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ORIGINAL ARTICLE

No reinduction of clinically relevant radioiodine uptake after lenvatinib treatment in radioidine-refractory differentiated thyroid cancer

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Abstract

Background Prior studies show that short-term treatment using tyrosine kinase inhibitors (TKIs) can reinduce radioiodine uptake and warrant ^{131}I therapy in radioiodine-refractory differentiated thyroid cancer (RAI-R DTC). We aim to evaluate the potential of standard-of-care TKI lenvatinib to reinduce clinically meaningful radioiodine retention.

Methods Nine RAI-R DTC patients starting lenvatinib treatment for progressive advanced or metastatic disease, were included and underwent rhTSH-stimulated ^{124}I dosimetric procedures at baseline, week 6 (N=7) and week 12 (N=8). At all timepoints, the fraction of patients eligible for ^{131}I therapy with a maximal activity of 7.4 GBq was assessed. Patients were considered eligible if at least one target lesion showed an expected mean absorbed dose ≥20 Gy. In total, 23 target lesions were segmented on ^{124}I PET/CT images and their volumes estimated using low-dose CT images. Lesion size-specific recovery correction was applied to the measured mean activity concentration at each timepoint. Tumor dosimetry was performed using a mono-exponential fit and S-values from an internal dosimetry program for diagnostic nuclear medicine based on the ICRP adult reference voxel phantoms (IDAC-Dose2.1). Mean absorbed lesion dose per administered activity (LDpA), 24h-uptake and residence time in target lesions were compared between time points.

Results By our definition, none of the patients were found eligible for ^{131}I therapy at any timepoint. Lenvatinib-induced partial response was observed in 59% and 75% of target lesions at week 6 and 12, respectively. Median LDpA was 0.08 (IQR: 0.04-0.17), 0.18 (0.08-0.36) and 0.17 (0.09-0.37) Gy/GBq for week 0, 6 and 12, respectively (p=0.08). The 24h-uptake and residence time were comparable between timepoints (p>0.22).

Conclusion Redifferentiation of RAI-R DTC to reinduce radioiodine uptake to a level that warrants ^{131}I therapy may not be established by short-term lenvatinib treatment. Multi-targeted TKIs may not be as potent as selective TKIs in reinducing clinically meaningful radioiodine retention.

Keywords Lenvatinib · Redifferentiation · Radioiodine refractory · Thyroid cancer · ^{124}I · Dosimetry

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Introduction

Locally advanced or metastatic differentiated thyroid cancer (DTC) is commonly treated with (repeated) ^{131}I therapy, thereby effectively targeting iodine-avid disease, resulting in a 10-year overall survival of over 92% [1–3]. However, over time, up to 50% of patients with metastatic DTC undergo dedifferentiation after which the cancer cells are no longer able to accumulate and/or respond to radioiodine. This results in radioiodine-refractory (RAI-R) disease in which ^{131}I therapy is deemed ineffective [4–6]. As management of these patients is a considerable challenge, the 10-year overall survival drops to < 10% [7]. In patients with RAI-R DTC, first-line treatment with tyrosine kinase inhibitor lenvatinib or sorafenib is an Food and Drug Administration (FDA-) and European Medicines Agency (EMA)-approved standard approach, offering disease control by targeting pathways involved in tumor growth and angiogenesis [1, 8]. However, it is associated with high toxicity, leading to dose reductions and interruptions in more than 60% of patients, and treatment withdrawal in approximately 15–20% of patients [9, 10].

In the last decade, a promising new approach for treating RAI-R DTC involves so-called redifferentiation of the tumor to restore its ability to accumulate radioiodine, followed by ^{131}I therapy [11–19]. This strategy involves short-term treatment with agents inhibiting the mitogen-activated protein kinase (MAPK) signaling pathway, which is overactivated in RAI-R disease. MAPK inhibition has been shown to upregulate the sodium-iodide symporter (NIS) which is involved in iodide uptake in thyroid (cancer) cells [20, 21]. Renewed or enhanced uptake has been observed for combination therapy with B-type rapidly accelerated fibrosarcoma kinase (BRAF) and mitogen-activated protein kinase kinase (MEK) inhibitors in median 61% (range: 35–83%) of patients, and 63% (range: 35–100%) was given subsequent ^{131}I therapy. Partial responses were observed in 50% (range: 14–75%) of treated patients [11–18].

Whether approved and in guidelines embedded TKIs can act as a redifferentiation agent is of great interest, as this could be a game changer in the management of RAI-R DTC. Lenvatinib is hypothesized to restore radioiodine uptake and accumulation through its indirect inhibition of the MAPK pathway [22]. In contrast to selective TKIs such as abovementioned BRAF and MEK inhibitors, which directly inhibit the MAPK pathway downstream, multi-targeted TKI lenvatinib reduces the MAPK pathway's (over)activation by blocking receptor tyrosine kinases at the top of the signaling cascade [20, 23]. Anschlag et al. showed in an in vitro experiment that lenvatinib and sorafenib increased ^{99m}Tc uptake, as surrogate for NIS expression, with a maximum of 326% and 312% in papillary DTC cell lines, respectively [24]. In a clinical study, multi-targeted TKI sorafenib was not successful in reinducing radioiodine uptake after 26 weeks [25]. It remains unclear whether there is an optimal time window during which redifferentiation maximizes, and how durable the effect is.

The RESET study was designed to evaluate the ability of lenvatinib treatment to reinduce radioiodine uptake to subsequently enable ^{131}I therapy in RAI-R DTC patients. To gain insight in the extent and timing of the redifferentiation effect, predicted efficacy and safety of ^{131}I therapy was quantified by dosimetry based on molecular imaging with ^{124}I PET/CT after 6 and 12 weeks of lenvatinib treatment.

Methods

Study design

The RESET trial was an investigator-initiated, open label phase II study, approved by the institutional review board (Medical Ethics Committee Leiden-Den Haag-Delft, P20.096) and registered at ClinicalTrials.gov (NTC04858867). The study was conducted following the principles of the Helsinki Declaration and Good Clinical Practice guidelines. All participants provided written informed consent to participate in the study.

Patient population

Adult patients with structural evidence of progressive, locally advanced or metastatic RAI-R thyroid cancer were considered eligible for the study if they had measurable lesions according to RECIST 1.1 criteria and a clinical indication for lenvatinib treatment. RAI-R disease was defined by the tumor board and included structural metastatic lesions that were not visible on diagnostic or post-therapeutic RAI scans, or lesions that have remained stable or show progression despite ^{131}I therapies in accordance with the Martinique principles [26]. Adequate blood coagulation function, bone marrow function, and renal and liver function were required. Patients were not considered eligible if they had concomitant or previous malignancies within the last 3 years or other conditions that would affect compliance to the study protocol. The complete inclusion and exclusion criteria are listed in the published study protocol [22].

Study procedures

An overview of the study procedures is illustrated in Fig. 1. In short, patients received standard-of-care lenvatinib treatment during which ^{124}I dosimetry procedures were performed to evaluate eligibility for ^{131}I therapy. Both safety

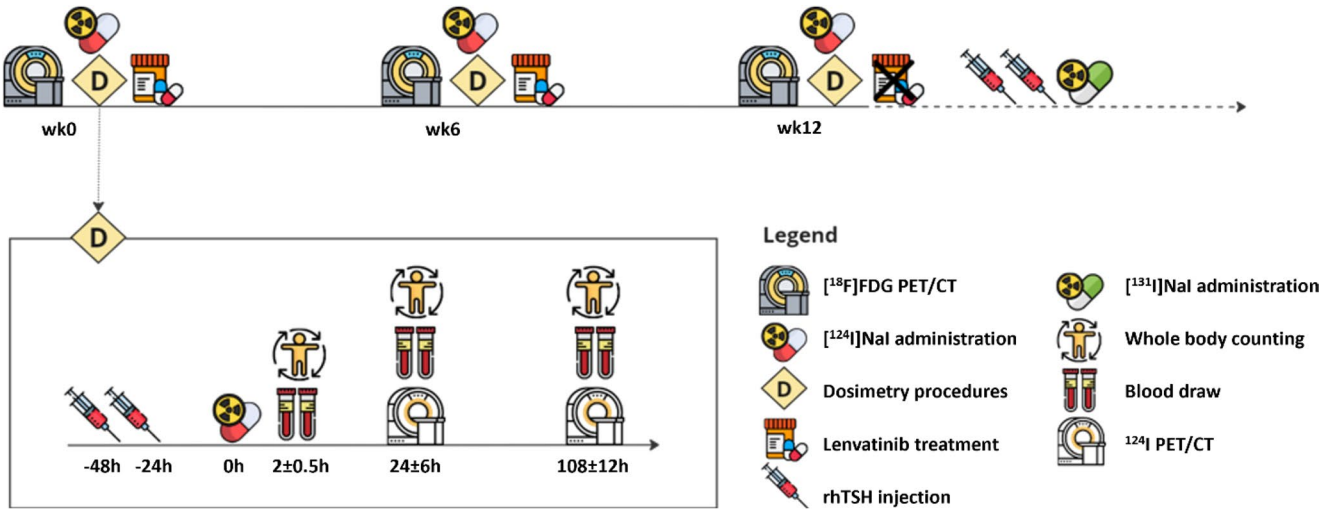

Fig. 1 Overview of the study procedures for cohort 1. wk: week; rhTSH: recombinant human thyroid stimulating hormone

(lung and bone marrow toxicity) and efficacy (absorbed dose in target lesions) of ^{131}I therapy were assessed. In cohort 1, planned to include six patients, eligibility for ^{131}I was assessed at 6 and 12 weeks after lenvatinib treatment to select the most optimal duration of lenvatinib treatment. An independent safety committee evaluated both safety, efficacy and subsequent time point selection to continue the study with cohort 2. In cohort 2, planned to include another 6 patients, eligibility was assessed at the selected time point (either 6 or 12 weeks). The study included evaluation of an early stopping criterion after enrollment of 9 patients: if all 9 patients demonstrated no eligibility for ^{131}I therapy, the study would be terminated. Patients in cohort 1 with unevaluable data at either week 6 or 12 were replaced, but their available data was included in the evaluation of the early stopping rule.

Lenvatinib treatment

Patients in the study received standard-of-care lenvatinib treatment at a start dose of 20 or 24 mg per day. Dose interruptions and reductions were allowed and induced at the discretion of the treating medical oncologist. In case of interruptions, ^{124}I dosimetry procedures were rescheduled.

^{124}I dosimetry procedures

^{124}I dosimetry procedures including PET/CT scans, blood sampling and whole body counting were performed prior to lenvatinib treatment, and after 6 and 12 weeks of treatment (cohort 1). Patients adhered to a low iodine diet 7 days prior to ^{124}I administration up to 24 h post-administration, and received recombinant human thyroid stimulating hormone (rhTSH) injections 24 and 48 h prior to administration. A total of 37 MBq (± 10%) [^{124}I]NaI was administered orally after TSH levels were confirmed to be >30 mIU/L. Dosimetry procedures were then performed following Jentzen et al. [27, 28]. After 24 ± 6 and 108 ± 12 h post-administration, PET/CT scans were acquired. Patients were scanned for 4 min per bed position using a Vereos (Philips Healthcare, Eindhoven, the Netherlands) or Omni Legend 32 (GE Healthcare, Milwaukee, WI, USA) PET/CT scanner. After 2 ± 0.5, 24 ± 6 and 108 ± 12 h post-administration, blood sampling and whole body counting was performed. Whole blood samples were measured in a calibrated 2480 Wizard gamma counter (Perkin Elmer, Waltham, MA, USA). Whole body counting was performed during 60 s using an uncollimated Discovery 670 Pro gamma camera (GE Healthcare, Milwaukee, WI, USA). Details regarding acquisition and reconstruction parameters for each scanner is listed in Supplementary Tables 1 and 2. Blood sampling and whole body counting were used to determine the mean absorbed dose in the blood and whole body retention at 48 h post-ingestion as a surrogate for bone marrow and lung toxicity risk, respectively [29].

^{131}I therapy

Patients were considered eligible for ^{131}I therapy if at least one target lesion showed an expected absorbed dose ≥ 20 Gy. This limit is in line with previous trials investigating redifferentiation of RAI-R DTC after treatment with BRAF/MEK inhibitors [13, 14, 17, 18]. Patients would receive 7.4 GBq ^{131}I or the maximum tolerable activity (MTA) if the MTA was < 7.4 GBq. ^{131}I therapy was considered tolerable and safe when the administered activity would result in an absorbed dose to the blood < 2.0 Gy and a whole body retention at 48 h post-ingestion < 4.4 or < 3.0 GBq in the

absence or presence of iodine-avid diffuse lung metastases, respectively [29].

Follow-up

Toxicity up to 30 days after ^{131}I therapy or the last ^{124}I scan was scored using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Response to treatment was assessed using [^{18}F]FDG-PET/CT imaging, to avoid the use of intravenous iodinated contrast, and was assessed by PERCIST criteria [30], at baseline and 6, 12, 24, 36 and 48 weeks after initiation of treatment or until lenvatinib was discontinued. Imaging was performed according to standard clinical protocol on the same scanner as ^{124}I imaging. All acquisitions were in accordance with European Association of Nuclear Medicine (EANM) guidelines for tumor PET imaging version 2 [31]. Patients fasted for at least six hours, were prehydrated using 1 L of water, and had blood glucose levels between 3.5 and 11.1 mmol/L before intravenous administration of [^{18}F]FDG. [^{18}F]FDG was administered using the quadratic formula: 379 or 132 (MBq·min·bed^{-1}·kg^{-2}, for Vereos and Omni, respectively) × [patient weight (kg)/75]^2/emission acquisition duration per bed position (min·bed^{-1}). As sensitivity was superior for the Omni, a reduction in administered activities was applied while being compliant with EANM Research Ltd (EARL) accreditation specifications [32]. Acquisition of PET images was commenced approximately 60 (55–75) minutes post-administration. Acquisition and reconstruction were EARL-compliant for both scanners, details are found in Supplementary Table 1.

Data analysis

Dosimetry

Dosimetry was performed following Jentzen et al. [27, 28] using Pmod Biomedical Image Quantification Software (v4.206, PMOD Technologies LLC, Zurich, Switzerland). Target lesions were delineated on ^{124}I PET/CT using a background-adapted 50% isocontour of the maximum value. To account for partial volume effects, the mean activity concentration was corrected for size-dependent recovery using phantom-derived recovery coefficients (RCs) [33]. ^{124}I and ^{131}I kinetics were assumed to be identical, and RC-corrected ^{124}I activity concentrations were corrected for the different half-lives. Subsequently, expected ^{131}I-uptake values were calculated and fitted with a mono-exponential curve. The resulting fit was used to estimate the ^{131}I absorbed dose calculated using ^{131}I S-values for spheric lesions (thyroid tissue density, $p = 1.04$ g/cm³) with homogenic distribution of radioiodine, derived from IDAC dose 2.1 [34]. Volumes of target lesions were estimated using all the three low-dose CT scans from the [^{18}F]FDG and both ^{124}I PET/CT images. Blood and whole body counting data was fitted according to a bi-exponential fit after which the MTA of ^{131}I was calculated following the EANM guidelines [29]. In all cases, physical decay was assumed after the last measured time point if the effective half-life of ^{131}I was larger than the physical half-life. Dosimetric results included absorbed dose per administered activity to target lesions (LDpA) and the blood, whole body retention at 48 h and the MTA. In addition, uptake at 24 h post-ingestion and residence time was obtained for the target lesions. Changes in LDpA, uptake and residence time were assessed per patient subgroup based on tumor histology.

Statistical analysis

The primary outcome was the fraction of patients eligible for ^{131}I therapy after 6 and 12 weeks of lenvatinib treatment. The study would be terminated prematurely if 0/9 patients were eligible for ^{131}I therapy, thereby confirming that the real fraction of reinduction of I-131 therapy is $<30\%$ (with one-sided binomial 95% confidence interval: 0–28.3.3%). Secondary outcomes included the variation of dosimetric parameters in time and toxicity of lenvatinib and subsequent ^{131}I therapy. Dosimetric results and target lesion volumes between time points were compared using Friedman's test, using a level of significance of 0.05. In case patients were not eligible for ^{131}I therapy, only CTCAE toxicity grades ≥ 3 were considered relevant.

Results

Patient population

Nine patients were enrolled between January 2022 and January 2024. The clinical characteristics of the enrolled patients are included in Table 1 and Supplementary Table 3. Six patients were evaluable for reinduction of RAI uptake after both 6 and 12 weeks of lenvatinib treatment and the remaining three patients were evaluated at one time point. Two patients were not evaluable at week 6: one due to logistical issues related to the scheduled replacement of the PET/CT scanner, and the other due to a contraindication (patient received iodinated contrast agent for suspicion of pulmonary embolism). Based on the results of cohort 1, one patient was evaluated at baseline and week 6. In total, 23 target lesions were identified and evaluated to assess the eligibility of ^{131}I therapy. The study was terminated after 9 patients as the early stopping rule was met.

Table 1 Baseline characteristic of all patients (N=9)

Characteristic	Values
Age	median: 63 (range: 55–79)
Sex	2 male, 7 female
Location of metastases at inclusion	4
Thyroid bed	7
Lymph nodes	6
Pulmonary	2
Liver	4
Bones	2
Other	
Tumor histology	6
Follicular, oncocytic cell type	3
Papillary	
Tumor genotype (available for 6/9 patients)	1
NRAS	1
MEK1	3
TP53	3
PTEN	1
NF1	1
TERT	
Prior ^{131}I treatment	9
Number of treatments	median: 3 (range: 1–5)
Other prior therapy	9
Surgery	4
Radiotherapy	1 (lenvatinib)*
TKI	
Other systemic therapy (study medication)	1 (digoxine)

TKI: tyrosine kinase inhibitor

*Lenvatinib was discontinued 22 months prior to study inclusion

Efficacy

Eligibility ^{131}I therapy and dosimetric results

None of the patients were considered eligible for ^{131}I therapy after 6 and 12 weeks of lenvatinib treatment. No clinically meaningful radioiodine uptake and retention was observed that lead to predicted ^{131}I mean absorbed doses in target lesions ≥ 20 Gy, except for one lesion at baseline. This was a heterogenous liver lesion (Fig. 3A) with an estimated absorbed dose of 20.6 Gy for a treatment with 7.4 GBq ^{131}I. Prior to inclusion of the study, the patient was considered not eligible for ^{131}I therapy and therefore not treated. An overview of the dosimetric results for all target lesions is given in Table 2 and Supplementary Fig. 1–3. Absorbed dose per administered activity was comparable between the different time points ($p = 0.08$, Fig. 2A). An overview of the change from baseline in dosimetric LDpA, uptake and residence time per tumor histology is given in Supplementary Table 4. Figure 3 illustrates ^{124}I PET/CT and [^{18}F]FDG scans of several target lesions before and during lenvatinib treatment.

Lenvatinib

According to PERCIST criteria, overall partial response (PR) to lenvatinib was observed in 4 patients, stable disease (SD) in 3 and progressive disease (PD) in 2 patients. Target lesion response was PR for 10/17 (59%) and SD for 7/17 (41%) at week 6, and 15/20 (75%) and 5/20 (25%) at week 12, respectively. The median volume of the target lesions was 6.3 mL (IQR: 2.4–12.3) and significantly decreased to 3.5 mL (IQR: 0.8–5.7) and 2.6 mL (IQR: 0.7–4.7) after 6 and 12 weeks lenvatinib treatment, respectively ($p < 0.01$).

Safety

MTA

All patients were deemed able to safely receive 7.4 GBq ^{131}I at all time points. MTA distribution over time is shown in Fig. 2B. MTA, WB retention and blood dose per administered activity was comparable between the different time points ($p > 0.1$, Table 3).

Toxicity

No combined toxicity of lenvatinib and subsequent ^{131}I therapy could be assessed. All nine patients were treated with lenvatinib using a start dose of 20 mg. No unexpected or new adverse events related to lenvatinib treatment were observed. During the study, lenvatinib dose was reduced in five patients. In two patients, lenvatinib was temporarily withdrawn. One serious adverse event (dyspnea grade 4) occurred in one patient. This patient received an iodinated contrast agent for a CT pulmonary angiogram to rule out pulmonary embolism. Grade 3 hypertension occurred in seven patients and one patient had a grade 3 impeding C2 fracture due to a metastasis, which was treated with external beam radiation therapy.

Discussion

The RESET study is the first prospective trial evaluating the ability of standard-of-care multi-target TKI lenvatinib to reinduce clinically meaningful radioiodine retention to enable ^{131}I in RAI-R DTC. Although lenvatinib resulted in a partial target response of 59% and 75% of the lesions at 6 and 12 weeks, respectively, none of the patients were found eligible for ^{131}I therapy. Dosimetric parameters LDpA, uptake at 24 h and residence time in the target lesions were

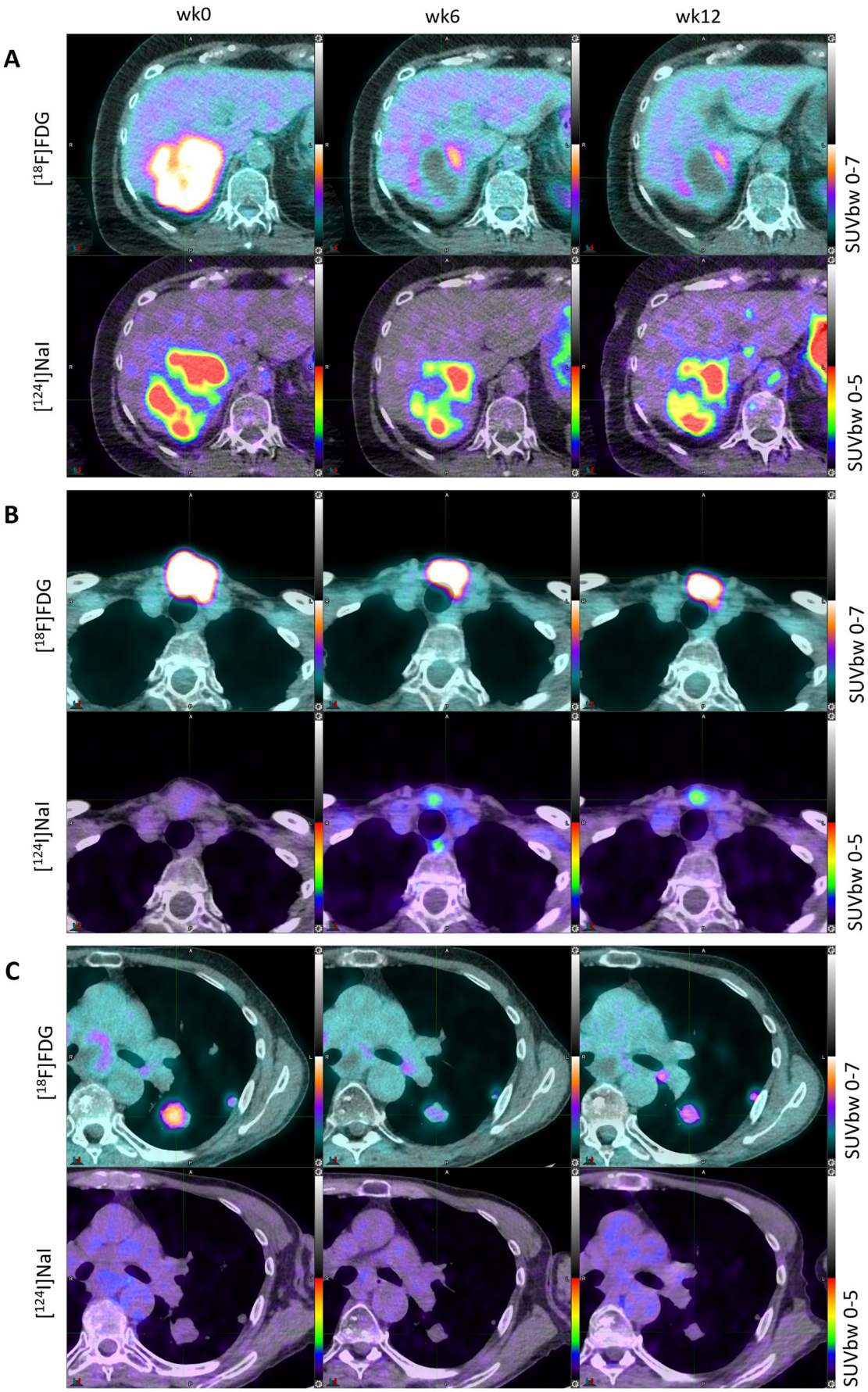
wk0
wk6
wk12
A
[18F]FDG
[124I]NaI
SUVbw 0-7
SUVbw 0-5
B
[18F]FDG
[124I]NaI
SUVbw 0-7
SUVbw 0-5
C
[18F]FDG
[124I]NaI
SUVbw 0-7
SUVbw 0-5

Fig. 3 [^{18}F]FDG and [^{124}I]NaI PET/CT scans of representative target lesions of the (**A**) liver, (**B**) thyroid bed, (**C**) lung at baseline and 6 and 12 weeks after lenvatinib treatment

comparable between the time points. This indicates that lenvatinib, when administered according to this protocol, does not lead to clinically relevant redifferentiation.

It is well established that overactivation of the MAPK signaling pathway promotes dedifferentiation of thyroid cancer cells, and that its inhibition leads to restoration of thyroid gene expression and subsequent thyroid functions as (radio)iodine uptake and organification [13, 20]. Inhibition of targets downstream the MAPK signaling pathway might be more potent to induce a redifferentiation effect [35]. Therefore, patients with therapeutically targetable tumor mutations in the MAPK pathway, such as BRAF and RAS, are more likely to show a redifferentiation effect. Case studies further support this as successful redifferentiation has been observed for patients with rare NTRK or RET fusions treated with larotrectinib or selpercatinib, respectively [36–39]. Besides, a combination of BRAF and MEK inhibitors seems more efficient, likely related to a more complete inhibition of the MAPK pathway [17]. In addition, Tchekmedyian et al. showed that combining vemurafenib and HER3 targeting might also lead to better redifferentiation results, as HER3 is involved in reactivation of the MAPK signaling pathway [18]. This might also explain the negative results of redifferentiation agents sorafenib [25], and lenvatinib in the present study, as these agents indirectly inhibit the MAPK pathway and are therefore less potent. Even though fairly positive results were found in pre-clinical studies for sorafenib and lenvatinib [24], these results are not directly translated to increased radioiodine uptake in clinical studies. This was also observed for digoxin, mediating the upregulation of NIS expression by intracellular Ca^{2+} and FOS activation rather than via the MAPK pathway [19, 40].

Van Houten et al. showed that restoration of RAI uptake can be achieved after only 5 days of digoxin treatment in a mouse model, and that it remains stable after 3 weeks of treatment [19]. Since pre-clinical data on lenvatinib and its effect on radioiodine uptake are limited, there is a possibility that the optimal treatment duration of lenvatinib to establish a redifferentiation effect might be missed in the current study. Treating patients even shorter can verify whether lenvatinib's primary benefit remains in disease control through anti-angiogenic and anti-proliferative mechanisms and not as redifferentiation agent, as this study shows. As predicted absorbed doses in target lesions were very limited, well below the threshold of 20 Gy, we believe the redifferentiation effect of lenvatinib will remain clinically insufficient to enable ^{131}I therapy.

It's important to note that decreased NIS functionality is not only affected by the overactivation of the MAPK pathway. Mechanisms involved in trafficking and localization of NIS to the cell membrane, alterations in NIS transcription factors and epigenetic suppression of NIS may also cause impaired radioiodine uptake [20, 21]. Besides that, enhanced radioiodine uptake will not directly mean ^{131}I therapy is effective if internalization is impaired and residence time of the radioiodine is limited. The definition of RAI-R disease and which patients are more likely to benefit in redifferentiation strategies need further research [41]. As pointed out by the previous redifferentiation trials, DTC subtype, mutation status, lesion size, tissue type radiosensitivity, and the extent of radioiodine uptake at baseline is likely to influence the success of redifferentiation [11, 12, 14–16, 18, 19]. Therefore, comparison of the results of redifferentiation studies is currently hampered by differences in patient groups. In our study, a relatively high fraction (67%) of patients with oncocytic follicular thyroid cancer was included, a subtype that is associated with decreased radioiodine avidity [42]. Whether redifferentiation rates would be higher in a population group that excludes oncocytic thyroid cancer cannot be entirely ruled out.

In this study, we chose for an approach with rhTSH-stimulated dosimetry procedures and subsequent ^{131}I therapy rather than thyroid-stimulating hormonal withdrawal (THW), to avoid a state of hypothyroidism for months and potential tumor growth. However, uptake and absorbed doses in lesions and healthy organs derived from ^{124}I PET and ^{123}I SPECT are known to be higher in case of THW in comparison to rhTSH-stimulated administrations [43–45]. The use of THW for both dosimetry procedures and ^{131}I therapy may therefore maximize redifferentiation and subsequent therapeutic efficacy, and might be preferred when lesion uptake is assessed at limited time points, provided it is not contra-indicated. We believe rhTSH stimulation rather than THW is justified in this clinical trial due to the need for ^{124}I procedures at multiple time points and the aim to reduce patient burden.

Limitations of the study include the small and heterogenous patient population, lack of paired biopsies prior and during lenvatinib treatment to assess the effectiveness on thyroid-specific gene expression in the target lesions and uncertainties in the quantification of radioiodine. Although we adhered to established ^{124}I dosimetry procedures, which are favored over ^{131}I or ^{123}I imaging [46], we observed significant decreases in volume of the target lesions over time in response to lenvatinib. Although we applied recovery correction curves derived from phantom data to account for partial volume effects [33], absorbed dose estimates remain less accurate in smaller volumes. Besides, we used an organ-level dosimetry approach rather than a voxel-based dosimetry approach, which could lead to an underestimation in heterogenous lesions.

Table 2 Dosimetric results of the target lesions (estimated for ^{131}I based on ^{124}I data)

Parameter	Median (IQR)			*p*-value
	wk0	wk6	wk12	
No. of patients	9	7	8	
No. of target lesions	23	17	20	
Absorbed dose (Gy/GBq)	0.08 (0.04–0.17)	0.18 (0.08–0.36)	0.17 (0.09–0.37)	0.08
Uptake (%) at 24 h p.i.	0.004 (0.001–0.025)	0.002 (0.002–0.011)	0.004 (0.002–0.016)	0.32
Residence time (min.)	0.22 (0.10–0.81)	0.11 (0.07–0.40)	0.16 (0.08–0.52)	0.22

IQR: interquartile range, p.i.: post-ingestion

Table 3 Dosimetric parameters regarding ^{131}I therapy safety (estimated for ^{131}I based on ^{124}I data)

Parameter	Median (IQR)			*p*-value
	wk0	wk6	wk12	
No. of patients	9	7	8	
MTA (GBq)	22.2 (16.2–25.7)	20.2 (9.4–28.1)	15.9 (12.7–23.6)	0.3
WB retention at 48 h (%)	9.4 (6.7–17.8)	14.3 (6.4–24.9)	13.3 (10.3–16.2)	0.8
Blood dose (Gy/GBq)	0.09 (0.07–0.11)	0.08 (0.7−0.13)	0.13 (0.08–0.15)	0.1

IQR: interquartile range; MTA: maximum tolerable activity

The patient population reflects different subtypes of DTC including papillary and follicular oncocytic cell type DTC. The latter is characterized by a reduced ability to take up iodine, resulting in limited effectiveness of ^{131}I therapy compared to papillary and follicular DTC [47]. Consequently, this may lead to less pronounced or measurable redifferentiation effects compared to papillary or follicular DTC. Even if redifferentiation occurs at a molecular level, the absolute amount of iodine uptake may remain insufficient to deliver a meaningful therapeutic dose of ^{131}I [48]. Our results suggest great variety in change from baseline in dosimetric results in both oncocytic and papillary DTC. Although the trial demonstrated that lenvatinib did not reinduce adequate radioiodine uptake to warrant ^{131}I therapy across all 9 patients, the absence of observed benefit may reflect the small sample size and variability within the heterogenous population rather than lenvatinib's true (in)efficacy to reinduce radioiodine uptake. Therefore, the findings of this study should be validated in larger, adequately powered studies, ideally with more homogenous populations or sufficient sample sizes to allow meaningful subgroup analyses in order to draw more robust, statistically supported conclusions. Based on the results of the RESET trial (0/9 patients with redifferentiation per protocol definition and timing), we confirm with 95% confidence that the true redifferentiation rate is < 30% (one-sided 95% CI: 0–28.3%), suggesting limited clinical relevance in this setting.

The strategy of short-term TKI treatment for redifferentiation and subsequent ^{131}I therapy is a sophisticated approach to reduce TKI-related toxicities and achieve tumor control in RAI-R disease. ^{131}I therapy responses in these patients can be enhanced when ^{131}I dose-response relationships for metastatic thyroid cancer lesions are more established. Tchekmedyian et al. noted that responders received an ^{131}I activity closer to the MTA in comparison to the patients in which SD was observed after redifferentiation and subsequent ^{131}I therapy [18]. Our study indicates that ^{131}I activities can safely be increased and that the MTA is stable in time and are median 2.1–3.0.1.0 times higher than the proposed activity of 7.4 GBq in our patient group. Leboulleux et al. noted that metastatic uptake decreases when redifferentiation and subsequent ^{131}I therapy is repeated [17], further implying that dosimetry-guided ^{131}I activities might be preferred in redifferentiation studies to maximize therapeutic effects. Nevertheless, the availability of the medication used as redifferentiation agents, radioisotopes and resources for radioiodine uptake assessment or dosimetry procedures remains pivotal in redifferentiation studies. Further studies

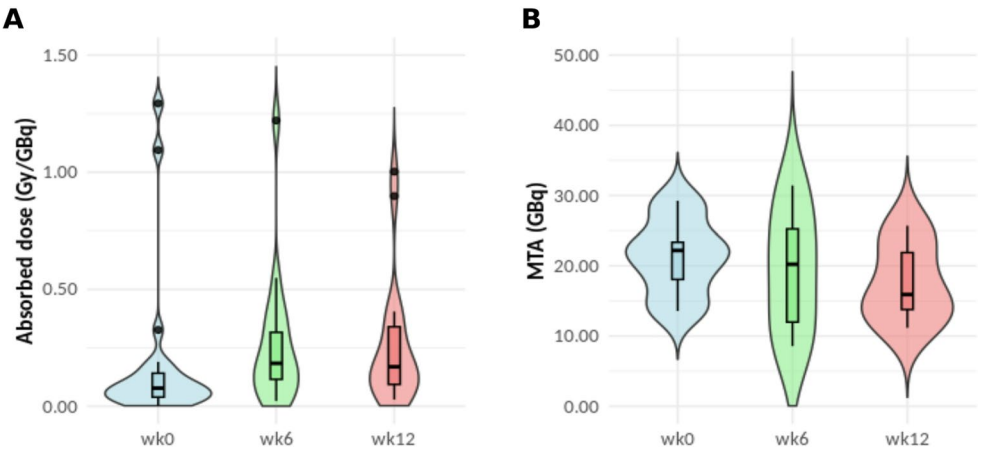

Fig. 2 Distribution of the (**A**) absorbed dose per administered activity in target lesions and (**B**) maximum tolerable activity over time (estimated for ^{131}I based on ^{124}I data)

are needed to optimize patient selection and treatment regimen in redifferentiation studies of RAI-R DTC.

Conclusion

The RESET study shows that lenvatinib treatment did not reinduce radioiodine uptake in patients with RAI-R DTC after 6 or 12 weeks. Multi-targeted TKIs may not be as potent as selective TKIs in reinducing clinically meaningful redifferentiation to warrant subsequent ^{131}I therapy.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00259-025-07662-9.

Author contributions The RESET trial was originally conceived by EK, DV and LG. MD, EK, DV and LG have made notable contributions to its conception and design and drafted the study protocol. FV, MS, JH, PD, MP and FS participated in critical review relating study design and protocol. MD, DV, LG, FV, MS, JH and PD were involved in preparation of and setting up all equipment used for the dosimetry procedures that are performed within this study. MP was involved in ^{124}I dispensing. EK screened and included all study patients. MD, EK, DV and LG were primarily involved in the study procedures. MD, EK, DV and LG drafted the manuscript, and revised it critically for important intellectual content. Critical review and contributions for finalizing the article were provided by all other authors. All authors have read and agreed to the published version of the manuscript.

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Data availability The results of the RESET trial will be disseminated after completion in peer-reviewed journals and presented at conferences. Data generated and analyzed within the RESET trial shall only be shared upon request with researchers who provide a methodologically sound research proposal, at the discretion of the principal investigators. Only de-identified participant data from the final research dataset used in the published manuscript can be shared.

Declarations

Ethics approval This study has been approved by the Medical Ethics Committee Leiden-Den Haag-Delft (ref. no. P20.096). The study was conducted according to the principles of the Declaration of Helsinki (10th version, Fortaleza 2013) and in concordance with the Dutch Medical Research Involving Human Subjects Act and other applicable guidelines, regulations, and acts.

Consent to participate Written informed consent was obtained from all individual participants included in the study.

Trial registration NIH ClinicalTrials.gov, NTC04858867, registered 26 April 2021.

Competing interests PD and FV have received speaker honoraria from GE HealthCare (fees received by institution). EK has consultancy/advisory relationships with Delcath, Immunocore and BMS, and received research grants not related to this paper from Bristol Myers Squibb, Delcath, Novartis and Pierre-Fabre (fees received by institution).

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