Treatment patterns among patients with advanced urothelial carcinoma following discontinuation of PD-1/L1 inhibitor therapy

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Background

- Locally advanced or metastatic urothelial carcinoma (la/mUC) is an aggressive disease that remains incurable despite recent advances.[1,2]
- Current treatment guidelines recommend programmed death receptor-1 or death-ligand 1 (PD-1/L1) inhibitor therapy second line (2L) after platinum-based chemotherapy, or first line (1L) in cisplatin-ineligible patients whose tumors express PD-L1 or who are ineligible for any platinum-containing chemotherapy regardless of PD-L1 expression.[3]
- However, only 23–29% of 1L and 13–21% of 2L patients (regardless of PD-L1 status) respond to PD-1/L1 inhibitor therapy based on results from clinical trials.[1,2,4]
- The PD-L1 inhibitor avelumab was also recently granted US Food and Drug Administration (FDA) approval (June 2020) as maintenance treatment for patients with la/mUC who have not progressed with 1L platinum-containing chemotherapy.[5]
- Historically, there has been a high unmet need for patients who discontinue PD-1/L1 inhibitors both in 1L and 2L.
  - For chemotherapy-naive patients discontinuing 1L PD-1/L1 inhibitor therapy, gemcitabine plus carboplatin or cisplatin (if eligible) are the preferred recommended 2L therapies.[3]
  - Until recently, few treatment options have been available for patients who discontinue 2L PD-1/L1 inhibitor therapy.[3]
    - Enfortumab vedotin-ejfv received FDA accelerated approval on December 18, 2019, for adult patients with la/mUC who have previously received a PD-1/L1 inhibitor and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced, or metastatic setting.[6]
  - Erdafitinib received FDA accelerated approval on April 12, 2019, and is limited to those patients with la/mUC whose tumors have susceptible fibroblast growth factor receptor 3 or 2 (FGFR3 or FGFR2) genetic alterations that has progressed during or following platinum-containing chemotherapy, regardless of PD-1/L1 inhibitor exposure status.[7]
- There is a lack of published real-world data on treatment patterns for patients with la/mUC previously treated with PD-1/L1 inhibitor therapy, particularly for those patients who received a PD-1/L1 inhibitor in the 1L (maintenance or non-maintenance) setting.

Objective

- To describe patient characterization and treatment patterns among patients with la/mUC following discontinuation of 1L or 2L PD-1/L1 inhibitor therapy.

Methods

- We performed a retrospective chart review in 26 geographically dispersed clinical sites in the US recruited at random from a nationally representative database.
  - Clinical sites were included if they treated/managed ≥4 patients with la/mUC who failed PD-1/L1 inhibitor therapy in the past 24 months and agreed to participate in data validation.
- Patients aged ≥18 years with histologically or cytologically confirmed urothelial carcinoma and radiographic evidence of metastatic or locally advanced disease were identified; the first 5 patients from each clinical site who met eligibility criteria were enrolled in the study.
- We included patients with newly initiated PD-1/L1 inhibitor therapy (nivolumab, atezolizumab, pembrolizumab, durvalumab, or avelumab) in 1L or 2L following chemotherapy for la/mUC at any point from May 15, 2016, to July 31, 2018, and subsequently discontinued PD-1/L1 inhibitor therapy prior to December 31, 2018. Follow-up continued through October 31, 2019, or death, whichever occurred first.
- Patients were excluded if they had (1) a history of another malignancy; (2) resectable disease; (3) participated in a clinical trial since la/mUC diagnosis; or (4) been lost to follow-up prior to death or end of study, or end of initial PD-1/L1 inhibitor therapy.
- Data were summarized using descriptive statistics and analyzed with Statistical Analysis System (SAS) version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Physician demographics

- Reporting oncologists were mostly male (84.2%), based in an urban setting (89.5%), and had >10 years in practice (68.4%).
- Approximately 40% of oncologists were academic, whereas the remaining 60% were practicing in the community setting.

Baseline demographics

- Among the 300 patients with la/mUC included in the study, 198 (66.0%) received initial PD-1/L1 inhibitor therapy as 1L and 102 (34.0%) as 2L therapy; median follow-up post–PD-1/L1 inhibitor discontinuation was 7.0 (range, 0–26.9) and 4.9 (range, 0–30.0) months for 1L and 2L groups, respectively.
- Mean (SD) age of the overall population at la/mUC diagnosis was 69.4 (8.7) years, and a majority of patients were male (66.0%) and White (74.7%; **Table 1**).
  - There was a trend toward younger age in patients who received their initial PD-1/L1 inhibitor therapy in 2L.

Table 1. Patient baseline demographics at time of advanced diagnosis

Characteristic[a,b]	All patients (N=300)	Initial PD-1/L1 inhibitor as 1L therapy (n=198)	Initial PD-1/L1 inhibitor as 2L therapy (n=102)
Age, years, mean (SD)	69.4 (8.7)	70.9 (8.9)	66.5 (7.6)
Gender, n (%)			
Male	198 (66.0)	126 (63.6)	72 (70.6)
Female	102 (34.0)	72 (36.4)	30 (29.4)
Race/ethnicity, n (%)			
White	224 (74.7)	149 (75.2)	75 (73.5)
Black/African American	60 (20.0)	40 (20.2)	20 (19.7)
Other	16 (5.3)	9 (4.5)	7 (6.9)
Tobacco use, n (%)			
Current	58 (19.3)	36 (18.1)	22 (21.6)
Former	194 (64.7)	134 (67.7)	60 (58.8)
Never/unknown	48 (16.0)	28 (14.1)	20 (19.6)
Most recent medical insurance, n (%)			
Medicare	186 (62.0)	130 (65.7)	56 (54.9)
PPO	71 (23.7)	41 (21.0)	30 (29.4)
Medicaid	22 (7.3)	16 (8.1)	6 (5.9)
Other	21 (7.0)	11 (5.6)	10 (9.8)

[a]At time of first radiographic evidence of metastatic or locally advanced disease.
[b]Median time between advanced diagnosis and start of PD-1/L1 inhibitor in 1L was 0.7 (range, 0–7.4) months. Median time between advanced diagnosis and start of PD-1/L1 in 2L was 7.1 (range, 1.4–29.4) months.
1L, first line; 2L, second line; PD-1/L1, programmed death receptor-1/death-ligand 1; PPO, preferred provider organization.

Table 2. Patient clinical characteristics at time of advanced diagnosis

Characteristic[a,b]	All patients (N=300)	Initial PD-1/L1 inhibitor as 1L therapy (n=198)	Initial PD-1/L1 inhibitor as 2L therapy (n=102)
Stage, n (%)			
III, inoperable	31 (10.3)	13 (6.6)	18 (17.6)
IV, TNM stage type	269 (89.7)	185 (93.4)	84 (82.4)
Any T, N1–N3, M0	33 (11.0)	13 (6.6)	20 (19.6)
Any T, any N, M1	236 (78.7)	162 (81.8)	64 (62.7)
Distant metastatic site, n (%)[c]			
Lung	163 (61.0)	109 (55.1)	54 (53.0)
Lymph nodes	121 (45.3)	78 (39.4)	43 (42.2)
Lymph node only	25 (8.3)	18 (9.1)	7 (6.9)
Bone	104 (39.0)	80 (40.4)	24 (23.5)
Liver	93 (34.8)	58 (29.3)	35 (34.3)
Brain	6 (2.2)	4 (2.0)	2 (1.9)
Other	4 (1.5)	4 (2.0)	0 (0.0)
ECOG PS score, n (%)			
0	43 (14.3)	24 (12.2)	19 (18.6)
1	159 (53.0)	101 (51.1)	58 (56.9)
≥2	96 (32.0)	73 (36.8)	23 (22.5)
Unknown	2 (0.7)	0 (0.0)	2 (2.0)
No. of comorbidities, n (%)			
0	47 (15.7)	24 (12.1)	23 (22.5)
1–2	162 (54.0)	110 (55.5)	52 (51.0)
>3	91 (30.3)	64 (32.3)	27 (26.5)
Most common comorbidities, n (%)			
Hypertension	119 (39.7)	69 (35.0)	50 (49.0)
Diabetes	78 (26.0)	54 (27.3)	24 (23.5)
Coronary artery disease	71 (23.7)	54 (27.3)	17 (16.7)
Chronic pulmonary disease	53 (17.7)	38 (19.2)	15 (14.7)
Moderate to severe renal disease	28 (9.3)	25 (12.6)	3 (2.9)
Cerebrovascular disease	22 (7.3)	12 (6.1)	10 (9.8)
PD-L1 expression testing conducted, n (%)[d]	201 (67.0)	141 (71.2)	60 (57.8)
Tumor proportion score ≥10%, n (% of tested patients)	159 (79.1)	115 (81.6)	44 (73.3)

[a]At time of first radiographic evidence of metastatic or locally advanced disease.
[b]Median time between advanced diagnosis and start of PD-1/L1 inhibitor in 1L was 0.7 (range, 0–7.4) months. Median time between advanced diagnosis and start of PD-1/L1 inhibitor in 2L was 7.1 (range, 1.4–29.4) months.
[c]Patients may have >1 site of metastasis.
[d]139 of 141 1L patients received PD-L1 testing at time of advanced diagnosis (prior to initiating 1L) and 2 received testing during 1L; 44 of 60 2L patients received PD-L1 testing at time of advanced diagnosis and 14 received testing after initiation of 1L.
1L, first line; 2L, second line; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD-1, programmed death receptor-1; PD-L1, programmed death-ligand 1; PPO, preferred provider organization; TNM, tumor node metastasis.

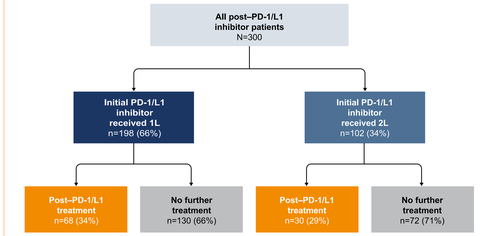
Clinical characteristics

- Most patients (89.7%) had stage IV disease with distant metastasis at diagnosis; common sites of metastases were lung (61.0%), bone (39.0%), and liver (34.8%; **Table 2**).
  - Less than a quarter of patients (n=66, 22.0%) were first diagnosed with localized bladder cancer before progressing to la/mUC.
- Most patients (84.3%) had comorbidities at la/mUC diagnosis, but these were considered well controlled.
- At initiation of therapy, a descriptively higher proportion of patients who received 1L PD-1/L1 inhibitor therapy had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of ≥2 than patients who received 2L PD-1/L1 inhibitor therapy (36.8% vs 22.5%, respectively).
- A descriptively higher proportion of patients receiving PD-1/L1 inhibitor therapy in 1L had PD-L1 expression testing (71.2%) compared with those receiving PD-1/L1 inhibitor therapy in 2L (57.8%).

Treatment patterns

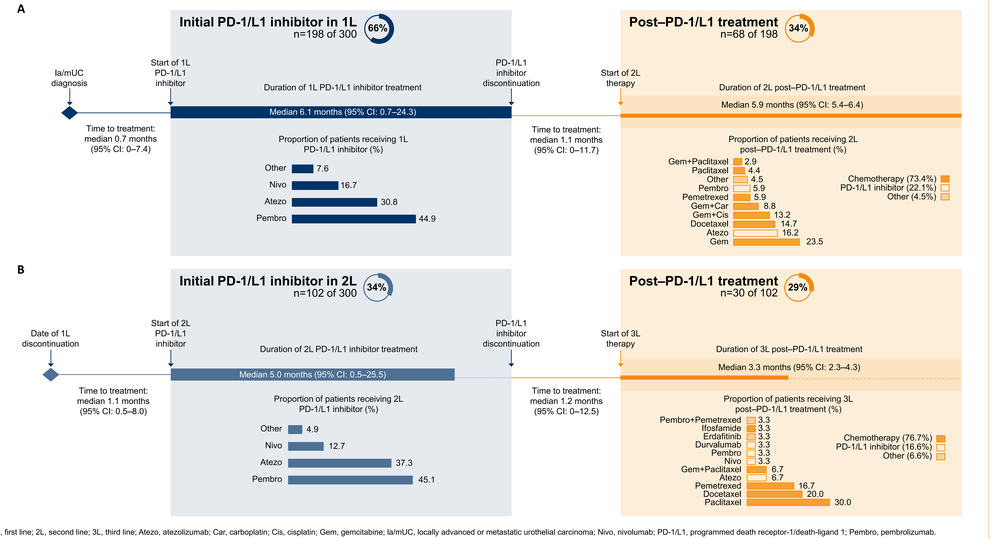
- Among the 300 patients in the study population, 198 (66.0%) received PD-1/L1 inhibitor therapy as 1L and 102 (34.0%) as 2L (**Figure 1**).
- Median time from la/mUC diagnosis to initiation of PD-1/L1 inhibitor in 1L was 0.7 (range, 0–7.4) months (**Figure 2**).
- Pembrolizumab was the most common PD-1/L1 inhibitor in 1L; median duration of treatment (all PD-1/L1 inhibitor therapies combined) was 6.1 months (95% CI: 0.7–24.3).
- Following discontinuation of 1L PD-1/L1 inhibitor therapy, 34.3% (n=68) received subsequent 2L therapy.
- The most common subsequent therapies following 1L PD-1/L1 inhibitor therapy discontinuation were gemcitabine monotherapy (23.5%), gemcitabine plus cisplatin or carboplatin (22.0%), another PD-1/L1 inhibitor therapy (22.1%), and taxane monotherapy (19.1%).
- For patients receiving their initial PD-1/L1 inhibitor in 2L, the time between discontinuation of 1L therapy and initiation of PD-1/L1 inhibitor therapy in 2L was 1.1 (range, 0.5–8.0) months (**Figure 2**).
  - Among patients who received their initial PD-1/L1 inhibitor in 2L, 53.6% were treated with 1L gemcitabine plus cisplatin, 34.0% with 1L gemcitabine plus carboplatin, and 12.4% with other chemotherapy.
- Pembrolizumab was the most common PD-1/L1 inhibitor in 2L; median duration of treatment (all PD-1/L1 inhibitor therapies combined) was 5.0 months (95% CI: 0.5–25.5) in the 2L subgroups.
- Following discontinuation of 2L PD-1/L1 inhibitor therapy, 29.4% (n=30) received subsequent therapy in the third line (3L).
- The most common subsequent therapies received following 2L PD-1/L1 inhibitor discontinuation were taxane monotherapy (50.0%), pemetrexed (16.7%), or another PD-1/L1 inhibitor therapy (16.6%).

Figure 1. Overview of treatment patterns



1L, first line; 2L, second line; PD-1/L1, programmed death receptor-1/death-ligand 1.

Figure 2. Treatment patterns among patients who received first PD-1/L1 inhibitor therapy in (A) 1L or (B) 2L



1L, first line; 2L, second line; 3L, third line; Atezo, atezolizumab; Car, carboplatin; Cis, cisplatin; Gem, gemcitabine; la/mUC, locally advanced or metastatic urothelial carcinoma; Nivo, nivolumab; PD-1/L1, programmed death receptor-1/death-ligand 1; Pembro, pembrolizumab.

- Switching from one PD-1/L1 inhibitor therapy to another distinct PD-1/L1 inhibitor therapy occurred in approximately 20% of both 1L and 2L patients, with "better efficacy/survival" noted by treating oncologists as the most common reason for switching therapy among this subgroup (**Table 3**).
- Of patients discontinuing post–PD-1/L1 inhibitor therapy during the study period, the majority (91.9%; 34 of 37) discontinued due to disease progression.

Table 3. Reasons for selection of treatment post–PD-1/L1 inhibitor

	Patients treated with any therapy post–PD-1/L1 inhibitor (n=98)
Reason(s) for prescribing regimen, n (%)	
Improved efficacy/survival benefit	53 (54.0)
Different class or mechanism of action	40 (43.3)
Different tolerability/safety profile	9 (9.2)
Other	4 (4.1)
	Patients treated with a second PD-1/L1 inhibitor (n=21)
Reason(s) for prescribing regimen, n (%)	
Improved efficacy/survival benefit	16 (76.2)
Different class or mechanism of action	1 (4.8)
Different tolerability/safety profile	3 (14.3)
Other	1 (4.8)

PD-1/L1, programmed death receptor-1/death-ligand 1.

Limitations

- The data in chart review studies reflect assessments by oncologists, which can include limitations such as reporting biases and inconsistency in data reported.
- We consider 1L as the first line of treatment initiated after a patient's advanced diagnosis, whereas clinically relevant definitions of 1L and 2L treatment might differ based on when patients may receive treatments earlier in their urothelial cancer journey and what treatments they receive.
- Patients were enrolled from selected clinical sites (first 5 patients meeting eligibility criteria), and results may not be generalizable to all patients at that site.

Conclusions

- Collectively, the data from the pre-enfortumab vedotin era highlight a significant unmet need for patients with la/mUC who discontinue PD-1/L1 inhibitor therapy.
- Clinical characteristics of patients treated with PD-1/L1 inhibitor therapy differed descriptively when examining the subgroups based on the line of therapy in which the initial PD-1/L1 inhibitor was received, including age, ECOG PS, and PD-1/L1 expression status.
- Only 34% and 29% of patients with la/mUC received subsequent treatment following discontinuation of PD-1/L1 inhibitor therapy in the 1L and 2L setting, respectively.
- Although a majority of patients received taxanes, there was no uniform standard-of-care treatment approach among patients who received subsequent therapy.
- A contemporary analysis following the approvals of 1L switch maintenance avelumab and 2L+ with enfortumab vedotin and erdafitinib is warranted.

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DISCLOSURES

AKM has received consulting/honoraria from Advanced Accelerator Applications, Astellas, AstraZeneca, Bayer, Clovis, Genentech, Janssen, Myovant, Sanofi, and Seagen Inc.; research support from Bayer and Sanofi; and honoraria for medical education work for Medscape, OncLive, and UroToday. SG and ZH are employees of and own stock at Seagen Inc. RF is an employee of Astellas Pharma. SO and CM are employees of Medical Data Analytics, which received consulting fees from Seagen Inc. ACS is an employee of EPI-Q Inc, which received consulting fees from Seagen Inc. GPS is a consultant for Amgen, Astellas/Agensys, AstraZeneca, Bayer, Bristol Myers Squibb, Eisai, EMD Serono, Exelixis, Genentech, Janssen, Merck, Novartis, Pfizer, Sanofi, and Seagen Inc.; has received research support to his institution from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Janssen, Merck, Pfizer, and Sanofi; is an author for UpToDate; serves on the steering committee for Astellas, AstraZeneca, Bavarian Nordic, Bristol Myers Squibb, and Debiopharm; and is a speaker for OncLive, Research to Practice, and Physician Education Resource.

ACKNOWLEDGMENTS

Medical writing support was provided by Jonathon Carthy of Curo, a division of Envision Pharma Group, and funded by Seagen Inc.

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Poster presented at the ASCO Genitourinary Cancers Symposium 2021 Virtual Meeting, February 11–13, 2021