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Optimizing immunotherapy in locoregional and metastatic urothelial cancer

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Clinical outcome after progressing to frontline and second-line anti-PD1/ PD-L1 in advanced urothelial cancer

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ABSTRACT

Background: Immune checkpoint inhibitors (ICIs) are approved for first-line (cisplatin unfit, PD-L1+) and platinum-refractory urothelial carcinoma (UC). Still, most patients experience progressive disease (PD) as the best response. Although higher response rates to subsequent systemic treatment (SST) have been described, post-PD outcome data are scarce.

Objective: To examine the outcome of UC patients who received SST and no SST after progressing to ICIs.

Design, setting, and participants: A retrospective analysis of UC patients progressing to frontline or later-line anti-PD-1/PD-L1 therapy in 10 European institutions was conducted between March 2013 and September 2017.

Intervention: Post-PD management as per standard practice.

Outcome measurements and statistical analysis: Overall survival (OS) was analyzed with a Kaplan-Meier model. Cox regression was used for multivariate analysis (MV). Impact of SST on OS was examined with a time-varying covariate model.

Results and limitations: A total of 270 UC patients with PD to ICIs (69 frontline, 201 later line) were analyzed. Of the patients, 57% of frontline-ICI-PD and 34% of later-line-ICI-PD patients received SST, and SST had an impact on OS in MV (frontline: hazard ratio [HR] 0.22, 95% confidence interval [CI] 0.10-0.51, $p < 0.001$; later line: HR 0.22, 95% CI 0.13-0.36, $p < 0.001$). In the frontline-ICI-PD group, median OS with and without SST was 6.8 mo (95% CI 5.0-8.6) and 1.9 mo (95% CI 0.9-3.0), respectively. High disease burden (three or more metastatic sites: HR 2.49, $p = 0.03$; simultaneous liver/bone metastases: HR 3.93, $p = 0.03$) predicted worse survival. In later-line-ICI-PD group, response to ICIs (HR 0.37, $p = 0.03$), longer exposure to ICIs (HR 0.89, $p = 0.002$), and bone metastasis (HR 2.42, $p < 0.001$) predicted survival. The retrospective nature of this study and a lack of certain parameters limit the interpretation of our analysis.

Conclusions: Patients progressing to frontline ICIs are at risk of early death, excluding them from experiencing potential benefit from chemotherapy.

Patient Summary

Our analysis suggests that outcomes after failing immunotherapy are poor, particularly in UC patients who received no prior chemotherapy.

INTRODUCTION

The first evidence that PD-L1 blockade might be beneficial in advanced urothelial cancer (UC) came from a phase I expansion cohort with atezolizumab (MPDL3280A). In this study, durable responses were observed in platinum-refractory UC patients (1). Other immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 axis also showed activity in metastatic UC (mUC). To date, several ICIs have been approved for second-line platinum-refractory UC patients; pembrolizumab is the only agent that has shown overall survival (OS) benefit in a randomized study (2–6). In 2017, the European Medicines Agency (EMA) and the Food and Drug Agency (FDA) granted accelerated approval to atezolizumab and pembrolizumab for first-line metastatic cisplatin-ineligible UC based on single-arm phase II clinical trial data (7,8). The label has recently been restricted by the EMA and FDA based on early preliminary data from ongoing first-line phase III clinical trials (9,10). These unpublished data suggest reduced survival in mUC patients treated with frontline ICIs with low PD-L1 status (5% in tumor-infiltrating immune cells or <10% combined positive score, assessed by Ventana SP142 and Dako 22C3, respectively) when compared with chemotherapy. As a result, the EMA/FDA restricted the use of first-line atezolizumab or pembrolizumab to cisplatin-unfit patients with PD-L1 high tumors. The lack of conclusive randomized clinical trial data complicates the debate on whether cisplatin-unfit patients should be treated with immunotherapy or carboplatin-based chemotherapy. Data on frontline ICIs in cisplatin-fit patients are currently unavailable. Beyond FDA/EMA restrictions for first-line ICIs, survival outcome and efficacy of subsequent systemic treatment (SST) after discontinuation of anti–PD-1/PD-L1 treatment are currently unclear, particularly for the frontline setting. Excellent responses to SST after progressing to frontline and second-line ICIs have been reported (11,12). However, a recent retrospective analysis revealed that only a third of patients received SST after immunotherapy progression (13). Unfortunately, this was only a small analysis (n = 62) and data were not stratified by treatment setting, precluding specific analysis for prognostic factors. To examine outcome and evolution beyond ICIs for all treatment settings, we retrospectively analyzed post-ICI outcomes and SSTs in front- and later-line patients with advanced or mUC.

PATIENTS AND METHODS

A retrospective analysis was performed using data obtained from advanced UC patients who progressed to front-, second-, or later-line anti–PD-1/PD-L1 monotherapy in phase I–IV trials and regular clinical care setting in 10 European institutions. Patients with ongoing response to ICIs were excluded. Both cisplatin-eligible and cisplatin-ineligible

patients were included in this analysis. Upper tract urothelial cancer (UTUC) and mixed/non-UC histology were allowed.

The patients in this study cohort were stratified into two groups:

1) Frontline-ICI-progressive disease (PD) group: cisplatin-eligible and cisplatin-ineligible mUC patients progressing to ICIs without previous exposure to platinum-based chemotherapy in the advanced disease setting (n = 69).
2) Later-line-ICI-PD group: mUC patients progressing to ICIs after previous exposure to chemotherapy (n = 201).

Patients progressing to ICIs according to radiological assessment (RECIST v1.1) or physician/investigator opinion were treated as per standard practice. In order to comply with confidentiality agreements from the clinical trials, no specified data on ICI agents are presented.

Objectives

The primary objective of this study was to analyze the OS of patients having SST or no SST after progressing to ICIs. Secondary objectives include objective radiological response (ORR) and progression-free survival (PFS) to subsequent therapies after previous exposure to ICIs. OS was calculated from the last administration of ICIs until death from any cause. In case patients were still alive, the date of the last follow-up (cutoff point July 31, 2017—the date of last update of database for all centers) was used to calculate survival. PFS was calculated from the time of first subsequent therapy dose infusion to the date of radiological progression or death, whichever occurred first. Radiological response was measured according to the RECIST 1.1 criteria.

Statistical analysis

Descriptive statistics were used for analyzing baseline characteristics, and differences were analyzed using the chi-square test and the Mann-Whitney U test. Survival times (OS and PFS) were analyzed using a Kaplan-Meier model. Univariate and multivariate (MV) analyses using Cox regression models were performed to examine the front-line-ICI-PD and later-line-ICI-PD groups. A cox proportional hazard regression with a time-dependent covariate was used to examine the association between subsequent therapy and survival, and this time-dependent covariate model was also used for MV analyses. Variables that achieved statistical significance in the univariate analysis, those that differed significantly at baseline, as well as known prognostic factors (eg, visceral disease in frontline patients) were included in a stepwise Cox regression model for MV. Factors included in MV analysis for frontline-ICI-PD patients were age, stage IV at presentation, histology, visceral disease (defined as presence of lung, liver, or bone metastasis), pres-

ence of simultaneous bone and liver spread, number of metastatic sites, ICI duration, and use of SST after ICI progression. For the later-line-ICI-PD population, MV analysis included age; previous treatment lines (1 vs ≥2); number of metastatic sites; liver, bone, visceral, and lymph node–only disease; ICI duration; ICI response; type of progression to ICIs (new lesions vs increased existing lesions); and SST exposure. Eastern Cooperative Oncology Group (ECOG) performance status and anemia were not included, since data on these variables were not collected consistently. Time variables were analyzed as continuous variables for MV analysis. All tests were two sided, and $p < 0.05$ was considered significant. All tests were performed using SPSS v15.0.1.

RESULTS

Study population

Between March 2013 and September 2017, 270 patients with locally advanced UC/mUC who started treatment with ICIs and became progressive were identified **(Fig. 1)**. Sixty-nine patients progressed to frontline ICIs (frontline-ICI-PD group) and 201 progressed to ICIs after previous platinum-based chemotherapy (later-line-ICI-PD group). After a median follow-up of 15.6 mo from ICI progression, 207 patients had died. The median follow-up for alive patients was 4.9 mo. A total of 107 patients in the total study population started at least one SST line after progressing to ICIs. In the frontline-ICI-PD group, 39 patients received SST, whereas 68 patients in the later-line-ICI-PD group had SST **(Fig. 1)**. Radiological response data to SST lines were available for 33/39 (85%) and 54/68 (79%) patients in the frontline-ICI-PD and later-line-ICI-PD groups, respectively. Baseline

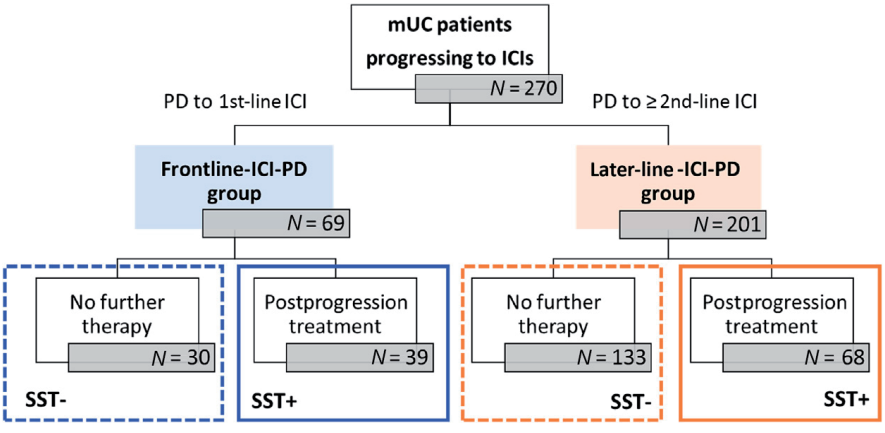


Fig. 1 – Flow diagram of patient cohorts. ICI = immune checkpoint inhibitor; mUC = metastatic urothelial carcinoma; PD = progressive disease; SST = subsequent systemic treatment

Table 1. Baseline characteristics and outcome of patients progressing to frontline ICIs (N=69)

Characteristics	SST- (N=30)	SST+ (N=39)	p-value
Gender: Male, N(%)	26 (87%)	34 (87%)	1
Age: median	71	68	0.16
Primary location: Bladder, N(%)	20 (67%)	30 (77%)	0.4
Histology: UC, N(%) *	26 (87%)	39 (100%)	0.032
Previous therapies in curative setting			
Intravesical BCG	7 (25%)	6 (15%)	0.4
Cystectomy/nephroureterectomy	14 (47%)	11 (28%)	0.13
Radical radiotherapy	2 (7%)	1 (3%)	0.6
Perioperative chemotherapy	6 (20%)	5 (13%)	0.5
Stage IV at initial diagnosis, N (%)	8 (27%)	23 (59%)	0.014
Metastatic sites at start IO			
LN only disease: N(%)	11 (37%)	8 (21%)	0.18
Visceral metastases: N(%)**	18 (60%)	27 (69%)	0.4
Bone mets: N(%)	8 (27%)	10 (26%)	1
Bone/liver mets: N(%)	13 (43%)	18 (46%)	1
Liver mets: N(%)	8 (27%)	10 (26%)	1
No. of metastatic sites at IO start			
1 or 2: N (%)	22 (73%)	31 (79%)	0.6
Pattern of IO progression (N,%)***			
New metastases: N (%)	18 (75%)	22 (56%)	0.1
Visceral involvement at ICI PD	unknown	34 (87%)	
Time from ICI to SST: median	NA	1.1	
1st SST after ICI PD			
Gem-Carbo		24 (62%)	
Gem-Cis		10 (26%)	
Other		5 (12%)	
2nd SST after ICI PD			
GemCis/GemCarboplatin		1 (3%)	
Taxanes		6 (15%)	
Other		3 (8%)	
Response to SST †			
CR/PR to 1st SST, N(%)		19 (58%)	
CR/PR to 2nd SST, N(%)		1 (14%)	

*UC defined as pure urothelial carcinoma or UC mixed with other variants in histology ** Visceral metastases defined as lung, liver or bone metastases.*** 3 patients were considered to be in clinical PD without radiological assessment, and 3 patients had confirmed PD, but lacked data on radiologic disease pattern at progression. Increasing metastases defined as RECIST 1.1 progressive disease in the absence of new metastases. † Radiological response to 1st and 2nd SST assessed in 33/39 and 7/10 respectively.

Table 2. Baseline characteristics and outcome of patients progressing to later-line ICIs (N=201)

Characteristics	SST- (N=133)	SST+ (N=68)	p-value
Gender: Male, N(%)	106 (80%)	58 (85%)	0.4
Age: median	61	61	0.6
Primary location: Bladder, N(%)	92 (69%)	47 (70%)	1
Histology: UC, N(%) *	124 (95%)	64 (99%)	0.3
Prior cisplatin-based chemotherapy, N(%)	85 (64%)	47 (72%)	0.3
No. of systemic lines prior to ICI (median)***			
1 (N, %)	79 (59%)	53 (78%)	0.012
≥2 (N,%)	54 (41%)	15 (22%)	
Stage IV at initial diagnosis	53 (40%)	24 (35%)	0.5
Metastatic disease sites at start IO			
LN only disease: N(%)	16 (12%)	16 (24%)	0.04
Visceral metastases: N(%)	104 (78%)	42 (62%)	0.02
Bone/liver mets: N(%)	78 (59%)	26 (38%)	0.01
Number of metastatic sites at start IO			
1 or 2	81 (61%)	53 (79%)	0.01
Pattern of IO progression: N(%)†			
Increasing metastases	22 (20%)	19 (29%)	0.3
Visceral spread at ICI PD	unknown	54 (85%)	
Time from ICI to SST: median	NA	1.2	
1st SST after ICI PD			
Gem-Carboplatin		18 (26%)	
Gem-Cisplatin		1 (1%)	
Other		46 (68%)	
Unknown		3 (5%)	
2nd SST after ICI PD		15 (22%)	
GemCis/GemCarboplatin		3 (4%)	
Taxanes		1 (1%)	
Other		12 (17%)	
Response to SST			
CR/PR to 1st SST, N(%) ‡		17 (31%)	
CR/PR to 2nd SST, N(%) ‡		3 (21%)	

* UC defined as pure urothelial carcinoma or UC mixed with other variants in histology ** Visceral metastases defined as lung, liver or bone metastases. *** Neoadjuvant and adjuvant chemotherapy were considered as 1st line if progression and subsequent treatment was started within 1 year of its ending. † based on data available in 174 patients, 5 patients were considered to be in clinical PD without radiological assessment, and 22 patients had confirmed PD, but lacked data on radiologic disease pattern at progression ‡ Radiological assessment to 1st and 2nd SST performed in 54/68 and 14/15 patients, respectively

Table 3. OS in patients progressing to frontline and laterline ICI. Uni and multivariate analysis

FRONTLINE-ICI-PD GROUP

Characteristic	Univariable analysis			Multivariable analysis		
	HR	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Sex, male	0.79	0.33-1.87	0.6			
Age	0.83	0.47-1.46	0.5	1.01	0.97-1.03	0.8
Primary bladder	0.80	0.43-1.48	0.5			
UC histology	0.61	0.19-2.0	0.4	0.62	0.17-2.34	0.5
Prior cystectomy/nephrectomy	1.34	0.75-2.38	0.3			
Stage IV at initial diagnosis	0.89	0.50-1.58	0.7	1.60	0.78-3.29	0.2
Metastatic sites at ICI start						
LN only disease	0.56	0.28-1.14	0.1	1.60	0.78-3.29	0.3
Visceral metastasis	1.77	0.92-3.42	0.08	3.93	1.22-12.7	0.02
Lung metastasis	1.75	0.99-3.1	0.06	2.49	1.10-5.77	0.03
Liver metastasis	1.75	0.95-3.24	0.07			
Bone metastasis	1.60	0.88-2.92	0.12			
Bone and liver metastasis	6.81	2.38-19.5	<0.001			
≥3 M1 sites	2.56	1.39-4.71	0.002			
Prior CR/PR RECIST response ICI	0.70	0.28-1.78	0.5			
ICI duration	0.49	0.28-0.88	0.016	0.99	0.93-1.07	0.9
Type of IO PD: new M1 sites	1.61	0.84-3.11	0.15			
SST+	0.42	0.22-0.81	0.009	0.22	0.10-0.51	<0.001

LATERLINE-ICI-PD GROUP

Characteristic	Univariable analysis			Multivariable analysis		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**P-value**
Sex, male	0.68	046-1.01	0.05			
Age	0.81	0.59-1.12	0.2	0.99	0.97-1.01	0.48
Primary bladder	1.25	0.88-1.76	0.2			
Number of previous lines (≥2 vs 1)	1.27	0.92-1.77	0.14	1.06	0.71-1.59	0.77
UC histology	0.99	0.47-2.14	0.9			
Prior cystectomy/nephrectomy	0.87	0.63-1.21	0.4			
Prior Cisplatin based CT	0.72	0.52-1.01	0.05			
CR/PR to prior plat-based CT	0.86	0.60-1.22	0.4			
Metastatic sites at ICI start						
LN only disease	0.56	0.36-0.89	0.013	0.60	0.27-1.33	0.2
Visceral metastasis	1.68	1.17-2.43	0.005	1.70	0.86-3.76	0.13
Lung metastasis	1.01	0.73-1.38	1	1.51	0.92-2.48	0.1
Liver metastasis	1.99	1.42-2.18	<0.001	2.42	1.55-3.78	<0.001
Bone metastasis	2.34	1.66-3.30	<0.001	1.01	0.61-1.70	1
≥3 M1 sites	2.03	1.44-2.86	<0.001			
Prior CR/PR RECIST response ICI	0.38	0.22-0.66	0.001	0.37	0.15-0.91	0.03
Prior ICI duration	0.34	0.24-0.47	<0.001	0.89	0.83-0.96	0.002
Type of IO PD: new M1 sites	1.83	1.15-2.92	0.01	1.35	0.77-2.345	0.3
SST+	0.41	0.28-0.61	<0.001	0.22	0.13-0.36	<0.001

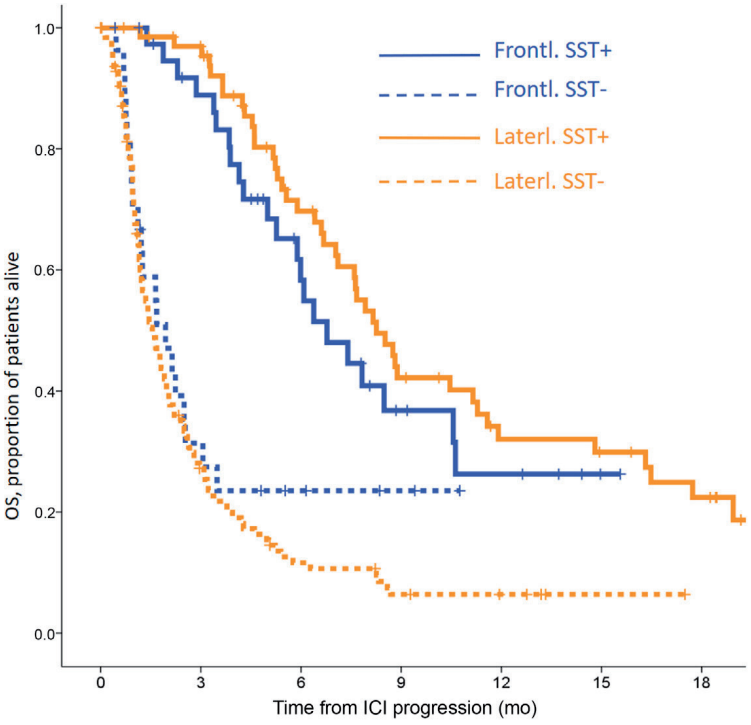
CI = confidence interval; CR = complete response; CT = chemotherapy; HR = hazard ratio; ICI = immune checkpoint inhibitor; IO = immuno-oncology; LN = lymph node; OS = overall survival; PD = progressive disease; PR = partial response; SST = subsequent systemic treatment; UC = urothelial carcinoma. Bold font highlights statistically significant differences.

characteristics were balanced between patients having SST or no SST in the frontline-ICI-PD group, except for histological subtype and stage IV disease at initial diagnosis. Patients with stage IV disease from initial diagnosis were more often exposed to SST (59% vs 27%). None of the non-UC patients received SST **(Table 1)**. In the later-line-ICI-PD group, baseline characteristics were balanced between SST + and SST– patients, except for meta-static site involvement and number of metastatic sites **(Table 2)**. Age, gender, and clinical features were typical for these populations. In the frontline-ICI-PD group, 11 (28%) patients received cisplatin-based chemotherapy and 25 (65%) received carboplatin as first SST, compared with eight (20%) and 17 (25%) in the later-line-ICI-PD group, respectively (SST specifics are shown in **Supplementary Table 1**).

Outcome after progressing to ICIs

In the frontline-ICI-PD group (cisplatin-eligible/ineligible), median OS for all 69 patients was 5.0 mo (95% confidence interval [CI] 2.9–7.0). Patients in the frontline-ICI-PD population that received no SST showed median OS of 1.9 mo (95% CI 0.9–3.0) compared with 6.8 mo (95% CI 5.0– 8.6) for patients who received SST **(Fig. 2)**. Cox regression with a time-dependent covariate model revealed a hazard ratio (HR) of 0.42 (95% CI 0.22–0.81, $p = 0.009$; **Table 3**) in favor of patients receiving SST. I addition, longer ICI exposure was correlated with better OS (HR 0.49). Factors associated with shorter OS were presence of liver and bone metastases (HR 6.81) and a high disease burden, qualified as three or more metastatic sites at the start of an ICI (HR 2.56). After correcting for baseline imbalances and relevant prognostic factors, multivariate HR demonstrated longer OS in patients receiving SST (HR 0.22, $p < 0.001$). A high disease burden (HR 2.49, $p = 0.03$) as well as the simultaneous presence of liver and bone metastases (HR 3.93, $p = 0.02$) was significantly associated with worse outcome. Frontline-ICI-PD patients receiving one or two or more SST lines showed median OS time of 6.1 mo (95% CI 4.6–7.6) and 10.6 mo (95% CI 6.9–14.4), respectively. Efficacy analysis of the first SST in the frontline-ICI-PD group showed median PFS of 5.6 mo (95% CI 1.2–8.0; **Fig. 2**) and 58% ORR in the evaluable population **(Supplementary Fig. 1)**. In the later-line-ICI-PD group, median OS for all 205 patients was 3.1 mo (95% CI 2.4–4.0).

Patients receiving SST showed median OS of 8.3 mo (95% 6.9–9.6) versus 1.5 mo (95% CI 1.2–1.9) for SST– patients **(Fig. 2)**. MV demonstrated that a previous response to an ICI (HR 0.37, $p = 0.03$), longer exposure to an ICI (HR 0.89, $p = 0.002$), and receipt of SST (HR 0.22, $p < 0.001$) were associated with better outcome in the later-line-ICI-PD group (**Table 3**). Bone metastases had a detrimental effect on OS (HR 2.42). Patients having one or two or more SST lines showed 7.1 mo (95% CI 5.7–8.5) and 19.2 mo OS time (95% CI 17.4–20.9), respectively ($p < 0.001$). Response to first SST was observed in 31% of evaluable patients in the later-line-ICI-PD group, and the median PFS was 3.8 mo



No. at risk

Frontl SST+	39	31	17	8	5	-	-	-
Frontl SST-	30	8	5	-	-	-	-	-
Laterl SST+	68	61	39	23	15	13	5	-
Laterl SST-	133	30	12	6	5	-	-	-

Fig. 2 - Kaplan-Meier plot displaying the OS of frontline-ICI-PD and laterline-ICI-PD patients who received SST or no SST.

Blue lines delineate patients progressing to front-line ICI, while orange lines indicate lateline-ICI progressors. Dotted lines represent patients without subsequent therapy after ICI progression (SST-), while continuous lines account for patients receiving further treatment (SST+). Median OS for front-line-ICI-PD was 1.9 months (95% CI 0.9-3.0) for SST-, compared to 6.8 months (95% CI 5.0-8.6) for SST+ patients. Regarding patients progressing to laterline ICI, median OS was 8.3 months (95% 6.9-9.6) versus 1.5 months (95% CI 1.2-1.9) for SST+ versus SST- patients, respectively.

(95% CI 1.2–8.0). Frontline and later-line-ICI-PD patients showed no differences in ORR to SST between different agents received after progression (cisplatin or carboplatin vs others). In the later-line-ICI-PD group, multivariate regression showed higher responses to SST in UTUC patients (OR 5.39) and patients with prior responses to ICIs (OR 6.9), while no statistically significant differences were found in subgroups of the frontline-ICI-PD group **(Supplementary Fig. 1)**.

DISCUSSION

Platinum-based chemotherapy (particularly cisplatin based) has been the standard first-line treatment in mUC for many decades, providing disease control and OS benefit (14,15). The introduction of ICIs rapidly evolved the treatment landscape of mUC. To date, several ICIs have been approved for the platinum-refractory setting and for first-line cisplatin-unfit patients. Although a proportion of UC patients have durable benefit from ICIs, 42–64% of patients show no response (2–5,7,8), and many of these patients clinically deteriorate upon ICI progression (16). Recently, the use of atezolizumab and pembrolizumab for first-line cisplatin-ineligible UC was restricted by the EMA and FDA to patients with PD-L1–positive tumors only, and this was based on preliminary data (unpublished) from the IMvigor130 and Keynote-361 studies (9).

To our knowledge, we provide the first post-ICI analysis based on a large stratified (frontline ICIs vs later-line ICIs) UC patient series (n = 270) that emphasizes the FDA/EMA concerns. Our data show that patients progressing to frontline ICIs performed very poorly in terms of OS, either with or without subsequent therapy (median OS 6.9 vs 1.9 mo), and these outcome data appear to be worse than historical data (cisplatin eligible: 15 mo, cisplatin ineligible: 9 mo (17,18)). Strikingly, 43% of patients progressing to frontline ICIs did not receive subsequent chemotherapy. Thus, patients are at risk of losing the opportunity to benefit from chemotherapy, whereas this is not much of a risk in the platinum-refractory setting. A larger number of metastatic sites involved and the presence of simultaneous bone and liver metastases were associated with frontline-ICI failure. Our analysis suggests that the use of frontline ICIs should be restricted to patients who are unlikely to deteriorate during immunotherapy and thus has important clinical implications that were previously not acknowledged. Our findings underline the need for randomized clinical trials that compare outcome of frontline ICIs with standard treatment in cisplatin-eligible and cisplatin-ineligible patients. Indirect comparisons between frontline single-agent ICIs and carboplatin-based chemotherapy favors chemotherapy in terms of disease control rate, as 36–42% of patients have progressive disease as the best response to a single ICI (7,8), compared with 14–18% with carboplatin-based chemotherapy (19,20). This lack of disease control in frontline ICI patients might facilitate clinical deterioration, precluding subsequent therapy. In the later-line-PD-group, our findings were in line with historical data (OS 8.3 mo; ORR 31%) (21,22), suggesting that later-line immunotherapy does not impair outcome to third-line treatment. Thus, these data support current-day clinical practice to offer ICIs to all patients in the platinum-refractory setting (23).

Our analysis revealed that patients with a previous response and longer exposure to ICIs showed longer OS after ICI progression. It could be hypothesized that tumors responding to immunotherapy harbor a favorable prognostic profile or may be more likely to benefit from other treatments. New metastatic lesions at PD to ICIs showed worse outcome compared with patients with increased size of known metastatic lesions at PD during radiological assessment (median OS 3.9 vs 6.8 mo and 3.3 vs 6.6 mo for frontline [HR 1.61, p = 0.15] and later-line [HR 1.83, p = 0.01] patients, respectively). Pseudo-progression to immune blockade, originally described in other tumors such as Kaposi sarcoma and melanoma (24–27), may be rare in UC. Therefore, continuation of ICIs beyond progression should not become a routine practice in UC, particularly when new metastatic lesions are observed at PD to ICIs. Our data show that patients benefit from subsequent therapy lines, providing better treatment options than continuing ICI treatment after progression.

Our work sets an example on how international collaborations can assess relevant questions in daily practice that go beyond the scope of clinical trials. In most clinical trials, post-progression data on efficacy of SST are not collected despite being relevant. Our collaborative group will continue to collect data on immunotherapy-treated mUC patients, providing a unique clinical database that might help shape treatment lines in mUC further.

Finally, there are several limitations to this analysis. The retrospective and time-to-event nature of the study constraints the interpretation of results. Selection bias is unavoidable; patients who were able to receive systemic treatment after progressing to immuno-oncology agents will have better prognosis than those who were not. Data on cisplatin eligibility are not presented due to clinical trial confidentiality and contracts. Furthermore, several prognostic factors associated with outcome (i.e., anemia and performance status) were not collected and could have influenced outcome (28,29).

CONCLUSION

Our data indicate that a substantial number of mUC patients who progress to ICIs do not receive further systemic treatment, including 43% of patients treated in the frontline ICI setting. The most striking finding is that patients treated with frontline ICIs are at risk of early death, excluding them from experiencing potential benefit from chemotherapy, whereas outcome of platinum-refractory patients was in line with historical data. Our data on frontline ICIs are worrisome and provide rationale to restrict frontline ICIs to patients with a low risk of clinical deterioration during the first months of immunotherapy

treatment. Predictive clinical factors of first-line immunotherapy failure may include a high disease burden, assessed by metastatic site involvement and disease patterns. Still, the retrospective nature of this analysis limits the interpretation of our data, encouraging further validation. Until randomized clinical trial data become available, these results add relevant information to medical decision making.

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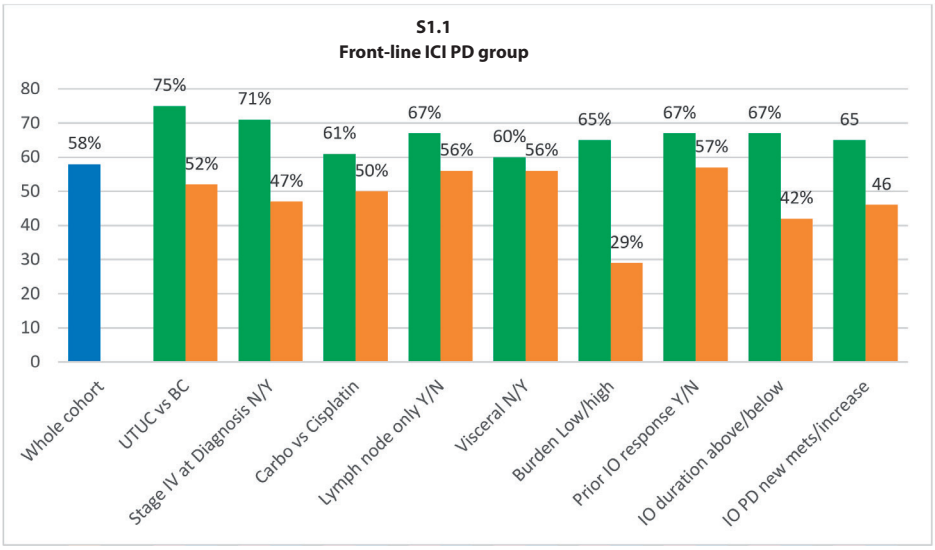
SUPPLEMENTARY MATERIAL

Table S1. Subsequent therapies received after ICI progression (PD)

1st agent received after ICI PD (N=107)		**Frontline-ICI-PD group (N=39)**	**Laterline-ICI-PD group (N=68)**
Gemcitabine-Carboplatin	30 (28%)	24 (61%)	6 (9%)
Gemcitabine-Cisplatin	14 (13%)	10 (26%)	4 (6%)
Taxanes (monotherapy)	18 (17%)	0	18 (26%)
Carboplatin-Paclitaxel	9 (8%)	0	9 (13%)
Other chemotherapies *	15 (14%)	3 (8%)	12 (18%)
Immunotherapy	3 (3%)	1 (2.5%)	2 (3%)
FGFR inhibitors	2 (2%)	0	2 (3%)
Other clinical trials	13 (12%)	1 (2.5%)	12 (18%)
Not reported	3 (3%)	0	3 (4%)
2nd agent received after ICI PD (N=26)		**Frontline-ICI-PD group (N=10)**	**Laterline-ICI-PD group (N=16)**
GemCis/GemCarboplatin	4 (15%)	1 (10%)	3 (19%)
Taxanes (monotherapy)	7 (27%)	6 (60%)	1 (6%)
Carbo-Paclitaxel	2 (8%)	1 (10%)	1 (6%)
Vinflunine	7 (27%)	2 (20%)	5 (32%)
Other chemotherapies**	4 (15%)	0	4 (25%)
Immunotherapy	1 (4%)	0	1 (6%)
FGFR inhibitors	1 (4%)	0	1 (6%)
3rd agent received after ICI PD (N= 6)		**Frontline-ICI-PD group (N=1)**	**Laterline-ICI-PD group (N=5)**
Gemcitabine-Carboplatin	2 (33%)	1 (100%)	1 (20%)
Immunotherapy	3 (50%)	0	3 (60%)
Other clinical trials	1 (17%)	0	1 (20%)

* Vinflunine (3), GemTaxol (3), MVAC (2), Gemcitabine (2), Platinum monotherapy (2), cabazitaxel (1), TIP (1), MOPq10 (1)
**MVAC, Adryamicin, Cisplatin-etoposide, Gemcitabine monotherapy



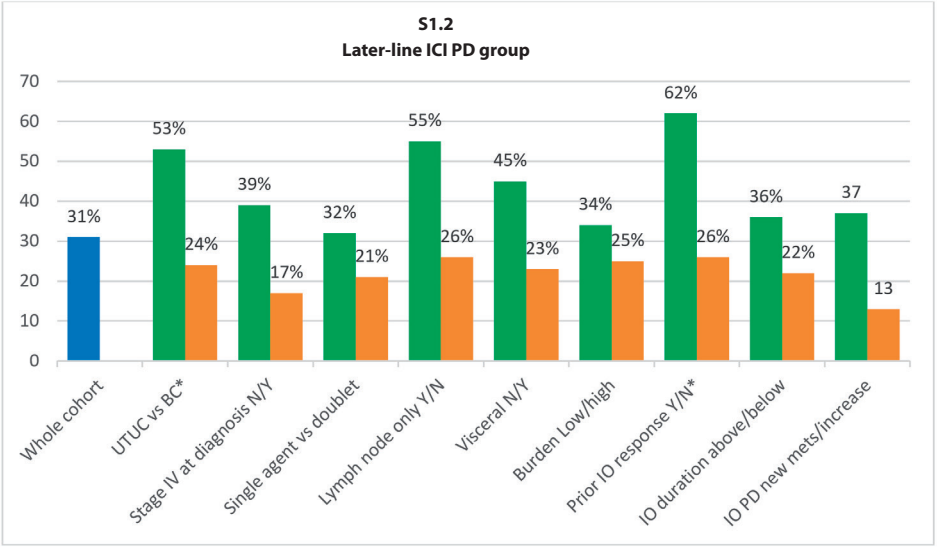


Figure S1. ORR to subsequent treatment by subgroups

Fig. S1.1 – Subgroup analysis of ORR to SST in front-line ICI PD patients (N=33). None of the differences were statistically significant. The pattern of spread (lymph node disease, visceral disease, burden of disease was measured at the time ICI was started. 6 patients had no radiological assessment for SST**.**

Fig. S1.2 – Subgroup analysis of ORR to SST in later-line ICI PD patients (N=54). * Both location and prior ICI response were independent variables predicting response to SST in the laterline population, applying a logistic regression analysis. There was no significant interaction between both variables. Both were included in a multivariate logistic regression analysis, showing an increased response in UTUC tumors (OR 5.39, 95% CI 1.29-22.5) and in those patients responding to prior ICI (OR 6.9, 95% CI 1.17-40.8).The pattern of spread (lymph node disease, visceral disease, and burden of disease) was measured at the time ICI was started. 14 patients had no radiological assessment for SST.