Evaluation of the TPO-R receptor agonist eltrombopag in the Pediatric Preclinical Testing Consortium osteosarcoma *in vivo* models

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Introduction

- Osteosarcoma (OS) is the most common primary bone malignancy in adolescents and young adults
- Overall survival rate for patients with metastatic or recurrent disease is <30%
- Survival outcomes have remained stagnant for the past 3 decades and new agents are needed to improve outcomes
- Eltrombopag (EP) is a small molecule thrombopoietin receptor (TPO-R) agonist and polyvalent cation chelator
- FDA-approved to threat chronic immune thrombocytopenia purpura (ITP) and severe aplastic anemia
- EP reduces leukemia cell proliferation via the depletion of intracellular iron levels, independent of TPO-R binding
- EP's inhibits osteosarcoma cell growth *in vitro* in a dose-dependent manner
- The PPTC sought to evaluate the potential anti-cancer efficacy of EP against *in vivo* osteosarcoma models

Methods

EP Administration:

- 5 mg/kg/day (low-dose) via oral gavage for 5 days per week over 4 weeks
- 50 mg/kg/day (high-dose) administered to 2 models (OS2, OS9) per the same schedule

Study Design and Analysis:

- Six OS patient-derived xenograft (PDX) models (OS-2, OS-9, OS-31, OS-33, OS-36, and OS-60-SJ) were heterotopically injected into the flanks of CB17SC *scid*$^{-/-}$ mice
- A control cohort that received vehicle was included for each PDX model
- Tumor volume was monitored in all cohorts
- Events defined as 4x initial tumor growth
- Tumor growth, Event Free Survival (EFS) compared between treatment and control groups
- p-values were two-sided and considered statistically significant if $p < 0.05$

Results

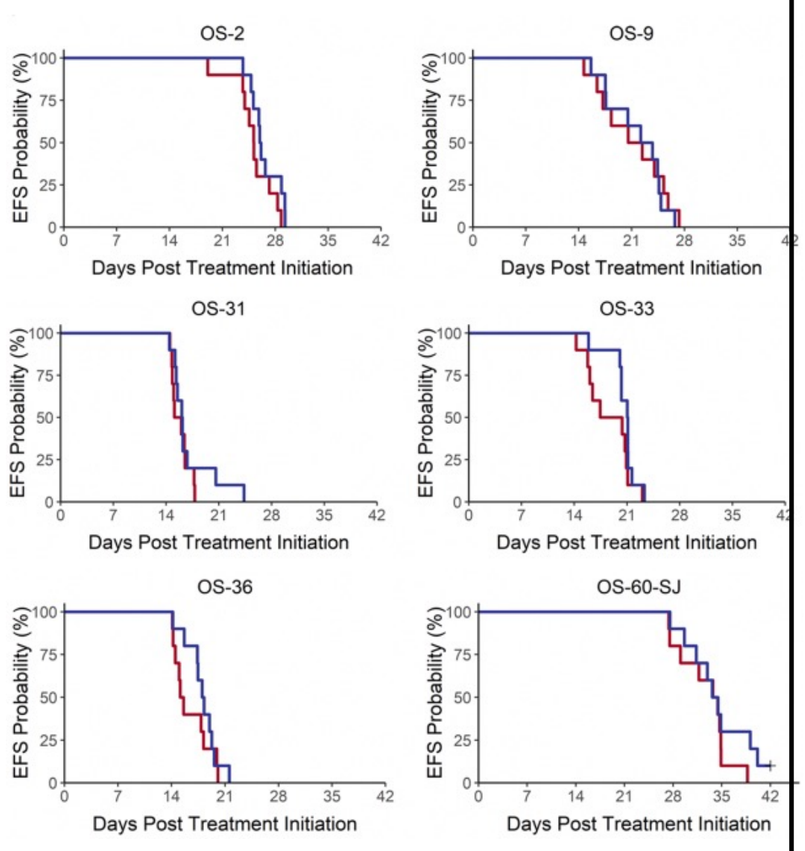
- No toxic deaths with either dose of EP
- EP dose 5 mg/kg/day:
  - No significant prolongation of time to event observed
  - No objective responses observed
  - All mice met criteria for PD1 (Table 1)
- EP dose 50 mg/kg/day:
  - Resulted in a small, but significant prolongation in time to event for both models tested No objective responses observed
  - All mice met criteria for PD1 (Table 1)

Table 1: Osteosarcoma PDX model response to EP

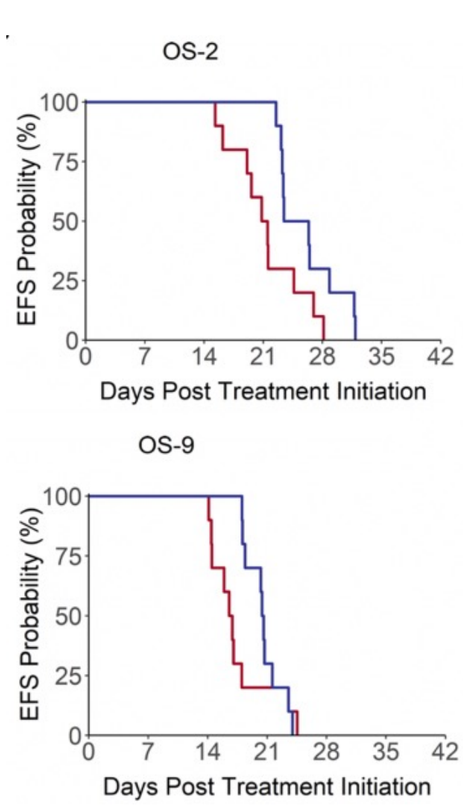
Model	KM med (days)	EFS T - C (days)	EFS T/C	p-value Gehan-Wilcoxon	minRTV mean±SD	minRTV p-value	Objective Response Measure
				5 mg/kg			
OS-2	26.0	0.9	1.03	p = 0.172	1.134±0.09	p = 0.631	PD1
OS-9	23.0	1.5	1.07	p = 0.881	1.686±0.46	p = 0.739	PD1
OS-31	16.1	0.6	1.04	p = 0.407	1.774±0.18	p = 0.011	PD1
OS-33	21.1	2.2	1.12	p = 0.109	1.472±0.23	p = 0.123	PD1
OS-36	18.1	2.8	1.18	p = 0.170	2.019±0.35	p = 0.684	PD1
OS-60-SJ	34.1	0.0	1.00	p = 0.452	1.228±0.11	p = 0.353	PD1
				50 mg/kg			
OS-2	24.9	3.7	1.2	p = 0.015	1.403±0.24	p = 0.529	PD1
OS-9	20.5	3.8	1.2	p = 0.014	1.752±0.19	p = 0.143	PD1

Results: Response to Low-Dose and High-Dose EP (EFS)

EP 5 mg/kg/day



EP 50 mg/kg/day



Discussion and Conclusions

- EP failed to exhibit significant anti-tumor activity in the osteosarcoma PDX models
- EP did not enhance tumor growth in any of the models tested
- Lack of meaningful EP anti-tumor activity suggests that leukemia and osteosarcoma may exhibit different dependencies on intracellular polyvalent cations
- EP may be considered as a potential supportive care agent in stimulating platelet recovery following chemotherapy-induced myelosuppression in patients with osteosarcoma

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