# *Frontline immune checkpoint inhibitors in patients ≥ 90 years with advanced urothelial cancer: a single center experience*

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***Introduction:*** *Immune checkpoint inhibitors (ICIs) are approved for advanced urothelial cancer alone and as first-line in combination with enfortumab vedotin. Platinum based chemotherapy which is another frontline choice is often not a treatment option for older patients due to comorbidities that increase with age. Despite ICIs being better tolerated compared to traditional chemotherapy little is known about their efficacy and toxicity in patients ≥ 90 years due to the rarity of this population in clinical trials. Our objective was to analyze the efficacy and toxicity of immune checkpoint inhibitors in patients ≥ 90 years.*

***Materials and methods:*** *We conducted a single center retrospective review of patients ≥ 90 years treated between July 2019 and September 2023 with standard of care ICIs for advanced urothelial cancer.*

***Results:*** *Six patients treated with pembrolizumab were identified. Four (66.7%) were male and mean age was 93.5 years at the time of treatment initiation. Response rate was 66.7% (4 patients) with 3 complete responses, which were durable off therapy. Median follow up was 18.2 months. Median progression free survival (PFS) was 10.2 months [95%confidence interval (95%CI): 1.77, not reached (NR)] and median overall survival (OS) was 18.2 months (95%CI: 12.1, NR). Side effects presented in 4 (66.7%) patients and included hypothyroidism, diarrhea, anemia, thrombocytopenia, rash, and bullous dermatitis. One patient developed grade 3 anemia and no patients experienced grade 4 events or required hospitalization due to treatment side effects.*

***Conclusions:*** *Our experience in a small cohort of patients ≥ 90 years indicate that ICIs are well tolerated and effective for the treatment of advanced urothelial carcinoma in this patient population.*

**Key Words:** bladder cancer, checkpoint inhibitors, elderly patients, immunotherapy, urothelial cancer

## Introduction

Bladder cancer is a disease of the elderly. It is the 7th most common cancer worldwide, and the 5th most common cancer in the United States in those over 70.[1]

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Platinum based chemotherapy has historically been the first line therapy for locally advanced and metastatic urothelial cancer (la/mUC) however many patients were ineligible due to comorbidities that increase with age.

Galsky et al proposed criteria defining cisplatin ineligibility, for patients with ≥ 1 of the following: Eastern Cooperative Oncology Group Performance Status (ECOG PS) of ≥ 2, creatinine clearance (Cr Cl) < 60 mL/min, hearing loss ≥ Grade 2, neuropathy ≥ Grade 2 and New York Heart Association (NYHA)

Class 3 heart failure.[2] Later Gupta et al proposed a definition for chemotherapy ineligibility, to describe those also not eligible for carboplatin. Criteria included patients with ECOG PS > 3, creatinine clearance (CrCl) < 30 mL/min, peripheral neuropathy > Grade 3, or NYHA Heart Failure Class > 3, or patients with both ECOG PS 2 and Cr Cl < 30 mL/min.[3]

Immune checkpoint inhibitors (ICIs) alone or in combination with enfortumab vedotin (EV) are a recently approved frontline option for la/mUC.[4-8] Even though ICIs and EV are better tolerated compared to chemotherapy little is known about their effects in patients > 90 years old.[8] An upper limit for age is rarely an eligibility criterion in clinical trials. However, enrolled patients were aged up to 92 and 94 in the frontline ICI trials[4,5] and 87, 90, 91 in the trials for pembrolizumab in combination with EV.[6,7]

Due to the rarity of this population, patients > 90 years old have not been separately analyzed. This patient group is often cisplatin and/or chemotherapy-ineligible, thus a better understanding of response and toxicity of ICI-therapy in this population is an unmet need. Herein we present our institutional experience in this population.

## Materials and methods

### *Population*

With Johns Hopkins Institutional Review Board approval, we performed a retrospective review of patients ≥ 90 years old with la/mUC treated with ICI as initial systemic treatment. We identified seven patients treated with ICI between July 2019 and September 2023. Informed signed consent was obtained from six patients and these were included in our analysis.

### *Study design*

Data were extracted from clinical notes. Response to therapy was determined by physician assessed RECIST criteria. ICI-related adverse events of any grade were identified according to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE). Summary statistics were calculated for baseline characteristics and treatment-related adverse events (TRAEs). Progression-free (PFS) and overall (OS) survival were calculated using Kaplan Meier estimates. PFS was defined as time in months from ICI initiation to the first documented evidence of disease progression (PD) on imaging or death of any cause. OS was defined as time in months from ICI initiation to death of any cause. Statistical analysis was performed using R 4.2.2.

## Report of cases

### *Case 1*

A 97-year-old white male presented with symptomatic muscle invasive urothelial cancer of the bladder (MIUCB) metastatic to the liver, PD-L1 positive (combined positive score CPS 77). He underwent palliative bladder radiotherapy for gross hematuria then initiated pembrolizumab 14 months later at age 98. Four months after treatment initiation, renal function deteriorated due to malignant ureteral obstruction, which was managed by percutaneous nephrostomy placement. Pembrolizumab was well tolerated and led to a mixed response with resolution of liver metastases, stable adenopathy, and lobular thickening of the bladder wall. He experienced intermittent cancer related hematuria throughout the course of treatment and grade 2 treatment related hypothyroidism which was well controlled with medication but remained otherwise asymptomatic. He received 18 cycles (15.6 months) of ICI which was discontinued due to multifactorial functional status decline. He passed away 5.7 months after treatment discontinuation without additional scans or overt IO-related toxicity.

### *Case 2*

A 95-year-old white male with prostate cancer history post radical prostatectomy and radiotherapy 30 years prior, presented with gross hematuria and was diagnosed with PD-L1 positive (CPS: 10-15) (MIUCB). Imaging was significant for a 5 cm lung mass, but the patient deferred biopsy. He initiated pembrolizumab at age 96, with a partial response in the bladder and lung after 2 months and complete response after 7 months. Following 7 months of pembrolizumab he developed grade 1 diarrhea and grade 2 bullous dermatitis. Pembrolizumab was held after 12 cycles (8.5 months) and dermatitis was managed with supportive care and resolved. After 19.7 months of durable complete radiographic response off treatment, scans showed disease progression with new right middle lobe pulmonary nodules. Pembrolizumab was not restarted due to risk of severe skin toxicity and the patient opted for symptomatic management. He remains alive 22 months after discontinuing pembrolizumab.

### *Case 3*

A 94-year-old African-American male with non-muscle invasive bladder cancer post BCG presented with gross hematuria and was diagnosed with PD-L1 positive (CPS 100) MIUCB. Lung metastases were identified,

and patient deferred a biopsy. Seven months after the initial diagnosis he underwent palliative bladder radiation for symptomatic MIUCB with gross hematuria and anemia. Pembrolizumab was initiated 1 month later, at age 94, with a partial response 2 months after initiation and a complete response after 13 months. He received 33 cycles of treatment with no significant side effects, but treatment was held after 27 months due to long treatment duration, sustained disease remission and progressive fatigue. Scans remain with durable complete response 22 months off ICI.

### *Case 4*

A 92-year-old white male who presented with gross hematuria and back pain and was diagnosed with high-grade upper tract urothelial cancer (UTUC) metastatic to the liver and bone. PDL-1 testing was not completed as outside tissue was not received. Chemotherapy was offered but deferred by the patient. He initiated pembrolizumab 4 months after the diagnosis and completed 2 cycles of treatment without significant side effects. He had symptomatic disease progression after 2 months, enrolled into hospice care and passed away 3 months after ICI discontinuation.

### *Case 5*

An African-American female with longstanding end stage renal disease on hemodialysis was diagnosed with PD-L1 low (CPS: 1-5) MIUCB metastatic to the lungs and initiated pembrolizumab 2 months later, at age 90. She received 17 cycles of pembrolizumab with partial response as best radiographic response. During treatment she experienced occasional grade 1 rash. After 11 months of treatment scans showed disease progression in the liver. She was subsequently treated with Enfortumab vedotin for 3 dose reduced cycles with disease progression as best response and enrolled to hospice care. She passed away 4 months after ICI discontinuation.

### *Case 6*

An 88-year-old white woman unnderwent a radical cystectomy for MIUCB with pathology demonstrating pT4a pN0 urothelial carcinoma with carcinoma in situ. Eighteen months later (at age 90), a routine follow up CT scan demonstrated a new left pelvic mass and pulmonary nodule determined to be PET avid. The patient refused chemotherapy, and had borderline functional status, thus, pembrolizumab was initiated (CPS was 7-8). Treatment was complicated by sepsis likely due to urinary source, grade 3 anemia that improved, and grade 1 thrombocytopenia that occasionally led to treatment delays. CT scans demonstrated partial response at 3 months and complete response at 6 months. She completes 9 cycles of therapy (7 months). Cycle 10 was deferred due to non-cancer and non-treatment related comorbidities. Two months later her scans demonstrated durable complete response. Shortly thereafter, she developed symptomatic COVID and requested hospice arrangements. She passed away 5 months after ICI discontinuation.

## Results

Baseline patient characteristics are summarized in Table 1. ICI was pembrolizumab for all patients. Tumor mutation burden and microsatellite instability were not available for all.

Median follow up was 18.2 months. Best response according to physician reported RECIST criteria was complete response (CR) for 3 (50.0 %) patients and partial response (PR), mixed response (MR) and progression of disease (PD) for 1 (16.7%) patient each. Objective response rate (ORR) was 66.7% (4 patients) with 3 (42.9%) patients having a durable complete

TABLE 1. **Baseline patient characteristics**

| **Characteristic** | **No. (%) Patients (n = 6)** |
|---|---|
| Age on C1D1, years, mean (range) | 93.5 (90-98) |
| Sex | |
| Female | 2 (33.3) |
| Male | 4 (66.7) |
| Race | |
| White or Caucasian | 4 (66.7) |
| African American | 2 (33.3) |
| Cancer primary location | |
| Bladder | 5 (83.3) |
| UTUC | 1 (16.7) |
| Metastatic sites | |
| Lymph nodes only | - |
| Visceral disease | 6 (100) |
| Liver | 2 (33.3) |
| Lungs | 4 (66.7) |
| Bones | 1 (16.7) |
| PDL-1 expression by combined positive score[1] | |
| < 10 | 2 (33.3) |
| ≥ 10 | 3 (50.0) |

[1]not available for 1 patient; C1D1 = cycle 1 day 1 of treatment

TABLE 2. **Treatment-related adverse events from ICI treatment (n = 6)**

| | No. (%) | | | |
|---|---|---|---|---|
| **Characteristic** | **Any grade** | **Grade 1** | **Grade 2** | **Grade ≥3** |
| Fatigue | 2 (33.3) | | 2 (33.3) | |
| Hypothyroidism | 1 (16.7) | - | 1 (16.7) | - |
| Rash | 1 (16.7) | 1 (16.7) | - | - |
| Bullous dermatitis | 1 (16.7) | - | 1 (16.7) | - |
| Diarrhea | 1 (16.7) | 1 (16.7) | - | - |
| Thrombocytopenia | 1 (16.7) | 1 (16.7) | - | - |
| Anemia | 1 (16.7) | - | - | 1 (16.7) |
| Overall events | 8 | 3 | 4 | 1 |

response off therapy. Median PFS was 10.2 months [95%Confidence Interval (95% CI): 1.77, Not Reached (NR)] and 5 (83.3%) patients eventually experienced disease progression or death. Median duration of ICI treatment was 9.8 months (range: 0.7-27.6). Median OS was 18.2 months (95% CI: 12.1, NR) with 2 (33.3%) patients still alive at the follow up cut off date. One patient had mixed response with complete resolution of his liver metastases and local progression of his bladder mass.

Three (50.0 %) patients had no significant TRAEs and one patient developed grade 3 transient anemia, Table 2.

## Discussion

The incidence of urothelial cancer increases with age. ICIs with or without EV are a first line treatment for la/mUC in cisplatin/chemotherapy ineligible patients, many of whom present at very advanced age. While other studies have investigated the use of ICIs in older patients,[9-11] our work focuses specifically on patients over 90 years old. As patients of that age are often chemotherapy ineligible, and age-related comorbidities often prevent the use of EV, a better understanding of ICI efficacy and toxicity in this patient group is of great importance.

In our small retrospective analysis of patients treated with first line pembrolizumab, ORR was 66.7% and median PFS was 10.2 months and OS was 18.2 months. Three (50.0%) patients had a durable complete response 2, 20 and 22 months after their last dose of ICI. ICIs were generally well tolerated without any reported grade 4 events and no patients required steroids or toxicity-related hospitalization.

We present our experience with patients over 90 years old treated with front-line ICIs for la/mUC. Response rates and toxicity were commensurate with frontline trails in larger populations. Though our dataset is small, it supports use of ICI in eligible patients > 90 years with locally advanced and metastatic urothelial cancer.

## Disclosures

Evangelia Vlachou has no conflict of interest to report. Burles Avner Johnson has served on an emerging thought leader advisory board for Seattle Genetics. BAJ, NMH, and JH-C are co-authors on a pending patent on utilizing an immune based gene signature to predict survival following immune checkpoint inhibitor therapy in patients with metastatic bladder cancer. Elizabeth Guancial, has no conflict of interest to report. Kara A. Lombardo has no conflict of interest to report. Noah M. Hahn discloses consulting compensation from AstraZeneca, Merck, Genentech, GlaxoSmithKline, Ferring, Champions Oncology, Health Advances, Keyquest Health, Guidepoint Global, Seattle Genetics, Mirati, Incyte, TransMed, CicloMed, Janssen, Pfizer, Boehringer Ingelheim, Pfizer, and EMD Serono; research support to the institution from HTG Molecular Diagnostics, AstraZeneca, Bristol Myers-Squibb, Genentech, Seattle Genetics, OncoGenex, Pieris, Inovio, Principia Biopharm; speaking honorarium from Creative Educational Concepts, and Large Urology Group Practice Association. Jean Hoffman-Censits discloses Genetntech research support and Institutional support for trials: EMD Serono, Astellas/Seagen, Ikena Oncology, Daiichi Sankyo. □

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