TPS11583 Poster Session

Phase I/II study to evaluate the feasibility and efficacy of sequential abemaciclib and gemcitabine treatment in patients with retinoblastoma (Rb)-positive leiomyosarcoma (LMS) and dedifferentiated liposarcoma (DDLPS).

Elise F. Nassif Haddad, Khandan Keyomarsi, Heather Y. Lin, Alexander J. Lazar, Wei-Lien Wang, Charles Manning, Guofan Xu, Osama F Mawlawi, Lorraine Cheryl Pelosof, Kelly Hunt, Funda Meric-Bernstam, Neeta Somaiah; Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX; University of Texas MD Anderson Cancer Center, Houston, TX; National Cancer Institute, Cancer Therapy Evaluation Program, Rockville, MD; Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center, Houston, TX

Background: LMS and DDLPS are aggressive malignancies with limited effective therapies in the advanced setting. Approximately 50% of LMS and nearly all DDLPS retain functional Rb protein, suggesting sensitivity to cell cycle inhibition. Our preclinical studies have demonstrated that combining sequential abemaciclib, a selective CDK4/6 inhibitor that induces cell cycle arrest, followed by gemcitabine timed with synchronized cell cycle reentry, results in synergistic antitumor activity in Rb-positive sarcomas. Sequential administration of abemaciclib followed by gemcitabine enhances apoptosis, impairs DNA repair mechanisms, and induces sustained cell cycle arrest. **Methods:** This is a multicenter, open-label, phase 1/2 clinical trial conducted through the National Cancer Institute (NCI), enabling broad, nationwide patient enrollment. The phase 1 dose-escalation portion will determine the maximum tolerated dose and recommended phase 2 dose of sequential abemaciclib and gemcitabine in patients with advanced/metastatic soft-tissue sarcomas. Part A of phase 1 will use biomarkers of cell cycle (functional positron emission tomography imaging using [18]F-fluoro-3'-deoxy-3'-L-fluorothymidine and thymidine kinase activity) to determine the optimal schedule of sequencing. Part B of the phase 1 will follow the BOIN design. Eligible patients must have histologically confirmed LMS or DDLPS with Rb positivity confirmed by immunohistochemistry, measurable disease, ECOG performance status ≤2, and adequate organ function. Prior gemcitabine therapy is permitted in phase 1 but excluded in phase 2. Phase 1 Part A is restricted to MD Anderson only enrollment due to the requirements of biomarker integration and timing. In the randomized phase 2 portion, patients will be randomized 1:1 (stratified by DDLPS vs LMS) to receive either (1) sequential abemaciclib followed by gemcitabine or (2) gemcitabine and docetaxel. The primary endpoint is progression-free survival, with secondary endpoints including objective response rate, overall survival, and safety. Correlative studies will analyze tumor biopsies and blood samples collected at baseline, after two treatment cycles, and at disease progression. Biomarker analyses will include RB1 expression profiling, whole exome sequencing, RNA sequencing, and circulating tumor DNA. Clinical trial information: NCT06498648. Research Sponsor: ETCTN - CTEP.