Phase II Study of AZD2171 in Patients with Malignant Pleural Mesothelioma: SWOG S0509

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Abstract

Background—Malignant pleural mesothelioma (MPM) tumors express VEGF and VEGF receptors. MPM patients have high circulating levels of VEGF, suggesting that tumor angiogenesis is a relevant therapeutic target for MPM. We conducted a phase 2 trial of the VEGFR1/2 TKI AZD2171 in patients with MPM after platinum-based systemic chemotherapy.

Patients and Methods—Patients (pts) with MPM previously treated with a platinum-containing chemotherapy regimen, good performance status, measureable disease and no significant bleeding diathesis or thrombotic history were eligible for enrollment. Pts were treated with AZD2171 45 mg/day on days 1-28 of each 28 day dosing cycle. Tumor measurements were made by RECIST criteria, with a subset analysis of modified RECIST. A two-stage design with a stopping rule based on number of patients with complete or partial response was utilized.

Results—Fifty-four patients were enrolled on study between 11/05 and 4/08. For 47 evaluable patients, 4 patients (9%) had objective responses, including two patients who had 91% and 56% responses in bulky pleural tumor; 16 patients (34%) had stable disease, 20 pts (43%) had disease progression; 2 pts (4%) had symptomatic deterioration and 1 pt (2%) had early death. Four were not assessable for response and assumed to be non-responders. The most common AZD2171-attributable toxicities were fatigue (64%), diarrhea (64%) and hypertension (70%); the majority 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.

Conclusions—The anti-angiogenic AZD2171 has modest single agent activity in MPM. However, several patient tumors were exquisitely sensitive to AZD2171. The starting dose was not well tolerated in this setting. Tumor response by Modified RECIST available for a small subset of patients correlated well with tumor response by RECIST. This study provides a rationale for further testing of AZD2171 with chemotherapy in MPM.

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INTRODUCTION

Malignant pleural mesothelioma (MPM) is a neoplasm that originates in the parietal pleura that 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 asbestos exposure.[1] MPM is a rare cancer, with between two and three thousand cases diagnosed in the United States per year; it is expected that the incidence of MPM will peak around 2010.[2] Globally, however, less stringent regulation of occupational asbestos has resulted in the more recent or continued exposure of large populations asbestos and to continued increase in new cases of MPM in Australia, Britain, 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 - 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] There currently 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.

There is evidence supporting the existence of an autocrine growth loop involving VEGF and its cognate receptors for MPM. VEGF and its cognate receptors VEGFR-1 (flt) and R-2 (KDR) are expressed in human MPM cell lines, with higher levels of VEGF detected in MPM cell line cultures than in normal mesothelial cell cultures. [8] The addition of rhVEGF to MPM cell line cultures stimulates cell proliferation in a dose-dependent manner, while inhibitors of VEGF and VEGF-C inhibit mesothelioma cell growth.[9,10] Human MPM tumors express the angiogenic cytokines VEGF, FGF-1 and -2, and TGFβ, [11,12]; additionally, the co-expression of VEGF and VEGF-R1 in human MPM has been reported.[13] MPM patients have high circulating levels of VEGF[14]. Some studies have reported tumor VEGF expression and tumor microvessel density to be independent prognostic markers.[15,16] These data suggest that tumor angiogenesis may be a relevant therapeutic target in MPM.

AZD2171 (Cediranib; AstraZeneca Pharmaceuticals, Wilmington, DE) is an orally active, potent, tyrosine kinase inhibitor (TKI) of VEGFR-1,-2 and -3 at nanomolar concentrations, as well as c-Kit and PDGFR-β.[17,18] In phase I studies the maximum tolerated dose was defined as 20-45 mg daily, with reported dose limiting toxicities of proteinuria, diarrhea, thrombocytopenia, hypertension and hypertensive crisis. [19-21] AZD2171 has single agent anti-tumor activity (partial responses and disease stabilization) in a number of solid tumors including ovarian cancer, alveolar soft tissue sarcoma, gastric cancer, biliary cancer, pancreatic cancer, CRC, prostate, RCC, breast cancer, thyroid cancer and NSCLC.[21-24]

Given that tumor angiogenesis is a potential therapeutic target in MPM and that AZD2171 has shown tolerability and anti-tumor efficacy in a number of solid tumors, we performed a Phase II trial of AZD2171 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 AZD2171 in second line MPM. Secondary objectives were to measure survival outcomes as well as to define the toxicity profile of AZD2171 in this setting. A protocol amendment was made to also capture tumor response by modified RECIST for pleural tumors.[25]

PATIENTS AND METHODS

Inclusion Criteria

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

Patients were not eligible if they had severe systemic co-morbid disease or a significant cardiac history, uncontrolled hypertension, significant proteinuria, a prolonged QTc interval, were either pregnant or breastfeeding, 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 (CTEP) of the National Cancer Institute and the institutional review boards of participating SWOG member sites. Written informed consent was obtained from all patients prior to enrollment. This study was monitored by the Data and Safety Monitoring Committee of the Southwest Oncology Group.

Study Design

The S0509 treatment protocol (ClinicalTrials.gov_Identifier: NCT0024307) consisted of single-agent AZD2171 administered orally at 45 mg/day on days 1-28 of each 28 day dosing cycle. No a priori limit on number of treatment cycles per patient was made. Adverse events were graded according to the CTC Version 3.0. Sequential dose modifications to 30 mg and 20 mg daily were allowed, although a further dose reduction to 10 mg daily was allowed for patients on study 3 months who were benefiting from treatment. Dose delay until toxicity resolved to Grade 1 and dose modification were made for Grade 3 non-hematologic and/or Grade 4 hematologic toxicities, and < Grade 3 but moderate hypertension, and proteinuria).

Patient history, physical examination, hematologic and chemical laboratory analyses were performed prior to beginning cycle 1 of therapy and prior to each subsequent treatment cycle. Tumor measurements were performed after every 2 treatment cycles. Tumor responses were judged by the response evaluation criteria in solid tumors (RECIST) guidelines.[26] A protocol amendment was made to capture tumor measurements using the Modified RECIST measurement system.[27] Patients were withdrawn from study for 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. A 2-stage design was employed such that 20 patients would be enrolled in the first stage, with an evaluation of response rate and safety performed. A response rate of 20% or higher would be sufficient to declare this regimen worthy of further study, while a response rate of 5% or lower would be indicate no further interest in this setting. If at least one confirmed partial response was noted, the study would continue accrual to a total of 40 patients. 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%.

Results

Patients

Patient recruitment was undertaken from November, 2005 through April, 2008, with a 3-month temporary closure for first stage evaluation. A total of 54 patients were registered, with 48 eligible for enrollment, but 1 patient not analyzable due to refusal of treatment. Patient characteristics for the 47 patients are presented in Table 1. The median patient age was 66.8 years (range 43 to 84 years). The majority of patients were male. Racial composition was white (94%), not available (6%); 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 < 5% loss of body weight within the 6 months prior to enrollment.

Tumor histologic subtype was classified as epithelial (60%), biphasic (6%); and not otherwise specified (23%) by local institution pathology review. No patient had a sarcomatous histology tumor. A formal central pathology review was not performed.

Response and Survival

For 4 patients, response was not able to be determined due to inadequate assessment. These four patients are assumed to be non-responders and are included in calculations of response rate. For 43 evaluable patients, response data are summarized in Table 2. There were no complete responses. Four patients (9%) had partial responses, including two patients with bulky disease who had 91% and 56% tumor shrinkage (See Figures 1a-d). Sixteen patients (34%) had stable disease, documented at least 6 weeks after registration and before progression or symptomatic deterioration range 2.4 to 13.7 months). Twenty patients (43%) had progressive disease, 2 patients (4%) had symptomatic deterioration, and 1 patient (2%) had early death.

Overall survival for 47 patients is shown in Figure 2. Forty-three had died at the time of analysis; the median overall survival was 9.5 months (95% C.I. 5.6-10.7 months) and one year survival was 36% (95% C.I. 23-50%). Progression-free survival (PFS) is shown in Figure 3. Forty-seven patients have progressed or died. Median PFS was 2.56 months (95% C.I 1.74-3.68 months) and one-year progression-free survival was 4% (95% C.I. 1-13 %). For 16 patients with stable disease, median time to progression is 4.9 months (95% C. I. 3.6 to 5.4 months).

Adverse Events

Forty-seven patients were assessable for adverse events. Hematological adverse events attributed to AZD2171 were infrequent and of grades 1-2 only (Table 3).

Grade 1-4 non-hematological adverse events noted in 10% of patients attributable to AZD2171 are listed in Table 4; the most common adverse events were fatigue, hypertension, and diarrhea. Rare (<10%) grade 3 and grade 4 events included apnea, ataxia, cognitive disturbance, intestinal pain, colitis, dizziness, encephalopathy, esophageal necrosis, ileal perforation, hand-foot syndrome, hypokalemia, hyponatremia, hypotension, chest wall pain, memory impairment, elevated serum ammonia, generalized muscle weakness, pain NOS, tumor pain, renal failure, speech impairment, and thrombosis/embolism. Biochemical abnormalities were infrequent and of grades 1-2 only (Table 5). There were no treatment-related deaths.

Dose de-escalation was made in 43 of 47 patients. Six patients were removed from the study due to adverse events attributed to treatment with AZD217. Two patients withdrew from the

study for reasons not related to adverse events. Thirty-six patients were withdrawn for disease progression, two patients were withdrawn due to early death, and one patient was withdrawn for unspecified reasons.

Modified RECIST correlation with RECIST

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

DISCUSSION

Interest in studying the anti-angiogenic agent AZD2171 in MPM was based on a significant body of evidence suggesting that angiogenesis is an important growth signaling pathway for MPM. In the second line setting, AZD2171 showed modest clinical activity as a single agent, with 9% of patients having had objective tumor responses, including 2 with marked shrinkage of bulky tumors. Because anti-angiogenic agents may induce a cytostatic rather than cytoreductive tumor response, stable disease is considered an important outcome measure in clinical trials of anti-angiogenics. In this uncontrolled trial, 34% of patients had stable disease, yielding a clinical benefit rate (CR, 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%) reported in a phase III study of second line pemetrexed vs. BSC.[28,29] There are, however, distinct limitations in using clinical benefit rate derived from single arm phase 2 studies in MPM due to confounding by the quite 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 anti-angiogenics and other potentially cytostatic agents in MPM.

For the entire study population the median PFS was short (2.56 months), similar to time to progression reported for some targeted agents that have been deemed inactive in MPM.[30-32] Looking at response rate and survival outcome measures together, this study's efficacy data are in concert with those for other agents that target multiple receptor tyrosine kinases including the VEGF receptors. 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/second-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.[33-35] In contrast, bevacizumab, a monoclonal antibody that blocks VEGF ligand binding to the VEGF receptors, did not have meaningful clinical activity when combined with the EGFR inhibitor erlotinib in previously treated MPM, nor did bevacizumab enhance the activity of cytotoxic chemotherapy for front-line treatment of pleural/peritoneal mesothelioma, for reasons that are not clear. [36,37]

PDGF-mediated signaling by AZD2171 may have played a role in the anti-tumor activity noted in the current study. PDGF receptor β is highly expressed in mesothelioma cell lines but not in normal human mesothelioma cells, and PDGF appears to be a paracrine growth factor for mesothelioma.[38,39] In vitro, imatinib mesylate, a potent inhibitor of PDGF α and β receptors and c-Kit, synergized with gemcitabine and pemetrexed in PDGFRβ-positive mesothelioma cells.[40] In a xenograft model of MPM, imatinib mesylate enhanced the activity of gemcitabine.[41] In the clinical setting, however, no significant efficacy was reported for single agent imatinib mesylate in unselected MPM patients.[42] We did not study the expression of PDGF receptor β in patient tumors and therefore, we were unable to determine a role for PDGF signaling inhibition by AZD2171 in this study.

In this study cohort of patients with a good performance status after one platinum-based prior systemic therapy, AZD2171 was not well tolerated at the starting dose of 45 mg daily, and the majority of patients required a dose reduction. Several phase I studies of AZD2171 in solid tumor patients determined the MTD to be lower than 45 mg.[20,21] The safety profile of AZD2171 as a second line agent in MPM was similar to that already reported for this and other VEGF receptor tyrosine kinase inhibitors.

MPM is a difficult tumor to measure accurately, as are other pleural-based tumor types, given the non-spherical pattern of growth. Limitations of RECIST in assessing response and outcome measures such as progression-free survival have been documented.[43] Other measurement systems for pleural tumors have been devised, including modified RECIST, in which pleural thickness is measured perpendicular to the chest wall and mediastinum.[27] To further investigate modified RECIST as a measurement system, we captured modified RECIST measurements via an amendment once the study had already been initiated and 27 patients had already been enrolled. We were only able to capture modified RECIST measurements for a small subset of patients, where tumor response assessment by modified RECIST correlated well with response by RECIST. Presumably, unfamiliarity with modified RECIST as well as difficulties in obtaining retrospective tumor measurements impacted on the collection of modified RECIST measurements. Modified RECIST and other means of assessing pleural tumor response such as PET imaging and volumetric measurement systems should be routinely incorporated into large clinical MPM trials in order to validate these measurement systems.

Anti-angiogenic 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.[44] Both VEGF and PDGF contribute to increased TIFP, while inhibitors of VEGF and/or PDGF signaling can reduce TIFP and augment chemotherapy effects in vivo.[45-50] Given that MPM is relatively resistant to standard cytotoxic chemotherapy, there is great interest in pursuing strategies that would improve the chemosensitivity of MPM. The addition of AZD2171 to cytotoxic chemotherapy in solid tumors is feasible as shown in a number of phase I studies[51-53], and an augmentation of the effect of chemotherapy by AZD2171 was reported in a randomized phase II study in NSCLC, where the addition of AZD2171 45 mg daily to Taxol plus Carboplatin resulted in improved tumor responses and PFS for AZD2171 compared with placebo with chemotherapy. Toxicities in the experimental arm led to a significant number of dose reductions, thus highlighting the challenges of adding targeted anti-angiogenics to standard chemotherapy.[54]

In summary, there appears to be a small subset of MPM patients whose tumors are highly driven by angiogenic signaling, thus conferring moderate to exquisite sensitivity to single agent tyrosine kinase inhibition of the VEGF receptors. It remains of paramount importance to develop strategies that would enable the selection of MPM patients for treatment with targeted anti-angiogenic therapies. While a large number of potentially predictive biomarkers for response to anti-angiogenic therapy have been studied, none have been validated for routine clinical use. The small number of responding patients in this study set did not allow us to investigate, with appropriate statistical power, potentially predictive tumor and surrogate serum-based markers of response to AZD2171. Given the signal of activity of single agent AZD2171 in second line MPM reported here, and the potential of anti-angiogenics to augment the activity of cytotoxic chemotherapy, the Southwest Oncology Group has initiated a Phase I/randomized Phase II clinical trial of pemetrexed plus cisplatin with or without AZD2171 for first-line treatment of MPM. Both tumor-based and surrogate biomarkers of angiogenesis will be collected in the context of this study, in order

to attempt to elucidate biomarkers that may allow for the personalization of anti-angiogenic therapy in MPM.

Acknowledgments

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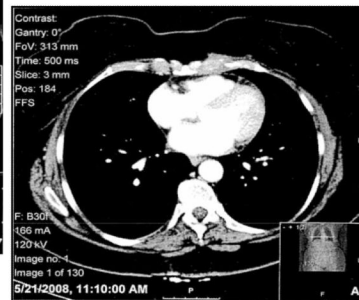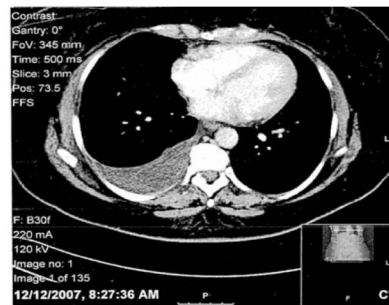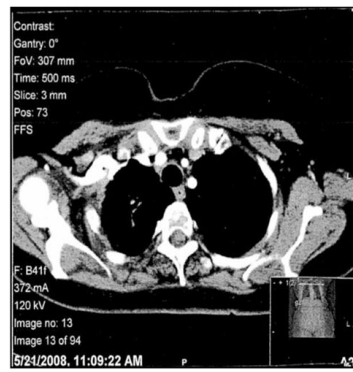
Figure 1. Tumor response after 5 weeks of AZD2171 treatment by CT imaging
1a: Pre-treatment, upper hemithorax
1b:Post-treatment, upper hemithorax
1c: Pre-treatment, lower hemithorax
1d: Post-treatment, lower hemithorax
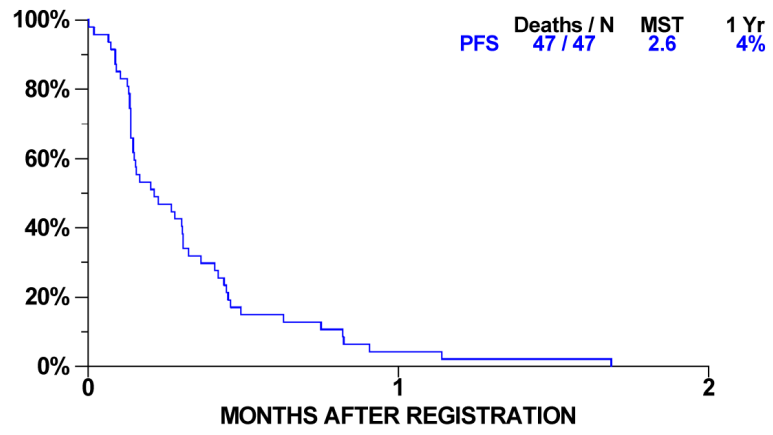
Figure 2. Progression Free Survival
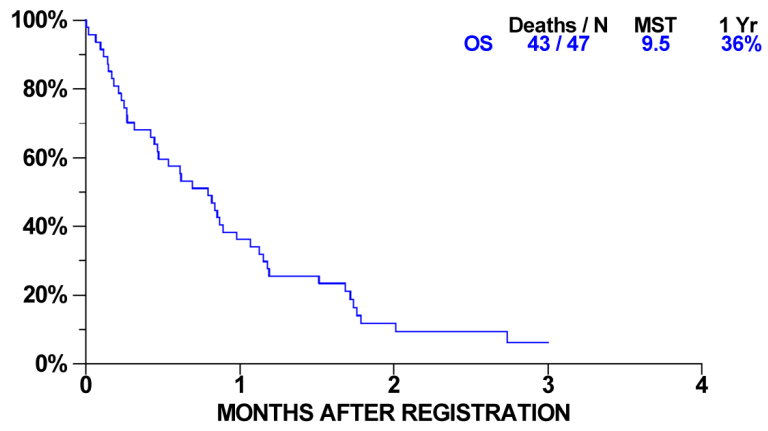
Figure 3. Overall Survival

Table 1

Patient Characteristics

N=47	
Median age (years)	66.8 (range 43-84)
Male:Female (%)	38:9 (81%: 19%)
Zubrod Performance Status	
	0: 1: 34% 53%
	2: 13%
Six month prior weight loss:	
	<5%: 70%
	5-<20%: 17%
	>20%: 4%
	Not reported: 9%

Table 2
Antitumor Activity – Best Overall Response

N=43	
Complete Response (CR)	0
Partial Response (PR)	4 (9%)
Stable Disease (SD)	16 (34%)
Progressive Disease (PD)	20 (43%)
Symptomatic Deterioration	2 (4%)
Early Death	1 (2%)

Table 3

Hematological Toxicity

N=47	Grade		
	1	2	% Pts
Anemia	5	1	13%
Leukopenia	1	0	2%
Neutropenia	1	0	2%
Thrombocytopenia	7	0	15%

Table 4

Grade 1-4 Non-Hematological Toxicity (≥ 10% Frequency)

N=47	Grade				% Pts
	1	2	3	4	
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					

N=47	Grade			
Hypothyroidism	2	4	0	0	13%

Table 5

Biochemical Toxicity

N=47	Grade		
	1	2	% Pts
Creatinine	3	2	11%
Alkaline phosphatase	4	1	11%
ALT	7	1	17%
AST	6	2	17%
Hyperglycemia	5	1	13%
Hypoalbuminemia	4	1	11%