Immune checkpoint inhibitors (ICIs) in advanced upper tract urothelial cancer (UTUC) with mismatch repair deficiency (dMMR) or microsatellite instability (MSI).

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Background: MSI-high (MSI-H) and dMMR are three times more common in UTUC than bladder cancer. While these features enhance ICI sensitivity in solid tumors, data on ICIs in advanced UTUC with dMMR/MSI-H remain scarce. **Methods:** We retrospectively reviewed records of patients (pts) with locally advanced (LA) or metastatic with dMMR/MSI-H UTUC treated with ICIs at MD Anderson (2015-2024). Descriptive statistics and the Kaplan-Meier method were used. **Results:** Twenty-four pts with LA/unresectable (n=8) or metastatic (n=16) disease were treated with ICIs (pembrolizumab, n=17; nivolumab, n=4; atezolizumab, n=3) (Table). Tumor origin was the ureter (10, 41.7%) or renal pelvis (14, 58.3%). Twenty-two (91.7%) pts had Lynch syndrome, mostly (n=20) detected by germline mutation testing (*MSH2*, n=12; *MLH1*, n=5; *MSH6*, n=3).Twenty-one (87.5%) pts had IHC-proven dMMR(MSH2/MSH6 loss, n=7; PMS2/MLH1 loss, n=5; MLH1 loss, n=4; MSH2 *loss*, n=3; MSH6 loss, n=3). The most frequent alterations in somatic genetic testing for 22 pts were *MSH2* (12 pts), *CREBBP* (7 pts), *ARID1A* (7 pts) and *NOTCH3* (7 pts). Fourteen (58.3%) pts received prior platinum chemotherapy: cisplatin (n=9) or carboplatin-based (n=5), with only 35.7% showing responses (one complete response [CR] and 4 partial responses [PR]).With a median follow-up of 54.3 months (mo) [95% CI: 19.5 – 87.1], median PFS was 55.8 mo [95% CI: 19.4 – NE]. Milestone PFS probabilities at 12 and 24 mo were 90.7% [95% CI: 79.2% – 100%] and 69.2% [95% CI: 51.3% – 93.4%], respectively.At a median follow-up of 51.3 mo [95% CI: 34 – 60.2], median OS was not reached. Median time on treatment was 13.5 mo [IQR: 4 – 25.8]. Eight (33.3%) pts remain progression-free beyond 4 years. ORR was 79.2%, including 16 CR (66.7%) and 3 PR (12.5%), while DCR was 95.8%.Median time to best response was 11.9 mo [IQR: 5.6 – 20]. Four (16.7%) pts were offered surgical consolidation with these outcomes: ypTaN0M0, ypT0N0M0, ypT1N0M0 and mypT1N0 M1-NED. Grade ≥3 immune-mediated toxicity events leading to ICI discontinuation (n=6) included hepatitis (n=3), pancytopenia (n=1), polyendocrinopathy (n=1) and diarrhea (n=1). **Conclusions:** Single-agentICIs show remarkable efficacy and durable responses in advanced dMMR/MSI-H UTUC, with one-third of pts remaining in remission after over 4 years. Our findings support dMMR/MSI-H as a predictive and prognostic biomarker in UTUC and the use of single-agent ICIs in this subpopulation. Research Sponsor: None.

Variable	Measure
Age at dx of advanced disease, median [ICR]	66 [55.8 – 72.3]
Sex, male (n, %)	14 (58.3%)
Race/Ethnicity, n (%)	
White	19 (79.2%)
Black	1 (4.2%)
Hispanic	2 (8.3%)
Asian	2 (8.3%)
Urothelial carcinoma mixed with variant histology, n (%)	3 (12.5%)
Liver mets at ICI start, n (%)	2 (8.3%)
Bone mets at ICI start, n (%)	5 (20.8%)
Hemoglobin <10 g/dL at ICI start, n (%)	5 (20.8%)
Bellmunt score, n (%)	
0-1	19 (79.2%)
2	3 (12.5%)
3	2 (8.3%)