Background Loss of the focal chromosomal region 9p21.3 is a common event in mUC (~25% of patients) that leads to loss of tumor suppressor genes CDKN2A/B and metabolic gene MTAP (Methylthioadenosine phosphorylase) and correlates with adverse clinical outcomes and resistance to immunotherapy. MTAP loss results in a buildup of its substrate, methylthioadenosine (MTA) which may act as an agonist of adenosine receptors and inhibit the anti-tumor immune response. However, MTAP loss creates a synthetic lethal vulnerability to de novo adenine synthesis inhibition with pemetrexed (Alhalabi et al, Nat Comm, 2022). Taken together, our data suggest that a rational triple combination therapy with pemetrexed (tumoricidal, increases tumor PD-L1 expression), A2AR/A2BR inhibitor (mitigates T cell inhibition caused by MTA), and anti-PD-1 (enhances T cell function) could represent a novel, biology-based therapeutic combination with much improved and durable activity against MTAP-deficient UC.

Methods A prospective phase II trial of patients with advanced MTAP-deficient urothelial cancer is being conducted under IRB-approved protocol NCT05335941. This study will enroll 20 patients at a single site (The University of TX, MD Anderson Cancer Center). Key eligibility criteria include advanced measurable previously treated UC. Prior therapy must include immunotherapy. MTAP-deficiency is confirmed with CLIA-approved immunohistochemistry or next-gen sequencing. Therapy consists of pemetrexed (500 mg/m2), and zimberelimab (AB122, 360 mg) intravenously every 3 weeks as well as etrumadenant (AB928, 150 mg) orally daily until disease progression, patient withdrawal, or unacceptable toxicity. Two tumor biopsies per patient (at trial baseline and between 2nd-3rd dose of combination therapy) will be obtained for correlative studies to identify biomarkers and inform mechanisms of response and/or resistance. The primary dual objective is to evaluate safety/tolerability and clinical activity of the triplet combination. The endpoint for this objective is adverse event rate by CTCAE v5.0 and response rate via RECIST v1.1. Secondary objective is to explore the biological changes in MTAP-deficient UC tumor microenvironment including tumor-infiltrating T-cells, macrophages, and myeloid-derived suppressor cell (MDSCs) at single-cell and molecular levels. Exploratory objective is to evaluate progression-free and overall survival. Interim analysis for futility and safety occurs in cohorts of 5 patients and is performed based on Bayesian sequential methods.

Trial Registration NCT05335941
Ethics Approval This protocol is approved by the MD Anderson Cancer Center IRB.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0660