Phase II Efficacy and Pharmacogenomic Study of Selumetinib (AZD6244; ARRY-142886) in Iodine-131 Refractory Papillary Thyroid Carcinoma with or without Follicular Elements

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Abstract

Purpose: A multicenter, open-label, phase II trial was conducted to evaluate the efficacy, safety, and tolerability of selumetinib in iodine-refractory papillary thyroid cancer (IRPTC).

Experimental Design: Patients with advanced IRPTC with or without follicular elements and documented disease progression within the preceding 12 months were eligible to receive selumetinib at a dose of 100 mg twice daily. The primary endpoint was objective response rate using Response Evaluation Criteria in Solid Tumors. Secondary endpoints were safety, overall survival, and progression-free survival (PFS). Tumor genotype including mutations in BRAF, NRAS, and HRAS was assessed.

Results: Best responses in 32 evaluable patients out of 39 enrolled were 1 partial response (3%), 21 stable disease (54%), and 11 progressive disease (28%). Disease stability maintenance occurred for 16 weeks in 49%, 24 weeks in 36%. Median PFS was 32 weeks. BRAF V600E mutants (12 of 26 evaluated, 46%) had a longer median PFS compared with patients with BRAF wild-type (WT) tumors (33 versus 11 weeks, respectively, HR = 0.6, not significant, P = 0.3). The most common adverse events and grades 3 to 4 toxicities included rash, fatigue, diarrhea, and peripheral edema. Two pulmonary deaths occurred in the study and were judged unlikely to be related to the study drug.

Conclusions: Selumetinib was well tolerated but the study was negative with regard to the primary outcome. Secondary analyses suggest that future studies of selumetinib and other mitogen-activated protein (MAP)/extracellular signal-regulated kinase (ERK; MEK) inhibitors in IRPTC should consider BRAF V600E mutation status in the trial design based on differential trends in outcome.

Introduction

The overall incidence of thyroid cancer in the United States rose at 5% to 6% annually from 1997 to 2006. New cases for 2009 are estimated at 37,200 (1). The prevalence is 410,404 and estimated deaths are 1,630 for 2009 (1). The most common type is papillary, comprising 70% to 80% of thyroid cancers. The prognosis is extremely good for papillary thyroid cancer (PTC) with overall 10-year survival rates of 98% (1–3). Once thyroid cancer is locally advanced or metastatic and no longer amenable to surgery, however, expected survival declines significantly (4, 5). The 10-year recurrence rate is 20% to 30% in high-risk patients, and approximately 5% will progress to radioiodine refractory disease. The 10-year survival rate is less than 15% (6, 7). Doxorubicin is the only U.S. Food and Drug Administration–approved therapy but is generally considered of low efficacy and high toxicity (8, 9).

Mutations in the mitogen-activated protein kinase (MAPK) signaling pathway involving the genes RET, BRAF, NTRK, and RAS have been reported in independent cohorts in up to 70% of patients with PTC (10–15). The high frequency and nonoverlapping nature of these mutational events suggests a high degree of dependency of thyroid
cancers on MAPK pathway signaling and its common downstream effectors, MEK1/2 [MAPK/extracellular signal-regulated kinase (ERK; MEK)]. Consequently, MEK inhibition represents a shared target for the common activating mutations in RET, RAS and BRAF that characterize PTC.

Selumetinib is a potent, selective, orally bioavailable, non-ATP competitive small-molecule inhibitor of the MAPK kinases, MEK-1/2. In vitro studies have shown that selumetinib and its N-desmethyl metabolite are potent and selective inhibitors of MEK (16, 17). Selumetinib was particularly potent in PTC cell lines with V600E BRAF gene mutation and some cell lines with RAS mutations (16–20).

In a phase 1 trial, oral selumetinib 100 mg twice daily was well tolerated with rash as the most frequent and dose-limiting toxicity. Most other adverse events were grade 1 or 2. Pharmacokinetics were less than dose proportional, with a median half-life of approximately 8 hours and inhibition of ERK phosphorylation in peripheral blood mononuclear cells at all dose levels. Nine patients had stable disease (SD) for 5 months or more, including one patient with thyroid cancer with SD for 19 months (21).

MEK inhibition with selumetinib represents a uniquely attractive therapeutic opportunity in patients with iodine-refractory papillary thyroid cancer (IRPTC) for whom there is no standard treatment. We conducted this phase 2 trial to determine the safety and efficacy of selumetinib in patients with IRPTC, including analyses of tumor genotype for mutations in BRAF, NRAS, and HRAS.

Materials and Methods

Patients

Patients eligible for this study had histologically or cytologically confirmed PTC with or without follicular elements with evidence for progressive disease (PD) that was no longer amenable to radioactive iodine therapy (iodine refractory) or curative surgical resection. Iodine refractory was defined as tumors that were no longer iodine avid, tumors that did not respond to the most recent radioactive iodine treatment, and patients who were ineligible for further radioactive iodine due to medical contraindications (e.g., lung toxicity). Disease progression had to be documented within the preceding 12 months by objective measurements on radiology evaluation. Progression as an entry criterion did not require that the change met Response Evaluation Criteria in Solid Tumors (RECIST) criteria (22). However, to be eligible, patients were required to have at least 1 RECIST-defined target lesion. There were no limitations on the number or nature of each patient’s prior therapies except as follows: at least 4 weeks elapsed since the most recent radiotherapy or chemotherapy (6 weeks for nitrosoureas or mitomycin C); and no prior treatments with tyrosine kinase inhibitors (TKI) that target RET, BRAF, or MEK. Other eligibility criteria included age more than 18 years; life expectancy more than 12 weeks; Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less; adequate hepatic, renal, and bone marrow function, and excluded HIV-positive patients on antiretroviral therapy and patients taking other simultaneous investigational agents, with known brain metastases, with QTc interval more than 450 msec, or other factors that increase the risk of QT prolongation or arrhythmic events and with uncontrolled intercurrent illness. Patients with refractory nausea and vomiting, chronic gastrointestinal diseases, or significant bowel resection that would preclude adequate absorption were also ineligible. Premenopausal women were required to have a negative pregnancy test and to avoid breastfeeding, and all patients of childbearing potential were required to use contraception. All patients provided written, informed consent before enrollment. The study protocol was approved by the Institutional Review Board at each of the participating centers and was carried out in accordance with the Declaration of Helsinki. The study was conducted and funded entirely through the National Cancer Institute’s Phase II Clinical Trials Consortium N01 mechanism except for the correlative studies which were supported by a grant from AstraZeneca.

Study design and endpoints

This study, NCI 7918, was conducted as an open-label, multi-institution, phase II study of selumetinib in IRPTC with or without follicular elements. Selumetinib was administered orally as a free base suspension at a dose of 100 mg twice daily for 28-day cycles. Those patients experiencing Common Terminology Criteria for Adverse Events (CTCAE) v3.0 grade 3 toxicity or worse had their dose reduced to 50 mg twice daily and then to 50 mg once
daily, if necessary. Selumetinib treatment was continued until disease progression, illness preventing further treatment, unacceptable toxicity, or patient withdrawal of consent. Disease progression was defined by RECIST. Patients were followed until disease progression, death, or for 2 years, whichever came first after removal from study. Patients removed from study for unacceptable adverse events were followed until resolution or stabilization of the adverse event. The primary endpoint was objective response (CR + PR), and secondary endpoints included progression-free survival (PFS), toxicity, and tumor genotyping. PFS is defined as the time from initiation of selumetinib to the date of progression or death.

Baseline evaluations including physical exam and laboratory assessments were done within 1 week prior to start of therapy. Scans and X-rays were done 4 weeks or less prior to selumetinib therapy. Physical exam and laboratories were repeated every 2 weeks for the first 6 weeks and then every 4 weeks thereafter. Radiographic tumor reassessments were carried out with RECIST every 8 weeks and at removal from study for PD. Confirmatory scans were obtained 4 weeks following initial documentation of objective response. Adverse events were reported and graded according to CTCAE v3.0.

Tumor genotyping

BRAF mutation testing was carried out by pyrosequencing. Previous investigators have confirmed that tissue from initial tumor resection is concordant with distant metastasis with regard to mutation genotype for BRAF in particular (10). For this reason, primary tumor was considered appropriate for tumor mutation testing. Formalin-fixed paraffin-embedded samples were macerated to enrich for tumor cells prior to DNA extraction. DNA was extracted by the QIAGEN DNeasy Tissue Extraction Kit from tissue embedded samples were macrodissected to enrich for appropriate for tumor mutation testing. Formalin-fixed paraffin-embedded samples were macerated to enrich for tumor cells prior to DNA extraction. DNA was extracted by the QIAGEN DNeasy Tissue Extraction Kit from tissue embedded samples were macrodissected to enrich for tumor cells prior to DNA extraction. DNA was extracted by the QIAGEN DNeasy Tissue Extraction Kit from tissue embedded samples were macrodissected to enrich for tumor cells prior to DNA extraction. DNA was extracted by the QIAGEN DNeasy Tissue Extraction Kit from tissue embedded samples were macrodissected to enrich for tumor cells prior to DNA extraction. DNA was extracted by the QIAGEN DNeasy Tissue Extraction Kit from tissue embedded samples were macrodissected to enrich for tumor cells prior to DNA extraction.

Pyrosequencing was carried out to identify the BRAF V600E mutation using the PyroMark BRAF RIO Kit (Qia-gen #40-0057), as per manufacturer instructions. PCR reactions were carried out on a Veriti thermal cycler (Applied Biosystems) and pyrosequencing was done on the PyroMark MD (Pyrosequencing AB). A positive control, normal control, and blank (no DNA template) PCR control were included in each assay. Pyrograms were analyzed by PyroMark 1.0 software with allele quantification mode to determine the percentage of mutant versus WT alleles according to relative peak height (23). Repeat genotyping of BRAF V600E and genotyping of NRAS Q61R, NRAS Q61K, and HRAS Q61R was carried out with PCR, and Pyrosequencing as previously described using the primer sets described by Volante and colleagues (24, 25).

Statistical analysis

A consensus standard of care for IRPTC does not exist. Historical data involving chemotherapy are difficult to interpret due to small sample sizes, retrospective reporting, inconsistent response assessment criteria, and lack of controls. A conservative estimate of the lower range of response rate of the best-studied agent in this disease, doxorubicin, is 5% using at least one published study (26). Therefore, we determined that selumetinib would be worthy of further evaluation if the response rate (CR + PR) were at least 20%. With a sample size of 32 patients, an exact binomial test with a nominal alpha = 0.1 (1-sided significance level) has 90% power to detect the difference between the null hypothesis proportion of 0.05 (or 5%) versus the alternative proportion of 0.20 (or 20%). Duration of response and PFS were assessed, and 95% CIs for the medians were provided. Differences in outcomes between patients with and without BRAF V600E mutation were assessed by Cox regression modeling. Demographic data were analyzed by summary statistics. Toxicities were reported as a proportion of patients with the event over the intention to treat population. All analyses were conducted with SPSS version 18 for Windows and the statistical programming language, R version 2.11.1.

Results

Patients

Between December 11, 2007 and June 30, 2009, 39 patients were enrolled and all were evaluable for toxicity from their first treatment with selumetinib. The number of evaluable patients for objective response, which was the primary endpoint of this study, was 32. These patients had measurable disease present at baseline and received at least one cycle of therapy and had a disease reevaluation. The demographics and baseline characteristics are summarized in Table 1. The median age of patients was 64 years (range, 37–86 years). The population was predominantly men (67%) and Caucasian (87%). Only 9 of 39 subjects (23%) had received prior systemic therapy. The majority of patients had an ECOG performance status of 0 or 1 (56% and 36%, respectively). The predominant age ranges at diagnosis for the evaluable patients were 40 to 49 (19%), 50 to 59 (28%), and 60 to 69 (22%). The number of patients over age 45 at diagnosis was 27 (69%). The time from original diagnosis to enrollment on trial was less than 5 years in 13 subjects (41%) and less than 2 years in 5 of these subjects (16%). When considering demographics based on BRAF V600E status (mutant vs. WT), more mutant patients were originally diagnosed at an age over 45 years (92 vs. 50%) but were similar in age at the time of study entry with a median age of 60 versus 56 years. Less prior systemic therapy (17 vs. 29%) was also noted in the patients with mutations versus the patients with tumors lacking defined mutations. The median time from diagnosis to initiation of selumetinib was similar in both groups (5 for mutant vs. 6 years for WT).

Efficacy and effectiveness

All analyses presented are based on intention to treat analysis (effectiveness) unless specifically stated otherwise. For the efficacy analyses only those patients who had measurable disease present at baseline, had received at least 1 cycle of therapy and had their disease reevaluated were considered evaluable for the primary endpoint of the study.
which was objective response. Seven (18%) enrolled patients were not evaluable. This was due to PD prior to completion of 1 cycle (1), adverse effects of therapy (1), withdrawal of consent prior to completion of 1 cycle (4), and no disease evaluation per protocol (1). The patient with PD prior to cycle 1 received less than 1 cycle of therapy and then was referred to hospice without disease reevaluation. By the protocol definitions, the patient was not evaluable but was considered to have PD for the intention to treat analysis. Table 2 shows the primary study outcome of objective response rate including 1 documented PR (3%), 21 SD (54%), and 11 PD (28%). One of the patients with SD met criteria for a PR but did not have confirmatory scans. PR + SD were seen in 57% at the initial evaluation. Stability of disease was maintained for 16 weeks in 49% of patients and in 36% at 24 weeks. Of the patients who obtained at least SD, the median duration of SD was 55 weeks (range, 3–98 weeks).

Figure 1 shows the percent change in size of the target lesions in patients with measurable disease. The mutational status for BRAF and NRAS is also identified in this figure for those patients with samples available for testing. Over half of the patients with measurable disease had a reduction in size of the target lesions from baseline.

Safety
The most common drug-related adverse events are summarized in Table 3 and included rash (77%), fatigue (49%), diarrhea (49%), and peripheral edema (5%). Fourteen patients required dose delays and 12 patients required dose reductions due to toxicity. Six enrolled patients (15%) discontinued treatment as a result of adverse events. In addition to the common toxicities listed above, 2 grade 3 toxicities occurred once during the study. One patient experienced a grade 3 episode of confusion that resolved spontaneously in cycle 1 of therapy. The patient was ultimately restarted on study drug without recurrence of the confusion. A second patient had a grade 3 cardiac event (takotsubo syndrome) possibly attributed to study drug after 3 cycles of therapy. The patient was withdrawn from the study when the symptoms returned after rechallenge with the drug. Four deaths occurred on study. Two of these patients were considered evaluable for response, and the causes of death were due to PD. The first patient completed 3.7 weeks of treatment and died with progression approximately 4 weeks after starting therapy. The second patient completed 1 cycle of therapy, was felt to have PD at the start of cycle 2 and died approximately 4 weeks later. Neither patient had BRAF or NRAS mutations. The other 2 deaths were due to pulmonary complications. The first patient who had a history of bilateral pulmonary metastases developed bilateral pneumonia and was treated emergently at an outside facility that never returned records for further clarification. The death occurred in cycle 2 of therapy and was felt by study investigators to be unrelated to the study drug. A second patient had a history of trachea-esophageal fistula and developed a cavitary pneumonia in cycle 1 of therapy that was felt to be unlikely to be related to the study drug.
Pulmonary toxicities have previously been reported in studies of selumetinib, but as in the current trial, the causality is undetermined.

Tumor genotype and survival analyses

Tissue samples were obtained from 26 of 32 evaluable patients. Most of these samples were from the date of the original diagnosis. BRAF mutation testing was carried out by pyrosequencing, and 12 of 26 (46%) samples were positive. The 2 patients with the greatest reduction in tumor volume (one partial responder and one unconfirmed partial responder) had documented BRAF V600E mutations. Genotypes passing quality assurances were obtained for all patients who provided tissue. Failure to obtain a genotype was entirely due to lack of tumor tissue. For example, in at least one case no tumor remained in the blocks that were

Table 2. Patient response and treatment status

<table>
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Evaluable patients

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Reason off study

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<td>3</td>
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<td>3</td>
<td></td>
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Abbreviations: CR, complete response; PR, partial response.

Figure 1. Percent change in target lesions by mutational status for BRAF and NRAS. The mutation status was unavailable if not shown.
received for genotyping. In other cases, no surgical blocks were retained from the primary surgery, the blocks could not be located, or the outside referring hospital failed to return repeated requests for the blocks.

Figure 2A shows the Kaplan–Meier curve for PFS. The median PFS for all patients was 32 weeks (95% CI = 8.4–56 weeks). The median length of treatment for all patients was 13 weeks (range: 0.3–98). This figure also reveals that patients with tumors containing the BRAF V600E genotype (12 of 26) had an improved median PFS of 33 weeks (95% CI = 30–35 weeks) compared with a median PFS of 11 weeks (95% CI = 5–16 weeks) in patients with tumors lacking this mutation, although this comparison did not reach statistical significance with CIs overlapping throughout the follow-up period (HR = 0.6, P = 0.3, 95% CI = 0.22–1.6).

To evaluate the possibility that BRAF mutation status might convey prognostic significance, and partially explain the difference in treatment outcomes by mutation status, we investigated the time from initial diagnosis to the time of initiation of therapy on the clinical trial (Fig. 2B). There was no difference according to mutation status, supporting the difference in time to progression as a function of differential response to selumetinib by mutation status.

Genotyping was also carried out for NRAS Q61K, NRAS Q61R, and HRAS Q61R. The samples were all negative for the NRAS Q61K and HRAS Q61R mutations. A single tumor specimen was positive for the NRAS Q61R genotype; it was negative for the BRAF V600E mutation and the best response in this patient was PD.

Discussion

Patients with PTC have few therapeutic options once surgery and radiotherapy (including radioactive iodine) have proven ineffective. There are currently no approved standards of care for patients in this setting. Although there are significant data about activation of oncogenic pathways mediated through MEK in PTC, until recently there was a paucity of agents available that target these proteins.
In this trial of selumetinib, a small-molecule inhibitor of the MAPK kinases MEK-1/2, the primary endpoint of an overall response rate of at least 20% in patients with IRPTC was not met. It is potentially useful to put the results of this study into the context of other recent clinical trials of IRPTC, with the caveat that direct comparison of phase II trials should be undertaken with caution (Table 4). A direct comparison is challenging because of small sample sizes, differences in the underlying risk of heterogeneous patient populations across studies, as well as any true differences in the effectiveness of the therapies under study. Allowing for these concerns, we report a distinctly lower objective response rate in the current trial of selumetinib compared with other TKIs recently studied. In addition, PD as “best response” was seen at rates that are 3 times the rate of other studies of IRPTC reported in Table 4. There were no complete responses reported in any of the studies. At the same time, using a modified definition of clinical benefit to standardize across studies (CB = CR + PR + SD) has been previously suggested, selumetinib compares more favorably with other recent studies with CB of 57% versus published rates of 61% to 81% (27). Although IRPTC studies generally report SD outcomes, it is worth recalling that the natural history of the disease is frequently characterized by prolonged periods of slow progression. In other words, reporting SD might overstate the activity of the therapy. To overcome this challenge to the evaluation of thyroid cancer therapy, 3 of the 4 studies included only patients with documented evidence of progression within the last 6 to 12 months (to enrich for actively progressing patients) and additionally reported outcomes for patients who attained longer periods of disease stabilization. Using prolonged SD measures as reported by other investigators, we observed 36% of patients with SD lasting over 24 weeks which compares favorably with the SD proportions with axitinib (38% over 16 weeks), sorafenib (53% from 14–89 weeks), and motesanib (33% over 24 weeks; refs. 27–29). Similar to the case for response rates, patients treated with selumetinib showed PFS rates that were shorter than for the 3 comparator studies. PFS in the current trial was short even for the group with the most favorable outcomes, the BRAF-mutant tumors (33 versus 40 weeks for motesanib). Survival in the BRAF WT patients was strikingly reduced compared with historic controls at a median of 11 weeks. We therefore conclude that there is little evidence going forward to suggest any benefit of selumetinib in BRAF WT tumors. In terms of best response to therapy, we note that only 2 of 9 (22%) patients who had PD as their best response exhibited a mutation in BRAF whereas 10 of 17 (59%) patients who attained SD or better had mutations.

There are at least 3 plausible explanations as to the differences in outcomes between the phase II studies described in Table 4. First, all 4 studies are small phase II trials and differences may simply relate to statistical chance or sampling in the setting of heterogeneous patient populations. Interestingly, all 4 studies document a fairly large fraction of patients who are not evaluable: 25%, 21%, 12%, and 15% for axitinib, sorafenib, motesanib, and selumetinib, respectively. Therefore, some variability in the underlying rates could be accounted for simply by missing data. Chance and missing data alone are unlikely to explain the consistent pattern of inferior outcomes in the current study of selumetinib. Next, we suggest that differences in outcomes could relate in part to differences in underlying risk factors between the patients treated on the different studies. There is evidence that underlying risks are different between the trials by considering known or suspected risk factors for poor outcome in IRPTC as shown in Table 4. For example, patients in the current trial were diagnosed with thyroid cancer much more remotely in the past (8.6 years) than patients in the motesanib trial (4.4 years), the only other study that reported data on duration of disease. BRAF WT patients, those with the most unfavorable outcomes had even longer times since their original diagnosis, 9.6 years.

Table 4. Comparative data for kinase inhibitors in thyroid cancer

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Sorafenib(a)</th>
<th>Axitinib(b)</th>
<th>Motesanib(b)</th>
<th>Selumetinib</th>
</tr>
</thead>
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<tr>
<td>Median age, y</td>
<td>63 (31–89)</td>
<td>59 (26–84)</td>
<td>62 (36–81)</td>
<td>64 (37–86)</td>
</tr>
<tr>
<td>Male, %</td>
<td>50</td>
<td>58</td>
<td>53</td>
<td>67</td>
</tr>
<tr>
<td>Prior systemic therapy, %</td>
<td>17</td>
<td>39</td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td>Median time from original diagnosis, y</td>
<td>4.4 (0.4–21.3)</td>
<td>8.6 (0.3–16.9)</td>
<td></td>
<td></td>
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<tr>
<td>Thyroid cancer subtype, papillary, %</td>
<td>60</td>
<td>50</td>
<td>61</td>
<td>100</td>
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<tr>
<td>Thyroid cancer subtype, papillary or follicular, %</td>
<td>90</td>
<td>75</td>
<td>96</td>
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</tr>
<tr>
<td>Clinical benefit (CR + PR + SD), %</td>
<td>76</td>
<td>68</td>
<td>81</td>
<td>57</td>
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<tr>
<td>CR, %</td>
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<tr>
<td>PR, %</td>
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<td>SD, %</td>
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<td>PD, %</td>
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Abbreviations: CR, complete response; PR, partial response.
(a)Study required PD using RECIST.

References
Although the impact of years since diagnosis is not an established stratification variable for IRPTC, it is at least plausible that patients farther into their disease course might be expected to have overall worse outcomes including rapid progression. Other factors including patient age and particularly male gender are reported to convey increased risk in IRPTC and were the most unfavorably represented in the current cohort relative to the 3 comparators (30). Finally, a plausible explanation for differences in outcomes across the studies is differences in the effectiveness of therapies. Certainly, there is no support in the current trial that selumetinib is as effective as the other agents considered, although such a comparison is not specifically relevant because its reported mechanism of action is different than that of the other TKIs. There is a distinct possibility that the drug is of low clinical potency overall in this disease and alternate inhibitors of MEK or BRAF might be more effective in targeting IRPTC. Finally, as with any phase II study without a placebo arm, particularly in which outcomes might be worse than one would generally anticipate, one must always be concerned that the therapy was detrimental to patient outcomes in some cases.

The toxicity profile of selumetinib compares favorably with other novel agents and to conventional chemotherapy. The most common side effects of selumetinib consisted of rash, fatigue, diarrhea, and peripheral edema. Only a small proportion of patients experiencing these side effects developed grades 3 to 4 toxicities. Only 16% of patients discontinued selumetinib therapy due to adverse events. Reported objective response rates have been greater in recent studies in advanced thyroid cancer of agents (axitinib, motesanib, sorafenib, and sunitinib) that target the vascular endothelial growth factor receptor (VEGFR) compared with agents such as selumetinib and gefitinib that do not target the VEGFR (27–29, 31, 32). This observation suggests that angiogenesis may be more important in progression of disease than signaling pathways known to be activated in the tumor such as RAS/RAF/MAPK activation.

This study reports mutation rates which are largely in line with data reported by at least one large repository of mutation data, the Catalogue of Somatic Mutations in Cancer (COSMIC, http://www.sanger.ac.uk/genetics/CGP/cosmic/ accessed November 1, 2011). Comparing rates from this study to previous reports show BRAF rates equal to the public repository at 46% in both cases. We observed NRAS in 1 of 26 (4%) and HRAS in 0 of 26 samples genotyped, which is lower than the 6% and 3% rate, respectively in COSMIC but within sampling error given the small study size. The recent motesanib trial genotyped 30 patients and reported a lower BRAF mutation rate of 30%, with HRAS 3%, and NRAS 12%. Again, while small sample size alone could explain any discrepancies, other factors such as different proportions of the morphologic variants of thyroid cancer included in the studies (i.e., follicular variant of PTC) might impact the mutation rates. Although morphology was an inclusion criterion in the study, details of morphology variants were not incorporated into the analysis plan and were therefore not systematically recorded. Future studies might consider more carefully the interactions of morphologic variants, genotypes, and outcome parameters.

When stratified by BRAF mutation status, patients with the V600E mutation show median PFS nearly 3 times that of patients with the WT allele (33 vs. 11 weeks, not statistically significant). By contrast, the time from the original diagnosis of PTC to the initiation of selumetinib therapy does not appear to be affected by the mutational status for BRAF. This offers additional evidence that the differences in outcomes observed in our study are related to the predictive nature of the BRAF V600E mutation in response to therapy rather than its prognostic significance.

The role of BRAF mutation in determining the response to targeted therapy has recently received increasing attention. This is of great relevance in cancers such as PTC in which the V600E mutation is observed in a median of 52% of cases (37%–73%) for studies reporting data on mutation frequency, and melanoma in which BRAF is mutated in 50% to 60% of advanced cases (14, 33–39). In a recent phase II study of selumetinib in advanced melanoma, a mutated BRAF status conferred a more favorable outcome. More strikingly, a recently completed phase I trial of the BRAF inhibitor PLX4032 in metastatic melanoma resulted in complete or partial tumor regression in the majority of patients carrying the BRAF V600E mutation (40). Unfortunately, the objective responses in PTC have not been as striking and may be explained by involvement of additional mutations of cell signaling pathways. For example, late acquisition of mutations in PIK3CA or AKT1 during tumor progression in thyroid cancer has been reported in some cases (10). When present, PIK3CA/AKT1 mutations would suggest coactivation of MAPK and PI3K in disease progression. Experimental compounds targeting effectors in the PI3K/AKT/mTOR pathway are being developed and could be considered in combination with a MEK inhibitor to improve response rates in future studies of thyroid cancer (41).

In conclusion, the selective MEK inhibitor selumetinib is well tolerated but the study was negative with regard to its primary endpoint. The drug showed modest activity at best as a single agent in unselected patients with PTC, mainly reflected as SD. When considering BRAF genotype, patients with tumors containing BRAF V600E mutations showed a trend (statistically not significant) to benefit preferentially although the best response was prolonged SD. The notable difference in outcome according to BRAF mutation status strongly suggests that future studies of selumetinib and other MEK inhibitors should consider BRAF genotyping in the design and analysis.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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