Efficacy and Safety of ^{177}Lu-DOTATATE in Lung Neuroendocrine Tumors: A Bicenter study

Lamiaa Zidan*[1], Amir Iravani*[1–3], Kira Oleinikov[4], Simona Ben-Haim[5,6], David J. Gross[4], Amichay Meirovitz[7], Ophra Maimon[7], Tim Akhurst[1,2], Michael Michael[2,8], Rodney J. Hicks[1,2], Simona Grozinsky-Glasberg*[4], and Grace Kong*[1,2]

[1]*Molecular Imaging and Therapeutic Nuclear Medicine, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia;* [2]*Sir Peter MacCallum Department of Oncology, The University of Melbourne, Melbourne, Victoria, Australia;* [3]*Washington University School of Medicine, Mallinckrodt Institute of Radiology, St. Louis, Missouri;* [4]*Neuroendocrine Tumor Unit, ENETS Center of Excellence, Department of Endocrinology and Metabolism, Hadassah-Hebrew University Medical Center, Jerusalem, Israel;* [5]*Department of Nuclear Medicine, Hadassah-Hebrew University Medical Center, Jerusalem, Israel;* [6]*Institute of Nuclear Medicine, University College London and UCL Hospitals NHS Trust, London United Kingdom;* [7]*Sharett Institute of Oncology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel; and* [8]*Division of Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia*

The purpose of this study was to assess the efficacy and safety of ^{177}Lu-DOTATATE in patients with somatostatin receptor (SSR)–positive lung neuroendocrine tumors (NETs). **Methods:** This is a retrospective review of the outcome of patients with typical carcinoid (TC) and atypical carcinoid (AC), treated with ^{177}Lu-DOTATATE at 2 ENETS Centers of Excellence. Morphologic imaging (RECIST 1.1) and ^{68}Ga-DOTATATE PET/CT responses were assessed at 3 mo after completion of ^{177}Lu-DOTATATE. Concordance between 2 response assessment methods was evaluated by κ statistics. Progression-free survival (PFS) and overall survival (OS) were estimated by Kaplan–Meier analysis and compared by Log-rank test. Treatment-related adverse events (AEs) were graded based on Common Terminology Criteria for Adverse Events, version 5. **Results:** Of 48 patients (median age, 63 y; 13 women), 43 (90%) had AC and 5 (10%) TC. Almost all patients (47, 98%) were treated due to progression. Most patients (40, 83%) received somatostatin analogs, and 10 patients (20%) had prior everolimus, chemotherapy, or both. All patients had high SSR expression ($\geq$ modified Krenning score 3) on pretreatment ^{68}Ga-DOTATATE PET/CT. Patients received a median 4 (range, 1–4) cycles of ^{177}Lu-DOTATATE (33% with concurrent radiosensitizing chemotherapy) to a median cumulative activity of 27 GBq (range, 6–43GBq). At a median follow-up of 42 mo, the median PFS and OS were 23 mo (95% CI, 18–28 mo) and 59 mo (95% CI, 50-not reached [NR]), respectively. Of 40 patients with RECIST-measurable disease and 39 patients with available ^{68}Ga-DOTATATE PET/CT, response categories were partial response, 20% (95% CI, 10%–35%) and 44% (95% CI, 30%–59%); stable disease, 68% (95% CI, 52%–80%) and 44% (95% CI, 30%–59%); and progressive disease, 12% (95% CI, 5%–27%) by both, respectively. There was a moderate concordance between response categories by RECIST and ^{68}Ga-DOTATATE PET/CT, weighted κ of 0.51 (95% CI, 0.21–0.68). Of patients with stable disease by RECIST, those with partial response on ^{68}Ga-DOTATATE PET/CT had a longer OS than those with no response, NR versus 52 mo (95% CI, 28–64), hazard ratio 0.2 (95% CI, 0.1–0.6), $P < 0.001$. Most grade 3/4 AEs were reversible and the most common was lymphopenia (14%) with no incidence of myelodysplasia or leukemia. **Conclusion:** In patients with advanced progressive lung NET and satisfactory SSR expression, ^{177}Lu-DOTATATE is effective and safe with a high disease control rate and encouraging PFS and OS.

Key Words: lung neuroendocrine tumor; bronchial carcinoid; peptide receptor radionuclide therapy; somatostatin receptor

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Well-differentiated lung neuroendocrine tumor (NET) or "lung carcinoid," classified into typical carcinoid (TC) and atypical carcinoid (AC), is a heterogeneous disease with variable clinical behavior and prognosis (*1*). TC rarely metastasizes and generally has a favorable prognosis, whereas AC is more likely to be metastatic at presentation and has a worse prognosis (*1*).

Surgery is the treatment of choice in patients with localized disease, whereas management of inoperable locally advanced and metastatic disease is complex and requires a multidisciplinary approach (*1*). For metastatic disease, the European Neuroendocrine Tumors Society (ENETS) guidelines recommend the mammalian target of rapamycin inhibitor everolimus as the first-line therapy for progressive lung NET; however, in patients with tumor of a low proliferative index, a somatostatin analog (SSA) can be considered as first-line therapy, especially when the uptake on somatostatin receptor (SSR) imaging is strongly positive (*2*). In the LUNA phase 2 trial, pasireotide (an agonist for SSR subtypes 1–3 and 5) alone or in combination with everolimus showed evidence of activity and safety (*3*). Chemotherapy is only considered in rapidly progressive metastatic pulmonary carcinoids and when no other treatment options are available. According to the National Comprehensive Cancer Network guidelines, platinum-based regimens or temozolomide can be used in stage IV AC with a high proliferation index (*4*).

Although lung NET frequently expresses SSR subtype 2 (SSR-2), the role of SSR-2–targeted peptide receptor radionuclide therapy (PRRT) with ^{177}Lu DOTA-0-Tyr3-Octreotate (^{177}Lu-DOTATATE) remains to be determined (*5*). Limited retrospective studies showed the efficacy of PRRT in lung NET, comparable to the results of the NETTER-1 trial, reflecting the generalizability of PRRT for any SSR-positive NET (*6–8*). Because of the lack of comparative

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For correspondence or reprints, contact Amir Iravani (Amir.iravani@wustl.edu).
*Contributed equally to this work.
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studies, after progression on SSA the selection of the next systemic treatment modality including everolimus, chemotherapy, or PRRT is at the discretion of physicians and depends on the access, expertise, and practice patterns of different institutions in the world. Besides, the efficacy of ^{177}Lu-DOTATATE in patients previously untreated with either chemotherapy or everolimus is unclear. This dual-center study aims to assess the safety and efficacy of patients with lung NET who received ^{177}Lu-DOTATATE.

MATERIALS AND METHODS

Patients

This is a retrospective review of all consecutive patients with biopsy-proven, well-differentiated lung NET (TC or AC), who received PRRT. Data are extracted from 2 ENETS centers of excellence—Peter MacCallum Cancer Centre (PMCC) in Melbourne, Australia, and Hadassah-Hebrew University Medical Center (HHUMC), Jerusalem, Israel—during the period from 2006 to 2019. This series shares a single patient with the series of Lim et al. (*8*). This shared patient underwent PRRT at PMCC but was comanaged at another institution involved in that publication. We consider it valuable to include this patient's data given the additional response assessment analyses and longer follow-up in our series.

Eligibility criteria for ^{177}Lu-DOTATATE therapy included positive SSR imaging in all lesions, with either imaging progression or uncontrolled symptoms related to the unresectable disease. Positive ^{68}Ga DOTA-0-Tyr3-Octreotate (^{68}Ga-DOTATATE) PET/CT or SSR imaging was defined as lesion uptake higher than liver and subgrouped to less than spleen or higher than spleen on the basis of tomographic imaging (modified Krenning score 3 and 4, respectively). Further eligibility criteria are listed in the supplemental materials (supplemental materials are available at http://jnm.snmjournals.org).

This study was conducted after receiving approval from the institutional ethics committee at the PMCC (Peter Mac project no. 19/214R) and the HHUMC (approval no. 0072-16). Details of access to PRRT at respective institutions are summarized in the supplemental materials.

Therapy

Each cycle of ^{177}Lu-DOTATATE was administered with premedication granisetron (2 mg), dexamethasone (8 mg), and renoprotective amino-acid infusion (25 g lysine and 25 g arginine in 1 L of normal saline) commencing 30 min before ^{177}Lu-DOTATATE and continuing for 3 h thereafter (*9*). Dexamethasone was used as an antiemetic medication per institutional protocol only at PMCC. The treatment regimen typically included up to 4 cycles of ^{177}Lu-DOTATATE given 6–10 wk apart. At PMCC, ^{177}Lu-DOTATATE was usually given with radiosensitizing chemotherapy unless contraindicated, based on prior experiences showing enhanced efficacy without additional toxicity (*10–12*). Further details of radiosensitizing chemotherapy are described in the supplemental materials. Patients at HHUMC did not receive concurrent chemotherapy.

Follow-up

Patients were clinically reviewed before, and after, each cycle of ^{177}Lu-DOTATATE and typically at 3 mo after the last cycle of treatment. Evaluation at 3 mo included assessment of symptoms; laboratory tests including full blood counts, renal function, hepatic function, and serum chromogranin A (supplemental materials); and imaging by CT or ^{68}Ga-DOTATATE PET/CT with or without ^{18}F-FDG PET/CT. Ongoing follow-up occurred at intervals of 3 to 6 mo. CT response was defined by RECIST 1.1 (*13*). Where available, contrast-enhanced CT images were directly compared. Otherwise, nonenhanced CT from the PET/CT component of the study was assessed, using ^{68}Ga-DOTATATE uptake as a guide to follow the dominant lesions. RECIST response was used to define the main outcomes and ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET response were used for exploratory outcome measures. Response assessments were performed blinded to the patient outcome.

A descriptor for pathologic uptake on ^{68}Ga-DOTATATE PET/CT was adapted from a semiquantitative visual scoring system originally designed for planar ^{111}In octreotide imaging known as the Krenning score. Scores were from 0 to 4 as follows: 0 = no uptake; 1 = uptake < liver; 2 = lesion uptake similar to liver;

TABLE 1
^{68}Ga-DOTATATE PET/CT Response Criteria

Response category	Description
Complete response	Disappearance of all tracer-avid lesions or If residual anatomic abnormality on CT with tracer uptake indistinguishable or less than background physiologic uptake
Partial response	Reduction in intensity of uptake by one modified Krenning score* in at least 1 tumor site associated with decrease/stable in size on CT (if measurable) or PET (if nonmeasurable on CT) or Reduction in size of tracer-avid lesions on CT (if measurable) regardless of intensity of uptake
Stable disease	Not partial response or progressive disease
Progressive disease	Development of new tracer-avid lesions or Increase in the size of the tracer-avid lesions on CT (if measurable) or on PET (if nonmeasurable on CT) regardless of intensity of uptake†

*Modified Krenning score, 0 = no uptake; 1 = uptake < liver; 2 = lesion uptake similar to liver; 3 = uptake > liver but < spleen; 4 = uptake ≥ spleen.

†Rarely an increase in the size of the lesion can be seen in responsive lesions. This may be associated with an increase in central hypodensity/necrosis on CT and a decrease in peripheral tracer uptake on PET. In this circumstance, a confirmatory follow-up study or correlation with other imaging modalities may be required.

3 = uptake > liver and < spleen; 4 = uptake ≥ spleen (*14*). Response by ^{68}Ga-DOTATATE PET/CT is described in Table 1.

In patients who underwent baseline ^{18}F-FDG PET/CT, positive lesion was defined as uptake above the liver, and metabolic responses were assessed on the ^{18}F-FDG PET images qualitatively according to the PMCC criteria (supplemental materials) (*15,16*).

Time to next treatment has been included to capture the timing of the next treatment from start of ^{177}Lu-DOTATATE. All hematologic and renal toxicities occurring from the time of the first ^{177}Lu-DOTATATE administration were recorded and defined according to the Common Terminology Criteria for Adverse Events (CTCAE; version 5.0).

Statistical Analysis

The continuous variables are summarized using the median (interquartile range [IQR] or range), and categoric variables are summarized using basic proportions. The concordance between RECIST and ^{68}Ga-DOTATATE PET/CT response was assessed by Cohen's κ statistics. Fisher's exact was used to evaluate the difference between response rates in different groups. Progression-free survival (PFS) was calculated from the start of ^{177}Lu-DOTATATE to clinical or imaging progression, new oncologic treatment, or death. Overall survival (OS) was recorded as the duration from the start of ^{177}Lu-DOTATATE to last follow-up or death. The patients who were alive at the last follow-up were censored on that date. The cutoff follow-up date was August 31, 2019. The Log-rank test and Cox regression model were used to compare survival of different groups. A Kaplan–Meier curve was used to depict the survival. Statistical analysis was performed using GraphPad Prism 8 (GraphPad Software).

RESULTS

Patient Characteristics

Of 51 consecutive patients with lung NET (22 from PMCC and 29 from HHUMC), 3 patients were removed from the analysis as they received at least 1 cycle of ^{90}Y-DOTATATE. Forty-eight patients were included for final analysis, including 43 (90%) with AC and 5 (10%) with TC. The median Ki-67 of the entire population was 10% (range, 1%–30%), and most patients (90%) had metastatic disease in the liver, bone, or multiorgan involvement. Most patients (83%) received SSAs, and 10 (20%) had prior everolimus, chemotherapy, or both. Almost all patients (47/48, 98%) were treated due to radiographic disease progression and 1 patient for uncontrolled symptoms (back pain correlated to sites of osseous metastasis). Most (94%) demonstrated high avidity on SSR imaging, with a Krenning score of 4. Of 25 patients who underwent baseline ^{18}F-FDG PET/CT, 16 (64%) had concurrent ^{18}F-FDG–avid disease (Table 2). The median cumulative activity of ^{177}Lu-DOTATATE was 27.4 GBq (range, 7.1–43.4 GBq) administered over a median of 4 cycles (range, 1–4). Sixteen patients (33%) had radiosensitizing chemotherapy (5FU or capecitabine with or without temozolomide) (Table 3).

TABLE 2
Patient Characteristics

Characteristic	Number (%)
Sex, male:female	35:13 (73:27)
Median age (y)	63 (range, 25–84)
Type	
Typical carcinoid	5 (10)
Atypical carcinoid	43 (90)
Ki-67	
≤2%	3 (6)
3%–20%	34 (71)
>20%	3 (6)
Unknown	8 (17)
Dominant site of disease	
Local/locoregional	5 (10)
Liver	10 (21)
Bone	3 (6)
Multiorgan	30 (63)
SSR expression by ^{68}Ga-DOTATATE (modified Krenning score)	
Score 3	3 (6)
Score 4	45 (94)
Baseline ^{18}F-FDG PE/CT	
No uptake	3 (6)
≤liver	6 (12)
>liver	16 (33)
Not available	23 (48)
Prior treatments	
SSA	40 (83)
Surgery	25 (52)
Chemotherapy	5 (10)
Everolimus	3 (6)
Everolimus and chemotherapy	2 (4)
Radiotherapy	2 (4)
Liver-directed therapy	2 (4)
None	1 (2)

Data in parentheses are percentages, unless otherwise noted.
SSR = somatostatin receptor; SSA = somatostatin analog.

Imaging Response

Of 40 patients with RECIST-measurable disease at 3 mo, 8 patients (20%; 95% CI, 10%–35%) had partial response and 27 patients (68%; 95% CI, 52%–80%) had stable disease resulting in a disease control rate (DCR) of 88% (95% CI, 73%–95%). Five patients (12%; 95% CI, 5–27) had progressive disease (Fig. 1). Five patients were lost to follow-up, 1 died early, and 2 had no available follow-up CT data (Supplemental Table1).

Of 39 patients with available ^{68}Ga-DOTATATE PET/CT at 3 mo, 17 patients (44%; 95% CI, 30%–59%) had partial response and 17 patients (44%; 95% CI, 30%–59%) had stable disease with a DCR of 88% (95% CI, 73%–95%) (Table 4 and Fig. 2). Five of those 39 patients (12%; 95% CI, 5%–27%) had progressive disease. Of the 9 patients with no available ^{68}Ga-DOTATATE PET/CT, 5 were lost to follow-up, 1 died, and 3 had Octreoscan as their posttreatment molecular imaging. In 39 patients with both RECIST-assessable disease and available ^{68}Ga-DOTATATE PET/CT results, only a moderate concordance in response categories of the 2 modalities was noted, weighted κ of 0.51 (95% CI, 0.21–0.68).

TABLE 3
Treatment Parameters

Parameter	Number
Indication of ^{177}Lu-DOTATATE (n = 48)	
Disease progression	47
Uncontrolled symptoms	1
No. of cycles	
1	3
2	6
3	13
4	26
Cumulative ^{177}Lu-DOTATATE activity in GBq	27 (range, 6–43)
Radiosensitizing chemotherapy (n = 16)	
1 cycle	3
2 cycles	3
3 cycles	4
4 cycles	6
Chemotherapy regimen	
5FU	4
Capecitabine	8
Combined capecitabine and temozolomide	4

Most patients with partial response or progressive disease by RECIST were also categorized similarly by ^{68}Ga-DOTATATE PET/CT, 4 of 5 (80%) and 7 of 8 (87%) patients, respectively. The discordant response categories were noted in stable disease by RECIST: in this category, 10 of 26 patients were classified as partial response and 1 patient as progressive disease by ^{68}Ga-DOTATATE PET/CT due to the development of new avid lesions.

Follow-up ^{18}F-FDG PET/CT was available in 12 of 48 patients. Although RECIST and ^{18}F-FDG PET/CT responses were in agreement in most cases, 3 cases with stable disease by RECIST were grouped as partial response by ^{18}F-FDG PET/CT.

In 30 patients from the AC cohort, although the rate of partial response was numerically higher in patients with a Ki-67 of >10% than in those with a Ki-67 of ≤10%, the difference did not reach statistical significance (36% and 16%, respectively; $P = 0.4$). Similarly, there was no significant difference in the rate of partial response in patients who received radiosensitizing chemotherapy, although a trend toward higher response rate was noted (36% and 12%, respectively; $P = 0.1$).

Survival Outcome

At a median follow-up of 42 mo, there were 16 (33%) deaths. The median PFS and OS of the entire cohort were 23 mo (95% CI, 18–28 mo) and 59 mo (95% CI, 50-not reached [NR]), respectively (Figs. 3A and 3B). The OS was not significantly different between the 2 institutions. The OS of the AC patients with Ki-67 ≤ 10% versus Ki-67 >10% and patients who received radiosensitizing chemotherapy versus those who did not receive chemotherapy were not significantly different ($P = 0.7$ and 0.4, respectively) (Supplemental Figs. 1A and 1B).

Of patients with stable disease by RECIST, those with partial response on ^{68}Ga-DOTATATE PET/CT had longer OS than those with no response (NR vs. 52 mo [95% CI, 28–65]; hazard ratio, 0.2 [95% CI, 0.1–0.6]; $P < 0.001$) (Fig. 4). Baseline ^{18}F-FDG PET/CT–positive disease (available for 25/48 patients) and follow-up ^{18}F-FDG PET/CT response (available for 12/48 patients) did not correlate with OS ($P = 0.2$ and 0.3, respectively).

During follow-up, 27 patients received further treatment. The median time to next treatment was 23 mo (range, 7–56). Fifteen patients received further PRRT, and 12 patients received other treatments, including everolimus ($n = 4$), liver-directed therapy ($n = 3$), or change or increase in the dosage of SSA ($n = 3$) or chemotherapy ($n = 2$). One patient who did show progressive disease at 3 mo after PRRT received no treatment but did not show any further progression up to 24 mo, possibly indicating pseudoprogression.

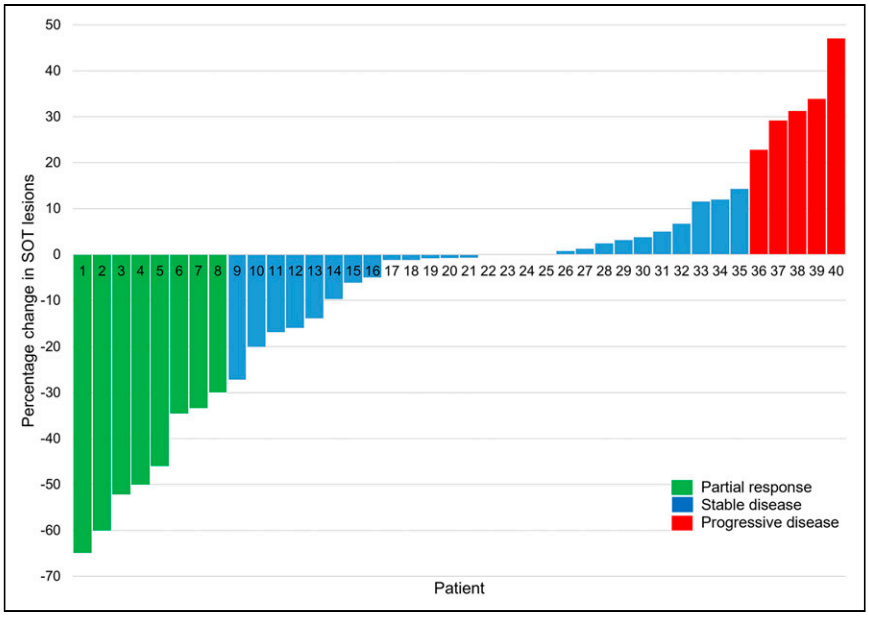

FIGURE 1. Waterfall plot of RECIST response at 3 mo after completion of PRRT. SOT lesions = sum of target lesions diameters.

Toxicity

^{177}Lu-DOTATATE was well tolerated with acceptable toxicity, and most CTCAE grade 3/4 hematologic toxicity during treatment reversed to CTCAE grade 1/2 or baseline (Table 5). The most common hematologic toxicity included thrombocytopenia and lymphopenia. There was no incidence of myelodysplasia/leukemia or renal toxicity on long-term follow-up.

DISCUSSION

PRRT is an effective treatment option for patients with advanced gastroenteropancreatic NET, with sufficient SSR expression after progression on SSA (*4,7*). We have recently reported that only a proportion of lung NET expresses SSR at sufficient levels

TABLE 4
Response to Treatment

Modality	Response	Number (% [95% CI]*)
CT-RECIST	Complete response	0
	Partial response	8/40 (20 [10–35])
	Stable disease	27/40 (67.5 [52–80])
	Progressive disease	5/40 (12.5 [5–27])
	Not available	8
^{68}Ga-DOTATATE PET/CT	Complete response	0
	Partial response	17/39 (43.5 [30–59])
	Stable disease	17/39 (43.5 [30–59])
	Progressive disease	5/39 (13 [5–27])
	Not available	9
^{18}F-FDG PET/CT	Complete response	0
	Partial response	5/12 (42)
	Stable disease	3/12 (25)
	Progressive disease	4/12 (33)
	Not available	36

*Not calculated for the sample sizes of <30.

to potentially benefit from PRRT (*17*). Although lung NETs were not included in the NETTER-1 trial, limited clinical studies have shown promising results (*6,7*). By pooling the patients from 2 ENETs centers of excellence, we have shown that ^{177}Lu-DOTATATE is an effective and safe treatment modality in lung NETs with high SSR expression after progression on SSA with a radiographic response of 20%, DCR of 88%, and favorable median PFS and OS of 23 and 59 mo, respectively. These results are largely consistent with those of previous studies, indicating the efficacy of this treatment (Supplemental Table 2) (*8,18–27*).

Effective treatment options for advanced progressive lung NET are limited, with no available data to guide the sequencing of therapy. Furthermore, the limited patient tolerability remains of serious consideration when deciding on further lines of treatment with the aim of preserving the quality of life. In the subcohort of 90 patients with lung NET in the RADIANT 4 trial, in 57 patients randomized to the everolimus arm a 50% reduction in risk of disease progression or death was reported compared with placebo (*28*). Although 58% of the patients achieved any tumor shrinkage, only 2% were evaluated as partial response by RECIST. The median PFS was 9.2 mo (95% CI, 6.8–10.9), with a 5.6-mo improvement compared with placebo (*28*). The phase II LUNA trial involving 112 patients, the majority with lung NET, supported the efficacy of pasireotide, everolimus, or their combination, with a radiographic DCR at 9 mo of 39%, 33%, and 58%, respectively (*3*). In line with the RADIANT-4 trial, the rate of partial response in the LUNA trial was 2% in all 3 groups. Adverse events (AEs) requiring dose adjustment or interruption were reported in 24%, 52%, and 61% of patients in the pasireotide, everolimus, and the combination arm, respectively (*3*). Chemotherapy remains an option as palliative therapy in lung NET, with a combination of various chemotherapeutic drugs showing a <30% objective response and median OS of 24.3 mo in a small retrospective series (*29*). Although PRRT is usually considered after progression on everolimus or chemotherapy, most patients (80%) in this study were untreated with either of those treatments. Although our result cannot be compared with prior trials or extrapolated to all patients with lung NET, the stringent patient selection based on sufficient SSR expression on pretreatment scanning remains a major advantage of this targeted treatment. Furthermore, attention to tumor heterogeneity of SSR expression is important as we have recently shown that up to 50% of patients with lung NET may demonstrate inter- and intrapatient heterogeneity on dual imaging by ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT (*17*).

PRRT has also shown an acceptable safety profile, with largely reversible short-term and limited long-term treatment-related AEs, with no cases of myelodysplasia or renal toxicity in our cohort, which is consistent with other studies (*18–21*). In a study by Sabet et al., grade 3 hematotoxicity was reported in 13.6% of patients at 3–10 wk after at least 1 cycle of PRRT with no grade 3 or higher nephrotoxicity (*19*). Mariniello et al. reported a <5% hematotoxicity after ^{90}Y-DOTATOC and no hematologic or renal AEs after ^{177}Lu-DOTATATE (*21*). In an Australian multicenter study, Lim et al. reported 2 of 48 (4%) patients with acute myeloid leukemia after PRRT; 1 patient was heavily pretreated including alkylating chemotherapy and the other patient was treated with SSA only (*8*).

Although previous studies and clinical trials have typically used CT or MRI for response assessment, it appears that the outcome of the patients with NET may not be adequately captured by RECIST 1.1 alone (*19–22,26,27,30*). In addition to standard RECIST, by combining the functional information provided by PET and morphologic change by CT, we also explored the use of ^{68}Ga-DOTATATE PET/CT for response assessment and found a moderate concordance between 2 modalities. Interestingly, the response by ^{68}Ga-DOTATATE PET/CT further stratified the OS of the patients who were otherwise grouped as stable disease by RECIST (Fig. 4). Such patients constituted almost two thirds of our cohort. The recent update on appropriate-use criteria indicated

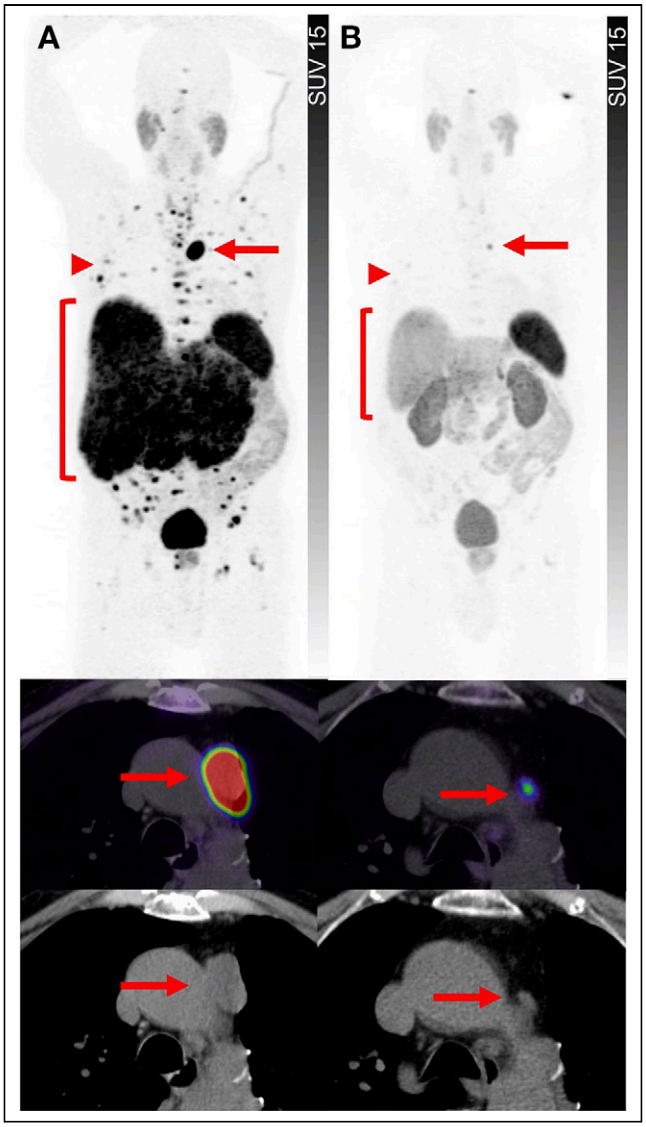

FIGURE 2. A representative patient with metastatic atypical lung carcinoid with partial response on ^{68}Ga-DOTATATE PET/CT and CT at 3 mo after PRRT. Maximum-intensity-projection PET (top), PET/CT (middle), and CT (bottom) at baseline (A) and 3-mo follow-up (B) show marked response to treatment in liver (brackets), bones (arrowheads), and lymph nodes (arrows).

the use of SSR PET as appropriate for restaging after completion of PRRT(*31*). On the basis of our experience, response should include the disappearance or significant reduction of ^{68}Ga-DOTATATE avidity such as a decline in the Krenning score of the known lesions without structural progression on CT or MRI. The response monitoring of nonmeasurable lesions such as osseous disease is also another advantage of SSR PET/CT. However, the exact role of ^{68}Ga-DOTATATE PET/CT in response monitoring remains to be determined without currently established or validated criteria but warrants further evaluation.

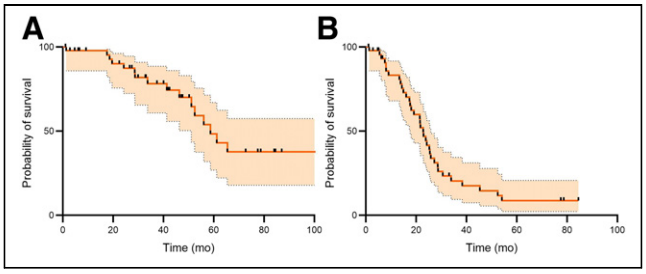

FIGURE 3. Kaplan–Meier plot depiction of OS (A) and PFA (B) of entire cohort.

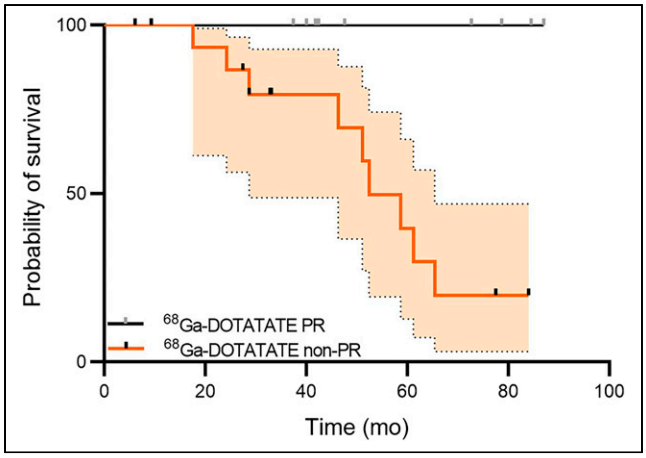

FIGURE 4. Of the patients with stable disease by RECIST, those with partial response (PR) on ^{68}Ga-DOTATATE PET/CT had longer OS than nonresponders (non-PR) on ^{68}Ga-DOTATATE PET/CT, as demonstrated by Kaplan–Meier plot.

The retrospective methodology of this study imposes some limitations, including potential selection bias, which we hope has been mitigated by combining the patients from the 2 institutions. Despite a relatively long follow-up time, death occurred only in around one third of patients, limiting the statistical power to robustly evaluate the prognostic implications of multiple clinical and imaging factors. In addition, the relatively low number of patients included further restricted the strength of statistical inference and precluded multivariate analysis. The use of different treatment protocols between the sites is also another limitation. For instance, dexamethasone was used as an antiemetic, and most patients at PMCC also received concurrent radiosensitizing chemotherapy. However, use of different procedures appears not to have had a major impact on outcomes, with comparable survival demonstrated at both centers. Lastly, 10% of patients had only locoregional disease, which may have better outcomes compared with those with bone, liver, or multiorgan involvement. We did not remove these patients from the analysis as this may have further reduced the statistical power of this study.

CONCLUSION

In patients with advanced progressive lung NET and satisfactory SSR expression, ^{177}Lu-DOTATATE is effective and safe, with a high DCR and encouraging PFS and OS. Further prospective studies comparing ^{177}Lu-DOTATATE with other systemic options are warranted.

DISCLOSURE

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TABLE 5
Hematologic Adverse Events of ^{177}Lu-DOTATATE

Adverse event	During treatment (%)				3-mo after treatment (%)			
CTCAE grade	1	2	3	4	1	2	3	4
Anemia	22 (43)	4 (8)			26 (51)	1 (2)		
Leukopenia	10 (20)		1 (2)	1 (2)	8 (16)	1 (2)	1 (2)	
Neutropenia	5 (10)	2 (4)		1 (2)	4 (8)			
Lymphopenia	9 (18)	13 (25)	6 (12)	1 (2)	11 (22)	12 (24)	1 (2)	
Thrombocytopenia	13 (25)	1 (2)		1 (2)	12 (24)			

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KEY POINTS

QUESTION: What is the role of ^{177}Lu-DOTATATE in patients with SSR-positive metastatic lung NET?

PERTINENT FINDINGS: In this retrospective study of 48 patients from 2 ENETS centers of excellence, ^{177}Lu-DOTATATE was safe and achieved a high disease control rate, with an objective response in one fifth of patients. In patients who achieved stable disease by RECIST at 3 mo after completion of ^{177}Lu-DOTATATE, the response by ^{68}Ga-DOTATATE PET/CT may have prognostic implication.

IMPLICATIONS FOR PATIENT CARE: In patients with advanced progressive lung NET and satisfactory SSR expression, ^{177}Lu-DOTATATE should be considered as an early effective and safe treatment modality.

REFERENCES

1. Caplin ME, Baudin E, Ferolla P, et al. Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids. *Ann Oncol.* 2015;26:1604–1620.
2. Pavel M, O'Toole D, Costa F, et al. ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. *Neuroendocrinology.* 2016;103:172–185.
3. Ferolla P, Brizzi MP, Meyer T, et al. Efficacy and safety of long-acting pasireotide or everolimus alone or in combination in patients with advanced carcinoids of the lung and thymus (LUNA): an open-label, multicentre, randomised, phase 2 trial. *Lancet Oncol.* 2017;18:1652–1664.
4. Shah MH, Goldner WS, Halfdanarson TR, et al. NCCN guidelines insights: neuroendocrine and adrenal tumors, version 2.2018. *J Natl Compr Canc Netw.* 2018;16:693–702.
5. Reubi JC, Waser B. Concomitant expression of several peptide receptors in neuroendocrine tumours: molecular basis for in vivo multireceptor tumour targeting. *Eur J Nucl Med Mol Imaging.* 2003;30:781–793.
6. Naraev BG, Ramirez RA, Kendi AT, Halfdanarson TR. Peptide receptor radionuclide therapy for patients with advanced lung carcinoids. *Clin Lung Cancer.* 2019;20:e376–e392.
7. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of ^{177}Lu-Dotatate for midgut neuroendocrine tumors. *N Engl J Med.* 2017;376:125–135.
8. Lim LE, Chan DL, Thomas D, et al. Australian experience of peptide receptor radionuclide therapy in lung neuroendocrine tumours. *Oncotarget.* 2020;11:2636–2646.
9. Kong G, Grozinsky-Glasberg S, Hofman MS, et al. Efficacy of peptide receptor radionuclide therapy for functional metastatic paraganglioma and pheochromocytoma. *J Clin Endocrinol Metab.* 2017;102:3278–3287.
10. Kong G, Johnston V, Ramdave S, Lau E, Rischin D, Hicks RJ. High-administered activity In-111 octreotide therapy with concomitant radiosensitizing 5FU chemotherapy for treatment of neuroendocrine tumors: preliminary experience. *Cancer Biother Radiopharm.* 2009;24:527–533.
11. Hubble D, Kong G, Michael M, Johnson V, Ramdave S, Hicks RJ. ^{177}Lu-octreotate, alone or with radiosensitising chemotherapy, is safe in neuroendocrine tumour patients previously treated with high-activity ^{111}In-octreotide. *Eur J Nucl Med Mol Imaging.* 2010;37:1869–1875.
12. Claringbold PG, Brayshaw PA, Price RA, Turner JH. Phase II study of radiopeptide ^{177}Lu-octreotate and capecitabine therapy of progressive disseminated neuroendocrine tumours. *Eur J Nucl Med Mol Imaging.* 2011;38:302–311.
13. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45:228–247.
14. Krenning EP, Valkema R, Kooij PP, et al. Scintigraphy and radionuclide therapy with [indium-111-labelled-diethyl triamine penta-acetic acid-D-Phe1]-octreotide. *Ital J Gastroenterol Hepatol.* 1999;31(suppl 2):S219–S223.
15. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. *J Nucl Med.* 2009;50(suppl 1):122S–150S.
16. Hicks RJ. The role of PET in monitoring therapy. *Cancer Imaging.* 2005;5:51–57.
17. Zidan L, Iravani A, Kong G, Akhurst T, Michael M, Hicks RJ. Theranostic implications of molecular imaging phenotype of well-differentiated pulmonary carcinoid based on ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET/CT. *Eur J Nucl Med Mol Imaging.* 2021;48:204–216.
18. Ianniello A, Sansovini M, Severi S, et al. Peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE in advanced bronchial carcinoids: prognostic role of thyroid transcription factor 1 and ^{18}F-FDG PET. *Eur J Nucl Med Mol Imaging.* 2016;43:1040–1046.
19. Sabet A, Haug AR, Eiden C, et al. Efficacy of peptide receptor radionuclide therapy with ^{177}Lu-octreotate in metastatic pulmonary neuroendocrine tumors: a dual-centre analysis. *Am J Nucl Med Mol Imaging.* 2017;7:74–83.
20. Parghane RV, Talole S, Prabhash K, Basu S. Clinical response profile of metastatic/advanced pulmonary neuroendocrine tumors to peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE. *Clin Nucl Med.* 2017;42:428–435.
21. Mariniello A, Bodei L, Tinelli C, et al. Long-term results of PRRT in advanced bronchopulmonary carcinoid. *Eur J Nucl Med Mol Imaging.* 2016;43:441–452.
22. Brabander T, van der Zwan WA, Teunissen JJM, et al. Long-term efficacy, survival, and safety of [^{177}Lu-DOTA(0),Tyr(3)]octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. *Clin Cancer Res.* 2017;23:4617–4624.
23. van Essen M, Krenning EP, Bakker WH, de Herder WW, van Aken MO, Kwekkeboom DJ. Peptide receptor radionuclide therapy with ^{177}Lu-octreotate in patients with foregut carcinoid tumours of bronchial, gastric and thymic origin. *Eur J Nucl Med Mol Imaging.* 2007;34:1219–1227.

24. Filice A, Fraternali A, Frasoldati A, et al. Radiolabeled somatostatin analogues therapy in advanced neuroendocrine tumors: a single centre experience. *J Oncol.* 2012;2012:320198.
25. Bodei L, Cremonesi M, Grana CM, et al. Peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE: the IEO phase I-II study. *Eur J Nucl Med Mol Imaging.* 2011;38:2125–2135.
26. Pfeifer AK, Gregersen T, Gronbaek H, et al. Peptide receptor radionuclide therapy with Y-DOTATOC and ^{177}Lu-DOTATOC in advanced neuroendocrine tumors: results from a Danish cohort treated in Switzerland. *Neuroendocrinology.* 2011;93: 189–196.
27. Garske-Román U, Sandström M, Fröss Baron K, et al. Prospective observational study of ^{177}Lu-DOTA-octreotate therapy in 200 patients with advanced metastasized neuroendocrine tumours (NETs): feasibility and impact of a dosimetry-guided study protocol on outcome and toxicity. *Eur J Nucl Med Mol Imaging.* 2018;45: 970–988.
28. Fazio N, Buzzoni R, Delle Fave G, et al. Everolimus in advanced, progressive, well-differentiated, non-functional neuroendocrine tumors: RADIANT-4 lung subgroup analysis. *Cancer Sci.* 2018;109:174–181.
29. Tsoukalas N, Baxevanos P, Aravantinou-Fatorou E, et al. Advances on systemic treatment for lung neuroendocrine neoplasms. *Ann Transl Med.* 2018;6:146.
30. Bodei L, Cremonesi M, Kidd M, et al. Peptide receptor radionuclide therapy for advanced neuroendocrine tumors. *Thorac Surg Clin.* 2014;24:333–349.
31. Hope TA. Updates to the appropriate-use criteria for somatostatin receptor PET [editorial]. *J Nucl Med.* 2020;61:1764.