-DOTATATE dose of less than 1 mCi and PD (HR, 2.718; 95% CI, 0.999–7.393; P = 0.028) (Fig. 4C; Supplemental Table 8). However, on multivariate analysis, only 177Lu-PRRT–refractory disease was significantly associated with a significantly reduced PFS (HR, 14.3; 95% CI, 1.853–97.6; P = 0.011).

Objective Response. Morphologic response to 225Ac-DOTATATE TAT according to the disease status on prior 177Lu-PRRT therapy is shown in Table 2. Two of the 79 evaluable patients (2.5%), both previously treated with 177Lu-PRRT, had a complete response; no complete responses were observed in the 177Lu-PRRT-naïve group. 68Ga-DOTANOC PET/CT revealed a partial response in 38
patients (48%) and stable disease in 23 (29%), for a disease control rate of 80%. Twelve and 4 progression events occurred in the prior-177Lu-PRRT and 177Lu-PRRT–naïve groups, respectively, representing a 40% lower estimated risk of progression in the 177Lu-PRRT–naïve group than in the prior-177Lu-PRRT group.

In the prior-177Lu-PRRT group, among 24 patients who experienced disease control with 177Lu-PRRT, 17 (74%) further showed a response to 225Ac-DOTATATE TAT. Promising response rates were also observed in 8 of 30 patients (27%; 1 complete response and 7 PRs) belonging to the prior-177Lu-PRRT–refractory group, with stable disease in a further 11 patients (36.6%; Fig. 1). PRs were observed in 15 of 27 patients (55.5%) in the 177Lu-PRRT–naïve groups.

Of the 17 patients with PD, 14 experienced disease-specific deaths, 2 have been rechallenged with an escalated 150 kBq/kg dose of 225Ac-DOTATATE and have shown disease stability, and the remaining patient refused to undergo any further treatment but is alive.

Clinical Response. Among the patients who were alive till the end of analysis, the median KPS significantly improved from 60 at baseline to 70 after treatment ($P < 0.0001$), and the median ECOG score enhanced from 2 to 1 ($P < 0.0001$). In the overall population, whereas the KPS improved from 60 to 70 ($P = 0.053$), ECOG status remained the same as the median baseline value of 2.

Toxicity and AEs

Treatment-related AEs occurring during 225Ac-DOTATATE TAT are shown in Supplemental Table 9. No renal or liver toxicity and no tumor-lysis syndrome were observed. One patient had grade 3 thrombocytopenia. Clinical disease-related symptoms, such as fatigue, loss of appetite, nausea, gastritis, abdominal pain, abdominal distension, and myalgia, were caused mainly by the nature of the cancer and the site of metastasis and were prevalent before the initiation of 225Ac-DOTATATE treatment. All the above symptoms improved after treatment.
Malignant ascites and pleural effusion, which are signs of PD, were observed in 14 and 2 patients, respectively. Grade 1 of 2 malignant ascites was present in 8 patients at baseline. Eventually, 4 patients experienced grade 2 malignant ascites, and 10 experienced life-threatening malignant ascites and died. One patient with pleural effusion also died.

Before initiation of $^{225}\text{Ac-DOTATATE}$, flushing was documented in 8 patients, 3 of whom had grade 3 flushing. After treatment, flushing improved to grade 1 in all patients.

Transient symptoms, including nausea, vomiting, and abdominal discomfort, were encountered in most patients during the amino acid infusion and $^{225}\text{Ac-DOTATATE}$ administration and settled within 24 h after treatment. Fatigue, myalgia, and loss of appetite were also observed and resolved within 1 wk after treatment.

**DISCUSSION**

In our short-term analysis on the first clinical experience with the $\alpha$-emitting conjugate $^{225}\text{Ac-DOTATATE}$ TAT in 32 patients with GEP-NETs who had exhausted or were refractory to $\beta$-emitting $^{177}\text{Lu-DOTATATE}$ therapy, we observed favorable responses with low toxicities (18). The study included an expanded cohort of 91 patients with an extended median follow-up of 24 mo, ranging from 5 to 41 mo. Our results provide further evidence that $^{225}\text{Ac-DOTATATE}$ is effective in patients with neuroendocrine tumors, a group with few therapeutic options, especially after progression on other therapies. Median OS and PFS were not attained. The objective response rate and disease control rates were 48% and 80%, respectively, and were lower than our previously reported short-term data showing a response rate of 63% and a disease control rate of 100%.

Though the current study had broad and heterogeneous inclusion criteria, it was conducted in a real-world setting based on everyday clinical practice that includes patients of poor performance status (31%) (ECOG status $\geq 3$)—a critical and optimistic perspective of this study. We believe that real-world–based clinical study results can be extended and translated to the general population. Moreover, in this study, several demographic and clinical variables were compared among 3 groups of patients whose categorization was based on the status of prior $^{177}\text{Lu-PRRT}$ therapy and who were matched (Supplemental Table 6), which ruled out the potential inherent bias.

Comparisons with the NETTER-1 median long-term OS result (23), 48 mo, revealed that $^{225}\text{Ac-DOTATATE}$ provided an additive OS benefit of 26 mo in the worst-outcome patient cohort, who were refractory to prior $^{177}\text{Lu-PRRT}$. Well in line with the phase III NETTER-1 (8) short-term result showing 14 deaths (12%) in the 116 neuroendocrine tumor patients who underwent $^{177}\text{Lu-DOTATATE}$ therapy as a first-line treatment option, our cohort of 34 $^{177}\text{Lu-PRRT}$–naïve patients reported a similar disease-specific death rate of 11.7% (4/34) in a median follow-up of 24 mo.

Another finding meriting comment is that in this cohort of patients from our group and the NETTER 1 group, the median OS was not attained. An interpretation of this finding is that the upfront use of $^{225}\text{Ac-DOTATATE}$ therapy in advanced neuroendocrine tumors may not be necessary as a mainstay option. Irrespective of the disease burden, patients can first be challenged with $^{177}\text{Lu-PRRT}$ and eventually be rechallenged with $\alpha$-based $^{225}\text{Ac-DOTATATE}$ therapy when a high disease burden is persistent despite attaining a maximum tolerable dose of $^{177}\text{Lu}$ ($\sim1.2$ Ci) or the patient is refractory to $^{177}\text{Lu-PRRT}$.

<table>
<thead>
<tr>
<th>Site of primary</th>
<th>Prior $^{177}\text{Lu-PRRT}$ naïve ($n = 57$)</th>
<th>177Lu-PRRT–naïve ($n = 34$)</th>
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<tbody>
<tr>
<td>Foregut ($n = 32$)</td>
<td>CR: 1 (3%) PR: 13 (40.6%) SD: 6 (18.7%) PD: 10 (31%) Not assessed: 3 (9.4%)</td>
<td>CR: 0 PR: 15 (44%) SD: 10 (29.4%) PD: 3 (8.8%) Not assessed: 7 (20.6%)</td>
</tr>
<tr>
<td>Midgut ($n = 11$)</td>
<td>CR: 0 PR: 6 (54.5%) SD: 3 (27.3%) PD: 2 (18.2%) Not assessed: 0</td>
<td>CR: 0 PR: 9 (55.6%) SD: 2 (12.2%) PD: 0 Not assessed: 4 (24.2%)</td>
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<td>Hindgut ($n = 7$)</td>
<td>CR: 1 (14.3%) PR: 2 (28.6%) SD: 2 (28.6%) PD: 2 (28.6%) Not assessed: 0</td>
<td>CR: 0 PR: 3 (42.8%) SD: 1 (14.3%) PD: 3 (42.8%) Not assessed: 0</td>
</tr>
<tr>
<td>Unknown ($n = 7$)</td>
<td>CR: 1 (28.6%) PR: 2 (28.6%) SD: 1 (28.6%) PD: 0 Not assessed: 0</td>
<td>CR: 0 PR: 3 (42.8%) SD: 1 (14.3%) PD: 3 (42.8%) Not assessed: 0</td>
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<tr>
<td>Total ($n = 57$)</td>
<td>CR: 2 (3.5%) PR: 23 (40.3%) SD: 16 (28%) PD: 12 (21%) Not assessed: 4 (7.0%)</td>
<td>CR: 0 PR: 15 (44%) SD: 7 (20.6%) PD: 4 (11.8%) Not assessed: 8 (23.6%)</td>
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**Table 2**

Morphologic Tumor Response Based on Primary Tumor Site

CR = complete response; PR = partial response; SD = stable disease.
Patients who achieved disease control (partial response or stable disease) with prior 177Lu-PRRT \( (n = 24) \) followed by retreatment with 225Ac-DOTATATE showed the best outcome, with a 24-mo OS probability of 95%, which was remarkably higher than in the 177Lu-PRRT-refractory \( (55.6\%) \) and naïve \( (62.6\%) \) groups. Moreover, only 3 deaths occurred in this group of patients, and none of the events was disease-specific. There may be 2 possible explanations for these findings. The first possibility is that 225Ac-DOTATATE significantly increased the OS as an adjuvant treatment option after 177Lu-PRRT. The alternative possibility is simply that patients had already achieved disease control on 177Lu-PRRT and could be followed up with a wait-and-watch approach until the disease progressed. However, only a double-arm randomized, controlled trial between the wait-and-watch group and the group receiving further 225Ac-DOTATATE treatment can be the definitive answer.

Rudisile et al. (24) studied the outcomes of 177Lu-PRRT retreatment in the salvage setting for all patients who responded to the initial standard 4 cycles of 177Lu-PRRT. They observed an additional response rate of 3%, PFS of 6 mo, and OS of 51 mo. The largest systematic review and metaanalysis, by Strosberg et al. (25), examined published evidence of 177Lu-PRRT retreatment efficacy and safety in patients with advanced progressive neuroendocrine tumors. 177Lu-PRRT retreatment provided encouraging results, with a median PFS of 12.5 mo and a median OS of 26.7 mo. In a similar salvage treatment setting, our results go beyond the previous reports, as we observed a remarkably higher response rate of 74% \( (17 \text{ with complete response and } 23 \text{ with partial response}) \), and promising prolonged survival benefits, as neither PFS nor OS was attained with 225Ac-DOTATATE therapy.

Although several groups reported variations in the site of metastases associated with poor survival, it is apparent that the presence of distant metastases has a significant impact on survival, irrespective of the treatment modality. Regarding the impact of bone metastases on survival, our results with 225Ac-DOTATATE TAT are similar to those reported by Rudisile et al. (24) and Swihla et al. (26), who demonstrated that the presence of bone metastases was associated with a shorter OS in patients with well-differentiated neuroendocrine tumors who received 177Lu-DOTATATE.

In addition to morphologic responses, improvements in overall patient well-being were observed, with the median KPS increasing from 60 before treatment \( (\text{patients requiring medical care and much assistance with self-care}) \) to 70 after treatment \( (\text{patients being able to care for themselves but unable to do their usual activities or active work}) \). This finding highlights the potential for 225Ac-DOTATATE to improve the quality of life in the worst-outcome patient population.

Treatment with 225Ac-DOTATATE TAT was well tolerated. As previously described, low-grade hematologic AEs were the most common side effect of treatment with 225Ac-DOTATATE. Grade 3 and higher AEs were uncommon and transient or unlikely to be treatment-related. The total amount of 225Ac administered \( (\leq 111 \text{ MBq}) \) did not correlate with AEs. Interestingly, AEs also did not correlate with 177Lu-naïve or prior 177Lu-PRRT therapy, which suggests that dosing with 225Ac-DOTATATE TAT should not be influenced by prior treatment with 177Lu. Moreover, similar to the short-term results \( (18) \) by our group on 225Ac-DOTATATE, there were minimal hematologic, kidney, and liver function toxicities. However, over time during the long-term follow-up, when making comparisons with our pilot results we observed a significantly high incidence of malignant ascites and pleural effusion; whether they were related to disease per se or were TAT-related, longer follow-up of this cohort will clarify. In agreement with our findings, another study using 225Ac-DOTATOC reported that cumulative doses of 60,000–80,000 kBq were tolerated with minimal acute and chronic grade 3 or 4 hepatotoxicity in patients with advanced-stage malignancies \( (27) \). Looking at the toxicity profile, it seems that there is scope to further escalate the individual activity per kilogram or use higher cumulative activity of 225Ac in the future. Thus, the only approach is to rigorously follow these patients for long-term side effects of 225Ac-DOTATATE TAT.

High-level evidence for long-term safety and sustained benefits to OS and radiologic PFS in patients with GEP-NETs treated with 225Ac-DOTATATE is crucial and warrants well-controlled, multicenter, randomized trials to determine its role and the best treatment algorithm for this challenging disease.

Our study had some limitations. The results are exploratory and single-center and are based on a heterogeneous patient population. Although not conducted as a clinical trial with strict inclusion criteria, we believe the study had the advantage of enrolling the largest (to our knowledge) GEP-NET population treated with 225Ac-DOTATATE therapy, including poor-outcome patients, and better reflects the results of treatment-related toxicity, confirming the benefit of efficacy, survival, and improvement in quality of life in a real-world clinical setting. Though all the CT scans of the CT component of PET/CT were of diagnostic quality, contrast was not administered to all patients, resulting in suboptimal-quality images.

CONCLUSION

225Ac-DOTATATE–based PRRT was effective in the heavily pretreated GEP-NET cohort of patients, with good survival rates, high response rates, improvements in KPS, and an acceptable toxicity profile. 225Ac-DOTATATE TAT may be a suitable treatment option for patients with stable disease or PD after 177Lu-DOTATATE β-therapy. Patients refractory to 225Ac-DOTATATE TAT have the worst outcome. We strongly advocate a large multicenter, randomized, controlled trial to assess the potential of this strategy as a new therapeutic paradigm for patients with GEP-NET who have exhausted all other options. Further, a balanced approach that exploits our long-term results and clinical trials can best aid the oncology community in delivering the most beneficial, individualized care to patients.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

**KEY POINTS**

**QUESTION:** What is the long-term outcome for GEP-NET patients treated with 225Ac-DOTATATE TAT?

**PERTINENT FINDINGS:** The median OS was not attained, and the 24-mo OS probability was 70.8%. Median PFS was also not reached, with a 24-mo PFS probability of 67.5%. A significant clinical benefit was achieved after 225Ac-DOTATATE therapy, with minimal treatment-related toxicities.

**IMPLICATIONS FOR PATIENT CARE:** Even in patients resistant to prior 177Lu-DOTATATE, 225Ac-DOTATATE TAT has shown promising long-term results, with transient and acceptable adverse effects.
REFERENCES


