664 A PHASE I TRIAL OF TREMELIMUMAB, DURVALUMAB (MEDI4736) AND BELINOSTAT IN *ARID1A* MUTATED CANCERS WITH FOCUS ON UROTHELIAL CARCINOMA (RESOLVE)

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Background *ARID1A* loss by mutation or deletion is the most common chromatin remodeling genomic alteration in cancer and occurs in about a fourth of all urothelial carcinoma (UC). Histone deacetylase inhibition (HDACi) has clinical benefit in *ARID1A* mutated UC.[1] *ARID1A* loss in cancer confers vulnerability to immune checkpoint inhibition (ICI) due to its association with microsatellite instability, high tumor mutational burden, increased expression of programmed death-ligand 1, and immune-active tumor microenvironment.[2] *ARID1A* mutation and inflammatory tumor microenvironment are associated with prolonged survival in metastatic UC treated with ICI.[3] The combination of HDACi plus ICI may enhance anti-tumor activity,[4] especially when used in a phased manner.[5] RESOLVE is a phase 1 study to study the dosing, safety, and efficacy of a phased regimen of tremelimumab and durvalumab (dual ICI) in combination with belinostat (HDACi) in advanced cancers with *ARID1A* loss, with a focus on UC.

Methods We are currently enrolling patients in this phase 1 open-label, dose-escalation, and safety-evaluating study of a phased triplet combination in a single cohort of patients with locally advanced or metastatic UC with *ARID1A* mutation. The primary objectives are to assess the recommended phase II dose of belinostat in combination with tremelimumab and durvalumab in advanced solid tumors harboring *ARID1A* mutations and to assess the ongoing safety of the combination. The secondary objective is to determine the efficacy of the triplet combination in patients with locally advanced or metastatic UC with *ARID1A* mutation.

Patients are treated with a fixed-dose intravenous regimen of tremelimumab 300 mg once with durvalumab 1500 mg on the first day of the first cycle. Belinostat is administered intravenously starting at cycle 2 in combination with durvalumab 1500 mg every three weeks for 6 cycles. This is followed by a maintenance phase of durvalumab 1500 mg every four weeks for a total treatment period of up to two years. Phase 1A begins with a single patient dose acceleration of belinostat from a dose of 750 mg/m^2 to 1000 mg/m^2 daily for five days, then administered every three weeks, with the expansion of cohort enrollment at the maximum-tolerated dose in phase 1B portion of the study. Patients with unresectable locally advanced or metastatic UC (variant histology is allowed) that harbor *ARID1A* loss of function genomic alterations are eligible for the study. Tissue and peripheral blood are collected at baseline, treatment, and progression for correlative studies. (NCT05154994)

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Trial Registration NCT05154994

REFERENCES

1. Gupta S, Albertson DJ, Parnell TJ, Butterfield A, Weston A, Pappas LM, *et al*. Histone deacetylase inhibition has targeted clinical benefit in ARID1A mutated advanced urothelial carcinoma. *Mol Cancer Ther*. 2018.
2. Hu G, Tu W, Yang L, Peng G, Yang L. ARID1A deficiency and immune checkpoint blockade therapy: From mechanisms to clinical application. *Cancer Letters*. 2020;**473**:148–55.
3. Goswami S, Chen Y, Anandhan S, Szabo PM, Basu S, Blando JM, *et al*. ARID1A mutation plus CXCL13 expression act as combinatorial biomarkers to predict responses to immune checkpoint therapy in mUCC. *Sci Transl Med*. 2020;**12** (548).
4. Borcoman E, Kamal M, Marret G, Dupain C, Castel-Ajgal Z, Le Tourneau C. HDAC Inhibition to Prime Immune Checkpoint Inhibitors. *Cancers*. 2021;**14**(1):66.
5. Hull EE, Montgomery MR, Leyva KJ. HDAC Inhibitors as Epigenetic Regulators of the Immune System: Impacts on Cancer Therapy and Inflammatory Diseases. *Biomed Res Int*. 2016;**2016**:8797206.

Ethics Approval This clinical trial is approved by the University of Utah Institutional Review Board (IRB 143952).

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