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Platinum Priority – Urothelial Cancer

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Primary Results from SAUL, a Multinational Single-arm Safety Study of Atezolizumab Therapy for Locally Advanced or Metastatic Urothelial or Nonurothelial Carcinoma of the Urinary Tract

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Abstract

Background: Atezolizumab, a humanised monoclonal antibody targeting PD-L1, is approved for locally advanced/metastatic urothelial carcinoma. SAUL evaluated atezolizumab in a broader, pretreated population, including patients ineligible for the pivotal IMvigor211 phase 3 trial of atezolizumab.
Objective: To determine the safety and efficacy of atezolizumab in an international real-world setting.
Design, setting, and participants: Between November 2016 and March 2018 (median follow-up 12.7 mo), 1004 patients with locally advanced or metastatic urothelial or nonurothelial urinary tract carcinoma who experienced progression during or after one to three prior therapies for inoperable, locally advanced, or metastatic disease were enrolled. Patients with renal impairment, treated central nervous system metastases, or stable controlled autoimmune disease were eligible; 10% had Eastern Cooperative Oncology Group performance status (ECOG PS) 2 and 98% were platinum pretreated (Clinicaltrials.gov: NCT02928406).
Intervention: Atezolizumab 1200 mg every 3 wk until progression or unacceptable toxicity.

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Outcome measurements and statistical analysis: The primary endpoint was safety. Secondary efficacy endpoints included overall survival (OS), progression-free survival (PFS), and overall response rate (ORR).
Results and limitations: The median treatment duration was 2.8 mo (range 0–19); 22% remained on treatment and 8% discontinued because of toxicity. Grade ≥3 adverse events occurred in 45% of patients. The most common grade ≥3 treatment-related adverse events were fatigue, asthenia, colitis, and hypertension (each in 1%). Median OS was 8.7 mo (95% confidence interval [CI] 7.8–9.9). The 6-mo OS rate was 60% (95% CI 57–63%), median PFS was 2.2 mo (95% CI 2.1–2.4), and the ORR was 13% (95% CI 11–16%; 3% complete responses). Among IMvigor211-like patients (excluding ECOG PS 2 and other IMvigor211 exclusion criteria), median OS was 10.0 mo (95% CI 8.8–11.9) and 6-mo OS was 65% (95% CI 61–69%).
Conclusions: SAUL confirms the tolerability of atezolizumab in a real-world pretreated population with urinary tract carcinoma. Efficacy overall and in the IMvigor211-like subgroup is consistent with previous pivotal anti-PD-L1/PD-1 urothelial carcinoma trials. These results support the use of atezolizumab in urinary tract carcinoma, including patients with limited treatment options.
Patient summary: In this international study we investigated the efficacy and safety of atezolizumab treatment for advanced urinary tract cancer in a large population of pretreated patients, including those who would not normally be candidates for clinical trials. Patients tolerated the treatment well, even if they had autoimmune disease, were being treated with corticosteroids, or had disease that had spread to their brain. Life expectancy in this study for patients typical of everyday clinical practice was similar to that seen in trials that enrolled only selected fitter patients.

1. Introduction

For 30 yr, chemotherapy was the mainstay of treatment for metastatic urothelial bladder cancer, with infrequent durable benefit. More recently, cancer immunotherapy has improved the treatment of urothelial carcinoma and five immunotherapeutic agents are approved in this setting [1,2]. Cancer immunotherapy simultaneously targets several steps in the cancerimmunity cycle [3]. The rationale for evaluating checkpoint inhibitors in urothelial carcinoma stemmed from the high unmet medical need, the immunotherapeutic effect of bacillus Calmette-Guérin in bladder cancer [4], the high incidence of somatic mutations, and the resulting increase in neoantigens [5–8].

Atezolizumab, a humanised monoclonal antibody, targets PD-L1, inhibiting its interaction with PD-1 receptors. Atezolizumab also blocks binding of PD-L1 to B7.1 (CD80), an interaction reported to provide additional inhibitory signals to T cells [9]. Atezolizumab demonstrated encouraging response rates in a phase 1 study in urothelial carcinoma [8]. Long-term follow-up showed that good tolerability was maintained with a durable clinical benefit [10]. The subsequent single-arm two-cohort IMvigor210 study of atezolizumab in advanced or metastatic urothelial carcinoma demonstrated median overall survival (OS) of 15.9 mo among 119 patients with advanced disease who were treatment-naïve but cisplatin-ineligible [11] and median OS of 7.9 mo among 311 patients whose disease had progressed on prior platinum-based chemotherapy [12].

In the subsequent IMvigor211 phase 3 trial, patients with disease progression during or following at least one platinum-containing regimen for metastatic urothelial carcinoma were randomised to either single-agent atezolizumab or investigator-selected chemotherapy (vinflunine or a taxane). Atezolizumab demonstrated a 13% overall response rate (ORR), median progression-free survival (PFS) of 2.1 mo, and median OS of 8.7 mo [13]. According to the hierarchical design, statistical significance was not met for the primary endpoint of OS for patients with PD-L1-positive tumours (≥5% PD-L1-expressing tumour-infiltrating immune cells [ICs]), precluding further statistical analysis. Together, the available clinical evidence suggests that the risk-benefit profile for atezolizumab is acceptable in patients with platinum-pretreated advanced urothelial carcinoma, and atezolizumab was approved for this indication in the USA and Europe. More recently, approval of atezolizumab (and pembrolizumab) in the first-line setting was restricted to patients considered cisplatin ineligible and with PD-L1-positive tumours (defined for atezolizumab as ≥5% PD-L1-stained ICs), although the US label allows atezolizumab for platinum-ineligible patients irrespective of PD-L1 expression.

Similar to many previous trials in metastatic urinary tract carcinomas, IMvigor211 excluded patients with Eastern Cooperative Oncology Group performance status (ECOG PS) >1, autoimmune disease, symptomatic brain metastasis, inadequate renal function, or nonurothelial histology. Such patients frequently present in clinical practice, yet clinical evidence in these difficult-to-treat populations is lacking [14]. To explore outcomes in these understudied but prevalent populations, we initiated the SAUL study in a population similar to that in IMvigor211 but allowing patients for whom atezolizumab is indicated but had not been systematically evaluated.

2. Patients and methods

SAUL (Clinicaltrials.gov NCT02928406) is a single-arm multicentre international open-label phase 3B safety study of atezolizumab in locally advanced (T4bN$_{any}$ or T$_{any}$N2–3) or metastatic (M1) measurable and/or nonmeasurable urothelial or nonurothelial carcinoma of the urinary tract (bladder, ureter, urethra, or renal pelvis). Nonurothelial carcinoma included all subtypes listed in the World Health Organization classification. Patients with Bellini collecting duct tumours were eligible if independently reviewed by two expert pathologists from different sites. All patients were required to have ECOG PS ≤2 and disease progression during or following one (subsequently amended to up to three) prior platinum- or nonplatinum-based treatments (or intolerance if they had received ≥2 cycles) for inoperable, locally advanced, or metastatic disease. Patients with relapse within 12 mo of (neo)adjuvant treatment were also eligible. If available, submission of representative formalin-fixed, paraffin-embedded tumour samples was mandatory.

Patients with treated asymptomatic central nervous system (CNS) metastases, autoimmune disease, concomitant corticosteroids, or renal impairment were eligible provided they met the criteria shown in Supplementary Table 1. Patients with prior allogenic stem cell or solid organ transplantation, a history of idiopathic pulmonary fibrosis, active hepatitis B or C, active tuberculosis, administration of a live attenuated vaccine within 4 wk before study treatment initiation, or prior treatment with CD137 agonists or immune checkpoint blockade therapies were ineligible.

Patients received atezolizumab 1200 mg intravenously every 3 wk until loss of clinical benefit, unacceptable toxicity, the patient's or investigator's decision to discontinue therapy, or death. Concomitant chemotherapy, hormonal therapy, immunotherapy, radiotherapy, or investigational agents were prohibited.

The primary objective was to evaluate the safety of atezolizumab, as measured by the nature, severity, duration, frequency, and timing of adverse events (AEs) as recorded by investigators and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Supplementary Table 2 details AEs of special interest (AESIs). Secondary objectives included evaluation of efficacy, including OS, investigator-assessed PFS (per Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1), ORR (defined as a best response of either confirmed complete or partial response per RECIST version 1.1), disease control rate (DCR; defined as the sum of complete or partial response, or stable disease for ≥4 wk), and duration of response (DoR; defined as the time from first documented response to disease progression or death from any cause). PFS, ORR, DCR, and DoR were also assessed using modified RECIST (Supplementary Table 3). Additional secondary objectives included evaluation of patient-reported outcomes and the EuroQoL 5-Dimensions 5-Levels-assessed utility, results of which will be reported separately, as will the duration and timing of AEs.

The planned sample size was 1000 patients. There was no formal statistical hypothesis and all analyses are descriptive using standard summary statistics. All time-to-event data (OS, PFS, and DoR) are summarised using Kaplan-Meier estimates; medians are reported with corresponding 95% confidence intervals (CIs). Subgroup analyses of safety and/or efficacy according to the following factors were prespecified: ECOG PS 2; presence of CNS metastases at baseline; renal impairment at study entry; positive human immunodeficiency virus (HIV) status; history of autoimmune disease; concomitant steroid therapy at baseline; and history of nonurothelial urinary tract carcinoma. Exploratory analyses were performed for all remaining patients, representing an "IMvigor211-like" more positively selected population. Analyses according to the number of prior treatment lines for metastatic disease were also prespecified.

During study treatment, patients were followed for safety at every cycle. Tumours were assessed every 9 wk for the first year and then every

Table 1 – Baseline characteristics (safety population, *n* = 997)

Characteristic	Result
Median age, yr (interquartile range)	68 (60–74)
Male, *n* (%)	772 (77)
ECOG PS at screening, *n* (%)	
0	427 (43)
1	469 (47)
2	101 (10)
PD-L1 expression score, *n* (%)[a]	
IC0	243 (24)
IC1	421 (42)
IC2/3	264 (26)
Missing	69 (7)
Number of prior lines for metastatic disease, *n* (%)[b]	
0	382 (38)
1	543 (54)
2	52 (5)
3	20 (2)
Smoking history, *n* (%)	
Current	167 (17)
Former	503 (50)
Never	327 (33)
Histological type, *n* (%)	
Urothelial	950 (95)
Nonurothelial/mixed	
Squamous cell carcinoma	18 (2)
Glandular	8 (1)
Bellini collecting duct	8 (1)
Neuroendocrine	7 (1)
Missing	6 (1)
Histological grade at diagnosis, *n* (%)	
1	54 (5)
2	116 (12)
3	780 (78)
Missing	47 (5)
Location, *n* (%)	
Bladder	744 (75)
Renal pelvis	122 (12)
Ureter	97 (10)
Urethra	10 (1)
Other	24 (2)[c]
TNM stage at diagnosis, *n* (%)	
0is	12 (1)
0a	28 (3)
I	123 (12)
II	187 (19)
III	147 (15)
IV	488 (49)
Missing	12 (1)
TNM stage IV at study entry, *n* (%)	997 (100)
Prior platinum regimens, *n* (%)[d]	
Any	975 (98)
Gemcitabine + cisplatin	530 (53)
Gemcitabine + carboplatin	416 (42)
MVAC	35 (4)

ECOG PS = Eastern Cooperative Oncology Group performance status; 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; MVAC = methotrexate, vinblastine, doxorubicin, cisplatin.

[a] PD-L1 expression was tested using the Ventana SP142 PD-L1 immunohistochemistry assay (Ventana Medical Systems, Tucson, AZ, USA).

[b] Patients whose disease relapsed within 12 mo of (neo)adjuvant treatment were counted (for the purposes of eligibility) as having received first-line treatment for metastatic disease.

[c] Includes eight with Bellini collecting duct tumours, ten with combinations of more than one location, one reported as urachus, one reported as intraprostatic, and four with unknown primary location.

[d] More than one answer was possible; treatment in the 22 patients (2%) with no prior platinum comprised single-agent gemcitabine (*n* = 18), single-agent vinflunine (*n* = 1), and other (*n* = 5).

Table 2 – Most common adverse events (any grade in 5% of patients, grade ≥3 or TR grade ≥3 in ≥1%; *n* = 997)

Adverse event	Patients, *n* (%)				
	All grades	Grade 3	Grade 4	Grade 5	TR grade ≥3
Any	880 (88)	352 (35)	59 (6)	37 (4)	127 (13)
Asthenia	184 (18)	20 (2)	2 (0.2)	0	8 (0.8)
Fatigue	173 (17)	24 (2)	0	0	10 (1)
Decreased appetite	163 (16)	10 (1)	1 (0.1)	0	1 (0.1)
Urinary tract infection	156 (16)	48 (5)	1 (0.1)	1 (0.1)	1 (0.1)
Anaemia	156 (16)	37 (4)	0	0	4 (0.4)
Pyrexia	137 (14)	5 (0.5)	0	0	3 (0.3)
Diarrhoea	137 (14)	8 (0.8)	0	0	4 (0.4)
Constipation	118 (12)	2 (0.2)	0	0	0
Nausea	109 (11)	2 (0.2)	0	0	0
Back pain	92 (9)	12 (1)	0	0	1 (0.1)
Pruritus	91 (9)	3 (0.3)	0	0	3 (0.3)
Vomiting	87 (9)	6 (0.6)	0	0	1 (0.1)
Arthralgia	82 (8)	10 (1)	0	0	2 (0.2)
Haematuria	78 (8)	14 (1)	0	2 (0.2)	0
Cough	70 (7)	1 (0.1)	0	0	0
Blood creatinine increased	60 (6)	6 (0.6)	1 (0.1)	0	0
Hypothyroidism	60 (6)	1 (0.1)	0	0	1 (0.1)
Dyspnoea	58 (6)	6 (0.6)	2 (0.2)	2 (0.2)	2 (0.2)
Abdominal pain	56 (6)	12 (1)	0	0	2 (0.2)
Rash	55 (6)	5 (0.5)	0	0	5 (0.5)
Peripheral oedema	51 (5)	3 (0.3)	0	0	1 (0.1)
Pain	41 (4)	13 (1)	2 (0.2)	0	0
Hyponatraemia	37 (4)	20 (2)	2 (0.2)	0	4 (0.4)
Hypertension	34 (3)	14 (1)	0	0	8 (0.8)
Urosepsis	14 (1)	10 (1)	2 (0.2)	2 (0.2)	0
Sepsis	13 (1)	6 (0.6)	4 (0.4)	2 (0.2)	1 (0.1)
Acute kidney injury	18 (2)	10 (1)	1 (0.1)	0	0
Intestinal obstruction	11 (1)	6 (0.6)	1 (0.1)	3 (0.3)	1 (0.1)

TR = treatment-related.

12 wk until confirmed disease progression. After atezolizumab discontinuation, patients were followed for safety for 30 d after the last dose (or until initiation of another anticancer therapy if earlier). Thereafter, patients were followed for disease progression, selected AEs, further anticancer therapy, and OS for up to 4 yr after enrolment of the last patient.

An independent data monitoring committee reviewed cumulative safety data at regular intervals to ensure patient safety. The protocol and all study-related materials were reviewed and approved by the institutional review board or ethics committee at each site before study initiation. All patients provided written informed consent before undertaking any study-specific procedures.

Table 3 – Subgroup analyses of safety

AE, n (%)	All (n = 997)	ECOG PS 2 (n = 101)	CNS metastases (n = 14)	Renal impairment (n = 46)	Auto-immune disease (n = 35)	Concomitant steroid use (n = 40)	Non-urothelial/ mixed (n = 47)	IMvigor211-like[a] (n = 643)	0 prior lines for metastatic disease (n = 382)[b]
Any grade AE	880 (88)	77 (76)	12 (86)	37 (80)	32 (91)	38 (95)	40 (85)	577 (90)	339 (89)
Grade 3/4	431 (43)	50 (50)	7 (50)	20 (43)	17 (49)	23 (58)	24 (51)	261 (41)	176 (46)
Grade 5	37 (4)	7 (7)	0	4 (9)	3 (9)	3 (8)	0	20 (3)	7 (2)
Treatment-related AE	530 (53)	35 (35)	6 (43)	18 (39)	24 (69)	22 (55)	25 (53)	355 (55)	210 (55)
Grade ≥3	127 (13)	13 (13)	2 (14)	3 (7)	9 (26)	4 (10)	5 (11)	81 (13)	52 (14)
Serious AE	327 (33)	40 (40)	5 (36)	17 (37)	11 (31)	19 (48)	16 (34)	200 (31)	123 (32)
AESI	305 (31)	20 (20)	5 (36)	7 (15)	16 (46)	14 (35)	15 (32)	201 (31)	124 (32)
Grade ≥3	67 (7)	5 (5)	0	1 (2)	5 (14)	2 (5)	3 (6)	46 (7)	27 (7)
AE leading to treatment discontinuation	57 (6)	3 (3)	0	3 (7)	3 (9)	2 (5)	2 (4)	37 (6)	24 (6)
Median treatment duration, months	2.8	0.7	1.4	3.0	5.6	1.4	2.1	3.5	2.8

AE = adverse event; AESI = AE of special interest; AID = autoimmune disease; CNS mets = central nervous system metastases; CSU = concomitant steroid use; ECOG PS = Eastern Cooperative Oncology Group performance status; MD = metastatic disease; NU/M = nonurothelial/mixed; RI = renal impairment; TD = treatment discontinuation; TRAE = treatment-related AE.

[a] All patients except those in subgroups excluded from the IMvigor211 phase 3 trial.

[b] Patients whose disease relapsed within 12 mo of (neo)adjuvant treatment.

3. Results

3.1. Patient population

Between November 30, 2016 and March 16, 2018, 1004 patients were enrolled from sites in Europe, Asia, South America, Australia, and Canada (Supplementary Table 4). Of these, 997 received atezolizumab. The remaining seven patients did not start treatment because of signs of clinical progression or deterioration or death.

Table 1 summarises the baseline characteristics. Overall, 35% of patients fell into at least one of the categories ineligible for IMvigor211, including 10% with ECOG PS 2. Only two patients with HIV-positive status were included. Almost all patients (98%) had received platinum at some stage during their previous therapy.

Among the 35 patients with autoimmune disease, the most common were psoriasis ($n = 15$), rheumatoid arthritis ($n = 4$), and autoimmune-mediated hypothyroidism or thyroiditis ($n = 3$). Two patients had ulcerative colitis and two had two concomitant autoimmune diseases. Among the 40 patients receiving corticosteroids at baseline, three (8%) also had CNS metastases (compared with a 1% overall incidence of CNS metastases). Eight (8%) of 101 patients with ECOG PS 2 were receiving corticosteroids at baseline compared with 4% overall. The most frequently administered corticosteroids were dexamethasone ($n = 14$) and prednisone ($n = 9$).

3.2. Treatment exposure

The data cutoff for the primary analysis was September 16, 2018. At this date, patients had received a median of five cycles (range 1–28), corresponding to a median duration of 2.8 mo (range 0–19). The mean dose intensity was 1154 mg (standard deviation 95) every 3 wk. Overall, 263 patients (26%) received ≥12 cycles, 131 (13%) received ≥18 cycles, and 39 (4%) received ≥24 cycles. Of the 600 patients with recorded disease progression at the data cutoff, 269 (45%) had received one or more cycles of atezolizumab after disease progression (≥5 cycles after progression in 105 patients).

The most common reason for treatment discontinuation was disease progression (66% of patients). Treatment was discontinued because of AEs in 8% and consent withdrawal in 3%. Treatment discontinuation peaked at cycle 3, corresponding to the first tumour assessment (Supplementary Fig. 1). Treatment was ongoing in 220 patients (22%) at the date of data cutoff.

3.3. Safety

The median duration of follow-up at the data cutoff was 12.7 mo (95% CI 11.8–13.2; range 0–19.7). AEs (any grade) occurred in 880 patients (88%), the most common being asthenia, fatigue, decreased appetite, urinary tract infection, and anaemia (Table 2). In 53% of patients, AEs were considered by the investigator to be treatment-related. Grade ≥3 AEs occurred in 45% of patients and were considered treatment-related in 13%. The most common grade ≥3 treatment-related AEs were fatigue, asthenia, colitis, and hypertension (each in 1%). There were 37 grade 5 events (4%), of which seven were considered treatment-related (colitis, intestinal perforation, dyspnoea [$n = 2$], respiratory failure, chronic kidney disease, and drug-induced liver injury).

AESIs were observed in 305 patients (31%); however, the majority were grade 1/2. Grade ≥3 AESIs occurred in 7% of patients, most commonly grade 3 immune-related hepatitis diagnosed as a laboratory abnormality (3%). Two-thirds of the grade ≥3 laboratory abnormalities were resolving or had resolved by the data cutoff date; one case of hyperbilirubinaemia was fatal.

Table 3 shows safety in difficult-to-treat populations that were excluded from IMvigor211. Although comparisons are

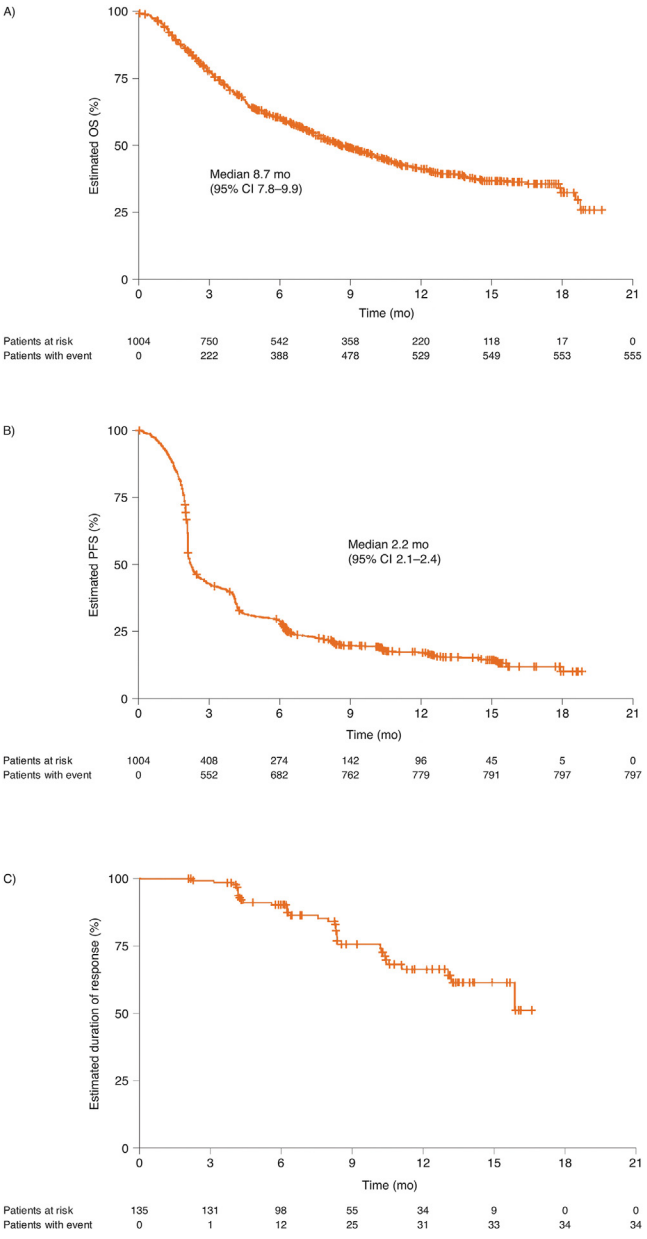

Fig. 1 – Efficacy in the intent-to-treat population: (A) overall survival (OS), (B) progression-free survival (PFS), and (C) duration of response. CI = confidence interval.

limited by small patient numbers in several subgroups, there was a suggestion that treatment-related AEs and AESIs were more frequent among patients with autoimmune disease than in the overall population, and grade ≥3 AEs were more common among patients receiving corticosteroids at baseline. Overall, however, incidences in most of the subgroups were similar to those in the overall population. There was no signal of greater toxicity in patients with ECOG PS 2.

3.4. *Efficacy*

At the data cutoff, 555 patients had died. Median OS was 8.7 mo (95% CI 7.8–9.9), the 6-mo OS rate was 60% (95% CI 57–63%), and the 1-yr OS rate was 41% (95% CI 38–44%; Fig. 1A). Median PFS based on 797 PFS events was 2.2 mo (95% CI 2.1–2.4; Fig. 1B) and 2.8 mo (95% CI 2.4–3.4) according to modified RECIST.

The RECIST ORR was 13% (95% CI 11–16%), including complete responses in 3%. The modified RECIST ORR was 14% (95% CI 12–17%). The DCR was 40% (95% CI 37–43%). Median DoR is not mature but the lower limit of the 95% CI for the median is 13.2 mo (upper limit not evaluable; Fig. 1C).

As shown in Table 4 and Fig. 2, efficacy in difficult-to-treat populations was generally consistent with results in the overall population treated in SAUL, except for shorter OS among patients with CNS metastases and significantly worse OS, PFS, ORR, and DCR among patients with ECOG PS 2. In the converse IMvigor211-like population, median OS was 10.0 mo (95% CI 8.8–11.9), the 6-mo OS rate was 65% (95% CI 61–69%), and the 1-yr OS rate was 46% (95% CI 41–50%). The ORR was 14% (95% CI 11–17%), including complete responses in 4%. Among patients with no prior treatment for metastatic disease (recurrence within 12 mo of [neo] adjuvant therapy), median OS was 9.9 mo (95% CI 7.8–12.4).

4. Discussion

SAUL is the first large prospective clinical trial designed to explore the safety of immunotherapy in advanced urothelial cancer, including patient populations that are rarely included in clinical trials. The prevalence of PD-L1 IC2/3 expression was similar in SAUL (26%) and IMvigor211 (25%). Atezolizumab was well tolerated and safety results in the SAUL real-world setting are consistent with previous atezolizumab experience, despite the less selected population. Treatment-related grade 5 AEs were observed in 0.7% of patients; immune-related AEs were relatively infrequent.

Efficacy in the real-world population enrolled in SAUL is similar to that in previous phase 3 trials of cancer immunotherapy [13,15]. Among the two-thirds of patients corresponding to an IMvigor211-like population (excluding difficult-to-treat subgroups ineligible for IMvigor211), median OS was 10.0 mo. This is within the range observed with pembrolizumab in KEYNOTE-045 [15] and atezolizumab in IMvigor211 [13]. These results further support the use of atezolizumab in IMvigor211-like patients. Notably, efficacy in patients who had received no prior therapy for

Table 4 – Subgroup analyses of efficacy

Endpoint	All (n = 1004)	ECOG PS 2 (n = 101)	CNS mets (n = 14)	RI (n = 46)	AID (n = 35)	CSU (n = 40)	NU/M (n = 47)	IMvigor211-like[a] (n = 643)	0 prior lines for MD (n = 384)[b]
Median OS, mo (95% CI)	8.7 (7.8–9.9)	2.3 (1.6–2.6)	3.7 (1.5–7.0)	5.7 (3.4–11.0)	8.2 (6.5–11.7)	4.2 (2.9–9.0)	7.3 (4.5–10.0)	10.0 (8.8–11.9)	9.9 (7.8–12.4)
6-mo OS rate, % (95% CI)	60 (57–63)	18 (11–26)	29 (9–52)	44 (29–58)	74 (56–86)	49 (32–63)	57 (42–70)	65 (61–69)	62 (56–66)
1-yr OS rate, % (95% CI)	41 (38–44)	11 (6–19)	19 (4–44)	21 (0–36)	31 (16–48)	31 (17–46)	28 (14–43)	46 (41–50)	45 (39–50)
Median PFS, mo (95% CI)	2.2 (2.1–2.4)	1.6 (1.5–1.9)	2.0 (1.5–2.3)	3.3 (2.1–5.9)	4.4 (2.2–6.3)	2.1 (1.9–6.1)	2.1 (1.9–3.1)	2.3 (2.2–2.6)	2.3 (2.1–3.2)
ORR, % (95% CI)	13 (11–16)	5 (2–11)	0 (0–23)	13 (5–26)	11 (3–27)	18 (7–33)	9 (2–20)	14 (11–17)	16 (13–20)
CR, %	29 (3)	0	0	0	0	0	1 (2)	23 (4)	18 (5)
DCR, % (95% CI)	40 (37–43)	14 (8–22)	29 (8–58)	46 (31–61)	51 (34–69)	35 (21–52)	36 (23–52)	41 (37–45)	42 (37–47)
Median DoR, mo (95% CI)	NE (13.2–NE)	6.4 (4.1–NE)	NE (NE–NE)	NE (4.2–NE)	10.6 (4.4–10.6)	NE (4.2–NE)	NE (6.4–NE)	15.9 (13.0–NE)	15.9 (10.6–NE)

AID = autoimmune disease; CI = confidence interval; CNS mets = central nervous system metastases; CR = complete response; CSU = concomitant steroid use; DCR = disease control rate; DoR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; MD = metastatic disease; NE = not evaluable; NU/M = nonurothelial/mixed; ORR = overall response rate; OS = overall survival; RI = renal impairment.

[a] All patients except those in subgroups excluded from the IMvigor211 phase 3 trial.

[b] Patients whose disease relapsed within 12 mo of (neo)adjuvant treatment.

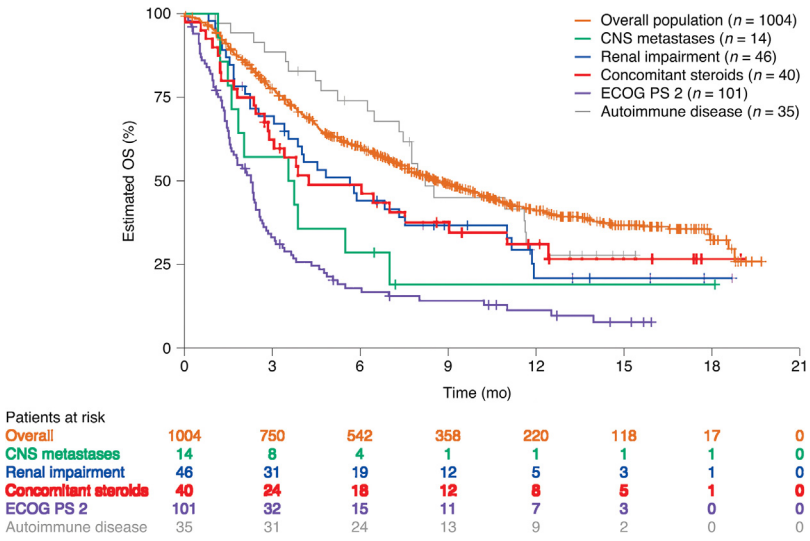

Fig. 2 – Efficacy in the overall population and prespecified difficult-to-treat subgroups. CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance status; OS = overall survival.

metastatic disease was in line with that in the overall population.

Currently many of the understudied patient populations deliberately included in SAUL do not receive chemotherapy and are ineligible for trials [16]. Results from SAUL provide information for clinicians and patients on the feasibility of immunotherapy in these populations. A previous retrospective analysis of patients with rheumatic disease before or during anti-PD-1 therapy suggested a high rate of rheumatoid flares [17]. In our analysis of patients with any autoimmune disease, AESIs appeared to be more common than in the overall population but treatment discontinuation was infrequent. Poor efficacy in patients with ECOG PS 2 is difficult to interpret. The literature includes minimal information on outcomes with chemotherapy or cancer immunotherapy in this setting, although Necchi et al. [18] reported more than twofold worse OS for metastatic urothelial carcinoma patients with ECOG PS $\geq$2 compared with ECOG PS 0. Similarly, outcomes for pembrolizumab-treated melanoma patients with ECOG PS $\geq$2 were significantly worse than for those with ECOG PS $\leq$1 [19]. We also observed short OS for patients with CNS metastases treated in SAUL. Such patients are usually excluded from clinical trials; the limited reports in the literature suggest poor outcomes in these populations irrespective of treatment [20,21]. The 95% CIs for efficacy parameters in the subgroup of patients receiving corticosteroids at baseline overlap with those for the overall population, although the suggestion of worse efficacy is consistent with a previous retrospective study describing significantly worse PFS and OS among patients with non-small-lung cell cancer treated with anti-PD-1/PD-L1 who were receiving steroids at baseline [22].

Limitations of SAUL include the single-arm design and the relatively small patient numbers in some of the understudied subgroups. Nevertheless, data for some of the difficult-to-treat populations provide information on the use of atezolizumab in patients for whom there was previously little or no information on treatment outcomes. For example, tolerability in patients with ECOG PS 2 was similar to that in the overall population.

5. Conclusions

Results from SAUL in a real-world population demonstrate that atezolizumab is a tolerable and effective treatment for urinary tract carcinoma, even in complex comorbid populations such as patients with renal impairment or autoimmune diseases. These results generated in an international real-world population provide reassurance that atezolizumab can be offered to a broader range of patients presenting in routine clinical practice and meeting the approved indication for atezolizumab. Notably, efficacy in SAUL was similar to that reported for atezolizumab in the IMvigor211 phase 3 trial and other clinical trials of PD-L1 and PD-1 inhibitors. Final results are expected in 2022, 4 yr after enrolment of the last patient.

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Study conception and design: Sternberg, Loriot, James, Choy, Castellano, Lopez-Rios, de Ducla, Fear, Merseburger.
Acquisition of data: Sternberg, Castellano, Banna, De Giorgi, Masini, Bamias, Garcia del Muro, Duran, Powles, Gamulin, Zengerling, Geczi, Gedye, Merseburger.
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Data sharing statement: Qualified researchers may request access to individual patient-level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on the Roche criteria for eligible studies are available at https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx. Further details on the Roche global policy on sharing of clinical information and how to request access to related clinical study documents are at www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2019.03.015.

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