Cancer Epidemiology 60 (2019) 121–127

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Treatment patterns and overall survival in metastatic urothelial carcinoma in a real-world, US setting

Jason C. Simeone[a,*], Beth L. Nordstrom[a], Ketan Patel[b], Helen Mann[c], Alyssa B. Klein[d], Laura Horne[e]

[a] Real-World Evidence, Evidera, Waltham, MA, USA
[b] Teradata UK Ltd, London, UK
[c] Global Medicines Development, AstraZeneca, Cambridge, UK
[d] Oncology Business Unit, AstraZeneca, Gaithersburg, MD, USA
[e] Independent Consultant, Fairfield, CT, USA

ARTICLE INFO

Keywords:
Chemotherapy
Electronic health records
Immunotherapy
Urinary bladder neoplasms

ABSTRACT

Background: Metastatic urothelial carcinoma (mUC) treated with chemotherapy is associated with poor survival; however, as the field of immuno-oncology continues to evolve, new immunotherapies have recently become available. The current study aimed to assess real-world characteristics, treatment patterns, and overall survival (OS) of patients with mUC treated in the United States (US).

Methods: We conducted a retrospective, observational analysis of patients with mUC from the Flatiron Health longitudinal database from 2011 to 2017. Treatment patterns of patients who started systemic first-line therapy (1 L cohort) or second-line therapy following platinum-based first-line therapy (2 L cohort) were described using medication order and administration data. Kaplan-Meier analyses were used to assess OS from the start of first- and second-line therapy in the 1 L and 2 L cohorts, respectively.

Results: A total of 1811 patients qualified for the 1 L cohort (median age [range], 72 [32–84] years); 476 met the criteria for the 2 L cohort (median age [range], 71 [40–84] years). The most common first- and second-line therapies were carboplatin + gemcitabine (n = 562 [34.6%]) and atezolizumab (n = 90 [13.1%]), respectively, in the 1 L cohort. Median OS was 12.7 months (95% confidence interval [CI] 11.8, 13.4) in the 1 L cohort and 8.3 months (95% CI 7.2, 8.9) in the 2 L cohort.

Conclusions: Consistent with clinical trial results, survival was poor in this real-world study in patients with mUC, indicating a continued unmet need. As immunotherapy becomes more commonplace in the treatment of mUC, future studies are needed to understand its real-world impact on survival.

1. Introduction

In the United States (US), bladder cancer is the sixth most common cancer, with an estimated 81,190 new cases and 17,240 deaths in 2018 [1]. The prognosis of advanced bladder cancer is poor, with a relative 5-year survival rate of approximately 15% for Stage IV (metastatic) disease [2]. Approximately 90% of bladder cancers are urothelial carcinoma (UC); standard of care (SoC) first-line treatment for metastatic UC (mUC) is cisplatin-based combination systemic therapy, with carboplatin + gemcitabine combination therapy utilized for cisplatin-ineligible patients [3–5].The median overall survival (OS) from the start of first-line platinum-based chemotherapy is approximately 9–15 months; however, many patients are not eligible for first-line chemotherapy due to their poor performance status [4–8]. Although chemotherapy-ineligible patients typically receive treatment with single agents, no clear SoC exists [4,5]. Following first-line therapy, only a small percentage of patients are offered second-line or later chemotherapy because of significant deterioration in performance status and/or renal function, or other comorbidities, and entry into a clinical trial is recommended [4,5,7,8]. For patients who receive second-line

Abbreviations: 1 L, first-line; 2 L, second-line; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EMR, electronic medical record; FDA, Food and Drug Administration; mUC, metastatic urothelial carcinoma; OS, overall survival; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; SD, standard deviation; SoC, standard of care; UC, urothelial carcinoma; US, United States

* Corresponding author at: Real-World Evidence, Evidera, Waltham, MA, 02451, USA.
E-mail addresses: Jason.Simeone@evidera.com (J.C. Simeone), Beth.nordstrom@evidera.com (B.L. Nordstrom), ketan.patel@teradata.com (K. Patel), helen.mann@astrazeneca.com (H. Mann), Alyssa.Klein@astrazeneca.com (A.B. Klein), lhorne@epiexcellence.com (L. Horne).

https://doi.org/10.1016/j.canep.2019.03.013
Received 18 December 2018; Received in revised form 18 March 2019; Accepted 21 March 2019
Available online 04 April 2019
1877-7821/

therapy, survival is progressively worse, with median OS ranging from approximately 5–8 months from the start of second-line therapy [6,9,10].

In recent years, immunotherapy has been used to treat mUC [4,7,8]. Immune checkpoint blockade is a promising anticancer strategy that has shown clinical activity in cisplatin-ineligible patients with mUC [11,12]. In May 2016, the anti-programmed cell death ligand-1 (PD-L1) agent atezolizumab was the first immunotherapy to receive US Food and Drug Administration (FDA) approval for the treatment of locally advanced UC or mUC that has progressed on or after platinum-based chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy, regardless of PD-L1 expression level [13]. This was followed by the US FDA approvals of the anti-programmed cell death-1 (PD-1) agents nivolumab and pembrolizumab in February and May 2017, respectively, along with the PD-L1 inhibitors durvalumab and avelumab in May 2017 in the post-platinum setting [14–21]. Atezolizumab and pembrolizumab were approved by the US FDA as first-line treatment for cisplatin-ineligible patients with mUC in April and May 2017, respectively [13,14]. However, in August 2018, their use was limited by the US FDA to cisplatin-ineligible patients whose tumors express PD-L1 based on the specific corresponding assay, or patients ineligible for any platinum-containing therapy regardless of their PD-L1 expression level [13,14]. To further explore first-line treatment options, a randomized, open-label, multicenter, Phase 3 study, DANUBE (NCT02516241), is designed to assess the efficacy and safety of durvalumab ± tremelimumab versus SoC chemotherapy in treatment-naïve patients with unresectable mUC [22]. Additionally, several other Phase 3 trials (e.g., IMvigor130 [NCT02807636], KEYNOTE-361 [NCT02853305], and CHECKMATE 901 [NCT03036098]) are ongoing to assess the benefit of first-line immunotherapy in patients with mUC [23–25]. In the second-line setting, the Phase 2, Hoosier Cancer Research Network GU14-182 trial (NCT02500121) is evaluating maintenance pembrolizumab versus placebo in patients with mUC who have achieved at least stable disease on first-line platinum-based chemotherapy [26]. The Phase 3, JAVELIN bladder 100 trial (NCT02603432) is comparing maintenance avelumab plus best supportive care versus best supportive care alone, in patients with locally advanced UC or mUC that did not worsen during or following completion of first-line platinum-based chemotherapy [27].

Real-world evidence in oncology can complement and expand the external validity of clinical trial data, informing patient care and therapeutic developments [28]. As the field of immuno-oncology continues to evolve and immunotherapy becomes SoC for a range of cancers, few real-world studies have assessed patient treatments and outcomes around the time of initial US FDA approvals [29]. Therefore, the aim of the current study was to provide real-world data on clinical characteristics, treatment patterns, and OS in patients diagnosed with mUC receiving first and subsequent lines of therapy from 2011 to 2017 in clinical practices across the US.

2. Materials and methods

2.1. Study design

We conducted a retrospective, observational analysis of electronic medical record (EMR) data from the Flatiron Health longitudinal database in the US [30]. The overall dataset included data for > 1.6 million patients across all tumor types from > 260 US community oncology clinics at the time of analysis. EMR data are anonymized and include structured data (e.g., cancer-related diagnoses and staging, laboratory data, and medications) as well as abstracted data derived from unstructured sources (e.g., physicians' notes, radiology/pathology notes, and discharge notes). The study selection period covered January 1, 2011, to June 30, 2016, with follow-up through June 30, 2017. Therefore, the study selection period ended shortly after the US FDA approval of atezolizumab for the second-line treatment of mUC and did not include patients treated with immunotherapies approved after June 30, 2016 (Supplementary Fig. 1).

All study data were fully compliant with US patient confidentiality requirements, including the Health Insurance Portability and Accountability Act (HIPAA) of 1996. This study used only de-identified patient records and, therefore, was exempted from Institutional Review Board approval. Informed consent was not required as this was a non-interventional study, and routinely collected, anonymized data were used for analysis.

2.2. Patients

Eligible patients had pathology consistent with UC documented in their medical records and were diagnosed with mUC on or after January 1, 2011, or were diagnosed with early-stage UC and subsequently developed mUC on or after January 1, 2011. Unresectable status was not captured in the Flatiron database and was not considered as an inclusion criterion. All patients were required to have ≥ 1 line of therapy for mUC on or after the date of diagnosis of metastatic disease and were divided into 2 cohorts. The 1 L cohort (first-line) included patients diagnosed with mUC who started systemic first-line therapy during the cohort selection period (January 1, 2011, to June 30, 2016). The 2 L cohort (second-line) included patients with mUC who started second-line therapy during the cohort selection period (January 1, 2011, to June 30, 2016) following 1 platinum-based first-line therapy.

Patients could enter both cohorts at different times during the cohort selection period. Analyses followed patients from the index date (defined as the start of first- and second-line therapy in the 1 L and 2 L cohorts, respectively) to the end of follow-up (i.e., the earlier of the following: date of death or date of last visit prior to data cutoff on June 30, 2017).

Patients with a histology other than UC and a primary site of malignancy other than the bladder, renal pelvis, ureter, or urethra were excluded from the study. Additional exclusion criteria included the presence of autoimmune disease; central nervous system metastases; human immunodeficiency virus infection, active tuberculosis, or hepatitis B or hepatitis C infection; evidence of other malignant neoplasms (except non-melanoma skin cancer and carcinoma in situ) prior to diagnosis of mUC; treatment with immunotherapy prior to the index date; and enrollment in other clinical trials.

2.3. Outcomes

Baseline demographics and clinical characteristics from the dataset were analyzed. Treatment patterns assessed were the type/class of therapy, including chemotherapy and immunotherapy. Number of therapy lines (first, second, and third or higher [referred to as third-line, hereafter]), time to start of therapy, time between lines of therapy, most frequently administered therapies, and OS from the start of first- and second-line therapy (index date) in the 1 L and 2 L cohorts, respectively, were also analyzed.

2.4. Statistical analyses

Demographics, clinical characteristics, and general treatment characteristics were summarized descriptively for both cohorts. Continuous study measures (e.g., age and body mass index) are reported descriptively with mean, standard deviation (SD), median, and range; where appropriate, these measures were presented in categories. Frequencies and percentages are reported for categorical measures (e.g., number and proportion of patients with biomarker testing). The Kaplan-Meier method was used to present OS from the index date, with the number of patients still alive and under follow-up indicated in 10-month increments. Median survival was calculated along with 95% confidence intervals (CIs). Data management and analyses were conducted using SAS

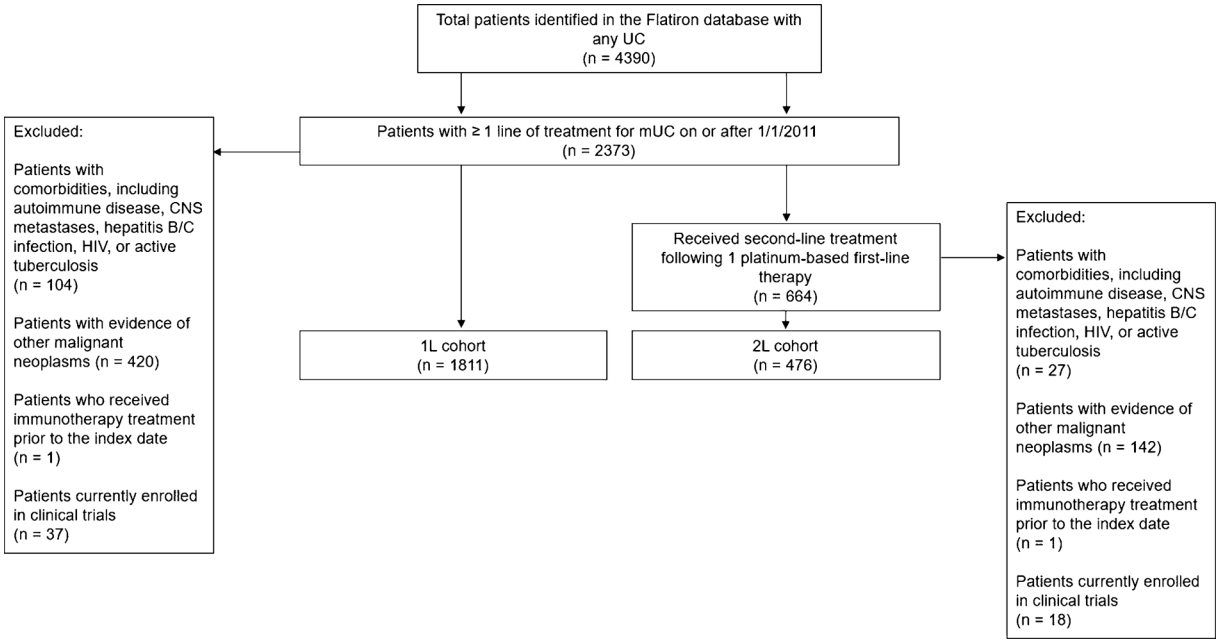

Fig. 1. Study flow diagram. 1 L, first-line; 2 L, second-line; CNS, central nervous system; HIV, human immunodeficiency virus; mUC, metastatic urothelial carcinoma; UC, urothelial carcinoma.

version 9.4 (Cary, NC) or higher. Statistical tests were 2-sided with a significance level of 0.05.

3. Results

3.1. Patient disposition and characteristics

A total of 4390 patients with a documented diagnosis of UC (all stages) and 2373 patients with ≥ 1 line of treatment for mUC on or after January 1, 2011, were available in the Flatiron database for analysis. Following implementation of exclusion criteria, 1811 patients and 476 patients qualified for the 1 L and 2 L cohorts, respectively (Fig. 1). Baseline demographics and clinical characteristics are reported in Table 1. In both cohorts, the median age of patients was approximately 70 years, approximately three-quarters of the patients were male, and 71%–73% were white.

3.2. Clinical characteristics during follow-up

Mean (SD) duration of follow-up was 561.7 (490.1) and 393.7 (401.6) days in the 1 L and 2 L cohorts, respectively. The site of metastases was unknown in n = 1116 (61.6%) and n = 266 (55.9%) patients in the 1 L and 2 L cohorts, respectively. In the n = 695 (38.4%) and n = 210 (44.1%) patients in the 1 L and 2 L cohorts, respectively, with a known site of metastases, bone was the most common site, observed in n = 319 (45.9%) and n = 101 (48.1%) patients in the 1 L and 2 L cohorts, respectively (Table 2). Of the patients with a known Eastern Cooperative Oncology Group performance status (ECOG PS), n = 700 (78.4%) and n = 172 (71.1%) had an ECOG PS of 0 or 1 in the 1 L and 2 L cohorts, respectively (Table 2). As expected, PD-L1 testing was only performed in n = 52 (2.9%) and n = 20 (4.2%) patients in the 1 L and 2 L cohorts, respectively, due to the lack of commercially available PD-L1 assays during the study period (Table 2).

3.3. Treatment patterns during follow-up

Treatment pattern data, including time from the diagnosis of mUC to the start of therapy, are reported in Table 3. Among patients in the 1 L cohort with available medication administration data on first-line therapy (n = 1622 [89.6%]), the most common first-line therapies were carboplatin + gemcitabine (n = 562 [34.6%]) and cisplatin + gemcitabine (n = 441 [27.2%]). Among patients with available medication administration data on second-line therapy (1 L cohort: n = 689 [38.0%]; 2 L cohort: n = 441 [92.6%]), the most common second-line therapies for patients in the 1 L cohort were atezolizumab (n = 90 [13.1%]) and carboplatin + gemcitabine (n = 88 [12.8%]). The most common second-line therapies in the 2 L cohort were carboplatin + gemcitabine (n = 68 [15.4%]) and paclitaxel (n = 66 [15.0%]). Among patients with available medication administration data on third-line therapy (1 L cohort: n = 269 [14.9%]; 2 L cohort: n = 183 [38.4%]), the most common third-line therapies in both cohorts were pemetrexed (1 L cohort: n = 64 [16.1%]; 2 L cohort: n = 49 [17.4%]) and atezolizumab (1 L cohort: n = 59 [14.8%]; 2 L cohort: n = 37 [13.1%]) (Fig. 2).

3.4. Overall survival

The median OS for patients in the 1 L cohort was 12.7 months (95% CI 11.8, 13.4) from the start of first-line therapy. The median OS for patients in the 2 L cohort was 8.3 months (95% CI 7.2, 8.9) from the start of second-line therapy (Fig. 3).

4. Discussion

This study provides real-world data on treatment patterns and survival outcomes in patients with mUC primarily treated in US community oncology clinics. At the time of analysis, we observed a greater use of carboplatin + gemcitabine compared with cisplatin-based combination chemotherapy, which suggests that the majority of patients may not have been cisplatin-eligible and/or carboplatin-based chemotherapy was favored by physicians in this sample [4,5]. The median OS rates of 12.7 months and 8.3 months for patients in the 1 L and 2 L cohorts, respectively, are broadly consistent with clinical trial data and corroborate the unmet treatment need in this patient population [9,31].

In this study, atezolizumab was the most frequently prescribed second-line therapy in the 1 L cohort and the second most frequently prescribed third-line therapy in both cohorts; however, it was not the most common second-line therapy in the 2 L cohort. This finding is

Table 1
Baseline demographics and clinical characteristics.

	1 L cohort (n = 1811)	2 L cohort (n = 476)
Age at index, years		
Mean (SD)	70.4 (9.5)	70.1 (9.2)
Median (range)	72 (32–84)	71 (40–84)
Sex, n (%)		
Male	1326 (73.2)	353 (74.2)
Female	485 (26.8)	123 (25.8)
Race/ethnicity, n (%)		
Asian	27 (1.5)	10 (2.1)
Black or African American	70 (3.9)	15 (3.2)
Hispanic or Latino	41 (2.3)	9 (1.9)
White	1299 (71.7)	345 (72.5)
Other	138 (7.6)	37 (7.8)
Missing	236 (13.0)	60 (12.6)
BMI, kg/m^2		
Mean (SD)	27.0 (5.4)	27.0 (5.4)
Days from initial UC diagnosis to index date		
Mean (SD)	550.9 (983.4)	743.0 (889.0)
Median (range)	161 (−14 to 8749)	456 (51 to 8436)
Stage of cancer at initial diagnosis, n (%)		
I	25 (1.4)	8 (1.7)
II	70 (3.9)	20 (4.2)
IIIA	109 (6.0)	33 (6.9)
IIIB	0	0
IV	711 (39.3)	187 (39.3)
Missing	896 (49.5)	228 (47.9)
Concomitant drugs[a], n (%)		
Anti-anemics	56 (3.1)	153 (32.1)
Anti-emetics	178 (9.8)	435 (91.4)
Anti-infectives	29 (1.6)	17 (3.6)
Bone-modifying agents	39 (2.2)	65 (13.7)
Granulocyte colony-stimulating factors	96 (5.3)	260 (54.6)
Pain agents	33 (1.8)	22 (4.6)
Solution fluids	176 (9.7)	264 (55.5)
Steroids	4 (0.2)	4 (0.8)
ECOG PS at index date, n (%)[b]		
0	319 (41.5)	77 (31.4)
1	313 (40.7)	121 (49.4)
2	118 (15.3)	40 (16.3)
3	18 (2.3)	7 (2.9)
4	1 (0.1)	0
Not documented	1042 (57.5)	231 (48.5)
Anatomical site of cancer, n (%)		
Bladder	1404 (77.5)	348 (73.1)
Renal pelvis	250 (13.8)	80 (16.8)
Ureter	141 (7.8)	45 (9.5)
Urethra	16 (0.9)	3 (0.6)
Site of metastases, n (%)[b]		
Brain	0	0
Liver	53 (15.1)	24 (16.7)
Bone	148 (42.0)	75 (52.1)
Other	151 (42.9)	45 (31.3)
Not documented	1459 (80.6)	332 (69.7)
PD-L1 expression, n (%)		
Positive	0	0
Negative	4 (0.2)	6 (1.3)
Not tested	1807 (99.8)	470 (98.7)
Presence of surgical procedure for bladder cancer[c], n (%)		
Yes	853 (47.1)	223 (46.8)
No	958 (52.9)	253 (53.2)

[a] Patients could receive > 1 concomitant drug.
[b] % calculated from documented cases.
[c] Defined as partial cystectomy, complete (radical) cystectomy, cystoprostatectomy, nephrectomy, nephroureterectomy, ureterectomy, urethrectomy, cystectomy, not otherwise specified, or other. 1 L, first-line; 2 L, second-line; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death ligand-1; SD, standard deviation; UC, urothelial carcinoma.

Table 2
Selected clinical characteristics during follow-up.

	1 L cohort (n = 1811)	2 L cohort (n = 476)
Concomitant drugs[a], n (%)		
Anti-anemics	572 (31.6)	172 (36.1)
Anti-emetics	1653 (91.3)	420 (88.2)
Anti-infectives	113 (6.2)	18 (3.8)
Bone-modifying agents	317 (17.5)	100 (21.0)
Granulocyte colony-stimulating factors	961 (53.1)	220 (46.2)
Pain agents	143 (7.9)	33 (6.9)
Solution fluids	1145 (63.2)	298 (62.6)
Steroids	31 (1.7)	13 (2.7)
ECOG PS < 60 days after index date, n (%)[b]		
0	313 (35.1)	62 (25.6)
1	387 (43.3)	110 (45.5)
2	151 (16.9)	52 (21.5)
3	42 (4.7)	16 (6.6)
4	0	2 (0.8)
Not documented	918 (50.7)	234 (49.2)
Site of metastases, n (%)[b]		
Brain	0	0
Liver	110 (15.8)	37 (17.6)
Bone	319 (45.9)	101 (48.1)
Other	266 (38.3)	72 (34.3)
Not documented	1116 (61.6)	266 (55.9)
PD-L1 expression, n (%)		
Positive	10 (0.6)	3 (0.6)
Negative	42 (2.3)	17 (3.6)
Not tested	1759 (97.1)	456 (95.8)

[a] Patients could receive > 1 concomitant drug.
[b] % calculated from documented cases. 1 L, first-line; 2 L, second-line; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death ligand-1.

Table 3
Treatment patterns in the 1 L and 2 L cohorts during follow-up.

	1 L cohort (n = 1811)	2 L cohort (n = 476)
Days from diagnosis of mUC to start of therapy, days		
Mean (SD)	92.9 (162.7)	78.0 (155.0)
Median (IQR)	43 (21–88)	35 (17–68)
Total number of systemic therapy treatment lines, n (%)		
1 line only	1122 (62.0)	N/A
2 lines only	420 (23.2)	293 (61.6)
3+ lines only	269 (14.9)	183 (38.4)
Mean (SD)	1.7 (0.96)	2.6 (0.93)
Median (range)	1 (1–7)	2 (2–7)
Days between end of first- and start of second-line therapy		
Mean (SD)	137.6 (201.6)	125.1 (173.5)
Median (range)	57 (1–1460)	53 (1–1460)
Days between end of second- and start of third-line therapy		
Mean (SD)	79.6 (155.3)	81.1 (133.9)
Median (range)	28 (1–1668)	28 (1–925)

1 L, first-line; 2 L, second-line; IQR, interquartile range (25th–75th percentiles); mUC, metastatic urothelial carcinoma; N/A, not applicable; SD, standard deviation.

attributable to the study design; to permit 12 months of follow-up for survival analyses, the cohort selection period ended shortly after the May 2016 US FDA approval of atezolizumab for the second-line treatment of mUC (Supplementary Fig. 1) [13]. Therefore, there was limited potential for second-line atezolizumab use to be captured during this study. Similarly, it is likely that cisplatin-ineligible patients in the 1 L cohort would have been candidates for first-line immunotherapy; however, the cohort selection period ended before the US FDA approval

Fig. 2. The 5 most common regimens in each line of therapy during follow-up. 1 L, first-line; 2 L, second-line.

of atezolizumab and pembrolizumab as first-line therapy in cisplatin-ineligible patients with mUC in April and May 2017, respectively (Supplementary Fig. 1) [13,14]. Currently, 5 immunotherapies have received US FDA approval for the treatment of mUC [13–17]. However, questions remain regarding their optimal use, impact on OS, and in which patient subgroups they may be particularly effective [32]. Consequently, additional real-world studies are needed to document the treatment patterns and survival outcomes in patients with mUC treated with the multiple immunotherapies currently approved in clinical practice [13–17]. PD-L1 testing rates were low, as anticipated, given the lack of companion diagnostic tests available during the study. Considering the requirement for companion diagnostic testing to accompany first-line atezolizumab or pembrolizumab treatment for cisplatin-ineligible patients with mUC, the extent to which PD-L1 testing will be more readily incorporated into future clinical practice remains unclear [13,14].

The current study has several limitations. There can be numerous sources of bias that threaten the internal validity of real-world studies [33–35]. Selection bias (i.e., where the study population is not representative of the true distributions in the overall population) can

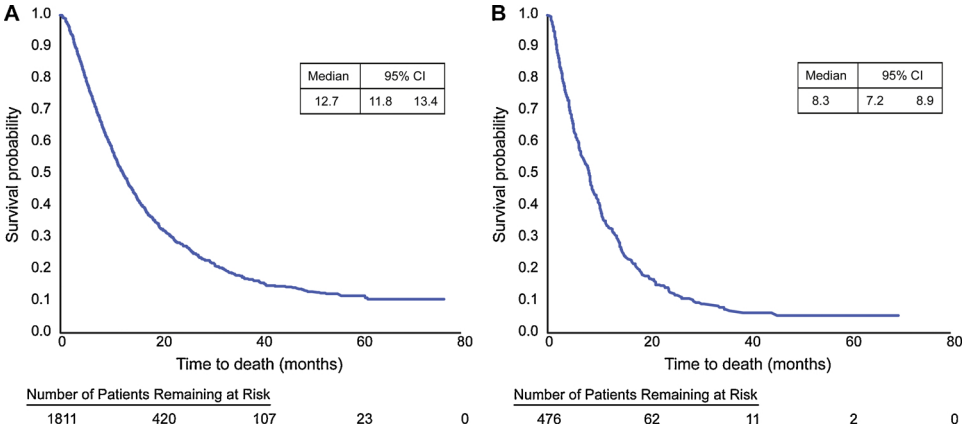

Fig. 3. Kaplan-Meier curves of OS from index date in (A) 1 L cohort and (B) 2 L cohort. 1 L, first-line; 2 L, second-line; CI, confidence interval; OS, overall survival.

arise from the use of diagnostic and therapeutic codes for patient selection [33]. Confounding bias (i.e., where extraneous variables influence the association between treatment and outcomes) can also arise from variance in patient characteristics and comorbidities [33]. Further, when compared with information typically captured in clinical trials, some clinical (e.g., site of metastases) and laboratory data were missing, and unresectable status was not captured in the Flatiron database. The number of cisplatin-ineligible patients was also unavailable. Information on comorbidities and radiation therapy/other treatment provided in settings outside of the oncology clinic (e.g., inpatient setting, primary care physician) was not available or may have been under-reported, and this may have resulted in misclassification of treatment and outcomes. Some patients had long gaps between treatment lines, which may have been the result of remission and recurrence, or of obtaining care at different clinics. As linkage between EMRs and additional datasets improves, future real-world studies with more complete patient-level data may address these limitations [34]. Lastly, the predominant use of atezolizumab is not surprising, as it was the only US FDA-approved immunotherapy available during the latter part of the cohort selection period (Supplementary Fig. 1).

5. Conclusions

As immunotherapy becomes SoC for a range of cancers, real-world evidence is vital to complement and expand clinical trial results. In this retrospective, real-world study in patients with mUC treated primarily in US community oncology clinics, the median OS for patients who started systemic, first-line therapy was approximately 1 year from the initiation of treatment. For patients previously treated with platinum-based first-line therapy, OS was approximately 8 months from the initiation of second-line treatment. Despite having only been available for a portion of the study period, atezolizumab was the most common second-line therapy among patients who started first-line therapy, suggesting the entry of immunotherapy as a valuable tool in the treatment of mUC. Additional studies are needed to understand if the increasing use of immunotherapy will affect survival rates.

Conflicts of interest

Jason Simeone and Beth Nordstrom are employees of Evidera, and Evidera received funding from AstraZeneca for this study. Alyssa Klein and Helen Mann are employees and stockholders of AstraZeneca. Laura Horne was a contractor for AstraZeneca at the time of the work and is a stockholder of AstraZeneca. Ketan Patel is a previous employee of AstraZeneca. Liam Gillies (medical writer) has no conflicts of interest to declare.

Author contributions

All authors have made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; have drafted the article and/or revised it critically for important intellectual content; and given final approval of the version to be published.

Funding

This work was supported by AstraZeneca. The sponsor was involved in the study design; collection, analysis, and interpretation of data; report writing; and the decision to submit.

Acknowledgments

The authors would like to thank William Sawyer, AstraZeneca, for review of the manuscript. Medical writing support was provided by Dr Liam Gillies, PhD, of Cactus Communications (London, UK) and was funded by AstraZeneca. The sponsor was involved in the study design; collection, analysis, and interpretation of data; report writing; and the decision to submit. Ketan Patel and Laura Horne are former employees of AstraZeneca.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.03.013.

References

[1] National Cancer Institute Surveillance, Epidemiology, and End Results Program, SEER Cancer Statistics Factsheets: Bladder Cancer, (2018) Available at https://seer.cancer.gov/statfacts/html/urinb.html (Accessed April 2018).
[2] American Society of Clinical Oncology (ASCO), Bladder Cancer: Introduction, (2018) Available at https://www.cancer.net/cancer-types/bladder-cancer/introduction (Accessed April 2018).
[3] American Cancer Society, Key Statistics for Bladder Cancer, Available at (2018) (Accessed April 2018), https://www.cancer.org/cancer/bladder-cancer/about/key-statistics.html.
[4] National Comprehensive Cancer Network (NCCN), NCCN Clinical Practice Guidelines in Oncology, Bladder Cancer. Version 3.2018, (2018) Available at https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf (Accessed April 2018).
[5] M.I. Milowsky, R.B. Rumble, C.M. Booth, et al., Guideline on muscle-invasive and metastatic bladder cancer (European Association of Urology Guideline): American society of clinical oncology clinical practice guideline endorsement, J. Clin. Oncol. 34 (2016) 1945.
[6] M. Fisher, R. Shenolikar, P. Miller, et al., Treatment patterns and outcomes in metastatic bladder cancer in community oncology settings, J. Clin. Oncol. 35 (2017) 396.
[7] S.S. Sridhar, Evolving treatment of advanced urothelial cancer, J. Oncol. Pract. 13 (2017) 309.
[8] B. Dietrich, S. Srinivas, Urothelial carcinoma: the evolving landscape of immunotherapy for patients with advanced disease, Res. Rep. Urol. 10 (2018) 7.
[9] D. Raggi, R. Miceli, G. Sonpavde, et al., Second-line single-agent versus doublet chemotherapy as salvage therapy for metastatic urothelial cancer: a systematic review and meta-analysis, Ann. Oncol. 27 (2016) 49.
[10] H. Gerullis, F. Wawroschek, C.H. Köhne, et al., Vinflunine in the treatment of advanced urothelial cancer: clinical evidence and experience, Ther. Adv. Urol. 9 (2017) 28.
[11] A.V. Balar, M.D. Galsky, J.E. Rosenberg, et al., Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial, Lancet 389 (2017) 67.
[12] A.V. Balar, D. Castellano, P.H. O'Donnell, et al., First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study, Lancet Oncol. 18 (2017) 1483.
[13] Genentech Inc, Tecentriq® Prescribing Information, (2018) Available at https://www.gene.com/download/pdf/tecentriq_prescribing.pdf (Accessed July 2018).
[14] Merck Sharp & Dohme, Keytruda® Prescribing Information, (2018) Available at https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf (Accessed July 2018).
[15] Bristol-Myers Squibb, Opdivo® Prescribing Information, (2018) Available at https://packageinserts.bms.com/pi/pi_opdivo.pdf (Accessed April 2018).
[16] EMD Serono and Pfizer, Bavencio® Prescribing Information, (2018) Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761078s000lbl.pdf (Accessed April 2018).
[17] AstraZeneca, Imfinzi® Prescribing Information, (2018) Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761069s002lbl.pdf (Accessed April 2018).
[18] J.E. Rosenberg, J. Hoffman-Censits, T. Powles, et al., Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial, Lancet 387 (2016) 1909.
[19] M.R. Patel, J. Ellerton, J.R. Infante, et al., Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial, Lancet Oncol. 19 (2018) 51.
[20] P. Sharma, M. Retz, A. Siefker-Radtke, et al., Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial, Lancet Oncol. 18 (2017) 312.
[21] T. Powles, P.H. O'Donnell, C. Massard, et al., Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: updated results from a phase 1/2 open-label study, JAMA Oncol. 3 (2017) e172411.
[22] S.H. Park, D. Castellano, D.P. Petrylak, et al., 285TiP: DANUBE: a phase 3 randomised study of first-line durvalumab (MEDI4736) ± tremelimumab vs standard of care (SoC) chemotherapy (CT) in patients (pts) with Stage IV urothelial carcinoma (UC), Ann. Oncol. 27 (2016), https://doi.org/10.1093/annonc/mdw583.011.
[23] M.D. Galsky, E. Grande, I.D. Davis, et al., IMvigor130: a randomized, phase III study evaluating first-line (1L) atezolizumab (atezo) as monotherapy and in combination with platinum-based chemotherapy (chemo) in patients (pts) with locally advanced or metastatic urothelial carcinoma (mUC), J. Clin. Oncol. 36 (suppl_15) (2018),

https://doi.org/10.1200/JCO.2018.36.15_suppl.TPS4589.
[24] T. Powles, J.E. Gschwend, Y. Loriot, et al., Phase 3 KEYNOTE-361 trial: pembrolizumab (pembro) with or without chemotherapy versus chemotherapy alone in advanced urothelial cancer, J. Clin. Oncol. 35 (suppl_15) (2017), https://doi.org/10.1200/JCO.2017.35.15_suppl.TPS4590.
[25] M.D. Galsky, T. Powles, S. Li, et al., A phase 3, open-label, randomized study of nivolumab plus ipilimumab or standard of care (SOC) versus SOC alone in patients (pts) with previously untreated unresectable or metastatic urothelial carcinoma (mUC; CheckMate 901), J. Clin. Oncol. 36 (suppl_6) (2018), https://doi.org/10.1200/JCO.2018.36.6_suppl.TPS539.
[26] ClinicalTrials.gov, Testing the PD-1 Inhibitor Pembrolizumab as Maintenance Therapy After Initial Chemotherapy in Metastatic Bladder Cancer. Identifier NCT02500121, (2019) Available at https://clinicaltrials.gov/ct2/show/NCT02500121 (Accessed February 2019).
[27] T. Powles, P. Grivas, A. Aragon-Ching, et al., A multicentre, international, randomised, open-label phase 3 trial of avelumab + best supportive care (BSC) vs BSC alone as maintenance therapy after first-line platinum-based chemotherapy in patients with advanced urothelial cancer (JAVELIN bladder 100), Ann. Oncol. 27 (suppl_6) (2016), https://doi.org/10.1093/annonc/mdw373.69.
[28] R.E. Sherman, S.A. Anderson, G.J. Dal Pan, et al., Real-world evidence—what is it and what can it tell us? N. Engl. J. Med. 375 (2016) 2293.
[29] J. O'Connor, K. Seidl-Rathkopf, P. You, et al., Adoption of immunotherapy into real-world practice: insights from the use of checkpoint inhibitors, J. Clin. Oncol. 35 (2017) e14583.
[30] Flatiron Health, (2018) Available at https://flatiron.com/real-world-evidence (Accessed April 2018).
[31] A. Necchi, G.R. Pond, D. Raggi, et al., Efficacy and safety of gemcitabine plus either taxane or carboplatin in the first-line setting of metastatic urothelial carcinoma: a systematic review and meta-analysis, Clin. Genitourin. Cancer 15 (2017) 23.
[32] J. Liu, C. Zhang, J. Hu, et al., Effectiveness of anti-PD-1/PD-L1 antibodies in urothelial carcinoma patients with different PD-L1 expression levels: a meta-analysis, Oncotarget 9 (2018) 12400.
[33] S. Khozin, G.M. Blumenthal, R. Pazdur, Real-world data for clinical evidence generation in oncology, J. Natl. Cancer Inst. 109 (11) (2017), https://doi.org/10.1093/jnci/djx187.
[34] M.L. Berger, M.D. Curtis, G. Smith, et al., Opportunities and challenges in leveraging electronic health record data in oncology, Future Oncol. 12 (2016) 1261.
[35] A.P. Abernethy, J. Gippetti, R. Parulkar, et al., Use of electronic health record data for quality reporting, J. Oncol. Pract. 13 (2017) 530.