A phase II study of pazopanib with oral topotecan in patients with metastatic osteosarcoma

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Background: Topotecan and pazopanib individually have clinical benefit in patients with sarcomas. Pazopanib is a multi-tyrosine kinase inhibitor and topotecan affects endothelial cells, and inhibits HIF-1, an upstream regulator of VEGF expression. The utilization of pazopanib with topotecan is anticipated to produce anti-tumor synergism in patients with osteosarcomas.

Methods: A phase II study of pazopanib/topotecan in patients with metastatic and non-resectable osteosarcomas was conducted by the Midwest Sarcoma Trials Partnership. Age >18, ECOG ≤1, adequate organ function, measurable disease and 1 prior therapy were required. Patients were treated with pazopanib 800mg oral daily, Topotecan 8mg orally day 1, 8, 15 on a 28-day cycle until disease progression or unacceptable toxicity. Primary endpoint: progression-free rate (PFR) at 12 weeks. Secondary endpoints: overall response rate (ORR), clinical benefit rate (CBR), OS, median progression free survival (PFS), and 3, and safety and tolerability. Lab correlates evaluated PFR and OS to levels of VEGFR2 and PDGF. Simon 2-stage design was used.

Results: A total of 21 pts were enrolled at 6 sites, with 17 evaluable for response. Mean age was 41 years, 48% of patients were female and 95% had metastatic disease. PFR at 12 weeks is 59% with a median PFS of 4.5 months and OS of 11.1 months. ORR is 6% and CBR is 85%. Grade 3-4 adverse events (%): neutropenia (42), thrombocytopenia (29), hypertension (16) and anemia (12). Correlate data will be presented.

Conclusions: The combination of pazopanib/topotecan proved extremely promising for patients with unresectable or metastatic osteosarcoma. To date 10 patients have met the primary endpoint. If an anticipate 11 or more patients/ 36 will have disease control at 4 months, the agent would be considered sufficiently efficacious for additional study.

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