TPS4611 Poster Session

STARLITE-1: Phase 1b/2 study of combination ^{177}Lu girentuximab plus cabozantinib and nivolumab in treatment naive patients with advanced clear cell RCC.

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Background: Complete response (CR) is a rare event in advanced clear cell renal cell carcinoma (ccRCC). The combination of nivolumab plus cabozantinib was approved for first-line treatment of ccRCC based on the CheckMate 9ER phase 3 study demonstrating improved progression-free survival (PFS) and objective response rate (ORR) in comparison to sunitinib. However, CR rate was only 9%. Drugs that could synergize with T cell anti-tumor activity can improve CR rates. Radiation-induced DNA damage to activate the cGAS-STING pathway is a promising mechanism. ^{177}Lu-girentuximab is an antibody-radioisotope that targets CAIX, a cell surface glycoprotein expressed in $>$ 95% of ccRCC. As a single agent in metastatic ccRCC, ^{177}Lu-girentuximab was safe and effective in stabilizing disease in 57% of patients. We hypothesize ^{177}Lu-girentuximab-induced DNA damage will potentiate the STING pathway, synergizing with nivolumab and cabozantinib to promote trafficking and infiltration of activated T cells and achieve higher CR rates. **Methods:** Up to 100 adults with treatment-naive, locally advanced or metastatic ccRCC, adequate organ/marrow function, and $\geq$1 measurable lesion by RECIST 1.1 will be enrolled. Patients will receive ^{177}Lu-girentuximab IV on day 1 of cycles 1, 4, and 7 (every 12 weeks) for up to 3 cycles. The starting dose of ^{177}Lu-girentuximab will be 1480 MBq/m^2 (61% of single agent maximum tolerated dose); subsequent doses in the same patient may be reduced to 1110 MBq/m^2 or 740 MBq/m^2 based on adverse events. Starting day 1 of cycle 2 (week 5), patients will receive nivolumab 480 mg IV every 4 weeks and cabozantinib 40 mg PO every day. All cycles are 28 days. A 5-patient safety lead-in will evaluate myelosuppression. The co-primary endpoints are safety and CR rate by RECIST 1.1. Secondary endpoints are ORR, PFS by RECIST 1.1, and overall survival. The sample size was chosen for reasonable operating characteristics to distinguish a desirable CR rate of 18% as better than the standard CR rate of 9%. To explore the effects of the treatment on inducing activated T cell infiltration, patients will undergo pre/post-treatment PET scan with ^{18}F-AraG radiotracer and biopsies will be obtained for single cell, spatial transcriptomics, and proteomics studies. Clinical trial information: NCT05663710. Research Sponsor: Telix Pharmaceuticals; DOD Kidney Cancer Research; W81XWH-22-1-0456.