CURRENT ONCOLOGY
A Canadian Cancer Research Journal

SHORT COMMUNICATION

Second-line systemic therapies for metastatic urothelial carcinoma: a population-based cohort analysis

E.S. Tsang MD,* C. Forbes MD,† K.N. Chi MD,* B.J. Eigl MD,* and S. Parimi MD‡

ABSTRACT

Introduction Patients with urothelial carcinoma (UC) have a poor prognosis after progression on first-line cisplatin-based chemotherapy. Real-world data about second-line cytotoxic therapies are limited. We sought to characterize patients with metastatic UC who receive more than 1 line of systemic therapy and to describe their treatments and outcomes.

Methods Using BC Cancer's pharmacy database, we identified patients with documented metastatic UC who had received more than 1 line of systemic therapy. A retrospective chart review was then performed to collect clinicopathologic, treatment, and outcomes data.

Results The 51 included patients, of whom 42 were men (82%), had a median age of 65 years (range: 38–81 years). Sites of metastasis included lymph nodes (n = 30), bone (n = 7), lung (n = 9), and peritoneum (n = 2). Second-line chemotherapy regimens included gemcitabine–cisplatin [GC (n = 14)], paclitaxel (n = 24), docetaxel (n = 12), and an oral topoisomerase I inhibitor (n = 1). Median time to progression (TTP) and overall survival (OS) were 2.0 and 6.83 months respectively. Compared with patients who received a different agent, patients who had experienced a prior response to first-line GC and who were re-challenged with second-line GC had a better median TTP (11.0 months vs. 6.0 months, p = 0.02) and survived longer (4.0 months vs. 1.0 months, p = 0.02). No differences in OS between non-GC regimens were evident.

Conclusions In patients with metastatic UC, overall outcomes remain poor, but compared with patients receiving other agents, the subgroup of patients re-challenged with second-line GC demonstrated improved TTP. Conventional chemotherapy regimens provide only modest benefits in the second-line setting and have largely been replaced with immunotherapy.

Key Words Bladder cancer, metastatic disease, urothelial carcinoma, second-line chemotherapy, systemic therapy

Curr Oncol. 2019 April;26(2):e260-e265 www.current-oncology.com

INTRODUCTION

Urothelial carcinoma (UC) of the bladder has an age-adjusted incidence of 18.8 per 100,000 population, with 21% of cases diagnosed when muscle invasion is already present[1]. Outside a clinical trial, cisplatin-based chemotherapy is still considered the standard first-line treatment in the metastatic setting, with a median survival of 13–15 months[2–5]. Upon progression, however, no standard second-line chemotherapy regimen has been established. Although phase III trials of second-line systemic therapies have included vinflunine and gemcitabine–paclitaxel, prognosis remains poor[6–8]. Real-world data about the relative efficacy of second-line cytotoxic chemotherapy are limited. We therefore undertook a retrospective patient-based institutional analysis to characterize patients with metastatic UC who received more than 1 line of systemic therapy and to describe their second-line treatments and outcomes.

Correspondence to: Sunil Parimi, BC Cancer–Vancouver Island Centre, 2410 Lee Avenue, Victoria, British Columbia V8R 6V5.
E-mail: sunil.parimi@bccancer.bc.ca ■ **DOI:** https://doi.org/10.3747/co.26.4070

METHODS

Patient Population

BC Cancer is a provincial institution that consists of 6 tertiary cancer centres located across British Columbia. It provides and funds systemic cancer therapy for the province's approximately 4.4 million residents. The BC Cancer pharmacy database was reviewed for the period 1 January 2007 to 12 October 2015 to identify patients with documented metastatic UC who received more than 1 line of systemic therapy, including docetaxel, paclitaxel, pemetrexed, carboplatin–paclitaxel, and gemcitabine–cisplatin (GC). Patients who received only 1 line of systemic therapy were excluded. Only patients with transitional cell histology were included; those with squamous or adenocarcinoma histologies were excluded. A retrospective chart review was then conducted to collect demographic, clinicopathologic, treatment, and outcomes data. This study was approved by the Research Ethics Board at the University of British Columbia.

Outcomes

The objective of the study was to characterize the second-line treatment patterns and outcomes for metastatic UC at BC Cancer. Outcomes included duration of second-line systemic therapy, time to progression (TTP), and overall survival (OS). Time to progression was calculated from the start date of a chemotherapy regimen to the date of progression or the start date of a new line of treatment. If both dates were available, the shorter of the latter two intervals was used in the analysis. Overall survival was calculated from the start date of the second-line chemotherapy regimen in the metastatic setting to the date of death or last documented follow-up. We compared outcomes for patients who received GC and non-GC chemotherapy regimens in the second line, and for patients who received various second-line non-GC chemotherapy regimens.

Statistical Analysis

Descriptive statistics were calculated to characterize our cohort with metastatic UC, and treatment groups were compared using the chi-square test. Durations of systemic therapies were compared using the Mann–Whitney *U*-test or Kruskal–Wallis test. Kaplan–Meier survival analyses were performed to estimate OS and TTP, and OS and TTP for each categorical variable were compared using the log-rank test. All tests were 2-sided, with $p \leq 0.05$ as the cut-off for statistical significance. The IBM SPSS Statistics software application (version 22.0: IBM, Armonk, NY, U.S.A.) was used for all statistical analyses.

RESULTS

We identified 51 patients with metastatic UC who received more than 1 line of systemic therapy. Median age in the cohort was 65 years (range: 38–81 years), and 42 of the patients (82%) were men. Sites of metastasis at diagnosis included lymph nodes ($n = 30$), bone ($n = 7$), lung ($n = 9$), liver ($n = 6$), and peritoneum ($n = 2$). Table I details the clinicopathologic data.

In the first-line metastatic setting, chemotherapy regimens consisted of GC ($n = 42$), MVAC [methotrexate–vinblastine–doxorubicin–cisplatin ($n = 1$)], and other ($n = 8$). The median number of treatment cycles was 4 (range: 1–10 cycles), with reasons for discontinuation including regimen completion ($n = 36$), disease progression ($n = 10$), drug toxicity ($n = 4$), and other ($n = 1$). Second-line chemotherapy regimens included GC ($n = 14$), paclitaxel ($n = 24$), docetaxel ($n = 12$), and a clinical trial of an oral topoisomerase inhibitor ($n = 1$). Median TTP on second-line chemotherapy was 2.0 months [95% confidence interval (CI): 1.18 months to 2.82 months; Figure 1(A)]. Median OS for our cohort was 6.83 months [95% CI: 5.44 months to 8.23 months; Figure 1(B)], with a 2-year survival rate of 8%.

Of the 51 patients receiving second-line chemotherapy, 14 (27%) received GC, and 37 (73%) received a non-GC regimen. Compared with patients who did not receive second-line GC, those who were re-challenged with second-line GC had a prior response to first-line GC [median TTP: 11.0 months (95% CI: 8.74 months to 13.26 months) vs. 6.0 months (95% CI: 4.94 months to 7.06 months), $p = 0.02$]. Of patients who received first-line GC, median TTP with second-line chemotherapy was longer in the GC re-challenge cohort than in the cohort receiving other agents (4.0 months vs. 1.0 months, $p = 0.02$). In all patients, mean duration of second-line chemotherapy was longer in the GC than in the non-GC cohort (3.54 months vs. 2.15 months, $p = 0.006$). Median TTP in the second-line setting was longer with GC than with a non-GC regimen [4.0 months vs. 2.0 months, $p = 0.01$, Figure 1(C)]. Median OS was not significantly different between the GC and non-GC cohorts [9.6 months vs. 5.6 months, $p = 0.26$, Figure 1(D)].

Of the 37 patients who received second-line non-GC chemotherapy, 24 received paclitaxel, 12 received docetaxel, and 1 was enrolled in a clinical trial of an oral topoisomerase I inhibitor (gimatecan). Table II reports the duration of second-line chemotherapy, showing no significant differences between the regimens. There were also no significant differences in median TTP or OS between the non-GC chemotherapy regimens (all $p > 0.05$, Table II).

DISCUSSION

Metastatic UC carries a poor prognosis, particularly once patients have progressed after first-line systemic therapy. In our retrospective study, we examined second-line treatment patterns and outcomes for patients with metastatic UC at BC Cancer. During the study period and in the absence of immunotherapy, options for effective second-line chemotherapy with significant survival benefits were limited. A retrial of cisplatin-based chemotherapy could be considered in select patients[9]. Overall outcomes remained poor with second-line chemotherapy, with an 8% 2-year survival rate and a median OS of 6.83 months; however, GC re-challenge was associated with longer median TTP. The re-challenge subgroup had experienced a prior response to GC (median first-line TTP: 11.0 months) and a longer interval to progression from first-line therapy (median: 9.0 months). There were no differences in outcome between the various second-line non-GC chemotherapies.

TABLE I Baseline clinicopathologic characteristics and first-line chemotherapy regimens in 51 patients with metastatic urothelial carcinoma who received more than 1 line of chemotherapy

Characteristic	Second-line chemotherapy regimen				*p* Value
	Gemcitabine–cisplatin (*n*=14)	Paclitaxel (*n*=24)	Docetaxel (*n*=12)	Clinical trial (*n*=1)	
Sex [*n* (%)]					0.59
Women	2 (14)	6 (25)	1 (8)	0	
Men	12 (86)	18 (75)	12 (92)	1 (100)	
ECOG PS [*n* (%)]					0.29
0	4 (29)	3 (13)	4 (33)	0	
1	6 (43)	11 (46)	4 (33)	1 (100)	
2	3 (21)	1 (4)	0	0	
3	0	0	1 (8)	0	
Unknown	1 (7)	9 (38)	3 (25)	0	
Metastatic burden at CTx initiation [*n* (%)]					0.003
Lymph node	7 (50)	13 (54)	9 (75)	1 (100)	
Bone	0	5 (21)	2 (17)	0	
Lung	3 (21)	4 (17)	2 (17)	0	
Liver	1 (7)	4 (17)	1 (8)	0	
Peritoneum	1 (7)	1 (4)	0	0	
Other	1 (7)	0	0	0	
Hemoglobin (g/L)					
Median	136	122	120	122	
Range	107–160	102–154	98–148		
Hemoglobin category [*n* (%)]					0.78
Low (<100 g/L)	0	0	0	0	
Normal	12 (86)	21 (88)	11 (92)	1 (100)	
Unknown	2 (14)	3 (13)	1 (8)	0	
LDH (U/L)					0.24
Median	187	179	196	251	
Range	80–408	113–591	138–397		
LDH category [*n* (%)]					
Elevated (≥250 U/L)	2 (14)	6 (25)	1 (8)	1 (100)	
Normal	6 (43)	11 (46)	6 (50)	0	
Unknown	6 (43)	7 (29)	5 (42)	0	
First-line CTx for metastatic disease [*n* (%)]					0.10
Gemcitabine–cisplatin	12 (86)	22 (92)	7 (58)	1 (100)	
MVAC	1 (7)	0	0	0	
Other	1 (7)	2 (8)	5 (42)	0	
Time between 1st- and 2nd-line CTx (months)					
Median	12.0	9.5	5.0	8.0	
IQR	10.8–17.5	6.0–12.5	4.0–7.0	0.56	

ECOG PS = Eastern Cooperative Oncology Group performance status; CTx = chemotherapy; LDH = lactate dehydrogenase; MVAC = methotrexate, vinblastine, doxorubicin, cisplatin; IQR = interquartile range.

Previously reported prognostic factors in metastatic UC have included poor Eastern Cooperative Oncology Group performance status, a hemoglobin level less than 100 g/L, the presence of liver metastases, and shorter time from the previous chemotherapy[10,11]. In our cohort, no significant differences were evident between the second-line regimens used, but that observation is likely limited by our small sample size. There appeared to be a trend toward longer time from first-line chemotherapy in patients who received second-line GC, but that trend was not statistically significant. The presence of those factors might help in risk stratification and the choice of subsequent therapies.

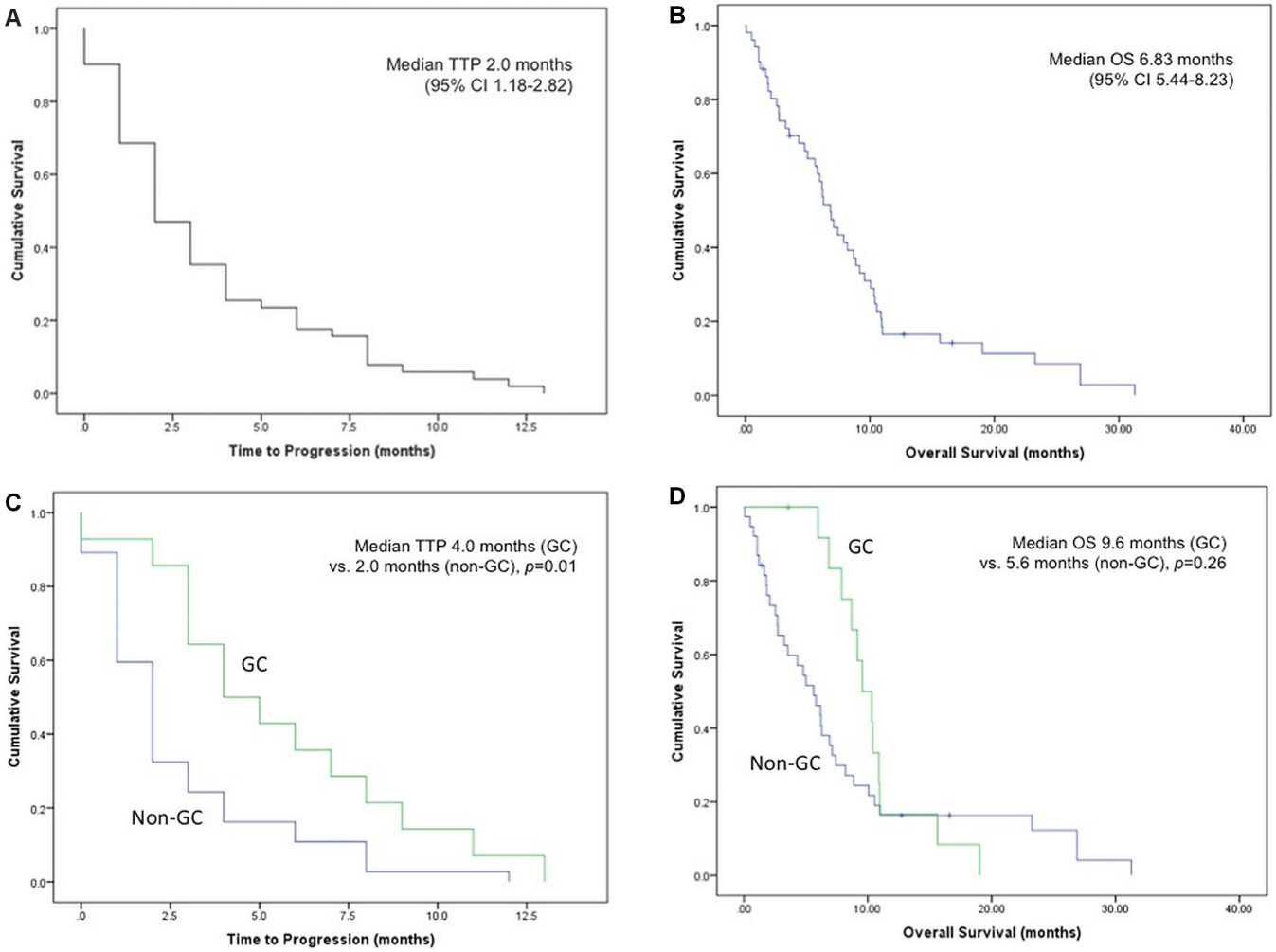

FIGURE 1 (A) Time to progression for patients with metastatic urothelial carcinoma who received second-line chemotherapy. (B) Overall survival for all patients with metastatic urothelial carcinoma who received more than 1 line of systemic therapy. (C) Kaplan–Meier survival curve for time to progression in patients who received second-line gemcitabine–cisplatin (GC) compared with non-GC chemotherapy regimens. (D) Kaplan–Meier survival curve for overall survival in patients who received second-line GC compared with non-GC chemotherapy regimens.

TABLE II Comparisons between patients who received second-line non-gemcitabine–cisplatin chemotherapy (CTx)

Variable	Chemotherapy regimen			*p* Value
	Paclitaxel	Docetaxel	Clinical trial	
Duration of CTx (months)				0.05
Median	2.0	1.0	6	
IQR	1.0–3.8	0–1.8		
Time to progression (months)				0.30
Median	2.0	2.0	6	
IQR	1.0–3.8	1.0–2.0		
Overall survival (months)				0.35
Median	5.3	3.5	8.2	
IQR	2.2–9.8	1.2–6.2		

IQR = interquartile range.

Given the poor outcomes with chemotherapy in metastatic UC, recent studies have also explored the emerging role of novel agents, including immunotherapy. Because of the high mutation burden in metastatic UC, various studies have reported improved outcomes using the new regimens. Table III summarizes recent trials in second-line metastatic UC. Notably, initial clinical trials with immunotherapy agents, including the phase III KEYNOTE-045 trial and a phase II trial of atezolizumab, demonstrated promising response rates[15,17]. More recently, vascular endothelial growth factor antagonists have been studied, with the RANGE trial showing increased progression-free survival with ramucirumab–docetaxel[18].

Limitations of our study include the small sample size, precluding a multivariate regression analysis with prognostic factors and survival outcomes. The second-line GC and non-GC groups showed significant differences (prior response or longer interval to progression), which might reflect an underlying selection bias in

TABLE III Summary of recent studies in the second-line treatment setting for metastatic urothelial carcinoma

Reference (study name)	Design	Pts (*n*)	Regimen	Results
Arranz *et al.,* 2015[12]	Prospective, phase II	71	Cabazitaxel	Study stopped; overall response rate: 4.9%
Quinn *et al.,* 2015[13]	Prospective, phase II	98	Eribulin	Overall response rate: 24% in tubulin-naïve and 28% in tubulin-exposed
Raggi *et al.,* 2016[14]	Meta-analysis	1910	Single-agent vs. doublet CTx	Improved pooled median PFS compared with single-agent (4.05 months vs. 2.69 months), but no difference in OS between groups
Rosenberg *et al.,* 2016[15] (IMvigor210)	Prospective, phase II	310	Atezolizumab	Overall response rate: 15%–27% vs. historical 10% (CTx)
Sonpavde *et al.,* 2016[16]	Retrospective (used trials with patient-level data)	370	Single-agent vs. combination chemotherapy	Improved OS with combination CTx (hazard ratio: 0.60)
Bellmunt *et al.,* 2017[17] (KEYNOTE-045)	Prospective, phase III	542	Pembrolizumab vs. investigator's choice (paclitaxel, docetaxel, or vinflunine)	Median OS: 10.3 months (pembrolizumab) vs. 7.4 months (CTx)
Petrylak *et al.,* 2017[18] (RANGE)	Prospective, phase III	530	Ramucirumab–docetaxel vs. placebo–docetaxel	Increased PFS with ramucirumab–docetaxel (4.07 months vs. 2.76 months)
Sharma *et al.,* 2017[19] (CheckMate 275)	Prospective, phase II	265	Nivolumab	Overall response rate: 16.1%–28.4%

Pts = patients; CTx = chemotherapy; PFS = progression-free survival; OS = overall survival.

the second-line GC population. Patients were generally re-challenged with GC in the second-line setting only if they had a prior response. In addition, information about clinical decision-making and the rationale for choice of agents were not available.

Our retrospective descriptive study serves largely to disseminate provincial findings and treatment practice patterns. It explores our institutional experience of patients with metastatic UC who received more than 1 line of systemic therapy. Survival outcomes remained poor with second-line chemotherapy, although the subgroup of patients who were re-challenged with GC experienced longer survival. Given the poor outcomes with chemotherapy, the level I survival data for pembrolizumab establishes immunotherapy as the new standard of care in the second-line setting for metastatic UC. More recent studies are setting out to elucidate the role for other agents such as ramucirumab in that setting.

CONCLUSIONS

We present our institutional experience of patients with metastatic UC who received more than 1 line of systemic therapy, characterizing their treatment and outcomes. In our relatively small cohort, patients who were re-challenged with GC experienced longer durations of chemotherapy and TTP, but not longer OS. This subgroup had already achieved a response to GC, with longer TTP on first-line treatment. As demonstrated by the poor survival outcomes, conventional chemotherapy regimens provide only modest benefits in the second-line setting. Novel agents, including immunotherapy, have been associated with more promising outcomes.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

*Division of Medical Oncology, BC Cancer–Vancouver Centre, Vancouver, †Department of Urology, University of British Columbia, Vancouver, and ‡Division of Medical Oncology, BC Cancer–Vancouver Island Centre, Victoria, BC.

REFERENCES

1. Nielsen ME, Smith AB, Meyer AM, *et al.* Trends in stage-specific incidence rates for urothelial carcinoma of the bladder in the United States: 1988 to 2006. *Cancer* 2014;120:86–95.
2. von der Maase H, Sengelov L, Roberts JT, *et al.* Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *J Clin Oncol* 2005;23:4602–8.
3. Bellmunt J, Orsola A, Leow JJ, Wiegel T, De Santis M, Horwich A on behalf of the ESMO Guidelines Working Group. Bladder cancer: ESMO practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014;25(suppl 3):iii40–8.
4. Loehrer PJ Sr, Einhorn LH, Elson PJ, *et al.* A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. *J Clin Oncol* 1992;10:1066–73. [Erratum in: *J Clin Oncol* 1993;11:384]
5. von der Maase H, Hansen SW, Roberts JT, *et al.* Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000;18:3068–77.
6. Albers P, Park SI, Niegisch G, *et al.* on behalf of the AUO Bladder Cancer Group. Randomized phase III trial of 2nd line gemcitabine and paclitaxel chemotherapy in patients with

advanced bladder cancer: short-term versus prolonged treatment [German Association of Urological Oncology (AUO) trial AB 20/99]. *Ann Oncol* 2011;22:288–94.
7. Bellmunt J, Theodore C, Demkov T, *et al.* Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. *J Clin Oncol* 2009;27:4454–61.
8. Bellmunt J, Fougeray R, Rosenberg JE, *et al.* Long-term survival results of a randomized phase III trial of vinflunine plus best supportive care versus best supportive care alone in advanced urothelial carcinoma patients after failure of platinum-based chemotherapy. *Ann Oncol* 2013;24:1466–72.
9. Bachner M, De Santis M. Second-line therapy in bladder cancer. *Curr Opin Urol* 2009;19:533–9.
10. Bellmunt J, Choueiri TK, Fougeray R, *et al.* Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. *J Clin Oncol* 2010;28:1850–5.
11. Sonpavde G, Pond GR, Fougeray R, *et al.* Time from prior chemotherapy enhances prognostic risk grouping in the second-line setting of advanced urothelial carcinoma: a retrospective analysis of pooled, prospective phase 2 trials. *Eur Urol* 2013;63:717–23.
12. Arranz JAA, Garcia del Muro X, Perez-Valderrama B, *et al.* JEVTCC: Phase II trial of cabazitaxel (Cbz) in patients (pt) with advanced or metastatic transitional-cell carcinoma (MTCC), who progressed before 12 months after cisplatin-based chemotherapy—a Spanish Oncologic Genitourinary Group (SOGUG) study [abstract 4525]. *J Clin Oncol* 2015;33:. [Available online at: http://ascopubs.org/doi/abs/10.1200/jco.2015.33.15_suppl.4525; cited 6 January 2019]
13. Quinn DI, Ruel N, Twardowski P, *et al.* Eribulin in advanced urothelial cancer (AUC) patients (pts): a California Cancer Consortium trial—NCI/CTEP 7435 [abstract 4504]. *J Clin Oncol* 2015;33:. [Available online at: http://ascopubs.org/doi/abs/10.1200/jco.2015.33.15_suppl.4504; cited 6 January 2019]
14. Raggi D, Miceli R, Sonpavde G, *et al.* Second-line single-agent versus doublet chemotherapy as salvage therapy for metastatic urothelial cancer: a systematic review and meta-analysis. *Ann Oncol* 2016;27:49–61.
15. Rosenberg JE, Hoffman-Censits J, Powles T, *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* 2016;387:1909–20.
16. Sonpavde G, Pond GR, Choueiri TK, *et al.* Single-agent taxane versus taxane-containing combination chemotherapy as salvage therapy for advanced urothelial carcinoma. *Eur Urol* 2016;69:634–41.
17. Bellmunt J, de Wit R, Vaughn DJ, *et al.* on behalf of the KEYNOTE-045 investigators. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med* 2017;376:1015–26.
18. Petrylak DP, de Wit R, Chi KN, *et al.* on behalf of the RANGE study investigators. Ramucirumab plus docetaxel versus placebo plus docetaxel in patients with locally advanced or metastatic urothelial carcinoma after platinum-based therapy (RANGE): a randomised, double-blind, phase 3 trial. *Lancet* 2017;390:2266–77.
19. Sharma P, Retz M, Siefker-Radtke A, *et al.* Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2017;18:312–22.