1-1-2018

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Recommended Citation

Noto, R., Pryma, D., Jensen, J., Lin, T., Stambler, N., Strack, T., Wong, V., & Goldsmith, S. (2018). Phase 1 Study of High-Specific-Activity I-131 MIBG for Metastatic and/or Recurrent Pheochromocytoma or Paraganglioma. *The Journal of Clinical Endocrinology & Metabolism, 103* (1), 213-220. https://doi.org/10.1210/jc.2017-02030

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The Journal of Clinical Endocrinology & Metabolism
Endocrine Society

Submitted: September 12, 2017
Accepted: October 18, 2017
First Online: November 01, 2017

The Journal of Clinical Endocrinology & Metabolism; Copyright 2017 DOI: 10.1210/jc.2017-02030

Phase 1 Study of High-Specific-Activity I-131 MIBG for Metastatic and/or Recurrent Pheochromocytoma or Paraganglioma

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Received 12 September 2017. Accepted 18 October 2017.

Context: There are no approved therapies for the treatment of metastatic and/or recurrent pheochromocytoma or paraganglioma (PPGL) in the United States.
Objective: To determine the maximum tolerated dose (MTD) of high-specific-activity I-131 meta-iodobenzylguanidine (MIBG) for the treatment of metastatic and/or recurrent PPGL.
Design: Phase 1, dose escalating study to determine the MTD via a standard 3+3 design; escalating by 37 MBq/kg starting at 222 MBq/kg.
Setting: Three centers.
Patients: Twenty-one patients were eligible, received study drug, and were evaluable for MTD, response, and toxicity.
Intervention: Open-label use of high-specific-activity I-131 MIBG therapy.
Main Outcome Measures: Dose-limiting toxicities, adverse events, radiation absorbed dose estimates, radiographic tumor response, biochemical response, and survival.
Results: The MTD was determined to be 296 MBq/kg based on two observed dose-limiting toxicities at the next dose level. The highest mean radiation absorbed dose estimates were in the thyroid and lower large intestinal wall (each 1.2 mGy/MBq). Response was evaluated by total administered activity: four (19%) patients, all of whom received >18.5 GBq of study drug, had radiographic tumor responses of partial response by RECIST. Best biochemical responses (complete or partial response) for serum chromogranin A and total metanephrines were observed in 80% and 64% of patients, respectively. Overall survival was 85.7% at 1 year and 61.9% at 2 years post-treatment. The majority (84%) of adverse events were considered mild or moderate in severity.
Conclusions: These findings support further development of high-specific-activity I-131 MIBG for the treatment of metastatic and/or recurrent PPGL at a MTD of 296 MBq/kg.

We studied the maximum tolerated dose (MTD) and preliminary efficacy of high-specific-activity I-131 MIBG therapy in patients with metastatic and/or recurrent PPGL, and found the MTD to be 296 MBq/kg.

Introduction

Pheochromocytomas and paragangliomas (PPGL) are rare neuroendocrine tumors arising from adrenal medullary chromaffin cells or extra-adrenal sympathetic neurons, respectively. Paraganglioma can also arise from parasympathetic neurons, largely in the head and neck, but these are not the subject of this report. The reported overall incidence varies between two and eight cases per million per year (1-4). Approximately 10-35% of PPGLs have been reported to present as metastatic at the time of diagnosis and primary treatment; metastases typically develop after a median interval of approximately 5.5 years (5-7). The most common sites of metastasis are lymph nodes, bone, lung, and liver (6). Five year survival rates vary (24-60%) based on the

location of metastatic lesions, with the worst prognosis reported for patients with liver and/or lung metastases (8). Shorter survival has also recently been correlated with older age at the time of primary tumor, synchronous metastases, larger primary tumor size, and unresectable disease (5). Once metastasis has occurred, treatment options are limited; there are currently no approved pharmacological treatments in the United States (US) for recurrent and/or metastatic (or previously referred to as malignant by WHO 2004 classification) PPGL. Conventional, low-specific-activity I-131 meta-iodobenzylguanidine (MIBG) therapy at high doses and cytotoxic chemotherapy with cyclophosphamide, vincristine, and dacarbazine (CVD) have been used in patients with recurrent and/or metastatic disease (9, 10). Tyrosine kinase inhibitors such as sunitinib and stable and/or radiolabeled octreotide derivatives are also being explored (11-13).

MIBG is a guanethidine derivative and is a substrate for the norepinephrine transporter (NET) present in the chromaffin cells of PPGLs. MIBG has been labeled with radioactive isotopes of iodine for both diagnostic and therapeutic applications. Conventional low-specific-activity I-131 MIBG has been commercially available in the US and Europe for the imaging of neuroendocrine tumors, including PPGL, since the 1990s. However, studies have reported that >99% of the MIBG molecules are not radiolabeled in commercial conventional preparations (14, 15). A major drawback of using high doses of conventional I-131 MIBG is the large amounts of unlabeled MIBG that compete for NET binding sites, lowering uptake of the therapeutically-active I-131 labeled MIBG while also disrupting the norepinephrine (NE)-reuptake mechanism (15). The resulting increase in circulating NE can lead to an elevated risk of significant cardiovascular side effects such as acute hypertensive crisis during or shortly after the infusion of conventional I-131 MIBG therapy (16, 17).

To improve the benefit to risk profile of I-131 MIBG, a novel manufacturing process (Ultratrace®) has been developed to produce AZEDRA® (iobenguane I 131; Progenics Pharmaceuticals, Inc., New York, NY), a drug product with high-specific-activity and little to no unlabeled MIBG; thus potentially providing advantages over conventional I-131 MIBG in safety and efficacy for the treatment of patients with PPGL (18). This open-label, multi-center, dose escalation phase 1 study was undertaken to determine the maximum-tolerated dose (MTD) of high-specific-activity I-131 MIBG in the treatment of metastatic and/or recurrent PPGL. Secondary measures included estimated radiation absorbed doses, objective radiographic tumor response by RECIST, biochemical response, survival, and safety and tolerability.

Patients and Methods

Patients

The study protocol (NCT00458952) and all procedures were approved by local Institutional Review Boards and the US Food and Drug Administration. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. All subjects provided written informed consent before study entry. To be eligible, patients 18 years of age or older had to have histologically confirmed evidence of PPGL with at least one measurable lesion on computed tomography (CT) or magnetic resonance imaging (MRI) that was also confirmed visible on diagnostic MIBG scan. Patients had disease that was metastatic or recurred following prior surgery. Key exclusion criteria were radiographic evidence for active central nervous system lesions within 3 months of study entry, previous systemic radiotherapy within 6 months or chemotherapy within 30 days of study entry, nursing or pregnant, and concurrent use of medications known to interfere with MIBG uptake.

Study Design and Assessments

This was a phase 1, open-label, single arm, multi-center, dose-finding study in patients with histologically confirmed PPGL that was metastatic and/or recurrent, regardless of disease progression status, designed to establish the MTD of high-specific-activity I-131 MIBG. To determine the MTD, sequential dose escalation cohorts began with 3 patients at 222 MBq/kg (6 mCi/kg), and proceeded according to a standard modified Fibonacci 3+3 trial design with dose increases at 37 MBq/kg (1 mCi/kg) increments, until the MTD was established (19). To guard against inadvertently administering high levels of radioactivity, an upper limit for administered activity was based on a body weight of 75 kg. Therefore, the first three dose levels were not to exceed 16.65, 19.43, or 22.2 GBq (450, 525, or 600 mCi). The 222 MBq/kg (6 mCi/kg) starting dose was less than the calculated maximum administered activity resulting in 23 Gray (Gy) of absorbed dose to the kidneys according to a prior dosimetry study (20). Toxicities were graded according to the US National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 3). Potential DLTs consisted of CTCAE grade 4 hematologic toxicity >1 week duration; or the occurrence of any grade 3-4 non-hematologic toxicity.

Key secondary objectives were to assess the radiation dose estimates, safety and tolerability, and preliminary efficacy of high-specific-activity I-131MIBG with regard to objective tumor response (OTR) by radiographic assessment, biochemical response, and survival. Patients were evaluated at 3, 6, 9, and 12 months following treatment. Safety was evaluated by collection of treatment emergent adverse events (AEs), ECGs, physical examination findings, vital sign measurements, and clinical laboratory data. The biodistribution of I-131 MIBG was assessed by determination of total body residence time and by visual examination of whole body planar images. Radiographic OTR was based on RECIST v1.0 and assessed by two blinded central independent reviewers and an adjudicator using CT or MRI scans of the chest, abdomen and pelvis performed at each assessment time point following investigational treatment. For the assessment of biochemical response, serum chromogranin A (CgA) and 24-hour levels of urinary catecholamines/metanephrines were collected at baseline and every 3 months for one year post-treatment. Complete response (CR) was defined as a tumor marker value above the Upper Limit of Normal (ULN) at baseline and at or below the ULN at the assessed time point; partial response (PR) was defined as a value above ULN at baseline and decreased by at least 50% from the baseline value but still above the ULN. Best overall tumor response by RECIST and best biochemical response were evaluated for treated patients during the 12-month efficacy period. After the first year, patients were followed every 6 months or until death (or withdrawal from the study) for overall survival (OS) and late radiation toxicity. Late radiation toxicity was assessed using Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) Late Morbidity Scoring Scheme (21).

Imaging

For imaging, each patient received a single intravenous (IV) bolus of approximately 185 MBq (5 mCi) high-specific-activity I-131 MIBG as the dosimetry (imaging) dose (20). Following the dosimetry dose, serial anterior and posterior whole body images were taken 30-60 minutes post injection and prior to patient voiding, and again at two to four days and following patient voiding. The geometric mean count of the first whole body studies represented 100% of administered activity. An imaging standard was prepared and placed in the field of view for all images and as a reference for correcting decay and camera sensitivity changes. Tumor uptake on the diagnostic MIBG scan was confirmed to correspond to a designated target lesion seen on CT or MRI. If at least one lesion observed on baseline CT or MRI was also visualized on the MIBG

scan, and the dosimetry dose showed typical biodistribution, the patient was administered a therapeutic dose 7 to 28 days following the dosimetry dose. Data were evaluated to determine human radiation absorbed dose estimates to target lesions and normal organs in accordance with the Medical Internal Radiation Dose schema to account for patient-to-patient variation in radiation-absorbed doses to individual organs (22). Absorbed radiation dose was calculated using OLINDA/EXM software (23).

Study Drug Administration

For the therapeutic dose administration of high-specific-activity I-131 MIBG, all patients were pre-treated with a saturated solution of potassium iodide for thyroid protection per standard practice. The recommended infusion rate of IV administration of the therapeutic dose was 50 mL over a period of 15 to 30 minutes. Due to the theoretical risk for hypertensive crisis during and after therapeutic administration of I-131 MIBG, investigators had phentolamine available during each infusion. ECGs and vital signs were obtained before and after each dose, Holter monitoring was initiated one hour pre-therapeutic dose and continued through approximately 23 hours post-therapeutic dose. A 12-lead ECG was performed upon the patient's release from isolation and prior to discharge. Any clinically significant ECG changes and findings were captured as reported AEs. The radioactive drug product was handled only by trained personnel with proper shielding and monitoring following institutional standard operating procedures and/or applicable guidance.

Statistical Analyses

The sample size was dictated by the '3+3' study design. Patients who received any dose of high-specific-activity I-131 MIBG were included in the safety analysis. The intent-to-treat (ITT) population was all patients who received a therapeutic dose; this was the primary analysis set for the determination of the MTD and efficacy measures. Quantitative values were reported as means ± sd or median and range, as appropriate. For categorical endpoints, Jonckheere-Terpstra test statistics were computed and *P* values presented ($P < 0.05$ was considered significant). Regression models for dose-response relationships were fit to the study data, and tests for the statistical significance of the association between dose level and response were conducted. Overall survival was defined as the time from the date of enrollment to the date of death from any cause or censored at the date the patient was last known to be alive. All statistical analyses were performed using SAS Statistical Software (version 9.2; SAS Institute Inc., Cary, NC).

Results

Baseline Characteristics of Patients

Of the 24 patients with metastatic and/or recurrent PPGL who consented for the trial, three patients did not meet all of the eligibility criteria at screening and did not receive study drug. The baseline characteristics of the 21 enrolled and dosed patients are presented in **Table 1**.

Radiation Absorbed Doses

The median dosimetry dose administered was 189 MBq (5.1 mCi), and the range was 181 to196 MBq (4.9 to 5.3 mCi). Target organ radiation dose estimates are presented in descending order of mean absorbed radiation dose in **Table 2**. One patient was excluded from the dosimetry analyses because no imaging standard was used. The highest estimated mean radiation absorbed dose estimates were observed in the thyroid and lower large intestinal wall (each 1.2 mGy/MBq). All other target organ mean radiation absorbed dose estimates were <1 mGy/MBq. The total mean radiation doses for kidneys, liver, and lungs were 0.42, 0.48, and 0.32 mGy/MBq,

respectively. Even at the highest dose level in our study, the radiation dose levels did not exceed critical organ radiation dose limits used in external beam radiation therapy (EBRT) (24). Estimated tumor radiation absorbed dose varied from 0.14 to 17 mGy/MBq with tumor volumes ranging from 5.9 cubic centimeters (cc) to 343 cc (mean, 79 cc).

Maximum Tolerated Dose

Due to the protocol-mandated dose ceilings for therapeutic doses relative to body weight, 12 (57%) of the 21 patients received doses lower than the planned levels on a per-body weight basis. The weight limit rendered a body weight-based dose analysis not feasible as essentially all of the patients in the later dose levels were above the upper body weight limit of 75 kg. The median therapeutic dose administered was 21.13 GBq (571 mCi), range 12 to 25.8 GBq (325-696 mCi), which resulted in a median activity by actual body weight of 240 MBq/kg (6.5 mCi/kg), range 167-311 MBq/kg (4.5-8.4 mCi/kg). To assess the results based on a fixed therapeutic dose in the study population, patients were grouped and analyzed by total administered activity, in two activity groups of ≤18.5 GBq (500 mCi) and >18.5 GBq.

Four patients experienced DLTs, all of which were hematological events. All of these patients received >18.5 GBq. **Figure 1** shows the administration of high-specific-activity I-131MIBG at sequential dose-escalating levels and occurrence of DLTs in the treated patients. Actual administered activities for the four patients who experienced DLTs were between 19.4 GBq (524 mCi) and 25.2 GBq (680 mCi). The DLTs were neutropenia (n=2), thrombocytopenia (n=1), and concurrent febrile neutropenia and thrombocytopenia (n=1). All observed DLTs resolved within a month. Based on the occurrence of DLTs in the planned 333 MBq/kg (9 mCi/kg) cohort, the MTD was determined to be 296 MBq/kg (8 mCi/kg). Six patients were treated in the MTD cohort.

Safety

The most frequently reported AEs were nausea (76%), fatigue (67%), dry mouth and vomiting (62% each), leukopenia, neutropenia, and thrombocytopenia (48% each), anemia, and salivary gland pain (43% each). The majority (84%) of AEs were CTCAE grade 1-2 in severity. Grade 3 or 4 AEs were reported in 16 (76%) of the 21 patients, including 5 (71%) of 7 patients who received ≤18.5 GBq and 11 (79%) of 14 patients who received >18.5 GBq (no statistically significant difference was observed between the dose groups). Overall, the most common (≥10%) grade 3/4 events were neutropenia, leukopenia, thrombocytopenia, nausea, and vomiting; and most of these were considered related to study drug. No patients were discontinued from the study due to AEs. There were five deaths during the study that occurred from approximately 2.5 months to up to 22 months after treatment, and all were assessed as unrelated to treatment. The majority of serious AEs were also not considered related to study drug. Hypertensive crises or cardiovascular risks were not observed in any patient. There was no evidence of a dose effect on ECG changes or clinically significant vital sign changes. Tachycardia was reported in four patients, and was not considered related to study drug. During the long-term follow-up period of up to 3.5 years, most patients did not experience radiation toxicity as assessed by the RTOG/EORTC Late Morbidity Scoring Scheme. The most clinically significant symptoms showing possible radiation toxicity was moderate bone pain/tenderness and/or moderate joint stiffness/pain reported by a total of 3 patients at 3-3.5 years post-treatment.

Tumor Response

Objective tumor response

Overall, 14 (58%) patients completed the 12-month efficacy phase. **Table 3** presents the best confirmed overall objective tumor response (OTR) to treatment during the efficacy phase as assessed by RECIST for each dose group, and all patients. The majority of patients had partial response (PR) or stable disease (SD) at 12 months. No patient had a CR to treatment, but four patients, all of whom received >18.5 GBq of high-specific-activity I-131 MIBG, had a best confirmed overall OTR of PR. The proportion of patients with evaluable responses (n=19) who were successful (PR or CR) overall was 21% (95% CI: 0, 0.42). However, the Jonckheere-Terpstra test for dose response in the evaluable population indicated there was no trend in OTR by dose group at any time point.

Biochemical tumor response

Analyses of biochemical tumor response to treatment were performed only on patients whose baseline blood and urine tumor markers were ≥ 1.5 x ULN. For most serum and urine (24 hour) tumor markers, mean baseline and mean maximum change values differed due to high patient variability. Jonckheere-Terpstra tests for dose-response at each time point indicated there were no trends by dose group for any of the tumor markers at any time point during the 12 months post-treatment ($p>0.05$). Tumor markers norepinephrine, normetanephrine, epinephrine, metanephrine, dopamine, total metanephrines, chromogranin A (CgA) and vanillylmandelic acid were assessed. **Table 4** presents the overall best biochemical responses for serum CgA and total urine metanephrines observed during the 12-month period. Based on the best biochemical response for serum CgA, 80% of patients with evaluable responses were successful overall (CR or PR). Based on the best biochemical response for total metanephrines, 64% (95% CI: 0.36, 0.93) of patients with evaluable responses were successful overall.

Survival

Survival time was calculated from the date of enrollment to the date of death from any cause or censored at the date the patient was last known to be alive. Overall survival was 85.7% (18/21) at one year post-treatment and 61.9% (13/21) at two years post-treatment.

Discussion and Conclusions

The objectives of this phase 1 study were to determine the MTD of high-specific-activity carrier-free I-131 MIBG for the treatment of metastatic and/or recurrent PPGL, evaluate the safety and tolerability, estimate radiation absorbed doses to target lesions and organs following dosimetry, and assess tumor response, biochemical response, and survival following treatment. Overall, four patients experienced DLTs and all were hematological events. Actual administered activities for these four patients were all >18.5 GBq (500 mCi). Of these four patients, three patients with the highest activity levels demonstrated the best radiographic tumor response to treatment, with PR as the best overall response. Tumor response for the other patient was not evaluated due to early discontinuation from the study. Because two patients experienced dose-limiting neutropenia in the 333 MBq/kg (9 mCi/kg) cohort, the MTD was determined to be 296 MBq/kg (8 mCi/kg).

Treatment success appeared to be related to total administered activity. The majority of patients had PR or SD by radiographic tumor response at 12 months. Four patients had best confirmed overall tumor response of PR, all of whom had received >18.5 GBq (500 mCi) of high-specific-activity I-131 MIBG. Overall, best treatment responses were also observed at doses >18.5 GBq, and no patients who received ≤18.5 GBq achieved PR by RECIST. For most tumor markers, mean baseline and mean maximum change values differed due to high patient

variability and small sample size. There were no dose-relationship trends for any of the tumor markers. Since hypertension is one of the symptoms in patients who have primarily norepinephrine secreting tumors, the use of antihypertensive medications was also analyzed as an exploratory endpoint evaluating clinical benefit in 15 patients who had documented use of baseline antihypertensive medications. Of these patients, five (33.3%) had either a decrease or discontinuation in the medications within 12 months of study drug treatment.

The majority of AEs in the phase 1 study were grade 1-2 in severity. Grade 3-4 AEs were consistent with the anticipated toxicities following radiotherapy and the expected pattern of AEs described in I-131 MIBG therapeutic studies (18, 23).

Limitations of this study are related to the small size of this trial, particularly with respect to interpretation of efficacy which is also impacted by the differences in therapeutic dose levels. Nonetheless, the preliminary safety and efficacy data from this phase 1 study support the clinical development of high-specific-activity I-131 MIBG in patients with metastatic and/or recurrent PPGL. Based on the MTD of 296 MBq/kg (8 mCi/kg) determined from this study, a target therapeutic administered activity of 18.5 GBq (500 mCi) was selected in the open-label, multicenter phase 2b study, which is currently ongoing in the long-term follow-up phase (NCT00874614).

There are no other comparative studies for any systemic therapeutic options in this ultra-rare disease. Only one phase 2 clinical trial with high dose conventional I-131 MIBG has been published, and no phase 3 clinical trials exist (25). Van Hulsteijn *et al* conducted a meta-analysis of radiographic and biochemical tumor response on 17 I-131 MIBG studies in a total of 243 patients with metastatic and/or recurrent PPGL (10). Response rates showed high variability; and treatment regimens, administered doses, and duration of follow-up also differed widely across studies. Individual tumor dosimetry was not routinely performed to optimize dose delivery, and version(s) of RECIST criteria was only used in four studies to assess objective tumor response. The analysis suggests that most patients experienced either PR (27% [radiographic], 40% [biochemical]) or SD (52% [radiographic], 21% [biochemical]) responses (mostly not by RECIST). An older meta-analysis by Loh *et al* reported similar radiographic response rates of 26% PR and 57% SD; while 13% of patients experienced PD (17). The large proportion of patients with SD is also observed in untreated patients with metastatic and/or recurrent PPGL, owing to perhaps the indolent nature of the disease (26). A single-arm phase 2 investigator-initiated study with sunitinib in locally advanced or metastatic PPGL has been published with interim results up to 12 weeks. The study reported that of 14 patients with evaluable radiological response, 3 patients (21.4%) had PR at 12 weeks with one unconfirmed response (27). Thus, based on the reported safety and tolerability, and efficacy of radiological response at 12 months, high-specific-activity I-131 MIBG may be an effective therapeutic option for patients with iobenguane-avid, metastatic and/or recurrent PPGL for whom there are no approved therapies.

Acknowledgements:
John W. Babich, PhD; R. Edward Coleman, MD; Shankar Vallabhajosula, PhD. Research funding was provided by Molecular Insight Pharmaceuticals, Inc., a wholly owned subsidiary of Progenics Pharmaceuticals, Inc.

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Disclosure: The authors report no conflicts of interest in this work. RBN has research funding and a consulting role with Eli Lilly and Avid Radiopharmaceuticals. DP consults for 511 Pharma. DP has received research funding from Progenics, Siemens, 511 Pharma. JJ, TL, NS, TS, and VW are employed by Progenics Pharmaceuticals, Inc. SJG receives royalties from Cornell University. The writing of the manuscript was not supported by any grant. The clinical trial is registered on ClinicalTrials.gov, NCT00458952.

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Figure 1. Administration of high-specific-activity I-131 MIBG at sequential escalating dose levels and occurrence of dose-limiting toxicities (DLTs) in 21 treated patients.

Table 1: Baseline characteristics of 21 treated patients

Characteristics	Value
Age (years)	
Median	49
Range	30-72
Male, n (%)	13 (61.9)
Race, n (%)	
White/Caucasian	16 (76.2)
Black	3 (14.3)
Asian	2 (9.5)
Height (cm)	
Median	172.7
Range	145-201
Weight (kg)	
Median	80.7
Range	42-126
Primary Diagnosis, n (%)	
Pheochromocytoma	10 (47.6)
Paraganglioma	11 (52.4)
Prior Anti-cancer Therapies for PPGL, n (%)	
Radiation therapy[1]	12 (57.1)
Chemotherapy (e.g., CVD and others)	6 (28.6)
Octreotide	3 (14.3)

1. Includes external beam radiation therapy and conventional I-131 MIBG

Table 2: Radiation absorbed dose estimates by target organ following dosimetry doses of high-specific-activity I-131 MIBG in 20 dosimetry-evaluable patients

Target Organ	Mean (mGy/MBq)	Minimum (mGy/MBq)	Maximum (mGy/MBq)
Thyroid	1.2	0.44	2.0
Lower large intestine wall	1.2	0.74	1.7
Salivary glands	0.87	0.28	1.9
Urinary bladder wall	0.67	0.62	0.71
Upper large intestine wall	0.51	0.34	0.71
Liver	0.48	0.16	2.7
Spleen	0.47	0.23	0.99
Kidneys	0.42	0.14	0.73
Heart wall	0.35	0.20	0.48
Lungs	0.32	0.13	0.63
Small intestine	0.19	0.14	0.26
Osteogenic cells	0.14	0.070	0.26
Gallbladder wall	0.13	0.065	0.36
Ovaries	0.13	0.094	0.20
Uterus	0.12	0.082	0.18
Pancreas	0.11	0.053	0.20
Adrenals	0.11	0.049	0.22
Total body	0.10	0.053	0.17
Stomach wall	0.094	0.050	0.16
Thymus	0.078	0.038	0.14
Muscle	0.077	0.041	0.13
Red marrow	0.074	0.041	0.13
Testes	0.072	0.042	0.13
Breasts	0.065	0.031	0.12
Skin	0.058	0.030	0.11
Brain	0.049	0.016	0.081

Table 3: Best overall objective tumor response as assessed by RECIST, categorized by total administered activity of high-specific-activity I-131 MIBG

Overall Response by RECIST	Total Administered Activity		Overall (N=21) n (%)
	≤18.5 GBq (N=7) n (%)	>18.5 GBq (N=14) n (%)	
Complete Response	0	0	0
Partial Response	0	4 (28.6)	4 (19.0)
Stable Disease	6 (85.7)	7 (50.0)	13 (61.9)
Progressive Disease	0	2 (14.3)	2 (9.5)
Not Evaluable	1[a] (14.3)	1[b] (7.1)	2 (9.5)

[a] Not evaluated because patient died of hepatic failure prior to any efficacy assessments.

[b] Not evaluated because patient was discontinued from the study for starting alternate chemotherapy.

Table 4: Best biochemical tumor response during 12 months post-treatment, categorized by total administered activity of I-131 MIBG and overall

Biochemical Tumor Response, Best Overall	Total Administered Activity		
	≤18.5 GBq (N=7) n (%)	>18.5 GBq (N=14) n (%)	Total (N=21) n (%)
Serum chromogranin A			
Complete Response (CR)	3 (42.9)	4 (28.6)	7 (33.3)
Partial Response (PR)	1 (14.3)	4 (28.6)	5 (23.8)
Stable Disease (SD)	0	3 (21.4)	3 (14.3)
Progressive Disease (PD)	0	0	0
Normal at Baseline (NNPD)	2 (28.6)	3 (21.4)	5 (23.8)
Not Evaluable (NE)	1 (14.3)	0	1 (4.8)
Proportion (of ITT) with Overall Response of CR or PR (95% CI)			0.75 (0.51, 0.99)
Proportion (of Evaluable) with Overall Response of CR or PR (95% CI) [a]			0.80 (0.56, 1.04)
Jonckheere-Terpstra test for dose response [a,b]			0.284
Total Metanephrines 24 hour			
Complete Response (CR)	2 (28.6)	3 (21.4)	5 (23.8)
Partial Response (PR)	0	4 (28.6)	4 (19.0)
Stable Disease (SD)	2 (28.6)	3 (21.4)	5 (23.8)
Progressive Disease (PD)	0	0	0
Normal at Baseline (NNPD)	1 (14.3)	1 (7.1)	2 (9.5)
Not Evaluable (NE)	2 (28.6)	3 (21.4)	5 (23.8)
Proportion (of ITT) with Overall Response of CR or PR (95% CI)			0.47 (0.22, 0.72)
Proportion (of Evaluable) with Overall Response of CR or PR (95% CI) [a]			0.64 (0.36, 0.93)
Jonckheere-Terpstra test for dose response [a,b]			1.000

a Excludes non-evaluable responses.

b p-value is exact and 2-sided.