Highlights in Sarcoma From the 2011 American Society of Clinical Oncology Meeting

June 3–7, 2011
Chicago, Illinois

Complete abstracts are available in *J Clin Oncol*. 2011;29 (Suppl).

LBA10002 PALETTE: Randomized, Double-Blind, Phase II Trial of Pazopanib Versus Placebo in Patients With Soft-Tissue Sarcoma Whose Disease Has Progressed During or Following Prior Chemotherapy–An EORTC STBSG Global Network Study

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The PALETTE (Pazopanib Explored in Soft-Tissue Sarcoma) study, a multicenter, international, double-blind, placebo-controlled phase III trial, examined the efficacy and safety of pazopanib compared to placebo as second-line or later treatment in patients with metastatic soft-tissue sarcoma (STS). Inclusion criteria included age of 18 years or older, angiogenesis inhibitor–naïve, histologically proven metastatic STS, and failure of at least 1 anthracycline-containing regimen. Patients also had 1 or more measurable baseline lesions, World Health Organization performance status of 0–1, adequate bone marrow, coagulation, hepatic and renal function, no poorly controlled hypertension, no bleeding diathesis, and no central nervous system involvement. A total of 369 patients were randomized 2:1 to receive either pazopanib 800 mg once daily (n=246) or placebo (n=123); patients were treated until tumor progression, unacceptable toxicity, death, or request to be discontinued from treatment. Median follow-up was 15 months. Patients receiving pazopanib had a significant improvement in progression-free survival compared to placebo (20 vs 7 weeks; HR, 0.31; 95% CI, 0.24–0.40; *P*=.0001). Although patients on pazopanib also had an improvement in overall survival, it was not significant (11.9 vs 10.4 months). Fatigue, hypertension, anorexia, and diarrhea were the main grade 3/4 adverse events, all occurring more frequently in the pazopanib arm compared to the placebo arm. The findings suggest that pazopanib is active in metastatic STS patients.

10026 A Dose-Finding Study of Temsirolimus and Liposomal Doxorubicin for Advanced Soft Tissue or Bone Sarcoma

DM Loeb, KA DeLorenzo, ARS Chen, CF Meyer, J Powell

In this dose-finding study, Loeb and colleagues hypothesized that the combination of liposomal doxorubicin and temsirolimus will result in improved overall survival in patients with advanced sarcoma. Enrolled patients were 1 year of age or older, had histologically confirmed recurrent or refractory sarcoma, and had adequate organ function. Patients were enrolled in cohorts of 3, with the first cohort receiving standard doses of both doxorubicin (30 mg/m^2 every 28 days) and temsirolimus (15 mg/m^2 weekly). A continual reassessment method was utilized in order to allow for more patients to be treated near the maximum tolerated dose. With this method, fatal toxicities were scored as a full event, reversible grade 4 toxicities were scored as 0.5 of an event, and reversible grade 3 toxicities were scored as 0.25 of an event; the total event score was restricted to 1 per patient. A total of 15 patients were accrued before the continual reassessment method determined an appropriate dosage of 30 mg/m^2 of liposomal doxorubicin and 20 mg/m^2 of temsirolimus. Grade 3/4 toxicities (n=14) occurred in 9 patients, with the following breakdown: 1 in dose level 1, 6 at dose level 2, and 2 at dose level 3. Loeb and colleagues concluded that the combination of liposomal doxorubicin and temsirolimus is tolerable and causes minimal grade 4 adverse events.

10025 A Phase II Trial of Sorafenib (S) and Dacarbazine (D) in Leiomyosarcoma (LMS), Synovial Sarcoma (SS), and Malignant Peripheral Nerve Sheath Tumor (MPNST)

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After response was seen in a study of single-agent sorafenib in leiomyosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumor, D'Adamo and associates

decided to evaluate the combination of sorafenib and dacarbazine in these same histologies. Enrolled patients had one of the histologies and adequate hepatic, renal, and marrow function. The primary endpoint was clinical benefit response (CBR) rate, which is complete response plus partial response plus stable disease times 18 weeks. A total of 31 patients were enrolled between February 2009 and December 2010; median age was 55 years, and 17 were female and 14 were male. Eastern Cooperative Oncology Group performance status was 0 in 16 patients and 1 in 14 patients, and 20 patients previously received an average of 1.6 lines of therapy. CBR was seen in 9 of 31 (29%) patients receiving sorafenib plus dacarbazine: 6 of 17 leiomyosarcoma patients, 3 of 10 synovial sarcoma patients, and 0 of 4 malignant peripheral nerve sheath tumor patients. The time to treatment progression was 11 weeks, and the 3 and 6 month progression-free rates were 35% and 26%, respectively. Patients had an overall survival of 13.2 months. In regard to safety, 15 of the first 25 patients required dose reductions of dacarbazine due to hematologic toxicity; after the dose was reduced to 850 mg/m^2, the remaining patients did not require any further reductions. Non-hematologic toxicities were consistent with the safety profiles of sorafenib and dacarbazine.

10005 Results of the Phase III, Placebo-Controlled Trial Evaluating the mTOR Inhibitor Ridaforolimus as Maintenance Therapy in Advanced Sarcoma Patients Following Clinical Benefit from Prior Standard Cytotoxic Chemotherapy: SUCCEED trial

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Previous trials have established that ridaforolimus, an oral mTOR inhibitor, has activity in advanced sarcomas after failure of chemotherapy. Therefore, Chawla and colleagues conducted a study to evaluate ridaforolimus versus placebo as maintenance therapy in metastatic sarcoma patients who had stable disease or better from prior chemotherapy. The primary endpoint was progression-free survival, with secondary endpoints of overall survival, best target lesion response, cancer-related symptoms, and safety and tolerability. A total of 711 patients were randomized, and only 53 were on blinded treatment at time of data cut-off. The analysis found that patients on ridaforolimus had a significant improvement in median PFS compared to those on placebo (17.7 vs 14.6 weeks). Similarly, overall survival was longer in patients receiving ridaforolimus (88 vs 78.7 weeks); follow-up for overall survival is ongoing. The incidence of adverse events was higher in patients receiving ridaforolimus compared to those patients on placebo; however, the safety analysis showed that ridaforolimus had a similar side effect profile to other mTOR inhibitors.

10080 Effect of the Combination of mTOR Inhibitor Ridaforolimus and HDAC Inhibitor Vorinostat on In Vitro Syngergism in Synovial Sarcoma, Osteosarcoma, and a Range of Other Tumor Subtypes

SS Morgan, LD Cranmer

In this analysis, Morgan and Cranmer examined combinations of molecularly targeted and cytotoxic agents in order to determine synergistic treatment combinations in 2 synovial sarcoma cell lines, HS-SY-II and SYO-I. These cell lines were treated with single agents or combinations of vorinostat and ridaforolimus and cytotoxic agents. Cell viability was measured after 72 hours (Table 1) and combination indices were used to determine whether each combination was synergistic, additive, or antagonistic. The analysis found that the ridaforolimus/vorinostat, ridaforolimus/doxorubicin, and ridaforolimus/melphalan combinations were synergistic. In the vorinostat/doxorubicin and vorinostat/melphalan combinations, the effect was additive. Because of the synergistic effects observed with the ridaforolimus/vorinostat combination, it was also evaluated in other tumor subtypes, including osteosarcoma, metastatic melanoma, pancreatic cancer, and lung cancer; the combination resulted in synergistic effects in all the cancer types.

Table 1. Cell Viability After 72 Hours

Drug	IC_{50} of Synovial Sarcoma Cell Lines	
	HS-SY-II	**SYO-I**
Ridaforolimus	10.9 nM	23.1 nM
Vorinostat	440 nM	561 nM
Doxorubicin	9.4 nM	7.4 nM
Melphalan	687 nM	859 nM

IC_{50}=half maximal inhibitory concentration.