TPS4621 Poster Session

A phase II trial to evaluate clinical efficacy, pharmacodynamics and exploratory analysis of pemetrexed in relation to MLL4 and UTX alteration status in patients with relapsed/refractory metastatic urothelial carcinoma and other solid tumors.

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Background: MLL4 (encoded by KMT2D) and UTX (encoded by KDM6A) are protein components of the epigenetic chromatin modifier complex COMPASS. MLL4 alterations are found in ~10% of all cancers including ~29% of bladder cancer (BLCA). UTX alterations are found in up to ~5% of all cancers including ~29% of BLCA. These alterations have not been previously therapeutically targeted as a precision oncology strategy in humans despite their frequency. We recently published the results of a CRISPR/Cas9 knockout screen in cells lacking MLL4/UTX-COMPASS function, which revealed synthetic lethality upon loss of genes that encode enzymes involved in de novo nucleotide synthesis (dnNS) [Zhao et al. J Clin Invest. 2023; Zhao et al. PNAS. 2023]. We also reported that MLL4 truncation mutations confer an inhibitor-targetable dependence on dnNS in colorectal cancer (CRC) and BLCA. We demonstrated sensitivity to lometrexol, which targets the enzyme GART (glycinamide ribonucleotide formyltransferase), in animal models of CRC and BLCA with MLL4 truncation. Our preclinical results clearly indicated the potential for dnNS inhibition as a targeted therapy for patients stratified by MLL4 or UTX status. Pemetrexed was identified as a more clinically relevant purine synthesis inhibitor for further development due to its well-established safety profile and prior use in BLCA. **Methods:** We have initiated an investigator-initiated, open-label phase II basket clinical trial at Northwestern University (NCT06630416). Patients with advanced, treatment-refractory tumors with MLL4 (KMT2D) or UTX (KDM6A) mutations (as identified by next generation sequencing) are enrolled in 2 cohorts: a) BLCA and b) other solid tumors. Other key inclusion criteria include ECOG performance status 0-2 and adequate organ function. Prior pemetrexed use is a key exclusion criterion. Patients are treated with pemetrexed 500mg/m2 IV Q 3 weeks. We intend to enroll up to 64 patients to allow for 58 evaluable patients (29 in each cohort) to achieve the null hypothesis. We will use a Simon 2-stage design, with 10 patients enrolled in each cohort in the first stage. The null hypothesis is that the true response rate is 0.1, and the alternative hypothesis is that the true response rate is 0.3. If there are 5 or more responses among these 29 patients, we reject the null hypothesis and claim that the treatment is promising. The design controls the type I error rate at 0.05 and yields a power of 0.8. This clinical trial has accrued 1 patient as of January 28th, 2025. Correlative studies will be carried out alongside the study to assess for mechanisms of resistance to pemetrexed. Molecular analysis of ctDNA will be performed on plasma for both arms and for plasma and urine for cohort A (bladder cohort) at pre-determined time points during treatment. Clinical trial information: NCT06630416. Research Sponsor: Robert Lurie Cancer Center, Northwestern Memorial Hospital, Chicago, IL, 60611.