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ORIGINAL RESEARCH

SAUL, a single-arm study of atezolizumab for chemotherapy-pretreated locally advanced or metastatic carcinoma of the urinary tract: outcomes by key baseline factors, PD-L1 expression and prior platinum therapy

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Background: The impact of pretreatment factors on immune checkpoint inhibition in platinum-refractory advanced urothelial cancer (aUC) deserves further evaluation. The aim was to study the association of Bellmunt risk factors, time from last chemotherapy (TFLC), previous therapy and PD-L1 expression with atezolizumab efficacy in platinum-refractory aUC.

Patients and methods: This was a *post-hoc* analysis of patients who had received prior cisplatin or carboplatin in the prospective, single-arm, phase IIIb SAUL study (NCT02928406). Patients were treated with 3-weekly atezolizumab 1200 mg intravenously. The primary outcome was overall survival (OS). Relationships were analysed using Cox regression and long-rank test.

Results: Of 997 patients in SAUL, 969 were eligible for this analysis. The number of Bellmunt risk factors was associated with OS ($P < 0.001$); median OS (mOS) for 0, 1 and 2-3 risk factors was 17.9, 8.9 and 3.3 months, respectively. Significant associations were also observed between OS and TFLC ($P < 0.001$), programmed death-ligand 1 (PD-L1) expression ($P = 0.002$), and prior perioperative chemotherapy ($P = 0.013$); mOS was 6.97 versus 11.63 months for TFLC $\leq$6 versus $>$6 months, 7.75 versus 11.6 months for PD-L1 expression on $<$1% of tumour-infiltrating immune cells (ICs) (IC0)/expression on 1% to $<$5% of tumour-infiltrating ICs (IC1) versus expression on $\geq$5% of tumour-infiltrating ICs (IC2/3) and 10.2 versus 7.8 months for prior versus no prior perioperative chemotherapy, respectively. The type of platinum compound and number of previous treatment lines were not associated with outcomes.

Conclusions: Post-platinum atezolizumab is active in aUC, irrespective of previous platinum compound and lines of therapy. Bellmunt risk stratification, PD-L1 expression, TFLC and perioperative chemotherapy were identified as prognostic factors for OS with second-line atezolizumab, indicating the need for novel prognostic signatures for immunotherapy-treated patients with aUC.

Key words: bladder cancer, immunotherapy, PD-L1, platinum, prognostic factors, urothelial carcinoma

INTRODUCTION

For 30 years, platinum-based combination chemotherapy was the only effective systemic therapy for advanced urothelial carcinoma (aUC).[1] Since 2016, five immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1) have been approved by the United States Food and Drug Administration and the European Medicines Agency for the treatment of relapsed aUC based on improved survival versus chemotherapy.[2,3] Nevertheless, not all patients benefit, with only ~20% of patients achieving long-term remission.[4] Identifying those patients is becoming particularly relevant since other novel agents are showing promising efficacy in patients who have failed ICI therapy and

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their earlier introduction may be beneficial in selected patients.[5,6] It is, therefore, important to develop effective selection tools for this new therapeutic paradigm.

Before the introduction of ICIs, prognosis of patients with aUC largely depended on the first-line therapy, with those treated with cisplatin-based combinations living longer than those who were not.[7] The impact of prior platinum therapy on the efficacy of second-line ICI, however, has not been studied. In addition, Eastern Cooperative Oncology Group performance status (ECOG PS) >0, anaemia (haemoglobin <10 g/dl) and presence of liver metastasis at the time of initiation of second-line therapy negatively impact on overall survival (OS), as shown by Bellmunt et al.,[8] while time from last chemotherapy (TFLC) has also been suggested as a useful predictor.[9] However, these factors have been developed using data from patients treated with second-line chemotherapy and their validity among patients receiving ICIs has not been studied. The use of biomarkers, such as PD-L1 expression or tumour mutational burden (TMB), has also been shown to hold promise as factors predicting benefit to ICIs.[10,11] Importantly, these data have been largely derived from cohorts from clinical trials.

Atezolizumab is a PD-L1 inhibitor approved for first-line treatment of aUC in platinum-ineligible patients and cisplatin-ineligible patients whose tumours have high PD-L1 expression (≥5%). It is also indicated after first-line platinum-based chemotherapy based on improved outcomes in clinical trials.[10-13] The prospective phase IIIb SAUL study ($N = 997$) of atezolizumab in relapsed aUC reported the largest 'real-world' series in this setting.[14] SAUL represents the ideal platform to study prognostic factors in ICI second-line therapy since it more accurately reflects everyday practice than interventional, randomised trials, while also including the PD-L1 status of the majority of patients. Importantly, the study included difficult-to-treat populations, such as non-urothelial carcinomas and patients with autoimmune diseases, which are underrepresented in clinical trials but frequently present in everyday practice, yet relevant clinical evidence is lacking. Therefore, we used the SAUL database to investigate the prognostic value of patient-related characteristics, factors related to previous chemotherapy as well as PD-L1 expression among patients with aUC treated with atezolizumab following failure of first-line, platinum-based chemotherapy.

PATIENTS AND METHODS

Patients

De-identified data including demographic, clinicopathologic, laboratory and outcomes from the complete SAUL database were provided by the sponsor. The data cut-off for the primary analysis was 16 September 2018. The database was not updated for this analysis. All patients provided written informed consent and the trial was approved by the institutional review board or ethics committee at each site before study start.

Inclusion criteria have been previously published.[14] Briefly, SAUL (NCT02928406) is a single-arm, phase IIIb safety and efficacy study of atezolizumab in locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract. All patients were required to have ECOG PS ≤2 and disease progression during or following one to three prior treatments for inoperable, locally advanced or metastatic disease. Patients with relapse within 12 months of perioperative (neoadjuvant or adjuvant) platinum-based chemotherapy, without any other line of chemotherapy for advanced/metastatic disease, were also eligible. Patients with treated central nervous system (CNS) metastases, autoimmune disease, concomitant corticosteroids or renal impairment were eligible. Patients were excluded from the current substudy if they had not received prior cisplatin or carboplatin.

Intervention

Patients received atezolizumab 1200 mg intravenously every 3 weeks until loss of clinical benefit, unacceptable toxicity, the patient's or investigator's decision to discontinue therapy or death. Tumours were assessed every 9 weeks for the first year and then every 12 weeks until confirmed disease progression. After atezolizumab discontinuation, patients were followed for disease progression and OS for up to 4 years after enrolment of the last patient.

Outcomes

The primary endpoint of this substudy was OS. Secondary endpoints were investigator-assessed progression-free survival (PFS) RECIST version 1.1 and objective response rate (ORR, complete/partial response) assessed by RECIST version 1.1 and modified RECIST. Immunohistochemical staining of PD-L1 expression was carried out on formalin-fixed, paraffin-embedded tissues using VENTANA SP142 rabbit monoclonal antibody (Ventana BenchMark ULTRA reader).[15]

Statistical analysis

All time-to-event data (OS, PFS) were calculated from day 1, cycle 1 of study treatment and were summarised using Kaplan–Meier estimates and medians reported with corresponding 95% confidence intervals (CIs). TFLC was calculated from the last day of the last chemotherapy line administered before study entry on day 1, cycle 1 of study treatment. *Post-hoc* subgroup analyses of efficacy according to the following factors were carried out: previous platinum compound (cisplatin versus carboplatin; patients who received both were categorised in the cisplatin group), number of previous lines of systemic therapy (0 versus ≥1), TFLC (cut-off points at 3, 6, 9 and 12 months), PD-L1 expression [tumour-infiltrating immune cell (IC) score of 0/1 versus 2/3], baseline haemoglobin (<10 versus ≥10 g/dl), liver metastases (yes versus no), ECOG PS (0 versus 1/2), number of Bellmunt risk factors (0 versus 1 versus 2/3) and adjuvant or neoadjuvant therapy (yes versus no). Associations [hazard ratio (HR) and 95% CI] of each of these factors with OS and PFS were evaluated using Cox proportional hazards model and survival was compared using the

Table 1. Key baseline characteristics of the 969 patients included in the study

Characteristic	Cohort ($N = 969$)
Median age[a], years (IQR)	68 (60-74)
Sex, *n* (%)	
Female	217 (22)
Male	752 (78)
ECOG PS, *n* (%)	
0	418 (43)
1	451 (47)
2	100 (10)
PD-L1 expression score[b], *n* (%)	
IC0	237 (24)
IC1	410 (42)
IC2/3	257 (27)
Missing	65 (7)
Number of prior lines for advanced/metastatic disease, *n* (%)	
0	369 (38)
1	531 (55)
2	49 (5)
3	20 (2)
Perioperative chemotherapy, *n* (%)	
No	506 (52)
Yes	463 (48)
Neoadjuvant	177 (18)
0 prior lines[c]	144 (15)
≥1 prior lines[c]	33 (3)
Adjuvant	272 (28)
0 prior lines[c]	214 (22)
≥1 prior lines[c]	58 (6)
Both	14 (1)
0 prior lines[c]	11 (1)
≥1 prior lines[c]	3 (<1)
Histological type, *n* (%)	
Urothelial	924 (95)
Non-urothelial/mixed	45 (5)
Squamous neoplasms	18 (2)
Glandular neoplasms	6 (<1)
Neuroendocrine tumours	7 (<1)
Bellini collecting duct	8 (<1)
Missing	6 (<1)
Haemoglobin, *n* (%)	
<10 g/dl	152 (16)
≥10 g/dl	794 (82)
Missing	23 (2)
Liver metastases, *n* (%)	
No	702 (72)
Yes	265 (27)
Missing	2 (<1)
Bellmunt risk factors[d], *n* (%)	
0	296 (31)
1	383 (40)
2	227 (23)
3	38 (4)
Missing	25 (3)
Prior platinum compound, *n* (%)	
Cisplatin	581 (60)
Carboplatin	388 (40)
Primary tumour location, *n* (%)	
Bladder	724 (75)
Renal pelvis	118 (12)
Ureter	94 (10)
Urethra	10 (1)
Other	23 (2)
Time since last therapy, *n* (%)	
≤3 months	353 (36)
>3 months	616 (64)
≤6 months	593 (61)
>6 months	376 (39)
≤9 months	765 (79)
>9 months	204 (21)

Percentages may not add to 100% due to rounding.
ECOG PS, Eastern Cooperative Oncology Group performance status; ICs, immune cells; IQR, interquartile range; PD-L1, programmed death-ligand 1.
[a] Missing: $n = 2$.
[b] IC0, expression on <1% of tumour-infiltrating ICs; IC1, expression on 1% to <5% of tumour-infiltrating ICs; IC2/3, expression on ≥5% of tumour-infiltrating ICs.
[c] Lines for advanced/metastatic disease before study treatment.
[d] Bellmunt risk factors: ECOG performance status ≥1, haemoglobin <10 g/dl and presence of liver metastasis.[8]

log-rank test. Associations with ORR were evaluated using Pearson's chi-squared test. To assess if the magnitude of the changes of survival due to each of the above factors depend on the other factors also studied, we included interaction terms in the Cox model. All tests were two-sided with a cut-off for statistical significance of $P < 0.05$.

Additional exploratory analysis of the importance of the prespecified factors on OS was carried out exclusively in two groups with special clinical interest: non-urothelial/mixed and human immunodeficiency virus (HIV)/autoimmune disease/steroid treatment populations. Since 148 patients received post-study anticancer therapies, we also carried out exploratory analysis of the impact of administration of post-study therapy on the prognostic significance of the prespecified factors.

RESULTS

Of 997 patients treated with atezolizumab in SAUL, 975 had received prior platinum treatment (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2021.100152). Of those, 6 patients who either had missing information on type of platinum treatment ($n = 3$) or had oxaliplatin ($n = 3$) were excluded, leaving 969 patients who were included in this substudy. Table 1 summarises baseline characteristics relevant for this analysis. Most patients received atezolizumab immediately after first-line platinum failure (55%). A substantial number of patients (38%) received atezolizumab following progression within 12 months after neoadjuvant or adjuvant chemotherapy, i.e. as first-line therapy for advanced/metastatic disease, while only 7% of patients had received ≥2 lines of therapy before enrolment. Of the 600 patients who had received previous lines of chemotherapy for advanced/metastatic disease, 94 (16%) had received perioperative chemotherapy. Among the 969 patients, 100 had ECOG PS of 2, 45 had non-urothelial histology, 14 had CNS disease, 2 were HIV positive, 34 had a history of autoimmune disease and 38 were on steroid treatment at study entry. One hundred and forty-eight patients (15%) received some form of anticancer therapy after atezolizumab (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2021.100152). No patient received erdafitinib or enfortumab vedotin.

At the time of database lock, median follow-up was 12.8 months (95% CI: 11.8-13.3), 539 (55.6%) patients had died, 492 (91.3%) due to urothelial cancer, while 212 (21.9%) were still on study treatment. Median OS for the cohort included in the current analysis was 8.6 months (95% CI: 7.6-9.7), the median PFS was 2.2 months (95% CI: 2.1-2.4) and ORR was 13.3%.

OS by Bellmunt risk stratification

Risk stratification according to the number of Bellmunt risk factors resulted in significant ($P < 0.001$) and clinically meaningful differences in prognosis: patients with no risk factors had a median OS of 17.9 months [95% CI: 12.7 to not reached (NR)], those with one factor had an OS of 8.9 months (95% CI: 7.5-10.9) and two-to-three factors 3.3 months (95% CI: 2.7-4) (Figure 1A, Table 2). Each of the factors was individually associated with OS. Worse ECOG PS, haemoglobin <10 g/dl and presence of liver metastases were predictors of shorter median OS (Supplementary Figure S2A-C, available at https://doi.org/10.1016/j.esmoop.2021.100152).

OS by previous therapy

Prior cisplatin-based chemotherapy was associated with a numerically longer median OS compared with carboplatin-based chemotherapy [9.4 months (95% CI: 8.1-10.9) versus 7.5 months (95% CI: 6.4-9.2)] but the difference did not reach statistical significance ($P = 0.056$; Figure 1B, Table 2). To evaluate whether this numerical difference was influenced by other factors (ECOG PS, haemoglobin <10 g/dl, liver metastasis, TFLC, PD-L1 expression, lines of previous therapy and perioperative chemotherapy), we carried out an exploratory analysis using Pearson's chi-square, *t*-test and other similar tests to assess if the distribution of these factors differed between the cisplatin/carboplatin groups. Cisplatin-based chemotherapy was associated with three favourable prognostic factors: no liver metastasis (75% versus 69%, $P = 0.044$), longer median TFLC (7.2 versus 5.4 months, $P < 0.001$) and prior perioperative chemotherapy (56% versus 35%, $P < 0.001$) versus carboplatin-based therapy. Including liver metastasis, TFLC and perioperative therapy as stratification factors in a log-rank test, we confirmed that there was no significant association between the type of previous platinum therapy and OS ($P = 0.731$). There was no association between OS and the number of previous lines of therapy ($P = 0.232$; Figure 1C, Table 2).

The administration of prior perioperative chemotherapy (neoadjuvant or adjuvant or both) was significantly associated with prolonged OS ($P = 0.013$; Figure 2A, Table 2). The median OS was 10.2 months (95% CI: 8.3-12.4) for perioperative chemotherapy versus 7.8 months (95% CI: 6.6-9) for none. After excluding the 369 patients who had received perioperative chemotherapy as their only therapy before atezolizumab, a significant difference in median OS in favour of perioperative chemotherapy was still observed: 12.5 (95% CI: 8-NR) versus 7.8 months (95% CI: 6.6-9) ($P = 0.011$; Figure 2B).

OS by TFLC

There was a significant association between TFLC and OS ($P < 0.001$; Figure 3A, Table 2). This was observed for all time periods studied (Supplementary Figure S3A-D, available at https://doi.org/10.1016/j.esmoop.2021.100152) with longer TFLC associated with longer OS. The sharpest difference in median OS was observed at the 6-month cut-off point [6.97 (95% CI: 5.88-7.95) versus 11.63 months (95% CI: 9.99-17.97)], which was therefore used as a cut-off point for a dichotomised interaction analysis with other factors included in this analysis. An interaction was identified between TFLC and the number of previous lines of therapy ($P = 0.034$) where TFLC >6 months was a positive prognostic factor for those patients who had received ≥1 previous line of systemic therapy for advanced/metastatic disease (HR 0.53; 95% CI: 0.41-0.68); in contrast, no association was found for patients who had not received prior chemotherapy for aUC (Figure 3B).

OS by PD-L1 expression

A PD-L1 IC score of 2/3 was significantly associated with prolonged OS ($P = 0.002$) with a median OS of 11.6 months (95% CI: 8.8-18.8) versus 7.75 months (95% CI: 6.5-9) in tumours with IC 0/1 (Figure 3C, Table 2). A similar benefit by high PD-L1 expression was observed across all subgroups analysed (Supplementary Figure S4, available at https://doi.org/10.1016/j.esmoop.2021.100152).

Other analyses

Fewer Bellmunt risk factors, stronger PD-L1 expression and longer TFLC were each significantly associated with prolongation of PFS (each $P < 0.001$) and higher ORR (each $P < 0.001$) (Table 2). ECOG PS 0, haemoglobin >10 g/dl and the absence of liver metastasis were each associated with longer PFS while only ECOG PS 0 and absence of liver metastasis were associated with higher ORR with similar results for ORR by modified RECIST (data not shown).

Exploratory analyses of the significance of the studied factors in non-urothelial/mixed tumours ($n = 45$), HIV/autoimmune disease/steroid therapy ($n = 72$) and according to the administration of post-study therapy yielded generally similar results to those of the whole population (Supplementary Tables S2 and S3, available at https://doi.org/10.1016/j.esmoop.2021.100152). Nevertheless, the power of these analyses is limited due to the low number of patients in each subgroup.

DISCUSSION

To our knowledge, this is the largest study to assess the impact of pretreatment factors on ICI efficacy outcomes in patients with aUC. The strengths of this study include utilization of 'real-world' but prospectively collected data, multi-institution global representation and the reasonable

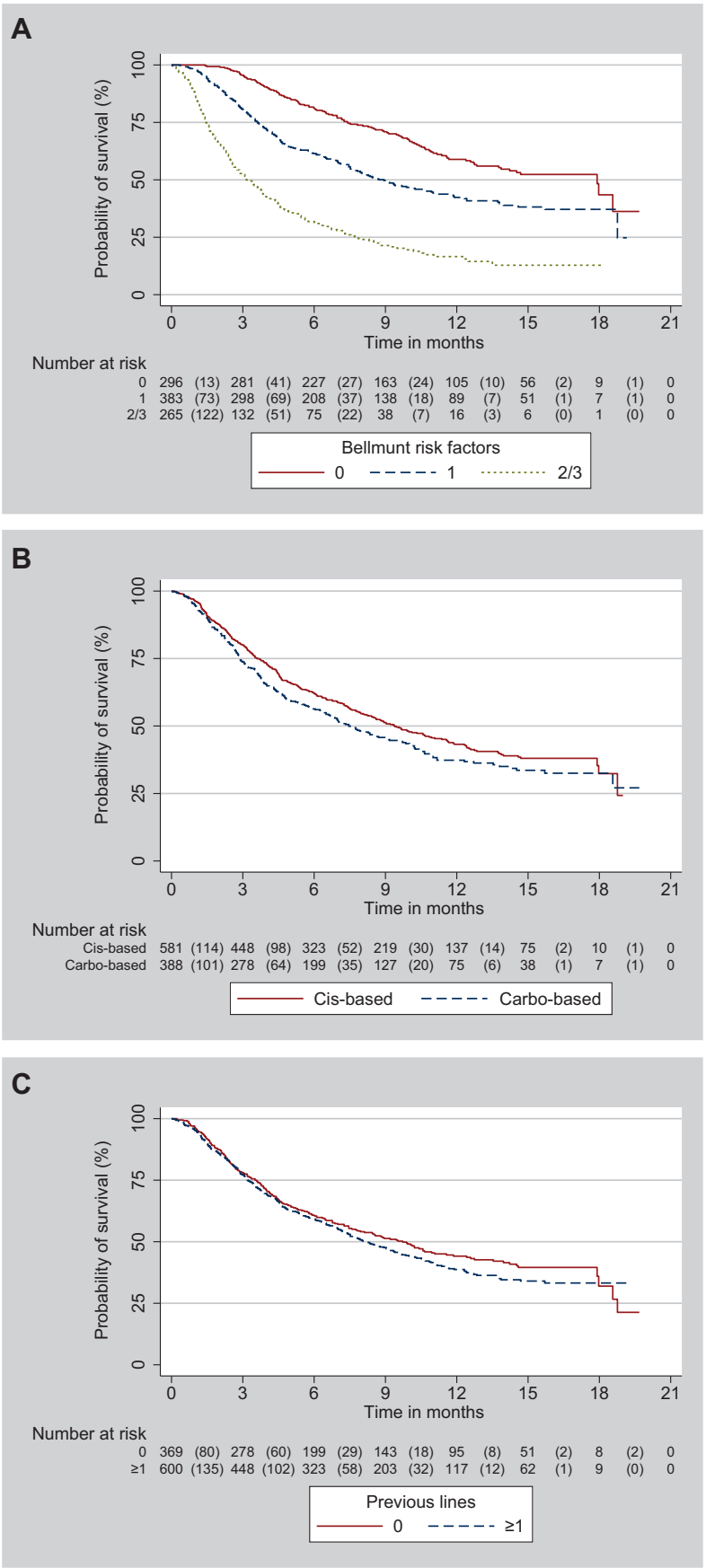


Figure 1. OS with atezolizumab according to (A) the number of Bellmunt risk factors[a], (B) the type of previous platinum therapy (cisplatin versus carboplatin) and (C) the number of previous lines of therapy (0 versus ≥1; *N* = 969).[8]

Carbo, carboplatin; Cis, cisplatin; ECOG, Eastern Cooperative Oncology Group; OS, overall survival.

[a] Bellmunt risk factors: ECOG performance status ≥1, haemoglobin <10 g/dl and presence of liver metastasis.

Table 2. Median OS, PFS and ORRs according to subgroups

	n	Median OS (95% CI)	*P*	HR (95% CI)	Median PFS (95% CI)	*P*	HR (95% CI)	ORR[a] (%)	*P*
Bellmunt risk factors[b]			<0.001			<0.001			<0.001
0	296	17.9 (12.7-NR)		1	4.1 (3.5-4.4)		1	19	
1	383	8.9 (7.5-10.9)		1.8 (1.4-2.2)	2.3 (2.1-2.8)		1.3 (1.1-1.6)	14	
2-3	265	3.3 (2.7-4)		4.3 (3.4-5.4)	2 (1.9-2.1)		2.3 (1.9-2.8)	7	
Previous therapy			0.056			0.162			0.095
Cisplatin-based	581	9.4 (8.1-10.9)		1	2.3 (2.1-2.5)		1	15	
Carboplatin-based	388	7.5 (6.4-9.2)		1.2 (0.9-1.4)	2.2 (2.1-2.4)		1.1 (0.9-1.3)	11	
Previous lines			0.232			0.394			0.084
0	369	9.7 (7.5-11.9)		1	2.2 (2.1-2.9)		1	16	
1-3	600	8.3 (7.2-9.4)		1.1 (0.9-1.3)	2.2 (2.1-2.4)		1.1 (0.9-1.2)	12	
PD-L1 expression[c]			0.002			<0.001			<0.001
IC0-1	647	7.75 (6.5-9)		1	2.1 (2.1-2.3)		1	10	
IC2-3	257	11.6 (8.8-18.8)		0.7 (0.6-0.9)	2.6 (2.1-4.1)		0.8 (0.6-0.9)	21	
TFLC (months)			<0.001			<0.001			<0.001
0-3	353	6.7 (5.4-7.8)		1	2.1 (2.1-2.2)		1	8	
3-6	240	7.5 (5.7-9.9)		0.9 (0.7-1.1)	2.1 (2.1-2.3)		0.9 (0.8-1.8)	12	
6-9	172	10.6 (8.4-18)		0.7 (0.5-0.9)	2.5 (2.2-4.1)		0.7 (0.6-0.9)	19	
9-12	96	NR (9.9-NR)		0.5 (0.3-0.7)	4.8 (2.5-6.5)		0.6 (0.4-0.8)	24	
>12	108	11 (7.75-NR)		0.6 (0.5-0.8)	3.7 (2.2-4.2)		0.7 (0.6-0.9)	15	
Neoadjuvant/adjuvant			0.013			0.139			0.077
No	506	7.8 (6.6-9)		1	2.2 (2.1-2.3)		1	11	
Yes	463	10.2 (8.3-12.4)		0.8 (0.7-0.9)	2.3 (2.1-3.2)		0.9 (0.8-1.04)	15	

CI, confidence interval; HR, hazard ratio; IC, immune cell; NR, not reached; ORR, objective response rates; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TFLC, time from last chemotherapy.

[a] ORR by RECIST version 1.1.

[b] Bellmunt risk factors: ECOG performance status ≥1, haemoglobin <10 g/dl and presence of liver metastasis.[8]

[c] IC0, expression on <1% of tumour-infiltrating ICs; IC1, expression on 1% to <5% of tumour-infiltrating ICs; IC2/3, expression on ≥5% of tumour-infiltrating ICs.

cohort sample size. This cohort closely resembles everyday practice since it includes 'trial-ineligible' patients, such as patients with poor performance status, poor renal function, CNS metastases, non-urothelial histology, autoimmune diseases and steroid treatment.

The validity of the Bellmunt prognostic factors are well established in patients treated with second-line chemotherapy for aUC. To our knowledge, this is the first study to statistically evaluate the prognostic value of these factors following a second-line ICI. We found that all factors, as well as the respective risk stratification, were associated with prognosis. Nevertheless, our results suggest that other factors may be useful in this respect.

Atezolizumab was equally effective following treatment with cisplatin and carboplatin which is of importance for the carboplatin group due to its high unmet need for effective treatment options. In contrast, we demonstrated that TFLC was an important determinant of atezolizumab efficacy and a potentially useful selection criterion. An interval of <6 months was associated with a median OS of only 6.97 months in contrast with 11.63 for >6 months, thereby clearly identifying a cohort in need of more effective therapies. The reasons for this association are unclear but similar findings have been described with non-ICIs,[9] indicating that TFLC may reflect a pragmatic measure of a fairly low pace of disease. Nevertheless, other factors may also play a role. Recent data from the IMvigor130 randomised study showed similar response rates for the combination of chemotherapy with atezolizumab versus chemotherapy alone, suggesting that chemotherapy and atezolizumab may benefit similar patient populations.[13] Thus, patients who remain on long remission from chemotherapy may have a better chance of response to subsequent ICI.

The association of perioperative chemotherapy with improved OS has to our knowledge not been reported before. In this group of patients, the disease would have initially been diagnosed at a localised state, which may imply a less aggressive course than in *de novo* metastatic disease. Biological factors may also explain these findings. Neoadjuvant chemotherapy has been shown to affect immune elements in the tumour microenvironment,[16] which may potentiate the effect of subsequent ICI therapy.[17,18] We also found that TFLC was associated with prolonged survival only in the population that had received ≥1 line of previous chemotherapy for aUC. This may be due to the fact that patients with only prior perioperative chemotherapy had relapsed within 12 months of treatment, thus excluding patients with longer treatment-free interval.

In concert with previous reports,[19,20] we found no impact of the number of previous lines of therapy on the efficacy of atezolizumab. Admittedly, only 7.1% of our patients received 2-3 previous lines of therapy, which reduces the power of the analysis for this subgroup. Nevertheless, given the convincing benefit of ICIs and the existing guidelines,[2,21] it is unlikely that patients will be treated with many lines of therapy before exposure to ICIs. Furthermore, in two other studies, which included patients receiving up to five lines of previous therapies, albeit in small numbers, heavily pretreated patients did not experience reduced efficacy of ICIs.[19,20]

The percentage of high PD-L1 expressing (IC2/3) tumours (27%) and the ORR (21%) and median OS (11.6

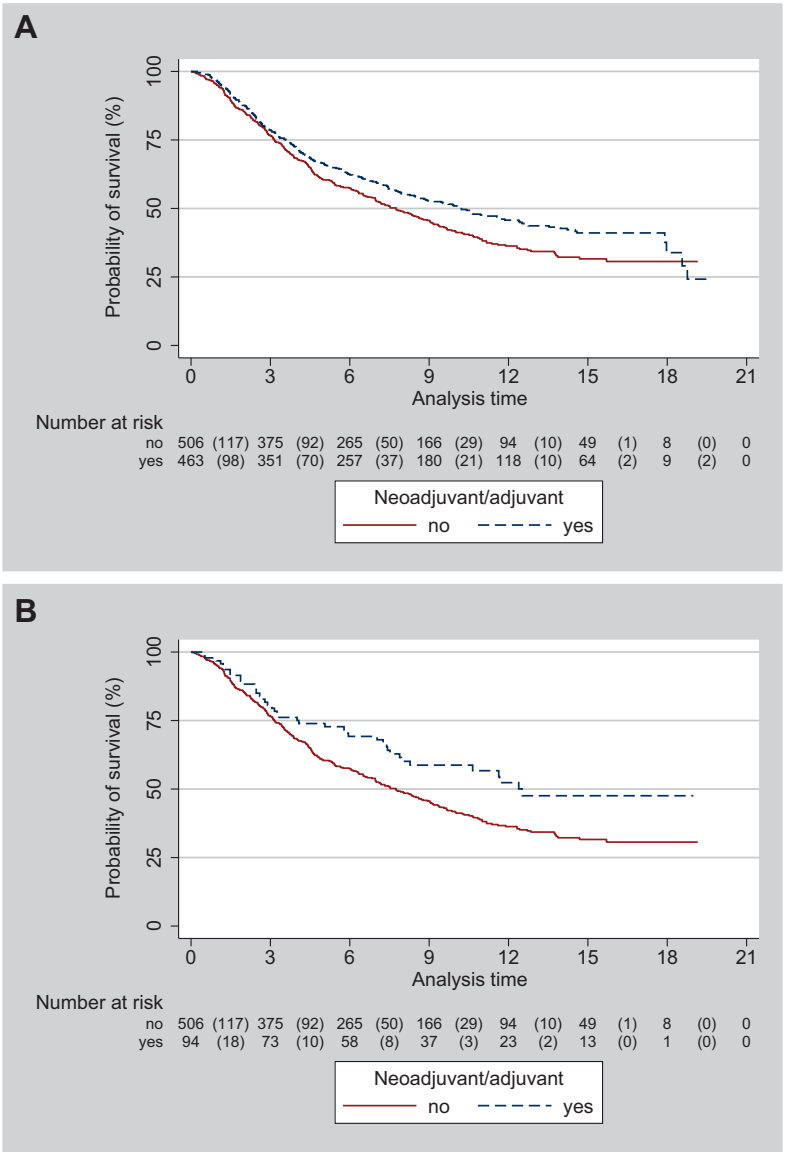
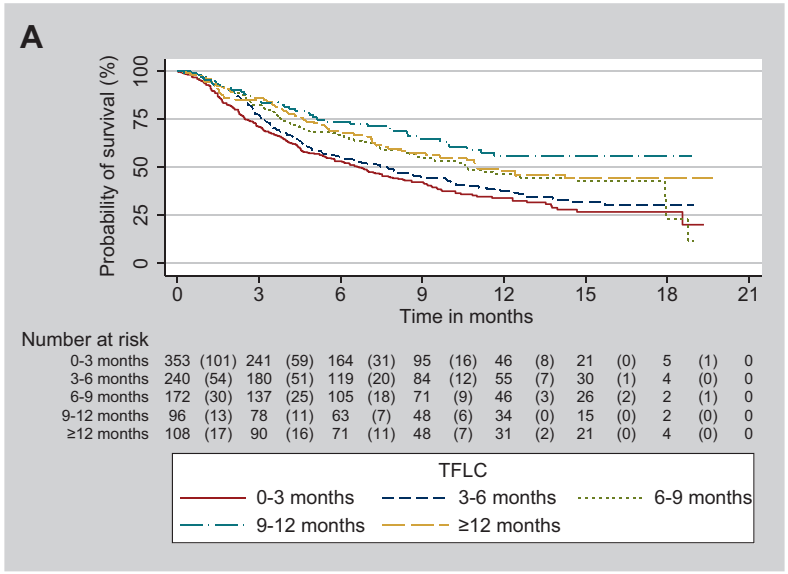


Figure 2. OS with atezolizumab according to prior perioperative (none versus adjuvant or neoadjuvant) chemotherapy for (A) the whole cohort (*N* = 969) and (B) patients with prior therapy for advanced/metastatic disease (*N* = 600).
OS, overall survival.

months) within the IC2/3 subgroup were in line with those reported in the IMvigor210 (32.2%, 26%, 11.4 months, respectively) and IMvigor211 (24.8%, 23%, 11.1 months, respectively) trials,[10,12] confirming the efficacy of atezolizumab in this patient group. We found a strong association of IC2/3 with response to atezolizumab: ORR was almost doubled compared with IC0/1. Similar convincing trends in OS and PFS were observed. Currently, PD-L1 expression is used only for the selection of cisplatin-ineligible patients to receive first-line ICIs, while no selection is recommended in the second-line setting.[2,22] Nevertheless, recent developments in other non-immunotherapy targeted therapies in post-first-line aUC, such as antibody-drug conjugates, will accelerate interest in the potential role of biomarkers. PD-L1 may be useful, especially since recent data suggest that its combination with other markers, such as TMB or molecular classification, may be more accurate tools to predict benefit from modern immunotherapy.[23]

Limitations of our study include the *post-hoc* nature of the analyses and the small sample size in some subgroups which limits the interpretation of those results and may have contributed to the large range for some 95% CIs. Further confirmatory analyses in larger patient populations are needed to validate these results.

This SAUL substudy identified factors for the selection of patients with aUC who were likely to derive a significant benefit from atezolizumab in the post-chemotherapy setting, while it may act as a 'benchmark' for efficacy assessment in single-arm phase II trials. Further research should focus on the development of prognostic signatures that would separate patients treated with immunotherapy into distinct prognostic groups, in accordance with findings from this study.



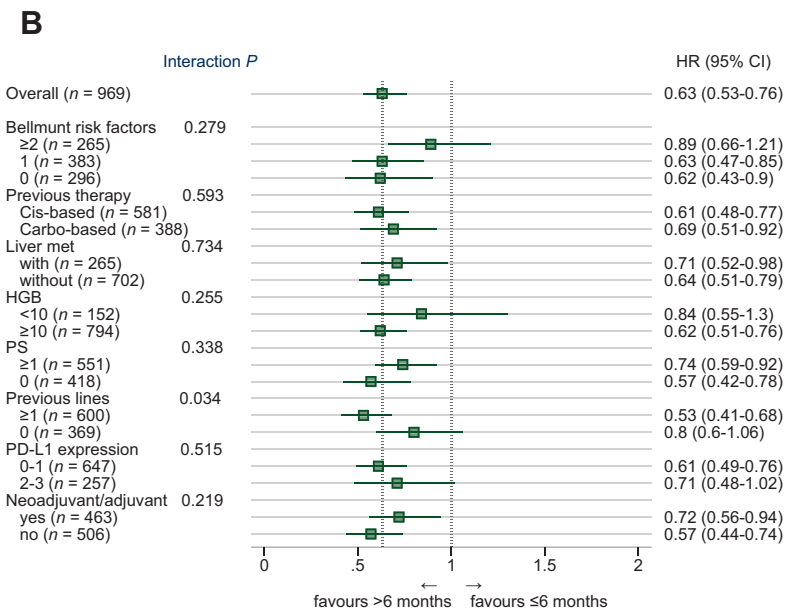


Figure 3. (A) OS with atezolizumab according to TFLC; (B) forest plot of OS depicting subgroup analysis and tests for interaction according to TFLC dichotomised at the 6-month cut-off point (*N* = 969); (C) OS with atezolizumab according to PD-L1 expression (IC0/1 versus IC2/3).
Carbo, carboplatin; CI, confidence interval; Cis, cisplatin; HGB, haemoglobin; HR, hazard ratio; IC0, expression on <1% of tumour-infiltrating immune cells; IC1, expression on 1% to <5% of tumour-infiltrating immune cells; IC2/3, expression on ≥5% of tumour-infiltrating immune cells; OS, overall survival; PD-L1, programmed death-ligand 1; PS, performance status (Eastern Cooperative Oncology Group); TFLC, time from last chemotherapy.

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DISCLOSURE

AB: honoraria, advisory and research funding from Roche, BMS, MSD, Ipsen, Debiopharm, Basilea, Pierre Fabre and

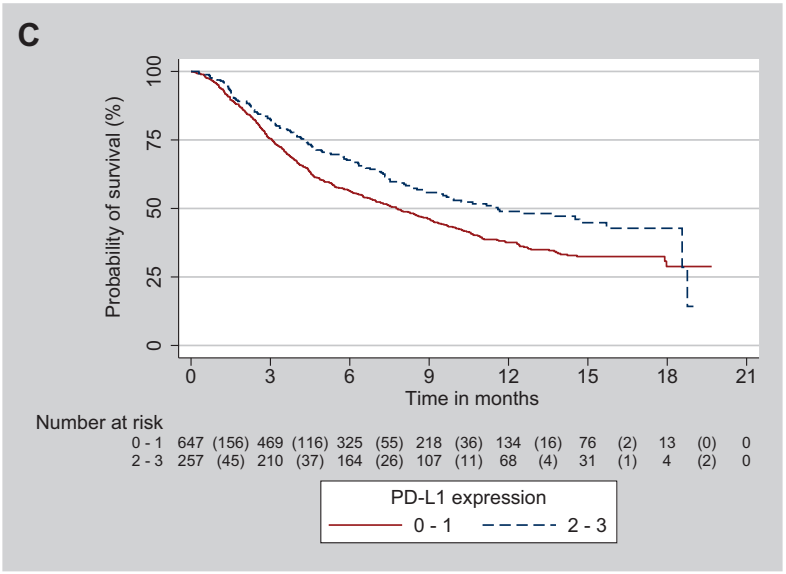

Figure 3. Continued.

Janssen; and steering committee member for Roche. ASM: lectures/speaker honoraria from AstraZeneca, Bristol-Myers Squibb, Eisai, Ipsen, MSD, Merck Serono, Janssen, Takeda, TEVA, Astellas, Novartis, Pfizer and Roche; consultant for AstraZeneca, Astellas, Bristol-Myers Squibb, Ipsen, Janssen, EUSA Pharma, MSD, Merck Serono, Novartis, Takeda, Teva, Pfizer and Roche; research and clinical trials support from AstraZeneca, Astellas, Bristol-Myers Squibb, Ipsen, Janssen, EUSA Pharma, MSD, Merck Serono, Novartis, Takeda, Teva, Pfizer and Roche. YL: personal fees from Roche, Janssen, Astellas, MSD, Pfizer, Roche, BMS, Immunomedics, AstraZeneca, Sanofi and Seattle Genetics; grants from Janssen, MSD and Sanofi; non-financial support from Janssen, Roche, AstraZeneca and Sanofi. NJ: consultancy from Merck, Roche and AstraZeneca; trial funding (to institution) from Merck, Roche and AstraZeneca. EC: research grants from BioCancer, Biogen, Novartis, Pfizer, Roche, Sanofi and UCB; consultancy from AbbVie, Amgen, Biogen, Biocon, Chugai Pharma, Eli Lilly, Gilead, Janssen, Merck Serono, Novartis, Pfizer, Regeneron, Roche, R-Pharm and Sanofi; and speakers fees from AbbVie, Amgen, Bristol Myer Squibb, Chugai Pharma, Eli Lilly, Galapagos, Gilead, Janssen, Novartis, Pfizer, Regeneron, Roche, Sanofi and UCB. DC: personal fees for advisory boards/speaker engagements from Roche, Janssen, Astellas, MSD, Ipsen, Pfizer, Bristol-Myers Squibb, Bayer, AstraZeneca, Novartis, Lilly, Sanofi, Pierre Fabre and Boehringer Ingelheim. FL-R: honoraria from AstraZeneca, Bayer, BMS, Lilly, MSD, Pfizer, Roche and Thermo Fisher; and research funding from Lilly, Roche and Thermo Fisher. FC: advisory role for BMS, MSD, Pfizer and AstraZeneca. MK: honoraria/consultation for Bayer, BMS, EUSAI, Novartis, Merck, MSD, Pfizer and Roche; travel grants from Ipsen, Janssen, Merck and Novartis. GdeV: support for clinical trials and scientific projects for Pfizer, Roche and Ipsen; and speaker fees and consulting for Pfizer, Novartis, Roche, MSD, Astellas, Bayer, Ipsen, Janssen, Merck, EUSA Pharma and BMS. CNS: consultant for Pfizer, MSD, Merck, AstraZeneca, Astellas, Sanofi-Genzyme, Roche-Genentech, Incyte, BMS, Foundation Medicine, Immunomedics (now Gilead), Medscape, UroToday, CCO Clinical, Janssen and NCI. All other authors have declared no conflicts of interest.

DATA SHARING

The data are available from the corresponding author upon reasonable request.

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