Title

Phase II Trial of Cediranib in Combination With Cisplatin and Pemetrexed in Chemotherapy-Naïve Patients With Unresectable Malignant Pleural Mesothelioma (SWOG S0905).

Journal

Journal of Clinical Oncology, 37(28)

ISSN

0732-183X

Authors

Tsao, Anne S
Miao, Jieling
Wistuba, Ignacio I
et al.

Publication Date

2019-10-01

DOI

10.1200/jco.19.00269

Peer reviewed

ORIGINAL ARTICLE

Phase I Trial of Cediranib in Combination with Cisplatin and Pemetrexed in Chemonaive Patients with Unresectable Malignant Pleural Mesothelioma (SWOG S0905)

Anne S. Tsao, MD,[a,*] James Moon, MS,[b] Ignacio I. Wistuba, MD,[c] Nicholas J. Vogelzang, MD,[d] Gregory P. Kalemkerian, MD,[e] Mary W. Redman, PhD,[b] David R. Gandara, MD,[f] Karen Kelly, MD[f]

[a]*Department of Thoracic and Head and Neck Medical Oncology, University of Texas M. D. Anderson Cancer Center, Houston, Texas*
[b]*SWOG Statistical Center, Seattle, Washington*
[c]*Department of Translational Molecular Pathology, University of Texas M. D. Anderson Cancer Center, Houston, Texas*
[d]*Comprehensive Cancer Centers of Nevada, Las Vegas, Nevada*
[e]*University of Michigan, Ann Arbor, Michigan*
[f]*University of California Davis Cancer Center, Sacramento, California*

Received 10 March 2017; revised 3 May 2017; accepted 4 May 2017
Available online - 6 June 2017

ABSTRACT

Introduction: In malignant pleural mesothelioma, targeting angiogenesis with cediranib, a vascular endothelial growth factor receptor and platelet-derived growth factor receptor inhibitor, may have therapeutic potential.

Methods: S0905 phase I combined cediranib (two dose cohorts [30 mg and 20 mg daily]) with cisplatin-pemetrexed for six cycles followed by maintenance cediranib in unresectable chemonaive patients with malignant pleural mesothelioma of any histologic subtype. The primary end point established the maximum tolerated dose in combination with cisplatin-pemetrexed in a dose deescalation scheme.

Results: A total of 20 patients were enrolled (seven to the 30-mg cohort and 13 to the 20-mag cohort). In the cediranib 30-mg cohort, two of the initial six patients reported dose-limiting toxicities and the dose was deemed too toxic to continue. In the next cohort, two patients experienced dose-limiting toxicities, and thus, the maximum tolerated dose of cediranib was established as 20 mg. During the six cycles of cisplatin-pemetrexed-cediranib, 20 mg, there were grade 3 toxicities (neutropenia and gastrointestinal) and grade 4 thrombocytopenia. No patients had any significant episodes of bleeding. According to the Response Evaluation Criteria in Solid Tumors (n = 17 evaluable patients), the median progression-free survival was 12.8 months (95% confidence interval [CI]: 6.9–17.2); according to the Modified Response Evaluation Criteria in Solid Tumors (n = 19 evaluable patients), the median progression-free survival was 8.6 months (95% CI: 6.1–10.9). For all patients, the disease control rate at 6 weeks was 90% and median overall survival time was 16.2 months (95% CI: 10.5–28.7).

Conclusions: Cediranib combined with cisplatin-pemetrexed has a reasonable toxicity profile and preliminary promising efficacy. The phase II S0905 trial will evaluate the efficacy of the triplet regimen compared with the current standard of care, cisplatin-pemetrexed.

Key words: Mesothelioma; Cediranib; Cisplatin; Pemetrexed

***Corresponding author.**

Disclosure: Dr. Kalemkerian reports grants from Merck, OncoMed, Pfizer, GlaxoSmithKline/Novartis, Astex, and Millennium outside the submitted work. Dr. Kelly reports personal fees from AstraZeneca outside the submitted work. Dr. Tsao reports research grants and compensation for advisory board service from AstraZeneca during the conduct of the study, as well as grants and personal fees from Bristol-Myers Squibb, Ariad, Boehringer-Ingelheim, and Polaris; personal fees from Genentech and Roche; and grants from Lilly, Millennium/Takeda, Seattle Genetics, Epizyme, and Merck outside the submitted work.

Trial Registration: Pemetrexed Disodium and Cisplatin with Cediranib Maleate in Treating Patients with Malignant Pleural Mesothelioma. NCT01064648.

Address for correspondence: Anne S. Tsao, MD, Department of Thoracic and Head and Neck Medical Oncology, Unit 432, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030. E-mail: astsao@mdanderson.org

ISSN: 1556-0864
http://dx.doi.org/10.1016/j.jtho.2017.05.021

Introduction

Malignant pleural mesothelioma (MPM) is a rare disease with limited treatment options and a median survival time of 12 months for unresectable patients.[1] In the frontline setting, cisplatin-pemetrexed has been the accepted standard of care since 2003.[1] Recently, the first therapeutic advance since the approval of pemetrexed and cisplatin was made when the addition of bevacizumab to the cisplatin-pemetrexed backbone prolonged survival over cisplatin-pemetrexed alone.[2] This success has provided the impetus to continue to evaluate angiogenesis inhibitors in this disease.

The angiogenic pathway plays an important role in mesothelioma. Preclinical studies have demonstrated a high dependency of MPM on the vascular endothelial growth factor (VEGF)/vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor (PDGF)/platelet-derived growth factor receptor (PDGFR) pathway.[3–5] Mesothelioma tumor cells have the highest secretion of VEGF ligand with pathway activation compared to other solid tumors and rely on the PDGF/PDGFR pathway for an autocrine loop proliferation.[3,6–13] In vitro and xenograft mesothelioma studies[14–16] have demonstrated that inhibition of the PDGF pathway leads to antitumor effects, and a phase I trial[17] of imatinib mesylate, a PDGFR inhibitor, combined with cisplatin-pemetrexed showed potential clinical benefit but low tolerance to therapy.

Previously, three small phase II trials[18–20] found that the addition of bevacizumab to platinum doublets in mesothelioma did not appear to augment clinical efficacy in the intent-to-treat population. In one of these studies,[18] patients with levels of serum VEGF higher than the median had a worse progression-free survival (PFS) and overall survival (OS), and they had less survival benefit with the addition of bevacizumab. As bevacizumab targets VEGF, an intrinsic mechanism of resistance may be present in mesothelioma that secretes high levels of VEGF. However, the French Intergroupe Francophone de Cancerologie Thoracique recently conducted the phase II/III Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS) trial[2] in 448 patients and demonstrated a greater than 2-month median OS benefit with the addition of bevacizumab to cisplatin-pemetrexed in the intent-to-treat population. This study supports the hypothesis that antiangiogenic agents have clinical efficacy in certain patients with mesothelioma.

We hypothesized that targeting the VEGF receptor would potentially bypass the potential resistance of high VEGF ligand secretion and ultimately provide clinical efficacy for patients with mesothelioma. In addition, targeting other angiogenic pathways, such as PDGF/PDGFR, made sense to enhance the antitumor effect.[21]

Cediranib (Recentin, AZD2171 [AstraZeneca Pharmaceuticals, Cheshire, United Kingdom]) is an oral tyrosine kinase inhibitor (TKI) of $VEGFR_{1,2,3}$, PDGFR, and c-KIT. Cediranib at a daily dose of 45 mg demonstrated antitumor activity in patients with mesothelioma in a second-line monotherapy trial, SWOG 0509.[22] This study reported a 9% response rate and 34% disease stabilization rate with a median PFS of 2.56 months and median OS of 9.5 months. Most patients did require a dose reduction from the daily dose of 45 mg.

A frontline trial, SWOG 0905, was therefore designed as a phase I/II combination trial of cisplatin-pemetrexed with and without cediranib. The phase I portion was designed as a safety study to evaluate two different doses of cediranib (30 mg and 20 mg) in combination with cisplatin-pemetrexed for six cycles of therapy followed by cediranib maintenance therapy. This article reports on the results of the phase I trial. The phase II portion of the trial has completed enrollment of 98 patients and data analysis is expected in winter 2017.

Methods

Patients and Methods

Adult patients with a histologically confirmed diagnosis of MPM of any histologic subtype were eligible. Other key inclusion criteria included disease measurable or not measurable by either Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 or Modified RECIST for Pleural Tumors; no prior systemic therapy (chemotherapy or other biologic therapy); a Zubrod performance status of 2 or less; and adequate hepatic (serum bilirubin level not exceeding the upper limit of normal and transaminase level of $\leq 1.5\times$ the upper limit of normal), hematologic (absolute neutrophil count of ≥ 1500/mL and platelet count of $\geq 100{,}000$/mL), renal (serum creatinine level $\leq 1.5\times$ the upper limit of normal or a measured creatinine clearance of ≥ 50 mL/min), and cardiac function. Patients may have undergone a prior surgical procedure (e.g., pleurectomy or pleurodesis) or received prior radiation therapy. Patients were not eligible if they had severe systemic comorbid disease or a history of significant cardiac disease, uncontrolled hypertension, significant proteinuria, a prolonged QTc interval, or gastrointestinal tract disease resulting in the inability to take oral medication. Patients could not have a history of clinically significant hemoptysis or other bleeding issues.

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 the 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 SWOG. Additional patient consent was required for the banking and future use of specimens.

Patient history taking, physical examination, and hematologic and chemical laboratory analyses were performed before cycle 1 and each subsequent cycle of therapy. Radiographic tumor measurements were performed after every two treatment cycles. Tumor response assessments were determined by RECIST 1.1. However, additional tumor measurements using the Modified RECIST measurement system as described in Tsao et al.[23] were also obtained for exploratory research purposes. Patients were withdrawn from the study in the event of disease progression or symptomatic deterioration, unacceptable toxicity as assessed by the study physician, treatment delay of greater than 3 weeks, need for more than the allowed number of dose modifications, or patient request.

Cisplatin (75 mg/m^2) and pemetrexed (500 mg/m^2) were administered intravenously on day 1 every 3 weeks. Dose modifications for chemotherapy were conducted per standard guidelines. Vitamin supplementation with folic acid, 400 μg daily, and vitamin B12, 1000 μg by intramuscular injection every 9 weeks, was mandatory for all patients and initiated 1 week (on day −7) before cycle 1 of cisplatin-pemetrexed and cediranib. Carboplatin substitution was allowed if toxicity to cisplatin developed. Cediranib was given concomitantly on day 1 and continued daily. Two doses of cediranib, 30 mg and 20 mg, were evaluated. No further dose reductions or modifications were allowed. No primary prophylaxis with granulocyte colony-stimulating factor or antibiotics was allowed.

Statistics

The primary end point of this study was to establish the maximum tolerated dose (MTD) and the recommended phase II dose of cediranib in combination with cisplatin and pemetrexed in patients with MPM. The phase I trial was a limited dose deescalation study with two potential doses of cediranib (30 mg and 20 mg daily). The dose-limiting toxicities (DLTs) were defined as febrile neutropenia, grade 4 neutropenia of more than 7 days' duration, grade 4 thrombocytopenia, or grade 3 or 4 nonhematologic toxicity (excluding alopecia). Only DLTs occurring during cycle 1 were used to guide dosing determination. Patients were considered evaluable for DLT if they received at least 14 doses (50% of the planned dose) of cediranib in combination with pemetrexed and cisplatin during cycle 1. Patients who were not evaluable for DLT were replaced. The regimen was considered safe and the MTD determined if the DLT rate of cediranib and cisplatin-pemetrexed was 33% or lower.

The following dosing scheme was used. Enroll six evaluable patients at the 30-mg dose level. If three or more patients experienced a DLT, enrollment would stop and the study would proceed to the 20-mg dose level. If zero to two patients experienced a DLT, four additional patients were accrued. If zero to three patients experienced a DLT, then the 30-mg dose would be declared the MTD. If four or more patients experienced a DLT, the trial would continue to the 20-mg dose level. At the reduced dose level the aforesaid rules would apply. If zero to three of 10 patients experienced a DLT, the 20-mg dose level would be the MTD. However, if three of the initial six or four or more out of 10 patients experienced a DLT, then neither the 30- mg nor the 20-mg would be considered the MTD.

Only patients with measurable disease at baseline, as defined by the specific criteria, were included in the response analysis. PFS, disease control rate, and duration of response were also analyzed by RECIST 1.1 and by Modified RECIST. Disease control was defined as absence of progression at the first follow-up assessment. Duration of response was defined as time from the date of initial documentation of partial or complete response until date of progression or death, with patients censored at date of last contact if last known to be alive and progression-free. OS, PFS, and duration of response were all estimated by the method of Kaplan-Meier.

Results

A total of 20 patients were enrolled into this study from March 15, 2010, until July 18, 2011. Patient demographics are listed in Table 1. There were seven patients in dose cohort 1 (30 mg) and 13 patients in dose cohort 2 (20 mg). Both cohorts were similar, with a median age of 64 years, predominantly white ethnicity (71% and 77%), and majority performance status of 0 or 1 (100% and 92%). However, whereas all patients enrolled in the 30-mg cohort had the epithelioid histologic subtype, the 20-mg cohort included two patients with the biphasic histologic subtype of mesothelioma and one with a not otherwise specified histologic subtype.

In the cediranib 30-mg dose cohort, one patient, who misunderstood instructions, took only four doses of cediranib during cycle 1 and was thus not evaluable for DLT. This patient was replaced per protocol. Two of the initial six evaluable patients reported DLTs and were dose-reduced—one on account of grade 3 fatigue and one owing to grade 3 fatigue and grade 3 diarrhea. Although technically this did not reach the formal stopping rule (three or more of the first six patients with a DLT), the Lung Committee leadership and treating investigators decided that the cediranib dose of 30 mg

Table 1. Patient Demographics

Characteristic	Cohort 1 Cisplatin-Pemetrexed Cediranib, 30 mg Daily (n = 7)	Cohort 2 Cisplatin-Pemetrexed Cediranib, 20 mg Daily (n = 13)
Median age (range), y	64.9 (47.5-83.6)	64.0 (43.7-74.1)
Sex (male-to-female ratio)	5:2	10:3
Race		
White	5 (71%)	10 (77%)
African American	1 (14%)	1 (8%)
Asian	1 (14%)	1 (8%)
Unknown	0 (0%)	1 (8%)
Hispanic	0%	1 (8%)
Performance status		
0-1	7 (100%)	12 (92%)
2	0 (0%)	1 (8%)
Histologic subtype		
Epithelioid	7 (100%)	10 (77%)
Biphasic	0 (0%)	2 (15%)
Sarcomatoid	0 (0%)	0 (0%)
Mesothelioma NOS	0 (0%)	1 (8%)
History of surgical procedure		
VATs procedure for pleural biopsy	6 (68%)	7 (54%)
Partial pleurectomy/decortication	0 (0%)	2 (15%)
Pleurectomy/decortication	0 (0%)	0 (0%)
Extrapleural pneumonectomy	0 (0%)	1 (8%)
History of radiotherapy		
Definitive (curative) intent	0 (0%)	1 (8%)
Palliative	3 (43%)	1 (8%)
Measurable disease per RECIST 1.1	7 (100%)	10 (77%)
Measurable disease per Modified RECIST for Pleural Tumors	7 (100%)	12 (92%)

NOS, not otherwise specified; VATS, video-assisted thoracoscopic surgery; RECIST, Response Evaluation Criteria in Solid Tumors.

was difficult for patients to continue, as two of the six patients required dose reductions to 20 mg of cediranib during cycle 1. Therefore, the study was not expanded to a total of 10 patients.

Six of the seven patients completed the six cycles of the triplet regimen, and five had nine or more cycles of maintenance therapy. The median number of cycles of all study treatment in the 30-mg cohort was 17 (range two to 32). The most common toxicities associated with therapy during cycle 1 in the 30-mg cediranib cohort included grade 2 or 3 fatigue, grade 1 or 2 nausea, and grade 1 or 2 lymphopenia, (Table 2). When all six cycles of therapy for the combination of cisplatin-pemetrexed in the 30-mg cediranib cohort were assessed (Table 3), five patients (71%) had grade 3 adverse events due to diarrhea (n = 1), fatigue (n = 2), lymphopenia (n = 2), and neutropenia (n = 1). The most common grade 1 or 2 toxicities during all six cycles of triplet therapy included gastrointestinal complaints (anorexia, diarrhea, nausea, and vomiting), fatigue, hypomagnesemia, hyponatremia, lymphopenia, neutropenia, and anemia. There were three reported cases of grade 1 or 2 hypertension. Five of the seven patients (71%) had chemotherapy delays and three patients required reductions of their cediranib dose, with one patient also requiring a dose delay of cediranib (Supplementary Tables 1 and 2).

In the maintenance cediranib 30-mg portion (n = 5 evaluable patients), the most common toxicities reported were diarrhea, hypomagnesemia, lymphopenia, neutropenia, nausea, vomiting, and proteinuria. There were five grade 3 events of diarrhea, hand-foot syndrome, hypomagnesemia, neutropenia, and weight loss (one each). Two of the five patients who received maintenance cediranib at a dose of 30 mg required dose delays (see Supplementary Table 1).

Thirteen patients were accrued to the lower dose level of cisplatin-pemetrexed and cediranib, 20 mg daily. One patient received only 13 daily doses of cediranib during cycle 1 because of a drug shipment error and was not evaluable for DLT. This patient was replaced per protocol. In addition, two patients who were in screening at the time of accrual completion were allowed to enroll. During cycle 1, two patients experienced DLTs, one due to grade 3 dehydration and one due to grade 3 hyponatremia. Thus, 20 mg of cediranib was determined to be the MTD.

Table 2. Number of Patients with Treatment-Related Adverse Events That Occurred during Cycle 1 among Patients Evaluable for Dose-Limiting Toxicities

	Cisplatin-Pemetrexed Cediranib, 30 mg (n = 6)		Cisplatin-Pemetrexed Cediranib, 20 mg (n = 12)	
	Grade		Grade	
Adverse Event	1-2	3	1-2	3
Nausea	3	0	8	0
Fatigue	3	2	5	0
Anorexia	2	0	4	0
Diarrhea	0	1	4	0
Hypomagnesemia	1	0	4	0
Hoarseness	2	0	2	0
Vomiting	2	0	2	0
Lymphopenia	4	0	0	0
Leucopenia	2	0	1	1
Abdominal pain	1	0	2	0
Constipation	2	0	1	0
Dehydration	0	0	2	1
Neutropenia	1	0	2	0
Anemia	1	0	1	0
Bllirubinemia	0	0	2	0
Edema, limbs	1	0	1	0
Hypertension	1	0	1	0
Hyponatremia	0	0	1	1
Mucositis, oral	1	0	0	1
Weight loss	0	0	2	0
Maximum grade of any adverse event	4	2	9	3

Note: Events less than grade 3 experienced by only one patient have been omitted.

Ten of the 13 patients completed six cycles of the triplet regimen. The median number of cycles of all study treatment received was 11 (range one to 41). During the triplet regimen, six of 20 patients (46%) required a chemotherapy delay and one patient also required a dose reduction of cisplatin (see Supplementary Table 1). Three patients required discontinuation of cisplatin-pemetrexed treatment, including two patients who were removed from all protocol treatment owing to toxicity. The most common toxicities during cycle 1 were grade 1 or 2 anorexia, grade 1 or 2 diarrhea, grade 1 or 2 fatigue, grade 1 hypomagnesemia, and grade 1 or 2 nausea (see Table 2). For all six cycles of combination cisplatin-pemetrexed with cediranib, 20 mg (see Table 3), the most common toxicities were grade 1 or 2 gastrointestinal symptoms (anorexia, nausea, vomiting, and diarrhea), dehydration, fatigue, hypomagnesemia, hyponatremia, hypokalemia, anemia, neutropenia, and proteinuria. Grade 3 toxicities were reported with neutropenia (n = 3), vomiting (n = 2), and one event each of abdominal pain, anemia, constipation, dehydration, diarrhea, fatigue, hypertension, hyponatremia, hypomagnesemia, mucositis, nausea, neuropathy, and pulmonary hypertension.

Two episodes of grade 4 thrombocytopenia were also reported. There were no patients with any significant episodes of bleeding. One patient in the cediranib 20-mg cohort was switched to carboplatin during cycle 4 on account of grade 3 neuropathy. One treatment-related death was noted in a patient who completed three cycles the triplet therapy and was suspected to have a septic event from pneumonia with associated hypotension and delirium.

Ten patients proceeded to maintenance therapy with cediranib. In the maintenance phase, the cediranib 20-mg cohort had grade 3 events of abdominal pain (n = 1), diarrhea (n = 1), heart failure (n = 1), and dyspnea (n = 2). Three patients required dose delays and one patient required a dose reduction (see Table 4).

Efficacy

The median follow-up among the four patients still alive as of last contact was 26 months (range 9–56). Table 5 summarizes the efficacy results. Two separate radiographic response measurements were utilized, RECIST 1.1 and Modified RECIST. In the 30-mg cohort, two out of seven evaluable patients had a partial response by RECIST 1.1, for a response rate of 29% (95% confidence interval [CI]: 0%–62%). The duration of these responses were 7.2 and 25.3 months. When

Table 3. Number of Patients with Treatment-Related Adverse Events during Cycles 1 to 6 of Cisplatin-Pemetrexed-Cediranib

	Cisplatin-Pemetrexed Cediranib, 30 mg (n = 7)				Cisplatin-Pemetrexed Cediranib, 20 mg (n = 13)			
	Grade				Grade			
Adverse Event	1-2	3	4	5	1-2	3	4	5
Nausea	5	0	0	0	11	1	0	0
Hypomagnesemia	6	0	0	0	9	0	0	0
Fatigue	4	2	0	0	6	1	0	0
Neutropenia	3	1	0	0	6	2	0	0
Vomiting	4	0	0	0	6	2	0	0
Anemia	4	0	0	0	7	1	0	0
Diarrhea	3	1	0	0	6	1	0	0
Leucopenia	6	0	0	0	4	1	0	0
Anorexia	5	0	0	0	6	0	0	0
Hyponatremia	4	0	0	0	4	1	0	0
Proteinuria	2	0	0	0	6	0	0	0
Thrombocytopenia	3	0	0	0	1	1	2	0
Dehydration	2	0	0	0	2	3	0	0
Weight loss	3	0	0	0	4	0	0	0
Constipation	3	0	0	0	2	1	0	0
Hypertension	3	0	0	0	2	1	0	0
Lymphopenia	3	2	0	0	0	0	0	0
Abdominal pain	2	0	0	0	2	1	0	0
Hoarseness	3	0	0	0	2	0	0	0
Hypoalbuminemia	3	0	0	0	2	0	0	0
Hypokalemia	0	0	0	0	3	1	0	0
AST level increased	3	0	0	0	1	0	0	0
Hypocalcemia	2	0	0	0	2	0	0	0
Mucositis oral	2	0	0	0	0	1	0	0
ALT level increased	2	0	0	0	1	0	0	0
Edema, limbs	2	0	0	0	1	0	0	0
Headache	1	0	0	0	2	0	0	0
Pain	2	0	0	0	1	0	0	0
Dyspnea	1	0	0	0	0	1	0	0
Peripheral sensory neuropathy	0	0	0	0	1	1	0	0
Alkaline phosphatase level increased	1	0	0	0	1	0	0	0
Arthralgia	2	0	0	0	0	0	0	0
Bilirubinemia	0	0	0	0	2	0	0	0
Creatinine level increased	1	0	0	0	1	0	0	0
Dizziness	0	0	0	0	2	0	0	0
Decreased oral intake	1	0	0	0	1	0	0	0
Generalized muscle weakness	0	0	0	0	2	0	0	0
Hyperkalemia	0	0	0	0	2	0	0	0
Hyperuricemia	0	0	0	0	2	0	0	0
Hypothyroidism	1	0	0	0	1	0	0	0
Myalgia	2	0	0	0	0	0	0	0
Altered mental status	0	0	0	0	0	0	0	1
Maximum grade of any adverse event	3	4	0	0	4	7	1	1

Note: Events less than grade 3 experienced by only one patient have been omitted.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Modified RECIST was applied, there were five patients with a partial response, including one that was unconfirmed, resulting in an estimated response rate of 71%, (95% CI: 38%–100%). The median duration of these responses was 5.9 months (95% CI: 3.0–9.7). The disease control rate was 86% (95% CI: 60%–100%) with both criteria.

In the 30-mg cohort, the median PFS by RECIST 1.1 was 12.8 months (95% CI: 3.1–14.6) and the median PFS by Modified RECIST was 10.1 months (95% CI: 4.5–10.9). The median OS was 16.2 months (95% CI: 7.5–28.7) (Fig. 1).

Within the 20-mg cohort, 10 of 13 patients had measurable disease. One patient withdrew consent after

Table 4. Number of Patients with Treatment-Related Adverse Events during Maintenance Cediranib Therapy (Cycle 7 or Later)

	Maintenance Cediranib 30 mg (n = 5)		Maintenance Cediranib 20 mg (n = 10)	
	Grade		Grade	
Adverse Event	1-2	3	1-2	3
Proteinuria	5	0	6	0
Hypomagnesemia	3	1	6	0
Anemia	3	0	7	0
Diarrhea	3	1	3	1
Anorexia	3	0	5	0
Creatinine level increased	1	0	6	0
Nausea	3	0	4	0
Vomiting	4	0	3	0
Leucopenia	5	0	2	0
Neutropenia	2	1	3	0
Weight loss	2	1	3	0
Fatigue	2	0	3	0
Thrombocytopenia	2	0	3	0
Dyspnea	1	0	1	2
Constipation	2	0	2	0
Hypertension	2	0	2	0
Metabolic/nutrition disorders, other	2	0	2	0
Abdominal pain	1	0	1	1
AST level increased	2	0	1	0
Bilirubinemia	1	0	2	0
Hoarseness	2	0	1	0
Hyperkalemia	0	0	3	0
Hyponatremia	2	0	1	0
Lymphopenia	3	0	0	0
Alkaline phosphatase level increased	2	0	0	0
Dysgeusia	1	0	1	0
Hyperglycemia	0	0	2	0
Hypoalbuminemia	1	0	1	0
Hypothyroidism	1	0	1	0
Pain	2	0	0	0
Diverticultis	0	0	0	1
Hand-foot syndrome	0	1	0	0
Heart failure	0	0	0	1
Maximum grade of any adverse event	2	3	6	4

Note: Events less than grade 3 experienced by only one patient have been omitted.
AST, aspartate aminotransferase.

completing the first cycle of treatment and did not have any follow-up disease assessments on protocol. This patient was counted in the denominator as a nonresponder for both RECIST 1.1 and Modified RECIST. A RECIST 1.1 response was observed in two patients (20% [95% CI: 0%–45%]). The durations of these responses were 17.1 and 1.5 months. By Modified RECIST, 12 patients had pleural thickness measurements reported at baseline. Seven patients had partial responses (three unconfirmed), for an estimated response rate of 58% (95% CI: 30%–86%). The median duration of these responses was 5.6 months (95% CI: 1.5–17.1). The disease control rate was 92% (95% CI: 78%–100%) with both criteria.

In the 20-mg cohort, the median PFS by RECIST 1.1 was 13.6 months (95% CI: 8.0–18.6), the median PFS by Modified RECIST was 8.6 months (95% CI: 6.9–13.1), and the median OS was 13.6 months (95% CI: 12.0–26.8) (see Fig. 1).

In total, 17 of 20 patients were evaluable for response by RECIST 1.1. The RECIST 1.1 response rate was 24% (95% CI: 3%–44%) and median PFS was 12.8 months (95% CI: 6.9–17.2). Nineteen patients were evaluable by Modified RECIST, with a response rate of 63% (95% CI: 41%–85%), a median duration of response of 5.6 months (95% CI: 3.0–9.7 months), and a median PFS of 8.6 months (95% CI: 6.1–10.9). For all patients, the disease control rate was 90% (95% CI:

Table 5. Efficacy Summary from All Patients from the Phase I SWOG 0905

Cohorts	RECIST 1.1 RR	RECIST 1.1 Median PFS	Modified RECIST RR	Modified RECIST Median PFS	DCR[a]	Median OS
All patients	n = 17 24%	n = 20 12.8 mo	n = 19 63%	n = 20 8.6 mo	n = 20 90%	n = 20 16.2 mo
30 mg of cediranib	n = 7 29%	n = 7 12.8 mo	n = 7 71%	n = 7 10.1 mo	n = 7 86%	n = 7 16.2 mo
20 mg of cediranib	n = 10 20%	n = 13 13.6 mo	n = 12 58%	n = 13 8.6 mo	n = 13 92%	n = 13 13.6 mo

[a]Identical for both RECIST 1.1 and Modified RECIST.
RR, response rate; PFS, progression-free survival; DCR, disease control rate; OS, overall survival.

77%–100%) and the median OS was 16.2 months (95% CI: 10.5–28.7).

Discussion

The phase I portion of SWOG0905 established that the MTD of cediranib was 20 mg daily in combination with cisplatin-pemetrexed. This triplet regimen was reasonably well tolerated with manageable toxicities. The main grade 3 or 4 adverse events were gastrointestinal toxicity, dehydration, and hematologic disorders. Cediranib certainly caused gastrointestinal toxicity and dehydration, which are not typically seen with cisplatin-pemetrexed alone.[1] It is also suspected that cediranib had an additive effect on hematologic toxicity. There was a 15% incidence of grade 3 or 4 thrombocytopenia with the triplet regimen, which is higher than the 5.4% seen in the Vogelzang trial[1] with cisplatin-pemetrexed alone. In the 30-mg cohort, grade 3 lymphopenia occurred in two patients, but no cases were reported in the cediranib 20-mg cohort. The addition of cediranib did not appear to increase the rates of grade 3 or 4 anemia or neutropenia, which were 4.2% and 23.2%, respectively, in the prior Vogelzang study.[1]

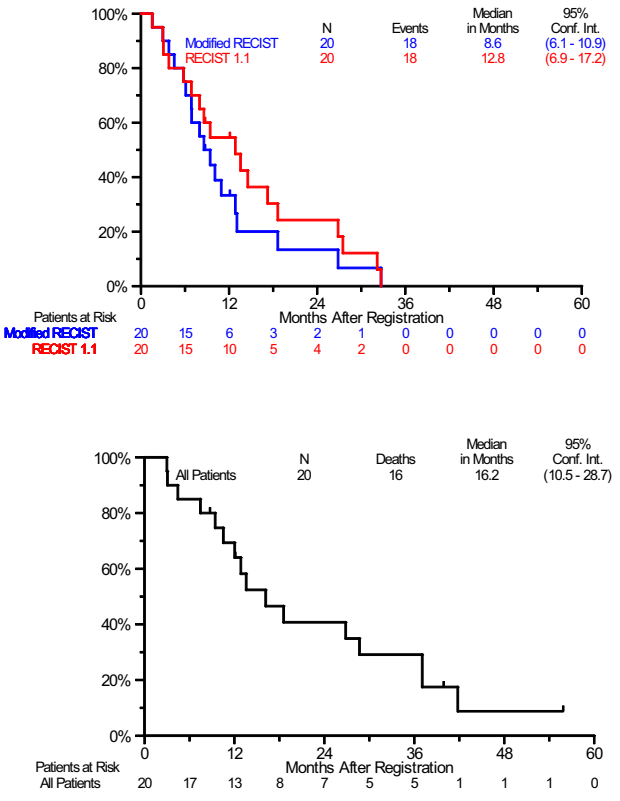

Figure 1. Progression-free and overall survival comparison in the intent-to-treat population. RECIST, Response Evaluation Criteria in Solid Tumors; Conf. Int., confidence interval.

Although the enrollment in S0905 was small when compared with the MAPS trial,[2] the toxicity of the current cisplatin-pemetrexed-cedirinib regimen appears to be comparable to that of the cisplatin-pemetrexed-bevacizumab regimen, for which a 71% grade 3 or 4 adverse event rate was reported. Cisplatin-pemetrexed-cediranib caused less thromboembolism, hypertension, and hemorrhage. The MAPS trial reported a 6% grade 3 thromboembolic rate, whereas there was only one grade 1 event in the S0905 trial. Grade 3 hypertension occurred in 23% of patients with bevacizumab-cisplatin-pemetrexed, compared with only one report with cediranib-based therapy. Notably, there were no reports of bleeding with cediranib-based therapy, whereas a 37.4% rate of hemorrhage (primarily grade 1 or 2 epistaxis) was reported for the bevacizumab-based regimen.

Cediranib-cisplatin-pemetrexed did have higher rates of proteinuria and gastrointestinal events compared with the MAPS regimen. The bevacizumab-based regimen reported a 16% rate of any grade proteinuria (3.2% grade 3), whereas S0905 noted a 60% rate of grade 1 or 2 proteinuria. The most common gastrointestinal side effect with cediranib was diarrhea. Cediranib-induced diarrhea was manageable with loperamide or lomotil; however, several patients needed to take the antidiarrheal agents prophylactically. In cohort 1, reducing the dose of cediranib to 20 mg daily improved diarrhea. Unfortunately, there are currently few data on the mechanism of action of VEGFR TKI–induced diarrhea. Although these VEGFR TKIs are cleared through the fecal pathway and the metabolites

may cause colonic irritation, there are potential effects from inhibition of intestinal microcirculation or even off-target effects on gut motility that could also have a significant role in causing diarrhea.[24]

Although the sample size of the current study was small and the patients were highly selected, there was a signal of clinical benefit with the addition of cediranib to cisplatin-pemetrexed. The median PFS noted with both the RECIST 1.1 and Modified RECIST criteria was better than that reported for platinum-based doublets (8.6 and 13.6 months versus 6.8 months).[25] Of note, the Vogelzang trial[1] did not report PFS but had a time to treatment failure of 5.7 months with cisplatin-pemetrexed. In addition, the OS times were 13.6 and 16.2 months in the two S0905 cohorts compared with 12.1 months in the Vogelzang trial.[1] This finding is consistent with the results of the French Intergroupe Francophone de Cancerologie Thoracique MAPs trial,[2] in which cisplatin-pemetrexed-bevacizumab had a median PFS (9.2 months versus 7.3 months [hazard ratio = 0.61, $p < 0.0001$]) and OS (18.8 months versus 16.1 months [hazard ratio = 0.77, $p = 0.0167$]) benefit over platinum-pemetrexed alone. Despite the control arm having better outcomes than historical studies,[1] the MAPs trial clearly demonstrated survival benefit with the addition of bevacizumab to cisplatin-pemetrexed.

Whether inhibition of VEGF ligand alone by bevacizumab is sufficient for survival benefit or whether targeting VEGFR along with PDGFR with cedirinib provides greater synergistic benefit remains to be seen. Given that mesothelioma is known to be reliant on the PDGF/PDGFR pathway for proliferation[14–16] and that prior studies with PDGFR inhibitors have shown a clinical benefit in mesothelioma,[17] it is suspected that multi-angiokinase inhibition may ultimately provide additive benefit. Cediranib has been studied in several other tumor types with variable results. In NSCLC[26] and colorectal cancer[27] the addition of cediranib to frontline chemotherapy failed to improve survival, whereas phase II and III trials in cervical[28] and ovarian cancer[29] have demonstrated increased response rates and survival outcomes.

For mesothelioma, the phase II portion of SWOG 0905, a randomized trial of cisplatin-pemetrexed with and without cediranib, has completed enrollment and is awaiting sufficient events to be analyzed. Molecular correlative studies in tumor tissue evaluating the VEGF/VEGFR and PDGF/PDGFR pathway by immunohistochemistry and plasma profiling through reverse phase protein arrays are planned. A randomized phase II trial of cisplatin-pemetrexed with and without nintedanib, an oral TKI targeting VEGFR, PDGFR, and fibroblast growth factor receptor (FGFR), has completed accrual and is now being expanded into a phase III randomized trial. Unlike cedirinib, nintedanib also targets FGFR, but whether the FGFR pathway is a clinically relevant target in mesothelioma remains unknown.[30,31] Overall, there is a growing body of literature indicating that anti-angiogenic therapy in combination with chemotherapy provides survival benefit for patients with malignant mesothelioma.

Conclusion

Cediranib in combination with cisplatin-pemetrexed has a reasonable toxicity profile and preliminary promising efficacy. The randomized phase II portion of the S0905 trial will evaluate the efficacy of the triplet regimen compared with the current standard therapy of cisplatin-pemetrexed.

Acknowledgments

This work was supported by National Institutes of Health National Cancer Institute grants (CA180888, CA180819, CA180858, CA180801, and CA180846).

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at http://dx.doi.org/10.1016/j.jtho.2017.05.021.

References

1. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol*. 2003;21:2636–2644.
2. Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2016;387:1405–1414.
3. Langerak AW, De Laat PA, Van Der Linden-Van Beurden CA, et al. Expression of platelet-derived growth factor (PDGF) and PDGF receptors in human malignant mesothelioma in vitro and in vivo. *J Pathol*. 1996;178:151–160.
4. Konig JE, Tolnay E, Wiethege T, Müller KM. Expression of vascular endothelial growth factor in diffuse malignant pleural mesothelioma. *Virchows Arch*. 1999;435:8–12.
5. Filiberti R, Marroni P, Neri M, et al. Serum PDGF-AB in pleural mesothelioma. *Tumour Biol*. 2005;26:221–226.
6. Ohta Y, Shridhar V, Bright RK, et al. VEGF and VEGF type C play an important role in angiogenesis and lymphangiogenesis in human malignant mesothelioma tumours. *Br J Cancer*. 1999;81:54–61.
7. Strizzi L, Catalano A, Vianale G, et al. Vascular endothelial growth factor is an autocrine growth factor in human malignant mesothelioma. *J Pathol*. 2001;193:468–475.
8. Honda M, Kanno T, Fujita Y, Gotoh A, Nakano T, Nishizaki T. Mesothelioma cell proliferation through

autocrine activation of PDGF-betabeta receptor. *Cell Physiol Biochem*. 2012;29:667–674.
9. Abdollahi A, Li M, Ping G, et al. Inhibition of platelet-derived growth factor signaling attenuates pulmonary fibrosis. *J Exp Med*. 2005;201:925–935.
10. Dorai T, Kobayashi H, Holland JF, Ohnuma T. Modulation of platelet-derived growth factor-beta mRNA expression and cell growth in a human mesothelioma cell line by a hammerhead ribozyme. *Mol Pharmacol*. 1994;46:437–444.
11. Gerwin BI, Lechner JF, Reddel RR, et al. Comparison of production of transforming growth factor-beta and platelet-derived growth factor by normal human mesothelial cells and mesothelioma cell lines. *Cancer Res*. 1987;47:6180–6184.
12. Klominek J, Baskin B, Hauzenberger D. Platelet-derived growth factor (PDGF) BB acts as a chemoattractant for human malignant mesothelioma cells via PDGF receptor beta-integrin alpha3beta1 interaction. *Clin Exp Metastasis*. 1998;16:529–539.
13. Walker C, Bermudez E, Stewart W, Bonner J, Molloy CJ, Everitt J. Characterization of platelet-derived growth factor and platelet-derived growth factor receptor expression in asbestos-induced rat mesothelioma. *Cancer Res*. 1992;52:301–306.
14. Li Q, Wang W, Yamada T, et al. Pleural mesothelioma instigates tumor-associated fibroblasts to promote progression via a malignant cytokine network. *Am J Pathol*. 2011;179:1483–1493.
15. Bertino P, Piccardi F, Porta C, et al. Imatinib mesylate enhances therapeutic effects of gemcitabine in human malignant mesothelioma xenografts. *Clin Cancer Res*. 2008;14:541–548.
16. Bertino P, Porta C, Barbone D, et al. Preliminary data suggestive of a novel translational approach to mesothelioma treatment: imatinib mesylate with gemcitabine or pemetrexed. *Thorax*. 2007;62:690–695.
17. Tsao AS, Harun N, Lee JJ, et al. Phase I trial of cisplatin, pemetrexed, and imatinib mesylate in chemonaive patients with unresectable malignant pleural mesothelioma. *Clin Lung Cancer*. 2014;15:197–201.
18. Kindler HL, Karrison TG, Gandara DR, et al. Multicenter, double-blind, placebo-controlled, randomized phase II trial of gemcitabine/cisplatin plus bevacizumab or placebo in patients with malignant mesothelioma. *J Clin Oncol*. 2012;30:2509–2515.
19. Dowell JE, Dunphy FR, Taub RN, et al. A multicenter phase II study of cisplatin, pemetrexed, and bevacizumab in patients with advanced malignant mesothelioma. *Lung Cancer*. 2012;77:567–571.
20. Ceresoli GL, Zucali PA, Mencoboni M, et al. Phase II study of pemetrexed and carboplatin plus bevacizumab as first-line therapy in malignant pleural mesothelioma. *Br J Cancer*. 2013;109:552–558.
21. Erber R, Thurnher A, Katsen AD, et al. Combined inhibition of VEGF and PDGF signaling enforces tumor vessel regression by interfering with pericyte-mediated endothelial cell survival mechanisms. *FASEB J*. 2004;18:338–340.
22. Garland LL, Chansky K, Wozniak AJ, et al. Phase II study of cediranib in patients with malignant pleural mesothelioma: SWOG S0509. *J Thorac Oncol*. 2011;6:1938–1945.
23. Tsao AS, Garland L, Redman M, Kernstine K, Gandara D, Marom EM. A practical guide of the Southwest Oncology Group to measure malignant pleural mesothelioma tumors by RECIST and modified RECIST criteria. *J Thorac Oncol*. 2011;6:598–601.
24. Bowen JM. Mechanisms of TKI-induced diarrhea in cancer patients. *Curr Opin Support Palliat Care*. 2013;7:162–167.
25. Fennell DA, Gaudino G, O'Byrne KJ, et al. Advances in the systemic therapy of malignant pleural mesothelioma. *Nat Clin Pract Oncol*. 2008;5:136–147.
26. Laurie SA, Solomon BJ, Seymour L, Mutti L, van Meerbeeck J. Randomised, double-blind trial of carboplatin and paclitaxel with daily oral cediranib or placebo in patients with advanced non-small cell lung cancer: NCIC Clinical Trials Group study BR29. *Eur J Cancer*. 2014;50:706–712.
27. Hoff PM, Hochhaus A, Pestalozzi BC, et al. Cediranib plus FOLFOX/CAPOX versus placebo plus FOLFOX/CAPOX in patients with previously untreated metastatic colorectal cancer: a randomized, double-blind, phase III study (HORIZON II). *J Clin Oncol*. 2012;30:3596–3603.
28. Symonds RP, Gourley C, Davidson S, et al. Cediranib combined with carboplatin and paclitaxel in patients with metastatic or recurrent cervical cancer (CIRCCa): a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Oncol*. 2015;6:1515–1524.
29. Ledermann JA, Embleton AC, Raja F, et al. Cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON6): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;387:1066–1074.
30. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med*. 2014;370:2071–2082.
31. Richeldi L, Cottin V, du Bois RM, et al. Nintedanib in patients with idiopathic pulmonary fibrosis: Combined evidence from the TOMORROW and INPULSIS(®) trials. *Respir Med*. 2016;113:74–79.