



# Response to first-line chemotherapy regimen is associated with efficacy of immune checkpoint blockade therapies in patients with metastatic urothelial carcinoma

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## Abstract

**Background** Atezolizumab (ATZ) has demonstrated antitumor activity in previous studies in patients with metastatic platinum-resistant urothelial carcinoma. However, the response rate of ATZ was modest. Therefore, finding biologic or clinical biomarkers that could help to select patients who respond to the immune checkpoint blockade remains important.

**Patients and methods** In this study, we present the retrospective analysis of 105 patients with urothelial cancer treated with ATZ after progression on first-line chemotherapy. Data of patients were obtained from patient files and hospital records. The association between response to first-line chemotherapy and ATZ was using Fisher's exact test. Median follow-up was calculated using the reverse Kaplan–Meier method. OS was estimated by using the Kaplan–Meier method.

**Results** The median follow-up time was 23.5 months. Forty (74.1%) of patients who experienced clinical benefit after first-line chemotherapy also had clinical benefit after atezolizumab, while only 14 (25.9%) of patients with initial PD after first-line chemotherapy subsequently experienced clinical benefit with ATZ ( $p=0.001$ ). The median OS on ATZ of 14.8 and 3.4 months for patients with clinical benefit and progressive disease in response to first-line chemotherapy, respectively ( $p=0.001$ ). Three of the adverse prognostic factors according to the Bellmunt criteria were independent factors of short survival: liver metastases {Hazard ratio [HR] = 1.9;  $p=0.04$ }, ECOG PS  $\geq 1$  (HR = 2.7;  $p=0.001$ ), and Hemoglobin level below 10 mg/dl (HR = 2.8;  $p<0.001$ ). In addition, patients with clinical benefit from first-line chemotherapy (HR = 0.39;  $p<0.001$ ) maintained a significant association with OS in multivariate analysis.

**Conclusions** Our study demonstrated that clinical benefit from first-line chemotherapy was independent prognostic factors on OS in patients' use of ATZ as second-line treatment in metastatic bladder cancer. Furthermore, these findings are important for stratification factors for future immunotherapy study design in patients with bladder cancer who have progressed after first-line chemotherapy.

**Keywords** Atezolizumab · Urothelial carcinoma · Bladder cancer · Chemotherapy · Immunotherapy · Outcomes

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## Introduction

Urothelial carcinoma, which is the ninth most common tumor worldwide, is an aggressive malignancy with a 5-year survival rate of about 5% in the metastatic setting [1, 2]. The standard first-line treatment in the metastatic urothelial carcinoma setting is cisplatin-based chemotherapy. Cisplatin-based chemotherapy-related objective response rates (ORR), disease control rates (DCR) and median overall survival (OS) times range between 40 and 50%, 75–80%, and 14–15.2 months, respectively [3]. Patients who relapse following cisplatin-based chemotherapy have a poor prognosis with median overall survival times ranging from 5 to 7 months [4].

In recent years, effective antitumor activity has been reported in association with the use of several immune checkpoint inhibitors targeting the programmed cell death protein 1 (PD-1) receptor and its ligand (PD-L1) during the course of first-line therapy or second-line therapy in metastatic urothelial carcinoma patients [5]. The antitumor activity of atezolizumab, one of these immune checkpoint inhibitors, has been demonstrated to have manageable safety in patients with locally advanced or metastatic platinum-resistant urothelial carcinoma [6–9]. Nevertheless, the reported ORRs associated with the use of atezolizumab as the second-line therapy in locally advanced and metastatic setting urothelial carcinoma patients range between 15 and 28.7% [6–9]. Therefore, it is important to identify the factors associated with acceptable efficacy levels of immune checkpoint inhibitors.

In this context, according to the Bellmunt criteria, three risk factors have been determined to predict overall survival (OS) in patients with platinum-refractory disease during second-line treatment. These risk factors are; Eastern Cooperative Oncology Group (ECOG) Performance Status, hemoglobin levels and liver metastases [10]. However, it is unclear whether these factors can be used to predict the efficacy of checkpoint inhibitors in patients with metastatic platinum-resistant urothelial carcinoma. There is still not any generally accepted biomarker indicated for use in patients with metastatic platinum-resistant urothelial carcinoma to predict the efficacy of checkpoint inhibitors. Thus, it is very important to find optimal predictive biomarkers in patients with advanced urothelial carcinoma that receive checkpoint inhibitors including atezolizumab.

There are studies in the literature in which cross-resistance was demonstrated between the chemotherapy regimens received as the first-line and the second-line therapy in metastatic urothelial carcinoma patients. However, given the fact that chemotherapy agents may also affect the immune checkpoint blockade responses in addition to their capacity to directly kill tumor cells, there are not

enough studies conducted on the cross-resistance between the immune checkpoint inhibitors and chemotherapy regimens [11, 12]. Accordingly, it may be possible to improve cytotoxic chemotherapy on the basis of the antitumor immune response.

In view of the foregoing, in this study, patients' responses to the first-line treatment were assessed in the context of immunotherapy checkpoint blockade in patients with metastatic urothelial carcinoma. Accordingly, patients' responses to the first-line treatment were assessed in terms of use as a clinical biomarker to predict the objective response rates and overall survival times in metastatic urothelial carcinoma patients receiving atezolizumab as the second-line treatment.

## Material and method

We evaluated patients who received cisplatin- or carboplatin-containing combination chemotherapy administered in the first-line metastatic setting, and the number of chemotherapy cycles. The research data of 140 metastatic urothelial carcinoma patients were collected from the hospital records and patient files, and were then analyzed retrospectively. Of these patients, 126 were determined to have received at least one cycle of atezolizumab treatment. The data of 21 patients were not available. Consequently, data of 105 patients that received at least one cycle of atezolizumab treatment as the second-line treatment following the disease progression despite first-line platinum base chemotherapy treatment were analyzed within the scope of the study.

In this context, responses to the first-line treatment and to atezolizumab as the second-line treatment, were retrospectively assessed on the basis of the relevant computed tomography data recorded every 12 weeks, according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Responses to the treatments were determined by the data collector on the basis of the relevant radiographic and clinical data. The respective analysis did not include a central evaluation carried out by a blinded radiologist according to RECIST version 1.1 criteria. Clinical benefit rates (CBR) were classified under three categories according to best responses exhibited by the patients, which are; cases with complete response to treatment, cases with partial response to treatment and cases with no response to treatment (stable disease). The relation between response to the first-line treatment and to atezolizumab was assessed using Fisher's exact test. Median follow-up times were calculated using the reverse Kaplan–Meier method. Overall Survival (OS) times were estimated using the Kaplan–Meier method. OS time was defined as the time elapsed from the administration of the first dose of atezolizumab till death for any reason. OS times were censored as of the date of last information and

were thus estimated using the Kaplan–Meier method. Exact 95% confidence intervals (CI) were used in the statistical analyses.

Univariate analysis was used to identify the clinical factors and laboratory parameters with a significant effect on OS. The variables that were found to have a statistical relationship with OS were analyzed within the scope of multivariate analysis ( $p < 0.1$ ). Subsequently, the variables in respect of which the associated probability ( $p$ ) values were found to be less than 0.05 were included in the final model. All statistical analyses were performed using the SPSS Statistics 23.0 (Statistical Package for Social Sciences version 23.0, IBM Corporation, USA) software package. The study was approved by the local ethics committee with approval no 2019–291.

## Results

Of the 105 patients that were determined to have met the inclusion criteria, 90 (85.7%) were male and 15 (14.3%) were female. The median age of the patients was 65 years (min.: 37 and max.: 86). The median follow-up time was 23.5 months. Median number of cycles of platinum-based first-line chemotherapy was 4 (2–8). The median OS for four cycles or less of platinum-based chemotherapy and > 4 cycles of platinum-based chemotherapy was 7.8 months and 11.7 months, respectively (log-rank  $p=0.1$ ). There was no significant difference between 4 cycles or less of platinum-based chemotherapy and > 4 cycles of platinum-based chemotherapy. It was determined that 5 (4.8%) patients exhibited complete response (CR) to the first-line treatment, that 38 (36.2%) patients exhibited partial response (PR) to the first-line treatment, that 16 (15.2%) patients had stable disease (SD) following the first-line treatment, and that 46 (43.8%) patients had progressive disease (PD) following the first-line treatment.

Additionally, it was determined that 9 (8.6%) patients exhibited CR to the atezolizumab treatment, that 22 (21%) patients exhibited PR to the atezolizumab treatment, that 23 (21.9%) patients had stable disease (SD) following the atezolizumab treatment, and that 51 (48.5%) patients had progressive disease (PD) following the atezolizumab treatment. Of the patients that received first-line treatment, 87 (83%) patients received second-line treatment in the form of atezolizumab in 3 months time or even before then as a result of disease progression following the first-line treatment. Forty-four percent (44%) of the patients received carboplatin-based chemotherapy. Patients' characteristics are shown in Table 1. Forty (74.1%) patients who were clinically benefited from the first-line treatment were determined to have also benefited from the atezolizumab treatment, whereas only 14 (25.9%) patients with disease progression

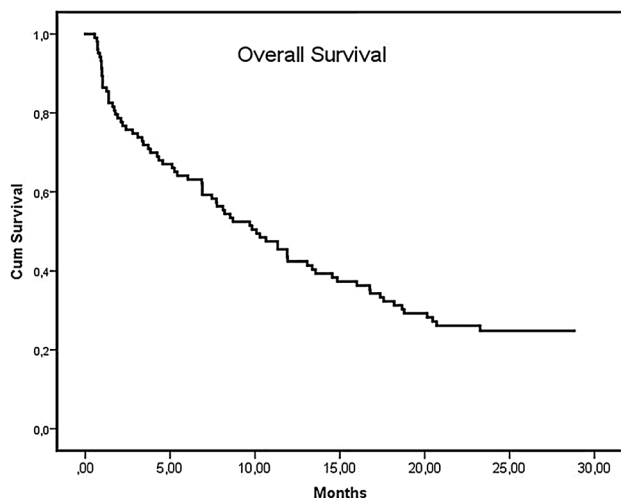
**Table 1** Patients' characteristics

Patient characteristics	<i>n</i>	%
Median age (years) 65 (min.:37; max.: 86)		
Gender (male)	90	85.7
Site of primary tumor		
Bladder	92	87.6
Upper tract	13	12.4
ECOG-PS		
0	27	25.7
1	74	70.5
2	4	3.8
Baseline creatinine clearance <60 ml/min	38	36.2
Baseline hemoglobin concentration < 10 g/dl	30	28.6
Smoking status		
Current smoker	27	25.7
Ex-smoker	53	50.5
Never smoker	25	23.8
Metastatic site at baseline		
Visceral	84	80
Liver	16	15.2
Lymph node only	15	14.3
Number of bellmunt risk factors		
0	19	18
1	55	52.4
2	26	24.8
3	5	4.8
Metastatic at the time of diagnosis	45	42.9
Neoadjuvant chemotherapy	21	20
Pelvic radiotherapy	33	31.4
Cystectomy	43	41
Previous chemotherapy		
Cisplatin-based	59	56
Carboplatin-based	46	44
Median Number of cycles of platinum-based first-line chemotherapy	4	2–6
Best response to first-line treatment		
Complete response (CR)	5	4.8
Partial response (PR)	38	36.2
Stable disease (SD)	16	15.2
Progressive disease (PD)	46	43.8
Time relapsed since the last chemotherapy		
3 months ≥	18	17
3 months<	87	83

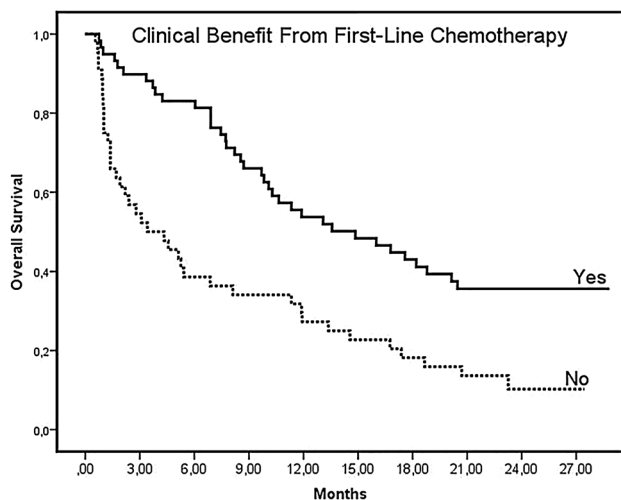
*Min.* minimum; *Max.* maximum; *ECOG-PS* eastern cooperative oncology group-performance status

after first-line treatment were determined to have also benefited from the ensuing atezolizumab treatment (Fisher's exact test,  $p=0.001$ ).

At the time of the analysis, the median OS of the patients treated with atezolizumab was determined to be 10 months



**Fig. 1** Kaplan–Meier curves for overall survival



**Fig. 2** Kaplan–Meier curves association of clinically benefited from the first-line treatment and overall survival

(95% CI 7–13.1 months) (Fig. 1). OS times of the patients calculated by taking the start of the atezolizumab treatment as the baseline were significantly different than the OS times of the patients calculated by taking the time of the best response given to the first-line treatment as the baseline. Patients who were clinically benefited from first-line treatment had higher OS times. The median OS calculated by taking the start of the atezolizumab treatment as the baseline was determined as 14.8 months in case of patients who were clinically benefited from the first-line treatment and as 3.4 months in case of patients who had a disease progression following the first-line treatment (log-rank  $p = 0.001$ ) (Fig. 2). Univariate analysis revealed that parameters such as liver metastases, baseline creatinine clearance

(GFR-glomerular filtration rate) less than 60 ml/min, Eastern Cooperative Oncology Group (ECOG) performance status  $\geq 1$ , and hemoglobin levels below 10 mg/dl were all significantly associated with OS in case of patients who were clinically benefited from the first-line treatment. The distribution of the OS times by all clinical subgroups as of the start of the atezolizumab treatment are shown in Table 2. According to the Bellmunt criteria, three of the adverse prognostic factors were determined to be independent factors of short-term survival, which are liver metastases (HR = 1.9; 95% CI 1.0–3.7;  $p = 0.04$ ), ECOG PS  $\geq 1$  (HR = 2.7; 95% CI 1.5–4.9;  $p = 0.001$ ), and Hemoglobin levels below 10 mg/dl (HR = 2.8; 95% CI 1.7–4.5;  $p < 0.001$ ). Additionally, the multivariate analysis also revealed a significant relationship between the OS of the patients and the clinical benefit they derived from the first-line treatment (HR = 0.39; 95% CI 0.24–0.65;  $p < 0.001$ ) (Table 3).

Thirty-four (32.4%) patients received third-line treatment. Median OS for patients who received third-line treatment and patient did not receive third-line treatment was 12.3 and 7.1 months, respectively (log-rank  $p = 0.1$ ). There was no statistically significant difference between the two groups.

## Discussion

The findings of this study indicated a significant relationship between the clinical benefit derived from the first-line treatment in patients with metastatic urothelial carcinoma and the clinical benefit derived from the atezolizumab treatment administered to these patients as the second-line treatment. Additionally, it was also determined that the patients who were clinically benefited from the first-line treatment had significantly longer overall survival times calculated by taking the start of the atezolizumab treatment as the baseline. These findings are very important in that they can be utilized as stratification factors in immunotherapy studies to be conducted on bladder cancer patients with disease progression following first-line treatment.

In the Javelin bladder 100 trial, a study of avelumab in patients with locally advanced or metastatic urothelial cancer, it was demonstrated that the patients who had non-progressive advanced urothelial carcinoma following the first-line platinum-based chemotherapy had significantly longer OS times following the administration of avelumab therapy as the maintenance therapy not later than 10 weeks after the completion of the first-line treatment, as compared to the patients that were provided the best supportive care [13]. In parallel to the results of the said trial, administration of avelumab therapy as the maintenance therapy has been accepted as the standard treatment protocol for patients who were clinically benefited from the platinum-based chemotherapy. The Javelin bladder 100 trial also revealed that the patients

**Table 2** Univariate analysis of clinical subgroups on overall survival

Patient sub-groups	OS (months)	95% CI	<i>p</i>
All patients	10	7–13.1	N/A
Best response to first-line treatment			
CR + PR + SD	14.8	8.3–21.4	0.001
PD	3.4	0.5–6.4	
Number of cycles of platinum-based first-line chemotherapy			
4 cycle ≤ 7.8	0.1		
4 cycle > 11.7			
Age (years)			
≤ 65	8.7	4.2–13.1	0.7
> 65	10	5.9–14.2	
Gender			
Male	9.8	6.9–12.7	0.5
Female	11.9	4.2–19.6	
Smoking status			
Yes	10.2	6.9–13.5	0.9
No	7.72	1.9–13.6	
Location of the tumor			
Upper tract	5.1	2.7–7.4	0.14
Bladder	10.3	6.9–13.6	
ECOG-PS			
0	18.4	14.5–22.3	0.002
1 ≥	8.1	4.2–12	
Baseline creatinine clearance			
< 60 ml/min	4.4	2.4–6.3	0.008
≥ 60 ml/min	14.5	8.3–20.8	
Baseline hemoglobin concentration			
< 10 g/dl	3.5	1.5–6.1	0.001
≥ 10 g/dl	13.4	8.5–18.2	
Metastatic at the time of diagnosis			
Yes	8.4	5.8–11.9	0.3
No	10.8	5.27–15.2	
Lymph node only metastasis			
Yes	14.5	3–26	0.2
No	8.5	5.6–11.4	
Visceral metastasis			
Yes	8.7	5.1–12.3	0.7
No	11.8	6.8–16.9	
Liver metastasis			
Yes	1.4	0.7–2.7	0.001
No	11.4	7.8–14.9	
Number of bellmunt risk factors			
0	20.2	16–24.3	0.001
1	14.2	11.4–16.9	
2	6	3.6–8.5	
3	1.2	0.6–1.9	
Cystectomy			
Yes	10.6	4.6–17	0.3
No	9.7	7.9–12.1	

**Table 2** (continued)

Patient sub-groups	OS (months)	95% CI	<i>p</i>
Neoadjuvant chemotherapy			
Yes	9.8	3–16.7	0.5
No	9.7	6.4–13	
Radiotherapy (palliative/curative)			
Yes	13.4	4–22.8	0.16
No	8.2	5.8–10.6	
Third line or treatment	0.1		
Yes	12.3	4.3–18.8	
No	7.1	2.2–13.8	
Time relapsed since the last chemotherapy			
3 months >	10.6	4.8–20.1	0.35
3 months ≤	9.7	5.8–13.6	
Neutrophil to lymphocyte ratio			
≤ 3	12.08	7.3–18.8	0.05
> 3	7.90	4.6–13.1	

OS overall survival; CI confidence interval; *p* probability; CR complete response; PR partial response; SD stable disease; PD progressive disease; ECOG-PS eastern cooperative oncology group-performance status

with advanced urothelial cancer were clinically benefited from the avelumab therapy, irrespective of whether they received cisplatin or carboplatin as the first-line treatment.

In comparison, in this study, from among the patients that received first-line treatment, 87 (83%) patients received second-line treatment in the form of atezolizumab in 3 months

**Table 3** Multivariate analysis of clinical subgroups on overall survival

Patient sub-groups	HR	95% CI	<i>p</i>
ECOG-PS			
≥ 1	2.7	1.5–4.9	0.001
Clinical benefit from the first-line treatment			
Yes	0.39	0.24–0.65	< 0.001
Baseline hemoglobin concentration			
< 10 gr/dl	2.680	1.558–4.608	< 0.001
Liver metastasis			
Yes	1.9	1.0–3.7	0.04

HR hazard ratio; CI confidence interval; *p* probability; ECOG-PS eastern cooperative oncology group-performance status

time or even before then as a result of disease progression following the first-line treatment, and forty-four percent (44%) of the patients received carboplatin-based chemotherapy. Similar to the findings reported in the Javelin bladder 100 trial, in this study as well, no significant differences

were found between the OS and the type of the chemotherapy administered and the period elapsed between the completion of the chemotherapy as the first-line treatment and the initiation of atezolizumab therapy as the second-line treatment.

CBRs of the patients that received cisplatin-based chemotherapy were calculated between 75 and 80%, nevertheless, nearly 50% of the patients who had metastatic urothelial carcinoma were not eligible to receive cisplatin-based chemotherapy [3, 4]. ORRs of the patients that were not eligible to receive cisplatin-based chemotherapy were around 40%, and lower than the ORRs of the patients that were eligible to receive cisplatin-based chemotherapy [14]. Therefore, many patients who have metastatic urothelial cancer do not actually meet the required eligibility criteria to receive avelumab therapy as the maintenance treatment.

In comparison, in this study, CBRs of the patients with metastatic urothelial cancer that received the first-line treatment was calculated as 56.2%. Forty (74.1%) patients, who were determined to have clinically benefited from the first-line treatment, were found to have clinically benefited from the atezolizumab treatment as well. On the other hand, only fourteen (25.9%) patients with a disease progression following the first-line treatment were found to have clinically benefited from the atezolizumab treatment. Therefore, in this study, unlike the Javelin bladder 100 trial, a group of stage IV bladder cancer patients, who were determined not to have clinically benefited from chemotherapy as the first-line treatment, were found to have benefited from the immune checkpoint inhibitors blockade treatment as the second-line treatment.

In the INDUCOMAIN study, it was demonstrated that the stand-alone use of immune checkpoint inhibitors prior to induction chemotherapy is not an adequate strategy, since it was found that the use of said strategy led to more frequent early disease progression [15]. In comparison, in this study, as was the case in the Javelin bladder 100 trial, the use of chemotherapy immune checkpoint inhibitors was demonstrated to be a good treatment option for metastatic urothelial carcinoma following the administration of induction chemotherapy [13]. Additionally, initial chemotherapy could potentially induce immunogenic cell death or depletion of suppressive immune cell populations such as myeloid-derived suppressor cells, thereby enhancing the effect of subsequently administered checkpoint inhibitors [16].

There were some limitations to this study. First, it was carried out as a retrospective study. Thus, responses to the treatments had to be determined by the data collector on the basis of the relevant radiographic and clinical data, and the respective analyses did not include a central evaluation carried out by a blinded radiologist according to RECIST criteria. Second, there were some potential confounder variables.

## Conclusion

It was concluded based on the findings of this study that the clinical benefit derived from the first-line treatment is an independent prognostic factor on OS in metastatic bladder cancer patients that received atezolizumab as the second-line treatment. Additionally, a group of stage IV bladder cancer patients, who were determined not to have clinically benefited from chemotherapy as the first-line treatment, were found to have benefited from the immune checkpoint inhibitors blockade treatment as the second-line treatment. Consequentially, the findings of this study can be utilized to develop the necessary stratification factors in immunotherapy studies to be conducted on bladder cancer patients with disease progression following the first-line treatment.

## Declarations

**Conflict of interest** There is no conflict of interest in connection with the publication of this manuscript. As the corresponding author, I declare on my own behalf that this study constitutes an original research, that is, it has not been published previously in any form and it is not under consideration for publication elsewhere, either in whole or in part. All the authors listed have approved the enclosed manuscript for publication. All authors have contributed to the collection of the research data, analyses of these data, compilation and presentation of the respective research findings in the form of an article.

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