Enhancing Radioiodine Incorporation into Radioiodine-Refractory Thyroid Cancer with MAPK Inhibition (ERRITI): A Single-Center Prospective Two-Arm Study

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ABSTRACT

Purpose: Restoration of iodine incorporation (redifferentiation) by MAPK inhibition was achieved in previously radioiodine-refractory, unresectable thyroid carcinoma (RR-TC). However, results were unsatisfactory in $BRAF^{V600E}$-mutant (BRAF-MUT) RR-TC. Here we assess safety and efficacy of redifferentiation therapy through genotype-guided MAPK-modulation in patients with BRAF-MUT or wildtype (BRAF-WT) RR-TC.

Patients and Methods: In this prospective single-center, two-arm phase II study, patients received trametinib (BRAF-WT) or trametinib + dabrafenib (BRAF-MUT) for 21 ± 3 days. Redifferentiation was assessed by ^{123}I-scintigraphy. In case of restored radioiodine uptake, ^{124}I-guided ^{131}I therapy was performed. Primary endpoint was the redifferentiation rate. Secondary endpoints were treatment response (thyroglobulin, RECIST 1.1) and safety. Parameters predicting successful redifferentiation were assessed using a receiver operating characteristic analysis and Youden *J* statistic.

Results: Redifferentiation was achieved in 7 of 20 (35%) patients, 2 of 6 (33%) in the BRAF-MUT and 5 of 14 (36%) in the BRAF-WT arm. Patients received a mean (range) activity of 300.0 (273.0–421.6) mCi for ^{131}I therapy. Any thyroglobulin decline was seen in 57% (4/7) of the patients, RECIST 1.1 stable/partial response/progressive disease in 71% (5/7)/14% (1/7)/14% (1/7). Peak standardized uptake value (SUV_{peak}) < 10 on 2[^{18}F]fluoro-2-deoxy-D-glucose (FDG)-PET was associated with successful redifferentiation ($P = 0.01$). Transient pyrexia (grade 3) and rash (grade 4) were noted in one patient each.

Conclusions: Genotype-guided MAPK inhibition was safe and resulted in successful redifferentiation in about one third of patients in each arm. Subsequent ^{131}I therapy led to a thyroglobulin (Tg) decline in more than half of the treated patients. Low tumor glycolytic rate as assessed by FDG-PET is predictive of redifferentiation success.

See related commentary by Cabanillas et al., p. 4164

Introduction

Radioiodine is the first-line treatment in patients with unresectable and/or metastatic thyroid carcinoma of follicular origin (i.e., follicular or papillary carcinoma; ref. 1). However, 60% to 70% of these patients are or eventually become refractory to radioiodine, a state that is associated with a considerable reduction in overall survival (2–5).

On a molecular level, radioiodine-refractoriness has been linked to mutually exclusive genetic alterations in genes encoding the growth factors RET, NTRK1, RAS, and BRAF. Constitutive activation of these oncoproteins stimulates MAPK signaling to activate downstream kinases MEK and ERK resulting in a disruption of follicular cell differentiation (6–9). This leads to upregulation of proliferation and suppression of key genes involved in iodine metabolism including the sodium iodide symporter (NIS), a protein critical for mediating iodide uptake into thyroid cells (10–15).

Preclinical and clinical studies have shown that oncogenic BRAF-induced gene patterns can be reversed by abrogation of MAPK signaling leading to a restoration of iodine uptake into thyroid carcinoma cells (16, 17). However, in the first translational study

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Translational Relevance

MAPK pathway inhibition can restore radioiodine uptake in previously radioiodine-refractory thyroid carcinoma (RR-TC) and thereby enable subsequent radioiodine therapy. However, redifferentiation rates were unsatisfactory in $BRAF^{V600E}$-mutant (BRAF-MUT) RR-TC thus far. In our cohort of 20 patients with unresectable RR-TC, treatment with trametinib [$BRAF^{V600E}$-wildtype (BRAF-WT)] or trametinib + dabrafenib (BRAF-MUT RR-TC) for 3 weeks restored radioiodine uptake in 7 of 20 (35%) patients and showed a favorable safety profile. Redifferentiation rates were comparable between patients with BRAF-WT and those with BRAF-MT RR-TC. Low glycolytic activity as assessed by 2[^{18}F]fluoro-2-deoxy-D-glucose (FDG)-PET predicted successful restoration of radioiodine uptake. Genotype-guided MAPK inhibition is feasible and holds promise to delay treatment with tyrosine kinase inhibitors for BRAF-WT and -MUT RR-TC.

using the MEK inhibitor selumetinib, despite convincing results in $BRAF^{V600E}$-wildtype (BRAF-WT) patients, only 1 in 9 patients with a $BRAF^{V600E}$-mutation (BRAF-MUT) achieved sufficient improvement in iodine incorporation to warrant radioiodine treatment (17). As the degree of iodine restoration has been linked to the extent of MAPK pathway inhibition (18), the findings imply that a more potent inhibition may improve NIS restoration in BRAF-MUT patients. Subsequent studies on these patients revealed improved radioiodine uptake by using the BRAF-inhibitors vemurafenib (18) and dabrafenib (19). Combined targeting of BRAF and downstream MEK kinase has been shown to lead to enhanced MAPK inhibition in a preclinical setting (20) resulting in a more profound expression of NIS.

These studies provide the rationale for our prospective study, in which we evaluate the efficacy and safety of radioiodine uptake restoration through genotype-guided MAPK modulation: MEK-targeted treatment with trametinib was performed for BRAF-WT, whereas combined MEK- and BRAF-inhibition with trametinib and dabrafenib was given in BRAF-MUT patients with radioiodine-refractory metastatic thyroid carcinoma (RR-TC). Redifferentiation success was quantified by baseline and follow-up ^{124}I PET with subsequent dosimetry-based ^{131}I therapy (21, 22).

Patients and Methods

Patients

Patients were eligible if they had unresectable and/or RR-TC of follicular origin. Radioiodine-refractoriness was defined as the presence of at least one metastatic lesion without therapeutically sufficient radioiodine accumulation on a diagnostic or therapeutic radioiodine scan performed less than 1 year prior to enrollment. Further requirements were the presence of at least one measurable lesion ≥15 mm (short-axis diameter for nodal lesions, long-axis diameter for nonnodal lesions) and confirmation of *BRAF V600E* mutation status. For all inclusion and exclusion criteria, see "Criteria for subject eligibility" in the supplementary appendix.

The study was registered as a prospective trial (clinicaltrials.gov, NCT04619316) and approved by the local institutional review board (IRB; University of Duisburg-Essen, Medical Faculty; Essen, Germany; protocol number: 17–7323-AF) and federal administrations (BfArM, BfS). The study was performed in concordance with the Declaration of Helsinki and all patients gave written informed consent for enrollment.

Study design and safety

The protocol design is shown in **Fig. 1**. Patients underwent ^{124}I-PET for baseline assessment of lesion size and iodine-avidity on clinical indication before entering the study. Treatment with 2 mg trametinib daily (and additional dabrafenib 75 mg twice daily in BRAF-MUT patients) was given for 21 days. After redifferentiation treatment, iodine uptake was assessed by ^{123}I scintigraphy and repeat ^{124}I-PET outside of the protocol. Patients in whom the posttreatment ^{123}I single-photon emission computed tomography (SPECT)/CT demonstrated a regional target/background ratio of more than 4 and a 2-fold higher iodine uptake than the mean uptake in liver parenchyma (in at least one tumor lesion) by visual assessment were considered responders, and ^{131}I therapy was performed. Images were assessed by single-session consensus of two Nuclear Medicine Physicians. Personalized ^{131}I therapy activity was derived from lung, blood, and lesion dosimetry. In all responders, redifferentiation treatment was continued until 2 days after ^{131}I administration and a posttherapy whole-body scintigraphy was performed 7 days after ^{131}I administration. In nonresponders the study medication was discontinued immediately and no ^{131}I therapy was performed.

Adverse events were monitored until 28 days after discontinuation of the study drugs and graded according to Common Terminology Criteria for Adverse Events (CTCAE; version 4.0) criteria.

Efficacy

In patients who underwent ^{131}I therapy, 2[^{18}F]fluoro-2-deoxy-D-glucose (FDG)-PET/CT imaging was performed between 3 and 12 months after ^{131}I therapy and best imaging response based on RECIST 1.1 (23) and PET response criteria in solid tumors (PERCIST) 1.0 (24) criteria was assessed by single-session consensus of two readers.

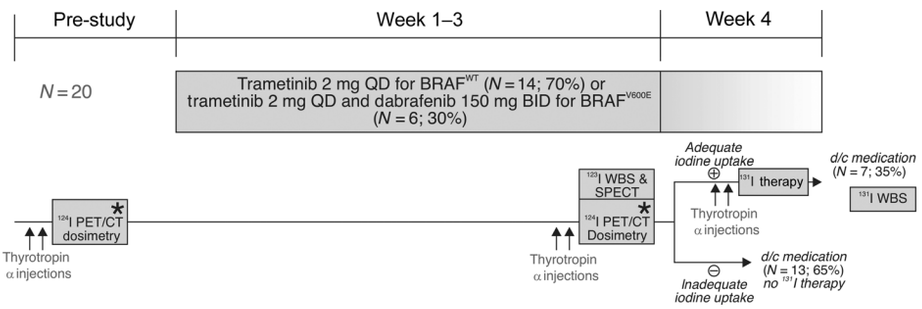

Figure 1.
Protocol design. QD, once daily; BID, twice daily; d/c, discontinue; WBS, whole body scintigraphy. Off-study examinations are marked with an asterisk.

Serum thyrotropin, thyroglobulin, and thyroglobulin antibody levels were monitored and the best thyroglobulin response within 1 year after ^{131}I therapy was assessed.

Iodine imaging studies and dosimetry

Before any iodine imaging, a minimum interval of 2 months after the last administration of iodinated contrast-medium was mandated, and patients were advised to follow a low-iodine diet for at least 5 days. A mean of 3.9 (interquartile range: 3.9–4.2) mCi [equivalent to 144.5 (interquartile range: 143–157) MBq] ^{123}I were administered after intramuscular injection of 0.9 mg recombinant thyrotropin on 2 consecutive days. After 4 hours, planar scintigraphy and–in the case of suspicious findings–additional SPECT/CT was performed. On the same day after ^{123}I scintigraphy, 1.0 (range: 0.8–1.1) mCi [equivalent to 36.3 (range: 31–40) MBq] ^{124}I were administered orally and PET/CT was acquired from skull to mid-thigh 20 and 120 hours after tracer ingestion.

Optimal ^{131}I therapy activity was determined using CT-derived lesion volume and the lesion activity concentration on ^{124}I PET for lesion dosimetry and repeated blood measurements for blood dosimetry in accordance with prior publications (25, 26).

Statistical analysis

The primary endpoint was the proportion of patients with successful redifferentiation on the ^{123}I SPECT/CT scan. Secondary endpoints were thyroglobulin response and safety. RECIST/PERCIST response was assessed posthoc. Posthoc analysis of the statistical association with redifferentiation rate was assessed for a maximum of six parameters that were previously associated with patient outcome or redifferentiation success [i.e., histopathology, cumulative previously administered radioiodine activity, *BRAF* mutation status, FDG-PET peak standardized uptake value (SUV_{peak}), unstimulated thyroglobulin (Tg) pre-redifferentiation] using Fisher exact test (17, 18, 27–29). Continuous variables were dichotomized by receiver operating characteristic analyses; Youden *J* was used for optimal cut-off point determination. Mean pre- and post-redifferentiation mean absorbed doses per administered activity were assessed using a Wilcoxon signed-rank test. *P* values <0.05 were regarded as statistically significant. Data were collected using electronic case report forms in a Research Electronic Data Capture (REDCap) database (30) hosted at University Hospital Essen (University Duisburg-Essen, Essen, Germany). All statistical analyses were performed using R v4.0.3 (The R Foundation, r-project.org).

Data availability statement

The data generated in this study are not publicly available due to privacy concerns but are available upon reasonable request from the corresponding author.

Results

Study population

Between March 2018 and March 2021, 40 patients were referred and screened for the study. 20 patients were eligible. The flow of patients is shown in Supplementary Fig. S1.

Baseline characteristics of the included patients are provided in **Table 1**. 10 (50%) patients had papillary thyroid carcinoma (PTC), 7 (35%) had follicular thyroid carcinoma (FTC), and 3 (15%) had poorly differentiated thyroid carcinoma (PDTC). 14 (70%) BRAF-WT and 6 (30%) BRAF-MUT patients were included. Sufficient histopathologic tissue for further assessment of the molecular profile was available in 15 of 20 (75%) patients. Using a previously published methodology (31), a solid tumor panel analysis of 26 different genes was performed (Supplementary Table S1). Telomerase reverse transcriptase (TERT) promoter mutations were detected in 10 of 15 (67%) patients, PTEN-mutations in 3 of 15 (20%) patients, and NRAS-mutations in 2 of 15 (13%) patients. 1 of 15 (7%) patients each had KRAS, AKT1, and APC (adenomatous polyposis coli) mutations, respectively.

Table 1. Patient characteristics.

Age, years	
Mean (range)	65.2 (48–83)
Sex, *n* (%)	
Male	9 (45)
Female	11 (55)
Tumor type, *n* (%)	
PTC	10 (50)
FTC	7 (35)
PDTC	3 (15)
Unstimulated serum Tg (ng/mL)	
Mean (range) median	4,213 (0–74,000)
Median	111
$BRAF^{V600E}$ mutation status, *n* (%)	
WT	14 (70)
MUT	6 (30)
Further mutation status, *n* (%)	
TERT promoter	10 (67)
PTEN	3 (20)
NRAS	2 (13)
KRAS	1 (7)
APC	1 (7)
AKT1	1 (7)
Prior treatments	
Cumulative ^{131}I activity in mCi, mean (range)	383.8 (162.2–805)
Cumulative ^{131}I activity in GBq, mean (range)	14.2 (6.0–29.8)
EBRT, *n* (%)	7 (35)
Tumor sites, *n* (%)	
Local	6 (30)
Cervical lymph nodes	9 (45)
Other lymph nodes	7 (35)
Lung	19 (95)
Bone	13 (65)
Other	3 (15)

Abbreviation: EBRT, external beam radiotherapy.

Efficacy

Seven of 20 (35%) patients demonstrated successful redifferentiation on study medication; 5 of 14 (36%) in the BRAF-WT, 2 of 6 (33%) in the BRAF-MUT arm. Four of 7 (57%) patients had shown some iodine uptake at baseline. A comparison of pre- and post-redifferentiation ^{124}I PET images of patients with successful restoration of radioiodine uptake are provided in Supplementary Fig. S2.

In patients with successful redifferentiation, dosimetry-guided ^{131}I therapy with a mean (range) activity of 300.0 (273.0–421.6) mCi [equivalent to 11.1 (range: 10.1–15.6) GBq] ^{131}I was performed.

Mean ± SD absorbed dose per administered activity was 0.03 ± 0.04 Gy/mCi (equivalent to 0.9 ± 1.2 Gy/GBq) before and 0.28 ± 0.22 Gy/mCi (equivalent to 7.6 ± 5.9 Gy/GBq) after successful redifferentiation (**Fig. 3A**).

Redifferentiation and ^{131}I therapy led to any decrease in thyroglobulin level in 4 of 7 (57%) patients (**Fig. 2A**). Mean thyroglobulin decline was 58% (range: 36%–93%), respectively.

Redifferentiation and ^{131}I therapy led to any decrease in RECIST summed lesion diameter in 6 of 7 (86%) and a 30% or higher decrease in 1 of 7 (14%) patients, respectively (**Fig. 2B**). In 1 of these patients, the occurrence of new lesions was observed. Thus, best RECIST 1.1 response within 1 year after radioiodine treatment was partial response (PR; $n = 1$, 14%), stable disease ($n = 5$, 71%), and progressive disease ($n = 1$, 14%), respectively.

Any decrease in mean SUV_{peak} on FDG-PET for five lesions with the highest uptake was observed in 3 of 6 (50%) patients, an increase was observed in 3 of 6 (50%). All changes in mean SUV_{peak} were ≥30%. The best PERCIST response was partial metabolic response ($N = 3$, 50%), and progressive metabolic disease ($N = 3$, 50%; **Fig. 2C**); in 1 patient PERCIST assessment was not possible due to missing baseline FDG-PET/CT. Changes in per-lesion absorbed dose are provided in **Fig. 2D** for RECIST 1.1 target lesions and in **Fig. 3A** across all lesions.

Between baseline and week 3 imaging RECIST 1.1 stable disease was observed in 18 of 20 (90%) patients and PR in 2of 20 (10%) patients. PR occurred in BRAF-MUT patients without restoration of radioiodine uptake.

Safety

A total number of 40 adverse events were observed in 17 of 20 (85%) patients. 38 of 40 (95%) events were graded as G1/2. Grade 3/4 events were observed in 2 (10%) patients: G3 pyrexia in 1 BRAF-MUT patient resolved after temporary discontinuation of trametinib + dabrafenib for 2 days and did not reoccur thereafter. Transient G4 rash in 1 BRAF-WT patient occurred 3 days after the termination of the study drug and occurred after the start of doxycycline intake. **Table 2** lists safety details.

Predictors of successful redifferentiation

An overview of factors and redifferentiation groups is provided in **Table 3**.

A mean SUV_{peak} <10 on FDG-PET for five lesions with the highest uptake was determined as the optimal cut-off value for discrimination of redifferentiation success. Baseline SUV_{peak} significantly predicted redifferentiation rate: Redifferentiation was successful in 6 of 9 (66.7%) patients with a mean SUV_{peak} <10 and unsuccessful in all 11 patients with a higher SUV_{peak} ($P = 0.01$). Redifferentiation was not successful in any ($n = 6$) of the patients with an unstimulated Tg < median (66 ng/mL) but statistical significance was not reached ($P = 0.05$). A comparison of pre-redifferentiation SUV_{peak} and lesion absorbed dose is shown in **Fig. 3B**.

Histopathology (FTC/PTC vs. PDTC), cumulative previously administered radioiodine activity, BRAF-mutation status, and unstimulated thyroglobulin pre-redifferentiation were not significantly associated with redifferentiation success.

In a subgroup analysis comparing FTC with BRAF-WT PTC no association with redifferentiation success was observed (**Table 3**).

Discussion

Here we demonstrate successful restoration of radioiodine uptake in about one third of patients with similar redifferentiation rate among patients with BRAF-MUT and BRAF-WT thyroid cancer. Subsequent ^{131}I therapy led to decreases in thyroglobulin levels in more than half of the ^{131}I-treated patients. Previous redifferentiation attempts using other substance classes, such as retinoids, resulted in only modest success (32–37). Further insight into molecular drivers of carcinogenesis and dedifferentiation led to improved redifferentiation outcomes by the use of MAPK pathway-targeting agents. In this redifferentiation trial, two arms were designed to assess genotype-guided MAPK inhibition with dual MEK and BRAF targeting for BRAF-MUT and single MEK targeting for BRAF-WT candidates. It is the first prospective study to employ combined BRAF- and MEK-targeting in BRAF-MUT unresectable RR-TC. Combination therapy demonstrated superior efficacy and safety when compared with monotherapy with BRAF small molecule inhibitors in BRAF-mutant melanoma patients (38, 39) and may be advantageous in the redifferentiation of RR-TC as well. Our study is the first redifferentiation trial using MAPK pathway-targeting that included a significant number of patients with FTC.

Successful redifferentiation was achieved by trametinib (BRAF-WT) or trametinib plus dabrafenib (BRAF-MUT) in about one third of patients in each group. The results of our study are in line with the findings of Ho and colleagues (17), Rothenberg and colleagues (19), Jaber and colleagues (40), and Dunn and colleagues (18), albeit with a lower redifferentiation rate.

Redifferentiation ^{131}I therapy led to thyroglobulin decline in more than half of successfully redifferentiated patients, RECIST 1.1 partial response in 1 patient, and stable disease in more than two thirds of patients, as well as PERCIST partial response in half of patients. Response rates were similar in both arms, which indicates additional value of combined therapy in BRAF-MUT patients.

An overview of redifferentiation trials involving MAPK and BRAF inhibitors is provided in **Table 4**. Treatment response to ^{131}I therapy was lower than in the trials of Rothenberg and colleagues (19), Ho and colleagues (17), Jaber and colleagues (40), Iravani and colleagues (41), and Dunn and colleagues (18), where partial responses were reported in 33%, 63%, 33%, 75%, and 50% of patients treated with radioiodine, respectively. Potential explanations include a lower rate of patients with radioiodine uptake present at baseline compared with Ho and colleagues (17), different definitions as to what constitutes radioiodine-refractoriness, and a shorter time span for redifferentiation treatment compared with Ho and colleagues (17), Rothenburg and colleagues (19), Iravani and colleagues (41), and Jaber and colleagues (40). In addition, in our study a minimum lesion size of 1.5 cm (short-axis diameter for nodal lesions, long-axis diameter for non-nodal lesions) was required for inclusion, whereas no size criteria were imposed in the other studies leading to the systematic exclusion of patients with lower tumor burden in our cohort. This may have negatively affected response rates, as small lesion size has previously been shown to be a positive predictor of response to ^{131}I therapy, partly because large lesions are more likely to show a nonuniform dose distribution (25, 26).

Redifferentiation treatment in both arms was safe with only two grade 3/4 events that were both manageable. Successful redifferentiation through genotype-guided MAPK modulation and subsequent ^{131}I therapy may delay the onset of tyrosine kinase inhibitors (TKI), especially in patients with low FDG avidity. Delayed onset of TKIs comes with potential benefits for safety, quality of life, and economic burden. In 1 patient successful redifferentiation was repeated a second time after 2 years leading to further decreases in tumor size and thyroglobulin levels (Supplementary Fig. S3).

The implementation of pre-therapeutic ^{124}I PET in this study enabled dosimetry of tumor lesions and organs-at-risk leading to the administration of higher activities than in previous redifferentiation trials. High ^{124}I PET-derived tumor absorbed doses after ^{131}I therapy were associated with thyroglobulin decline (**Fig. 2D**). In addition, in patients with extensive prior ^{131}I therapy pretherapeutic ^{124}I PET dosimetry allows for a deescalation of treatment activity to reduce the risk of side effects.

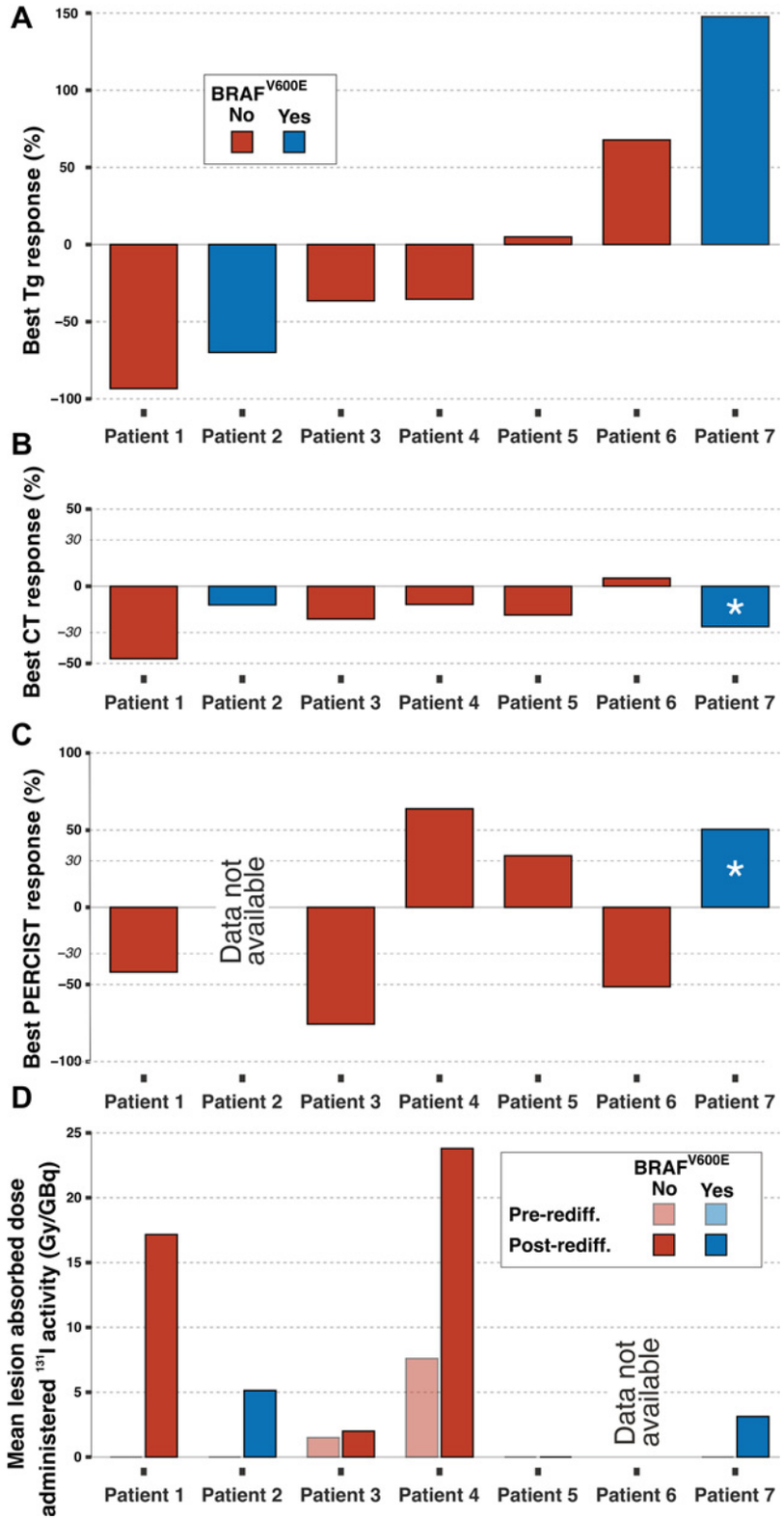

Figure 2.

Efficacy of redifferentiation therapy. Treatment response of patients with successful restoration of radioiodine uptake by change in (**A**) Tg level, (**B**) RECIST summed diameter (asterisk: occurrence of new lesions), (**C**) PERCIST SUV_{peak} (asterisk: occurrence of new lesions), and (**D**) mean absorbed dose on a per-patient level. Waterfall plots of individual patients are sorted by best Tg response. Of note, persistence of iodine-negative lesions after redifferentiation was observed in patients 5, 6, and 7 with a consecutive increase in Tg levels at follow-up. Pre-rediff, pre-redifferentiation; post-rediff, post-redifferentiation.

Table 2. Adverse events stratified by BRAF status from treatment start until follow-up 28 days after discontinuation of the study medication.

	BRAF-WT ($n = 14$)		BRAF-MUT ($n = 6$)	
Side effect	**All grades, *n* (%)**	**Grade 3/4, *n* (%)**	**All grades, *n* (%)**	**Grade 3/4, *n* (%)**
Rash	14 (100.0)	1 (7.1)	1 (16.7)	–
Diarrhea	4 (28.6)	–	–	–
Oral mucositis	2 (14.3)	–	–	–
Hypertension	2 (14.3)	–	1 (16.7)	–
Dyspepsia	1 (7.1)	–	–	–
Nausea	1 (7.1)	–	2 (33.3)	–
Oral pain	1 (7.1)	–	–	–
Vomiting	1 (7.1)	–	1 (16.7)	–
Fatigue	1 (7.1)	–	–	–
Dizziness	1 (7.1)	–	–	–
Syncope	1 (7.1)	–	–	–
Epistaxis	1 (7.1)	–	–	–
Scalp pain	1 (7.1)	–	–	–
Erythema	–	–	1 (16.7)	–
Palpitations	–	–	1 (16.7)	–
Pyrexia	–	–	2 (33.3)	1 (16.7)

In a posthoc analysis, we assessed predictors of therapy response. Low tumor glycolytic rate by FDG-PET was a significant predictor of redifferentiation success, which is likely due to the known association between FDG uptake and dedifferentiation in thyroid carcinoma (42, 43) and a variety of other tumor entities (44–46). As previously shown (18), low Tg values as a biochemical sign of dedifferentiation might be associated with a lower redifferentiation rate.

Our study benefits from systematic baseline and follow-up ^{124}I PET dosimetry and additional FDG-PET assessment. However, several limitations are noted:

The small number of included patients may affect the reliability of the study results. In addition, a larger range for imaging follow-up of 3 to 12 months may have reduced the consistency of RECIST/PERCIST assessments. In addition, the follow-up period does not yet allow drawing reliable conclusions on late toxicity, such as radiation fibrosis and hematopoietic disorders, as well as the extent to which systemic treatment can be delayed. Due to the trial design, no comparison with standalone MEK- and BRAF-targeting without subsequent ^{131}I therapy or TKI treatment was performed. Of note, 2 of 6 BRAF-MUT patients demonstrated partial response after dabrafenib + trametinib treatment without sufficient restoration of radioiodine uptake. This suggests that combined MAK- and BRAF-targeting itself may have been efficacious, which is in line with the findings of performed trials (47, 48).

Furthermore, BRAF mutation status was only evaluated in one lesion per patient potentially leading to misclassification of patients with a discordant molecular profile among tumor lesions. However, the published literature implies a high concordance of BRAF mutation status between primary tumor, lymph node metastases, and remote metastases (49–51).

Conclusion

Genotype-guided MAPK inhibition was safe and resulted in successful redifferentiation in about one third of patients. The redifferentiation rate was similar in BRAF-MUT and -WT arms indicating additional value of combination therapy for BRAF-MUT cancer.

Table 3. Predictors of successful redifferentiation.

		Successful redifferentiation, *n* (%)		
Parameter		**No**	**Yes**	***P***
Histopathology	PTC/FTC	11 (65)	6 (35)	1.00
	PDTC	2 (67)	1 (33)	
Cumulative previous radioiodine activity	≤432 mCi (∼16 GBq)	12 (75)	4 (25)	0.10
	>432 mCi (∼16 GBq)	1 (25)	3 (75)	
$BRAF^{V600E}$ mutation	No	9 (64)	5 (36)	1.00
	Yes	4 (67)	2 (33)	
SUV_{peak} (FDG-PET)[a]	≤10	3 (33)	6 (67)	0.01[b]
	>10	7 (100)	0 (0)	
Unstimulated Tg pre-redifferentiation (ng/mL)	≤66	6 (100)	0 (0)	0.05
	>66	7 (50)	7 (50)	
Histopathology/$BRAF^{V600E}$ mutation[c]	FTC/no	4 (57)	3 (43)	1.00
	PTC/no	3 (60)	2 (40)	

[a]Mean of five lesions with highest uptake.
[b]$P < 0.05$ by Fisher exact test.
[c]The lower row presents a subgroup analysis for BRAF-WT PTC versus FTC.

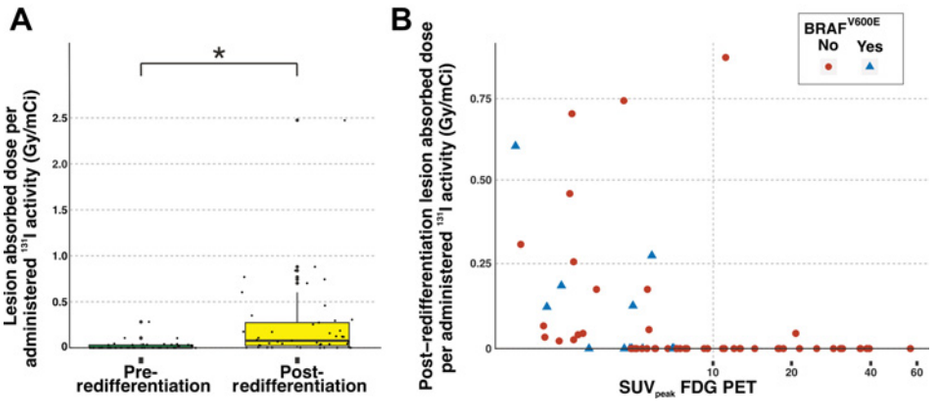

Figure 3.
Association of lesion absorbed doses as assessed by ^{124}I PET/CT and FDG-PET. **A,** Box plot showing pre- and post-redifferentiation therapy lesion-based mean absorbed dose per administered ^{131}I activity (statistical significance in Wilcoxon test indicated by an asterisk; $P < 0.00001$) for all patients with successful restoration of radioiodine uptake. **B,** Dot plot showing the per-lesion association of post-redifferentiation absorbed dose and pre-redifferentiation FDG uptake on a per-lesion level for all patients with available FDG-PET ($n = 16$).

Table 4. Comparison of studies on redifferentiation involving MAPK and/or BRAF inhibitors identified via a PubMed database search using the search strings "Redifferentiation MEK" and "Redifferentiation BRAF" and the initial Ho and colleagues trial.

Study	Cohort	BRAF status	Study drugs	Drug intake until iodine imaging	^{131}I treatment, *n* (%)	RECIST response
Ho (17)	13 PTC, 7 PDTC	9 BRAF-MUT, 11 BRAF-WT	Selumetinib	4 weeks	8/20 (40)	5 PR, 3 SD
Dunn (18)	10 PTC	10 BRAF-MUT	Vemurafenib	4 weeks	4/10 (40)	2 PR, 2 SD
Jaber (40)	10 PTC, 1 FTC, 2 PDTC	9 BRAF-MUT, 4 BRAF-WT	Dabrafenib, vemurafenib, trametinib, investigational MEK inhibitor	14.3 months	9/13 (69)	3 PR, 6 SD
Rothenberg (19)	10 PTC	10 BRAF-MUT	Dabrafenib	25 days	6 (60)	2 PR, 4 SD
Iravani (41)	3 PTC, 2 FTC, 1 PDTC	3 BRAF-MUT, 3 BRAF-WT	Dabrafenib + trametinib, trametinib	4 weeks	4 (66)	3 PR, 1 SD

Abbreviations: PR, partial response; SD, stable disease.

Following successful redifferentiation, dosimetry-guided ^{131}I therapy resulted in Tg decline in more than half of patients and morphologic and metabolic disease control was noted. Low tumor glycolytic rate by FDG-PET, i.e., SUV$_{peak}$ of 10 or less, was a predictor of redifferentiation success.

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Note

Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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