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Pedicratic Preclinical Testing Consortium (PPTC) of eribulin in osteosarcoma (OS)

patient-derived xenograft (PDX) model

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1. Introduction

Eribulin is a synthetic analogue of halichondrin B and inhibits cancer cell proliferation via blockade of microtubule function. It is FDA approved for patients with breast cancer with two prior chemotherapy regimens for the treatment of metastatic disease and for previously treated patients with inoperable or metastatic liposarcoma. In vivo testing of eribulin against osteosarcoma (OS) Pediatric Preclinical Testing Program (PPTP) PDX models, developed from primary tumors, demonstrated significant single agent activity. However, a Children's Oncology Group (COG) phase 2 trial of eribulin in patients with relapsed OS did not demonstrate significant responses to single agent eribulin (Isaakoff M et al.). In the current study, the efficacy of eribulin in PDX models generated from primary and relapsed tumors, as well as dose-response, were assessed.

2. Study Methods

Eribulin was evaluated in 10 PPTC models. 6 models were treated at 1mg/kg IP injection on days 1 & 4, repeated at day 21: 4 from primary OS specimens (OS46, OS51, OS55, OS65) and 2 from relapsed specimens (OS39R, OS60). Response to treatment was determined based on PPTP-established endpoints (Houghton PJ, et al.; Kolb EA, et al.). In an additional 4 models, 3 dose levels of eribulin were evaluated in 3 primary tumors (OS1, OS17, OS33) and 1 relapsed tumor (OS60). In the dose response studies, eribulin was administered IP at 1mg/kg, 0.5mg/kg, and 0.25mg/kg on day 1 & 4, repeated at day 21 with follow-up through day 42.

3. Results: OS PDX model dose response to Eribulin

Eribulin was tested at the following dose level: 0.25mg/kg. 1mg/kg (SDIR in 2/4), 0.5mg/kg (1/4) and 0.25mg/kg (0/4). Median tumor volumes showed significant decreases when compared to controls. Minimum relative tumor volumes also showed a dose response effect from 0.25 to 1.0mg/kg.

4. Discussion and Conclusions

Eribulin demonstrated antitumor activity against OS PDX models generated from primary and relapsed tumors at a dose level of 1mg/kg. Eribulin showed a clear dose-response effect in terms of its ability to induce SD/PR responses, highlighting the importance of dose selection. This dose response effect suggests the possibility that an inability to achieve comparable serum concentrations in human clinical trials may explain the limited tumor responses observed in the COG phase 2 trial of eribulin. Pharmacokinetic studies from the COG phase 2 study are ongoing in an effort to understand the disparate tumor responses seen in vivo studies and the phase 2 clinical trial.

5. References

Isaakoff M, Villanova D, Cronin MD, et al. AOST1322: A phase II study of eribulin in recurrent or refractory soft tissue sarcoma. 2013 ASCO meeting. poster.

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