Epidemiology and treatment patterns for locally advanced or metastatic urothelial carcinoma: a systematic literature review and gap analysis

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What is already known about this subject

- Several immuno-oncology (IO) agents targeting programmed death-1/death-ligand 1 (PD-1/L1) are now approved second-line treatment options in the United States and Europe for patients with locally advanced or metastatic urothelial carcinoma (la/mUC) previously treated with platinum-based chemotherapy or first-line options in patients ineligible for cisplatin whose tumors express PD-L1 or for any platinum-based chemotherapy regardless of PD-L1 expression levels.
- There is a need to summarize the current literature on the epidemiology of la/mUC and the real-world treatment patterns since the introduction of these novel therapies to have a better understanding of what has already been published and identify evidence gaps for future research.

What this study adds

- The study found that there is a lack of up-to-date, country-specific epidemiological data on urothelial carcinoma (UC) and la/mUC, including rates of progression from early-stage disease to la/mUC.
- There was a large variation in the rates of treatment, particularly with cisplatin, both within and among countries.
- The few published real-world IO studies indicate there has been an increase in the use of IO therapy for la/mUC in recent years; however, relatively high levels of treatment discontinuation were reported in patients treated with IO, and only a small percentage of patients received subsequent therapy.

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ABSTRACT

BACKGROUND: Several immuno-oncology (IO) agents targeting programmed death-1 or programmed death-ligand 1 (PD-1/L1) are approved second-line therapy options for patients with locally advanced or metastatic urothelial carcinoma (la/mUC) previously treated with platinum-based chemotherapy or first-line options in patients ineligible for cisplatin whose tumors express PD-L1 or for any platinum-based chemotherapy regardless of PD-L1 expression levels. However,

literature on the epidemiology of la/mUC is limited, and real-world treatment patterns are not well established, especially with respect to therapies used following IO.

OBJECTIVES: To (a) report the epidemiology of urothelial carcinoma (UC) and la/mUC; (b) identify and summarize the published literature on la/mUC treatment patterns, including IO and post-IO treatment; and (c) identify evidence gaps.

METHODS: A systematic literature review was conducted using Cochrane dual-reviewer

methodology and the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols. Literature databases and selected congress abstracts (2017-2018) were searched for retrospective studies published January 2013-August 2018 in English reporting epidemiological and treatment data (all lines of therapy) for adult patients with la/mUC.

RESULTS: Among 6,584 database references and 1,832 congress abstracts screened, 45 publications (29 manuscripts, 1 poster, 15 abstracts; reporting 37 unique studies) were retained. All studies related to

treatment patterns, and the majority were from the United States (n=17), Japan (n=8), and the United Kingdom (n=5). Epidemiological data were not identified among the searches thus online registries were leveraged. Among the identified publications, 21 (20 unique) reported on cisplatin versus non-cisplatin regimens, 14 (8 unique) on IO, and 9 (7 unique) on vinflunine. Cisplatin use varied both within and among countries (ranging from 18.4% in 1 U.S. study to 87.9% in 1 Japanese study). The use of IO was higher in later lines of therapy, ranging from 1.4% to 7.9% as first-line therapy to 57.8% as second-line and 64.4% as third-line therapy. Among studies reporting IO discontinuation rates, 41.4%-71% of patients were reported to discontinue IO across the studies, and the median time to discontinuation ranged from 2.7 to 5.8 months. Only 25%-35.5% of patients received subsequent therapy following IO discontinuation; post-IO treatments varied widely.

CONCLUSIONS: Additional published data on the country-specific epidemiology of UC and la/mUC are needed, including rates of progression from early-stage disease to la/mUC. There was large variation in treatment rates, particularly cisplatin use, within and across countries. The few published real-world IO studies reported high levels of discontinuation with only a small percentage of patients receiving subsequent therapy. As IO therapies continue to be granted regulatory approval in countries outside the United States and novel therapies gain approval in the post-IO setting, the treatment paradigm for patients with la/mUC is shifting, and future studies with more recent data will be required.

Bladder cancer is the most common malignancy in the urinary system with an estimated 549,393 new cases and 199,922 deaths worldwide in 2018.¹ Urothelial carcinoma (UC) is the most common histological form of bladder cancer and accounts for >90% of all cases.^{2,3} Although the majority of UC cases are superficial, an estimated 25% are muscle invasive,⁴ and 11% are locally advanced or metastatic (la/mUC) at diagnosis.⁵ Prognosis is poor for patients with la/mUC and <15% survive beyond 5 years⁶; metastatic disease is considered incurable, and the 5-year survival rate is 4.6% in the United States.⁵

Cisplatin-containing combination chemotherapy remains the standard of care for the first-line treatment of patients with la/mUC.⁷ However, approximately 30%-50% of patients are unfit for cisplatin-containing chemotherapy due to an Eastern Cooperative Oncology Group performance status ≥ 2 , creatinine clearance <60 mL/min, presence of significant hearing loss or peripheral neuropathy, or heart failure.^{8,9} In patients for whom cisplatin-containing chemotherapy is unsuitable, carboplatin-based therapy may be offered as alternative first-line treatment.¹⁰ Overall survival

ranges between 9 and 15 months in patients with la/mUC treated with first-line platinum-based chemotherapy.^{6,10}

In recent years, several immuno-oncology (IO) agents targeting programmed death-1 or programmed death-ligand 1 (PD-1/L1) have gained full or accelerated approval in multiple countries for patients with la/mUC (the first U.S. Food and Drug Administration [FDA] approval for atezolizumab was in May 2016, with other agents approved February-May 2017).¹¹ Current National Comprehensive Cancer Network (NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) recommend the use of anti-PD-1/L1 therapy as preferred second-line options following platinum-based chemotherapy; atezolizumab and pembrolizumab are also recommended as preferred first-line options in patients ineligible for cisplatin-based chemotherapy whose tumors express PD-L1 or who are not eligible for any platinum-based chemotherapy regardless of PD-L1 expression levels.^{12,13} The European Society for Medical Oncology (ESMO) treatment guidelines recommend pembrolizumab in patients with la/mUC who progress after platinum-based chemotherapy; atezolizumab and nivolumab can be considered in this setting although they are supported by lower levels of evidence (avelumab and durvalumab have not received European Medicines Agency [EMA] approval in this setting).¹⁴ ESMO also recommends atezolizumab and pembrolizumab as first-line therapy options in cisplatin-ineligible patients with PD-L1-positive la/mUC.¹⁴ Although some patients with la/mUC may experience durable responses with anti-PD-1/L1 therapy, data from clinical trials show objective response rates ranging from 23% to 29% as first-line therapy in unselected populations and from 13% to 21% as second-line therapy.¹⁵⁻¹⁷

For patients with la/mUC who are refractory to platinum-based chemotherapy and IO, treatment options have been limited (as of the time of publication). In December 2019, enfortumab vedotin-ejfv (EV) received FDA accelerated approval for adult patients with la/mUC who have previously received a PD-1/L1 inhibitor and a platinum-based chemotherapy in the neoadjuvant/adjuvant, la/mUC setting.¹⁸ EV is now recognized as a recommended, preferred subsequent treatment option in this setting in the NCCN and ESMO guidelines.^{12,14} Erdafitinib, a fibroblast growth factor receptor (FGFR) inhibitor, although not specifically indicated for use in the post-IO setting, has FDA regulatory approval in the post-platinum setting for patients with la/mUC who harbor susceptible FGFR3 or FGFR2 genetic alterations and is a recommended and preferred option in this specific population in the NCCN and ESMO guidelines.^{12,14,19} EV and erdafitinib are not approved outside the United States. Before these agents, vinflunine was approved by the EMA in 2009 for patients with la/mUC

after failure of platinum-containing therapy and has been a treatment option specifically in Europe, although its use is now only recommended if IO or combination chemotherapy are unsuitable.^{7,20} Vinflunine is not approved in the United States and not recommended in the United Kingdom.²¹

Given the relatively short time period since IOs were first approved for the treatment of la/mUC, there is limited literature on real-world treatment patterns after the introduction of these therapies, especially pertaining to novel therapies that may be used following discontinuation of IO. Although Cumberbatch et al. (2018) recently published a detailed review of the epidemiology of bladder cancer, it focused on the contemporary risk factors associated with the disease and did not cover treatment patterns.²² The present systematic literature review (SLR) was conducted to (a) report the epidemiology of UC and la/mUC; (b) identify and summarize the published literature on la/mUC treatment patterns, including the percentage of patients treated with cisplatin- versus non-cisplatin-based regimens, IO therapy (by line of therapy [LOT]), and subsequent drug therapy after receipt of IO therapy; and (c) identify gaps in the literature on epidemiology and treatment patterns and assess unmet needs post-IO.

Methods

SEARCH STRATEGY

The SLR was conducted using Cochrane dual-reviewer methodology and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) checklist. To capture contemporary data spanning the pre- and postregulatory approval of IO agents for la/mUC, searches were focused on studies published from January 1, 2013, to August 24, 2018, in MEDLINE with MEDLINE epubs ahead of print, Embase, and Cochrane via Ovid. Supplementary searches were performed in PubMed (past 2 years) using text word or Medical Subject Headings to identify retrospective studies published in English that reported epidemiology or treatment data for adult patients with UC or la/mUC.

In addition to the literature database searches, the reference section of identified review articles was reviewed for relevant studies. Abstracts presented at the following conferences held in 2017 and 2018 were also searched: International Society for Pharmacoeconomics and Outcomes Research, American Society of Clinical Oncology, American Urological Association, European Association of Urology, ESMO, and AMCP. Supplemental searches of recognized national and international epidemiology websites were conducted, including Surveillance, Epidemiology,

and End Results; European Cancer Observatory; Cancer Research UK; U.K. Office for National Statistics; European Cancer Information System; Bladder Cancer Canada; Cancer Information Service (Japan); and GLOBOCAN (International Association of Cancer Registries). Websites were re-reviewed during manuscript preparation to capture 2019 data where available. For situations where ≥ 1 congress abstract reported the same study or data as a more recent full-text manuscript, all associated publications were captured and reported in the PRISMA diagram, but only data from the full-text manuscript were reported in the SLR to avoid duplication.

INCLUSION CRITERIA

Included studies were defined according to the PICOS (population, intervention, comparator, outcome, study type) framework using the following criteria: (a) population: adult patients aged ≥ 18 years with UC or bladder cancer, further subdivided into those with bladder cancer, UC, or la/mUC; (b) intervention: any or none; (c) comparator: any or none; (d) outcomes: epidemiology (incidence and prevalence) or treatment patterns; and (e) study type: retrospective observational studies and retrospective or ad hoc analyses of data from clinical trials.

Included studies were from the following countries/regions of interest: United States, Canada, Japan, United Kingdom, France, Germany, Italy, Spain, and Nordic countries.

EXCLUSION CRITERIA

Publications were excluded if they reported on animal, preclinical, pediatric, clinical trial, or economic modeling studies. Studies of primary urethral carcinoma, small cell carcinoma of the urinary bladder, upper tract UC, or studies in patients with any involvement of the urachus (if they did not also include data on patients with la/mUC) were also excluded to ensure data that related only to earlier-stage disease such as nonmuscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC) were not included. Reviews, meta-analyses, notes, case reports, comments, editorials, letters, or opinion articles were excluded, as were studies not published in English.

LITERATURE SCREENING, DATA REPORTING, AND CRITICAL APPRAISAL

Following initial searches, all citations were combined and duplications were removed. In level 1 screening, 2 independent reviewers assessed the titles and abstracts of identified publications against study inclusion/exclusion criteria. Full-text manuscripts retained after level 1 screening were then reviewed in level 2. Disagreements during level 1 or

level 2 screening were resolved through discussion, with a third independent senior reviewer making the final decision if needed. All excluded studies were documented along with the reason for exclusion. Data collection from the included publications and epidemiology websites were reported in prespecified data extraction tables. Data were extracted by 1 reviewer and validated by a second reviewer for quality assurance. Critical appraisal of research quality was conducted using the Newcastle-Ottawa Scale to assess risk of bias.²³

Among epidemiology publications, UC and la/mUC prevalence, incidence, and mortality or survival rates were reported. Among publications reporting treatments for patients with UC or la/mUC, the number and percentage of patients receiving cisplatin- versus carboplatin-containing regimens or classified as cisplatin-eligible versus -ineligible, patients treated with vinflunine, or patients treated with an IO agent (including the specific therapy where available), as well as those who received treatment after IO were reported. LOT for each of these treatments and number of patients discontinuing IO therapy were also reported.

Results

SEARCH RESULTS

Among 6,584 database references and 1,832 congress abstracts screened, 45 publications (29 manuscripts, 1 poster, 15 abstracts; reporting 37 unique studies) were retained after full-text review (Figure 1). The 29 manuscripts and 1 poster were critically appraised for risk of bias using the Newcastle-Ottawa Scale. Of these, 10 (33%) had a low risk, 14 (47%) moderate risk, and 6 (20%) high risk; abstracts were not critically appraised. The sample size in these 30 studies ranged from 16 to 1,333 patients. The mean (SD) and median sample size were 174 (270) and 74.5, respectively; 7 studies had <30 patients, and 12 had <50 patients. Of these studies, 16 (53%) were single center and thus may not have been representative of the population with mUC, 13 (43%) did not control for potential confounders that could affect comparability of cohorts, 7 (23%) included univariate between-group comparisons only, and 10 (33%) used multivariate analyses. All 30 studies that were critically appraised were longitudinal and identified exposure (treatment) and outcome from medical charts or claims data.

Most publications meeting inclusion criteria (n=45) reported data from the United States (n=17), Japan (n=8), and the United Kingdom (n=5); 3 reported data from Italy, 2 each from Germany and France, and 1 each from Canada, Spain, and Nordic countries; some reported on >1 country. Two studies were multinational, and 4 did not report the country, although they did report sufficient other data for

inclusion. No epidemiological publications met inclusion criteria; although 8 publications were identified for data extraction, all were excluded due to outdated data (n=4),^{4,24-26} not reporting data for a country of interest (n=2),^{27,28} insufficient reporting (n=1),²⁹ or other exclusion criteria (n=1).³⁰ Because no published epidemiology data meeting study inclusion criteria were available, national and international epidemiology websites were used, as these provided the most recent data on incidence, prevalence, and mortality rates for bladder cancer. Data from these online resources were identified for bladder cancer only; no data were available for UC or la/mUC specifically.

All 45 included studies reported data on treatment patterns, which may have included specific treatment regimens or outcomes in patients who had received certain treatments by design. With respect to prespecified treatments of interest, 21 publications (20 unique studies) reported data on cisplatin versus non-cisplatin regimens, 14 (8 unique studies) on IO, and 9 (7 unique studies) on vinflunine. Other named agents identified in the studies that were not prespecified as of interest included gemcitabine monotherapy; gemcitabine plus carboplatin; gemcitabine plus paclitaxel; paclitaxel plus ifosfamide and nedaplatin; and paclitaxel plus carboplatin, docetaxel, and pemetrexed.

INCIDENCE AND PREVALENCE

Data extracted from national and international epidemiology websites are reported in Figures 2 and 3. Globally, the estimated annual bladder cancer incidence rate ranged from 6.9 per 100,000 in the United Kingdom to 15.9 per 100,000 in Italy.¹

CISPLATIN- VERSUS NON-CISPLATIN-BASED REGIMENS

A total of 31 papers reported on cisplatin versus non-cisplatin treatment regimens. Of these, 10 were not considered representative of treatment patterns because they had <30 patients (n=5),³¹⁻³⁵ were clinical studies restricted to investigator-selected treatments (n=3),³⁶⁻³⁸ or both (n=2).^{39,40} Twenty-one unique publications reported sufficient data to determine the percentage of patients receiving cisplatin-versus non-cisplatin-based regimens (Table 1).

Approximately half of patients with la/mUC who received treatment received a first-line cisplatin-based regimen, as reported in 4 studies: 42% (United States: n=1,703; 2004-2011),⁴¹ 40% (United States: n=9,436; 2005-2015),⁴² 50.9% (multinational: n=1,160; 2000-2013),² and 46% (multinational: n=1,020; year not reported).⁴³

A large variation in cisplatin use was observed both within and across countries. Among 10 studies from the United States, the proportion of patients receiving first-line

FIGURE 1 PRISMA Diagram of Study Selection

^aPapers not specific to la/mUC were excluded and coded as "wrong population"; papers outside the countries of interest were excluded and coded as "wrong country"; papers on surgery or radiation were excluded and coded "wrong intervention"; papers on pathology/histology/biomarkers/genotyping were excluded and coded "wrong outcome"; and clinical trials were excluded and coded as "wrong study type."

^bNo epidemiological publications reporting current data for qualitative synthesis were identified; supplemental searches of national and international epidemiology websites were conducted.

FIGURE 2 Estimated Annual Number of New Bladder Cancer Cases (2018) and 5-Year Prevalence (2018), by Country ^aDenoted by reference numbers.^bData are from 2019.^cData are from 2017.^dData are from 2016.

GLOBOCAN = Global Cancer Incidence, Mortality and Prevalence.

cisplatin-based treatment ranged from 18.4% to 60.2%.^{44,45} In the 2 qualifying studies from Japan, >80.0% of patients received cisplatin-based treatment as first line.^{46,47} An additional study from Japan of 47 patients all receiving carboplatin-based chemotherapy reported that 62% of these patients were considered unfit to receive cisplatin; patients in this study had an average age of 77.1 years.³⁸

In 3 studies, cisplatin eligibility was evaluated against established criteria.⁹ In these studies, a substantial proportion of cisplatin-eligible patients were not administered cisplatin. A multinational study of 1,160 patients found that >25% of cisplatin-eligible patients did not receive cisplatin (patients received carboplatin or other therapies mainly due to advanced age and comorbidities), whereas nearly 35% of cisplatin-ineligible patients received cisplatin-based therapy.² A study from the United States (2010–2014 data) reported that 48.7% of cisplatin-eligible patients were not treated with cisplatin (alternative therapies not

provided), whereas 25.4% of cisplatin-ineligible patients received cisplatin anyway.⁴⁸ In 1 retrospective Japanese study (not included in Table 1 due to the treatments being restricted by design), all 47 patients received carboplatin-based first-line treatment despite 38.3% of patients being cisplatin-eligible.³⁸

IMMUNO-ONCOLOGY AGENTS TARGETING PD-1/L1

IO data were reported in 8 unique studies, 4 with real-world data,^{35,44,49,50} 3 retrospective/post hoc analyses of patients who had received IO agents as part of a clinical trial,^{51–53} and 1 comparison of a clinical trial population with a real-world cohort.⁵⁴ Seven of these studies provided detailed information (Table 2). Data were most commonly reported for IO therapies collectively, with treatment-specific data reported only for atezolizumab.^{50,54}

The percentage of patients receiving IO therapy in real-world clinical practice was reported in 3 studies

FIGURE 3 Estimated Annual Incidence Rate (Number of Age-Standardized New Cases per 100,000), by Country (2018)

^aDenoted by reference numbers.

^bData are from 2017.

GLOBOCAN = Global Cancer Incidence, Mortality and Prevalence.

(1 additional study reported real-world data, but all included patients had received IO therapy⁵⁰). Two of these studies, which included pre-IO approval data from Canada (2002–2016) and the United States (2011–2016), reported that only 1.3% and 4.4% of patients received first- and second-line IO, respectively.^{49,52} A more recent (2015–2017) study from the United States showed higher rates, with 7.9%, 57.8%, and 64.4% of patients receiving IO in first, second, and third lines, respectively.⁴⁴

Real-world discontinuation rates were reported in 2 U.S. studies (discontinuation reasons not assessed). In the first study, IO discontinuation rates were 64.7% (n=22 of 34), 54.0% (n=68 of 126), and 41.4% (n=12 of 29) for first, second, and third LOT, respectively.⁴⁴ In this study, patients were reported to stay on IO therapy for a median of 3.0 months (95% CI=2.3–5.9), 3.1 months (2.1–4.9), and 5.8 (1.6 to not reported) months by LOT, respectively.⁴⁴ In the other study reporting discontinuation rates, patients receiving atezolizumab remained on therapy (LOT not reported) for a median of 2.7 months (95% CI=1.8–3.6), with 71% (n=56 of 79) discontinuing treatment.⁵⁰

The percentage of patients receiving subsequent therapy after discontinuing IO was reported in 2 studies and

ranged from 25.0% to 35.5%.^{50,51} Post-IO treatments varied widely and included chemotherapy, IO, targeted therapies, clinical trial agents, or best supportive care. In 2 other studies, chemotherapy response rates were similar when administered before or after IO therapy in patients whose disease had relapsed.^{35,53} In a study of 115 patients receiving IO sequenced with carboplatin chemotherapy, the rates of partial response (PR)/complete response (CR) to carboplatin-based chemotherapy were 49% PR (0% CR) when administered before IO, compared with 40% PR (4% CR) when administered after IO.⁵³ In a second study, patients receiving chemotherapy after IO had a PR of 64% (n=9 of 14) if they were chemotherapy-naïve and a PR of 21% (n=3 of 14) if they had previously discontinued a chemotherapy treatment.³⁵

VINFLUNINE STUDIES

Vinflunine data were presented in 7 unique studies ([Supplementary Table 1](#), available in online article).^{31,33,34,55–58} All 7 studies were retrospective analyses reporting data from real-world clinical practice in Europe.

Real-world treatment patterns by LOT were reported in 1 study (2009–2016) from Germany (N=435), of which 3%,

TABLE 1 Studies Reporting First-Line Cisplatin- Versus Non-Cisplatin-Based Regimens, by Country (Studies with ≥ 30 Patients and $<10\%$ Missing Data)

Author, Year	Country and Data Source	Publication Type	Study Period	Patients with Drug Data, n	LOT	Patients with Cisplatin- vs. Non-Cisplatin-Based Regimen, n (%)
Bamias A, 2018 ²	Multinational RISC 29 centers	Manuscript	2000-2013	TCC ^a : 1,160 (of 1,174) with drug data TCC + mixed: 1,260 (of 1,278) with drug data	1L	TCC Cis: 591 (50.3) Non-cis: 569 (48.5) Car: 348 (29.6) Other: 221 (18.8) NR: 14 (1.2) TCC + mixed Cis: 636 (50.5) Non-cis: 624 (49.5) Car: 377 (29.6) Other: 247 (19.6) NR: 18 (1.4)
Necchi A, 2018 ⁴³	Multinational (RISC) Number of centers not reported	Abstract	NR	472	1L	Cis: 338 (71.6) Non-cis: Car: 134 (28.4)
Locke JA, 2016 ⁶⁶	Multinational 12 centers	Manuscript	1995-2014	145	1L	Cis: 91 (62.8) Non-cis: 54 (37.2)
Galsky MD, 2018 ⁴¹	United States SEER-Medicare database	Manuscript	2004-2011	717	1L	Cis: 192 (26.8) Non-cis: 465 (64.8) NR: 60 (8.4)
Barata PC, 2018 ⁵⁰	United States Single center (Cleveland Clinic)	Manuscript	2016-2017	79	1L, 2L, 3L	Cis: 34 (43.0) Non-cis: 45 (57.0) Atezolizumab: 20 (25.3) Clinical trial IO: 2 (2.5) Car/other: 23 (29.1) (cannot differentiate LOT)
Doshi G, 2018 ⁴⁴	United States U.S. Oncology Network, iKnowMed	Poster	2015-2017	430	1L	Cis: 79 (18.4) Non-cis: 351 (81.6) Car: 154 (35.8) IO: 34 (7.9) Other: 163 (37.9)
Malangone-Monaco E, 2017 ⁴²	United States U.S. insurance claims database	Abstract	2005-2015	3,750	1L	Cis: 935 (24.9) Non-cis: 2,815 (75.1) Car: 1,505 (40.1) Other: 1,310 (34.9)
Kunthur A, 2017 ⁴⁵	United States VA central cancer registry	Abstract	2000-2010	196	1L	Cis: 118 (60.2) (100% gem-cis) Non-cis: 78 (39.8) (100% gem-car)

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TABLE 1 Studies Reporting First-Line Cisplatin- Versus Non-Cisplatin–Based Regimens, by Country (Studies with ≥ 30 Patients and <10% Missing Data) (continued)

Author, Year	Country and Data Source	Publication Type	Study Period	Patients with Drug Data, n	LOT	Patients with Cisplatin- vs. Non-Cisplatin–Based Regimen, n (%)
Flannery K, 2017 ⁶⁷	United States Electronic health records of McKesson Specialty Health/ U.S. Oncology Network	Abstract	2010-2014	1,155	1L	Gem-cis: 310 (26.8) Car: 409 (35.4) Gem: 96 (8.3) NR (may include cis): 341 (29.5)
Fisher M, 2017 ^{68,b}	United States 10 U.S. community oncology practices	Abstract	2008-2015	508 mBC 286 (56.3%) had 1L platinum	1L	Cis: Gem-cis: NR (17.0) Non-cis: Gem-car: NR (23.6) Unknown: NR (59.4)
Zargar-Shoshtari K, 2016 ^{69,c}	United States Single institution database	Manuscript	2001-2013	88 (neoadjuvant data) 29 with adjuvant data	Adjuvant	Cis: 8 (27.6) Non-cis: 21 (72.4) Car: 16 (55.2) Other: 5 (17.2)
Bambury RM, 2015 ⁷⁰	United States Institutional database (Memorial Sloan Kettering Cancer Center)	Manuscript	2008-2013	129	1L, 2L	Cis: 74 (57.4) Non-cis: Car: 55 (42.6) (cannot differentiate LOT)
Yelfimov DA, 2014 ⁷¹	United States Single center (Mayo Clinic Minnesota)	Manuscript	1980-2005	80	Adjuvant	Cis: 43 (53.8) Non-cis: Car: 17 (21.2) Unknown: 20 (25.0)
Kikuchi E, 2016 ⁴⁶	Japan 17 centers	Manuscript	2004-2010	107 with mUC	1L	Cis: 87 (81.3) Non-cis: 20 (18.7) Car: 10 (9.4) Other: 10 (9.4)
Muto S, 2015 ^{47,d}	Japan Teikyo University Hospital, Tokyo and Dokkyo Medical University Hospital, Tochigi	Manuscript	2008-2014	N=66: 33 (2L gem monotherapy) 33 (2L best supportive care control group)	1L	Cis: 58 (87.9) Gem group: 28 (84.8) Control: 30 (90.9) Non-cis: 8 (12.1) Gem group: 5 (15.2) Control: 3 (9.1)
Yip SM, 2018 ⁵²	Canada 5 cancer centers in Alberta, Canada	Manuscript	2002-2016	233	1L	Cis: 130 (55.8) Non-cis: 103 (44.2) Car: 87 (37.3) Other: 16 (6.9)
Niegisch G, 2018 ⁵⁵	Germany GermanOncology (GO) network, office-based sites, nonacademic clinics, and academic clinics	Manuscript	2009-2016	435	1L	Cis: 309 (71.0) Non-cis: 126 (29.0) Car: 56 (12.9) Other: 70 (16.1)

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TABLE 1 Studies Reporting First-Line Cisplatin- Versus Non-Cisplatin–Based Regimens, by Country (Studies with ≥ 30 Patients and <10% Missing Data) (continued)

Author, Year	Country and Data Source	Publication Type	Study Period	Patients with Drug Data, n	LOT	Patients with Cisplatin- vs. Non-Cisplatin–Based Regimen, n (%)
Passalacqua R, 2017 ⁵⁶	Italy 28 Italian cancer centers	Manuscript	2011-2014	217	1L	Cis: 122 (56.2) Non-cis: 95 (43.8) Car: 91 (42.0) Other: 4 (1.8)
Laurent M, 2016 ⁷²	France AGEVIM multicenter cohort	Manuscript	1999-2011	193 with mBC 178 (92.2%) with mUC	1L	Among 193 mBC patients Cis: 84 (43.5) Non-cis: 109 (56.5) Car/oxaliplatin: 70 (36.3) Other: 39 (20.2)
Hussain S, 2017 ⁵⁸	United Kingdom and Ireland 9 sites	Manuscript	1999-2013	43	1L	Cis: 13 (30.2) Non-cis: Car: 16 (37.2)
Holmsten K, 2016 ⁵⁷	Denmark and Sweden	Manuscript	2010-2013	100	1L	Cis: 76 (76.0) Non-cis: 24 (24.0) Car: 17 (17.0) Other: 7 (7.0)

^aUC is also known as TCC.

^bIn Fisher et al. (2017),⁶⁸ data on the total number of patients receiving cisplatin was not provided (only the proportion receiving gemcitabine-cisplatin combination was reported).

^cZargar-Shoshtari et al. (2016)⁶⁹ reported on 29 patients receiving cisplatin versus non-cisplatin adjuvant therapy (2001-2013).

^dIn Muto et al. (2015),⁴⁷ patients received either 2L gemcitabine maintenance therapy or best supportive care.

1L=first line; 2L=second line; 3L=third line; AGEVIM=AGE-Vessle-chiMiotherapie or Age-Bladder-Chemotherapy; car=carboplatin; cis=cisplatin; gem=gemcitabine; IO=immuno-oncology; LOT=line of therapy; mBC=metastatic bladder cancer; mUC=metastatic urothelial carcinoma; NR=not reported; RISC=Retrospective International Study of Invasive/Advanced Cancer of the Urothelium; SEER=Surveillance, Epidemiology, and End Results; TCC=transitional cell carcinoma; UC=urothelial carcinoma; VA=Veterans Administration.

47.2%, and 32.4% of patients were treated with vinflunine in the first, second, and third line, respectively.⁵⁵ In the remaining 6 studies, all patients received vinflunine; sample sizes ranged from 19³³ to 217.⁵⁶ In a study from the United Kingdom/Ireland, vinflunine was provided as second-line treatment to 49 patients in a Free of Charge Program, as it was not available through the National Health Service.⁵⁸

PATIENT ESTIMATES

The findings from this SLR were summarized into a flow model to estimate the number of U.S. patients with la/mUC whose disease progressed after receipt of IO therapy, including those who received subsequent therapy. Approximately 22,542 patients are diagnosed with or progress to la/mUC annually, of whom 11,600 received first-line therapy. An estimated 1,795 patients would be eligible to receive therapy post-IO, including 1,352 patients who progress after chemotherapy and an IO agent ([Supplementary Figure 1](#), available in online article). Due to the extent of

missing data for numerous inputs, an accurate estimate of the number of patients receiving IO for other countries of interest was not possible.

Discussion

With the emergence of novel therapy options for patients with la/mUC, assessment of the current epidemiology and treatment landscape is important to provide an evidence base for their evaluation. This SLR was conducted to identify and summarize the published literature on UC and la/mUC incidence and prevalence rates and la/mUC treatment patterns and to identify evidence gaps. A total of 45 publications on la/mUC treatment patterns, comprising 37 unique studies, were retained after full-text review; no studies on the epidemiology of UC and la/mUC were found and epidemiological data were obtained from the national and international websites. The limited number of retained

TABLE 2 Retrospective Studies Reporting IO Treatment Patterns

Author, Year	Agent	Country and Data Source	Study Period	Patients with Drug Data, n	Patients with IO, by LOT, n (%)	Patients with Progression, Discontinuation, or Response, by IO LOT	Patients with Subsequent Treatment Among Those Who Discontinue IO, by IO LOT, n (%)
Doshi G, 2018 ⁴⁴	IO ^a	United States U.S. Oncology Network, iKnowMed	2015-2017	1L: 430 2L: 218 3L: 45	1L: 34 (7.9) 2L: 126 (57.8) 3L: 29 (64.4)	Tx failure event 1L: 22 (64.7%); median TTF 13.0 weeks 2L: 68 (53.9%); median TTF 13.3 weeks 3L: 12 (41.4%); median TTF 25.3 weeks	NR
Vander Velde N, 2019 ⁵⁴	Atezolizumab	United States IMvigor210 and VHA ^b	2006-2017	1L: 392 110 in IMvigor210	1L: 110 (100.0) atezolizumab ^c	NR Mean duration of treatment: 11.0 months	NR
Barata PC, 2018 ⁵⁰	Atezolizumab	United States Single center (Cleveland Clinic)	NR	1L: 20 2L: 47 3L: 9 4L: 3	100% received atezolizumab ^c 1L: 20 (25.3) 2L: 47 (59.5) 3L: 9 (11.4) 4L: 3 (3.8)	NR Median duration of treatment all LOT: 2.7 months, 56 (70.9%) discontinued	25% of 56 discontinued patients (LOT not specified)
Sonpavde G, 2017 ⁵¹	Anti-PD-1/L1 therapy ^a	United States, Italy, and United Kingdom 4 institutions (Dana-Farber Cancer Institute, Comprehensive Cancer Centers of Nevada, Istituto Nazionale dei Tumori, and Barts Cancer Institute)	NR	All LOT: 62	NR	By design: 100% progressed in all LOT During IO therapy, progressive disease: 31 (50.0%) Post-IO therapy, progressive disease: 5 (22.7%)	22 (35.5) of 62 who discontinued (any LOT) Study does not report patients who responded to PD-1/PD-L1 inhibitor

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publications likely reflects the relatively small volume of patients with la/mUC, as well as the lack of treatment options for these patients (besides chemotherapies) until 2016.

Bladder cancer was the tenth most common cancer, with an estimated 549,393 new cases worldwide in 2019.¹ In the United States, there are an estimated 80,400⁵ to 82,501¹ new bladder cancer cases annually, with an estimated 5-year prevalence of 277,255.¹ Among the countries investigated, the highest bladder cancer incidence rates (per 100,000) were seen in Italy (15.9-36.9), Germany (15.7-37.9), and Spain (15.6-37.8)^{1,59}; the United Kingdom had the lowest incidence rates (6.9-19.0 per 100,000).^{1,59} Although epidemiology

websites provided clear estimates of bladder cancer incidence and prevalence, little data were available pertaining to la/mUC. Although studies published before the SLR study period report rates of progression from early-stage disease to la/mUC,^{60,61} no new studies were found in this SLR suggesting there is a lack of up-to-date information. Additional studies in large databases or patient registries are needed to identify the country-specific epidemiology of UC and la/mUC, including the rates of progression from early-stage disease. This evidence gap is especially important to address given the potential effect of new and emerging therapies on disease progression.

TABLE 2 Retrospective Studies Reporting IO Treatment Patterns (*continued*)

Author, Year	Agent	Country and Data Source	Study Period	Patients with Drug Data, n	Patients with IO, by LOT, n (%)	Patients with Progression, Discontinuation, or Response, by IO LOT	Patients with Subsequent Treatment Among Those Who Discontinue IO, by IO LOT, n (%)
Szabados B, 2018 ³⁵	Anti-PD-1/L1 therapy ^a	United Kingdom and Netherlands 2 institutional databases from clinical trials (Barts Health and Netherlands Cancer Institute)	NR	All LOT: 28	By design: 1L: 14 (50.0) 2L: 14 (50.0) IO/CT sequencing study	By design: 28 (100.0%) progressed in all LOT Median follow-up: 8.2 (IQR, 6.5-11.3) months	By design, 100% of pts received subsequent CT
Simeone JC, 2018 ⁴⁹	IO ^a	United States Flatiron Oncology	2011-2016	476 1L: 476 2L: 476	1L: 0 (all platinum-based) 2L: 21 (4.4)	NR	NR
Wei X, 2018 ⁵³	Anti-PD-1/L1 therapy ^a	NR; multinational/multiple institutions assumed based on author list	NR	All LOT: 115	1L: 33 (28.7) 2L: 82 (71.3) IO/car regimen sequencing study	1L: PR: 9%; CR: 0% 2L: PR: 22%; CR: 4%	By design, 100% of pts with 1L IO received 2L car-based treatment

Note: Yip et al. (2018),⁵² a Canadian study not listed here, reported that in 2L, 1 of 79 patients received IO.

^aAgent not specified.

^bStudy compared cisplatin-ineligible patients with mUC from the phase 2 trial IMvigor210 (treated with atezolizumab) with patients from the VHA health care system (treated according to normal clinical practice) using IMvigor210 eligibility criteria applied by proxy measurements.

^cNon-IO data not included.

1L = first line; 2L = second line; 3L = third line; 4L = fourth line; car = carboplatin; CR = complete response; CT = chemotherapy; IO = immuno-oncology; IQR = interquartile range; LOT = line of therapy; mUC = metastatic urothelial carcinoma; NR = not reported; PD-1/L1 = programmed death-1 or programmed death-ligand 1; PR = partial response; pts = patients; TTF = time to treatment failure; Tx = treatment; VHA = Veterans Health Administration.

A large variation in cisplatin use was observed both within and among countries, with a trend toward lower cisplatin use in studies with the most recent data periods (evaluating data post-2010, cisplatin use was 43.0% for 2016-2017 [United States],⁵⁰ 56.2% for 2011-2014 [Italy],⁵⁶ and 76.0% for 2010-2013 [Denmark and Sweden]⁵⁷), although studies spanned multiple years across different countries making conclusions difficult to establish. This trend was further substantiated by a recent study identified outside the SLR period that showed a decrease from 53% to 33% in the proportion of eligible patients who received first-line cisplatin-based therapy in the United States between 2015 and 2018.⁶² The data also suggest that patients are not being consistently treated according to recommendations based on cisplatin-eligibility criteria. For example, a large multinational analysis of Retrospective International Study of Invasive/Advanced Cancer of the Urothelium (RISC) data established that eligibility criteria accounted for only 56% of the cases in which the investigator provided a reason

for not using cisplatin,² suggesting other considerations in addition to cisplatin-eligibility are important to treatment decisions in real-world clinical practice. It should be noted that patients included in this analysis were treated before the publication of cisplatin-eligibility criteria by Galsky et al. (2011).⁹ Much of the identified published evidence on cisplatin versus non-cisplatin use was outdated and therefore may not reflect current treatment patterns. Further, not all data were specific to patients with la/mUC, and studies may have reported on the overall population with UC or only some stages/extent of disease. The most recent data (2015-2017) available were from the United States,⁴⁴ with limited data overall on cisplatin versus non-cisplatin use outside the United States and Japan.

Given IO therapy for la/mUC has only been approved since 2016, few studies reporting real-world treatment patterns have been published to date. Overall, the use of IO therapy has been increasing, as reflected by higher IO treatment rates in more recent studies. This trend

was confirmed in an additional study published after the SLR study period that found the quarterly proportion of patients who received first-line IO increased from 1.4% to 42.0% between 2015 and 2018.⁶² In a separate analysis by Parikh et al. (2019), IO use decreased from 51.9% to 30.3% between May 2018 and January 2019 following the FDA's decision to restrict the first-line use of atezolizumab and pembrolizumab to cisplatin-ineligible patients with PD-L1-positive tumors.⁶³ Nonetheless, the overall increase in the use of IO for patients with la/mUC represents a major shift in clinical practice that is continuing to evolve.

Despite increased use, most patients discontinue IO, with 1 study reporting that up to 71% of patients discontinued atezolizumab across all LOT.⁵⁰ Median IO treatment duration reported in clinical trials is 2–3 months,^{15–17} whereas studies identified in the SLR indicated patients often discontinued IO treatment within 3–6 months in the real-world setting.^{44,50} Limited data have been published on IO treatment duration in the real-world setting since the SLR was conducted. One recent analysis reported a median duration of IO treatment ranging from 2.1 to 2.8 months.⁶⁴ Few patients receive subsequent therapy following IO, reflecting a persisting unmet need, in particular for those patients whose disease progressed after IO treatment.^{50,51} The emergence of novel therapies may help fill this unmet need. For example, EV was approved by the FDA under accelerated approval in December 2019 based on results from the EV-201 trial in 125 adult patients with la/mUC previously treated with platinum and anti-PD-1/L1 therapy, which showed a confirmed objective response rate of 44% (95% CI=35.1%–53.2%) and a CR rate of 12%.^{18,65} Further study is needed on the number of patients who receive a subsequent therapy following progression

on IO since the introduction of new therapies in this setting.

LIMITATIONS

The study reflects a period in time shortly after approvals for IOs and, as such, a limited number of studies were identified with data on IO and, in particular, post-IO treatment patterns. Differences in study design and data reporting made comparisons across studies and within and among countries difficult. LOT was not specified in many studies. Many of the identified studies included <30 patients or reported data that were >5 years old, and so may not be reflective of current treatment patterns. The majority of published studies were from the United States and Japan and cannot be considered representative of other countries. In particular, very limited data were available for Canada and Spain. Because no epidemiology studies meeting inclusion criteria were identified, epidemiology websites were used. The websites reported data for bladder cancer overall; epidemiology data on urothelial carcinoma specifically were not available.

Conclusions

Bladder cancer remains one of the most prevalent cancers worldwide with a significant number of new cases and deaths each year. Use of cisplatin, the recommended first-line treatment for patients with la/mUC, varies widely both within and among countries, indicating that many eligible patients are not receiving guideline-recommended therapy. There has been an increase in the use of IO therapy for la/mUC in recent years, however, due to a lack of published real-world studies as well as the relative recency of these clinical practice changes, very little is known outside clinical trials. The few published real-world studies reported relatively high levels of

treatment discontinuation in patients treated with anti-PD-1/L1 therapies, yet only a small percentage received subsequent therapy, indicating a high need for novel therapies that are safe and efficacious.

DISCLOSURES

This study was funded by Astellas/Seagen. Hepp is an employee of and owns stock in Seagen. Shah was a contractor for Astellas Pharma at the time of the study and owns stock in Pfizer. Smoyer is an employee and shareholder of Envision Pharma Group, paid consultants to Seagen. Vadagam was an employee of Envision Pharma Group, paid consultants to Seagen, at the time of the study.

Parts of these data have been presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 2019 Annual Meeting; May 18–22, 2019; New Orleans, LA.

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