Phase II Study of the Mitogen-Activated Protein Kinase 1/2 Inhibitor Selumetinib in Patients With Advanced Hepatocellular Carcinoma

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A B S T R A C T

Purpose

Hepatocellular carcinoma (HCC) is a common and deadly malignancy with few systemic therapy options. The RAF/mitogen-activated protein kinase kinase (MEK)/extracellular signal-related kinase (ERK) pathway is activated in approximately 50% to 60% of HCCs and represents a potential target for therapy. Selumetinib is an orally available inhibitor of MEK tyrosine kinase activity.

Patients and Methods

Patients with locally advanced or metastatic HCC who had not been treated with prior systemic therapy were enrolled on to the study. Patients were treated with selumetinib at its recommended phase II dose of 100 mg twice per day continuously. Cycle length was 21 days. Imaging was performed every two cycles. Biopsies were obtained at baseline and at steady-state in a subset of patients, and pharmacokinetic (PK) analysis was performed on all patients.

Results

Nineteen patients were enrolled, 17 of whom were evaluable for response. Most (82%) had Child-Pugh A cirrhosis. Toxicity was in line with other studies of selumetinib in noncirrhotic patients. PK parameters were also comparable to those in noncirrhotic patients. No radiographic response was observed in this group, and the study was stopped at the interim analysis. Of 11 patients with elevated α -fetoprotein, three (27%) had decreases of 50% or more. Median time to progression was 8 weeks. Inhibition of ERK phosphorylation was demonstrated by Western blotting.

Conclusion

In this study of selumetinib for patients with HCC, no radiographic responses were seen and time to progression was short, which suggests minimal single-agent activity despite evidence of suppression of target activation.

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INTRODUCTION

Hepatocellular carcinoma is one of the most common cancer killers worldwide. Treatment of locally advanced (unresectable) and metastatic HCC is generally palliative in nature. Sorafenib is currently considered the therapy of choice for patients with advanced HCC on the basis of a randomized trial in which median overall survival (OS) was improved from 7.9 months for placebo-treated patients to 10.7 months with sorafenib.¹ Although this result is promising, it is still the case that agents targeting new mechanisms are an urgent priority for patients with HCC.

The RAF/mitogen-activated protein kinase kinase (MEK)/extracellular signal-related kinase (ERK) signaling pathway plays a central role in the regulation of many cellular processes, including proliferation, survival, differentiation, apoptosis, motility, and metabolism.² Activated RAS triggers the phosphorylation and activation of RAF kinase, which then phosphorylates MEK1 and MEK2 on two serine residues.² Activated MEK phosphorylates its only known substrates, ERK1 and ERK2. Phosphorylated ERK dimerizes and translocates to the nucleus,³ where it is involved in several important cellular functions, including cell proliferation.

RAS and RAF mutations are relatively uncommon in HCC,⁴⁻⁶ but there is evidence that, despite this, the RAF/MEK/ERK pathway may have significance in the progression of HCC. Activation of this pathway has been demonstrated in 50% to 100% of human HCCs.⁷⁻⁹ This may be in large part due to autocrine/paracrine signaling through receptor tyrosine kinases, such as epidermal growth factor receptor, the insulin-like growth factor receptor, or c-MET.¹⁰ Additionally, it was recently noted that HCCs appear to have decreased expression of inhibitors of the RAS pathway, possibly via methylation of the promoter of the *RASSF1A* and/or *NORE1A* genes.^{11,12} MEK/ERK inhibition has been studied in HCC cell lines and xenografts with mixed results. A preclinical study by Klein et al¹³ utilized several means of inhibition of the MEK/ERK pathway and demonstrated decreased proliferation and increased apoptosis in several HCC cell lines. Huynh et al¹⁴ utilized selumetinib against HCC cell lines and again demonstrated activity in vitro and in xenograft models in more than one HCC cell line. This group noted decreased activity in one cell line that did not express significant phospho-MEK.

Selumetinib (AZD6244, ARRY-142886) is a potent, selective, orally available, and non-ATP-competitive small-molecule inhibitor of the mitogen-activated protein (MAP) kinase kinase, MEK1/2.¹⁶ The recommended phase II dose of selumetinib has previously been established as 100 mg twice per day orally.¹⁷ To our knowledge, this study represented the first trial of an inhibitor of MEK in patients with HCC. Because the metabolism of selumetinib is also primarily hepatic, the study also represented an opportunity to investigate the pharmacokinetics (PKs) and safety profile of selumetinib in a population of patients who have underlying liver disease.

PATIENTS AND METHODS

Patient Selection

This study was an open-label, single-arm, phase II clinical trial evaluating the efficacy of selumetinib in advanced or metastatic HCC. The study was performed by the Southeastern Phase II Consortium and the Ohio State University Phase II Consortium. The human participants committees at each participating center approved this study, and all patients provided written informed consent before participation. All trial procedures were conducted in accordance with the principles established by the Helsinki Declaration.

Patients enrolled on this study had either histologically proven or α -fetoprotein (AFP > 1,000 ng/dL) –confirmed HCC. They could not be considered candidates for potentially curative therapies. Prior regional therapy or ablative therapy was allowed, but prior systemic therapy (including sorafenib) was not. History of liver transplantation was exclusionary (CONSORT, Fig 1).

Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 was required in addition to the following laboratory criteria: leukocytes greater than 3,000/ μ L, absolute neutrophil count greater than 1,500/ μ L, platelets greater than 75,000/ μ L, total bilirubin less than two times the upper limit of normal (ULN), AST/ALT less than five times institutional ULN, creatinine less than 1.5 mg/dL (or creatinine clearance greater than 60 mL/min), and INR less than 1.4.

If cirrhosis was present, the patient had to meet criteria for Child-Pugh class A or B. If Child-Pugh B cirrhosis was present, the patient could not have significant encephalopathy or ascites that required ongoing paracentesis, and the patient had to meet the stated laboratory criteria.

Treatment

Selumetinib was formulated as a mix and drink preparation by using captisol as the diluent. Dosing was 100 mg orally twice per day to patients who had fasted for a minimum of 2 hours before dosing. Days 1 through 3 of the

Fig 1. CONSORT diagram.

study constituted the initial PK analysis; the patient took a single morning dose of 100 mg selumetinib followed by PK sampling. After the 48-hour PK sample, patients began twice-daily therapy continuously. A cycle of therapy was 21 days of therapy.

Dose modifications were planned for any grade 3 or 4 toxicities. Up to two dose reductions were allowed; the first was a reduction to 50 mg twice per day, and the second was a reduction to 50 mg once daily. Rash was managed with interruption of therapy for intolerable grade 2 or greater severity followed by dose reduction after resolution to grade 1 or tolerable grade 2.

PK sampling was performed for the first 15 patients on days 1 through 3 (single-dose PK) and days 15 to 17. Tumor biopsies were performed before day 1 with a 14-gauge to 20-gauge needle and up to four passes. Biopsies were immediately frozen in liquid nitrogen and were not used for diagnostic purposes. Paired tumor biopsies were obtained in the first five patients; subsequently, funding issues required us to amend the protocol to obtain only a baseline tumor biopsy. Analyses presented are based on the paired biopsy samples. Imaging for tumor response was performed after every two cycles.

Tumor Biopsy and Western Blot Analysis

Patients who consented to an optional biopsy had paired tumor biopsies performed before treatment and during treatment with selumetinib 100 mg orally twice per day on day 7, approximately 2 hours after selumetinib dose (presumed to be at steady-state). Specimens were snap frozen in liquid nitrogen and stored at -80°C until they were additionally processed. Weighted tumor samples were mixed with the appropriate amount of the T-PER tissue protein extraction reagent (Thermo Scientific, catalog No. 78,510; Rockford, IL) containing protease inhibitor cocktail, 2 mmol/L phenylmethyl sulfonyl fluoride, 2 mmol/L Na_3VO_4 , and 6.4 mg/mL *p*-nitrophenylphosphate. Samples were homogenized with the polymerase chain reaction tissue homogenizing kit (Fisher Scientific, Rockford, IL). The homogenate was centrifuged at $13,000 \times g$ for 30 minutes at 4°C , the supernatant was collected, and the protein concentration was determined by the Bradford assay. Proteins were separated by sodium dodecyl sulfate–polyacrylamide gel electrophoresis and were transferred to nitrocellulose membranes, which were then blotted with phospho-p44/42 map kinase (*p*-ERK; Thr202/Tyr204; 9101; Cell Signaling, Danvers, MA), p44/42 MAP kinase (9102; Cell Signaling), phospho-MEK1/2 (Ser 217/221; 9121; Cell Signaling), MEK1/2 (9122; Cell Signaling), phospho-p38 MAPK (Thr180/Tyr182; 12F8; 4631, Cell Signaling), p38 MAP kinase (9212, Cell Signaling), phospho-Akt (Ser473; 9271; Cell Signaling), Akt1/2 (N-19; SC-1619, Santa Cruz Biotechnology, Santa Cruz, CA), phospho-STAT3 (Tyr 705; 9131L; Cell Signaling), STAT3 (F-2; SC-8019; Santa Cruz Biotechnology, Santa Cruz, CA), GAPDH (MMS-580S; Covance, Princeton, NJ).

PK Analysis

Blood samples for determination of selumetinib and N-desmethyl selumetinib were taken on day 1 and day 15. The PK analyses were performed at Clinical Pharmacology and DMPK, Alderley Park, AstraZeneca, United Kingdom. The PK variables for the patients with comprehensive PK sampling were estimated by noncompartmental analysis by using WINNonlin (version 5.2, Scientific Consultant, Apex, NC). The actual sampling time, as opposed to the protocol-scheduled time, was used in the derivation of PK parameters.

The following parameter estimates were estimated for selumetinib from the observed concentration-time profiles: maximum plasma concentration (C_{max}), the C_{max} at steady-state ($C_{ss\ max}$), the time of maximum concentration (t_{max}), and the t_{max} at steady-state ($t_{ss\ max}$). Parameters were determined by inspection of the concentration-time profiles.

The apparent clearance (CL/F after the single dose and CL_{ss}/F after multiple dosing) were determined from the ratio of dose to area under the concentration curve (AUC) or dose to AUC_{ss} . Apparent volume of distribution (V_z/F) after oral dosing was calculated by dividing the dose by the product of $\lambda_z \times AUC$. The estimated volume of distribution at steady-state after oral dosing (V_{ss}/F) was determined from the mean residence time (MRT) $\times CL/F$.

The accumulation ratio (RAC) was calculated as the ratio of the AUC_{ss} and $AUC_{(0-12)}$ on day 1. The $AUC_{(0-12)}$ was determined for N-desmethyl selumetinib on days 1 and 15 to enable the calculation of the metabolite-to-parent percentage on days 1 and 15 (N-desmethyl selumetinib $AUC_{(0-12)} \div$ selumetinib $AUC_{(0-12)} \times 100$). The time dependency (T_c or linearity factor) of the pharmacokinetics on multiple dosing was assessed by the calculation of the ratio of AUC_{ss} to AUC on day 1.

Statistical Methods

The primary end point was the objective response rate. Secondary end points included the time to event functions of progression, progression-free survival (PFS), and overall survival (OS). For sample size calculation, an optimal two-stage design¹⁸ was used. The information used in the calculations of this design were the values of $P_0 = .03$, $P_1 = .15$, $\alpha = .1$, and power = 90%.

In the first stage, 19 patients were entered, with the assumption that at least 17 would be eligible. If there was at least one response among these 17 eligible patients, an additional 25 patients would have been entered for the second stage, of whom 22 would be assumed to be eligible. Thus, a total of 44

Fig 2. Western blot derived from frozen biopsy samples taken at baseline and day 8 (± 3 days) of selumetinib therapy demonstrating baseline and post-treatment phosphorylation of ERK1/2, MEK1/2, p38, Akt, and STAT3. Samples demonstrated baseline activation of ERK1/2 in all samples tested and inhibition of ERK phosphorylation after selumetinib therapy but, as expected, no changes in MEK phosphorylation status.

patients could have been enrolled on the study. The probability of early stopping was 0.60 if the true response rate was 0.03, and it was 0.06 if the true response rate was 0.15. Moreover, the overall probability of rejecting the treatment was 0.90 if the true response rate was 0.03, and it was 0.10 if the true response rate was 0.15.

Statistical Analysis

The Kaplan-Meier (or product-limit) method was used to estimate all time-to-event functions. Time to disease progression (TTP) has been defined as the time from the start of treatment to disease progression. Deaths occurring in the absence of proven disease progression were censored. PFS has been defined as time from the start of treatment to disease progression or death as a result of any cause. OS has been defined as time from the start of treatment to death as a result of any cause. Exact 95% CIs were calculated for each proportion of interest. These proportions have been reported as percentages. Statistical analyses were performed with SAS statistical software (version 9.2, SAS Institute, Cary, NC). PK analysis was performed with software noted in the Methods section, and parameter estimates were summarized with descriptive statistics.

RESULTS

Patient Demographics and Clinical Outcomes

Nineteen patients were enrolled between November 8, 2007, and January 28, 2009. Demographic variables and tumor characteristics at

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	Patients (n = 17)	
	No.	%
Age, years		
Median	57	
Range	48-77	
Male sex	13	76
ECOG PS*		
0: fully active	5	31
1: restricted	9	56
2: ambulatory	2	13
Child-Pugh		
A/B/not reported†	14	21
HCV/HBV/both	13	11
No viral infection	2	
PV thrombus	6	35
Prior embolization	3	18
Total bilirubin		
Median	0.87	
Range	0.6-1.8	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status; HCV, hepatitis C virus; HBV, hepatitis B virus; PV, portal vein. *n = 1 missing.

†Includes patients with no cirrhosis clinically.

Table 2. Grades 3 to 4 Treatment-Related Toxicity at Least Possibly Related to Therapy

CDUS Toxicity Code	Patients	
	No.	%
ALT	1	5
AST	1	5
Alkaline phosphatase	1	5
Bilirubin for hyperbilirubinemia	1	5
Fatigue (ie, asthenia, lethargy, malaise)	1	5
Glucose, serum high (ie, hyperglycemia)	1	5
Potassium, serum low (ie, hypokalemia)	1	5
Sodium, serum low (ie, hyponatremia)	1	5

Abbreviation: CDUS, clinical data update system.

baseline are listed in Table 1. All 19 patients were considered evaluable for toxicity. Of the 19, two patients failed to complete a full cycle of therapy, one because of elevated serum transaminases that did not resolve after holding study medication (which was felt to be secondary to rapid disease progression) and the second as a result of voluntary withdrawal from protocol after 1 week of therapy without any grade 3 toxicities. As such, 17 patients were considered evaluable for the primary end point of radiographic response. Among these 17 patients, there was no partial response or complete response; therefore, enrollment to the trial was halted at the interim analysis. With a median time on study of 6 weeks (range, 1 to 33 weeks), the best response rate of stable disease (SD) was six (35%) of 17 patients (exact 95% CI, 14% to 62%).

Eleven (65%) of 17 evaluable patients (exact 95% CI, 38% to 86%) had elevated AFP at baseline (> 200 ng/dL). Among these patients, AFP decreased by 50% or more in three patients (27%; exact 95% CI, 6% to 61%). One patient's AFP decreased significantly after 3 weeks of therapy from a peak of 79,725 ng/dL to 700 ng/dL. That patient went on to demonstrate radiographic progression at the subsequent (second) magnetic resonance imaging evaluation. After removal from protocol, the patient was started on sorafenib and demonstrated a relatively dramatic partial response at the first evaluation roughly 12 weeks later. This patient is represented as patient five (far right) in Figure 2, in which it can be seen that the patient had high levels of phospho-ERK and MEK at baseline, with significant inhibition of phospho-ERK by selumetinib.

Of the 17 evaluable patients, 14 patients died, two patients experienced progression, and one patient neither experienced progression nor died. The median PFS was 1.4 months (95% CI, 1.2 to 2.5

months). Median TTP was essentially the same. Median OS was 4.2 months (95% CI, 1.9 to 6.0). Follow-up times for the three surviving patients were 3.4, 12.5, and 15.2 months.

Toxicity

Toxicity was no greater than expected from prior studies of selumetinib. The main toxicities were low-grade but persistent nausea and maculopapular rash. The most commonly observed grade 3 and 4 toxicities possibly related to treatment are listed in Table 2. No ocular toxicity was noted, although ocular acuity testing was not required; hence, minor ocular toxicities may have been underreported. There were no significant cardiac events, although, again, repeated testing of ejection fraction was not required by the protocol.

PKs

The PK parameters are listed in Tables 3 and 4. Absorption was rapid, with median t_{max} and $t_{max ss}$ of 1.5 hours and 1 hour, respectively; $C_{max ss}$ was achieved in the majority of individuals (12 of 13) between 0.5 and 2 hours after dosing. The variability in the peak plasma concentration was moderate to high. After the peak, plasma concentrations declined (Fig 3) with a mean terminal elimination half-life ($t_{1/2}$) of 10 hours and a range of 6 to 16 hours. The mean apparent oral plasma clearance (CL_{ss}/F) was 36L/h (range, 16 to 82 L/h). The N-desmethyl metabolite was approximately 5% of the parent AUC on day 1 and AUC_{ss} on day 15 (range, 2% to 11%). The mean accumulation for selumetinib to steady-state was approximately 1.5-fold and ranged from 0.2-fold to 4.3-fold for AUC_{ss}.

There was no apparent relationship between exposure and liver function, as measured by albumin and bilirubin (Fig 4), although the number of patients with levels consistent with Child-Pugh scoring of ≥ 6 was low. Three patients had Child-Pugh class B liver disease; PK data were available for two of these, and one of these patients had the highest observed exposure in the study population. The exposure in patients in this study was generally in a similar range to that observed in patients with other tumor types in the selumetinib clinical program (data not shown).

MEK Inhibition in Tissue Samples

To determine the effects of selumetinib on the activities of MEK and other signal transduction pathways in patients with locally advanced or metastatic HCC, pre- and post-tumor biopsies were analyzed for the phosphorylation levels of ERK1/2, MEK1/2, p38, Akt, and STAT3. Figure 2 shows that four of five patients (patients 1, 2, 4, and 5) achieved significant inhibition of phospho-ERK1/2 levels in tumors. As would be expected, selumetinib treatment resulted in little

Table 3. Pharmacokinetic Parameters After Selumetinib Single Oral 100-mg Dose to Steady-State

Parameter Measure on Day 1	Parameter							
	t_{max} (hours)	C_{max} (ng/mL)	AUC ₍₀₋₁₂₎ (ng $\times$ h/mL)	AUC (ng $\times$ h/mL)	CL/F (L/h)	Vz/F (L)	$t_{1/2}$ (hours)	N-desmethyl/Selumetinib AUC ₍₀₋₁₂₎ (%)
No. evaluated	14	14	14	13	13	13	13	12
Mean		734	3,299	5,219	29	415	10	5.7
SD		795	2,690	3,697	20	309	3	2.4
Min	0.5	123	777	1,300	7	114	6	1.7
Max	4	3,140	10,384	14,251	77	1,126	16	10.8

Abbreviations: t_{max} , time of maximum concentration; C_{max} , maximum plasma concentration; AUC₀₋₁₂, area under the concentration curve from 0 to 12 hours; AUC, area under the concentration curve; CL/F, apparent clearance; Vz/F, apparent volume of distribution; $t_{1/2}$, half life; SD, standard deviation; Min, minimum; Max, maximum.

Table 4. Pharmacokinetic Parameters After Selumetinib Oral 100-mg Oral Twice-Daily Dose to Steady-State

Parameter Measure on Day 15	Parameter							
	$t_{\max ss}$ (hours)	$C_{\max ss}$ (ng/mL)	AUC_{ss} (ng $\times$ h/mL)	CL_{ss}/F (L/h)	V_{ss}/F (L)	RAC (hours)	Tc	N-desmethyl/Selumetinib AUC_{ss} (%)
No. evaluated	13	13	13	13	13	12	11	12
Mean		647	3,473	36	328	1.5	0.9	4.9
SD		401	1,613	19	289	1.1	0.5	1.7
Min	0.5	135	1,220	16	88	0.2	0.2	2.2
Max	4	1600	6175	82	1023	4.3	1.9	7.8

Abbreviations: $t_{\max ss}$, time of maximum concentration at steady-state; $C_{\max ss}$, maximum plasma concentration at steady-state; AUC_{ss} , area under the concentration curve at steady-state; CL_{ss}/F , apparent clearance at steady-state; V_{ss}/F , estimated volume of distribution at steady-state; RAC, accumulation ratio; Tc, temporal change (ratio of AUC_{ss} /single-dose AUC); SD, standard deviation.

effect on the phospho-MEK1/2 levels in four of the five patients (because this is mediated by RAF upstream).

To determine the selectivity of selumetinib we also analyzed its effects on the phosphorylation of another MAP kinase protein, p38. Figure 2 shows that treatment with selumetinib resulted in a decrease of phospho-p38 in patient 1, an increase in patients 2 and 3, and little effect on patients 4 and 5. These results suggest that the inhibition of MEK kinase in these patients is complex and has different consequences depending on the individual patient tumor.

We next evaluated the effect of selumetinib on other oncogenic pathways, such as Akt and STAT3. Whereas the effects of selumetinib on the phospho-STAT3 levels were subtle, the effects on phospho-Akt were pronounced in some tumors (Fig 2). Furthermore, the results show that treatment with selumetinib resulted in mixed effects on the phosphorylation levels of Akt.

DISCUSSION

To our knowledge, this study represented the first study of an inhibitor of MEK in patients with HCC. The preclinical rationale for the use of this class in this population was strong. However, in the patient pop-

ulation studied, monotherapy activity of selumetinib was minimal despite treatment with the agent at full dose. Tolerability of the drug was similar in this population to that reported in other populations^{17,19} and cannot be considered the principal reason for lack of efficacy in this trial. Our study utilized RECIST (Response Evaluation Criteria in Solid Tumors) to evaluate response. RECIST has been criticized in HCC because of inherent difficulty in imaging HCCs and because devascularization rather than tumor shrinkage may be a hallmark of response in HCC. Recently, a modified RECIST has been proposed,²⁰ but it is not yet considered standard for clinical trials of systemic agents.

Interestingly, Abou-Alfa et al¹⁵ described improved prognosis in HCC patients treated with sorafenib whose tumors demonstrated high nuclear phospho-ERK levels by immunohistochemistry on paraffin-embedded samples. This analysis was difficult to interpret, however, given lack of placebo-treated patients in the study. As such, the question remains about whether ERK activation is prognostic or predictive of response to sorafenib activity. Our results suggest that this finding was not likely due to the effects of sorafenib on the

Fig 3. Mean and standard deviation selumetinib and N-desmethyl selumetinib plasma concentrations after single and twice daily dosing of selumetinib to patients with hepatocellular carcinoma.

Fig 4. Selumetinib area under the concentration curve (AUC) as a function of serum albumin on days 1 and 15 demonstrates no trend toward increased or decreased exposure on the basis of albumin (as a surrogate for severity of liver disease). AUC_{ss} , AUC at steady-state.

RAF/MEK/ERK pathway, but rather they suggest the possibility that phospho-ERK expression represented a favorable prognostic factor (rather than a predictive one, as suggested in the discussion of the study by Abou-Alfa et al¹⁵). Little other data on this topic exist in the literature. Of note, we recently identified increasing degrees of phospho-ERK expression as a positive prognostic factor in rectal cancer (O'Neil et al, manuscript in preparation). The data from this study along with other studies of other vascular endothelial growth factor pathway antagonists suggest vascular endothelial growth factor receptor inhibition as the main activity of sorafenib in HCC.²¹ Additionally, our data suggest that phospho-ERK expression may not be an adequate selection factor for therapy with MEK inhibitors. Studies in several tumor types, particularly melanoma, suggest that cancers harboring *BRAF* mutations may be particularly sensitive to MEK inhibition.²² Some in vivo experiments have demonstrated that tumors with *KRAS* mutations may also be sensitive,²³ although others have refuted this.²⁴ Interestingly, in a recently completed trial of selumetinib in cholangiocarcinoma, responding patients harbored neither *KRAS* nor *BRAF* mutations,²⁵ so true predictors of response remain elusive in many, if not most, disease states.

In a subset of patients, we demonstrated that MEK phosphorylation was present in all patient cases sampled and that, at day 8 of therapy, MEK phosphorylation was in fact inhibited in the tumor by the studied dose of selumetinib in four of five patients. This suggests that inactivity of the compound was not explained by lack of target inhibition. Our studies of downstream effects of MEK inhibition on Akt, STAT, and p38 showed mixed effects of MEK inhibition, and our conclusions in this regard are quite limited because of small numbers.

Another potential explanation for lack of activity of this compound in HCC could relate to differential exposure in the cirrhotic population compared with a noncirrhotic one. Fifteen of 19 patients in our study had cirrhosis, and the vast majority were Child-Pugh class A. PK analysis of our population is again somewhat limited by numbers, but there was no suggestion of a significant difference in PK parameters between patients in our study and those in prior studies of AZ6244 (Maria Learoyd, AstraZeneca, personal communication).

In summary, this study represented, to our knowledge, the first study of an inhibitor of MEK in HCC. The study was terminated early because of a lack of radiographic responses and short PFS, which both reflect the lack of adequate antitumor activity with selumetinib as monotherapy.

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.

Employment or Leadership Position: Ruey-min Lee, Merck (C); Maria Learoyd, AstraZeneca (C) **Consultant or Advisory Role:** Bert H. O'Neil, AstraZeneca (C) **Stock Ownership:** Maria Learoyd, AstraZeneca **Honoraria:** None **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

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