ORIGINAL ARTICLE

Selumetinib-Enhanced Radioiodine Uptake in Advanced Thyroid Cancer

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ABSTRACT

BACKGROUND

Metastatic thyroid cancers that are refractory to radioiodine (iodine-131) are associated with a poor prognosis. In mouse models of thyroid cancer, selective mitogen-activated protein kinase (MAPK) pathway antagonists increase the expression of the sodium–iodide symporter and uptake of iodine. Their effects in humans are not known.

METHODS

We conducted a study to determine whether the MAPK kinase (MEK) 1 and MEK2 inhibitor selumetinib (AZD6244, ARRY-142886) could reverse refractoriness to radioiodine in patients with metastatic thyroid cancer. After stimulation with thyrotropin alfa, dosimetry with iodine-124 positron-emission tomography (PET) was performed before and 4 weeks after treatment with selumetinib (75 mg twice daily). If the second iodine-124 PET study indicated that a dose of iodine-131 of 2000 cGy or more could be delivered to the metastatic lesion or lesions, therapeutic radioiodine was administered while the patient was receiving selumetinib.

RESULTS

Of 24 patients screened for the study, 20 could be evaluated. The median age was 61 years (range, 44 to 77), and 11 patients were men. Nine patients had tumors with *BRAF* mutations, and 5 patients had tumors with mutations of *NRAS*. Selumetinib increased the uptake of iodine-124 in 12 of the 20 patients (4 of 9 patients with *BRAF* mutations and 5 of 5 patients with *NRAS* mutations). Eight of these 12 patients reached the dosimetry threshold for radioiodine therapy, including all 5 patients with *NRAS* mutations. Of the 8 patients treated with radioiodine, 5 had confirmed partial responses and 3 had stable disease; all patients had decreases in serum thyroglobulin levels (mean reduction, 89%). No toxic effects of grade 3 or higher attributable by the investigators to selumetinib were observed. One patient received a diagnosis of myelodysplastic syndrome more than 51 weeks after radioiodine treatment, with progression to acute leukemia.

CONCLUSIONS

Selumetinib produces clinically meaningful increases in iodine uptake and retention in a subgroup of patients with thyroid cancer that is refractory to radioiodine; the effectiveness may be greater in patients with *RAS*-mutant disease. (Funded by the American Thyroid Association and others; ClinicalTrials.gov number, NCT00970359.)

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Metastatic disease is the most frequent cause of death related to thyroid cancer.[1] Radioiodine (iodine-131) remains a mainstay of therapy for patients with metastatic thyroid cancer of follicular origin (i.e., papillary thyroid cancer or follicular thyroid cancer). Unfortunately, many patients have tumors that do not concentrate iodine, resulting in radioiodine resistance and a poor prognosis (the 10-year survival rate among patients with metastatic thyroid cancer that retains radioiodine avidity is approximately 60%, whereas it is only 10% if the metastases are refractory to radioiodine therapy).[2] Several trials have evaluated strategies to "redifferentiate" metastatic thyroid cancers and render them responsive to radioiodine, including trials evaluating retinoids[3-5] and lithium,[6] which only yielded a modest clinical benefit. These studies were also limited by methodologic issues such as the inability to quantify radioiodine uptake and retention in tumors, so the effect of the interventions was difficult to assess.

Approximately 70% of papillary thyroid cancers have mutually exclusive gene mutations encoding the growth factor receptors RET or NTRK1, the three isoforms of *RAS* (N, H, K), and BRAF.[7-10] Constitutive activation of these proteins stimulates mitogen-activated protein kinase (MAPK) signaling, which inhibits the expression of thyroid hormone biosynthesis genes, including the sodium–iodide symporter and thyroid peroxidase, which facilitate iodine uptake and organification, respectively.[11-15] Cancers that do not concentrate radioiodine develop in transgenic mice in which mutant BRAF is expressed in thyroid cells.[16] When BRAF activation is switched off genetically or its downstream signaling is inhibited with kinase inhibitors targeting either MAPK kinase (MEK) or BRAF, the tumors regain the ability to trap radioiodine.

These preclinical observations provided the rationale for our pilot clinical study, in which patients who were found to have metastases that were refractory to radioiodine were treated with the selective, allosteric MEK 1 and MEK 2 inhibitor selumetinib (AZD6244, ARRY-142886),[17] and changes in iodine uptake were assessed by means of serial iodine-124 positron-emission tomography (PET)–computed tomography (CT). The use of iodine-124 PET-CT rather than traditional whole-body iodine-131 scintigraphy allowed for precise quantification of iodine uptake before and after selumetinib treatment in individual metastatic lesions ("lesional dosimetry") and prediction of the dose of radiation that could be delivered with iodine-131.[18,19]

Methods

Study Conduct

The trial was conducted in accordance with the study protocol, available with the full text of this article at NEJM.org. All patients provided written informed consent. The study was approved by the research committees of the Departments of Medicine, Radiology, and Medical Physics at Memorial Sloan-Kettering Cancer Center (MSKCC) and by the center's institutional review board. All authors vouch for the data, the fidelity of the study to the protocol, and the analysis. No one who is not listed as an author contributed to the manuscript.

Patients

Patients were required to have differentiated thyroid carcinoma of follicular-cell origin, or its respective variants, histopathologically confirmed at the MSKCC. Patients also had to meet at least one of the following criteria for radioiodine-refractory disease: an index metastatic lesion that was not radioiodine-avid on diagnostic radioiodine scanning performed up to 2 years before enrollment; a radioiodine-avid metastatic lesion that remained stable in size or progressed despite radioiodine treatment 6 months or more before entry into the study; and ^{18}F-fluorodeoxyglucose (FDG)–avid lesions on PET scanning (FDG avidity is indicative of less differentiated thyroid tumors with impaired iodine uptake[20] and resistance to radioiodine,[21] which are associated with a poor prognosis[22]). (For additional inclusion and exclusion criteria, see the Supplementary Methods section in the Supplementary Appendix, available at NEJM.org.) Thyrotropin alfa (Thyrogen) was provided by Genzyme, and selumetinib was provided by AstraZeneca. IBA Molecular provided the iodine-124 for the study. These companies did not participate in any aspect of the study design, data accrual, data analysis, or manuscript preparation. The investigational new drug application for selumetinib was held by MSKCC.

STUDY DESIGN

After adhering to a low-iodine diet for 5 days, patients underwent a thyrotropin alfa–stimulated iodine-124 PET-CT study, followed by treatment with selumetinib at a dose of 75 mg given orally twice daily for 4 weeks. In the fourth week of selumetinib treatment, patients underwent a second iodine-124 PET-CT study. Spot urinary iodine measurements were performed before each iodine-124 PET evaluation (median urinary iodine value during the study, 99 μg per liter; range, 0 to 374) to rule out clinically significant iodine contamination before each scan. Patients discontinued the study if the second iodine-124 PET evaluation did not show an increase in iodine uptake to a prespecified dosimetry threshold. If this dosimetry threshold was met, then patients continued to receive selumetinib (and a low-iodine diet) as thyrotropin alfa–stimulated whole-body and blood dosimetry studies were performed to determine the maximum tolerable activity pursuant to the standard of care at MSKCC.[23] After determination of the maximum tolerable activity, a therapeutic dose of iodine-131 was administered after stimulation with thyrotropin alfa.[24] Selumetinib was continued until 2 days after ingestion of therapeutic iodine-131. Toxic effects were monitored for 30 days after the last dose of selumetinib. Patients continued to receive suppressive thyroid hormone treatment throughout the protocol. The second iodine-124 PET-CT study in one patient was delayed by a week because of a temporary shortage of the iodine-124 radionuclide; this study showed no appreciable change in iodine uptake.

In patients who received iodine-131, CT imaging, magnetic resonance imaging, or both was performed 2 and 6 months after radioiodine therapy. One radiologist assessed the radiologic response in all patients, as compared with prestudy scans, according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Levels of serum thyrotropin, free thyroxine, thyroglobulin, and thyroglobulin antibodies were measured 1, 2, and 6 months after administration of radioiodine.

IODINE-124 PET-CT STUDIES

Patients received 0.9 mg of thyrotropin alfa intramuscularly once daily for 2 consecutive days, and then 6 mCi of iodine-124 orally the next day. Two days later, imaging was performed with the use of a PET-CT scanner (Discovery STE, GE Healthcare), without the administration of contrast material. The patient was scanned from the canthomeatal line (the line between the center of the ear canal and the junction of the upper and lower eyelids) to the midthigh with the use of seven to nine bed positions, with scans of 6 minutes per bed position. The images in all the patients were interpreted in a blinded fashion by the same board-certified nuclear-medicine physician, and the number, size, and maximal standardized uptake value of the lesions in each body region were recorded.

If the second iodine-124 PET-CT study indicated increased iodine uptake in the index lesion (or lesions), an estimate was made of the administered activity of iodine-131 required to deliver a projected absorbed dose of 2000 cGy or more to the lesion. This estimate was based on the lesion activity concentration measured on PET multiplied by a recovery coefficient based on the lesion dimensions measured on CT and on an assumed biologic half-life of at least 2 days. If it appeared that one or more lesions could be treated with a dose of 2000 cGy or more with an iodine-131 administered activity of up to 300 mCi, the patient was then eligible for the standard iodine-131 dosimetry protocol to determine the actual activity to be administered. In addition, as previously described, an imaging analysis tool was used with the GE PET volume computer-assisted reading system to localize individual iodine-124 uptake to a specific, corresponding lesion on CT.[25]

TISSUE GENOTYPING

Mutation detection in DNA isolated from formalin-fixed, paraffin-embedded archival samples was performed with the use of the mass-spectrometry genotyping assay (MassArray, Sequenom), as previously described.[26] This assay interrogated for mutations in some of the most common thyroid oncogenes, including *BRAF*, *NRAS*, *KRAS*, *PIK3CA*, and *AKT1*. Since the mass-spectrometry assays for codons 12 and 13 of *HRAS* were not informative, these sites were evaluated by means of Sanger sequencing. If mass spectrometry analysis failed, samples were assayed for *BRAF*, *NRAS*, *KRAS*, and *HRAS* mutations by means of Sanger sequencing. Samples that were wild-type for oncogene point mutations were screened for *RET*

Table 1. Baseline Characteristics of the 20 Patients.

Characteristic	Value
Age — yr	
Median	61
Range	44–77
Sex — no.	
Male	11
Female	9
Type of tumor — no./total no. (%)	
Classic papillary	5/20 (25)
Tall-cell papillary	8/20 (40)
Poorly differentiated	7/20 (35)
Tumor genotype — no./total no. (%)	
BRAF V600E	9/20 (45)
NRAS Q61R and *Q61K*	5/20 (25)
RET/PTC	3/20 (15)
Wild type	3/20 (15)
Median no. of prior radioiodine treatments per patient	2.1
Other treatments for thyroid cancer — no. of patients/total no. (%)	
External-beam radiation therapy	7/20 (35)
Targeted therapies*	2/20 (10)

* These patients received sorafenib in combination with an mTORC1 (mammalian target of rapamycin complex 1) inhibitor before enrollment in the study.

and *PAX8*–peroxisome proliferator–activated receptor gamma (*PPARG*) rearrangements. Tumor complementary DNA (cDNA) was used as a template for a quantitative polymerase-chain-reaction assay to identify unbalanced expression of exons 10 and 11 relative to 12 and 13 of *RET*, which flank the rearrangement site in intron 11 (Table S1 in the Supplementary Appendix). Samples with greater expression of exons 12 and 13 than of exons 10 and 11 were considered to be positive for an *RET/PTC* translocation. Cell-line cDNA from medullary thyroid cancers (TT cells) and papillary thyroid cancers (TPC1 cells) were used as positive controls for expression of full-length *RET* and *RET* fusion messenger RNA, respectively.

STATISTICAL ANALYSIS

The primary end point was the percentage of patients with selumetinib-induced increases in iodine uptake in the index tumor (or tumors), as quantified by iodine-124 PET at baseline and after 4 weeks of selumetinib. We adopted as the null hypothesis an increase in iodine-124 PET–quantified iodine uptake in 5% of patients, with increased uptake in 25% of patients considered to be desirable. With a type 1 error of 5% and a power of 85%, increased iodine uptake in the second iodine-124 PET scan would need to be observed in at least three patients for the study to be considered positive. A second primary end point was the tumor response at approximately 2 and 6 months after iodine-131 treatment according to RECIST, version 1.1.

A secondary end point was an assessment of whether treatment with iodine-131 after selumetinib was associated with decreased serum thyroglobulin levels at 2 and 6 months. A Wilcoxon signed-rank test for paired samples was used for this landmark comparison at each follow-up assessment. Undetectable thyroglobulin values clinically reported as less than 0.2 ng per milliliter were assigned a value of 0.2 ng per milliliter for calculations. An additional, exploratory end point was an assessment of differences in selumetinib efficacy for enhancing radioiodine uptake between patients with *BRAF* mutations and patients with wild-type *BRAF* (additional details of the statistical design are included in the Supplementary Appendix). We used descriptive statistics for this assessment.

RESULTS

STUDY POPULATION

Between August 2010 and December 2011, a total of 24 patients were referred and screened for the study. Two patients were ineligible because of baseline measurements of the QT interval corrected for heart rate which were outside the study range. Two patients were enrolled but discontinued the study before selumetinib was administered: 1 in whom a new brain metastasis was diagnosed and 1 in whom iodinated contrast material was used for a diagnostic scan that revealed a pulmonary embolism.

Baseline clinical characteristics of the 20 patients who could be evaluated are listed in Table 1. Five patients (25%) had classic papillary thyroid cancer, 8 (40%) had tall-cell–variant papillary thyroid cancer, and 7 (35%) had poorly differentiated carcinoma. Nine patients had a *BRAF V600E* mutation, 5 had an *NRAS* mutation at codon 61 (Q→R or K), 3 had *RET/PTC* rearrange-

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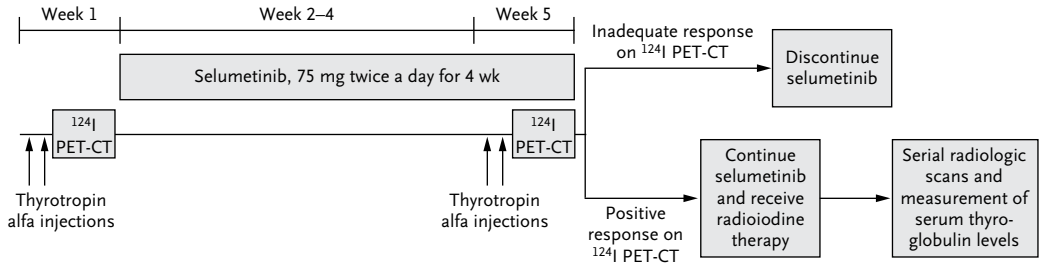

B

Tumor Genotype	Patients with Increased Iodine Uptake in a Lesion after Selumetinib	Patients Who Received Radioiodine
	no./total no. of patients	
BRAF	4/9	1/9
NRAS	5/5	5/5
RET/PTC	2/3	1/3
Wild-type	1/3	1/3
Total	12/20	8/20

Figure 1. Protocol Design and Changes in Iodine Uptake.

Panel A shows the protocol design. Baseline iodine avidity in the lesion was first assessed with thyrotropin alfa–stimulated iodine-124 positron-emission tomographic–computed tomographic (PET-CT) scanning. Patients were then treated with selumetinib at a dose of 75 mg given orally twice a day for 4 weeks. In the final week of treatment, a second thyrotropin alfa–stimulated ^{124}I PET-CT study was performed. The double arrows indicate the two thyrotropin alfa injections. Patients with ^{124}I dosimetry that predicted tumor uptake of less than 2000 cGy discontinued the study. If the absorbed dose of radioiodine in the lesion was predicted to be 2000 cGy or greater, full dosimetry with iodine-131 was performed to calculate the maximum tolerable activity that could be administered safely. Patients then received a therapeutic dose of radioiodine the next week after preparation with thyrotropin alfa. Selumetinib was continued until 2 days after the administration of therapeutic radioiodine. Thyroglobulin levels and the radiographic response were assessed at 2 and 6 months after radioiodine administration. Panel B shows a summary of the changes in iodine uptake quantified by ^{124}I PET-CT and the number of patients who met the criteria for treatment with iodine-131.

ments, and 3 had tumors that were wild-type for all genes examined. No *PAX8-PPARG* rearrangements were detected. One *BRAF*-mutant tumor and one *RET/PTC* tumor were poorly differentiated carcinomas; the remaining tumors of these genotypes were papillary thyroid cancers. All five *NRAS*-mutant tumors were poorly differentiated carcinomas.

EFFICACY

Figure 1A shows the protocol design. Of the 20 patients who could be evaluated, 12 (60%) had iodine-124 uptake that was new, increased, or both after selumetinib (Fig. 1B). In 8 patients (40%), the second iodine-124 PET study indicated that the absorbed radiation dose in the lesion would equal or exceed 2000 cGy with 300 mCi of radioiodine or less; these patients continued to receive selumetinib, and they received therapeutic radioiodine. In all 5 patients with *NRAS*-mutant tumors, this dosimetry threshold was exceeded, and these patients were treated with radioiodine. In contrast, 4 of 9 patients with *BRAF* mutations had selumetinib-induced increases in iodine-124 uptake, but only 1 had an increase that exceeded the threshold for radioiodine treatment. Two of 3 patients with *RET/PTC* and 1 of 3 patients with wild-type tumors had greater iodine uptake on the second iodine-124 PET study; 1 patient in each of those genotype groups went on to be treated with iodine-131. Increases in iodine uptake were achieved in patients with papillary thyroid cancers and those with poorly differentiated carcinomas (Table S2 in the Supplementary Appendix), as well as in patients in each protocol-specified category of radioiodine refractoriness

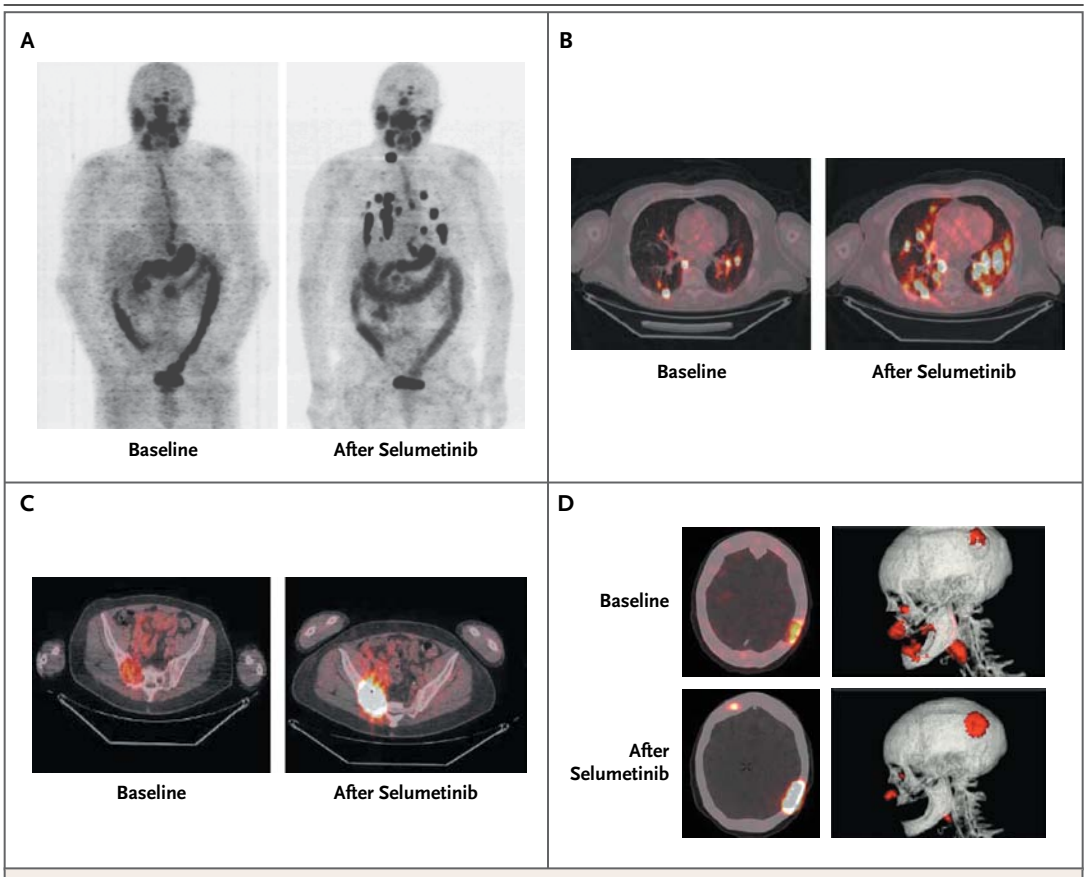

Figure 2. Iodine-124 PET-CT Scans Obtained before and after Selumetinib Treatment in Selected Patients with Positive Responses.

Panel A shows whole-body maximum-intensity projection images of a patient with a *BRAF*-mutant papillary thyroid cancer. New iodine uptake is shown in nearly all previously negative lung and neck metastases. Panel B shows fused axial PET-CT images of a patient with an *NRAS*-mutant, poorly differentiated thyroid cancer. Both new and significantly increased iodine uptake in lung metastases is shown. Panels C and D show PET-CT images from another patient with an *NRAS*-mutant, poorly differentiated thyroid cancer. In Panel C, fused axial PET-CT images show significantly increased iodine uptake in a sacroiliac bone metastasis after administration of selumetinib (right). In Panel D, fused axial images (top and bottom left) show new iodine uptake in a previously negative site as well as increased avidity in a large left parietal skull metastasis. Three-dimensional rendering highlights changes in the left parietal skull metastasis before and after selumetinib (top and bottom right).

(Table S3 in the Supplementary Appendix). Of the 10 patients with no detectable iodine-124 uptake at baseline, 2 had increased uptake after receiving selumetinib, 1 of whom went on to receive iodine-131.

The selumetinib-induced changes in the iodine-124 PET-CT scans are shown in Figure 2. The only patient with a *BRAF* mutation who qualified for radioiodine therapy had dramatic increases in iodine uptake in a right cervical lymph node and lung metastases that showed no uptake at baseline (Fig. 2A). In other patients, iodine uptake was enhanced both in lesions with low-level iodine avidity and those with no avidity at baseline (Fig. 2B). Striking increases in selumetinib-induced iodine-124 uptake were also observed in bone metastases (Fig. 2C and 2D).

Quantification of baseline and post-selumetinib iodine-124 in each tumor in a patient with an *NRAS* mutation who qualified for radioiodine therapy revealed either new iodine uptake or more than a 100% increase in uptake in nearly every lesion (Fig. 3). Analysis of every lesion in all eight patients treated with radioiodine showed

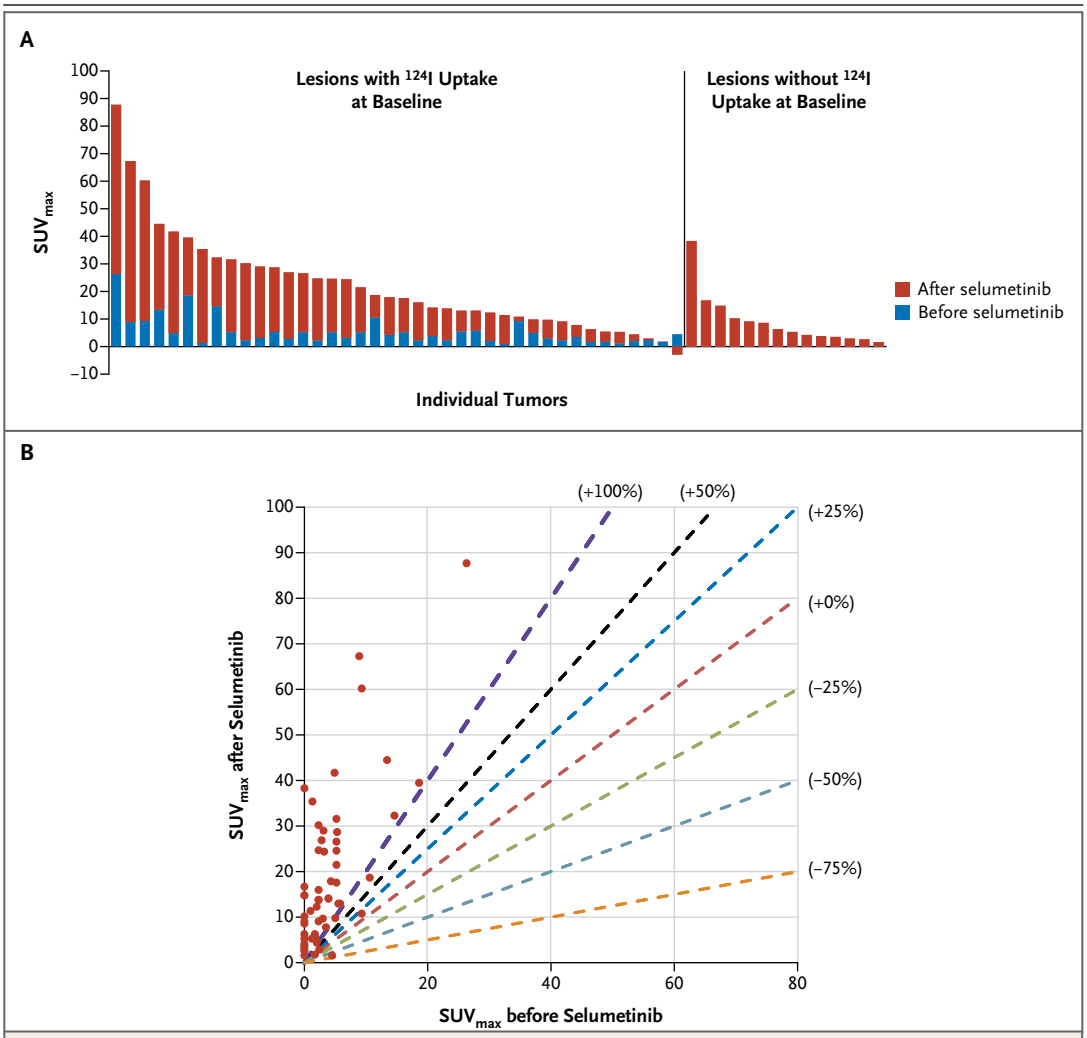

Figure 3. Quantification of Iodine-124 PET Uptake in a Lesion in a Patient with an *NRAS* Mutation Who Later Received Radioiodine.

Panel A shows the maximal standardized uptake value (SUV_{max}) for iodine in all tumors in a patient with an *NRAS*-mutant, poorly differentiated thyroid cancer. Each bar represents one malignant lesion identified on the iodine-124 PET-CT scan. The bars to the left indicate the increases in iodine-124 avidity achieved after selumetinib administration in lesions that absorbed some iodine at baseline. The bars on the right indicate selumetinib-induced changes in lesions that were negative for iodine at baseline. Panel B shows the SUV_{max} in every metastatic lesion identified in the same patient before and after the administration of selumetinib. The dashed lines mark points on the graph corresponding to different degrees of change in the SUV_{max} in the lesion after the administration of selumetinib. The red dashed line demarcates no change in iodine uptake after the administration of selumetinib (0%). Dashed lines to the left of the red dashed line represent graded percentage increases in iodine-124 uptake (+25%, +50%, and +100%), whereas the lines to the right represent graded percentage decreases (–25%, –50%, and –75%). Nearly all the metastatic lesions in this patient (circles) had more than a 100% increase in iodine uptake after administration of selumetinib. The SUV_{max} for a sternal metastasis was off the scale (it increased from 220 to 599 with selumetinib) and thus could not be included in these graphs without obscuring the data for the other 54 lesions analyzed.

that selumetinib increased iodine-124 uptake in nearly all lesions, with more than a 100% increase in uptake in most lesions (Fig. S1 in the Supplementary Appendix). Iodine uptake in salivary glands was not significantly affected by selumetinib (Fig. S2 in the Supplementary Appendix); this suggests that the effect was restricted to thyroid tumors.

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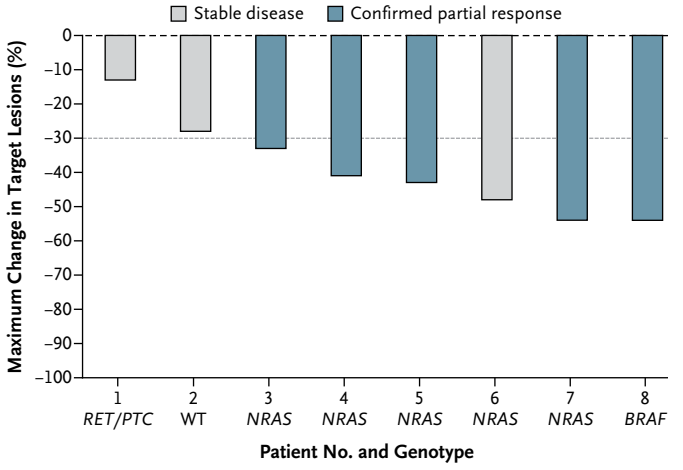

B

Patient No.	Serum Thyroglobulin Values				
	Before Selumetinib (wk 1)	After Selumetinib (wk 5)	1 Mo after Radioiodine Therapy	2 Mo after Radioiodine Therapy	6 Mo after Radioiodine Therapy
			ng/ml		
1	650	780	240	200	740
2	360	880	270	210	194
3	2700	3200	3700	740	480
4	510	1300	NA	31	22
5	220	530	11.3	0.4	<0.2
6	840	570	46	31	100
7	6500	1070	170	66	57
8	82	650	NA	23	14

Figure 4. Response to Iodine-131 Therapy with Selumetinib Treatment.
Panel A shows a waterfall plot of the maximum change in target lesions (relative to a prestudy scan) in the eight patients who received therapeutic radioiodine. The best overall response in each patient according to the Response Evaluation Criteria in Solid Tumors, version 1.1, is also shown. The dashed line indicates a 30% reduction in tumor dimensions. WT denotes wild-type. Panel B shows serum thyroglobulin values in the eight patients treated with radioiodine. NA denotes not available.

During 6 months of follow-up, a reduction in the size of target lesions was observed in all patients after the administration of radioiodine, with confirmed partial responses in five patients and stable disease in three as the best overall response (Fig. 4A, and Fig. S3 in the Supplementary Appendix). Significant decreases in thyrotropin-suppressed serum thyroglobulin levels after radioiodine administration were achieved in all eight patients at 2 months and 6 months after radioiodine administration, with mean reductions of 89% (P=0.004) and 80% (P=0.004), respectively, as compared with the value measured within 3 weeks before radioiodine administration (Fig. 4B). In seven of the eight patients, confirmed partial responses and stable disease outcomes were durable over the 6-month period of follow-up after radioiodine administration. The remaining patient had a 48% reduction in tumor dimensions 2 months after receiving radioiodine but then had tumor progression at 6 months, representing a best overall response of stable disease.

SAFETY

All patients who could be evaluated completed the full course of selumetinib without a dose reduction or delay in administration. All toxic effects attributed to selumetinib were grade 1 or 2 and were consistent with adverse events reported in larger studies of selumetinib,[27,28] including fatigue (in 80% of patients), maculopapular rash (70%), and acneiform rash (25%). Fourteen patients (70%) had grade 1 elevations in liver aminotransferase levels, possibly related to selumetinib; these levels reverted to baseline values after drug discontinuation. (Tables S4 and S5 in the Supplementary Appendix list all the toxic effects reported during the study.) One patient who was treated with 139 mCi of radioiodine during the study received a diagnosis of the myelodysplastic syndrome more than 51 weeks later; the disease eventually progressed to acute leukemia. Before enrollment, this patient had received three courses of radioiodine (a cumulative prestudy dose of 976.2 mCi), as well as 8640 cGy of external-beam radiation therapy, for prostate cancer, and thrombocytopenia developed when the patient was treated with sorafenib and temsirolimus in a clinical trial.

DISCUSSION

Previous studies using various compounds to promote radioiodine uptake in refractory metastatic thyroid cancers have not shown a clinically significant benefit.[3,6] The approach undertaken in this study was facilitated by several developments: the discovery that genetic alterations that constitutively activate MAPK signaling can promote the dedifferentiation of thyroid-cancer cells,[12,29,30] the clinical availability of a selective MEK inhibitor,[17] and the development of iodine-124 PET-CT technology to quantify the uptake of iodine in a lesion.[18]

Our results show that inhibition of the MAPK pathway with selumetinib can renew the therapeutic efficacy of radioiodine by enhancing uptake in patients with thyroid cancer that is refractory to radioiodine. All five patients with *NRAS*-mutant tumors had increased iodine uptake in response to selumetinib; four had confirmed partial responses and one had stable disease after radioiodine administration. This finding is of particular interest, given the well-documented challenges of developing therapeutic approaches for *RAS*-driven cancers, and it is consistent with preclinical data showing that a *RAS* mutation can suppress thyroid-specific gene expression in a MEK-dependent manner.[12,31] Only one of nine patients with *BRAF* mutations received radioiodine therapy. That patient had a particularly striking conversion of lesions from negative to positive on iodine-124 PET after treatment with selumetinib and had a confirmed partial response. Three other patients with *BRAF* mutations also had increased uptake on the post-selumetinib iodine-124 PET study, even though the threshold required for therapy was not reached. The differences observed between *RAS*-mutant and *BRAF*-mutant tumors remain to be explained, but it is possible that MAPK signaling is incompletely inhibited in some *BRAF*-mutant tumors because of higher flux through the pathway.

These results provide a proof of principle that MEK inhibitors can induce iodine uptake and retention in thyroid tumors. An advantage of this therapeutic strategy over long-term treatment with small-molecule kinase inhibitors alone[32] is that only a short course of drug therapy is required to elicit a durable clinical effect. Enhanced iodine uptake was also observed in bone and nodal metastases, niches that have been comparatively refractory to treatment with kinase inhibitors.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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