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ORIGINAL ARTICLE

A phase IIa trial of molecular radiotherapy with 177-lutetium DOTATATE in children with primary refractory or relapsed high-risk neuroblastoma

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Abstract

Purpose The objective of this phase IIa, open-label, single-centre, single-arm, two-stage clinical trial was to evaluate the safety and activity of 177-lutetium DOTATATE (LuDO) molecular radiotherapy in neuroblastoma.

Methods Children with relapsed or refractory metastatic high-risk neuroblastoma were treated with up to four courses of LuDO. The administered activity was 75 to 100 MBq kg^{-1} per course, spaced at 8- to 12-week intervals. Outcomes were assessed by the International Neuroblastoma Response Criteria (primary outcome), progression-free survival (PFS), and overall survival (OS).

Results The trial recruited 21 patients; eight received the planned four courses. There was dose-limiting haematologic toxicity in one case, but no other significant haematologic or renal toxicities. None of 14 evaluable patients had an objective response at 1 month after completion of treatment (Wilson 90% CI 0.0, 0.16; and 95% CI is 0.0, 0.22). The trial did not therefore proceed to the second stage. The median PFS was 2.96 months (95% CI 1.71, 7.66), and the median OS was 13.0 months (95% CI 2.99, 21.52).

Conclusion In the absence of any objective responses, the use of LuDO as a single agent at the dose schedule used in this study is not recommended for the treatment of neuroblastoma. There are several reasons why this treatment schedule may not have resulted in objective responses, and as other studies do show benefit, the treatment should not be regarded as being of no value. Further trials designed to overcome this schedule's limitations are required.

Trial registration ISRCTN98918118; URL: https://www.isrctn.com/search?q=98918118

Keywords Neuroblastoma · Molecular radiotherapy · Lutetium DOTATATE · Toxicity

Abbreviations

AE	Adverse event
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
FDG	Fluorodeoxyglucose
GaDO	68-Gallium DOTATATE
GFR	Glomerular filtration rate
Gy	Gray
h	Hour
INRC	International Neuroblastoma Response Criteria
kg	Kilogram
kVp	Kilovoltage peak
l	Litre
L	Levo
LuDO	177-Lutetium DOTATATE
m	Metre
mA	Milliamperes
MBq	Megabecquerel
mIBG	Meta-iodobenzylguanidine
MRI	Magnetic resonance imaging
OS	Overall survival
PET	Positron emission tomography

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This article is part of the Topical Collection on Pediatric

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PFS	Progression-free survival
PRRT	Peptide receptor radionuclide therapy
SAE	Serious adverse event
SIOPEN	International Society of Paediatric Oncology European Neuroblastoma clinical research group
SPECT	Single-photon emission computed tomography
SUV_{max}	Maximum standardized uptake value
UK	United Kingdom
USA	United States of America
USAN	United States Adopted Name

Introduction

Neuroblastoma most commonly affects younger children [1]. Patients are stratified by age [2], stage [3], and molecular pathology [4] into low-, intermediate-, and high-risk groups [5]. High-risk neuroblastoma requires systemic therapies (induction [6] and high-dose chemotherapy [7,8] followed by immunotherapy [9,10]) and local approaches (surgery [11] and radiotherapy [12]). Around 25% respond poorly to induction chemotherapy, or may progress on initial treatment, and require alternative treatments before high-dose (myeloablative) chemotherapy [13]. These are referred to as refractory patients. Others may respond well initially, but relapse before or following high-dose chemotherapy, and are referred to as relapsed patients [14]. Patients in both groups have low survival rates, so new treatments are needed.

Neuroblastoma is radiosensitive [15], and radiotherapy is important [16]; however, full coverage of disseminated disease with external beam radiotherapy is not feasible. Molecular radiotherapy can potentially target all cells expressing the relevant receptor. 131-Iodine-labelled metaiodobenzylguanidine (^{131}I-mIBG) therapy [17], targeting the norepinephrine transporter molecule [18], is widely used [19].

Peptide receptor radionuclide therapy (PRRT) targets somatostatin receptors. Radiolabelled somatostatin analogues are used for adult neuroendocrine cancers [20,21]. 177-Lutetium DOTATATE (LuDO) prolongs survival in metastatic gastroenteropancreatic neuroendocrine tumours [22,23]. Toxicity is limited to myelotoxicity and nephrotoxicity [24].

Neuroblastoma cells express somatostatin receptors [25]. We used 68-gallium DOTATATE (GaDO) positron emission tomography (PET) computed tomography (CT) imaging to select patients with relapsed or refractory neuroblastoma with a high level of GaDO avidity, and treated six with LuDO molecular radiotherapy [26]. Two had partial metabolic responses. The role of PRRT in neuroblastoma has been reviewed by others [27].

Objectives

The objective of the study was to evaluate the safety and activity of LuDO molecular radiotherapy in metastatic high-risk relapsed or refractory neuroblastoma.

Patients and methods

Trial design

This is a phase IIa, open-label, single-centre, single-arm, two-stage clinical trial.

Patients

Patients (aged > 18 months and < 18 years) with histologically confirmed relapsed or refractory metastatic high-risk neuroblastoma were eligible if they had an estimated life expectancy > 3 months and good performance status (Lansky > 50% for patients ≤ 12 years of age; Karnofsky > 50% for those > 12 years of age) and had recovered from any major prior surgery. Tracer uptake in tumour deposits, measured by SUV_{max} on GaDO PET CT, had to be at least as high as in the liver. A 2-week washout from any prior treatment, with haematologic recovery, was required. Confirmation of adequate organ function was required prior to commencing trial treatment. Written informed consent from parents, or patients if aged 18 years or older, and agreement to abide by the radiation protection rules for comforters and carers [28] were required.

Exclusion criteria included as follows: patients not fit enough to undergo treatment; pregnant or lactating patients; concurrent treatment with any anti-tumour agents; and prior treatment with radiolabelled somatostatin analogues (any other prior treatment was permitted).

Disease and normal organ function assessments

Baseline disease assessments included ^{123}I-mIBG scintigraphy, which was scored according to SIOPEN criteria [29]; GaDO PET CT; cross-sectional imaging with CT or magnetic resonance imaging (MRI) of the primary tumour or bulky metastatic sites if appropriate; urinary catecholamine metabolites; and bone marrow aspirates and trephine biopsies. Routine haematology and biochemistry profiles and glomerular filtration rate (GFR) measurement were also performed. A pregnancy test was required in females of reproductive potential.

All patients were imaged with GaDO PET CT according to local protocol, on a Discovery STE PET CT system (GE Healthcare, Chicago, IL, USA). Patients were injected intravenously with at least 100 MBq GaDO for adequate image

quality. Imaging took place 45 to 60 min after injection. A total body protocol for transmission and emission imaging was acquired. CT was performed at 80–140 kVp and modulated mA. PET was performed in 3-dimensional mode with 4 min per bed position. Iterative reconstruction with 21 subsets was performed with attenuation correction. Patients who required general anaesthesia had images acquired with the same protocol.

Following each course of treatment, routine bloods were performed weekly. A GFR was calculated prior to subsequent courses [30]. The GaDO and ^{123}I-mIBG imaging were performed prior to the third course of treatment, to ensure that no further LuDO was given if the disease had progressed. One month following completion of the planned four courses of LuDO, reassessments were performed as at baseline.

Treatment schedule

Patients were admitted to a radiation protection suite on the paediatric oncology ward, and remained there, as inpatients, until there were no longer any radiation restrictions. The investigational medicinal product LuDO ([^{177}Lu-DOTA^{0},Tyr^{3}]octreotate; United States Adopted Name (USAN) lutetium (^{177}Lu) DOTATATE; also called lutetium oxodotreotide in Europe; brand name Lutathera®) was supplied by Advanced Accelerator Applications, Saint-Genis-Pouilly, France, a Novartis company. Hydration with 0.9% sodium chloride 3 l m^{-2} 24 h^{-1} was commenced 6 h prior to the LuDO administration and continued for 24 h. Thirty minutes before treatment, anti-emetics were given, and an amino acid solution infusion (L-lysine hydrochloride 2.5% w/v, L-arginine hydrochloride 2.5% in water for injection) 1 l 1.73 m^{-1} was commenced and administered over 4 h (that is 250 ml 1.73 m^{-1} h^{-1}) to protect the kidneys. The LuDO was administered intravenously over about 20 min.

The aim was to give a total of four courses. The intercourse interval was a minimum of 8 weeks, and this could be extended to a maximum of 12 weeks if necessary to allow for haematologic recovery.

Dose prescription

The dosing schedule was designed to mitigate the main potential toxicities of LuDO: myelosuppression and late nephrotoxicity. Dosimetry was performed in respect of both whole-body radiation absorbed dose, which may correlate with haematological toxicity, and kidney radiation absorbed dose, which may correlate with nephrotoxicity. Blood dose was not measured. We recognize that the relationship between absorbed dose and toxicity is controversial. With ^{131}I-mIBG therapy for neuroblastoma, some authors have demonstrated a relationship [31], while others have not [32]. The aim was to err on the side of safety and tolerability and to administer an activity of LuDO per course which would result in a whole-body dose of about 0.5 Gy, with a cumulative whole-body dose of about 2 Gy over four courses, so that peripheral blood stem cell support was not required; and not to exceed a cumulative renal dose of 23 Gy, to avoid nephrotoxicity. No account was taken of any prior external beam radiotherapy which may have affected renal function, except for ensuring that all patients had an adequate GFR before trial entry. Toxicity and dose-limiting toxicity criteria are shown in Table 1.

For the first administration, a weight-based activity of 75 MBq kg^{-1} was used. Following administration, a series of radiation measurements were taken using a ceiling-mounted monitor according to a standard protocol to enable the whole-body radiation dose to be calculated. Subsequently, over the next 4 days, a series of at least three whole-body scans were acquired to enable the whole-body dose to be verified by a second method, as well as to confirm uptake in known areas of disease. In addition, single-photon emission computed tomography (SPECT) CT scans were performed to allow tumour and normal organs (principally the kidney) absorbed radiation doses to be estimated.

The administered activity for the second and subsequent courses was calculated on the basis of the whole-body dose measured following the previous administration, and the haematological toxicity (Table 1).

Dosimetry

Whole-body dosimetry was performed using in-room ceiling scintillation monitors (Southern Scientific Ltd., Henfield, UK). The first measurement was performed immediately after administration of LuDO, prior to the patient emptying his or her bladder. Subsequent measurements were taken by comforters and carers, and activity at these time points normalized to the first measurement. For each fraction of treatment, a time-activity graph was generated and the whole-body dose calculated from the product of cumulated activity and relevant *s*-factor.

Whole-body planar scans and SPECT CT were obtained after treatment to evaluate tumour and normal organ-at-risk dosimetry and to confirm the whole-body dose. All patients who had dosimetric analysis had 3–5 imaging sessions after each fraction of treatment. All images were acquired on a Discovery 670 Gamma Camera (GE Healthcare, Chicago, IL, USA). Whole-body planar scans were obtained with an emission window of 208 keV ± 10%. SPECT CT was performed with the same emission window and triple-energy scatter correction. A total of 120 projections were acquired at 30 s per projection. Iterative reconstruction was used (20 subsets) with attenuation and scatter correction. Dosimetry was performed by contouring on the CT transaxial slices and transposing to the SPECT dataset. Based on phantom SPECT sensitivity measurements, the activity in the organ at each time

Table 1 Definitions of haematological and renal toxicity and dose-limiting toxicity and their use to determine subsequent administered activities

Haematological toxicity			
Mild	Neutrophil and/or platelet toxicities grade 1 or grade 2 with recovery by week 10 after administration of LuDO.		
Moderate	Neutrophil and/or platelet toxicities grade 3 or grade 4 with recovery by week 10 after administration of LuDO.		
Severe	Neutrophil and/or platelet toxicities grade 3 or grade 4 failing to recover by week 10 after administration of LuDO.		
The grading system used for neutrophil and platelet toxicity was CTCAE v4.0.			
Renal toxicity			
○ Prior to the first LuDO administration, a formally measured GFR had to be > 50 ml min^{-1} 1.73 m^{-2} (eligibility criterion).			
○ Prior to subsequent cycles, an estimated GFR was performed, and if it fell below 50 ml min^{-1} 1.73 m^{-2}, a formally measured GFR was performed, and if that confirmed it as less than 50 ml min^{-1} 1.73 m^{-2}, no further LuDO was given.			
○ Following each LuDO administration, renal dosimetry was performed to ensure that the cumulative renal dose did not exceed 23 Gy.			
Dose-limiting toxicity			
○ Severe haematological toxicity encountered after any course.			
○ Fall in the GFR below 50 ml min^{-1} 1.73 m^{-2}.			
○ Cumulative renal dose likely to exceed 23 Gy.			
Activities to be administered for subsequent courses			
Haematological toxicity from previous administration	Whole-body absorbed dose from previous administration		
	< 0.4 Gy	0.4–0.6 Gy	> 0.6 Gy
Mild	100 MBq kg^{-1}	75 MBq kg^{-1}	75 MBq kg^{-1}
Moderate	75 MBq kg^{-1}	75 MBq kg^{-1}	50 MBq kg^{-1}
In the absence of haematological toxicity, the dose for the subsequent cycles was 100 MBq kg^{-1}, regardless of the whole-body dose.			
No further LuDO to be given if dose-limiting toxicities are observed:			
○ Severe haematological toxicity was encountered after any course.			
○ GFR falls below 50 ml min^{-1} 1.73 m^{-2}.			
○ Cumulative renal dose threatens to exceed 23 Gy.			

point was calculated so that a time-activity curve could be generated. Dose was calculated by multiplying the cumulated activity by the relevant *s*-factor.

Outcomes

The primary outcome measure was response (complete, very good partial, and partial) assessed by the International Neuroblastoma Response Criteria (INRC) [33,34] at 1 month after the completion of therapy, defined as the last administration of LuDO. Patients who did not have response assessment at 1 month after the completion of therapy were considered non-responders. The data were also analyzed by the recently published Revisions to the INRC [35].

Secondary outcome measures were as follows: toxicity, progression-free survival (PFS), overall survival (OS), and response by INRC at 4 months after the completion of therapy (defined as per primary outcome measure). Toxicity was assessed according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. PFS time was defined as the time from trial inclusion until objective tumour progression, death without progression, or second malignancy. OS time was calculated from the date of inclusion into the trial until date of death. For all survival outcomes, patients who did not experience an event during trial follow-up were censored at their last assessment date.

Sample size

The sample size calculation was based on a Simon two-stage minimax design [36]. A rate of 40% or more was defined at the outset as the acceptable level of response. A response rate of 20% or less was considered unacceptably low. The probability of obtaining a false negative result, β (i.e. incorrectly

rejecting for further study a treatment with a true response rate of ≥ 40%), was set at 20%. The probability of obtaining a false positive result, α (i.e. incorrectly accepting for further study a treatment that has a true response rate of ≤ 20%), was set at 10%. Stage 1 required 14 eligible and evaluable patients, with a minimum of three responders to proceed to stage 2. A further 10 patients were needed to be recruited in stage 2. A minimum of 8 out of 24 responses would indicate that the treatment schedule was active and should go onto further studies to evaluate efficacy (while taking account of toxicity). Sample size calculations were performed using Sample Size Tables for Clinical Trials [37].

Statistical methods

The analysis of the primary outcome measure was carried out on an eligible and evaluable patient basis. Patients who did not start treatment, and those who died due to any cause within 3 months from registration (i.e. time between death date and registration date is less than 92 days), were excluded from this analysis. All other analyses were carried out according to an intention-to-treat (ITT) principle, defined as all patients registered in the trial. Descriptive statistics were used to summarize baseline characteristics, treatment, report harms, and response outcomes. Data is expressed as mean (standard deviation (SD)), median (minimum, maximum), or number (percent). Kaplan-Meier plots with median survival and estimate at 6 and 12 months are presented. Two-sided confidence intervals (CIs) at 90% and 95% levels are reported; for the response outcome, one- and two-sided Wilson CIs were calculated.

Ethical and research governance considerations

This trial was conducted in accordance with the recommendations of guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996; and with the Research Governance Framework for Health and Social Care, UK law, and the applicable UK Statutory Instruments. The trial received a favorable opinion from the National Research Ethics Service's London – Hampstead Research Ethics Committee; a Clinical Trial Authorization from the Medicines and Healthcare products Regulatory Agency (MHRA); approval from the Administration of Radioactive Substances Advisory Committee (ARSAC); and local Research And Development approval. The Sponsor was the University of Birmingham, and data management and monitoring was undertaken by the Cancer Research UK Clinical Trials Unit at the University of Birmingham. Parents or legal guardians of patients, or patients if aged over 18 years, were given verbal and written information about the trial to consider for a period of at least 1 day, before being asked to give written informed consent for trial entry at a subsequent consultation.

An independent Data Monitoring Committee was established to review safety and outcome data at six monthly intervals. The trial terminated recruitment when the data for the primary outcome measure for the eligible and evaluable patient population was available on the database for stage 1 of the trial and the number of responders was insufficient to carry on to stage 2.

The trial was registered in the European Clinical Trials Database (EudraCT number 2012-000510-10), and in the International Standard Randomized Controlled Trials Number Registry (ISRCTN98918118).

Results

Patient population

In total, 43 patients were screened. Between 19 September 2013 and 28 July 2017, 21 patients were registered in the trial; all had ^{123}I-mIBG-positive disease on imaging. Participants were followed up after the end of treatment until progression of disease and death. At the date of data analysis, 14 September 2018, 18 patients had died from their disease. Median follow-up for alive patients was 17.3 months (13.1 to 37.4). The other 22 patients were not entered because of the following: low SUV_{max} on the GaDO scan (11); rapid disease progression, poor performance status or estimated life expectancy, or out of range organ function (6); a medical decision for alternative treatment (3); or parental wishes (2). Figure 1 is a CONSORT diagram of patients screened for this study.

Table 2 shows patient demographics and disease characteristics at baseline.

Treatment delivery

Of the 21 registered patients, 20 received at least one course of LuDO treatment. One patient was withdrawn before the start of treatment because of progressive disease. The median time between enrollment and start of treatment for the 20 patients was 3 days (range 0–26 days). Of the 20 treated patients, eight received four courses of LuDO, two received two courses, and ten received only one course. The reasons for early discontinuation were progression or death in 11 and severe haematological toxicity in one. A total of 46 courses of treatment were given.

The administered activity of LuDO was 75 MBq kg^{-1} for the first course, in all twenty treated patients. The administered activity in all subsequent courses was 100 MBq kg^{-1}, because no patients needed dose modifications for toxicity, other than

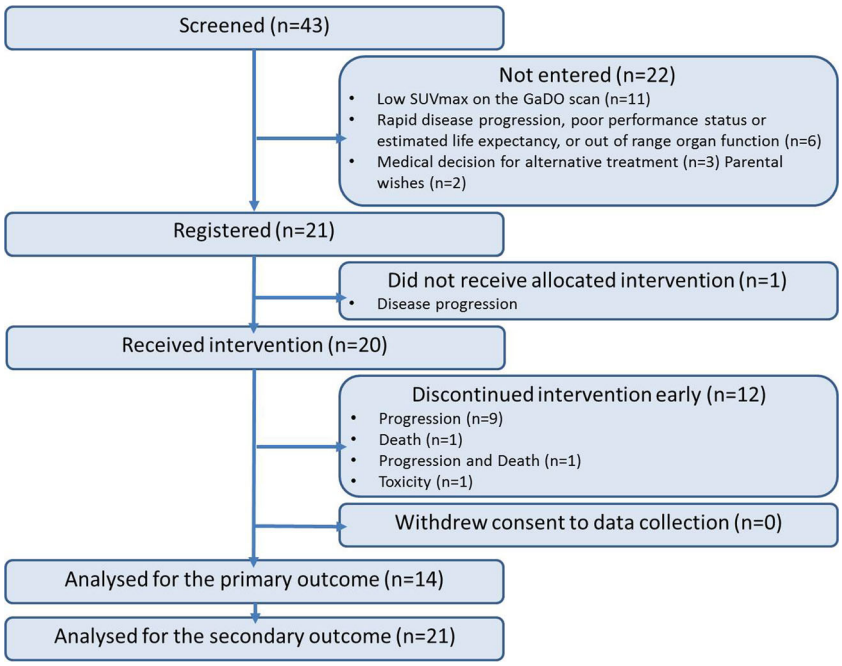

Fig. 1 CONSORT diagram of all patients enrolled in this study

one patient who stopped treatment because of severe haematological toxicity.

Safety and toxicity

There was no treatment-related mortality. There were 151 adverse events (AE) among 19 of the 20 treated patients. The median AE number was 6.5 (range 0–20). The highest grade of AE was grade 1 in five patients, grade 3 in 12 patients, and grade 4 in 2 patients. Grade 3 and 4 toxicities are listed in Table 3. There were 10 serious adverse events (SAE) reported in six patients. Four patients experienced one SAE, and two patients experienced three SAE each. In each case, the reason for SAE reporting was unexpected hospitalization. In nine cases, the SAE was categorized as being unrelated to trial treatment. The one serious adverse reaction was caused by neutropenic sepsis. There were no serious unexpected serious adverse reactions. There was one case of dose-limiting haematological toxicity. This was after the first course of treatment, when an administered activity of 75 MBq kg^{-1} resulted in a whole-body dose of only 0.21 Gy, below the median. The observed haematological toxicity may have been due to

Table 2 Patient demographics and disease characteristics at baseline ($n = 21$)

Sex	Male	10 (48%)
	Female	11 (52%)
Age at diagnosis	Median 3.6 years (range 0.7–16.1 years)	
Age at registration	Median 5.4 years (range 1.7–16.9 years)	
Weight	Median 19.5 kg (range 11.5–47.0 kg)	
MYCN status	Amplified	1 (5%)
	Not amplified	20 (95%)
Disease status	Refractory	8 (38%)
	Relapsed	13 (62%)
Prior surgery	No	5 (24%)
	Yes	16 (76%)
Prior radiotherapy	No	11 (52%)
	Yes	10 (48%)
Prior chemotherapy	Median 4 regimens (range 2–7 regimens)	
Prior high dose Chemotherapy	No	13 (62%)
	Yes	8 (38%)

Table 3 CTCAE v4.0 grade 3 and grade 4 toxicities reported

Toxicity (CTCAE term)	Grade 3 events	Grade 4 events
Increased alanine aminotransferase	0	1
Increased bilirubin	1	0
Decreased white blood cell count	4	0
Decreased lymphocyte count	7	0
Decreased neutrophil count	6	0
Decreased platelet count	3	1
Anaemia	2	0
Febrile neutropenia	1	0
Bronchial infection	1	0
Skin infection	1	0
Upper respiratory infection	1	0
Urinary tract infection	1	0
Wound infection	1	0
Abdominal pain	1	0

concurrent use of myelosuppressive antibiotics, rather than an actual side effect of the trial treatment. No significant renal toxicity was observed.

SUV_{max} uptake levels and whole-body and tumour dosimetry

Only patients with a higher somatostatin receptor expression in tumour than in the normal liver were included in this trial. The median SUV_{max} for the liver measured on pre-treatment GaDO PET CT scans was 4.7 (range 2.1 to 9.0), and the median highest tumour SUV_{max} measurement for each patient was 11.2 (range 5.7 to 44.2).

The median whole-body radiation absorbed dose (as estimated from the ceiling-mounted monitor data) was 0.24 Gy (range 0.14 to 0.42 Gy) following the first course when the administered activity was 75 MBq kg^{-1}, and 0.33 Gy (range 0.16 to 0.61 Gy) following subsequent courses when the administered activity was 100 MBq kg^{-1}. The median cumulative whole-body absorbed dose in those patients who received all four courses for whom complete data were available was 1.26 Gy (range 0.97 to 1.48 Gy).

The median cumulative mean renal radiation dose in the six patients who received four courses of treatment and for whom full dosimetric data were recorded was 16.5 Gy (range 9.5 to 21.5 Gy).

The tumour dose per course was measured in 24 lesions, and the median was 2.43 Gy (range 0.04 to 13.50 Gy).

Response

Of the 20 treated patients, six were considered ineligible for the primary outcome assessment as they died within 92 days of enrollment: median 62 days, range 28–91 days. This left 14 evaluable patients, of whom none had a response either by the original or by the revised INRC criteria at 1 month after completion of treatment (Wilson 90% CI 0.0, 0.16; and 95% CI is 0.0, 0.22). Of these 14, eight patients had progressed and six were non-responders at that time point. In view of this, the trial was closed and did not move on to the second stage. Of 21 patients analyzed for the secondary outcome measure, response at 4 months post end of treatment, no patients responded (Wilson 90% CI 0.0, 0.11; and 95% CI is 0.0, 0.16): one was non-responder, one did not start treatment, and 19 had progressive disease. Eight patients had stable disease at reassessment after two cycles of treatment, and four had stable disease at reassessment after four cycles of treatment.

Survival

For all 21 patients, one (5%) patient had no event, two (10%) progressed without death, and 18 (85%) progressed and died. The median PFS was 2.96 months (95% CI 1.71, 7.66). The PFS at 6 months was 38% (95% CI 18%, 58%) and PFS at 12 months was 5% (95% CI 0%, 20%) (Fig. 2).

At the time of analysis, 18 of 21 patients had died. The median OS for the 21 patients was 13.0 months (95% CI 2.99, 21.52). The OS at 6 months was 62% (95% CI 38%, 79%) and OS at 12 months was 52% (95% CI 30%,71%) (Fig. 3).

At least ten of the patients went on to receive other treatments following progression.

An unplanned analysis assessed PFS and OS for 13 relapsed patients and for the eight refractory patients (Table 2). For relapsed patients, the median PFS was 1.87 months (95% CI 0.72, 82.96) and the median OS was 5.45 months (95% CI 2.23, 17.31). For refractory patients, the median PFS was 7.66 months (95% CI 1.71, 10.78) and the median OS was 24.74 (95% CI 1.87, 27.89) months.

Although no response by the INRC criteria was noted at 1 month after completion of treatment, an unplanned analysis showed a reduction in the SIOPEN semi-quantitative ^{123}I-mIBG scan skeletal score in three patients between baseline and prior to the third administration of LuDO. The paired values were 9, 5; 19, 18; and 17, 12.

Discussion

This is the first formal phase II trial of LuDO molecular radiotherapy in children with neuroblastoma. As no objective responses by the INRC criteria were seen in 14 evaluable patients, we do not recommend the use of LuDO as a single agent at the dose schedule used in this study for the treatment of patients with neuroblastoma. This is disappointing, as we have seen responses in patients treated outside this trial [26,38], and an independent group observed objective responses in all of four patients treated similarly [39]. In this trial, we did observe an objective improvement on

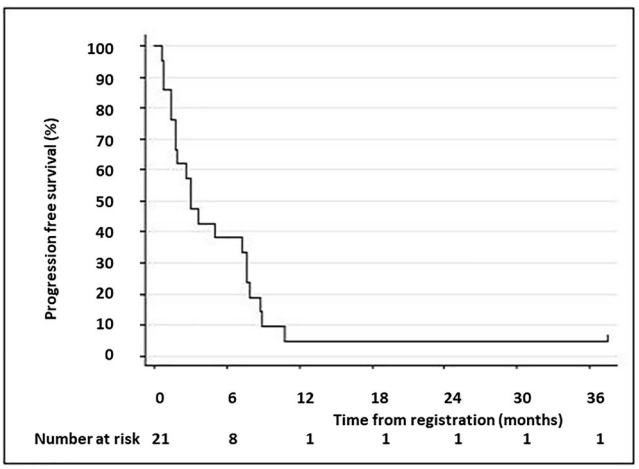

Fig. 2 Progression-free survival

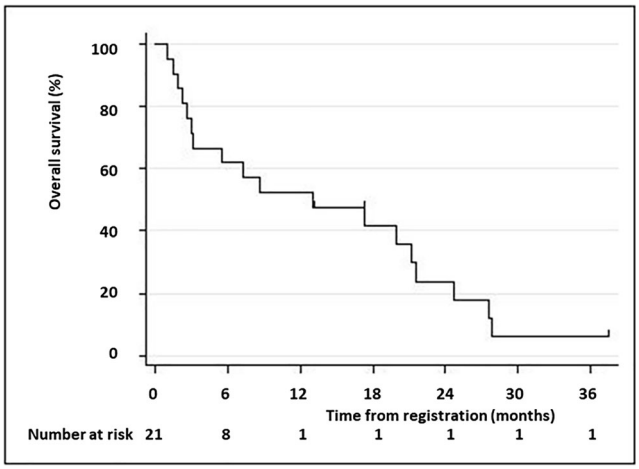

Fig. 3 Overall survival

independent blinded ^{123}I-mIBG semi-quantitative scoring after two courses of treatment in three patients, although this was insufficient to count as a partial response and was not sustained at the primary evaluation time point.

The poor survival observed in this trial is in keeping with that seen in similar patients enrolled in other early phase clinical trials. A meta-analysis of European phase II trials in neuroblastoma showed a median PFS of 5.7 months and a median OS of 11.0 months in relapsed disease, compared with our figures of 1.87 and 5.45 months respectively. In refractory disease, the median PFS was 12.5 months and median OS was 27.9 months, compared with our figures of 7.66 and 24.74 months respectively [40]. The better survival of refractory patients compared with relapsed patients is expected [41].

We feel it is important to report our data for these subgroups, even though the analysis was not planned at the outset, for several reasons. There is a growing recognition in the literature that results vary between refractory patients who have failed to respond adequately to induction chemotherapy, and move onto alternative treatments, and those who relapse after a good initial response chemotherapy [40,41]. Therefore, overall results may differ depending on the relative proportions of the two groups. We have previously observed that studies which fail to report the two groups separately limit the value of the data presented [19].

It is important to note (Fig. 1), as this is an imaging biomarker–driven study, that 11 of 43 patients screened did not have adequate uptake as measured by tumour SUV_{max} on the baseline GaDO PET CT scan to allow entry to the trial. This means that a significant proportion of patients will not be eligible for inclusion in any future trials of this agent. While all patients included in the trial had a higher tumour SUV_{max} than the liver, it is possible that those with a greater somatostatin receptor expression might have better outcomes; however, as no patients met the pre-defined response criteria, it is not possible to say from this patient population whether or not that was in fact the case.

There may be several reasons why, in this trial, LuDO did not prove to be as effective as anticipated:

The scheduling at two monthly intervals, based on adult neuroendocrine tumour experience, may have been too spaced out for a rapidly proliferating tumour like neuroblastoma, and permitted repopulation between treatments.

Only one patient was withdrawn from study treatment because of haematological toxicity. The measured cumulative renal radiation dose was in all cases lower than the 23-Gy objective, and at 16.5 Gy, the median value was about 70% of that. The measured cumulative whole-body dose was in all cases lower than the 2-Gy objective, and at 1.26, the median value was 63% of that. These factors indicate that with personalized dosing, the administered activity could have been substantially increased in many patients without excess toxicity.

Our observed whole-body doses are substantially less than the 4 Gy we use routinely in ^{131}I-mIBG therapy with peripheral blood stem cell support [42]. Tumour doses measured after administration of ^{131}I-mIBG to a whole-body dose of 4 Gy may vary by an order of magnitude—from about 10 to 100 Gy, depending on the avidity of the tumour and retention of the radiopharmaceutical over time [43]. Our tumour dose measurements using the described schedule of LuDO administration also vary widely, but with a median of 2.43 Gy per course, are substantially below those seen with ^{131}I-mIBG therapy.

We have demonstrated heterogeneity in somatostatin receptor expression and a lack of concordance between somatostatin and norepinephrine transporter expression in tissue bank samples [25]. Using PET CT and scintigraphy, we have sometimes observed anatomical disparity in the distribution of neuroblastoma deposits taking up GaDO and ^{123}I-mIBG; and another group has reported similar findings [39]. This microscopic and macroscopic diversity may be a factor contributing to a poor response to single-agent LuDO. We may hypothesize that a combination of LuDO and mIBG therapy may overcome this limitation and be more effective than either agent alone.

The concomitant use of radiation sensitizers has been demonstrated in laboratory models to potentiate mIBG therapy [44,45], and synergy between radiosensitizing drugs and LuDO has also been similarly shown [46].

Despite the negative result of this study, we believe that PRRT in general, and LuDO in particular, may have value as a treatment for neuroblastoma. Our view is supported by the fact that other groups are planning trials of different theranostic imaging and treatment radiopharmaceuticals targeting SSTR, for example 64-copper SARTATE PET imaging and 67-copper SARTATE molecular radiotherapy [47]. We propose further clinical trials bringing together increased

activities of LuDO with mIBG in a dose-dense schedule, as this may potentially overcome some of the limitations discussed here. When an optimal dose schedule has been identified, further studies on the addition of radiation sensitizers may be considered.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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