

# Treatment of relapsed urothelial bladder cancer with vinflunine: real-world evidence by the Hellenic Genitourinary Cancer Group

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Nikolaos Pistamaltzian<sup>a</sup>, Kimon Tzannis<sup>b</sup>, Vassiliki Pissanidou<sup>e</sup>, Stavros Peroukidis<sup>g</sup>, Georgia Milaki<sup>h</sup>, Vasilis Karavasilis<sup>e</sup>, Iraklis Mitsogiannis<sup>c</sup>, Ioannis Varkarakis<sup>c</sup>, Athanasios Papatsoris<sup>c</sup>, Athanasios Dellis<sup>d</sup>, Ioannis Adamakis<sup>d</sup>, Konstantinos Stravodimos<sup>d</sup>, Dimitra Molyva<sup>f</sup>, Ilias Athanasiadis<sup>a</sup>, Nikos Androulakis<sup>h</sup>, Charalambos Andreadis<sup>f</sup>, Charalambos Kalofonos<sup>g</sup>, Dionisios Mitropoulos<sup>d</sup>, Charalambos Deliveliotis<sup>c</sup>, Constantinos Constantinides<sup>d</sup>, Meletios A. Dimopoulos<sup>b</sup> and Aristotelis Bamias<sup>b</sup>

Relapsed urothelial cancer represents an unmet medical need. Vinflunine is a third-generation antimicrotubuline inhibitor and is currently the only approved drug for second-line treatment across European Union. We conducted a retrospective analysis assessing the efficacy and safety of vinflunine in 71 Greek patients with relapsed urothelial cancer who were treated between 2005 and 2014. An overall 84% of our patients received vinflunine as second-line treatment, 77% had a performance status of Eastern Cooperative Oncology Group scale 0 or 1, and 30% had liver metastasis at the time of vinflunine administration. A median of four cycles of vinflunine were administered (range 1–16). The most common reported adverse events were constipation, fatigue, and anemia. Median progression-free survival was 6.2 months (95% confidence interval: 4.4–8.8) and overall survival was 11.9 months (95% confidence interval: 7.4–21). Two patients (3%) achieved a complete remission, seven a partial remission (10%), and 22 (31%) had stable disease according to an intention-to-treat analysis. Hemoglobin level less than 10 g/dl and Eastern Cooperative Oncology Group performance status greater than 1 were independent adverse prognostic factors.

## Introduction

Urothelial bladder cancer (UBC) is the sixth more common type of cancer in the European Union and is the cause of 40 000 cancer-related deaths every year [1]. Most deaths are attributed to muscle-invasive disease, which is curable in about 50% of cases after cystectomy, but cure is exceptional in stage IV disease. Chemotherapy is the mainstay of therapy for patients with advanced or relapsed disease [2]. Cisplatin-containing regimens represent the standard of care for the first-line treatment, with response rates as high as 60%. Unfortunately, the duration of response is short, and the median survival is 12–14 months [2–4]. Optimal therapy of relapses after

Stratification according to the Bellmunt risk model was also associated with progression-free survival and overall survival in our population. Vinflunine appears to be a safe and effective treatment modality for relapsed urothelial cancer. More effective therapies and more accurate prognostic algorithms should be sought. *Anti-Cancer Drugs* 00:000–000 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

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<sup>a</sup>Second Oncology Department, MITERA Hospital, Maroussi, <sup>b</sup>Department of Clinical Therapeutics, Medical School, <sup>c</sup>Second University Urological Clinic, Sismanoglio General Hospital, <sup>d</sup>First University Urological Clinic, Laiko General Hospital, University of Athens, Athens, <sup>e</sup>Oncology University Clinic, General Hospital of Thessaloniki Papageorgiou, <sup>f</sup>Third Oncology Clinic, Theagenio Cancer Hospital of Thessaloniki, Thessaloniki, <sup>g</sup>Oncology University Clinic, Patras University Hospital, Patras and <sup>h</sup>Oncology Unit, Venizeleio General Hospital, Heraklion, Greece

Correspondence to Nikolaos Pistamaltzian, MD, PhD, Mitera Hospital, Maroussi, Greece  
e-mail: nfpist@gmail.com

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first-line treatment remains an unmet medical need. Although several agents and regimes have been studied so far in second line [5–9], results have been generally disappointing. Patients who relapse after cisplatin-containing chemotherapy rapidly progress and die of their disease irrespective of the treatment utilized, with a median overall survival (OS) usually below 10 months. The use of modern targeted therapies has not changed the limited efficacy pattern of the treatment of relapsed disease [10,11]. Understandably, no agents have been approved for this indication until recently.

Vinflunine is a third-generation antimicrotubuline agent of the vinca alkaloid class, with well-established activity against urothelial cancer [12,13]. In a randomized study, a prolongation of OS was shown in eligible patients [14]. On the basis of these results, vinflunine was granted approval across European Union as a second-line treatment, after the failure of platinum-containing combination chemotherapy regimens [15]. To date, vinflunine remains the only approved drug in this setting. Nevertheless, its efficacy outside the context of clinical trials has been reported only by a few investigators following its approval [16–19]. In this retrospective analysis, the efficacy and safety of vinflunine in advanced urothelial cancer among Greek patients were assessed.

## Patients and methods

Patients with advanced or recurrent UBC, treated with vinflunine for disease progression after previous platinum-based chemotherapy, were included in this analysis. Prior chemotherapy could have been used as adjuvant or neoadjuvant treatment provided that it had been completed within the last 6 months preceding the administration of vinflunine. Data from medical files were obtained from seven oncology centers across Greece, representative of all types of institutions (cancer centers, university, NHS, or private hospitals) for this retrospective analysis. Patients had consented for the use of their data for research purposes. Age, sex, time since initial disease presentation, initial treatment modality/ies, the use of adjuvant or neoadjuvant therapy, previous lines of therapy, starting of vinflunine dose, the type and duration of response to vinflunine treatment, and adverse events related to vinflunine administration were assessed. Hemoglobin levels ( $\leq$  or  $>10$  g/dl), liver involvement, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) were also considered as factors for stratification to risk groups, according to Bellmunt *et al.* [20]. Toxicity and tumor responses were evaluated by treating physicians. Adverse events were reported according to National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE; v4.0).

## Data collection and statistical analysis

Data were entered anonymously into a common data sheet to ensure homogeneity of data entry. Checks of the data for consistency, missing values, errors during transmission, and for data out of range were made by two authors (K.T. and A.B.). Regular visits to participating centers were not made, but queries were resolved by communicating with the respective centers.

Medians (range) and means (SD) were used for asymmetrical and normal distributions, respectively, simple tabulations for quality characteristics, and the  $\chi^2$ -test for variable correlations. Survival analysis was carried out using Kaplan–Meier estimators with long-rank tests. Cox

proportional hazard regression was used for univariate and multivariate analysis to obtain hazard ratio and their 95% confidence intervals (95% CIs). Progression-free survival (PFS) and OS were calculated for the time of vinflunine initiation, whereas time to progression (TTP) was calculated from the end of first-line chemotherapy until the initiation of vinflunine. All statistical analyses were performed using STATA/SE 11.2 software (Copyright 1985–2009; StataCorp LP, College Station, Texas, USA).

## Results

### Patient characteristics

Seventy-one patients (65 men and six women) were treated with vinflunine between July 2005 and July 2014. The first three patients had been included in the pivotal randomized trial [14], whereas all remaining patients received vinflunine after its approval in Greece. Baseline patient characteristics are listed in Table 1. Vinflunine was given as second-line treatment in 60 cases (84%), as third line in nine cases (13%), and after adjuvant chemotherapy (first line for advanced disease) in two cases (3%). The combinations of carboplatin/gemcitabine and cisplatin/gemcitabine were the most preferred treatments in previous lines of therapy. An overall 28% of patients had achieved an objective response with previous chemotherapy. Mean TTP after completion of first-line chemotherapy was 3.3 months (range 0–42 months), with 25% of patients having achieved a TTP of more than 6 months. Only 17 patients received subsequent chemotherapy after cessation of vinflunine.

At the time of vinflunine initiation most patients (77%) had a PS of ECOG scale 0 or 1. The most common site of metastasis was pelvic or para-aortal lymph nodes (44%), with 62% of patients having more than one metastatic site, whereas liver metastases were present in 30% of the included patients. The majority of the patients (74%) had one or two Bellmunt risk factors at the beginning of vinflunine administration.

### Vinflunine administration and tolerance

Vinflunine had been administered according to the manufacturer's instructions [15]. Starting dose was  $320 \text{ mg/m}^2$  except for 17 patients, who were started at  $280 \text{ mg/m}^2$ . At the time of analysis six patients were still on treatment with vinflunine. The median number of vinflunine cycles administered was 4 (range: 1–16). Data regarding toxicity were available for 49 patients. The most frequently reported toxicities are shown in Table 2. The most common hematologic toxicity was anemia (44%), whereas the most common grade III/IV hematologic toxicity was neutropenia (16%). Of the non-hematologic adverse events, the most commonly reported were constipation (65%) and fatigue (67%), with incidence of grade III or more in 12 and 16% of the patients, respectively. In addition, there were two

**Table 1** Baseline characteristics of 71 patients treated with vinflunine for relapsed urothelial bladder cancer

Characteristics	n (%)
Age [mean (SD)]	66.8 (8.4)
Total	71 (100)
Sex	
Male	65 (92)
Female	6 (8)
Prior cystectomy	
Yes	43 (61)
No	28 (39)
Prior radiation (pelvic)	
Yes	12 (17)
No	59 (83)
Prior adjuvant/neoadjuvant chemotherapy	
Yes	19 (27)
No	50 (70)
Missing	2 (3)
Prior chemotherapy for advanced disease	
Prior lines	
0	2 (3)
1	60 (84)
2	9 (13)
Prior chemotherapy regimens <sup>a</sup>	
MVAC	5 (7)
DD MVAC	2 (3)
GC	23 (32)
DD GC	3 (4)
CaG	40 (56)
MCAVI	3 (4)
Other	2 (3)
Outcome of previous therapy	
Objective response	
CR	2 (3)
PR	18 (25)
SD	26 (37)
PD	21 (29)
NE/unknown	4 (6)
Time to progression	
Median	3.3
> 6 months	18 (26)
≤ 6 months	51 (74)
ECOG PS	
0	17 (24)
1	38 (53)
2	14 (20)
3	2 (3)
Hb (mg/dl)	
> 10	55 (78)
≤ 10	16 (22)
Metastatic sites <sup>a</sup>	
Local	17 (24)
Lymph nodes	31 (44)
Liver	21 (30)
Lung	30 (42)
Bone	18 (25)
Other	5 (7)
Number of disease sites	
1	27 (38)
2	26 (37)
3	16 (23)
4	1 (1)
5	1
Bellmunt risk factors	
0	13 (18)
1	31 (44)
2	21 (30)
3	6 (8)

<sup>a</sup>Not mutually exclusive.

CaG, carboplatin, gemcitabine; CR, complete remission; DD, dose dense; ECOG PS, Eastern Cooperative Oncology Group performance status; GC, gemcitabine, cisplatin; Hb, hemoglobin; MCAVI, methotrexate, carboplatin, vinblastine; MVAC, methotrexate, vinblastine, doxorubicin, cisplatin; PD, progressive disease; PR, partial remission; SD, stable disease.

**Table 2** Worst toxicities reported for 49 patients treated with vinflunine for relapsed urothelial cancer

Toxicity	Grade [N (%)]				
	0	1	2	3	4
Neutropenia	32 (65)	8 (17)	1 (2)	3 (6)	5 (10)
Thrombocytopenia	42 (86)	5 (10)	1 (2)	1 (2)	0 (0)
Anaemia	27 (56)	10 (20)	10 (20)	2 (4)	0 (0)
Constipation	17 (35)	8 (16)	18 (37)	5 (10)	1 (2)
Diarrhea	46 (94)	1 (2)	2 (4)	0 (0)	0 (0)
Neurotoxicity	29 (59)	6 (12)	14 (29)	0 (0)	0 (0)
Nausea and vomiting	26 (53)	14 (29)	6 (12)	3 (6)	0 (0)
Fatigue	16 (33)	7 (14)	18 (37)	8 (16)	0 (0)
Renal	40 (82)	7 (14)	2 (4)	0 (0)	0 (0)
Cardiac	44 (90)	0 (0)	0 (0)	5 (10)	0 (0)

episodes of neutropenic fever and two major thrombotic events (one deep venous thrombosis and one pulmonary embolism). Treatment was discontinued because of the following toxicities in five cases: PE, ileus, fatigue grade III, repeated episodes of constipation grade II, and a combination of constipation, fatigue, and neurotoxicity, all of grade II. There was no report of toxicity-related death.

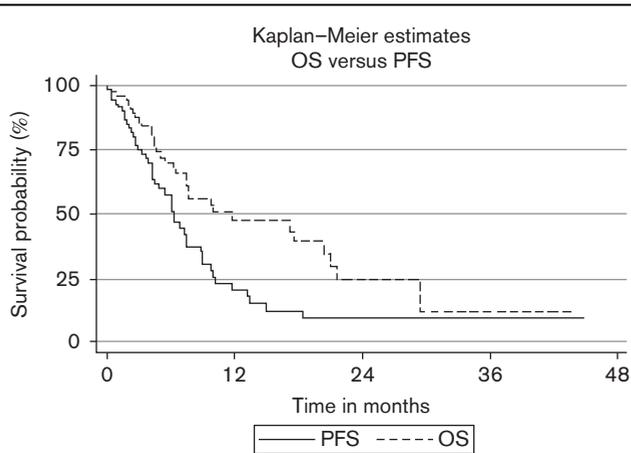
### Efficacy results

Data regarding response to vinflunine were available for 55 patients: two patients (3%) achieved a complete remission, seven a partial remission (12%), 22 had stable disease (41%), and 24 patients (44%) had progressive disease. According to an intention-to-treat analysis (nonevaluable patients were considered as having experienced progression) these percentages were modified as follows: 3, 10, 31, and 54%. Patients who had achieved an objective response during previous chemotherapy had a higher probability of achieving a response with vinflunine (33 vs. 9%,  $P=0.052$ ). This trend was stronger in the intention-to-treat analysis (30 vs. 6%,  $P=0.017$ ).

Four patients were lost to follow-up after initiation of vinflunine and were not included in the survival analysis. Of the 67 evaluable patients 35 were alive and 32 had died at the time of analysis. After a median follow-up time of 11.8 months (95% CI: 6.9–19.4), median PFS was 6.2 months (95% CI: 4.4–8.8) and OS was 11.9 months (95% CI: 7.4–21) (Fig. 1). Neither TTP from the end of the previous therapy nor response to previous therapy was correlated with PFS or OS. Similarly, no statistical association was found with sex, age, history of prior cystectomy, or previous pelvic irradiation, the administration of adjuvant or neoadjuvant chemotherapy, the number of previous lines of chemotherapy or the regimens used, as well as the administration of further therapy after vinflunine.

ECOG PS, hemoglobin level, and liver involvement were found to be associated with OS on the univariate analysis (Table 3). In contrast, metastases in other sites

Fig. 1



Median progression-free survival (PFS) and overall survival (OS) of patients.

had no prognostic value. Hemoglobin level and ECOG PS retained their significance in multivariate analysis (Table 3). Stratification according to Bellmunt risk factors was significantly associated with PFS and OS (Fig. 2).

**Discussion**

There is relatively scarce information regarding the efficacy and tolerability of vinflunine (Table 4, [13,14,16–20]), especially outside the context of a clinical trial. This report contributes real-world data from a Greek cohort who mainly received vinflunine after its approval in Greece and we believe that it adds useful information to recent similar reports from other European countries [16–19]. Our study has all the limitations of a retrospective analysis: no control group, no central evaluation of efficacy (and hence PFS), possible inhomogeneity in dose modifications and toxicity assessment, and

introduction of several biases. However, in contrast to the reported clinical studies, patients with ECOG PS of more than 1 were included in our study (23 vs. 0% in the pivotal trial), prior cisplatin and carboplatin were equally distributed (in contrast to the 70% of cisplatin-pretreated patients in the pivotal trial), and there was no restriction in the number of previous lines of therapy. We therefore believe that we depict a situation close enough to everyday clinical practice.

Median TTP from the end of first-line chemotherapy was around 3 months and only a quarter of patients experienced a TTP over 6 months. In addition, only 13% of our patients received vinflunine in third line and fewer than 30% received chemotherapy following completion of vinflunine. These results are in concert with data from France [17] and highlight two major limitations in our current therapeutic approaches for advanced bladder cancer: lack of sustained disease control by first-line therapy, lack of effective options for relapsed disease, and rapid deterioration of patients with advanced bladder cancer after failure of first-line chemotherapy. Overcoming such limitations could probably lead to considerable improvement in the prognosis of these patients.

Our experience appears similar to that of other European colleagues regarding the satisfactory tolerability of vinflunine in this setting. Only five patients discontinued treatment because of drug-related complications. The incidence of febrile neutropenia is similar to that of the pivotal trial (4 vs. 6%), without any reported death attributed to vinflunine in our study. The response rate was also similar to those of other studies. Nevertheless, the median OS of 11.9 months and the median PFS of 6.2 months are longer than expected from the pivotal trial (6.9 and 3.0 months, respectively) [14] and other similar studies [13,16–20]. More specifically, studies from the

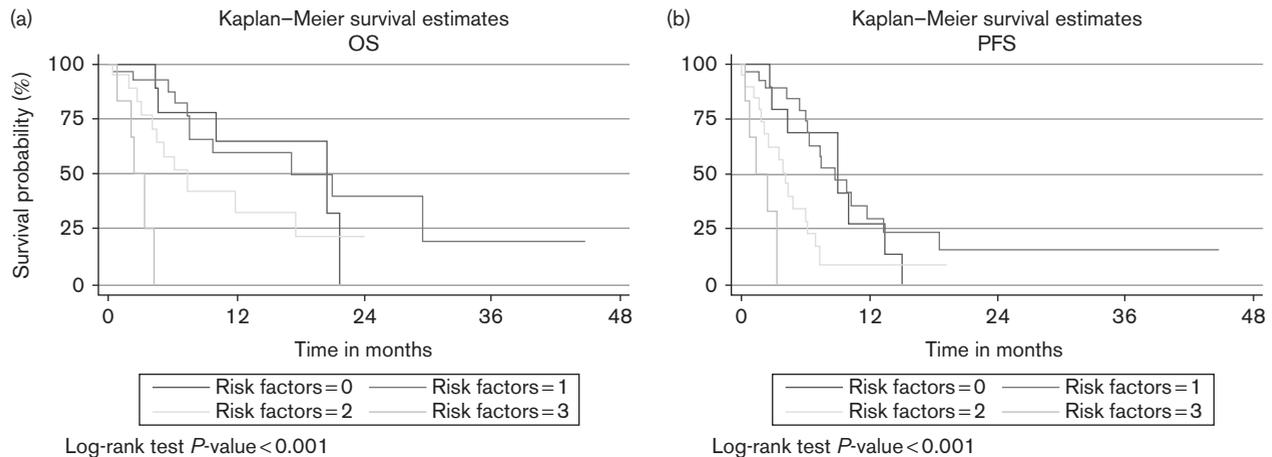
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Table 3 Univariate and multivariate analysis for overall survival

	N (%)	Median	95% CI	Log rank	Multivariate		
					HR	95% CI	P
ECOG PS				0.002			
0+1	52 (78)	17.6	7.7–21.6		3.32	1.41–7.80	0.006
1+2	15 (22)	4.5	1.9–11.9				
Hb					2.99	1.28–6.95	0.011
> 10	52 (78)	17.3	7.7–21.6				
≤ 10	15 (22)	4.2	2.1–17.6				
Number of metastatic sites							
1	25 (37)	21.6	6.2-.NE				
≥ 2	42 (63)	9.8	4.7–17.6				
Liver metastases				0.085			
No	46 (69)	17.6	7.7–21.6				
Yes	21 (31)	6.2	2.7-.NE				
Bellmunt				<0.001			
0	13 (19)	20.5	4.4-.NE				
1	28 (42)	17.3	7.7-.NE				
2	20 (30)	7.4	3.1–17.6				
3	6 (9)	2.4	0.8-.NE				

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, hemoglobin; HR, hazard ratio. .NE, non evaluable

Fig. 2



(a) OS according to prognostic factors. (b) PFS according to prognostic factors. OS, overall survival; PFS, progression-free survival.

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Table 4 Current data regarding vinflunine in relapsed urothelial cancer

References	<i>n</i>	PS [ <i>n</i> -(%)]	Anaemia (%)	Liver M (%)	TTP	RR (%)	PFS	OS
Bellmunt <i>et al.</i> [14]	253	0 (28) 1 (72)	15		< 6 months, 82%	8.6	3.0	6.9
Palacka <i>et al.</i> [19]	16	0 (75) 1 (25)	25	44		13	2.3	5.2
Vaughn <i>et al.</i> [13]	151	0 (100) <del>1 (100)</del>		50	< 6 months, 77%	14.6	2.8	8.2
Culine <i>et al.</i> [20]	51	0 (98) <del>1 (98)</del>		32	< 3 months, 38%	18	3.0	6.6
Castellano <i>et al.</i> [16]	102	0 (31) 1 (61)		17		24	3.9	10
Medioni <i>et al.</i> [17]	134	0 (25) 1 (47%)	24	28	< 6 months, 84%	22	4.2	8.2
Hegele <i>et al.</i> [18]	21					19	4.4	6.2
This study	71	0 (24) 1 (53)	22	30	<6 months, 74%	15	6.2	11.9

M, metastases; OS, overall survival, PFS, progression-free survival, PS, performance status; RR, response rate, TTP, time to progression.

USA, Spain, France, Germany, and Slovakia have reported median OS ranging from 5.2 to 10 months and median PFS from 2.3 to 4.4 months. The reason for this discrepancy is not entirely clear but it could be, at least up to a point, attributed to differences in clinical characteristics with prognostic significance among the populations of these studies. Recently, Bellmunt *et al.* [21] proposed a model with four risk categories based on the presence of three risk factors – namely, ECOG PS greater than 1, liver involvement, and hemoglobin less than 10 g/dl. This model has been validated in patients treated with second-line paclitaxel/gemcitabine [22]. Our study also confirms the prognostic significance of these factors and the validity of this risk stratification model. Patients with all three risk factors do not benefit from vinflunine, as their median OS has been consistently below 3 months in our analysis as well as in those of Bellmunt and Niegisch [21,22]. Differences in the distribution of the prognostic factors included in this model might account for the variable outcomes across different studies. For

example, liver metastases occurred less frequently in our population and this could account for the better survival in our cohort. Nevertheless, according to this model, the expected OS based on the percentage of our patients with 0 and 2 risk factors is 6 months, whereas the median OS for our patients with 0 or 1 risk factor is numerically longer than that reported by Bellmunt *et al.* [21]. A similar discrepancy was described by the German investigators who reported shorter respective median OS compared with those of Bellmunt and colleagues [22]. It is possible that factors not included in the model may be of significance. The importance of the platinum-free interval has been previously proposed [22]: the percentage of our patients with a platinum-free interval less than 6 months is lower than that reported in two previous studies. In addition, reduction of the sum of the long-axis diameter by 10% or more has been suggested as another important prognostic factor [23]. Such data were not available in our analysis. It is therefore plausible that factors not included in the risk model may be of significance and could add to

the accuracy of this prognostic tool. In this context, the identification of molecular factors predicting response (or resistance) to vinflunine, alone or in combination with molecular factors [24], might lead to the selection of patients likely to benefit from this therapy. Indeed, bcl-2 has been implicated in the development of resistance to vinflunine [25]. Other factors, such as b-tubulin III, which have been shown to be of prognostic significance in patients not treated with vinflunine [26], may be relevant for this agent, taking into consideration its mechanism of action.

Our study represents the first experience with vinflunine in Greek patients in daily clinical practice. Vinflunine appears to be a safe and useful agent for good prognosis patients with metastatic UBC who fail platinum-based, first-line chemotherapy. The prognosis of these patients, however, remains poor. Efforts to further refine the prognostic models in this setting and to develop more active therapies should continue.

## Acknowledgements

### Conflicts of interest

None declared.

## References

- 1 GLOBOCAN. 2012. Cancer fact sheets. Available at: [globocan.iarc.fr](http://globocan.iarc.fr). [Accessed 1 March 2015].
- 2 Bamias A, Tiliakos I, Karali M-D, Dimopoulos MA. Systemic chemotherapy in inoperable or metastatic bladder cancer. *Ann Oncol* 2006; **17**:553–561.
- 3 Sternberg CN, de Mulder PHM, Schornagel JH, Theodore C, Fossa SD, van Oosterom A, et al. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumors. *Eur J Cancer* 2006; **42**:50–54.
- 4 Von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced metastatic bladder cancer: results of a large, randomized, multicenter, phase III study. *J Clin Oncol* 2000; **18**:3068–3077.
- 5 Yafi FA, North S, Kassouf W. First and second – line therapy for metastatic urothelial carcinoma of the bladder. *Curr Oncol* 2011; **18**:e25–e34.
- 6 Sweeney CJ, Roth BJ, Kabbinavar FF, Vaughn DJ, Arning M, Curiel RE, et al. Phase II study of pemetrexed for second-line treatment of transitional cell cancer of the urothelium. *J Clin Oncol* 2006; **24**:3451–3457.
- 7 Sternberg CN, Calabro F, Pizzocaro G, Marini L, Schnetzer S, Sella A. Chemotherapy with an every-2-week regimen of gemcitabine and paclitaxel in patients with transitional cell carcinoma who have received prior cisplatin-based therapy. *Cancer* 2001; **92**:2993–2998.
- 8 Kanai K, Kikuchi E, Ohigashi T, Miyajima A, Nakagawa K, Nakashima J, et al. Gemcitabine and paclitaxel chemotherapy for advanced urothelial carcinoma in patients who received prior cisplatin-based chemotherapy. *Int J Clin Oncol* 2008; **13**:510–514.
- 9 Karadimou A, Lianos E, Pectasides D, Dimopoulos MA, Bamias A. Efficacy of methotrexate/vinblastine/doxorubicin cisplatin combination in gemcitabine-pretreated patients with advanced urothelial cancer: a retrospective analysis. *J Urol* 2010; **2**:193–199.
- 10 Grivas PD, Daignault S, Tagawa ST, Nanus DM, Stadler WM, Dreicer R, et al. Double-blind, randomized, phase 2 trial of maintenance sunitinib versus placebo after response to chemotherapy in patients with advanced urothelial carcinoma. *Cancer* 2014; **120**:692–701.
- 11 Pili R, Qin R, Flynn PJ, Picus J, Millward M, Ho WM, et al. A phase II safety and efficacy study of the vascular endothelial growth factor receptor tyrosine kinase inhibitor pazopanib in patients with metastatic urothelial cancer. *Clin Genitourin Cancer* 2013; **11**:477–483.
- 12 Bachner M, De Santis M. Vinflunine in the treatment of bladder cancer. *Ther Clin Risk Manag* 2008; **4**:1243–1253.
- 13 Vaughn DJ, Srinivas S, Stadler WM, Pili R, Petrylak D, Sternberg CN, et al. Vinflunine in platinum-pretreated patients with locally advanced or metastatic urothelial carcinoma: results of a large phase 2 study. *Cancer* 2009; **115**:4110–4117.
- 14 Bellmunt J, Theodore C, Demkov T, Komyakov B, Sengelov L, Daugaard G, 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**:4454–4461.
- 15 ■ ■. *Javlor (vinflunine) 25mg/ml injection [prescribing information]*. Boulogne, France: Pierre Fabre Medicament; 2014.
- 16 Castellano D, Puente J, de Velasco G, Chirivella I, Lopez-Criado P, Mohedano N, et al. Safety and effectiveness of vinflunine in patients with metastatic transitional cell carcinoma of the urothelial tract after failure of one platinum-based systemic therapy in clinical practice. *BMC Cancer* 2014; **14**:779.
- 17 Medioni J, Guillot A, Spaeth D, Di Palma M, Theodore C. Historical data in real life from patients treated by vinflunine for an advanced or metastatic urothelial carcinoma: results of the CURVE study. *Eur J Cancer* 2013; **2** (Suppl):S646–S647.
- 18 Hegele A, Goebell P, Marz U, Neuhaus T. Monotherapy with intravenous vinflunine in patients with advanced or metastatic urothelial cancer after failure of a platinum-containing regimen: a retrospective analysis of German routine data. *Urol Int* 2014; **92**:174–179.
- 19 Palacka P, Mego M, Obertova J, Chovanec M, Sycova-Mila Z, Mardiak J. The first Slovak experience with second-line vinflunine in advanced urothelial carcinomas. *Klin Onkol* 2014; **27**:429–433.
- 20 Culine S, Theodore C, De Santis M, Bui B, Demkow T, Lorenz J, et al. A phase II study of vinflunine in bladder cancer patients progressing after first-line platinum-containing regimen. *Br J Cancer* 2006; **94**:1395–1401.
- 21 Bellmunt J, Choueiri TK, Fougeray R, Schutz FA, Salhi Y, Winquist E, 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**:1850–1855.
- 22 Niegisch G, Fimmers R, Siener R, Park S-I, Albers P. German Association of Urological Oncology Bladder Cancer Group. Prognostic factors in second-line treatment of urothelial cancers with gemcitabine and paclitaxel (German Association of Urological Oncology Trial AB20/99). *Eur Urol* 2011; **60**:1087–1096.
- 23 Harshman LC, Fougeray R, Choueiri TK, Schutz FA, Salhi Y, Rosenberg JE, et al. The impact of prior platinum therapy on survival in patients with metastatic urothelial cancer receiving vinflunine. *Br J Cancer* 2013; **109**:2548–2553.
- 24 Buti S, Ciccarese C, Zanoni D, Santoni M, Modena A, Maines F, et al. Prognostic and predictive factors in patients treated with chemotherapy for advanced urothelial cancer: where do we stand? *Future Oncol* 2015; **11**:107–119.
- 25 Massari F, Santoni M, Ciccarese C, Brunelli M, Conti A, Santini D, et al. Emerging concepts on drug resistance in bladder cancer: Implications for future strategies. *Crit Rev Oncol Hematol* 2015.
- 26 Massari F, Bria E, Ciccarese C, Munari E, Modena A, Zamboni V, et al. Prognostic value of beta-tubulin-3 and c-Myc in muscle invasive urothelial carcinoma of the bladder. *PLoS One* 2015; **10**:e0127908.

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