MATERIALS AND METHODS

Patients

Patients were deemed unsuitable for ^{177}Lu-DOTATATE if disease demonstrated low avidity SSR imaging (uptake equal to or less than liver activity), hypoalbuminemia (albumin level ≤ 25 g/L), thrombocytopenia (platelet count < 50 × 109/L at PMCC and < 70 ×109/L at HHUMC), pancytopenia (hemoglobin level < 10 g/dL and white cell count < 3 × 109/L for the Israeli center), Eastern Cooperative Oncology Group (ECOG) performance score of 4, expected survival < 3 months, or confirmed pregnancy.

Ethical Approval

All patients at PMCC were treated on compassionate grounds under the Special Access Scheme (SAS), which allows treatment of patients with life-threatening diseases with experimental therapies that have demonstrated efficacy in other studies. The use of SAS provisions was approved by the institutional ethics committee (Peter Mac Project No: 19/214R) and all patients provided written informed consent to undergo treatment and follow-up. The Israeli Ministry of Health approves PRRT treatment for patients with metastatic progressive NETs and the study was approved by the HHUMC institutional ethical committee (approval number: 0072–16).

Therapy

At PMCC radio-labelling and administration of ^{177}Lu-DOTATATE was performed under local institutional protocol as previously published(*1*). Radiolabelling of ^{177}Lu-DOTATATE at HHUMC was also published previously (*2*).

At PMCC, an earlier protocol used infusional fluorouracil (5-FU) as a radiosensitizer (typically 200 mg/m2 daily, starting 2 days before ^{177}Lu-DOTATATE for 2 weeks in total). With the availability of oral capecitabine, a 5FU prodrug, this substituted 5FU at the dosage of 825 mg/m2 twice daily commencing 2 days before ^{177}Lu-DOTATATE for 2 weeks. At the discretion of the oncologist following discussion at the multidisciplinary team meeting, if temozolomide was combined with capecitabine, this was administered at 100mg/m^2 twice daily for 5 days commencing on the day of ^{177}Lu-DOTATATE for 5 days.

Follow-up

Chromogranin A (CgA) assessment at baseline and follow-up was not included in the manuscript due to the different reference ranges of the two institutions' laboratories and to avoid any possible flaws related to the inter and intra-laboratory variations and also several interfering factors with CgA levels.

^{18}F-FDG PET/CT response was based on PMCC criteria and grouped : complete response (^{18}F-FDG–avid lesions revert to the background of normal tissues in which they are located), partial response (significant reduction in tumor uptake), stable disease (no visible change in metabolic activity of tumors), progressive disease (increase in intensity or extent of tumor metabolic activity or new sites) (*3,4*).

Supplemental Table 1. Imaging response of all patients

Patient	^{68}Ga-DOTATATE PET/CT response	^{18}F-FDG PET/CT response	RECIST 1.1 response
1	Partial response	na	Partial response
2	Partial response	na	Partial response
3	Partial response	Partial response	Partial response
4	Partial response	na	Partial response
5	Partial response	na	Partial response
6	Stable disease	na	Partial response
7	Partial response	Partial response	Partial response
8	Partial response	na	Partial response
9	Partial response	Partial response	Stable disease
10	Partial response	na	Stable disease
11	Partial response	na	Stable disease
12	Partial response	na	Stable disease
13	Partial response	na	Stable disease
14	Partial response	Partial response	Stable disease
15	Stable disease	na	Stable disease
16	Partial response	na	Stable disease
17	Stable disease	na	Stable disease
18	Stable disease	na	Stable disease
19	Partial response	na	Stable disease
20	Stable disease	na	Stable disease
21	Partial response	Stable disease	Stable disease
22	Stable disease	na	Stable disease
23	Stable disease	Stable disease	Stable disease
24	Stable disease	Partial response	Stable disease
25	Stable disease	Stable disease	Stable disease
26	Stable disease	na	Stable disease
27	Stable disease	na	Stable disease
28	Stable disease	na	Stable disease
29	Stable disease	na	Stable disease
30	Stable disease	na	Stable disease
31	Partial response	na	Stable disease
32	na	na	Stable disease
33	Stable disease	na	Stable disease
34	Progressive disease	na	Stable disease
35	Stable disease	na	Stable disease
36	Progressive disease	na	Progressive disease
37	Progressive disease	Progressive disease	Progressive disease
38	Progressive disease	Progressive disease	Progressive disease

39	Stable disease	Progressive disease	Progressive disease
40	Progressive disease	Progressive disease	Progressive disease
41	na	na	na
42	na	na	na
43	na	na	na
44	na	na	na
45	na	na	na
46	na	na	na
47	na	na	na
48	na	na	na

na: not available

Supplemental Table 2. Summary of the studies of PRRT in lung neuroendocrine neoplasia (carcinoid)

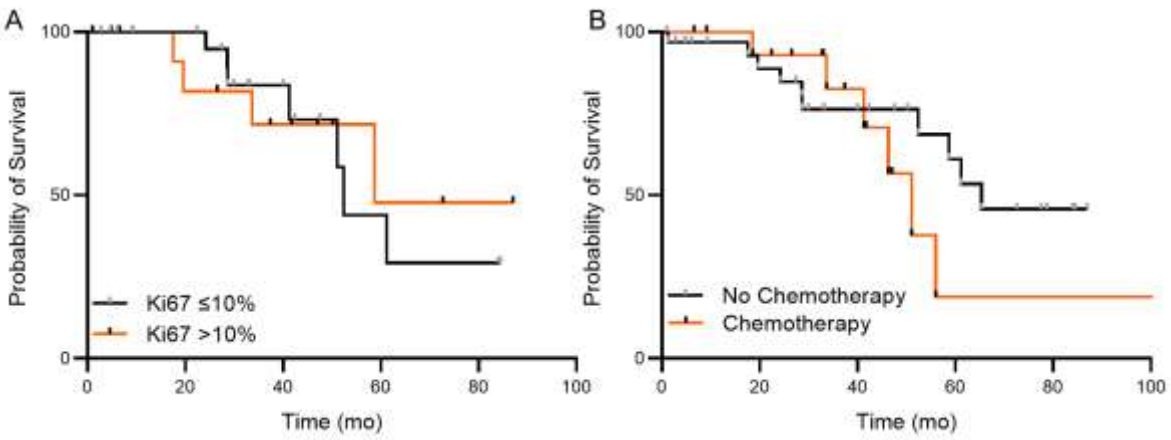
Reference	Study	n (TC: AC)	Therapy	Response Criteria	CR n (%)	PR n (%)	SD n (%)	Progressive disease n (%)	Follow-up (mo)*	PFS mo (95% CI)*	OS mo (95%CI)*
Current study	Retrospective	48 (5:43)	^{177}Lu	RECIST	0	8/40 (20)	27/40 (68)	5/40 (12)	42	23 (18-28)	59 (50-NR)
(*5*)	Prospective	34 (15:19)	^{177}Lu	SWOG	1 (3)	4 (12)	16 (47)	13 (38)	29	18 (13-26)	49(26-69)
(*6*)	Retrospective	22 (5:17)	^{177}Lu	RECIST	0	6 (27)	9 (41)	7(32)	54	27 (9-45)	42 (25-59)
(*7*)	Retrospective	22 (13:8) 1 SCLC	^{177}Lu	RECIST	1/19 (5)	1/19 (5)	11/19 (58)	6/19 (32)	NS	NS	40
(*8*)	Retrospective	48 (15:32) 1 unknown	^{177}Lu	Review of notes/radiology reports/correspondence	0	16 (33)	24† (50)	8 (17)	33	NS	43
(*9*)	Retrospective	114 (34:40) 40 NOS	^{177}Lu or ^{90}Y or combined	RECIST	0	15 (13)	61 (54)	38 (33)	45	28	59
(*10*)	Retrospective	23‡	^{177}Lu	RECIST	0	7 (30)	7 (30)	6 (26)	64	20	52 (49-55)
(*11*)	Retrospective	9 (4:5)	^{177}Lu	SWOG	0	5 (56)	3† (33)	1 (11)	20	31	NS
(*12*)	Prospective	13	^{177}Lu or ^{90}Y or combined	Functional response on PET/CT	0	8 (62)	3 (23)	2 (15)	NS	NS	NS
(*13*)	Prospective	5	^{177}Lu	RECIST	0	2 (40)	3† (60)	0	29	NS	NS
(*14*)	Retrospective	6	^{177}Lu or ^{90}Y or combined	RECIST	0	1 (17)	3 (50)	2 (33)	17	NS	NS
(*15*)	Prospective	6	^{177}Lu	RECIST	0	1 (17)	5 (83)	0	31	NS	NS

*Figures have been rounded off

† minor response is grouped as stable disease

‡ Including 3 not evaluable patients

AC: atypical carcinoid; CI: confidence interval; CR: complete response; ^{177}Lu: ^{177}Lu-DOTATATE; n: number of patients; NR: Not reached; NS: not stated; NOS: Not otherwise specified; OS: overall survival; Progressive disease: progressive disease; PR: partial response; RECIST: response evaluation criteria for solid tumors; SCLC: small cell lung carcinoma; TC: typical carcinoid; SWOG: Southwest Oncology Group; ^{90}Y: ^{90}Y-DOTATATE



Supplemental Figure 1. Kaplan Meier plot of atypical carcinoid showing no significant difference in OS of the patients with Ki67≤10% compared to those with Ki67>10% (A). No significant difference in OS of the patients treatment with concurrent chemosensitizing chemotherapy and those without chemotherapy (B).

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