SWOG S0722: Phase II Study of mTOR Inhibitor Everolimus (RAD001) in Advanced Malignant Pleural Mesothelioma (MPM)

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Introduction: The PI3K/Akt/mammalian target of rapamycin pathway is activated in a majority of malignant pleural mesotheliomas (MPM). We evaluated the activity of everolimus, an oral mammalian target of rapamycin inhibitor, in patients with unresectable MPM.

Methods: MPM patients who had received at least one but no more than two prior chemotherapy regimens, which must have been platinum-based, were treated with 10 mg of everolimus daily. The primary endpoint was 4-month progression-free survival (PFS) by RECIST 1.1.

Results: A total of 59 evaluable patients were included in the analysis. The median duration of treatment was 2 cycles (56 days). Overall response rate was 2% [95% confidence interval (CI): 0–12%] by RECIST 1.1 and 0% (0–10%) by modified RECIST for MPM. The 4-month PFS rate was 29% (95% CI: 17–41%) by RECIST 1.1, and 27% (95% CI: 16–39%) by modified RECIST. The median PFS was 2.8 months (95% CI: 1.8–3.4) by RECIST 1.1. The median overall survival was 6.3 months (95% CI: 4.0–8.0). There was no difference in PFS among patients who received one or two prior chemotherapy regimens ($p = 0.74$). There was no difference in overall survival between patients with epithelioid histology versus other types ($p = 0.47$). The most common toxicities were fatigue (59%), hypertriglyceridemia (44%), anemia (42%), oral mucositis (34%), nausea (32%), and anorexia (32%). The most common grade 3 to 4 toxicities were fatigue (10.2%), anemia (6.8%), and lung infection (6.8%).

Conclusion: Everolimus has limited clinical activity in advanced MPM patients. Additional studies of single-agent everolimus in advanced MPM are not warranted.

Key Words: Malignant pleural mesothelioma, mTOR inhibitor, Everolimus, Modified RECIST.

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Multiple signaling pathways are activated in malignant pleural mesothelioma (MPM) including the PI3K-Akt-mammalian target of rapamycin (mTOR) pathway. MPM cell lines[1] and tumor samples[2–4] frequently exhibit highly activated Akt, leading to phosphorylation of mTOR, 4EBP1, and FKHD, among others.[3,4] Inhibition of the Akt pathway by the mTOR inhibitor rapamycin in MPM cells leads to G1 arrest,[2] overcomes acquired resistance to apoptosis in MPM,[5] and inhibits cell migration on extracellular matrix.[6] Sirolimus, another mTOR inhibitor, led to cell death of MPM cell lines alone and to a much greater extent in conjunction with cisplatin.[7] Furthermore, temsirolimus alone or in combination with cisplatin inhibited MPM cell growth both in vitro and in vivo xenograft models.[8] Thus, mTOR inhibitors demonstrated compelling preclinical activity in MPM models.

Everolimus is an orally available inhibitor of mTOR that has been approved for use in renal cell carcinoma, pancreatic neuroendocrine tumors, angiomyolipoma in patients with tubular sclerosis complex, and in combination with exemestane in hormone receptor-positive breast cancer patients after progression on letrozole or anastrozole.[9] Here, we report the results of a phase II study investigating the clinical activity of single-agent everolimus in advanced MPM patients who have progressed after platinum-based chemotherapy.

PATIENTS AND METHODS

Inclusion Criteria

Eligible patients must be 18 years or older with histologically proven epithelioid, sarcomatoid, or biphasic unresectable

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MPM, zubrod performance status of 0 to 1, adequate hematologic function (absolute neutrophil count > 1500/ml and 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).

Patients were required to have failed at least one prior platinum-based therapy but no more than two prior systemic therapeutic regimens (including biologics, targeted and immunotherapies). Pleural space washing with cisplatin was not considered systemic treatment. Neoadjuvant and/or adjuvant systemic therapy was not considered as a prior regimen if more than 12 weeks had elapsed between treatment and disease progression. Patients may have received prior surgery (e.g., pleurectomy) provided that at least 28 days had elapsed and all toxicities surgery had resolved. Patients must not have had any prior mTOR inhibitor therapy or central nervous system metastasis.

Patients were ineligible if they had severe systemic comorbid disease. Pregnant or breast-feeding patients were excluded. Patients who had prior pulmonary emboli could be on therapeutic low-molecular heparin. However, patients on coumadin anticoagulation must have had an international normalized ratio of less than 1.5 within 28 days before registration to the trial. Patients must not be on chronic, systemic immunosuppressive treatment; however, a stable regimen of topical or inhaled corticosteroids or corticosteroids given at doses equivalent to prednisone less than 20 mg/day and given for a minimum of 4 weeks were allowed before the first dose of everolimus.

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 Southwest Oncology Group (SWOG) member sites. Written informed consent was obtained from all patients before enrollment.

Study Design and Protocol Treatment

The S0722 treatment protocol (ClinicalTrials.gov_identifier: NCT00770120) consisted of single-agent everolimus administered orally at 10 mg once daily until disease progression or unacceptable toxicity. Adverse events were graded according to the National Cancer Institute CTC Version 3.0. Patients who experienced more than grade 3 nonhematologic and/or grade 4 hematologic toxicities were allowed two sequential dose modifications to 5 mg once daily and 5 mg once every other day. Treatment was held until all toxicities resolved to less than grade 1.

Patient history, physical examination, and laboratory analyses were performed within 28 days before cycle 1 and on day 1 of each subsequent treatment cycle. Radiographic tumor measurements were performed after every two treatment cycles. Tumor responses were determined by RECIST 1.1 and modified RECIST.[10] Patients were withdrawn from the study due to disease progression, unacceptable toxicity, treatment delay of more than 2 weeks for pneumonitis, treatment delay of more than 3 weeks for any other reason, or if more than 2 dose reductions were required.

Statistical Considerations and Statistical Analysis

The primary objective of this study was 4-month progression-free survival (PFS) rate using RECIST 1.1.[11] It was assumed that if the true 4-month PFS is less than 30%, everolimus would not warrant further investigation, while if the true 4-month PFS is more than 50%, it will be of considerable interest. Using a two-stage design, initially 20 patients would be enrolled. If more than 5 of those 20 patients were alive and progression-free at 4 months, additional 35 patients would be enrolled. If 23 of 55 patients were alive and progression-free at 4 months, everolimus would be considered as having potential activity in MPM. This design had 91% power to detect an increase from a 4-month PFS of 30% to 4-month PFS of 50% using a one-sided significance test of 4%. Secondary objectives included evaluating overall response rate (ORR) and overall survival (OS) using RECIST 1.1, and ORR and PFS using the modified RECIST for pleural tumors. PFS and OS estimates were calculated using the method of Kaplan-Meier. Confidence intervals (CI) for median PFS and median OS were constructed using the method of Brookmeyer-Crowley.[12]

TABLE 1. Clinicopathologic Characteristics of Advanced MPM Patients

	N (%)
Median age (yrs) (range)	67.0 (45.8–81.3)
Sex	
Male	45 (76)
Female	14 (24)
Race	
White	55 (93)
Black	1 (2)
Unknown	3 (5)
Histology	
Epithelial	36 (61)
Biphasic	4 (7)
Sarcomatous	0 (0)
NOS	17 (29)
Not reported	2 (3)
Prior systemic regimens	
1	34 (58)
2	25 (42)
Zubrod performance status	
0	13 (22)
1	46 (78)
No. of metastatic sites	
None	5 (8)
Single	23 (39)
Multiple	31 (53)
Weight loss past 6 months	
<5%	47 (80)
5–<10%	6 (10)
10–20%	6 (10)
>20%	0 (0)

NOS, not otherwise specified.