

Research Paper

# A Real-World Data Study to Evaluate Treatment Patterns, Clinical Characteristics and Survival Outcomes for First- and Second-Line Treatment in Locally Advanced and Metastatic Urothelial Cancer Patients in Germany

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## Abstract

**Background:** Worldwide, urothelial carcinoma (UC) is a common cause of morbidity and mortality. In particular, the incidence of bladder cancer varies widely across Europe; Germany has the ninth highest international age-standardized incidence. For advanced UC or metastatic UC (mUC), platinum-based combination chemotherapy is the standard first-line (1L) treatment; however, there is wide heterogeneity of second-line (2L) treatments, ranging from vinflunine in parts of Europe to taxanes and other agents elsewhere in Europe, in the United States and globally. Limited data exist on treatment patterns and outcomes in patients with advanced UC or mUC in the routine clinical setting in Germany. The objective of this study was to describe clinical characteristics, treatment patterns and subsequent outcomes in this setting.

**Methods:** This retrospective observational cohort analysis evaluated 1L and 2L treatment patterns and overall survival (OS) in patients aged  $\geq 18$  years with advanced UC or mUC (T4b, N2-3 and/or M1) at office-based urology and academic as well as nonacademic urology clinics throughout Germany between 1 November 2009 and 2 June 2016. Data were obtained through the GermanOncology database and additional treatment centers using similar electronic case report forms.

**Results:** Among the 435 patients included in the analysis, 435 received 1L treatment and 125 received 2L treatment. Median age at start of 1L treatment was 69 years, 75% of patients were male, 75% were current or ex-smokers, 15% had hemoglobin  $< 10$  g/dL and 44% had creatinine clearance  $< 60$  mL/min/1.73; proportions were similar with 2L treatment. Cardiovascular disease was the most frequently reported comorbidity (65%), followed by diabetes (19%). Most patients (77%) received 1L platinum-based combination treatment (most commonly gemcitabine + cisplatin, 83%). Of those treated with 2L treatment, 66% received a single agent (most commonly vinflunine, 71%). Median OS (95% CI) with 1L treatment was 16.1 months (13.7-19.2) overall and 17.7 months (14.4-24.2) with 1L cisplatin + gemcitabine. In the 1L setting, 12-month OS was 61%, 24-month OS was 39% and

36-month OS was 26%. Median (95% CI) OS with 2L treatment was 9.2 months (5.5-11.6) overall and 5.9 months (4.1-12.6) with 2L vinflunine. In the 2L setting, OS rates for the same time periods were 40%, 22% and 8%, respectively. Median (95% CI) progression-free survival was 7 months (6.4-8.1) and 4 months (3.0-4.8), respectively, in the 1L and 2L settings. Objective response rates were 34% in the 1L setting and 14% in the 2L setting. No difference in OS by sex or smoking status was noted. Patients with or without renal impairment had a 12-month OS of 54% or 69%, respectively. OS at 12 months was 63% among patients with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1 vs 53% among patients with an ECOG PS of  $\geq 2$ . Cox regression analysis found no difference in OS between vinflunine and other 2L treatments ( $P = 0.69$ ).

**Conclusions:** This study provides a contemporary multicenter assessment of real-world treatment patterns and outcomes among palliatively treated patients with UC in Germany. The findings were generally consistent with the poor treatment outcomes observed globally, underscoring the need for effective 1L and 2L treatment for advanced UC or mUC.

Key words: first-line treatment, German clinical practice, metastatic urothelial carcinoma, second-line treatment, treatment patterns

## Introduction

Globally, there were approximately 430,000 new cases of and 165,000 deaths due to bladder cancer in 2012 [1]; it was the ninth most common cancer among both sexes and was the thirteenth most common cause of death due to cancer [1]. The incidence and prevalence of bladder cancer varies widely across European countries [1, 2]. In Germany, urothelial carcinoma (UC) constitutes one of the most common cancers [3]. Based on 2012 data, Germany had the ninth highest international age-standardized incidence of bladder cancer in men and women [4]. For bladder cancer, of which UC accounts for >90% of cases, an incidence of 28,910 newly diagnosed cases per year was reported in Germany, of which 15,400 were invasive [1, 4]. In Germany, non-UCs of the urinary bladder are infrequent (<10%) [5, 6]. Similarly, UC of the upper urinary tract, ureters and renal pelvis accounts for <10% of urothelial bladder cancers [7-9], with 2770 incident cases per year in Germany, in both sexes [10].

The clinical course of patients with UC varies widely, with approximately two-thirds of patients experiencing an uncomplicated clinical course due to a relatively low risk of invasion and metastasis. However, the remaining patients face an aggressive disease with often rapid local and systemic progression [1, 11]. As many as 50% to 70% of non-muscle-invasive bladder cancers recur, and approximately 10% to 20% progress to muscle-invasive disease [1, 12] that may portend a worse prognosis. For instance, according to the large US-based Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, approximately 34% of bladder cancers are localized and associated with a 5-year survival of approximately 70%. Comparatively, patients with

regional (7% of diagnoses) or distant (4% of diagnoses) spread have 5-year survival rates of 35% and 5%, respectively [13].

In the palliative setting, cisplatin-based combination chemotherapy is the standard first-line (1L) treatment [11], and median overall survival (mOS) with such regimens is 13 to 16 months [11, 14-16]. However, cisplatin eligibility remains a limiting factor in elderly patients because renal dysfunction (creatinine clearance [CrCL] <60 mL/min), poor performance status (Eastern Cooperative Oncology Group performance status [ECOG PS] of  $\geq 2$ ) and comorbidities (eg, New York Heart Association Class III heart failure, grade  $\geq 2$  hearing loss, grade  $\geq 2$  neuropathy) exclude many patients ( $\approx 50\%$ ) from recommended 1L treatment [17-20]. Treatment of patients who progress after 1L treatment remains a challenge, because second-line (2L) treatment options are limited. Current practice guidelines in Europe recommend vinflunine as 2L treatment [11, 17]; however, 2L treatment of mUC varies geographically because there is no global standard of care for 2L treatment. Vinflunine was approved by the European Medicines Agency in 2009 but is not used throughout all of Europe [21]. Support for vinflunine in the 2L setting was based on the results from a phase 3 study showing that vinflunine + best supportive treatment resulted in an overall response rate of 8.6% compared with 0% with best supportive treatment alone [22]. Although no survival advantage was found in the intent-to-treat population ( $n = 370$ ), improvement in mOS favored vinflunine (4 vs 7 months) in the eligible population ( $n = 357$ , which excluded 13 intent-to-treat patients who had  $\geq 1$  major protocol violation at baseline;  $P = 0.036$ ) [22]. In countries where vinflunine is not approved, including

the United States, taxanes or taxane-based combinations are considered an appropriate alternative [11, 23, 24].

Data are limited on treatment patterns and outcomes in patients with advanced UC or metastatic UC (mUC) in the routine clinical setting in Germany. The primary objective of this retrospective, observational cohort analysis was to describe treatment patterns and survival outcomes among patients with a diagnosis of incurable locally advanced UC or mUC treated with 1L and 2L systemic chemotherapy in the palliative setting in Germany.

## Materials and Methods

### Study design

This noninterventive, retrospective analysis evaluated the 1L and 2L treatments and survival outcomes of patients with locally advanced UC or mUC in the real-world clinical practice setting in Germany. The study protocol (MO39086) was approved by the ethics committee at the Medical Faculty of the Heinrich-Heine-University Düsseldorf (study number 5566). The protocol was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

### Contributing databases

Data for this study were obtained through 2 sources, and the overall study and observation periods are outlined in Figure S1. The GermanOncology (GO) network contributed data from office-based urology clinics, distributed across Germany, which collect patient characteristics, treatment data and outcome data using a standardized electronic case report form (eCRF). The GO database began in January 2012 and currently includes patient clinical characteristics, chemotherapy and radiotherapy treatment regimens, comorbid conditions and supportive therapy use from >12,500 patients being treated for cancer. To reach the appropriate sample size of patients with advanced or mUC, 25 additional treatment centers were recruited to contribute patient data by means of a modified eCRF. This modified eCRF extended the GO eCRF to enable more tailored and detailed data collection by including prognostic variables (eg, PS, hemoglobin, CrCl and site of metastases). For the newly accrued patients from these additional data sources, only data from up to June 2, 2016 (submission of protocol to institutional review boards) were considered in accordance with the requirements of the ethical permission obtained for the study.

### Patient population and definitions

Eligible patients included adults aged  $\geq 18$  years with a diagnosis of locally advanced (transitional cell) UC of the upper and lower urinary tracts, defined as T4b, N(any), M0, T(any), N2-3, M0 or metastatic cancer defined as T(any), N(any), M1 (with clinical, radiological or pathological confirmation of metastasis) who received palliative 1L or 2L treatment starting on or after November 1, 2009 (Figure S1). Patients were excluded if their medical records were missing data on critical variables (Figure 1). Critical variables included age, sex, stage at study entry, line of therapy, start date of first or second line of therapy, end date of 1L or 2L treatment and therapeutic agents. Patients included in this registry were eligible for 1L, 2L or both cohorts depending on the treatments (lines of therapy) received. Patients in the 2L cohort, if data were complete for their 1L treatment, were also included in the 1L analysis if otherwise eligible for that analysis. Patients with nonmuscle invasive bladder cancer were not included.

### Treatment and outcome definitions

For 1L treatment, the index date for study participants was the start date of the 1L systemic treatment. For 2L treatment, the index date was the date when the 2L chemotherapeutic treatment for recurrence after previous treatments/treatment failure of 1L treatment was initiated (Figure S1). Treatment response was assessed by the treating physician. The objective response rate was defined as the number of patients with a complete or partial response divided by the total number of patients.

### Statistical analysis

Results for treatment patterns and clinical characteristics were reported as the numbers and percentages of patients, and descriptive analyses including means and SDs or 95% CIs and/or medians and interquartile ranges (Q1-Q3) were used for continuous variables. The numbers and percentages of patients were used for categorical variables. All statistical analyses were conducted using SAS 9.4.

### Survival analyses

OS was defined as the interval between the index date of 1L treatment or 2L treatment and the date of death; patients lost to follow-up or alive at the end of the study period were censored at the last available date known to be alive. The mOS was estimated in months using the Kaplan-Meier method with 95% CIs. Milestone survival rates at 6, 12, 24 and 36 months were calculated with 95% CIs around the estimates using the Life Table (actuarial) method.

Cox regression analysis was used to compare outcomes in patients receiving vinflunine with other 2L treatments, adjusted for hypothesized prognostic factors based on the vinflunine phase 3 study (ECOG PS [ $>0$  vs  $0$ ], liver metastases [yes vs no], hemoglobin level [ $<10$  vs  $\geq 10$  g/dL]), age at index ( $\geq 68$  vs  $<68$  years) and sex [25]. Patients with missing covariates in the Cox regression were excluded from the regression analysis. All prognostic factors were included in the model at the same time. However, because information on hemoglobin level was not available for patients from the GO database, survival differences between vinflunine vs any other non-vinflunine-containing therapy using the Bellmunt model could only be assessed in a subset of the total 2L-treated patient population.

Progression-free survival (PFS) was measured from the index date to the date of progression or death due to any cause or initiation of new regimen, censoring patients who were still alive and did not progress at the last visit date. Median PFS (mPFS) was estimated, with 95% CIs, in months using the Kaplan-Meier method.

## Results

### Sites and geographic representation

Care settings included office-based sites (1L: 229 patients; 2L: 61 patients), nonacademic clinics (1L: 70 patients; 2L: 8 patients) and academic clinics (1L: 136 patients; 2L: 56 patients). Contributing centers covered most of Germany in a manner reflecting the distribution of the population. As such, most patients came from North Rhine-Westphalia ( $n = 183$ , 42%), followed by Bavaria ( $n = 42$ , 10%) and Berlin ( $n = 63$ , 15%), which are all densely populated federal states. A large hospital in Berlin provided coverage to patients in nearby Mecklenburg-Vorpommern and Brandenburg. Less densely populated states such as Saxony-Anhalt ( $n = 19$ , 4%) or Saxony ( $n = 5$ , 1%) had a lower contribution of patients, and federal states that were not covered mainly reflect low-populated states such as Saarland or Thuringia.

### Patient population and baseline characteristics

Of the 444 eligible patients, 9 were excluded for missing data on critical variables during 1L treatment. Overall, 435 patients were included in the 1L analysis, of which 125 were also included in the analysis of 2L treatment. Details of patient attrition by data source are shown in Figure 1. In general, of the 184 patients with UC extracted from the GO database, 118 met the inclusion criteria—112 of whom received 1L chemotherapy and 30 of whom received 2L chemotherapy. Of the 326 patients obtained from the other contributing centers, all met the inclusion

criteria—of whom 323 received 1L chemotherapy and 95 received 2L chemotherapy (Figure 1).

In patients treated with 1L treatment, the mean age was 66 years at the time of primary diagnosis and 67.4 years at the time of 1L treatment (Table 1). Patients treated with 2L chemotherapy had a mean age of 64.3 years at the time of initial diagnosis and of 66.6 years at the time of 2L index date. The majority of 1L- and 2L-treated patients were male, were current or former smokers and had metastatic (M1) disease (Table 1). A large number of patients had missing baseline smoking status ( $n = 225$ , 52%), CrCl levels ( $n = 183$ , 42%) and hemoglobin levels ( $n = 182$ , 42%). The most common distant metastatic sites in 1L-treated patients were the liver (42%) and other visceral organs (38%). In those who received 2L treatment, the most common metastatic sites also included the liver (32%), other visceral organs (30%) and bone (30%). A higher percentage of 2L-treated than 1L-treated patients had an ECOG PS of  $\geq 2$ , CrCl  $<60$  mL/min and hemoglobin  $<10$  mg/dL (Figure 2A). The most common comorbidities were cardiovascular disease, diabetes and renal insufficiency, which were similar in frequency between the 1L and 2L treatment groups (Figure 2B, Table 1).

### Treatment patterns

The median time from primary diagnosis to any 1L palliative treatment was 4.9 months, and the median time from diagnosis to any 2L palliative treatment was 7.5 months. A graphic illustration of treatment flow across 1L, 2L and 3L treatments is provided in Figure 3. Approximately 77% ( $n = 334$ ) of 1L-treated patients received platinum-based combination treatment. The most common 1L combination treatment was gemcitabine + cisplatin ( $n = 276$ , 83%), followed by gemcitabine + carboplatin ( $n = 47$ , 14%). A minority of patients ( $n = 75$ , 17.2%) were treated with 1L single-agent treatment. Gemcitabine ( $n = 38$ , 51%) was the most common 1L single agent, followed by vinflunine ( $n = 12$ , 16%) and cisplatin ( $n = 11$ , 15%). In this analysis, approximately 29% ( $n = 125$ ) of 1L-treated patients received 2L treatment, and 9% ( $n = 37$ ) received 3L treatment (Figure 3). However, subsequent treatment data may not be fully captured due to ongoing treatment, progression or death, as discussed below. Of the 2L-treated patients, 66% ( $n = 83$ ) received single-agent treatment. The most common was vinflunine ( $n = 59$ , 71%), followed by gemcitabine ( $n = 7$ , 8%) and paclitaxel ( $n = 5$ , 6%). Approximately one-third ( $n = 40$ , 32%) of 2L-treated patients received combination treatment, and the most common combinations were gemcitabine + cisplatin ( $n = 15$ , 37%), gemcitabine + paclitaxel ( $n = 15$ , 37%) and gemcitabine + carboplatin ( $n = 8$ , 20%).

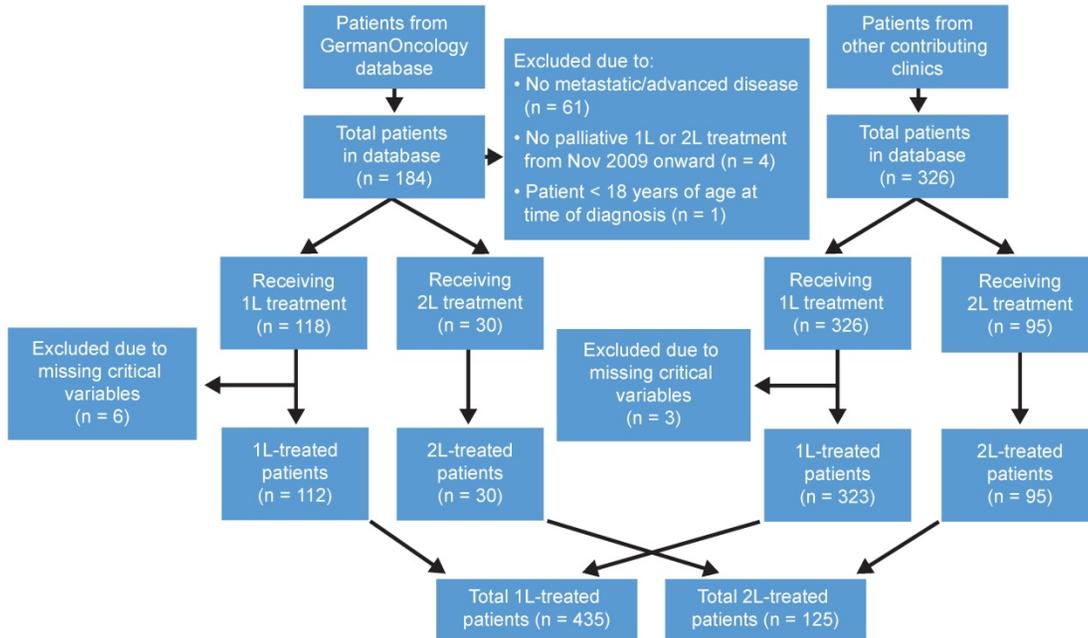


Figure 1. Patient attrition. Schematic flow diagram indicating study databases, reasons for exclusion and analysis populations. 1L: first line; 2L: second line.

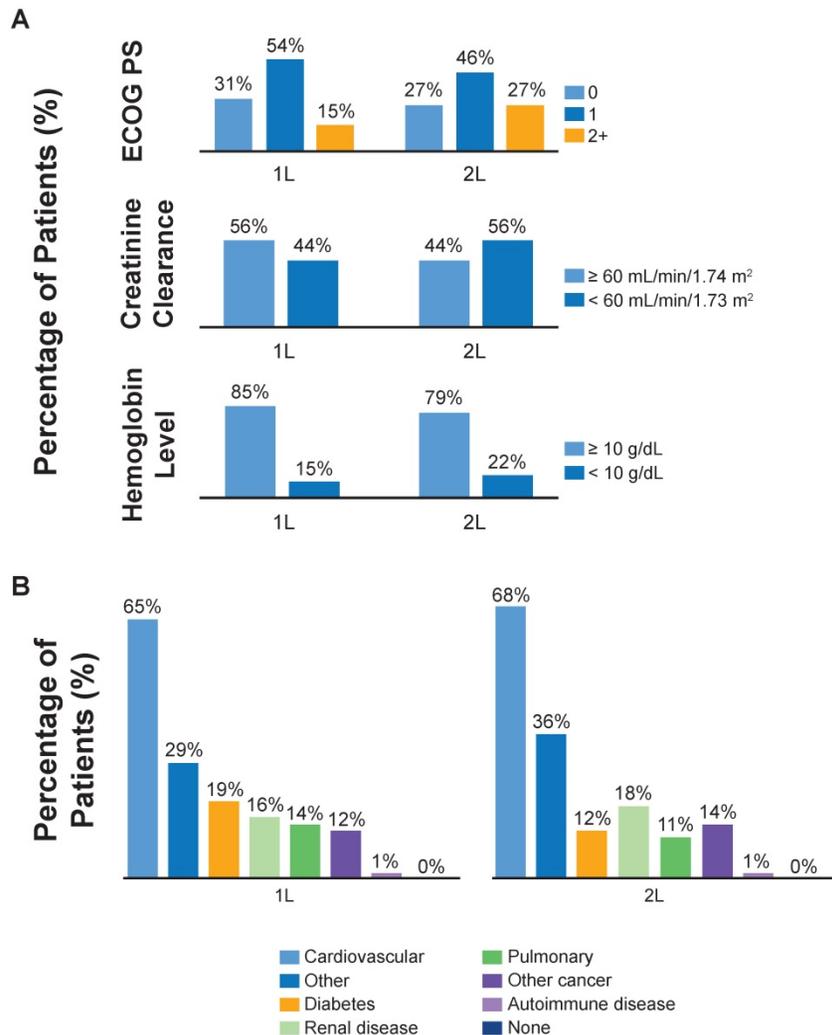


Figure 2. Baseline characteristics and comorbidities by line of therapy. (A) Eastern Cooperative Oncology Group performance status (ECOG PS), creatinine clearance and hemoglobin levels by line of therapy. Percentages of patients with missing baseline ECOG PS, creatinine clearance and hemoglobin were 7%, 42% and 42%, respectively. (B) Common comorbidities by line of therapy.

**Table 1.** Baseline characteristics by line of therapy and most common 1L and 2L treatments

Characteristic	Patients With 1L Treatment	1L Cisplatin + Gemcitabine <sup>a</sup>	Patients With 2L Treatment	2L Vinflunine <sup>b</sup>
Patient count at start, n	435	276	125	59
Age at primary diagnosis, years <sup>c</sup>				
Mean (SD)	66.0 (10)	64.9 (9)	64.3 (10)	65.1 (10)
Median	67	66	65	67
Age at index date, years <sup>d</sup>				
Mean (SD)	67.4 (10)	66.2 (9)	66.6 (10)	66.6 (10)
Median	69	67	69	69
Baseline characteristic, n (%)				
Sex				
Male	326 (75)	204 (74)	87 (70)	40 (68)
Female	109 (25)	72 (26)	38 (30)	19 (32)
Smoking status				
Never	53 (25)	27 (18)	18 (32)	9 (35)
Current/former	157 (75)	122 (82)	39 (68)	17 (65)
Missing	225 (52)	127 (46)	68 (54)	33 (56)
Tumor stage at study entry				
IV (only IV is permitted, if available)	363 (100)	260 (100)	103 (100)	46 (100)
Missing	72 (17)	16 (6)	22 (18)	13 (22)
Primary tumor grade				
Low grade	299 (931)	235 (96)	88 9 (94)	40 (98)
High grade	22 (7)	9 (4)	6 (6)	1 (2)
Missing	114 (26)	32 (12)	31 (25)	18 (31)
Metastatic status at study entry <sup>e</sup>				
M0	142 (39)	106 (41)	32 (31)	16 (35)
M1 primary	136 (37)	97 (37)	33 (32)	16 (35)
M1 recurrent	89 (24)	58 (22)	39 (38)	14 (30)
Missing	68 (16)	15 (5)	21 (17)	13 (22)
Extent of disease at study entry <sup>f</sup>				
Locally advanced, moderate lymph node involvement <sup>g</sup>	9 (2)	8 (3)	4 (3)	2 (3)
Bladder confined, extensive lymph node involvement <sup>g</sup>	133 (31)	98 (36)	28 (22)	14 (24)
Location of distant metastasis (if M1) <sup>e</sup>				
Liver	56 (42)	44 (48)	17 (34)	8 (38)
Other visceral <sup>h</sup>	50 (38)	31 (34)	15 (30)	7 (33)
Bone	41 (31)	30 (33)	15 (30)	5 (24)
Other nonvisceral <sup>h</sup>	33 (25)	20 (22)	14 (28)	5 (24)
Missing	93 (41)	63 (41)	22 (31)	9 (30)
ECOG PS				
0	125 (31)	96 (36)	31 (27)	18 (33)
1	218 (54)	141 (52)	54 (46)	18 (33)
2+	62 (15)	32 (12)	32 (27)	18 (33)
Missing	30 (7)	7 (3)	8 (6)	5 (8)
Hemoglobin level				
< 10 g/dL	39 (15)	29 (15)	17 (22)	6 (17)
≥ 10 g/dL	214 (85)	161 (85)	62 (78)	29 (83)
Missing	182 (42)	86 (31)	46 (37)	24 (41)
CrCl				
< 60 mL/min/1.73 m <sup>2</sup>	110 (44)	71 (38)	45 (56)	22 (61)
≥ 60 mL/min/1.73 m <sup>2</sup>	142 (56)	118 (62)	35 (44)	14 (39)
Missing	183 (42)	87 (32)	45 (36)	2 (39)
Comorbidities <sup>e,h</sup>				
Pulmonary	46 (14)	26 (12)	10 (11)	5 (11)
Cardiovascular	222 (65)	128 (60)	64 (68)	32 (70)
Diabetes	66 (19)	49 (23)	11 (12)	6 (13)
Renal disease	53 (16)	23 (11)	17 (18)	8 (17)
Autoimmune disease <sup>i</sup>	4 (1)	4 (2)	1 (1)	0 (0.0)
Other	100 (29)	59 (27)	34 (36)	16 (35)
Other cancer	41 (12)	21 (10)	13 (14)	8 (17)
Missing	93 (21)	61 (22)	31 (25)	13 (22)
Insurance type				
Private	48 (11)	29 (11)	20 (16)	7 (12)
Public	387 (89)	247 (90)	105 (84)	52 (88)

1L: first line; 2L: second line; CrCl: creatinine clearance; ECOG PS: Eastern Cooperative Oncology Group performance status.

<sup>a</sup> Most common 1L treatment.<sup>b</sup> Most common 2L treatment.

<sup>c</sup>Primary diagnosis was the initial diagnosis of urothelial carcinoma, independent of stage.

<sup>d</sup>For 1L treatment, the index date was the start date of the 1L systemic treatment. For 2L treatment, the index date was the date when the 2L chemotherapeutic treatment for recurrence after previous treatments/treatment failure of 1L treatment was initiated.

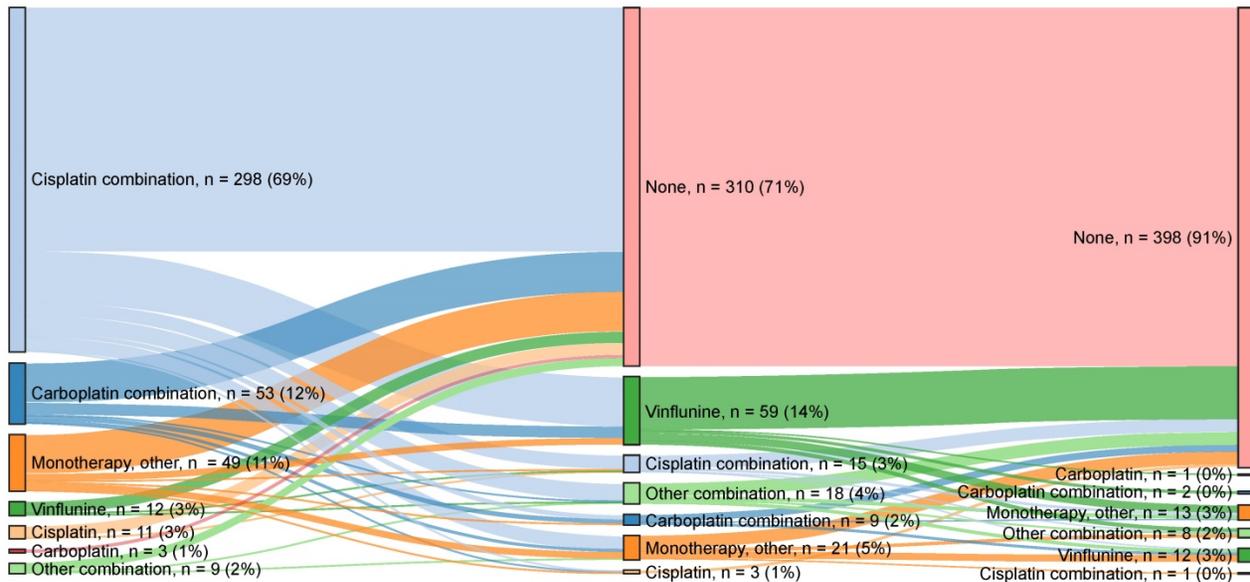
<sup>e</sup>Values within categories do not necessarily add up to 100% due to non-mutually exclusive groups and/or missing values, which do not contribute to the denominators used for percentages.

<sup>f</sup>For patients with non-M1 or non-missing status. Locally advanced disease with moderate lymph node involvement refers to T<sub>b</sub>, N ≤1, M0 (includes N<sub>x</sub> or M<sub>x</sub>, if T4<sub>b</sub> confirmed). Bladder-confined disease with extensive lymph node involvement refers to T4<sub>b</sub>, N2-3 M0 (includes T<sub>x</sub> or M<sub>x</sub> if N2-3 confirmed)

<sup>g</sup>Other metastatic sites, including the lung, peritoneum, non-visceral: brain, skin and other sites.

<sup>h</sup>Variable not collected by GermanOncology; total N = 112 for 1L and 30 for 2L.

<sup>i</sup>Including ≥1 of the following diseases: myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with anti-phospholipid syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis or glomerulonephritis.



**Figure 3.** Treatment patterns across lines of therapy. Sankey diagram of treatments received. Possible reasons for not receiving second-line treatment include death, still receiving first-line treatment, clinical factors and patient preference.

## Treatment outcomes

### OS by treatment type

OS by line of treatment and most common vs other treatments is shown in Figure 4A. Of the patients who received 1L treatment, a total of 206 (47%) deaths occurred, and a total of 229 (53%) were censored. Of the patients who received 2L treatment, a total of 79 (63%) deaths occurred and 46 (37%) were censored. The mOS (95% CI) with 1L treatment overall was 16.1 months (13.7-19.2) and with cisplatin + gemcitabine was 17.7 months (14.4-24.2) (Table 2). In the 1L setting, OS rates at 6, 12, 24 and 36 months were 80%, 61%, 39% and 26%, respectively (Figure 4A). The mOS (95% CI) with 2L treatment overall was 9.2 months (5.5-11.6) and 5.9 months (4.1-12.6) with 2L vinflunine (Table 2). In the 2L setting, OS rates at the same time periods were 57%, 40%, 22% and 8%, respectively. Survival rates with the 1L combination of gemcitabine + cisplatin at 6, 12, 24 and 36 months were 82%, 66%, 43% and 26%, respectively. OS was numerically higher for the combination of gemcitabine + cisplatin at 6 and 12 months compared with other 1L treatments. This difference became less apparent at 24 and 36 months. OS with 2L treatment

with vinflunine was similar to that with other 2L agents at all time points. OS rates with vinflunine at 6, 12, 24 and 36 months were 49%, 39%, 20% and 9%, respectively, in the 2L setting (Figure 4A). Cox multivariate regression analysis found no difference in survival between vinflunine and other 2L treatments (adjusted *P* value = 0.69) (Figure 5A).

### OS by clinical characteristics

OS in the 1L setting was similar by age (<65 or ≥65 years) at 6, 12 and 24 months and was numerically higher at 36 months in favor of patients aged <65 years (Figure 4B). OS at 6, 12, 24 and 36 months was similar by sex and smoking status (Figure 4B). In 1L-treated patients, those without renal insufficiency had numerically higher OS at 6 and 12 months but not thereafter. In 1L-treated patients, survival appeared higher in patients with an ECOG PS of 0 to 1 compared with an ECOG PS of ≥2 (Figure 4C). No difference in survival in the 2L setting was found based on Bellmunt risk factors [25] (Figure 5B).

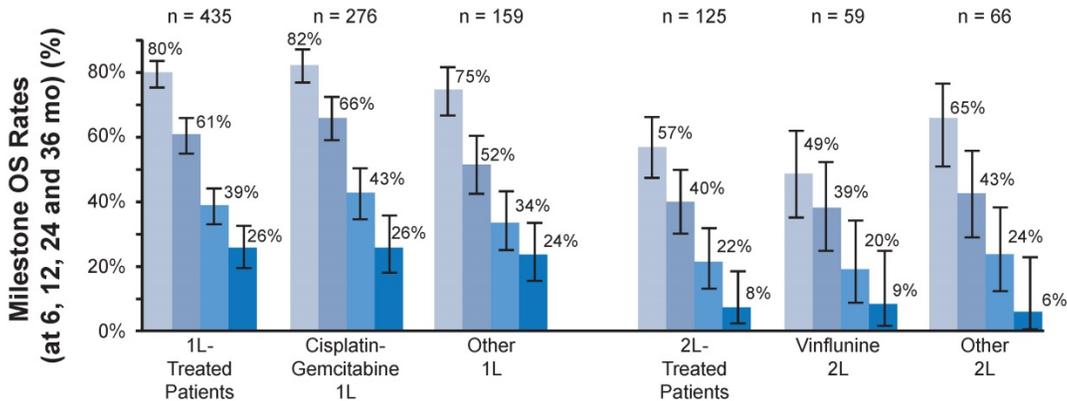
### Treatment response and progression by line of therapy

Key measures of response and progression by line of therapy are shown in Table 2. Objective

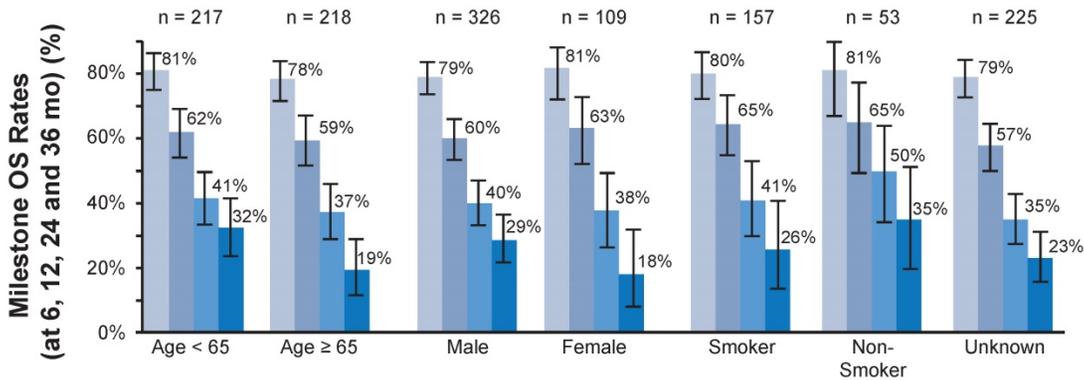
responses occurred in 34% of patients treated with any 1L treatment, 35% of patients treated with 1L cisplatin + gemcitabine, 13% of 2L-treated patients and 5% of patients treated with 2L vinflunine (Table 2). The mPFS (95% CI) values in patients treated with any 1L treatment, 1L cisplatin + gemcitabine, any 2L treatment and 2L vinflunine were 7 months (6.4-8.1), 7 months (6.4-9.1), 4 months (3.0-4.8) and 3 months (2.5-4.2), respectively. Of the patients who received 1L treatment, a total of 228 (66%) PFS events (death or

progression) occurred, and 147 (34%) were censored. In the patients who received 2L treatment, a total of 99 (79%) PFS events (death or progression) occurred – 26 (21%) of which were censored. Early disease progression within 6 and 12 months of start of treatment occurred in 26% (n = 115) and 43% (n = 186) of patients treated in the 1L setting and in 43% (n = 54) and 55% (n = 69) of patients treated with 2L chemotherapy, respectively (Table 2).

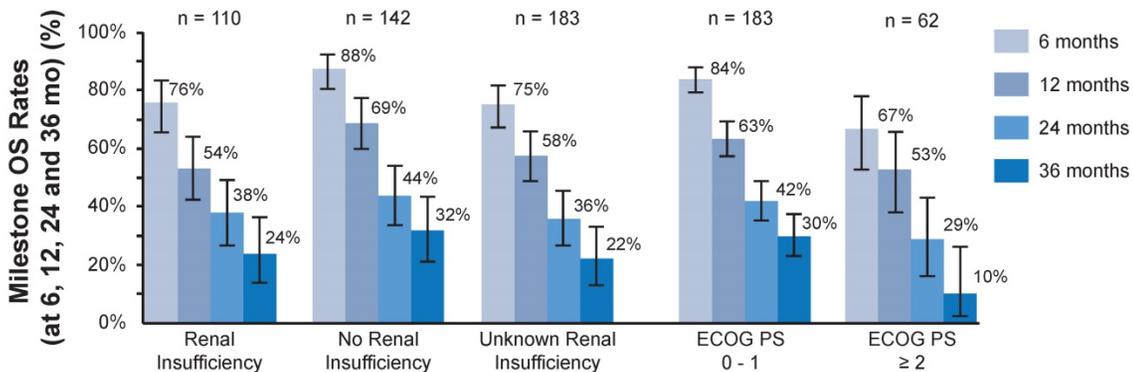
**A** Line of therapy and most frequent treatment vs. other treatments



**B** 1L therapy by age, sex and smoking status subgroup



**C** 1L therapy by renal function and ECOG PS



**Figure 4.** First-line (1L) treatment outcomes. (A) Milestone overall survival (OS) at 6, 12, 24 and 36 months by line of therapy and most frequent vs other treatments. (B) Milestone OS at 6, 12, 24 and 36 months for 1L treatment by age, sex and subgroups of smoking status. (C) Milestone OS at 6, 12, 24 and 36 months for 1L treatment by renal function and Eastern Cooperative Oncology Group performance status (ECOG PS). Bars show 95% CIs.

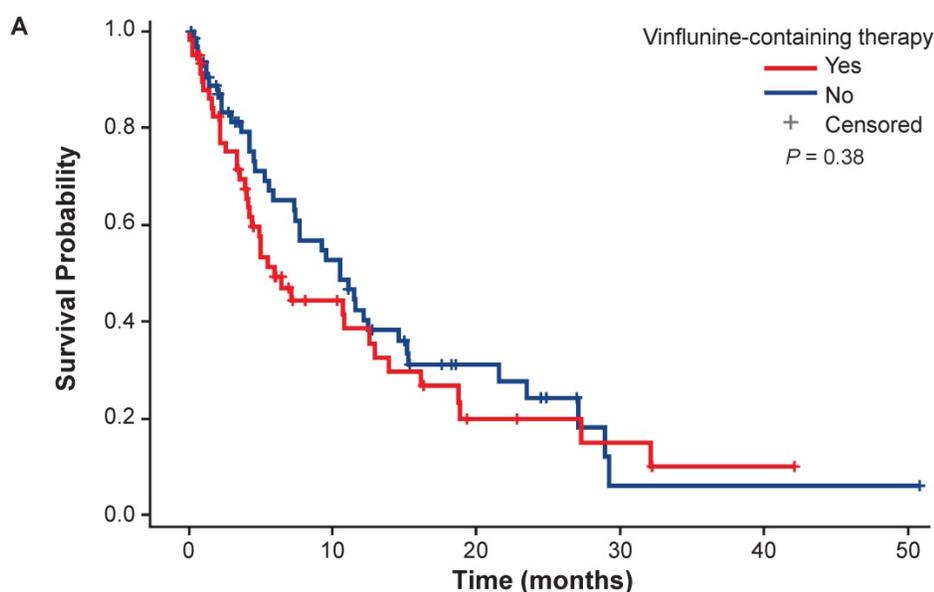
**Table 2.** Clinical outcomes by line of therapy

	1L-Treated Patients (n = 435)	1L Cisplatin + Gemcitabine <sup>a</sup> (n = 276)	2L-Treated Patients (n = 125)	2L Vinflunine <sup>b</sup> (n = 59)
PFS, median (95% CI), months	7.2 (6.4-8.1)	7.6 (6.4-9.1)	4.0 (3.0-4.8)	3.1 (2.5-4.2)
OS, median (95% CI), months	16.1 (13.7-19.2)	17.7 (14.4-24.2)	9.2 (5.5-11.6)	5.9 (4.1-12.6)
Objective response, n (%) <sup>c</sup>	117 (34)	86 (35)	15 (14%)	3 (6)
Best overall response rate, n (%) <sup>d</sup>				
Complete response	38 (11)	29 (12)	2 (2)	0 (0.0)
Partial response	79 (22)	57 (23)	13 (12)	3 (6)
Stable disease	89 (26)	62 (25)	29 (26)	16 (30)
Progressive disease	104 (30)	76 (31)	45 (41)	26 (48)
Not clearly definable	38 (11)	21 (9)	22 (20)	9 (17)
Missing or unknown	87 (20)	31 (11)	14 (11)	5 (9)
Early disease progression, n (%)				
6 months	115 (26)	78 (28)	54 (43)	28 (47)
12 months	186 (43)	131 (47)	69 (55)	34 (58)

<sup>a</sup> Most common first-line treatment.

<sup>b</sup> Most common second-line treatment.

<sup>c</sup> Defined as the number of patients who achieved a complete or partial response (with percentages based on the total number of patients).



**B** Adjusted multivariate model including prognostic factors suggested by Bellmunt [25], n = 70<sup>a</sup>

Prognostic Factors <sup>b,c</sup>	Hazard Ratio (95% CI)	P Value
<b>Vinflunine vs other therapy</b>	<b>1.15 (0.58-2.25)</b>	<b>0.69</b>
Age at index $\geq$ vs $<$ 68 years	0.45 (0.23-0.88)	0.02
Female vs male	1.90 (0.92-3.86)	0.08
ECOG PS $>$ 0 vs 0	1.38 (0.57-3.38)	0.49
Liver metastasis yes vs no	0.95 (0.32-2.41)	0.92
Hemoglobin $<$ 10 vs $\geq$ 10 g/dL	0.68 (0.18-1.90)	0.51

**Figure 5.** Cox regression analysis comparing overall survival with second-line vinflunine vs other second-line treatments. (A) Overall survival analysis comparing second-line vinflunine-treated vs other treatments. (B) Cox regression analysis using the Bellmunt prognostic model for vinflunine vs other second-line treatments. <sup>a</sup> 70 patients remained after all patients with missing covariates were excluded. <sup>b</sup> The model was stratified by center type. <sup>c</sup> The reference groups for each factor were as follows: other therapy, age  $<$ 68 years, male sex, ECOG = 0, no liver metastasis, hemoglobin  $\geq$ 10 g/dL. ECOG PS: Eastern Cooperative Oncology Group performance status.

## Discussion

In this analysis, baseline characteristics and demographics of patients with advanced UC or mUC in Germany were consistent with expectations ( $>$ 65 years of age, mostly male and current or former smoker) [11, 13, 17]. The 1L treatment regimens were

also consistent with international guideline recommendations, as the majority of patients were treated with 1L cisplatin-based combination treatment (71%) [11, 17].

Furthermore, the remaining patients were preferably treated with carboplatin-based combinations, most commonly carboplatin +

gemcitabine. Although high estimated rates of cisplatin ineligibility ( $\approx 50\%$ ) have been reported [26], it is interesting to note that in our study the combination of gemcitabine + cisplatin was the most common 1L treatment among patients with an ECOG PS of  $\geq 2$  and renal insufficiency (CrCL  $< 60$  mL/min) (76% and 79%). Patients with these characteristics could be considered cisplatin ineligible [18-20] and could be excluded from randomized clinical trials, suggesting different treatment patterns between randomized clinical trials and those in the real-world practice setting. Furthermore, the mOS in patients in this subgroup was worse than that in their healthier counterparts, reflecting the great medical need for these underrepresented patients (ECOG PS of 0 to 1 and  $\geq 2 = 17.8$  and 12.6 months, respectively; CrCl  $\geq$  and  $< 60$  mL/min: 19.2 and 12.8 months respectively; and no liver metastases and liver metastases: 14.9 and 11.0 months, respectively). Indeed, the high percentage of cisplatin-treated patients may be due to the common practice of administering cisplatin-based treatment to those technically ineligible given the superiority of cisplatin-based combination therapy in this setting [27].

In our study, the mPFS and mOS in all patients who received 1L treatment were 7.2 and 16.1 months, respectively, which is comparable with data from randomized clinical trials among patients with locally advanced UC or mUC (eg, mPFS of 8 months and mOS of 13 of 16 months [15, 16]). Less than one-third (29%) of 1L-treated patients went on to receive 2L treatment. The 1L-treated patients who did not receive 2L chemotherapy (71%) may have experienced stable disease that did not require additional lines of therapy, may have experienced progressive disease and refused treatment, may have died before 2L chemotherapy or may have not received 2L chemotherapy for unknown reasons. Patients in our study who received any 2L treatment had an mPFS and mOS of 4 and 9 months, respectively—in line with previously reported randomized data with taxanes and vinflunine: mPFS of 2 to 3 months and mOS of 6 to 7 months [22, 28]. In addition, our real-world results from Germany show the overall 2L mOS ( $\approx 9$  mo) is in line with the  $\approx 8$ -mo mOS demonstrated in a US population-based study previously reported [29].

The most common 2L treatment in our study was single-agent vinflunine (71%). This finding is consistent with current European guideline recommendations to offer vinflunine to patients progressing after platinum-based combination chemotherapy for metastatic disease [11]. In our study, the mOS (95% CI) among patients treated with 2L vinflunine ( $n = 59$ ) was 5.9 months (4.1-12.6),

shorter than that in those treated with any 2L agents (9.2 months; 5.5-11.6;  $n = 125$ ). The mPFS was similar between the 2 groups: 3.1 and 4.0 months, respectively. These findings are consistent with those of contemporary studies that showed that mOS ranged from 5 to 10 months and mPFS from 2 to 6 months in patients with advanced UC treated with vinflunine [22, 30-34]. However, multivariate Cox regression analysis found no significant difference in OS between vinflunine and other 2L treatment regimens. However, results should be interpreted with caution due to small sample sizes. This finding agrees with data from a recent phase 3 trial comparing the checkpoint inhibitor pembrolizumab with the standard 2L chemotherapies vinflunine, docetaxel or paclitaxel. In this trial, the efficacy of standard 2L chemotherapeutic drugs was similar as well in 2L-treated patients [35]. However, results from a phase 3 trial comparing atezolizumab versus chemotherapy in patients with locally advanced or mUC who progressed after platinum-based chemotherapy found that survival with vinflunine was better than hypothesized compared with taxane-based treatment [36].

This study had several strengths and limitations. The results presented here are descriptive, and any comparisons of outcomes should be interpreted with caution because the patients were treated in routine clinical practice and not randomized to treatment arms; thus, unmeasured confounding variables may exist. The practice patterns described here may be applicable to Germany but not generalizable to practice patterns outside of Germany. Differences in treatment patterns may exist between office and academic care settings, but were not differentiable in this analysis. No detailed safety data was available as this study focused on treatment patterns and efficacy outcomes. The sample sizes of the subgroups were small, so limited statistical analyses were conducted. This study described several outcomes, including objective response rate, treatment response, PFS and OS, which is unusual for observational research studies. However, a large number of patients had missing baseline characteristics that may have affected outcome estimates (OS and PFS) within a specific subgroup as well as estimates of best overall response. Data collection relied on eCRF and responses of physicians and their staff, who transferred information from patient medical records; not only could there have been bias in the selection of patient records from which to transcribe the data, but there could have been errors introduced when the eCRFs were completed.

Overall, the results of this and previous studies of advanced UC and mUC show that outcomes are

generally poor, because progression after 1L failure is common and portends a worse prognosis. Effective treatment options in 1L and 2L settings are scarce, and many patients do not receive 2L treatment. These results underscore the large unmet need for new therapeutic options for patients who progress after 1L treatment. Therefore, a better understanding of the real-world patterns of chemotherapy use and its impact on survival is warranted due to the emergence of cancer immunotherapy in the 1L and 2L settings [35, 37-41].

## Supplementary Material

Supplementary figure S1.

<http://www.jcancer.org/v09p1337s1.pdf>

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## Competing Interests

Günter Niegisch has served in a consulting or advisory role with Roche Pharma AG, has received research funding from 4SC and has received travel and accommodations from Pfizer. Shih-Wen Lin and Julie Pavlova are employees of Genentech and Roche and have stock ownership.

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