Phase II Study of Cediranib in Patients with Malignant Pleural Mesothelioma

SWOG S0509

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Introduction: Malignant pleural mesothelioma (MPM) tumors express vascular epithelial growth factor (VEGF) and VEGF receptors. We conducted a phase II study of the oral pan-VEGF receptor tyrosine kinase inhibitor, cediranib, in patients with MPM after platinum-based systemic chemotherapy.

Methods: Patients with MPM previously treated with a platinum-containing chemotherapy regimen and a performance status 0 to 2 were eligible for enrollment. Cediranib 45 mg/d was administered until progression or unacceptable toxicity. The primary end point was response rate. Tumor measurements were made by RECIST criteria, with a subset analysis conducted using modified RECIST. A two-stage design with an early stopping rule based on response rate was used.

Results: Fifty-four patients were enrolled. Of 47 evaluable patients, 4 patients (9%) had objective responses, 16 patients (34%) had stable disease, 20 patients (43%) had disease progression, 2 patients (4%) had symptomatic deterioration, and 1 patient (2%) had early death. The most common toxicities were fatigue (64%), diarrhea (64%), and hypertension (70%); 91% of patients required a dose reduction. Median overall survival was 9.5 months, 1-year survival was 36%, and median progression-free survival was 2.6 months.

Conclusion: Cediranib monotherapy has modest single-agent activity in MPM after platinum-based therapy. However, some patient tumors were highly sensitive to cediranib. This study provides a rationale for further testing of cediranib plus chemotherapy in MPM and highlights the need to identify a predictive biomarker for cediranib.

Key Words: Phase 2, Angiogenesis inhibitor, Pleural mesothelioma.

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Malignant pleural mesothelioma (MPM) is a neoplasm that originates in the parietal pleura and is strongly associated with asbestos exposure through chronic environmental or occupational exposure. The lag time between exposure and presentation of the disease ranges between 5 and 20 years, although cases have been diagnosed more than 40 years after exposure.[1] MPM is a rare cancer with 2000 to 3000 new cases diagnosed in the United States per year; it is estimated that the incidence of MPM in the United States is currently peaking.[2] Worldwide, however, less stringent regulation of occupational asbestos has resulted in the continued exposure of large populations to asbestos and has, therefore, fostered continued increases in new cases of MPM in Australia, Europe, and Asia.[3–5]

MPM is a relatively chemotherapy- and radiation-resistant tumor. The median survival for untreated patients is in the range of 4 to 12 months.[6] Currently, platinum-based therapy in combination with newer generation antifolate drugs such as raltitrexed and pemetrexed remains a benchmark for standard front-line therapy for MPM, with median survival times of 11.4 and 12.1 months, respectively, reported in phase III trials in combination with cisplatin.[7,8] At this time, there are no well-accepted standard therapies in the setting of second-line MPM, and no targeted therapies have been approved for clinical application in MPM.

In preclinical models with MPM cell lines, vascular epithelial growth factor (VEGF) and its cognate receptors, VEGF receptor (VEGFR)1 (flt) and VEGFR2 (KDR), are highly expressed on tumor cells, and a proposed autocrine growth loop involving VEGF and its cognate receptors has been identified.[9] Recombinant human VEGF added to MPM cell line cultures stimulates cell proliferation in a dose-dependent manner, whereas inhibitors of VEGF and VEGF-C inhibit mesothelioma cell growth.[10,11] In support of this autocrine growth loop, human MPM tumors express the

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angiogenic cytokines VEGF, fibroblast growth factor-1, fibroblast growth factor-2, and transforming growth factor-β,[12,13] and the coexpression of VEGF and VEGFR1 in human MPM has been reported.[14] In clinical studies, patients with MPM have high circulating levels of VEGF.[15] Some studies have reported tumor VEGF expression and tumor microvessel density to be independent prognostic markers.[13,15] These data support the targeting of tumor angiogenesis as a therapeutic strategy in MPM.

Cediranib (Recentin, AZD2171; AstraZeneca Pharmaceuticals, Cheshire, United Kingdom) is an orally active, potent, tyrosine kinase inhibitor (TKI) of VEGFR1 to 3 at nanomolar concentrations, as well as c-Kit and platelet-derived growth factor receptor-β.[16,17] In phase I studies, the maximum tolerated dose was defined as 20 to 45 mg daily, with reported dose-limiting toxicities of proteinuria, diarrhea, thrombocytopenia, hypertension, and hypertensive crisis.[18–20] Partial tumor responses and disease stabilization have been observed in a number of solid tumors.[18–21]

Given that tumor angiogenesis is a potential therapeutic target in MPM and that cediranib has shown tolerability and antitumor efficacy in a number of solid tumors, we performed a phase II trial of cediranib in patients with advanced or recurrent MPM after platinum-based chemotherapy. The primary objective of the trial was to assess the objective response rate of cediranib in second-line MPM. Secondary objectives were to measure survival outcomes and to define the toxicity profile of cediranib in this setting. A protocol amendment was made to also capture tumor response by modified RECIST for pleural tumors.[22]

PATIENTS AND METHODS

Inclusion Criteria

Patients who were at least 18 years of age with histologically proven epithelioid, sarcomatoid, or biphasic mesothelioma of the pleura (by pathology evaluation at local institutions) whose disease was not resectable were eligible for enrollment. Patients were required to have had prior platinum-based chemotherapy, and only one prior chemotherapy regimen was allowed. Only patients with measurable disease by RECIST criteria[23] were eligible. Prior radiation or surgical procedures for MPM for diagnostic or therapeutic purposes were allowed. A Zubrod performance status of 0 to 2 and adequate hematologic function (absolute neutrophil count $\geq$1500/ml and platelets $\geq$100,000/ml), hepatic function (serum bilirubin $\leq$ upper limit of normal and transaminases $\leq$1.5 times upper limit of normal), and renal function (serum creatinine $\leq$1.5 times upper limit of normal or a measured creatinine clearance $\geq$50 ml/min) were required.

Patients were not eligible if they had severe systemic comorbid disease or a significant cardiac history, uncontrolled hypertension, significant proteinuria, a prolonged QTc interval, were either pregnant or breast-feeding, or had gastrointestinal tract disease resulting in inability to take oral medication or altered gastrointestinal absorption.

The protocol and informed consent document were approved by the Cancer Therapy Evaluation Program of the National Cancer Institute and the institutional review boards of participating SWOG member sites. Written informed consent was obtained from all patients before enrollment. This study was monitored by the Data and Safety Monitoring Committee of the Southwest Oncology Group.

Study Design and Protocol Treatment

The S0509 treatment protocol (ClinicalTrials.gov_ Identifier: NCT00243074) consisted of single-agent cediranib administered orally at 45 mg/d every day and were treated until progression or unacceptable toxicity. Adverse events were graded according to the NCI CTC Version 3.0. Sequential dose modifications to 30 mg (dose level 1) and 20 mg daily (dose level 2) were allowed, although a further dose reduction to 10 mg daily was allowed for patients on study $\geq$3 months who were benefiting from treatment. A treatment delay until toxicity resolved to $\leq$ grade 1, and dose modifications were made for patients with $\geq$ grade 3 nonhematologic and/or grade 4 hematologic toxicities, and moderate hypertension and proteinuria.

Patient history, physical examination, hematologic, and chemical laboratory analyses were performed before cycle 1 of therapy and each subsequent treatment cycle. Radiographic tumor measurements were performed after every two treatment cycles. Tumor responses were judged by RECIST. A protocol amendment was made to capture tumor measurements using the modified RECIST measurement system. Patients were withdrawn from the study due to disease progression or symptomatic deterioration, unacceptable toxicity as assessed by the study physician, treatment delay of greater than 3 weeks, or if more than the prescribed dose modifications were required.

Statistical Considerations and Statistical Analysis

A two-stage design was used such that 20 patients would be enrolled in the first stage, with an evaluation of response rate and safety performed. If at least one confirmed partial response (PR) was noted, the study would continue accrual to a total of 40 patients. A response rate of 20% or higher would be sufficient to declare this regimen worthy of further study, whereas a response rate of 5% or lower would indicate no further interest in this setting. This design has a significance level (probability of false declaring an agent with a true 5% response probability to warrant further study) of 5% and a power (probability of correctly declaring an agent with a 20% response probability to warrant further study) of 92%.

Progression-free survival (PFS) was calculated as the time elapsed between study enrollment and first documented tumor progression, death, or last contact. Overall survival (OS) was defined as the time elapsed between study enrollment and death from any cause or last contact. Patients alive or progression free at last contact were censored for the respective outcomes. Median PFS and OS, 95% confidence intervals (CIs), and associated survival curves were estimated by Kaplan-Meier methods.

TABLE 1. Patient Characteristics

N = 47	*n* (%)
Median age (yr)	66.8 (range 43–84)
Men:women (%)	38:9 (81:19)
Zubrod performance status	
0	16 (34)
1	25 (53)
2	6 (13)
Six-month before weight loss	
<5%	33 (70)
5 to <20%	8 (17)
>20%	2 (4)
Not reported	4 (9)
Histologic subtype	
Epitheliod	28 (60)
Sarcomatoid	0
Biphasic	3 (6)
Not otherwise specified	11 (23)
Not reported	5 (11)

TABLE 2. Antitumor Activity—Best Overall Response

N = 43	*n* (%)
CR	0
PR	4 (9)
SD	16 (34)
PD	20 (43)
Symptomatic deterioration	2 (4)
Early death	1 (2)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

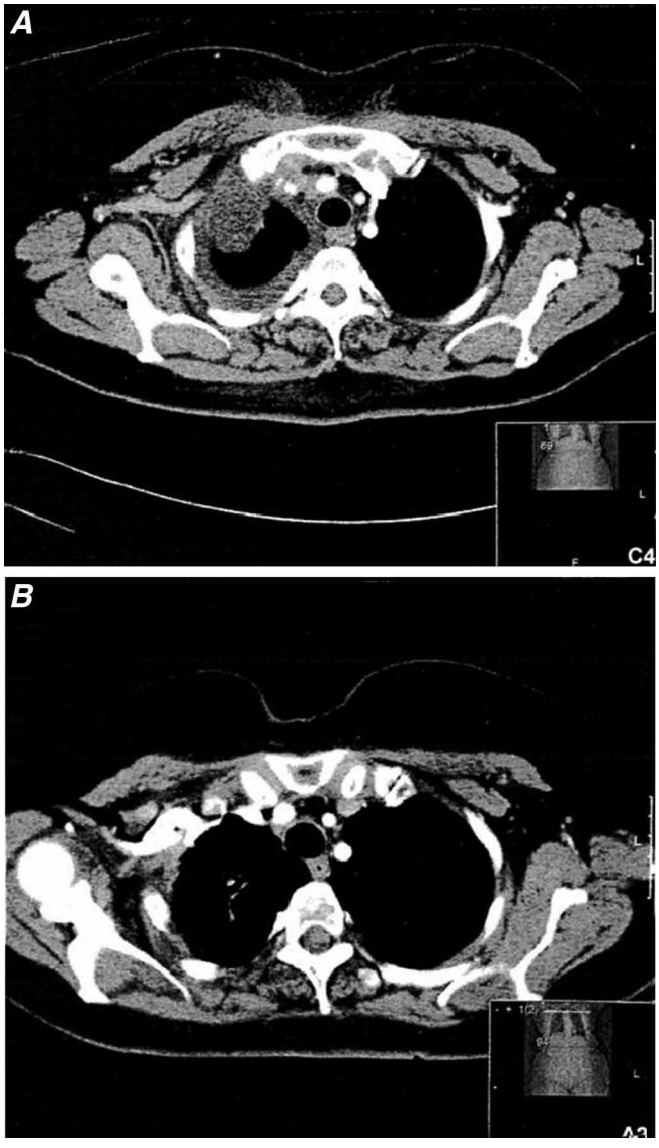

FIGURE 1. *A* and *B*, Computed tomography scans of the thorax over the course of cediranib therapy.

RESULTS

Patients

Patient recruitment was undertaken from November 2005 through April 2008, with a 3-month temporary closure for the first-stage evaluation. A total of 54 patients were registered, with 48 patients eligible for enrollment. One patient was not assessable because of refusal of treatment. Patient characteristics for the 47 patients are presented in Table 1. The median age was 66.8 years (range 43–84 years); the majority of patients were men. Racial composition was predominantly white (94%) with 6% race not available. Ethnic composition was Hispanic 4%, non-Hispanic 87%, and unknown 9%. Patient performance status was 0 in 34%, 1 in 53%, and 2 in 13% of patients. The majority of patients had less than 5% loss of body weight within the 6 months before enrollment.

Tumor histologic subtype was classified as epithelioid (60%), biphasic (6%), and mesothelioma, not otherwise specified (23%) by local institution pathology review. No patients with sarcomatoid subtype were enrolled. Histologic subtype was not reported for 11%. A formal central pathology review was not performed. All patients had multiagent first-line chemotherapy.

Response and Survival

There was one patient with an objective response in the first 20 accrued to the first stage of the trial. The second stage of the study was then opened for accrual as per the study design mentioned earlier in the text. For the entire study cohort (first and second stages combined), response was not able to be determined because of inadequate assessment for four patients (8%). These four patients are assumed to be nonresponders and are included in calculations of response rate. For the 43 evaluable patients, response data are summarized in Table 2. There were no complete responses. Four patients (9%) had PRs, including two patients with bulky disease who had 91% (see Figures 1*A*, *B*) and 56% tumor shrinkage. Sixteen patients (34%) had stable disease (SD),

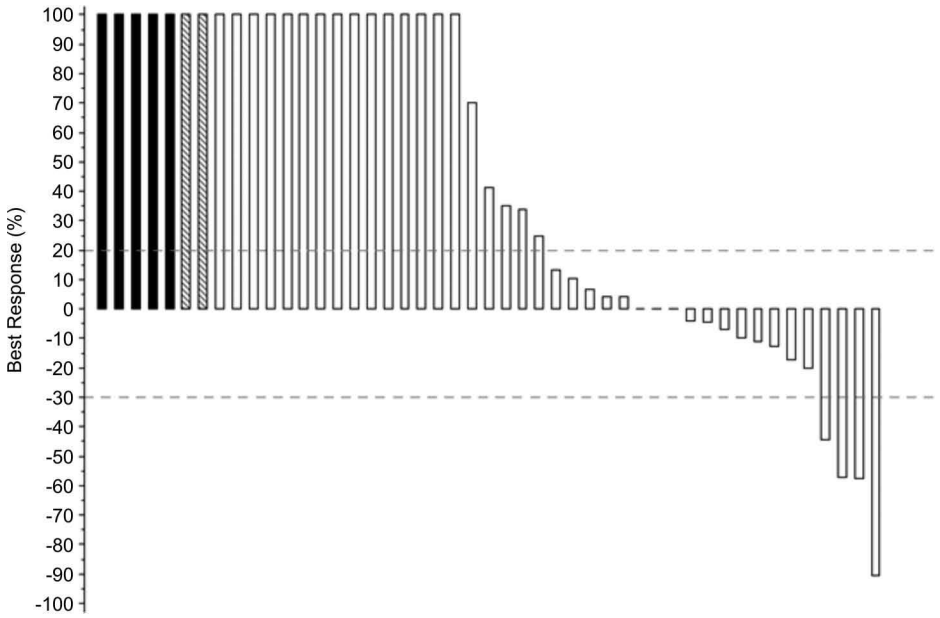

FIGURE 2. Waterfall plot of best response.

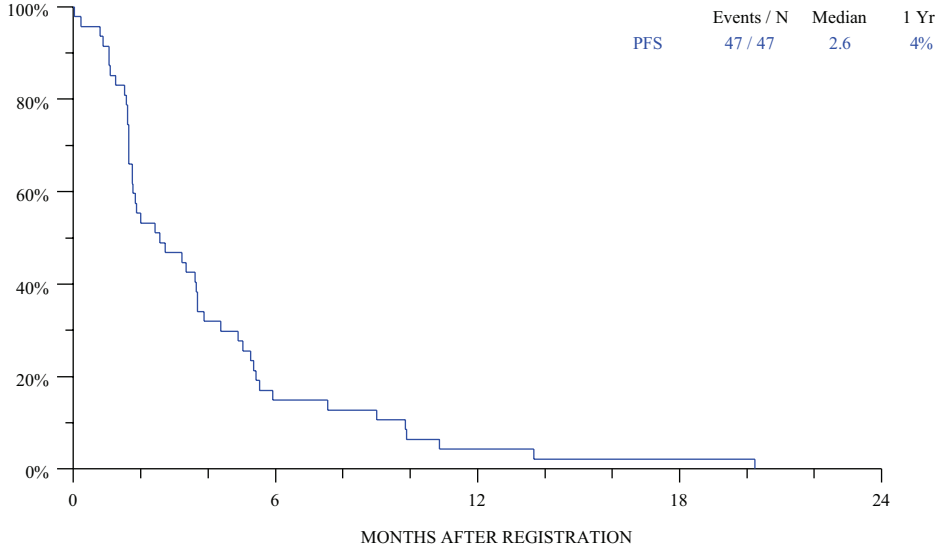

FIGURE 3. Progression-free survival.

documented at least 6 weeks after registration and before progression or symptomatic deterioration (range 2.4–13.7 months). Twenty patients (43%) had progressive disease, two patients (4%) had symptomatic deterioration, and one patient (2%) had early death. A waterfall plot of best response is shown in Figure 2.

OS for 47 patients is shown in Figure 3. Forty-three patients had died at the time of analysis; the median OS was 9.5 months (95% CI: 5.6–10.7 months) and 1-year survival was 36% (95% CI: 23–50%). PFS is shown in Figure 4. Forty-seven patients have progressed or died. Median PFS was 2.56 months (95% CI: 1.74–3.68 months) and 1-year PFS was 4% (95% CI: 1–13%). For 16 patients with SD, median time to progression was 4.9 months (95% CI: 3.6–5.4 months).

For 11 patients, modified RECIST data were reported. There was 100% correlation in response assessment for modified RECIST with RECIST measurements.

Adverse Events

Forty-seven patients were evaluable for adverse events. Hematological adverse events attributed to cediranib were infrequent and of grades 1 and 2 only (Table 3).

Grades 1 to 4 nonhematological adverse events that occurred in ≥9% of patients attributable to study treatment are listed in Table 4; the most common nonhematologic adverse events were fatigue, hypertension, and diarrhea. Grade 3 and 4 events of frequency less than 9% included apnea, ataxia, cognitive disturbance, intestinal pain, colitis, dizziness, encephalopathy, esophageal necrosis, ileal perfo-

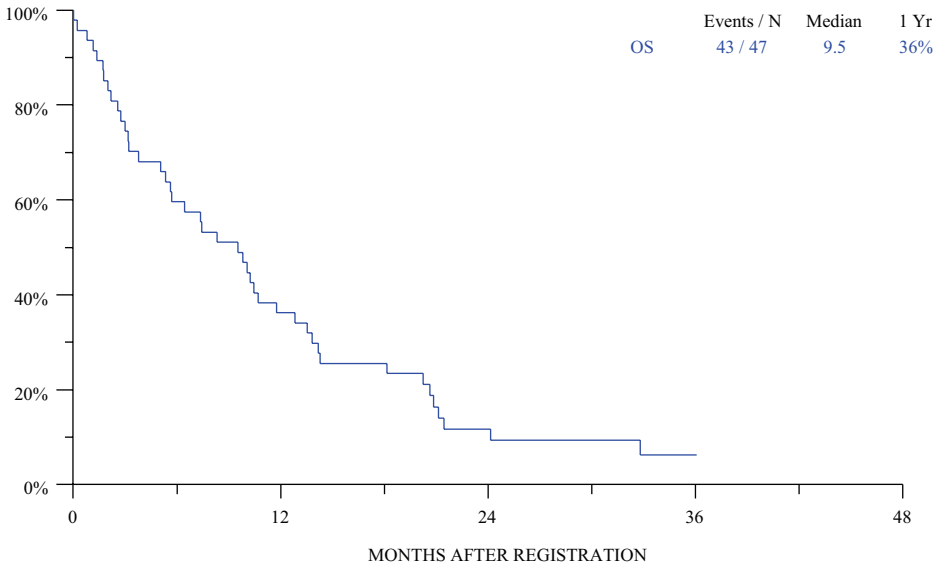

FIGURE 4. Overall survival.

TABLE 3. Hematological Toxicity

	Grades		
N = 47	1	2	Percentage of Patients
Anemia	5	1	13
Leukopenia	1	0	2
Neutropenia	1	0	2
Thrombocytopenia	7	0	15

TABLE 4. Grade 1 to 4 Nonhematological Toxicity (≥9% Frequency)

	Grades				
N = 47	1	2	3	4	Percentage of Patients
Constitutional					
Anorexia	7	5	3	0	32
Weight loss	7	5	2	0	30
Fatigue	13	10	7	0	64
Dehydration	0	3	3	0	13
Gastrointestinal					
Nausea	10	4	2	0	34
Vomiting	5	3	1	0	19
Diarrhea	14	12	4	0	64
Constipation	4	1	1	0	13
Heartburn	3	2	0	0	11
ENT					
Dry mouth	4	1	0	0	11
Voice changes	14	3	0	0	36
Cardiac					
Hypertension	5	14	14	1	70
Respiratory					
Cough	5	1	0	0	13
Renal					
Proteinuria	8	4	2	0	30
Musculoskeletal					
Muscle pain	3	1	0	0	9
Neurologic					
Headache	4	1	1	0	13
Sensory neuropathy	3	0	1	0	9
Endocrine					
Hypothyroidism	2	4	0	0	13

ENT, ear, nose, and throat.

ration, hand-foot syndrome, hypokalemia, hyponatremia, hypotension, chest wall pain, memory impairment, elevated serum ammonia, generalized muscle weakness, pain not otherwise specified, tumor pain, renal failure, speech impairment, and thrombosis/embolism. Biochemical abnormalities were infrequent and of grades 1 and 2 only (Table 5). There were no treatment-related deaths.

A dose deescalation was made in 43 of 47 patients. Six patients were removed from the study due to adverse events attributed to treatment with cediranib. Two patients withdrew from the study for reasons not related to adverse events. Thirty-six patients were withdrawn for disease progression, two patients died early, and one patient was withdrawn for unspecified reasons.

DISCUSSION

Interest in studying the antiangiogenic agent, cediranib, in MPM was based on a significant body of evidence supporting the role of angiogenesis as an important growth signaling pathway for MPM. In the second-line setting, the objective response rate for single-agent cediranib was 9%, which did not meet the prespecified 20% response rate of interest. Notably, however, there was marked shrinkage of bulky tumors in two of the four patient responders. In this uncontrolled trial, 34% of patients had SD, yielding a clinical benefit rate (complete response, PR, and SD) of 43%, which compares favorably to the clinical benefit rate of 46.6% for second-line pemetrexed in patients enrolled in an expanded access program, but less favorably to that reported for second-line pemetrexed (clinical benefit rate of 59.3%) in a

TABLE 5. Biochemical Toxicity

	Grades		
N = 47	1	2	Percentage of Patients
Creatinine	3	2	11
Alkaline phosphatase	4	1	11
Alanine aminotransferase	7	1	17
Aspartate aminotransferase	6	2	17
Hyperglycemia	5	1	13
Hypoalbuminemia	4	1	11

phase III study of second-line pemetrexed versus best supportive care in MPM.[24,25] The utility of the clinical benefit rate derived from single arm phase 2 studies is limited by the variable natural history of untreated MPM. Thus, there is great interest in the development and validation of functional imaging studies and surrogate biomarkers of antitumor activity to augment the assessment of antiangiogenics and other classes of agents that might be cytostatic for cohorts of patients with MPM.

For the entire study population, the median PFS was short (2.56 months) but similar to reported time to progression for other targeted agents in MPM.[26–28] Specifically, the clinical efficacy reported in this study for cediranib is in line with other multitargeted VEGFR receptor TKI agents. In single-agent studies, front-line vatalanib for pleural and peritoneal mesothelioma yielded a response rate of 11% and a 3-month PFS of 55%; front-line/s-line sorafanib therapy for pleural and peritoneal mesothelioma yielded a response rate of 4% and a median failure-free survival of 3.7 months; and second-line sunitinib in MPM yielded a response rate of 23% with a median time to progression of 3.5 months.[29–31] In contrast, bevacizumab, a monoclonal antibody that blocks VEGF ligand binding to the VEGFRs, did not have meaningful clinical activity when combined with the EGFR inhibitor erlotinib in previously treated MPM, nor did bevacizumab enhance the activity of gemcitabine/cisplatin chemotherapy for front-line treatment of pleural/peritoneal mesothelioma in the intent to treat population.[32,33] However, in subgroup analysis, patients on the bevacizumab/gemcitabine/cisplatin arm who had low circulating levels of VEGF had longer PFS and OS.

In this study of patients with a good performance status after one platinum-based prior systemic therapy, cediranib was not well tolerated at the starting dose of 45 mg daily, and the majority of patients required a dose reduction. In fact, in several phase I studies of cediranib in solid tumor patients, the maximum tolerated dose was reported to be lower than 45 mg.[19,20] The safety profile of cediranib as a second-line agent in MPM was similar to that already reported for this and other VEGFR TKIs.

MPM is a difficult tumor to measure accurately, as are other pleural-based tumor types, given the nonspherical pattern of growth. The limitations of RECIST in assessing response and outcome measures such as PFS have been documented for MPM.[34] Other measurement systems proposed for pleural tumors include modified RECIST, in which pleural thickness is measured perpendicular to the chest wall and mediastinum.[22] We captured modified RECIST measurements for a small subset of patients and found that tumor response measured by modified RECIST correlated well with that measured by RECIST. For this subset, assessment of the activity of single-agent cediranib was not influenced by measurement system.

Because MPM is relatively resistant to standard cytotoxic chemotherapy, there is great interest in pursuing strategies that would improve the chemosensitivity of MPM. Antiangiogenic agents can augment the activity of cytotoxic chemotherapy; one proposed mechanism is through the modulation of tumor interstitial fluid pressure (TIFP) as in vivo, elevated TIFP is a barrier to drug delivery to the tumor.[35] Both VEGF and platelet-derived growth factor contribute to increased TIFP, whereas inhibitors of VEGF and/or platelet-derived growth factor signaling can reduce TIFP and augment chemotherapy effects in vivo.[36–41] The addition of cediranib to cytotoxic chemotherapy in solid tumors is feasible as shown in a number of phase I studies,[42,43] and an augmentation of the effect of chemotherapy by cediranib was reported in a randomized phase II study in non-small cell lung cancer, whereas the addition of cediranib to paclitaxel plus carboplatin resulted in improved tumor responses and PFS for cediranib compared with placebo and chemotherapy. Toxicities in the experimental arm led to a significant number of dose reductions, thus highlighting the challenges of adding targeted antiangiogenics to standard chemotherapy.[44]

In summary, the activity of cediranib monotherapy in MPM after platinum-based therapy was modest, although we identified a small subset of patients with MPM whose tumors seem to be highly driven by angiogenic signaling, thus conferring high sensitivity to this agent. The challenge remains to develop strategies that would enable the selection of patients with MPM for treatment with targeted antiangiogenic therapies. Although a large number of potentially predictive biomarkers for response to antiangiogenic therapy have been studied, none have been validated for routine clinical use. Given the signal of activity of single-agent cediranib reported in this study, and the potential of antiangiogenics to augment the activity of cytotoxic chemotherapy, the Southwest Oncology Group has initiated a phase I/randomized phase II clinical trial of cediranib versus placebo in combination with pemetrexed/cisplatin for first-line treatment of MPM. Both tumor-based and surrogate biomarkers of angiogenesis will be collected in the context of this study, to elucidate biomarkers that may allow for the personalization of antiangiogenic therapy in MPM.

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