CONCURRENT TREATMENT WITH GM-CSF IMMUNOEMBOLIZATION OF HEPATIC METASTASES AND SYSTEMIC IMMUNE CHECKPOINT INHIBITORS TO OVERCOME IMMUNE EVASION IN PATIENTS WITH METASTATIC UVEAL MELANOMA

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Background
Uveal melanoma (UM) is a poorly immunogenic melanoma subtype with low objective response rate (ORR) to immune checkpoint inhibitors (ICI). With a strong predilection for hepatic metastases, UM patients often receive liver-directed therapies, such as hepatic artery embolization. We hypothesized that transarterial immune-embolization (TAIE) with GM-CSF to treat hepatic metastases may synergize with concurrent use of ICIs, plausibly through improved antigen presentation.

Methods
This single-center retrospective study includes UM patients with liver-predominant metastatic disease who received TAIE using a combination of GM-CSF (2000 mcg) and lipiodol for up to 10 treatments in an alternating lobar fashion, with/without concurrent systemic ICI (defined as administered within 3 months of starting TAIE). Efficacy endpoints included investigator-assessed ORR per RECIST 1.1, progression-free survival (PFS) and overall survival (OS). Safety endpoints included adverse events (AEs), related to TAIE and/or ICI.

Results
Between 2016–2023, 18 metastatic UM patients (8M; 10F) with median age 64 (range 46–80) years received 83 IE treatments (median 3, range 1–10). Median follow up was 19.3 (range 1.7 – 47.1) months. Fourteen of 18 (78%) patients received concurrent ICI (n = 10 with combination anti-CTLA-4/PD-1, n = 4 with anti-PD-1). ORR was 17% (3/18), with all 3 patients experiencing partial responses lasting 4.2, 28.1+ and 38.6 months, respectively, while receiving concurrent ICI. Seven (39%) patients had stable disease as best response, resulting in a disease control rate of 56% (10/18). Median OS from first TAIE treatment was 35 (range 1.7–39.2+) months. Concurrent IE with ICI was generally tolerated well, except one of 13 (8%) patients requiring hospitalization for transient distributive shock (n=1), which resolved with supportive care. Immune-related AE (IRAE) were only observed in patients receiving combination ICI with anti-CTLA-4/PD-1, including hepatitis (n= 5; G2 in 1 and G3 in 4; 4 required steroids and all resolved), pneumonitis (n=1; G1), pancreatitis (n=1, G2), colitis (n=1; G3) and adrenal insufficiency (n=1; G3); four of these seven patients resumed PD-1 monotherapy without further AEs.

Conclusions
Concurrent administration of liver-directed therapy with GM-CSF TAIE and systemic ICI, including anti-CTLA4/PD-1 combination, is safe and feasible, and can lead to sustained clinical benefit in a subset of UM patients. For this poorly immunogenic cancer with a characteristic predilection for hepatic metastases, liver-directed novel immunotherapy approaches offer a unique opportunity to synergize with systemic immunotherapies.

Ethics Approval
University of Washington IRB Committee D approved the study: Clinical Outcome of Immunotherapy in Melanoma and Other Skin Cancer
Patients, Investigator: Shailender Bhatia, IRB ID: STUDY00011495. IRB determined that consent was waived due to minimal risk.

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