Objective Response Rate is a Surrogate Marker for Long-Term Overall Survival in Metastatic Urothelial Carcinoma Patients Treated With Immune Checkpoint Inhibitors

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Abstract

In this study, we evaluated RECIST criteria-based objective response rate (ORR) as potential surrogate endpoints for overall survival (OS) in patients who were treated with immune checkpoint inhibitors (ICIs) and with long-term follow-up in metastatic urothelial carcinoma.

This 5-year analysis of real-world data indicated a significant correlation between ORR, especially CR, and OS in patients who received ICIs in metastatic urothelial cancer. Therefore, identifying a potential surrogate marker for survival in patients treated with ICT would represent an important advance in the early identification of patients' response or resistance to ICT.

Background: This study aimed to evaluate the utility of RECIST criteria-based objective response rate (ORR) as a potential surrogate endpoint for long-term overall survival (OS) in patients with metastatic urothelial carcinoma who were treated with immune checkpoint inhibitors (ICIs). **Methods:** The primary endpoint was overall ORR and OS, duration of treatment (DoR) with ICIs. ORR was analyzed using Fisher's exact test. Median follow-up and OS were estimated by using the Kaplan–Meier method. **Results:** The median follow-up was 58 (1.15-71) months. Progression developed in 94 (47%) patients during the first 3 months of ICIs therapy. The treatment response to ICIs included complete response (CR), partial response (PR) and stable disease in 10% (n = 20), 23% (n = 46), and 20% (n = 41) of patients, respectively. The responder and nonresponder groups differed in terms of certain baseline characteristics, such as Bellmunt risk factors, and neutrophil-to-lymphocyte ratio (NLR). The 5-year OS rates for patients with CR and PR were 73% and 23%, respectively. The median DoR for CR, PR, and SD were 51.8 months (44.5-59.1), 20.7 months (16.7-24.6), and 8.8 months (5.5-12.1), respectively. Overall, 16(80%) patients with CR and 14(30%) patients with PR had an ongoing response at the time of the analysis. In the univariate analysis, NLR $>$ 3, liver metastases, ECOG PS $\geq$ 1, and hemoglobin levels $<$ 10 mg/dl, as well as the PR and CR, were all significantly associated with OS. In multivariate analysis, presence of liver metastases (HR 2.3; 95% CI, 1.3-4.2; $P < .004$) was found to be an independent determinant of short OS, while PR (HR 0.3; 95% CI, 0.15-0.5; $P < .001$) and CR (HR 0.06; 95% CI, 0.014-0.27; $P < .001$) were associated with improved OS. **Conclusions:** In conclusion, this 5-year analysis of real-world data in the setting of metastatic urothelial cancer indicated a significant correlation between ORR, especially CR, and OS in

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Introduction

Many clinical trials and real-world data in the setting of metastatic urothelial carcinoma demonstrated the association of immune checkpoint inhibitors (ICIs), as a first- or second-line treatment, with an effective antitumor activity.[1,2] In a study by Bellmunt et al.,[3] use of pembrolizumab versus chemotherapy as a second line treatment in metastatic urothelial carcinoma was associated with a longer median overall survival (OS; 10.3 months vs. 7.4 months), while the 2 treatment arms were found to be similar in terms of progression-free survival (PFS; 2.1 months vs. 3.3 months, respectively). In contrast to its utility as a surrogate endpoint in cytotoxic chemotherapy studies, PFS is not considered a suitable surrogate primary endpoint for the ICIs in metastatic urothelial carcinoma.[3]

In this regard, OS has become the primary endpoint in many ICIs studies, whereas the need for a long-term follow up is considered likely to delay the access to novel effective treatments for many patients during this period.[4]

Therefore, Response Evaluation Criteria in Solid Tumors (RECIST) criteria-based objective response rate (ORR) has been evaluated as a potential surrogate in predicting OS in patients who were treated with ICIs.[4-6] However, OS may differ with respect to achievement of complete response (CR), partial response (PR), and stable disease (SD) in ICIs-treated advanced urothelial cancer patients.[4]

Another critical point is the emergence of recurrence in majority of metastatic urothelial cancer patients who achieved a CR or PR after chemotherapy, within a few months. The median duration of response (DoR) for the gemcitabine plus cisplatin (GC) and the methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) regimens were reported to be 9.6 months and 11 months, respectively.[7] However, in patients who achieved an objective response with ICIs, the median DOR was reported to be 34.8 months along with an ongoing response rate of 42% at the 5-year long-term follow-up.[2]

Moreover, given that majority of clinical studies have not extensively included real-world populations and the patients included in trials often have lower risk than the real-world populations, these factors may limit the external validity of clinical trials in real-life clinical practice.[8]

To the best of our knowledge, limited real-life data exist regarding the long-term follow-up of patients treated with ICIs in the setting of metastatic urothelial carcinoma. Therefore, this real-life 5-year follow-up study aimed to evaluate the utility of RECIST criteria-based ORR as a potential surrogate endpoint for long-term OS in metastatic urothelial carcinoma patients treated with ICIs.

Patients and Methods

Study Population

A total of 201 patients who received at least 1 cycle of ICIs for metastatic urothelial carcinoma were included in this retrospective study conducted between June 15, 2017, and June 21, 2023. Although, 215 patients were enrolled initially, 201 patients were considered eligible for the study, due to lack of available data in 14 patients.

The study was approved by the institutional ethics committee (Protocol no: 2019–291).

Assessments

Data on patient demographics, clinicopathological, laboratory, and clinical outcome were retrieved from hospital records. The primary endpoint was ORR, OS, and DoR.

The Bellmunt model demonstrated the 3 risk factors to predict OS in patients with platinum-refractory disease on second-line chemotherapy, including the Eastern Cooperative Oncology Group (ECOG) performance status greater than 0, the serum hemoglobin level less than 10 g/dL, and the presence of liver metastasis.[9] The patients were risk-stratified according to the criteria defined in this classification.

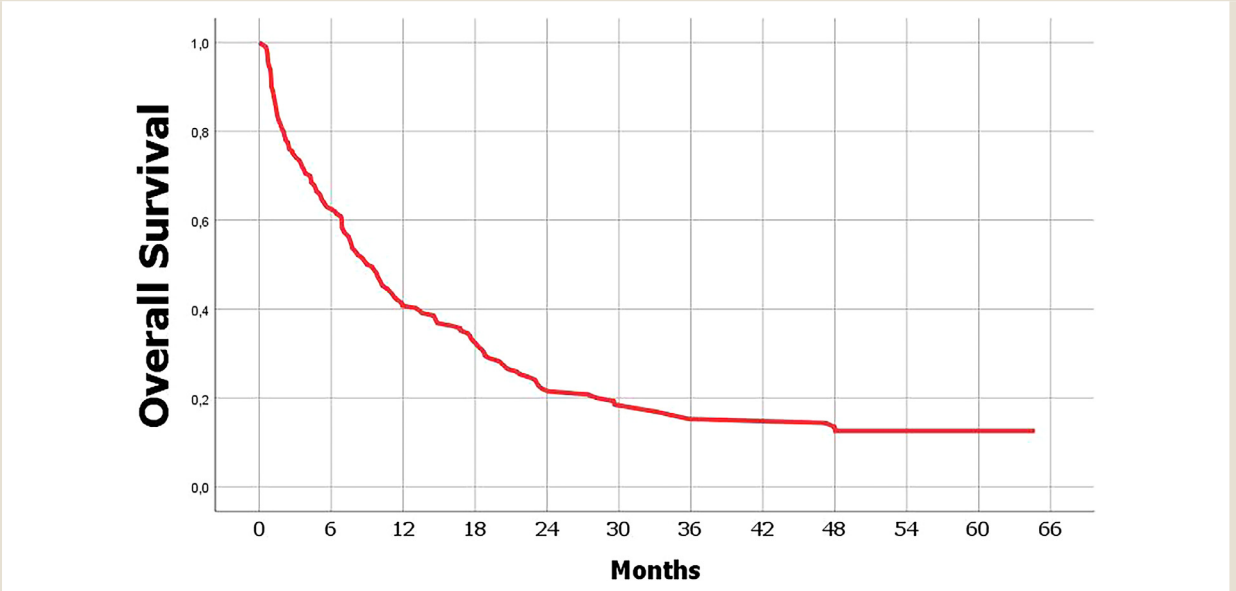
Twenty-two cisplatin-ineligible patients (10.9%) received first-ICIs. Cisplatin eligibility was determined based on Galsky criteria, which include glomerular filtration rate > 60 mL/min, ECOG performance status 0-1, congestive heart failure New York Heart Association (NYHA) class ≤ III, and neuropathy/hearing loss grade ≤ 2.[10]

Treatment response was assessed by computed tomography every 12 weeks according to RECIST, version 1.1, and determined by the data collector based on radiography and clinical notes. ORR was defined as the best response, either a confirmed CR or PR. DOR was defined as the time from the first documented response to disease progression or death from any cause, whichever occurred first.

Statistical Analysis

All statistical analyses were performed using SPSS Statistics, Version 23.0 (IBM Corporation, USA). OS was defined as the time from the first dose of ICIs to death of any cause. The data were censored on the date of the last information available and estimated using the Kaplan–Meier method. Exact 95% confidence intervals (CIs) were used. ORR was analyzed using Fisher's exact test. Median follow-up and OS were estimated by using the Kaplan-Meier method and the log-rank test was used for the comparison between different subgroups.

Figure 1 Kaplan Meier analysis for overall survival.



Results

Baseline Characteristics

Data of 201 eligible patients were analyzed. The median (min-max) age of the patients was 66 (37-86) years, and 156 (84.3%) were males. The majority of patients (94.6%) had ECOG performance status scores of 0-1, and the primary tumor in the bladder was predominant (87.5%) (Table 1).

Overall, 10.9% of patients received ICIs as a first-line treatment and 77.6% as a second-line treatment, while ICIs were received at the third or later lines by 11.5% of patients (Table 1).

Treatment Response

The median follow-up time was 58 months (range, 1.15-71 months). Progression developed in 94 (47%) patients during the first 3 months of ICIs therapy.

The treatment response to ICIs included CR, PR and SD in 10% (n = 20), 23% (n = 46), and 20% (n = 41) of patients, respectively. The responder and nonresponder groups of ICIs-treated patients showed difference in terms of certain baseline characteristics, such as Bellmunt risk factors, and neutrophil-to-lymphocyte ratio (NLR). The patient characteristics according to response rate are summarized in Table 1.

Survival Outcome

The median OS for all patients was 9.4 (7.4-11.4) months (Figure 1).

The 5-year OS rates for patients with CR, PR, and SD were 73%, 23%, and 0%, respectively (Figure 2).

The median DoR for patients with CR, PR, and SD were 51.8 months (44.5-59.1), 20.7 months (16.7-24.6), and 8.8 months (5.5-12.1), respectively. Overall, 16 (80%) patients with CR and 14 (30%) patients with PR had an ongoing response at the time of the analysis.

Univariate and Multivariate Analyses for Determinants of Survival

In univariate analysis, NLR > 3, liver metastases, ECOG performance status ≥ 1 and hemoglobin levels below 10 mg/dl, and the PR and CR rates, were all significantly associated with OS (Table 2).

In multivariate analysis, presence of liver metastasis (HR 2.3; 95% CI, 1.3-4.2; $P < .004$) was found to be an independent determinant of short OS, while PR (HR 0.3; 95% CI, 0.15-0.5; $P < .001$) and CR (HR 0.06; 95% CI, 0.014-0.27; $P < .001$) were associated with improved OS (Table 3).

Discussion

In general, surrogate endpoints based on tumor measurements in relation to OS have been used in ICIs studies. Many studies reported weak associations between PFS and OS.[6] The DoR of ICIs was longer in advanced bladder cancer.[1,2] In the long-term result of KEYNOTE-052 trials, OR was 28.6%, and responder patients maintained their responses.[3] However, the majority of ICIs trials of advanced bladder cancer did not evaluate the long-term outcome effects of ICIs separately based on SD, PR, and CR. Therefore, in this study, we evaluated RECIST criteria-based ORR and SD as potential surrogate endpoints for OS in ICIs-treated metastatic urothelial carcinoma patients over a long-term follow-up.

In this retrospective cohort of ICIs-treated metastatic urothelial carcinoma patients, the 5-year OS rate was 73% in those with CR and the median DoR was 51.8 months, while 80% of patients with CR had an ongoing response. Therefore, our findings

Table 1 Baseline Characteristics by the Best Overall Response

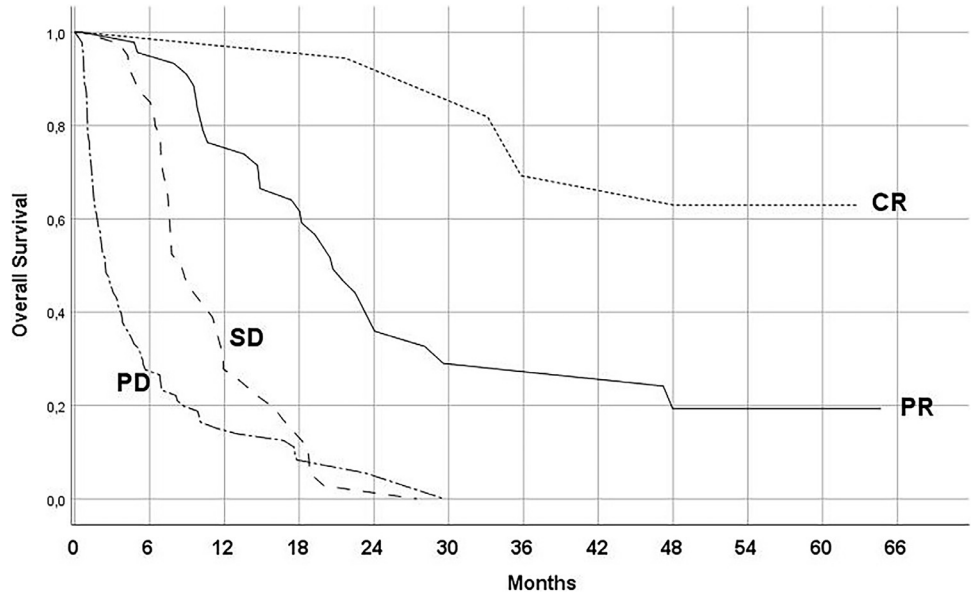
Total n = 201	Immune Checkpoint Inhibitor Response Group				
	CR, n (%)	PR, n (%)	SD, n (%)	PD, n (%)	*P*-Value
Age					
≤ 65 (n = 93)	14 (15.1)	19 (20.4)	19 (20.4)	41 (44.1)	.154
> 65 (n = 108)	6 (5.6)	27 (25)	22 (20.4)	53 (49.1)	
Sex					
Male (n = 171)	15 (8.8)	39 (22.8)	34 (19.9)	83 (48.5)	.472
Female (n = 30)	5 (16.7)	7 (23.3)	7 (23.3)	11 (36.7)	
Smoking History					
Yes (n = 162)	16 (9.9)	36 (22.2)	36 (22.2)	74 (45.7)	.697
No (n = 35)	4 (11.4)	10 (28.6)	5 (14.3)	16 (45.7)	
ECOG Performance Status					
ECOG 0 (n = 48)	10 (20.8)	17 (35.4)	13 (27.1)	8 (16.7)	**< .001**
≥ ECOG 1 (n = 152)	9 (5.9)	29 (19.1)	28 (18.4)	86 (56.6)	
Bellmunt Prognostic Risk Factor Score					
0 (n = 31)	8 (25.8)	13 (41.9)	8 (25.8)	2 (1.1)	**< .001**
1 (n = 95)	9 (9.5)	17 (17.9)	22 (23.2)	47 (49.5)	
2 (n = 50)	2 (4)	5 (10)	9 (18)	34 (68)	
3 (n = 10)	0 (0)	0 (0)	0 (0)	10 (100)	
Baseline Hemoglobin concentration					
< 10 gr/dl (n = 50)	1 (2)	6 (12)	11 (22)	32 (64)	**.016**
≥ 10 gr/dl (n = 140)	18 (12.9)	34 (24.3)	27 (19.3)	61 (43.6)	
Neutrophil to Lymphocyte Ratio					
≤ 3 (n = 55)	7 (12.7)	11 (20)	16 (29.1)	21 (38.2)	**.033**
> 3 (n = 61)	2 (3.3)	14 (23)	9 (14.8)	36 (59)	
Tumor Location					
Upper Tract (n = 25)	2 (8)	2 (8)	4 (16)	17 (68)	.114
Bladder (n = 172)	17 (9.9)	43 (25)	37 (21.5)	75 (43.6	
Cystectomy					
Yes (n = 92)	11 (12)	20 (21.7)	18 (19.6)	43 (46.7)	.735
No (n = 108)	8 (7.4)	26 (24.1)	23 (21.3)	51 (47.2)	
De novo Metastatic disease					
Yes (n = 76)	6 (7.9)	17 (2.4)	17 (22.4)	36 (47.4)	.904
No (n = 124)	13 (10.5)	29 (23.4)	24 (19.4)	58 (46.8)	
Visceral Metastasis					
Yes (n = 135)	13 (9.2)	30 (22.2)	27 (20)	65 (48.1)	.963
No (n = 65	6 (9.2)	16 (24.6)	14 (21.5)	29 (44.6)	
Liver Metastasis					
Yes (n = 39)	3 (7.7)	4 (10.3)	3 (7.7)	29 (74.3)	.006
No (n = 161)	16 (9.9)	42 (26.1)	38 (23.6)	65 (40.4)	
Lymph Node Metastasis					
Yes (n = 67)	9 (13.4)	15 (22.4)	11 (16.4)	32 (47.8)	0.077
No (n = 133)	10 (7.5)	31 (23.3)	30 (22.6)	62 (46.6)	
Neoadjuvant Chemotherapy					
Yes (n = 35)	2 (5.7)	11 (31.4)	6 (17.1)	16 (45.7	.532
No (n = 165)	17 (10.3)	35 (21.2)	35 (21.2)	78 (47.3)	

(*continued on next page*)

Table 1 (*continued*)

Total n = 201	Immune Checkpoint Inhibitor Response Group				
	CR, n (%)	PR, n (%)	SD, n (%)	PD, n (%)	*P*-Value
Palliative/Curative Radiotherapy to Bladder					
Yes (n = 49)	5 (10.2)	13 (26.5)	8 (16.3)	23 (46.9)	.791
No (n = 149)	14 (9.4)	32 (21.5)	33 (22.1)	70 (47)	
ICI					
Atezolizumab (n = 165)	15 (9.1)	36 (21.8)	34 (20.6)	80 (48.5)	.220
Pembrolizumab (n = 26)	2 (7.7)	9 (34.6)	4 (15.4)	11 (42.3)	
Nivolumab (n = 10)	3 (30)	1 (10)	3 (30)	3 (30)	
Treatment Setting					
First Line (n = 22)	2 (9.1)	5 (22.7)	6 (27.39	9 (40.9)	.190
Second Line (n = 145)	13 (9)	29 (20)	31 (21.4)	72 (49.7)	
Third Line (n = 19)	2 (10.5)	3 (15.8)	3 (15.8)	11 (57.9)	
Fourth Line (n = 4)	3 (75)	0 (0)	0 (0)	1 (25)	
Response to chemotherapy prior to ICT					
CR (n = 7)	1 (14.3)	4 (57.1)	1 (14.2)	1 (14.3)	.128
PR (n = 40)	2 (5)	15 (37.5)	6 (15)	17 (42.5)	
SD (n = 22)	2 (9.1)	3 (13.6)	6 (27.3)	11 (50)	
PD (n = 91)	11 (12.1)	16 (17.6)	17 (18.7)	47 (51.6)	

Figure 2 The 5-year OS rates for all RECIST subgroups.



indicate the presence of a significant relationship between CR and OS in the long-term outcome. Likewise, the solid tumor immune checkpoint studies demonstrated a strong correlation between CR and OS.[4]

The CR rate in our study (10%) seems consistent with the CR rates (ranges, 5%-10%) with ICIs reported in previous studies in metastatic urothelial carcinoma.[1] Furthermore, in the 5-year clinical update from the Phase II IMvigor210 study (cohort 1), first-line atezolizumab monotherapy in cisplatin-ineligible patients demonstrated durable antitumor activity with an ORR of 23.5% and a median DoR of 59.1 months where 53.6% of patients had an ongoing response at the time of the analysis.[11] The current real-

Table 2 Median Overall Survival Results of Subgroups of Patients

Subgroups		Months	%95 CI	*P*
All patients		9.4	7.4-11.4	NA
Age (y)	≤ 65	8.97	6.86-11.07	.178
	> 65	9.69	6.23-13.15	
Sex	Male	8.97	7.15-10.78	.467
	Female	11.93	1.76-22.09	
Smoking History	Yes	9.53	7.28-11.77	.430
	No	8.71	0.6-16.81	
Tumor Localization	Upper tract	5.12	0-14.41	.226
	Bladder	9.53	7.3-11.76	
Cystectomy	Yes	8.71	5.73-11.68	.372
	No	9.43	7.19-11.66	
ECOG-PS	0	18.79	16.33-21.26	**.003**
	≥ 1	7.06	5.27-8.86	
Baseline Hemoglobin concentration	< 10 gr/dl	4.30	2.41-6.17	**< .001**
	≥ 10 gr/dl	10.65	6.88-14.41	
Metastatic at the time of diagnosis	Yes	7.59	4.39-10.79	.346
	No	9.86	7.45-12.26	
Lymph Node Metastasis	Yes	9.69	6.99-12.39	.661
	No	8.54	6.22-10.86	
Visceral Metastasis	Yes	8.54	6.33-10.76	.920
	No	9.69	6.66-12.72	
Liver Metastasis	Yes	4.73	2.93-6.53	**< .001**
	No	11.04	8.18-13.9	
Number of Bellmunt Risk Factors	0	22.47	17.54-27.41	< .001
	1	10.09	7.11-13.07	
	2	4.30	2.9-5.71	
	3	1.18	0.57-1,8	
Immunotherapy Use	First line	7.26	1.9-12.62	.332
	Second line	10.09	7.22-12.95	
	Third line	4.73	0.34-9.12	
ICI	Atezolizumab	9.43	7.21-11.65	.876
	Pembrolizumab	7.72	4.88-10.56	
	Nivolumab	11.04	3.03-19.04	
Response to immunotherapy	Complete (CR)	Not reached		**< .001**
	Partial (PR)	20.7	16.74-24.65	
	Stable (SD)	8.84	5.58-12.1	
	Progression (PD)	2.5	1.62-3.37	
Response to Chemotherapy prior to ICI	Complete (CR)	16.79	0.09-33.48	.482
	Partial (PR)	7.95	6.68-9.22	
	Stable (SD)	7.06	3.09-11.03	
	Progression (PD)	11.89	6.83-16.96	
Neoadjuvant Chemoterapy	Yes	9.82	5.22-14.43	.772
	No	8.97	6.77-11.17	
Radiotherapy (Palliative/Curative)	Yes	16.79	7.88-25.7	.146
	No	7.72	6.22-9.22	

Table 3 Multivariate analyses

Subgroups	HR	95% CI	*P*
Complete Response			
Yes	0.06	0.014-0.27	< .001
Partial Response			
Yes	0.3	0.15-0.5	< .001
Liver Metastasis			
Yes	2.3	1.3-4.2	.004
ECOG-PS			
0	0.83	0.5-1.4	.4
Baseline Hemoglobin concentration			
< 10 gr/dl	1.4	0.8-2.2	.2

world data on long-term response rates and ORR are comparable to the results of previous clinical trials.[1,3,11]

In the current study, PR was %23, the 5-year OS rate for PR was 23%, the median DoR was 20.7 months, and 30% of patients who had PR had an ongoing response at the time of the analysis. Bedke et al.[12] evaluated clinical outcomes in patients with PR or SD on atezolizumab therapy for metastatic urothelial carcinoma, and reported that patients who received atezolizumab with PR had a longer duration of disease control and OS than those who received chemotherapy. In the current study, we demonstrated that approximately one of the 3 patients with PR had an ongoing long-term DoR and this was consistent with atezolizumab trials in which PR of ICIs was different than chemotherapy.[12]

In addition, our findings revealed that SD was %20, and the DoR for patients with SD was 8.8 months. Bedke et al.[12] showed that there was no clear difference between ICIs and chemotherapy in terms of the DoR, which was approximately 3-4 months in both arms. In contrast, DoR was longer for patients with SD in our cohort.

Many ICIs studies evaluated the pretreatment prognostic factors routinely measured for OS in patients with metastatic urothelial carcinoma. In this context, the peripheral blood NLR, platelet, neutrophil count, serum lactate dehydrogenase, CRP, albumin level, and DoR to first-line platinum-based chemotherapy have been demonstrated to be prognostic factors for ICIs in patients with metastatic urothelial carcinoma.[13-19] However, extended follow-up and observation periods are required to confirm the validity of these pretreatment prognostic factors.[13-19] Therefore, RECIST criteria-based ORR, enabling an assessment within 8–12 weeks, may be a faster tool to predict patients who may or may not benefit from the treatment.

There are some limitations of the current study. First, owing to the retrospective study design, treatment response was determined by the data collector based on radiography and clinical evaluations and did not include a central evaluation by a blinded radiologist according to the RECIST criteria. Second, we did not use the immune-related response criteria (irRC) which is used to generally evaluate ICIs responses.[20] Third, our study population included heterogeneous groups such as 10.9% cisplatin-ineligible patients who received first-line ICIs, treatment lines were different for each other, and the patients received different types of ICIs.

In conclusion, this 5-year analysis of real-world data in the setting of metastatic urothelial cancer indicated a significant correlation between ORR, especially CR, and OS in patients who received ICIs. Therefore, identifying a potential surrogate marker for survival in patients treated with ICIs would represent an important advance in the early identification of patients' response or resistance to ICIs.

Clinical Practice Points

- This 5-year analysis of real-world data in the setting of metastatic urothelial cancer indicated a significant correlation between ORR, especially CR, and OS in patients who received ICIs. Therefore, identifying a potential surrogate marker for survival in patients treated with ICIs would represent an important advance in the early identification of patients' response or resistance to ICIs.

Disclosure

No conflict of interest exists in the submission of this manuscript, and the manuscript is approved by all authors for publication. I would like to declare on behalf of my co-authors that the work described was original research that has not been published previously, and is not under consideration for publication elsewhere, in whole or in part. All the authors listed have approved the manuscript that is enclosed.

All authors have contributed to the collection of the data, analysis, and writing of the article.

CRediT authorship contribution statement

Deniz Tural: Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Cagatay Arslan:** Methodology, Writing – review & editing. **Fatih Selcukbiricik:** Data curation, Investigation, Project administration. **Omer Fatih Olmez:** Data curation. **Mustafa Erman:** Data curation, Formal analysis, Writing – review & editing. **Yüksel Ürün:** Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing. **Dilek Erdem:** Data curation. **Saadettin Kilickap:** Conceptualization, Data curation, Software, Visualization, Writing – review & editing.

References

1. Hussain SA, Birtle A, Crabb S, et al. From Clinical trials to real-life clinical practice: the role of immunotherapy with pd-1/pd-l1 inhibitors in advanced urothelial carcinoma. *Eur Urol Oncol*. 2018;1:486–500.
2. Tural D, Arslan C, Selcukbiricik F, et al. Five-Year outcome and safety in patients treated with immune checkpoint blockade therapies for urothelial carcinoma: experience from real-world clinical practice. *Clin Genitourin Cancer*. 2022;7673:00256–00257.
3. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med*. 2017;376:1015–1026.
4. Kartolo A, Yeung C, Hopman W, et al. Complete response and survival outcomes in patients with advanced cancer on immune checkpoint inhibitors. *Immunotherapy*. 2022;14:777–787.
5. Roviello G, Andre F, Venturini S, et al. Response rate as a potential surrogate for survival and efficacy in patients treated with novel immune checkpoint inhibitors: a meta-regression of randomized prospective studies. *Eur J Cancer.*. 2017;86:257–265.
6. Mushti S, Mulkey F, Sridhara R. Evaluation of overall response rate and progression-free survival as potential surrogate endpoints for overall survival in immunotherapy trials. *Clin Cancer Res*. 2018;24:2268–2275.
7. 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;18:3068–3077.
8. Kennedy-Martin T, Curtis S, Faries D, Robinson S, Johnston J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. *Trials*. 2015;495:16.
9. Bellmunt J, Albanell J, Paz-Ares L, et al. Pretreatment prognostic factors for survival in patients with advanced urothelial tumors treated in a phase I/II trial with paclitaxel, cisplatin, and gemcitabine. *Cancer*. 2002;95:751–757.
10. Galsky MD, Hahn NM, Rosenberg JE, et al. Defining "cisplatin ineligible" patients with metastatic bladder cancer. *J Clin Oncol*. 2011;29(7_suppl):238. doi:10.1200/JCO.2011.34.8433.
11. Rosenberg JE, et al. Atezolizumab monotherapy in cisplatin-ineligible patients with previously untreated metastatic urothelial carcinoma: 5-year response and survival analysis from the phase II IMvigor210 study (cohort 1). Poster presented at ESMO. *Abstract 699P. Ann. Oncol.*. 2021;32(suppl_5):S678–S724.
12. Bedke J, Merseburger AS, Loriot Y, et al. Partial response and stable disease correlate with positive outcomes in atezolizumab-treated patients with advanced urinary tract arcinoma. *Eur Urol Focus*. 2021;7:1084–1091.
13. Ogihara K, Kikuchi E, Shigeta K, et al. The pretreatment neutrophil-to–lymphocyte ratio is a novel biomarker for predicting clinical responses to pembrolizumab in platinum-resistant metastatic urothelial carcinoma patients. *Urol Oncol*. 2020;38:602.e1–602.e10.
14. Yamamoto Y, Yatsuda J, Shimokawa M, et al. Prognostic value of pre-treatment risk stratification and post-treatment neutrophil/lymphocyte ratio change for pembrolizumab in patients with advanced urothelial carcinoma. *Int J Clin Oncol*. 2021;26:169–177.
15. Kobayashi T, Ito K, Kojima T, et al. Risk stratification for the prognosis of patients with chemoresistant urothelial cancer treated with pembrolizumab. *Cancer Sci*. 2021;112:760–773.
16. Yasuoka S, Yuasa T, Nishimura N, et al. Initial experience of pembrolizumab therapy in japanese patients with metastatic urothelial cancer. *Anticancer Res*. 2019;39:3887–3892.
17. Tural D, Ölmez ÖF, Sümbül AT, et al. Prognostic factors in patients with metastatic urothelial carcinoma who have treated with Atezolizumab. *Int J Clin Oncol*. 2021;26:1506–1513.
18. Tural D, Selçukbiricik F, Ölmez ÖF, Sümbül AT, et al. Response to first-line chemotherapy regimen is associated with efficacy of ımmune checkpoint blockade therapies in patients with metastatic urothelial carcinoma. *Int J Clin Oncol*. 2022;27(3):585–591.
19. Tural D, Ölmez ÖF, Sümbül AT, et al. Atezolizumab in patients with metastatic urothelial carcinoma who have progressed after first-line chemotherapy: results of real-life experiences. *Eur Urol Focus*. 2021;7:1061–1066.
20. Fojo AT, Noonan A. Why RECIST works and why it should stay: counterpoint. *Cancer Res*. 2012;72:5151e7.