DOI:10.31557/APJCB.2022.7.3.207

RESEARCH ARTICLE

A Prospective Study of I.V. Vinflunine in the Treatment of Patients with Advanced or Metastatic Urothelial Carcinoma after Failure of a Platinum-containing Regimen and Biomarker Correlates

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Abstract

Background: Vinflunine is the only cytotoxic agent that had been tested as a second line therapy in platinum refractory urothelial carcinoma patients in a phase III clinical trial. The aim of our study was to evaluate the efficacy and safety of vinflunine as a second line after failure of platinum containing regimen. **Patients and methods:** We prospectively included 27 patients of locally advanced or metastatic urothelial cancer who presented to the National Cancer Institute (NCI) of Egypt. The primary objective was to assess the disease control rate. However, the secondary objectives were to assess the progression free survival (PFS) and overall survival (OS). **Results:** A total of 27 patients were treated at the NCI of Egypt. Median age was 64.1 years (42.3-76.8). Male to female ratio was 26:1. Eastern Cooperative Oncology Group performance status was zero in 2 patients, one in 23 patients while the ECOG PS 2 was in only 2 patients. The vast majority of the patients received 2 cycles (12 patients), one patient received 3 cycles, 5 patients received 4 cycles, and 8 patients received 6 cycles while one patient received 8 cycles. A complete response was observed in one patient, partial response in 9 patients and stable disease in 12 patients and progressive disease in 5 patients with a disease control rate of 81.4%. Median progression free survival (PFS) and overall survival for the entire population were 3.45 months and 3.22 months respectively. Median OS for the responders was 7.24 months. Toxicity was mild, and grade 3-4 adverse events were anemia (11.1%), neutropenic fever (4%), fatigue (14.8%) and constipation (7.4%). **Conclusion:** Vinflunine is an efficient and tolerable second line treatment in advanced urothelial carcinoma.

Keywords: Vinflunine- urothelial carcinoma- platinum failure- second line

Asian Pac J Cancer Biol, **7 (3)**, 207-214

Submission Date: 08/11/2021 Acceptance Date: 04/17/2022

Introduction

Urothelial tract carcinoma represents a major health problem worldwide. In fact, it is the sixth most common type of cancer in western countries [1]. Traditionally, advanced urothelial carcinomas have been considered chemo sensitive tumors based on high radiological response rates of 40-70% with cisplatin-based schemes such as gemcitabine-cisplatin (GC), methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) or paclitaxel, cisplatin, and gemcitabine (PCG) [2]. Unfortunately, responses are not maintained over time and median progression free and overall survivals rarely exceed 8 and 15 months, respectively, when metastatic urothelial carcinoma patients are treated in first-line [3]. Patients who fail the initial systemic approach for advanced disease represent a challenge in daily clinical practice.

In the last decade, wide ranges of single agents or combination schemes have been tested for activity in patients who are resistant to previous platinum approaches. The drugs explored in this setting included paclitaxel,

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nab- paclitaxel, irinotecan, ixabepilone, bortezomib, pemetrexed, oxaliplatin, ifosfamide, lapatinib, docetaxel, gemcitabine, topotecan, gefitinib, sorafenib, sunitinib, and pazopanib. The most promising combined chemotherapy schemes among those studied were paclitaxel plus gemcitabine [4], ifosfamide plus gemcitabine [5] or carboplatin plus paclitaxel [6]. Despite the great efforts and resources devoted to all these trials, together with the number of patients involved, in most cases the clinical outcomes were disappointing with objective response rates ranging between 10 and 20%, median progression free survivals of 2–3 months, and median overall survivals of 6–9 months [7]. However other agents have been introduced and are showing promising results [8].

Vinflunine is the newest member of the vinca alkaloids family available to clinical practice [9]. As with other tubulin inhibitors, vinflunine prevents microtubule assembly during mitosis and induces apoptosis [10]. The main differentiating feature that distinguishes vinflunine from others vinca alkaloids is the affinity profile of vinflunine which has a greater effect on mitotic rather than axonal tubulin. Therefore, the result is a significantly reduced rate of neurotoxicity which allows for greater plasma concentrations of the drug [11]. The clinical activity of vinflunine in patients with metastatic transitional cell carcinoma of the urothelial cancer (TCCU) was initially assessed in two non-randomized phase II trials [12]. The earlier phase II trials showed that the activity of vinflunine in 51 and 175 platinum-resistant urothelial carcinoma patients achieved response rates of 18% and 15%, respectively, and median duration of responses were 9.1 and 6 months. Median progression free survival and overall survival were 3.0 and 6.6 months in the first trial, and 2.8 and 8.2 months in the second one. These consistent results led to a pivotal, multinational, and randomized study that compared vinflunine and best supportive care in the second-line treatment of advanced urothelial carcinoma patients who had previously progressed after a platinum-containing regimen [13]. A total of 370 patients were recruited and vinflunine had shown to be superior to the control arm in terms of the considered primary endpoint of the study which was overall survival in the intention to treat population (6.9 months vs. 4.6 months).

However, these results were not found to be statistically significant (HR 0.88; 95% CI, 0.69-1.12: P = 0.287).

All other efficacy parameters favored vinflunine clinically and were statistically significant, such as overall survival in the analysis per protocol population (6.9 vs. 4.3 months: P = 0.04), overall response rate (16% vs 0%: P = 0.0063), disease control rate (41.1% vs. 24.8%: P = 0.0024), and median progression free survival (3.0 months vs. 1.5 months: P = 0.0012). The duration of objective responses was 7.4 months (95% CI 4.5 to 17.0 months) in those patients treated with vinflunine.

Long-term overall survival data from this registration trial after a follow-up of more than 45 months confirmed the increase in total median overall survival with vinflunine compared to best supportive care in the intention to treat population (6.9 months vs. 4.6 months) and the statistically significant increase in the eligible population (6.9 vs. 4.3 months; HR 0.78; 95% CI 0.61- 0.96: P = 0.00227) [14]. As a result of this study, vinflunine was the first drug to receive approval from the European Medicine Agency (EMA) for use in platinum resistant metastatic urothelial carcinoma patients. A study was conducted retrospectively, observational, and a non-interventional study (according to the classification of the Spanish Health Authorities) to assess the impact of treatment with vinflunine in the daily practice in terms of toxicity, response rate, duration of response, progression free survival, and overall survival in an unselected subgroup of patients with metastatic urothelial carcinoma who had progressed after only one previous line of platinum-containing regimen for advanced disease, and furthermore assessed the reproducibility of the clinical trial results in routine clinical practice.

Materials and Methods

Patients

This is a prospective single center open label phase II study conducted at the medical oncology department of the National Cancer Institute of Cairo University. Patients were randomly assigned to receive second line single agent vinflunine chemotherapy drug after documented progression on the first line platinum containing regimen of locally advanced or metastatic carcinoma of the urothelial tract.

Twenty-seven patients were enrolled from August 2013 till October 2017. The study duration was planned to continue until the last patient withdrawn from the treatment. After withdrawal from the study treatment each patient was be followed until death.

Our primary objective was to evaluate the disease control rate as defined by RECIST (version 1.1) assessment criteria [Complete Response (CR) + Partial Response (PR) + Stable Disease (SD) rates] in patients with advanced or metastatic urothelial carcinoma previously treated with a platinum-containing chemotherapy as 1st line treatment. However, the second objective was to evaluate other efficacy parameters as objective response rate (ORR) = CR + PR Rate, time to response, duration of response, progression free survival (PFS) as well as to assess the safety profile of vinflunine (Javlor®) in this category of patients.

We calculated the number of risk factors exhibited by each patient including:

- The time from previous chemotherapy (less than 3 months),

- ECOG PS (more than zero),

- Liver metastasis,

-Hemoglobin level (less than 10gm/dl) and

- Albumin level (< LLN)

We calculated the overall survival for risk factors (0-1), (2) and (3+).

Furthermore, we have applied the Bajorin risk stratification by using the performance status and the visceral metastasis (liver, lung, bone) [15]. We calculated the risk factors based on (zero), (1 risk factor) and (2 risk factors).

Results

We prospectively included 27 patients of locally advanced or metastatic urothelial cancer who presented to the National Cancer Institute (NCI) of Egypt. The baseline characteristics of the study population are listed in Table 1.

The male to female ratio was 26:1. The median age group was 64.1 years ranging from 42.3 to 76.8 years. Out of the 27 patients, 11 patients had bilharzial history. Two patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of zero while the vast majority (23 patients) had ECOG PS 1, and two patients had ECOG PS of 2.

Table 1. Characteristics of the 27 Patients at Presentation

Characteristics	Total, N=27 (%)
Gender:	
· Male	26 (96.3)
· Female	1 (3.7)
Age:	
·Median	64.1 years
·Range	42.3-76.8
Age group:	
·≤50	2 (7.4)
· >50---≤60	8 (29.6)
· >60---≤70	13 (48.2)
· >70	4 (14.8)
ECOG PS when starting vinflunine	
· PS 0	2 (7.4)
· PS 1	23 (85.2)
· PS 2	2 (7.4)
Hemoglobin level (gm/dl):	
· Median	10.8g/dL
· Range	8.1-15
Creatinine level (mg/dl)	
· Median	1.4
· Range	0.7-3.7
Total Bilirubin (mg/dl)	
· Median	0.9
· Range	0.1-6.6
Bilharzial history:	
· Yes	11 (40.7)
· No	16 (59.3)
Prior surgery for cancer:	
· None	13 (48.1)
· Radical cystectomy	7 (25.9)
· Partial cystectomy	1 (3.7)
· TURBT	5 (18.5)
· Radical nephrectomy	1 (3.7)
Prior radiotherapy:	
· Yes (bladder and pelvis)	3 (11.2)
· No	24 (88.8)

Table 2. Tumor Characteristics

Location of the disease	
· Locally advanced	4 (14.9%)
· Metastatic	23 (85.1%)
Visceral metastasis:	
· Liver	8
· Lung	6
· Pleural effusion	1
· Pancreas	1
· Peritoneum	1
Non visceral metastasis	
· Lymph nodes	6

The tumor characteristics at the time of first diagnosis are shown in Table 2. Four patients presented with locally advanced disease and 23 patients had metastases. Liver metastases were present in 8 patients and 6 patients had lung metastases. Distant lymph nodal metastases were present in 6 patients. Finally, pleural effusion was present in one patient.

Tumor characteristics at the time of first diagnosis are shown in Table 3. Twenty-two patients (81.5%) presented with transitional cell carcinoma of the urothelial tract while five patients (18.5%) had squamous cell carcinoma of the urothelial tract.

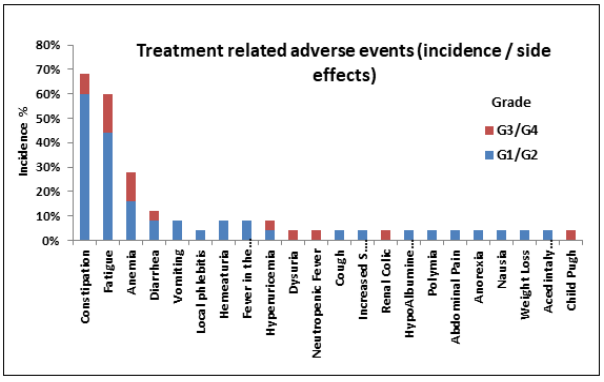

Figure 1. Treatment Related Adverse Events

Table 3. Tumor Description at the Time of First Diagnosis

Tumor description	Number (%)
Primary tumor type:	
· Squamous cell carcinoma of the urothelial tract (Sq cell Ca)	5 (18.5)
· Transitional cell carcinoma of urothelial tract (TCC)	22 (81.5)
Primary tumor location	
· Upper urinary tract/urethra	4 (14.8)
· Bladder	23 (85.2)
T-stage	
· T2	4 (14.8)
· T3	21 (77.8)
· T4	2 (7.4)
N-stage	
· N0	6 (22.2)
· N1	12 (44.4)
· N2	3 (11.1)
· N3	6 (22.2)
M-stage	
· M0	4 (22.2)
· M1	23 (70.4)

Table 4. Prognostic Factors Classification

Prognostic factors	Yes	No
Time from prior chemotherapy (<3 months)	14	13
Performance status (> 0)	25	2
Liver metastases	8	19
Haemoglobin level (<10gm/dl)	4	23
Albumin level (<LLN)	13	14

The primary tumor was located in the bladder in 23 (85.2%) patients. However, in 4 (14.8%) patients the primary tumor was located in the upper urinary tract/ urethra.

Based on the American Joint Committee on Cancer (AJCC, 8th edition) TNM staging system for bladder cancer, 4 patients (14.8%) presented with T2 disease and 21 patients (77.8%) presented with T3 disease, while only 2 patients (7.4%) presented with T4 disease. While 6 patients (22.2%) had N0 disease, 12 patients (44.4%) presented with N1 disease. Three patients (11.1%) had N2 disease and 6 patients had N3 disease. Finally, 4 patients (14.8%) had M0 and 23 patients (85.2%) had M1 disease.

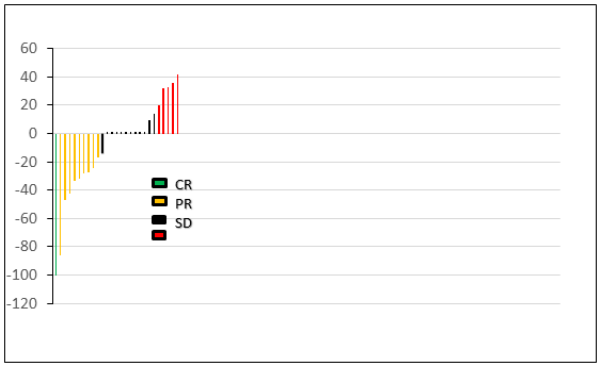

Figure 2. Change in Tumour Size by Waterfall Plot

Twelve patients (44.5%) received 2 cycles. one patient received 3 cycles (3.7%), and 5 patients (18.5%) reached to 4 cycles. Furthermore, 8 patients (29.6%) continued to 6 cycles, and only one patient (3.7%) succeeded to receive a total of 8 cycles.

Patients were then classified as: low risk if had 0-1 risk factors, intermediate risk with 2 risk factors and high risk with 3+ risk factors.

Fourteen patients out of the 27 patients had the time progression from the prior chemotherapy less than 3 months. Twenty-five patients had PS more than zero. Liver metastases were present in 8 patients, 4 patients had haemoglobin level less than 10gm/dl, and 13 patients had an albumin level less than the normal level. This is shown in Table 4.

So, only 5 patients were at low risk. Nine patients were classified with an intermediate risk, and 13 patients were classified with high risk factors (Table 5).

Furthermore, we have applied the Bajorin risk stratification by using the performance status and the visceral metastasis (liver, lung, bone). As shown in Table 6, 25 patients had ECOG PS (0-1) and visceral metastases were present in 13 patients.

Accordingly, 12 patients had zero risk factors and 15 patients had one risk factor while none of the patients had 2 risk factors (Table 7).

Table 5. Risk Factors Classification

Risk factors groups	Number of patients	Percentage (%)
Low risk (0-1)	5	(18.50)
Intermediate risk (2)	9	(33.30)
High risk (3)	13	(48.20)

The figure shows the change in the tumour size from baseline (sum of the largest diameter) in relation to the number of cycles by SPIDER chart.

Figure 3. Change in Tumour Size from Baseline by Spider Plot

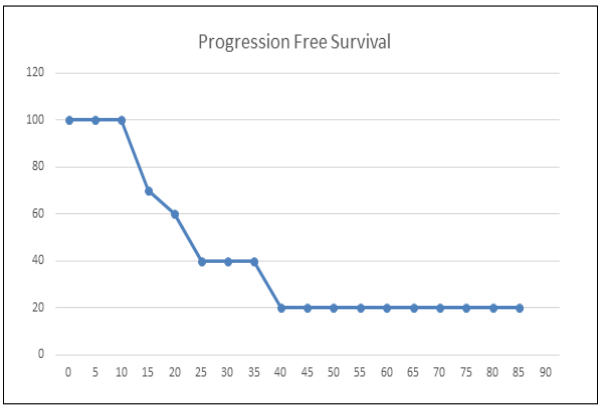

Figure 4. Progression Free Survival Rates of the 10 Patients who have Achieved PR/CR.

Toxicity

The most common adverse event as shown in Table 8 and Figure 1 presented to us during the treatment course was the constipation. Seventeen patients (68%) developed constipation ranging from grade 1 to grade 3 toxicity. The second evident adverse event was the fatigue in 15 patients (60%). That was followed by anemia where 8 patients suffered from grade 1 to grade 3 toxicity. Fatigue, anemia and finally constipation were the most common side effects that developed grade 3 toxicity without any grade 4 toxicity. Four patients (16%) developed grade 3 fatigue while 3 patients (12%) developed grade 3 anemia. However, 2 patients only (8%) developed grade 3 anemia.

Table 6. Bajorin Prognostic Factors

Prognostic factors	Yes	No
Performance status (2 or more)	2	25
Visceral metastasis (liver, lung, bone)	13	14

Three patients (12%) developed diarrhea where 2 of them had grade 2 toxicity and only one patient developed grade 3 diarrhea. Grade 2 vomiting was associated with 1 patient only and the other one was of grade 3. Local phlebitis developed in 2 patients only with grade 2 toxicity.

There were no statistically significant differences in the previously reported adverse event except in constipation with a p value of 0.012.

Disease control rate included patients who achieved a partial response, complete response and stable disease and who maintained this response for duration of at least one month. Evaluation was done every 2 cycles.

The median observation time of the study was 14 weeks (range: 5-92 weeks). The overall response rate was 37% (10/27 patients). Twenty-two out of 27 (81.4%) of enrolled subjects achieved positive disease control (partial response, complete response and stable disease) and maintained this response for a duration of at least one month. Five patients had disease progression (Table 9, and Figure 2).

Response duration was calculated from the time that measurement criteria are met for complete or partial response until the documentation of progression or death or start of new anticancer therapy. As shown in Figure 3, out of the 10 responding patients, response duration was assessed for 8 patients. The other 2 patients were lost to follow up after responding.

The median estimate response duration for patients who received vinflunine was 17.5 weeks with a mean value of 29 weeks (range: 4-86 weeks) [95% Confidence Interval (CI) 10.72 – 47.28 weeks] before disease progression or death.

The Progression free survival (PFS) was calculated from the date of study entry until the date of first progression or the date of death (whatever the reason of death) if no progression was recorded before.

For the 10 patients who have achieved PR/CR on treatment, 22 weeks (ranging from 12 to 90 weeks) was the median duration time before disease progression or death with a mean value of 35.6 [95% Confidence Interval (CI) 17.03 – 54.17 weeks]. Three patients had disease progression, and one of them died and the other 2 were lost to follow up. Two other patients died, 3 patients were alive at the end of the study, and the remaining 2 cases were lost to follow up after final evaluation (Figure 4).

On the other hand, the median PFS for the whole group of patients (22 cases) who have achieved disease control (SD, PR, and CR) was 15 weeks (3.45 months) (range: 7-90 weeks) with a mean value of 23.59 [95% Confidence Interval (CI) 15.52 – 31.66 weeks].

Overall survival was calculated from the date of study entry up to the date of death or last follow up. Mean overall survival time for the total population was 25.1 weeks

Table 7. Bajorin Risk Factors

Bajorin risk factors group	Number of patients	Percentage (%)
Zero risk factors	12	(44.40)
(1) Risk factor	15	(55.60)
(2) Risk factors	0	(0)

Table 8. Adverse Events

AE	N (%)	G1	G2	G3
None	1 (4)			
Constipation	17 (68)	1	14	2
Fatigue	15 (60)	3	8	4
Anemia	8 (32)	1	3	3
Diarrhea	3 (12)		2	1
Vomiting	2 (8)		1	1
Local phlebitis	2 (8)		2	
Hematuria	2 (8)		2	
Fever in absence of neutropenia	2 (8)		1	
Hyperuricemia	1 (4)			
Dysuria	1 (4)			1
Neutropenic fever	1 (4)			1
Cough	1 (4)			
Increased creatinine	1 (4)		1	
Renal colic	1 (4)			1
Hypoalbuminemia	1 (4)		1	

[95% confidence interval (CI) ranging from 16.24 to 33.86 weeks] with a median value of 14 weeks (3.22 months).

For the 10 responding patients the median survival time was 31.5 weeks (7.24 months) with a mean value of 40.1 weeks (9.22 months) [95% confidence interval (CI) ranging from 22.37 to 57.73 weeks]. On the other hand, the median survival time for non-PR/CR patients was 13 weeks with a mean value of 15.3 weeks [95% confidence interval (CI) ranging from 11.5 to 19.1weeks] with a p value of 0.01 between both groups (Figure 5).

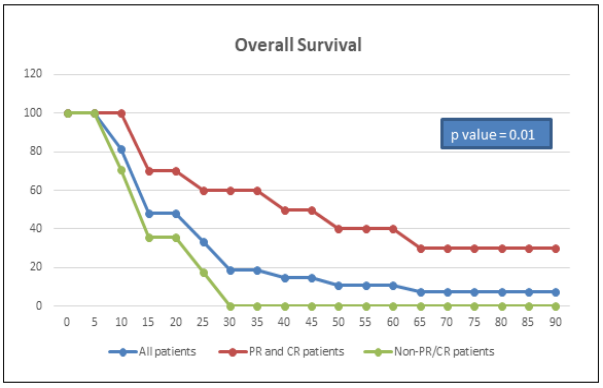

Figure 5. Overall Survival Rates of the 27 Patients Included in the Study.

Discussion

This study aimed at assessing the impact of the drug Vinflunine prospectively in terms of efficacy and safety in the treatment of Egyptian patients with advanced or metastatic urothelial carcinoma progressing after a platinum-containing regimen.

Our current study included 27 patients. Most of them were males with a median age group of 64.1 years ranging from 42.3 to 76.8 years which is concordant to [16] who reported a range from 50 to 75 years. The study showed that vinflunine is an active and safe drug for patients who had previously failed to one prior platinum containing regimen. The safety and efficacy of vinflunine that we obtained were comparable to the results achieved in most of the other published trial.

To support the concept of good tolerability and comparing several adverse events of grade 3 and grade 4 observed in different trials, constipation in our study was 7.4% while the percentage of constipation was 5.9% in Castellano study and 5% in Passalacqua trial and finally 8% in Hussein et al trial. Four per cent of our patients had vomiting grade 3 and 4 while it was 2% in Castellano, 3% in Karin trial and 6% in Pistamaltzian trial. In our study, neutropenia and neutropenic fever occurred in 4% while neutropenia was present in 12.8% in Castellano study and 10.7% in Schinzari trial and 50% in Bellmunt trial. Shah

Table 9. Disease Control Rate

Response after 30 days		N	%
Positive Disease Control	Complete Response	1	3.7
	Partial Response	9	33.3
	Stable Disease	12	44.4
	Disease control	22	81.4
Negative Disease Control	Progressive Disease	5	18.6
Total		27	100

et al, reported neutropenic fever in 27% while Karin et al reported 31% febrile neutropenia. Finally anemia was present in 11% of our patients while Passalacqua trial reported 6% and Bellmunt trial 19%.

As per the efficacy that our data were similar to the results achieved in most of previous trials. In our 27 patients, the CR and PR rates were 3.7%, and 33.3% respectively with a DCR of 81.4% and ORR of 37%. The median PFS for the whole group was 3.45 months. These data are concordant with the above mentioned different responses of the controlled trials. Our median OS for the whole group was 3.22 months. However, in the subgroup analysis the OS for the 10 responder patients (CR/PR) was 7.24 months while the OS for the non CR/PR patients was 2.99 months with a p value 0.01. So this data was expected because of small sample size and substantial heterogeneity.

Recently, the IMvigor 210 study using the immune checkpoint inhibitor, atezolizumab, the median progression free survival was 2.1 months and an overall survival of 9 months [17, 18]. Also, in Key Note 045 study using the drug pembrolizumab, a progression free survival of 2.1 months and an OS of 10.3 months were reported [19]. Furthermore, in Check Mate 275 which used the nivolumab a progression free survival of 2 months and an OS of 7.74 months were reported [20]. Finally, Durvalumab was used showing a PFS of 1.5 months and an OS of 18.2 months [21].

So, in countries with limited resources like Egypt, and in view of the very high cost of the immune checkpoint inhibitors, it is possible to use Vinflunine as second line therapy for patients with advanced/metastatic bladder cancer patients.

In conclusion, our study showed the benefit of vinflunine and its impact on treatment in the daily practice in terms of toxicity, disease control rate, duration of response, progression free survival and overall survival in an unselected subgroup of patients with metastatic urothelial carcinoma who had progressed after only one previous line of platinum-containing regimen for advanced disease.

So, this consolidated the data that JAVLOR has demonstrated to be effective after failure of a platinum-based regimen and the consistency of results with significant and meaningful benefits through the different efficacy parameters.

The value of Ki-67 for molecular staging of urinary bladder cancer needs to be further confirmed in adequately designed prospective trials involving larger number of patients before any definitive conclusions can be made.

Nevertheless, there is an overwhelming need to incorporate new objective translational biomarkers that might help us better select the right treatment for our patients.

Multivariate analysis is the best way to evaluate independent factors that may affect treatment outcome. However due to the relatively small number of patients included in the current study, application of multivariate analysis may not be optimum.

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