TPS11585 Poster Session

ETCTN 10563: A phase I study of peposertib and liposomal doxorubicin for advanced or metastatic leiomyosarcoma and other sarcomas.

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Background: Soft tissue sarcomas (STS) with genomic complexity are often aggressive but may be sensitive to further genotoxic stress. Leiomyosarcoma (LMS), a common STS, frequently harbors genomic complexity and DNA damage response (DDR) dysregulation. Preclinical data showed hyper-dependency on DNA-PK-mediated non-homologous end joining (NHEJ) DDR, and low-dose liposomal doxorubicin (LD-LPD) synergized with the DNA-PK inhibitor peposertib to inhibit tumor growth in LMS models. We hypothesize that a low, sensitizing dose of LPD enhances DNA damage and safely synergizes with peposertib in LMS and other genomically complex STS. **Methods:** This phase 1, open label, multicenter dose escalation and dose expansion study (NCT05711615) evaluates LD-LPD given intravenously (IV) on day 1 of 28-day cycles with peposertib given orally (PO) twice daily (BID) continuously (Table). Up to 18 patients (pts) over 18 years-old with advanced or unresectable LMS, undifferentiated pleomorphic sarcoma, myxofibrosarcoma, dedifferentiated liposarcoma, and synovial sarcoma, ECOG performance status ≤2, who received ≥1 prior line of systemic therapy (including anthracycline ≤300 mg/m^2) are eligible for dose escalation. Dose expansion will include 12 pts with LMS. The primary objective is to determine the recommended phase 2 dose of LPD+peposertib based on the dose limiting toxicity rate. The Bayesian Optimal Interval (BOIN) design will inform dose escalation decisions. Secondary endpoints for the expansion cohort include adverse event rate, progression-free survival, and objective response rate per RECIST v1.1. Potential predictive biomarkers and changes in DDR biomarkers will be evaluated on biopsies during screening and at cycle 1 day 7. Circulating tumor DNA (ctDNA) collected at baseline (dose escalation and dose expansion), on treatment and at progression (dose expansion) will be correlated with disease activity and response. This trial activated on 8-May-2023 through the Experimental Therapeutics Clinical Trials Network (ETCTN) and is enrolling at select sites in the United States. Dose escalation is ongoing as of January 2025. Clinical trial information: NCT05711615. Research Sponsor: National Institutes of Health/National Cancer Institute (NIH/NCI); National Cancer Institute/U.S. National Institutes of Health; Merck KGaA, Darmstadt, Germany CrossRef Funder ID: 10.13039/100009945.

Planned dose levels for dose escalation.

Dose Escalation Schedule

	Dose	
Dose Level	**Liposomal doxorubicin**	**Peposertib (tablet)**
-1	10 mg/m^2 IV	50 mg PO BID
0*	10 mg/m^2 IV	100 mg PO BID
+1	10 mg/m^2 IV	150 mg PO BID
+2	10 mg/m^2 IV	200 mg PO BID
+3	15 mg/m^2 IV	200 mg PO BID
+4	20 mg/m^2 IV	200 mg PO BID

*Starting dose.