Title

Redifferentiation of iodine-refractory BRAF V600E-mutant metastatic papillary thyroid cancer with dabrafenib.

Authors

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Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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Statement of Translational Relevance

Radioactive iodine is a highly specific and effective treatment for patients with differentiated thyroid cancer that is residual after surgery, unresectable or metastatic. However, many patients have primary resistance to radioiodine or become refractory over time. Mutations in the MAPK pathway are frequent in thyroid cancer, and prior studies have shown that inhibiting this pathway can restore radioiodine uptake in thyroid cancer cells. This trial treated patients with iodine-refractory, \textit{BRAF}-mutant papillary thyroid cancer with a short course of the BRAF inhibitor dabrafenib. This led to new radioiodine uptake in the majority of patients, leading to dramatic tumor responses. Our study adds to growing evidence for the potential clinical efficacy of this novel, iodine resensitization approach in this difficult to treat patient population.
Abstract

Purpose

To determine whether the selective BRAF inhibitor, dabrafenib, can stimulate radioiodine uptake in BRAF V600E mutated unresectable or metastatic iodine-refractory papillary thyroid cancer (PTC).

Patients and Methods

Ten patients with BRAF V600E-mutant iodine-refractory PTC were enrolled. Absence of radioiodine uptake on iodine-131 whole body scan obtained within 14 months of study entry was required. Each patient received dabrafenib (150 mg twice daily) for 25 days prior to thyrotropin alfa-stimulated iodine-131 whole body scan (4 mCi/148 MBq). Patients whose scan showed new sites of radioiodine uptake remained on dabrafenib for 17 more days, then were treated with 150 mCi (5.5 GBq) iodine-131. The primary end point of the study was the percentage of patients with new radioiodine uptake after treatment with dabrafenib.

Results

Six of ten patients (60%) demonstrated new radioiodine uptake on whole body scan after treatment with dabrafenib. All six were treated with 5.5 GBq iodine-131. Two patients had partial responses and four patients had stable disease on standard radiographic restaging at three months. Thyroglobulin decreased in four of six treated patients. One patient developed squamous cell carcinoma of the skin. There were no other significant adverse events attributed to dabrafenib.

Conclusion
Dabrafenib can stimulate radioiodine uptake in patients with metastatic \textit{BRAF} V600E-mutant iodine-refractory PTC, representing a potential new therapeutic approach for these patients.
Introduction

Papillary thyroid carcinoma (PTC) is the most common form of thyroid cancer. The incidence of PTC has dramatically increased over the past forty years. In 2013 over 80% of the newly-diagnosed thyroid cancers in the USA were PTCs.(1) The majority of PTCs have activating mutations within gene that make up of the MAPK pathway. Approximately 50% of PTCs harbor \textit{BRAF} activating mutations (98-99% encoding V600E), 20% have \textit{RET/PTC} rearrangements and a small percentage have \textit{NTRK} rearrangements.(2-5) Although PTC is usually indolent, tumors harboring \textit{BRAF} mutations are more aggressive, with an increased risk of lymph node metastasis, extra-thyroidal extension, insensitivity to radioiodine and death.(6)

Radioiodine is the most effective therapy available for patients with residual PTC after surgery, unresectable disease, or distant metastasis.(7, 8) For patients whose tumors are either resistant to radioiodine \textit{de novo} or become refractory to radioiodine over time, new therapies are needed. This is particularly true for patients with low volume, asymptomatic disease that is not rapidly progressive.

PTCs harboring \textit{BRAF} mutations are insensitive to radioiodine in part due to low expression of the sodium-iodide symporter (NIS). (9-12) When BRAF V600E is expressed in thyroid cancer cell lines, NIS expression and/or proper localization is suppressed, interfering with the cells’ ability to take up radioiodine. (13-15) Insensitivity to radioiodine was overcome in a genetically engineered mouse model of \textit{BRAF} V600E thyroid cancer by treatment with \textit{BRAF} and MEK inhibitors, which induced re-expression of NIS and radioiodine uptake.(16) In humans, the MEK
inhibitor, selumetinib, increased radioiodine uptake in 12 of 20 patients with iodine-refractory differentiated thyroid cancer and led to significant tumor shrinkage in 5 of 8 patients treated with radioiodine.(17) Together, these results demonstrate the potential clinical benefit of an iodine re-sensitization approach by pre-treating patients with MAPK pathway inhibitors.

In BRAF-mutant thyroid cancers, direct inhibition of BRAF may be more effective than downstream MEK inhibition in stimulating NIS re-expression and radioiodine uptake(16). Therefore, we investigated the potential of the selective BRAF inhibitor, dabrafenib, to restore radioiodine uptake in patients with BRAF-mutant PTC that does not take up radioiodine.

**Methods**

**Patient Selection**

Eligible patients had histologically confirmed PTC that was metastatic or unresectable and harbored a mutation encoding BRAF V600E. Additional inclusion criteria included: absence of tumor iodine-131 uptake on whole body scan within 14 months of study entry (either low-dose--74-148 MBq or high-dose--≥ 1.1 GBq), evaluable disease by CT scan or ultrasound, age ≥ 18 years, Eastern Cooperative Oncology Group performance status ≤ 1 and adequate liver, renal and bone marrow function. Exclusion criteria included prior treatment with BRAF or MEK inhibitors, brain metastases, symptomatic, large volume or rapidly progressive disease, as judged by the treating physician, and prolonged QTc interval. The study (ClinicalTrials.govIdentifier NCT01534897) was approved by the Institutional Review Board of the Dana-Farber/Harvard

CCR-14-2915 resubmission, 12/15/2014, page 6
Cancer Center. All patients provided written informed consent. Dabrafenib was provided by GlaxoSmithKline, Thyrotropin alfa was purchased from Genzyme and iodine-131 was purchased from Jubilant DraxImage Inc.

**Treatment**

Patients were treated with dabrafenib 150 mg orally twice daily until their diagnostic radioiodine scan was performed on day 25. Adverse events (AEs) were graded according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Patients began a low-iodine diet on day nine. On days 21 and 22, each patient received thyrotropin alpha 0.9 mg IM, and on day 23, each received 148 MBq iodine-131. A whole body scan was performed on day 25. Spot urinary iodine measurements were performed before each scan to exclude intake of excess iodine. Dabrafenib was discontinued if there was no radioiodine uptake on whole body scanning. If radioiodine uptake was seen (in any abnormal site—new uptake at all known sites of disease was not specifically required), patients continued on dabrafenib and a low-iodine diet for two additional weeks. On day 37, iodine-131, 5.5 GBq, was administered (after thyrotropin alpha for two days).

On day 42, a whole body scan was performed and dabrafenib was discontinued. Patients continued to receive their usual levothyroxine suppressive therapy throughout the protocol.

Computed tomography (CT) imaging of the neck and chest was performed within 30 days prior to the first dose of dabrafenib and again at three and six months in all patients. Response was determined according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Serum concentrations of thyrotropin (TSH), free thyroxine (FT4), thyroglobulin (Tg) and Tg.
antibodies were measured on day one prior to the first dose of dabrafenib, on day 21 prior to thyrotropin alfa, on day 42, and at three months.

**Whole Body Scanning**

Whole body scans were performed using a dual head, large field of view gamma camera (Siemens Symbia S, Siemens Medical Systems) equipped with high energy collimation two (for diagnostic 148 MBq dose) or five (for treatment 5.5 GBq dose) days after administration of Iodine-131. Immediately before imaging, patients were injected with one mCi (37 MBq) of $^{99m}$Tc pertechnetate to permit anatomic localization of lesions, a routine procedure at our institution. Simultaneous dual tracer iodine/pertechnetate images were obtained for anatomic localization. Anterior and posterior planar spot images of the head and neck were recorded for 15 minutes using a 256 x 256 image acquisition matrix. Images of the chest, abdomen, and pelvis/proximal thighs were recorded for ten minutes each. For each focus of abnormal radioiodine uptake identified by the nuclear medicine physician, a region of interest was drawn and the geometric mean counts in the region were identified. Images were windowed on a digital workstation to ensure that the region of interest size was correctly matched to the lesion and did not include extended artifactual uptake. Therefore, “star” artifacts did not obscure any areas of bona fide uptake. A radioiodine standard of approximately 100 microcuries (3.7 MBq) was prepared and imaged. All areas of abnormal radioiodine uptake were identified. The uptake within these regions was quantified as a percentage of the total administered radioiodine dose, based on counts recorded from the iodine-131 standard after correcting for radioactivity decay. The images in all patients were interpreted in a blinded fashion by an experienced nuclear medicine physician.
Baseline scans were performed both at MGH (n=4) and at outside (n=6) facilities, either after rhTSH injection or after thyroid hormone withdrawal, with serum TSH >25 uU/ml. All baseline scans were reviewed by the same nuclear medicine physician who interpreted the on-treatment scans, to confirm negative baseline status.

Tissue Genotyping

Mutation detection in DNA-isolated, formalin-fixed, paraffin-embedded archival samples was performed at MGH with the SNaPshot multiplexed allele-specific tumor genotyping analysis as described previously.(18) For one patient, BRAF mutational status was determined by real-time PCR assay performed by NorDx Laboratory (Scarborough, ME).

Data Analysis

The primary end point was the percentage of patients with dabrafenib-induced radioiodine uptake determined by whole body scan. Secondary end points included best tumor response at three after radioiodine treatment according to RECIST 1.1 and change in serum Tg concentration from baseline to three months after radioiodine treatment.

Results

Study Patients

Figure 1 shows the study schema. Ten patients were screened for the study, deemed eligible and were enrolled between July, 2012 and July, 2013. Clinical characteristics of the ten patients are
presented in Table 1. The median age was 66 years (range 61-84 years); six patients were male and four patients were female; five had classical variant, four had tall cell variant and one had clear cell PTC. Although evidence of disease progression was not required for study entry, five patients had progression per RECIST v1.1 within the 14 months prior to enrollment. Four of the five patients who had PET imaging prior to study entry had FDG-avid disease. All patients had been previously treated with radioiodine (median = two treatments; range = one to four; all patients received at least one 5.5 GBq treatment dose). Three patients received prior external beam radiation therapy; no patient had received prior cytotoxic chemotherapy or targeted therapy. Baseline serum TSH range was 0.02-1.09 uU/ml (median = 0.05).

Efficacy

Six of ten patients (60%) developed new radioiodine uptake while on dabrafenib, including all four patients with tall cell and two of five patients with classical variant PTC (Supplementary Table 1). Urinary iodine measurements confirmed that in patients with negative whole body scans, the absence of radioiodine uptake was not due to contamination by excess dietary iodine (Supplementary Table 2). Three of four patients with FDG-avid and one patient with FDG-negative disease developed new radioiodine uptake while on dabrafenib (Supplementary Table 1). New radioiodine uptake was found in four of five patients with documented progressive disease and in two of three patients documented to have stable disease within 14 months prior to enrollment (Supplementary Table 1), and as expected, scans after the 5.5 GBq iodine-131 dose revealed novel sites not appreciated on the lower dose scans (Supplementary Figure 2).
Figures 2A and B demonstrate a typical patient’s negative whole body scan prior to protocol entry. Figure 2C demonstrates new radioiodine uptake in known sites of disease on dabrafenib. Supplementary Figure 1 displays the pre- and post-treatment radioiodine scans in the six patients with new uptake. Physiologic uptake in sites such as the salivary glands, nasopharynx and stomach was not affected by dabrafenib (Figure 2 and Supplementary Figure 1).

Six months after treatment with radioiodine, there was a reduction in the size of target lesions on CT imaging in five of the six treated patients (Figure 3). Two patients met criteria for partial responses (PR) (Figures 3, 4), including one with a nearly 60% reduction in the size of the target lesion, a mediastinal lymph node metastasis (Figure 4A). Of the four patients who were treated with radioactive iodine with stable disease (SD), three demonstrated a reduction in the size of the target lesions (by 12-20%) and one had a slight increase (3%). By comparison, one of four patients who failed dabrafenib-induced radioiodine redifferentiation experienced progressive disease (PD), while the other three patients had SD (Supplementary Table 1). Although TSH-suppressed Tg concentrations decreased in four of six patients with new iodine-131 uptake at three months, the differences were not statistically significant (Table 2). It is worth noting that serum Tg concentration increased in two patients with new radioiodine uptake, both of whom had PRs, whereas serum Tg at three months increased in all four patients without radioiodine uptake (Table 2). These increases are not accounted for by variation in the degree of TSH suppression (Supplementary Table 3). While rising Tg is generally indicative of tumor growth, the target lesions in both patients maintained their decreased size following radioiodine treatment, and no new foci of disease have been apparent on CT imaging.
Safety

All patients completed the full course of dabrafenib without dose modification. There were no unexpected AEs. AEs occurring in more than a single patient included new skin lesions or changes (80%), fatigue (50%), gastrointestinal symptoms (50%), electrolyte abnormalities (50%-two with hypocalcemia and one each with hypophosphatemia, hyperglycemia and hyponatremia), palmar-plantar erythrodysethesia (PPE) (40%), headache (30%), nausea (20%), weight loss (20%), creatinine increase (20%) and epistaxis (20%) (Table 3). One of the skin lesions was a new squamous cell carcinoma attributed to dabrafenib that was excised with clear margins. Other skin changes included darkening skin (20%), actinic keratosis (20%) and verrucous keratosis (20%). The hypocalcemia and PPE AEs were grade 2. All other AEs were grade 1. All AEs resolved upon completion of the study treatment. There were no AEs attributed to iodine-131.

Discussion

Post-surgical radioiodine therapy remains the standard of care for patients with potentially aggressive or advanced differentiated thyroid cancer. Based on randomized phase III trial results, the multikinase inhibitor, sorafenib, was recently approved by the U.S. Food and Drug Administration for patients with locally advanced or metastatic iodine-refractory thyroid cancer (including Hürthle cell, papillary, follicular, and poorly differentiated).(19) Compared to placebo, sorafenib extended progression-free survival (PFS) from 5.8 to 10.8 months. Partial responses were noted in 12.2% of patients. Of note, drug toxicities were frequent and required dose reductions or discontinuation of therapy in many patients. In addition, self-reported quality of life
of life scores were lower in the sorafenib group than in the placebo group, despite the PFS benefit. Thus, while new therapies, such as sorafenib and other TKIs, are emerging for patients with iodine-refractory disease, treatment with a TKI may not be appropriate for all patients after weighing the possible risks against the potential for benefit. This may be particularly true for patients who are asymptomatic and have low-volume, slow-growing disease.

For patients whose tumors are either resistant to radioiodine de novo or become refractory to radioiodine over time, more effective therapeutic approaches with less toxicity are needed. Redifferentiation of advanced thyroid cancer to facilitate treatment with radioiodine represents a novel approach for iodine-refractory patients for whom treatment with a TKI may not be appropriate. Preclinical studies in vitro and in genetically engineered mice have demonstrated that inhibitors of the MAPK signaling pathway can restore iodine uptake in BRAF V600E mutant, iodine refractory thyroid cancer. Blockade of this pathway with the MEK inhibitor, selumetinib, for redifferentiation and enhancement of radioiodine uptake in iodine-refractory thyroid cancer in humans was recently demonstrated. Notably, all five patients with RAS-mutant follicular thyroid cancer experienced selumetinib-induced increase in radioiodine uptake, while only four of nine patients with BRAF mutations developed uptake.

Our results with the selective BRAF inhibitor, dabrafenib, provide additional support for the hypothesis that MAPK pathway inhibition can restore sensitivity to radioiodine by facilitating redifferentiation of iodine-refractory advanced thyroid cancer. The percentage of patients with new or enhanced radioiodine uptake in BRAF-mutant PTC is similar with dabrafenib (6/10) and
selumetinib (4/9); taken together, these data indicate the potential for MAPK pathway inhibitors to reverse insensitivity to iodine-131 in these more aggressive thyroid cancers. Although not pre-specified, using a one sample exact binomial test with a one-sided type 1 error of 10%, with our study design there would have been 85% power to rule out a null hypothesis of new uptake in 5% of patients (5% was adopted as the null hypothesis in the selumetinib study as well) and target a rate of 30% if at least two patients demonstrated new uptake.

There are several important differences between our trial and the selumetinib trial by Ho, et al.(17) First, our study of dabrafenib was limited to BRAF V600E-mutant thyroid cancers, whereas the selumetinib study was not limited to a specific genotype. Second, we used traditional iodine-131 whole body scanning with quantification of regions of interest to determine radioiodine uptake; Ho et al. used iodine-124 PET-CT lesional dosimetry to predict which patients were most likely to respond to radioactive iodine. Iodine-124 PET-CT has two potential advantages over traditional iodine-131 whole body scanning: it can more accurately quantify iodine uptake in individual tumors; and it can be used to predict the radiation dose that will be delivered to each lesion with subsequent iodine-131 therapy. I-124 PET dosimetry is a promising technique for more precise quantitation of radioiodine uptake; however, it is not an FDA-approved study, requires an institutional IND and is not available in most clinical centers.(21, 22) Third, our study required absence of radioiodine uptake on whole body scanning within 14 months of study entry; Ho et al. recruited patients with iodine-refractory disease defined as those without radioiodine uptake, those with radioiodine uptake if the lesions were stable or progressed after radioiodine treatment, or those with 18F-fluorodeoxyglucose (FDG)-avid disease. Fourth, any patient in our study who developed new iodine-131 uptake was treated
with a fixed dose of 5.5 GBq iodine-131; Ho, et al. limited radioiodine treatment to patients whose lesions could be treated with a minimal dose of 2000 cGy as predicted by iodine-124 PET-CT lesional dosimetry. Therefore, doses of up to 11 GBq iodine-131 were employed, and while four of nine BRAF-mutant patients had increased radioiodine uptake after selumetinib, only one of these four reached the pre-defined dosimetry threshold for treatment with radioiodine (this patient had a PR accompanied by a sustained decrease in serum Tg). Due to these differences, it is not possible to quantitatively compare the degree of radioiodine uptake between patients in the two studies. Also, the true threshold of iodine-131 uptake required for clinical benefit after radioiodine therapy is not known. Further study will be necessary to determine whether there is a true benefit from treating redifferentiated tumors with relatively low levels of radioiodine uptake, and whether dose estimates based on Iodine-124 lesional dosimetry are necessary to predict response or lack of response.

In the current study, it is not possible to distinguish between tumor response resulting from a direct cytotoxic effect of dabrafenib, versus the induction of new radioactive iodine uptake. However, the short duration of dabrafenib therapy and the sustained response off dabrafenib suggests that a response to radioactive iodine is more likely. Furthermore, no responses were seen in patients who did not develop new radioactive iodine uptake. Notably, six of ten patients demonstrated a clear increase in TSH after just three weeks of dabafenib (Supplementary Table 3), prior to receiving radioactive iodine, and four of these six (patients 1, 2, 4 and 10) showed concomitant, clear increases in Tg during that same time frame (Table 2). For these patients, such increases may represent an increased thyroid hormone requirement induced by dabrafenib, leading to a rising TSH and TSH-stimulated Tg production, although a tumor differentiating
effect of dabrafenib cannot be excluded. Other patients (e.g. patients 7 and 8) demonstrated decreased Tg (with relatively stable TSH) during the same time frame, suggesting an antitumor effect (or less likely inhibition of Tg release by dabrafenib). Finally, both patients with partial tumor responses by RECIST demonstrated both early (before low-dose radioactive iodine) and late (after high-dose radioactive iodine) increases in Tg over time (Table 2). Although the increases could suggest progressive disease, the stability of these patients’ tumor responses and lack of new sites of disease on imaging could be due to a beneficial effect of dabrafenib on tumor differentiation. Additional study will be necessary to determine whether such early increases in TSH or Tg might provide an early indication of efficacy.

These data provide strong support for the concept that BRAF inhibition can induce radioactive radiiodine uptake in BRAF V600E-mutant iodine-refractory PTC, representing a form of tumor redifferentiation. Whether this approach will lead to long-term benefit for our patients is not yet known. Although two patients experienced PRs, as discussed above, their Tgs rose, and the declines in serum Tg overall in patients with new radioactive iodine uptake was modest. Compared with conventional or targeted chemotherapy, the ability to induce radioidine uptake in iodine-refractory, advanced thyroid cancer has the potential advantage of requiring only a short course of minimally toxic targeted therapy in order to maximize the potential long-term therapeutic effect from radiiodine therapy.

Why only some patients with BRAF V600E-mutant disease developed new uptake with BRAF inhibition is not known. We do know that mutant BRAF-mediated inhibition of iodine transport
is only partially ERK dependent, inhibition of the MAPK pathway with a BRAF or MEK inhibitor does not completely restore iodine uptake, and the effects of either RAF or MEK inhibitors on downstream signaling in thyroid cancer cells may be limited by feedback mechanisms. (15) (16) (23) An important area of future investigation will be to study BRAF inhibitors in combination with other inhibitors of the MAPK or feedback pathways to achieve even more robust radioactive iodine uptake in BRAF V600E-mutant, iodine-refractory PTC. (24, 25)

**Figure/Table Legends**

**Figure 1. Study design.**

**Figure 2. Example Iodine-131 whole body scans.** (A). Image of the whole body in a patient prior to study enrollment showing sites of physiologic uptake in the nasopharynx, salivary glands, stomach, faint activity in the bowel and excreted activity in the bladder (black arrows) (B) Left Magnification of area from the whole body scan corresponding to known sites of disease in the neck and upper mediastinum, which show no radioiodine uptake. Right Repeat iodine-131 on Day 25 after treatment of dabrafenib. There are no new areas of uptake despite treatment with dabrafenib. (C) Left Area from whole body scan prior to dabrafenib treatment in a second patient. Middle Corresponding image after 148 MBq iodine-131 on Day 25 after dabrafenib. Blue arrows indicate new uptake corresponding to known sites of disease in the neck. (Right) Corresponding image on Day 42 after 5.5 GBq iodine-131.

**Figure 3. Best response by RECIST 1.1.** Blue, partial response (PR); gray, stable disease (SD); red; progressive disease (PD).
Figure 4. Examples of tumor responses in patients with dabrafenib-stimulated new iodine-131 uptake. (A) Patient four demonstrated a nearly 60% reduction in the size of the target lesion on CT imaging, a mediastinal lymph node metastasis. (B) Patient eight demonstrated a nearly 40% reduction in the size of multiple target lesions in both lungs. Blue arrows indicate the location of the target lesions.

Table 1. Baseline Characteristics of the Ten Patients.

Table 2. Change in Thyroglobulin Levels.

Table 3. Adverse Events.
References


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**Days 1-28**

**Dabrafenib 150mg PO BID (n=10)**

- rhTSH days 21,22
- 131I 4mCi day 23
- Whole body radioiodine scan day 25

- No 131I uptake → No further treatment

- + 131I uptake

**Continue therapy days 29-42**

- rhTSH days 35,36
- 131I 150mCi day 37
- Whole body radioiodine scan day 42

**Figure 1**
Figure 2
Figure 3
Figure 4

A

B

baseline

after dabrafenib + iodine-131
<table>
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<th>Table 1. Baseline Characteristics of the Ten Patients.</th>
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<td>Range</td>
</tr>
<tr>
<td><strong>Sex--no. (%)</strong></td>
</tr>
<tr>
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<td><strong>Sites of disease--no. (%)</strong></td>
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Table 2 Change in Thyroglobulin Levels.

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<th>RECIST Response at 3 mo</th>
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<th>Before 148 MBq Iodine-131 scan (day 21)</th>
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<td>9</td>
<td>N</td>
<td>20.6</td>
<td>PD</td>
<td>14.5</td>
<td>16.5</td>
<td>23.2</td>
<td>30.80</td>
<td>60%</td>
<td>112%</td>
</tr>
<tr>
<td>10</td>
<td>Y</td>
<td>-17.6</td>
<td>SD</td>
<td>2.6</td>
<td>8.9</td>
<td>1</td>
<td>1</td>
<td>-62%</td>
<td>-62%</td>
</tr>
</tbody>
</table>

*TSH was administered on Days 21, 22, 35 and 36.
<table>
<thead>
<tr>
<th>Table 3. Adverse Events.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient</strong></td>
</tr>
<tr>
<td>Skin*</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Electrolyte**</td>
</tr>
<tr>
<td>Gastrointestinal****</td>
</tr>
<tr>
<td>PPE*****</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Epistaxis</td>
</tr>
<tr>
<td>Eye disorders*****</td>
</tr>
<tr>
<td>Cr increase</td>
</tr>
</tbody>
</table>

*darkening (2) actinic keratosis (2) verrucous keratosis (2) SCC (1) erythematous (1) papular (1) pinpoint (1) callus (1) pruritis (1) not specified (3) 
**hypocalcemia (2) hypophosphatemia (1) hyponatrema (1) hyperglycemia (1) 
***nausea (2) weight loss (2) poor appetite (1) cramping (1) dysphagia (1) constipation (1) 
****palmar-plantar erythrodysthesias 
*****watery eyes (1) kaleidoscope vision (1--preexisting) 

All toxicities were graded as mild (CTCAE v 4.0 grade 1) except for hypophosphatemia in patient 2 (severe but deemed unrelated to study drug), hypocalcemia in patient 7 (moderate) and PPE in patient 10 (moderate)
Redifferentiation of iodine-refractory BRAF V600E-mutant metastatic papillary thyroid cancer with dabrafenib.


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