Multi-Institutional Phase II Study of Selumetinib in Patients With Metastatic Biliary Cancers

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ABSTRACT

Purpose

Biliary cancers (BCs) carry a poor prognosis, but targeting the RAS/RAF/mitogen-activated protein kinase kinase (MEK)/extracellular signal-related kinase (ERK) pathway is of significance. Selumetinib is an inhibitor of MEK1/2, so this trial was designed to determine the safety and efficacy of selumetinib in BC.

Patients and Methods

This was a multi-institutional phase II study of selumetinib at 100 mg given orally twice per day to patients with advanced BC. The primary end point was response rate. All patients were required to provide tissue before enrolling. The levels of phosphorylated ERK (pERK) and AKT (pAKT) were assessed by immunohistochemistry. Tumors were genotyped for the presence of *BRAF*- and/or *RAS*-activating mutations.

Results

Twenty-eight eligible patients with a median age of 55.6 years were enrolled. Thirty-nine percent of patients had received one prior systemic therapy. Three patients (12%) had a confirmed objective response. Another 17 patients (68%) experienced stable disease (SD), 14 of whom (56%) experienced prolonged SD (> 16 weeks). Patients gained an average nonfluid weight of 8.6 pounds. Median progression-free survival was 3.7 months (95% CI, 3.5 to 4.9) and median overall survival was 9.8 months (95% CI, 5.97 to not available). Toxicities were mild, with rash (90%) and xerostomia (54%) being most frequent. Only one patient experienced grade 4 toxicity (fatigue). All patients had tissue available for analysis. No *BRAF* V600E mutations were found. Two patients with short-lived SD had *KRAS* mutations. Absence of pERK staining was associated with lack of response.

Conclusion

Selumetinib displays interesting activity and acceptable tolerability in patients with metastatic BC. Our results warrant further evaluation of selumetinib in patients with metastatic BC.

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INTRODUCTION

Biliary cancers (BCs) are the second most common primary liver cancers.¹ The tumor arises from the ductular epithelium of the biliary tree within the liver (intrahepatic), the extrahepatic ducts (extrahepatic), or the gallbladder.² Intrahepatic cancer is steadily increasing in the Western world.^{1,2} Most patients present with advanced disease and die within a few months of diagnosis because of severe cachexia.² Survival rate at 5 years is less than 5% and has remained unchanged for 30 years. Historically, there has been no satisfactory treatment available for patients with metastatic BC; patients faced a low

response rate and poor survival.²⁻⁴ A recent phase II/III randomized study (Advanced Biliary Cancer [ABC] 01/02) suggested a superior outcome when cisplatin was added to gemcitabine versus gemcitabine alone.⁵ A subgroup analysis suggested that the observed advantage might be derived from the large proportion of patients (25%) with locally advanced disease.⁵

The RAS/RAF/MEK/ERK signaling pathway plays a central role in the regulation of cellular processes, including proliferation, apoptosis, and metabolism.^{6,7} This pathway is one of the most important and best understood mitogen-activated protein (MAP) kinase signal transduction pathways and is activated by a diverse group

of extracellular signals, including growth factor receptors (eg, epidermal growth factor receptor, platelet-derived growth factor receptor) and cytokines.⁸ Activated RAS triggers the phosphorylation and activation of the RAF kinase, which then phosphorylates MEK1 and MEK2 on two serine residues.⁹ Activated MEK phosphorylates its only known substrates: ERK1 and ERK2. Phosphorylated ERK (pERK) dimerizes and translocates to the nucleus,¹⁰ where it is involved in several important cellular functions.

RAS and BRAF mutations are rarely found together in tumors, and this absence of overlap implies an important role for the RAS/RAF/MEK cascade in tumor formation.^{11,12} Although RAS mutations do not clearly determine whether a cell line will be sensitive to MEK inhibition, BRAF mutations are frequently associated with the more sensitive phenotype¹³ and may constitute a key survival mechanism for those cells.¹⁴ Selumetinib (AZD6244, ARRY-142886; AstraZeneca, Manchester, United Kingdom) is a second-generation, potent, selective, orally available, and uncompetitive small molecule inhibitor of the MAP kinase, MEK1/2.¹⁵ Selumetinib's activity was examined in a panel of human cancer cell lines that showed broad activity, particularly in lines containing the BRAF V600E-activating mutation.¹⁶

There is evidence that the frequencies of mutations of RAS and RAF in BC are distinctly different. In one study evaluating 69 patients with BC, 31 (45%) and 15 (22%) had KRAS mutations or V600E BRAF missense mutation, respectively; no patients had both.¹⁷ Mutations of the RAS genes have been observed in 10% to 57% of gallbladder carcinomas.¹⁸ In one study from Greece, mutations were observed in seven (335) of 21 gallbladder carcinomas.¹⁹ In another study, the V600E somatic mutation of BRAF was absent in all 62 archival biliary tract cancers analyzed.²⁰

Considering these findings, we hypothesized that selumetinib would be active in patients with advanced BC. We also hypothesized that beneficial clinical effects of selumetinib would correlate with the presence of activating mutations in BRAF, activation of ERK, and/or lack of activation of the AKT pathway. We conducted and report here a phase II study of single-agent selumetinib in BC to evaluate its efficacy and tolerability at a dose of 100 mg given orally twice daily.

PATIENTS AND METHODS

Eligible patients were required to have histologically confirmed advanced biliary tract carcinoma. All patients were required to have either fresh or paraffin-embedded tissue from tumor blocks before enrolling onto the study. Patients had to have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST),²¹ ≤ 1 prior systemic anticancer therapy; patients with prior cryotherapy, radiofrequency ablation, ethanol injection, transarterial chemoembolization, or photodynamic therapy were included provided that greater than 6 weeks had elapsed and indicator lesion(s) were outside the area of prior treatment. Additional criteria included life expectancy ≥ 12 weeks, Eastern Cooperative Oncology Group performance status of less than 2, and the ability to take and absorb oral medications. Patients had to have normal organ function, including total bilirubin ≤ 2 times the upper limit of normal and AST/ALT ≤ 3 times the upper limit of normal. Selected exclusion criteria included prior treatment with MEK inhibitors or sorafenib; major surgery within three weeks; brain metastases; history of malignancy other than BC within the previous three years except for adequately treated basal cell carcinoma, squamous cell cancer, or carcinoma of the cervix; uncontrolled intercurrent illness;

pregnancy; HIV infection; QT interval greater than 500 milliseconds; and concomitant medication that can prolong the QT interval.

Study Design

This was a National Cancer Institute (NCI)/Cancer Therapy Evaluation Program (CTEP)–sponsored phase II, open label, multicenter trial led by The Ohio State University with the participation of Vanderbilt University, Emory University, and University of North Carolina. Selumetinib was provided by NCI/CTEP. The primary objective of this study was to determine the overall response rate (complete response and partial response) as defined by RECIST.²¹ Tissue samples were required from all patients before enrollment. Secondary objectives included evaluation of toxicity, overall survival (OS), progression-free survival (PFS), assessment of BRAF and KRAS mutations and measurement of pERK and pAKT as indicators for the activation of relevant pathways.

Selumetinib Administration and Dose Modifications

The starting dose and schedule of selumetinib was 100 mg given orally twice daily in a mix and drink formulation in 28-day cycles without interruption. Treatment was administered on an outpatient basis. The two parts of the formulation were selumetinib, supplied as a powder in glass bottles/vials, and an aqueous solution of the Captisol vehicle (Cydex Pharmaceuticals, Lenexa, KS), which was mixed and reconstituted as a suspension immediately before use. There were two levels of dose reductions planned (50 mg twice per day and 50 mg once per day) with patients taken off the study for additional dose reductions.

Assessment of Response and Toxicity

Radiologic assessment was done by computed tomography or magnetic resonance imaging (as long as the same consistent measure was used serially) every 8 weeks, and responses were measured according to RECIST.²¹ Toxicities were defined by the NCI–Common Terminology Criteria of Adverse Events version 3.0.

Correlative Studies

Tissue samples. Formalin-fixed/paraffin-embedded (FFPE) or fresh frozen tissue samples were obtained from all patients before treatment. Portions of fresh frozen tissue were later fixed in formalin and paraffin embedded. Slides of 4 or 10 μ m were prepared from FFPE blocks and used for immunohistochemistry or DNA extraction, respectively. From each paraffin block, one or more sections was stained with hematoxylin and eosin, and tumor-containing regions were identified by a pathologist.

Immunohistochemistry

FFPE tissue blocks were stained for pAKT and pERK as previously described.²² Briefly, FFPE tissue sections were dewaxed, soaked in alcohol, and incubated in hydrogen peroxide after microwaving in antigen-unmasking solution (Vector Lab, Burlingame, CA). Samples were then incubated with anti-pAKT (Ser473 specific) or anti-pERK (Thr 202/Tyr 204) antibodies from Cell Signaling Technology (Beverly, MA). Staining was performed with the Vectastain Universal Quick Kit (Vector Lab) using the manufacturer's protocol. Negative controls were produced with omission of primary antibodies, and positive controls included tissue samples previously examined and identified as positive for pAKT or pERK. Staining was scored (scale 0 to 3) by four independent investigators in a blinded review.

DNA Extraction and Genotyping

FFPE tissue was scraped from slides and placed into 200 μ L 0.5% Tween 20. Samples were heated to 90°C for 10 minutes and then digested with proteinase K (0.2 mg/mL) at 55°C for 3 hours. After digestion, 400 μ L of 5% Chelex 100 (Bio-Rad, Hercules, CA) in Tris-EDTA was added, and samples were heated to 99°C for 10 minutes followed by centrifugation at 4°C and 10,500 rotations per minute for 15 minutes. Supernatants were extracted with chloroform before ethanol precipitation of DNA. Extracted genomic DNA was quantified and evaluated for KRAS and BRAF mutations. DNA Extraction and allele-specific polymerase chain reaction mutational assays (using KRAS and BRAF kits [DxS, Manchester, United Kingdom]) were conducted at AstraZeneca in the United Kingdom to identify KRAS (G12C, A, D, V, S, R, G13D) and BRAF (V600E) mutational status.

Statistical Methods

Simon's two-stage minimax design was used; the true overall response rate was set at 10% and 30%, respectively, under null and alternative hypothesis. With type I and type II error rates both at 10%, a total of 25 evaluable patients were needed. If two or more responses were seen in the 16 patients from the first stage, the study would proceed to the second stage. If more than four responses were observed in the whole cohort, the agent would be considered promising. If efficacy goals were met in the first two stages, an additional 10 evaluable patients were to be treated to allow the evaluation of correlative end points with adequate statistical power. The Kaplan-Meier method was used to analyze data on secondary end points including PFS and OS. For each patient, the staining scores for pERK or pAKT from four raters were averaged and then dichotomized. For different subgroups created based on baseline pERK or pAKT status, median PFS and OS, together with their 95% CIs, were reported. Group difference was assessed with log-rank test. All data analyses were conducted using SAS (SAS/STAT User's Guide, Version 9, 1990; SAS Institute, Cary, NC). *P* values less than .05 were considered statistically significant.

RESULTS

Patient Characteristics

Twenty-nine patients were enrolled between December 2007 and January 2009. Patient characteristics are listed in Table 1. Of the 29 patients enrolled, 25 were evaluable for response. One patient was found to be ineligible, because of an incorrect diagnosis on pathologic review, and was removed from study 2 weeks after therapy. All remaining 28 patients were evaluable for toxicity and survival analysis (Fig 1). Representing the majority of patients enrolled onto the study, 17 (61%) had intrahepatic cholangiocarcinoma. Eleven (39%) had exposure to prior chemotherapy. All patients had metastatic disease, and the average number of target lesions was 4. As of August 2010, there were no patients treated on the study, and seven patients were alive.

Treatment Toxicity

The most common toxicities (Table 2) included rash (90%), xerostomia (54%), and nausea (51%). Most toxicities were grade 1 or 2. Only one patient suffered grade 4 toxicity (fatigue). No ocular toxicities were reported. All toxicities were manageable and reversible. Only 14% (4 of 28) of patients required dose reductions because of grade 3 fatigue, diarrhea, rash, or cellulitis.

Treatment Efficacy

A median of 4 cycles were administered per patient (range, 1 to 16). Three patients had an objective response, including three with confirmed partial response (one of those had an unconfirmed complete response; Table 3). Seventeen patients (68%) experienced stable disease (SD), including 11 (44%) with SD duration $\geq$ 16 weeks and three (12%) with duration of more than 1 year. Study radiographs and responses were independently reviewed and found acceptable by CTEP. Median PFS (mPFS) was 3.7 months (95% CI, 3.5 to 4.9), and median OS (mOS) was 9.8 months (95% CI, 5.97 to not available; Fig 2). Figure 3 shows that the majority of patients (52%) experienced target lesion decrease. There was no correlation between rash or CA 19-9 levels with efficacy parameters. Exposure to prior therapy did not seem to influence the rate or duration of response. OS was lower for patients with prior exposure to therapy versus for patients with no

Table 1. Patient Demographics and Characteristics

Characteristic	No. of Patients (n = 28*)
Sex	
Male	19
Female	9
Age, years	
Median	55.6
Range	26-79
Race/ethnicity	
White	27
African American	1
ECOG performance status	
0	11
1	17
Prior treatment	
X-ray treatment	4
Surgery	8
Chemotherapy	11
Metastatic	7
Adjuvant	4
Gemcitabine-based	8
Other†	3
Biologic therapy‡	2
Biliary drainage/stenting	4
Disease site	
Intrahepatic	17
Gallbladder	7
Extrahepatic	4
Metastasis site	
Liver only	7
Liver and other§	16
Other¶	5
Number of target lesions	
Average	4
Range	1-13

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
 *Total of 29; one patient found ineligible after starting therapy and removed after review as a result of incorrect pathologic diagnosis.
 †Includes oxaliplatin, irinotecan, or capecitabine.
 ‡Includes sunitinib and bevacizumab.
 §Includes lymph nodes, soft tissue, gallbladder fossa, lung, pericolic, peritoneal, adrenal gland, and pancreas.
 ¶Includes soft tissue, lymph nodes, and lungs.

prior exposure (5.43 v 18.1 months). Patients receiving selumetinib on this study experienced an average of 5% confirmed nonfluid weight gain (results are being published separately).

Biologic Markers

Tissue specimens were available for all patients (n = 28). One sample for a patient with a best response of SD was found to contain insufficient tumor for correlative studies.

Immunohistochemistry Analysis of pERK and pAKT

Staining for pAKT and pERK were evaluated in tumor samples from 27 individual patients. Independent scoring from four investigators ranged from 0 to 3 for pERK and pAKT (0 indicated no staining for the specific marker), and mean scores were calculated. The intraclass correlation coefficient between raters was 0.963 for pAKT and 0.977 for pERK, which suggests good agreement. There was no correlation between absent or low versus high

Fig 1. CONSORT diagram.

pAKT or pERK status (average score, < 1 v ≥ 1) and mPFS. There was a numeric advantage with mOS with pERK ≥ 1 or pAKT ≥ 1 compared with pERK less than 1 or pAKT less than 1, although the difference did not reach statistical significance (Table 3). Because tumors with an average score between 0 and 1 had some scores of 0 and others higher, we also analyzed the data when grouping the samples as no detectable immunostaining (scored 0 by all reviewers) versus having detectable immunostaining. When analyzed in this manner, positive immunostaining for pERK was associated with improved OS ($P = .0083$, Appendix Tables A1 and A2, online only). It is notable that none of the 11 patients with pERK scores less than 1 were responders, and four of five patients with progressive disease were included in this group (Table 4). Representative immunohistochemistry results are shown in Appendix Figure A1 (online only).

Table 2. Common Toxicities (n = 28)

Toxicity	All Toxicities (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Rash	90	68	18	4	0
Xerostomia	54	25	29	0	0
Nausea	51	39	4	8	0
Vomiting	50	25	21	4	0
Fatigue	49	25	16	4	4
Diarrhea	45	4	25	16	0
Bloating	43	18	21	4	0
Dry skin	40	32	8	0	0
Dysgeusia	29	21	8	0	0
Mucositis	24	16	8	0	0
Flatulence	20	16	4	0	0
Thrombocytopenia	12	8	4	0	0
Pruritus	16	12	4	0	0
Alopecia	12	12	0	0	0
Hypokalemia	12	8	4	0	0

Table 3. Efficacy Results

Result	No. of Patients	%
Response*		
Overall response rate	3	12
Complete response	0	0
Partial response†	3	12
Stable disease	17	68
Stable disease > 16 weeks	14	56
Progressive disease	5	20
Nonevaluable	3	12
mPFS, months	3.7	
95% CI	3.5 to 4.9	
pAKT < 1	3.6	
pAKT ≥ 1	3.7‡	
pERK < 1	3.5	
pERK ≥ 1	3.7§	
mOS, months	9.8	
95% CI	5.97 to NA	
pAKT < 1	6.5	
pAKT ≥ 1	9.9¶	
pERK < 1	5.4	
pERK ≥ 1	11.4	
Weight gain, pounds#		
Mean	8.6	
Range	1.0-33.0	

NOTE. Only 25 patients were evaluable for response; 28 were evaluable for PFS and OS.

Abbreviations: mPFS, median progression free survival; mOS, median overall survival; pAKT, phosphorylated AKT; pERK, phosphorylated ERK; NA, not available; CTEP, Cancer Therapy Evaluation Program.

*All responses were independently confirmed by CTEP.

†All partial responses were confirmed. One patient experienced an unconfirmed complete response.

‡ $P = .5$.

§ $P = .4$.

¶ $P = .8$.

|| $P = .5$.

#All 25 evaluable patients experienced weight gain.

Mutational Analysis of BRAF and KRAS

One or more slides (10 μ m) from each block was used for DNA extraction and genotyping. Slides from 28 individuals were genotyped for *BRAF* and *KRAS* mutations. *BRAF* evaluation was successful on all 28 samples, and 25 of 28 samples were sufficient for *KRAS*. All samples had wild-type *BRAF* sequencing. Of the 25 samples successfully evaluated for *KRAS* G12/13X mutations, two were positive, which indicates the presence of G12S and G12D mutations.

DISCUSSION

BC remains a challenging cancer. The rationale for this study was based on the demonstration of a potential role for *BRAF* and *KRAS* signaling pathways in the carcinogenesis of BC. Results from this study reveal interesting activity for selumetinib as a single agent in this patient population with metastatic BC that included patients (39%) with prior exposure to systemic therapy. There were three objective responses and another 14 patients with meaningful SD. Additionally, both mPFS and mOS compare favorably with published historical controls.²⁻⁵ Consistent with the PFS and response results was the target lesion decrease in 52% of patients as shown in Figure 3.

Fig 2. Kaplan-Meier plots for overall survival (OS) and progression-free survival (PFS). mOS, median OS; NA, not available; mPFS, median PFS.

Selumetinib was fairly well tolerated with predominantly GI and cutaneous toxicities. Fourteen percent of treated patients required dose reduction for grade 3 diarrhea, fatigue, rash, or cellulitis. We did not observe any ocular toxicity with this MEK inhibitor.

In our population, no patients had a *BRAF* V600E mutation, and there was a low occurrence (approximately 8%) of *KRAS* G12/13X mutations. Although other published studies suggest these mutations can be found in up to 60% of patients with BC,¹⁷⁻²⁰ our study is the only prospective analysis of *BRAF/KRAS* mutational status in this patient population in the United States. Several published studies suggest that the presence of an activating mutation of *BRAF* in cancer cell lines predicts sensitivity to MEK inhibition in vitro. In our study and despite the presence of several patients who experienced clinical benefit, there were no *BRAF* V600E mutations. Of note, our study included a larger proportion of patients with intrahepatic disease compared with the general population of BC patients. This could limit the generalizability of our findings, including the interpretation of the molecular correlates, especially the mutational analyses.

Fig 3. Waterfall plot showing maximum percentage decrease in target lesions. (*) Patients with 0% change as maximum response. PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response.

Table 4. Results for Immunohistochemistry, Response, PFS, and OS

Patient ID	Best Response	PFS (months)	OS (months)	Mean pAKT Score*	Mean pERK Score*
1	SD	14.7	31.0†	0.5	0.75
2	PD	1.6	5.4	1.0	0.5
3	SD	4.9	7.6	2.25	0.0
4	NE	1.4	2.1	0.25	0.25
5	PD	1.2	2.1	1.5	0.0
6	SD	9.1	23.1	2.75	3.0
7	PR	4.4	8.2	1.0	1.0
8	NE	NE	10.0	2.0	1.0
9	PD	1.7	2.8	1.5	0.0
10	SD	3.6	23.3	0.0	0.875
11	SD	3.5	23.4†	0.0	0.625
12	PD	1.1	1.5	0.0	0.0
13	SD	3.7	6.5	0.0	0.0
14	PR	10.3	24.4†	1.5	2.0
15	SD	11.5	23.5†	2.25	2.75
16	SD	14.9	18.0	3.0	2.0
17	NE	NE	0.5	2.75	3.0
18	SD	13.0	22.0†	NA	NA
19	SD	3.4	11.5	1.0	1.0
20	PR	3.5	6.0	2.0	2.875
21	PD	2.0	19.4	1.125	2.625
22	SD	3.7	9.8	3.0	2.5
23	SD	2.7	19.2†	0.75	1.0
24	SD	4.1	5.0	0.5	0.25
25	SD	4.1	11.3	0.5	2.0
26	SD	3.7	18.9†	1.25	2.875
27	SD	3.9	4.8	0.0	1.5
28	SD	2.4	2.4	0.875	2.25

NOTE. Patients with PD are shown in bold.

Abbreviations: PFS, progression-free survival; OS, overall survival; pAKT, phosphorylated AKT; pERK, phosphorylated ERK; SD, stable disease; PD, progressive disease; NE, nonevaluable; NA, not available.

*Mean pAKT and pERK scores were based on four blinded and independent readings of immunohistochemistry slides.

†Patient still alive.

Another finding in our study was the lack of a clear correlation between pERK or pAKT immunostaining and mPFS. Interestingly, patients with pERK score lower than 1 included 80% of patients whose disease progressed and none of the patients who experienced objective response. In addition, OS was lower in patients in whom pERK immunostaining was absent. Patients with pERK ≥ 1 or pAKT ≥ 1 had an improved but not statistically significant survival advantage. These findings raise the possibility that pERK and/or pAKT may have prognostic but not predictive relevance and suggest that tumor sample AKT activity may not predict resistance. We recognize that immunohistochemistry is qualitative and that staining can be heterogeneous. However, it is important to note that the agreement in scores between the independent observers was high and tissue samples were available from 95% of study patients, including every patient who experienced objective response or whose disease progressed. Given the exploratory nature of the correlative analyses and the limitation of such analyses in the setting of a small sample size, additional studies using robust and more objective measures are needed to confirm this potentially important finding. Finally, sequential biopsies in patients on therapy were not available to confirm pharmacodynamic inhibition of ERK activation.

Given the absence of clear predictors from the correlative studies presented, several other mechanisms may explain the interesting activity noted with selumetinib in BC. Alternative genetic or epigenetic alterations for this malignancy, such as activation as a result of *BRAF* gene mutations at other nucleotide positions or newly described *MEK* mutations,^{23,24} are certainly possible. A recent study identified transcriptional pathway signatures that could predict for MEK addiction and response to selumetinib with no absolute correlation with mutational or phosphoprotein markers of *BRAF/MEK*, *RAS*, or *PI3K*.²⁵ Finally, immune modulation can potentially explain the observed activity of selumetinib, including the documented nonfluid weight gain. Selumetinib has been previously shown to inhibit secretion of interleukin (IL) -6²⁶ as well as of other cytokines including IL-1 and tumor necrosis factor. IL-1, IL-6, and tumor necrosis factor have all been implicated in the origins of cachexia in cancer.²⁷⁻²⁹ Cholangiocarcinoma cells constitutively secrete IL-6, a vital cytokine for cholangiocarcinogenesis, with a major role on survival signaling pathways and growth of these cells,^{30,31} and inhibition of IL-6 has been shown to attenuate growth of cholangiocarcinoma cell lines.³²

A review of published results on selumetinib in various malignancies revealed few reported responses,^{15,33-38} specifically in melanoma (< 5%),³⁶ lung cancer (5%),³⁸ and thyroid cancer (< 3%).³⁵ In our study, 12% of patients experienced objective responses, and 56% experienced prolonged SD; the majority of those with prolonged SD had target lesion decrease. Our study fell short of achieving the number of responses required to consider moving forward with single-agent selumetinib in patients with BC. One may argue that our choice of primary end point was not optimal, and our target response rate may have been ambitious. Nonetheless, with the presence of preliminary evidence of activity for selumetinib, development of this agent is warranted in combination with other promising agents, such as inhibitors of epidermal growth factor receptor³⁹ or AKT.^{40,41}

In conclusion, MEK inhibition with selumetinib was well tolerated and shows evidence of promising activity in BC. Correlative studies confirming the potential negative predictive value of

absence of ERK phosphorylation and identifying new positive predictors of clinical response are needed to better understand the mechanisms of activity and to better select patients for treatment. The results of the present study suggest that selumetinib monotherapy has clinical activity in BC and may represent a particularly promising compound for inclusion in combinatorial strategies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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