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Safety and Efficacy of Atezolizumab in Under Studied Populations with Pretreated Urinary Tract Carcinoma: Subgroup Analyses of the SAUL Study in Real-World Practice

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Purpose: Atezolizumab is an established treatment option for pretreated urothelial carcinoma, demonstrating efficacy in phase II/III trials. The SAUL study enrolled a broader patient population to determine safety and efficacy in under represented subgroups.

Abbreviations and Acronyms

AE = adverse event
CrCl = creatinine clearance
DCR = disease control rate
ECOG PS = Eastern Cooperative Oncology Group performance status
IC = immune cell
ORR = overall response rate
OS = overall survival
PD-L1 = programmed cell death ligand-1
PFS = progression-free survival
UTUC = upper tract urothelial carcinoma

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Data Statement: Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available at https://vivli.org/members/ourmembers/. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

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Materials and Methods: Patients with metastatic urinary tract carcinoma received atezolizumab 1,200 mg every 3 weeks until disease progression, unacceptable toxicity, loss of clinical benefit or patient/physician decision. The primary endpoint was safety. Efficacy was a secondary endpoint. Analyses by programmed cell death ligand-1 (PD-L1) status, age, Eastern Cooperative Oncology Group performance status (ECOG PS) and renal impairment were prespecified; post hoc analyses explored outcomes by tumor location.

Results: A total of 1,004 patients were enrolled. Subgroup analyses in patients with older age, renal impairment or upper tract urothelial carcinoma showed safety and efficacy similar to those in patients without these characteristics. Patients with ECOG PS 2 had clinical features typically associated with aggressive disease; median overall survival was 2.3 months versus 10.0 months in patients with ECOG PS 0/1. Patients with PD-L1 expression on ≥5% of tumor-infiltrating immune cells tended to have better outcomes than those with <5% PD-L1 expression, although conclusions on the relative efficacy of atezolizumab cannot be drawn from this single-arm study.

Conclusions: The under studied populations included in the SAUL study had similar outcomes to those in more selected populations included in phase II/III trials of atezolizumab, except for those with ECOG PS 2. Age ≥80 years and/or creatinine clearance <30 ml/minute does not preclude administration of atezolizumab; however, treatment risk vs benefit must be carefully assessed in patients with ECOG PS 2.

Key Words: atezolizumab, PD-L1, renal impairment, unmet need, urothelial carcinoma

THE humanized monoclonal antibody atezolizumab, which targets programmed cell death ligand-1, is a recommended monotherapy option for patients with locally advanced or metastatic urothelial carcinoma who have received prior platinum-containing chemotherapy.[1,2] Guideline recommendations are supported by the phase II and III IMvigor210 and IMvigor211 trials.[3–5] The subsequent single-arm SAUL study (NCT02928406) evaluated atezolizumab in a "real-world" population more representative of patients presenting in everyday oncology practice. Inclusion criteria were broadened to evaluate the safety and efficacy of atezolizumab in under studied patient populations, including those with autoimmune disease, renal impairment or poor performance status. Primary results demonstrated median overall survival of 8.7 (95% CI 7.8–9.9) months and a safety profile consistent with previous atezolizumab trials in more selected populations.[6] The primary report included findings in the "IMvigor211-like" patient population, ie without characteristics and comorbidities that would have excluded them from the pivotal IMvigor211 trial.[5] Here we describe subgroup analyses according to PD-L1 status and age, and focus on patient populations of particular clinical interest that were ineligible for previous atezolizumab studies in urothelial carcinoma and for whom there is limited understanding of the safety and efficacy of immunotherapy. These include patients with Eastern Cooperative Oncology Group performance status 2, renal impairment and upper tract urothelial carcinoma or Bellini collecting duct tumors. Outcomes in patients with autoimmune disease have been reported previously.[7]

MATERIALS AND METHODS

The trial design has been described previously.[6] Briefly, patients with metastatic urinary tract carcinoma (urothelial or nonurothelial [all subtypes in the WHO classification], including Bellini collecting duct tumors if independently reviewed by 2 expert pathologists from different sites) received atezolizumab 1,200 mg every 3 weeks until disease progression, unacceptable toxicity, loss of clinical benefit, or patient/physician decision. The primary endpoint was safety (National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0). Secondary endpoints included OS, progression-free survival, overall response rate (assessed by Response Evaluation Criteria in Solid Tumours, version 1.1) and disease control rate (proportion of patients with complete or partial response, or stable disease for ≥4 weeks). PD-L1 expression was assessed on immune cells using the Ventana SP142 assay.[8] Patients with available PD-L1 status were analyzed according to PD-L1 IC 0/1 (PD-L1 expression on <5% of tumor-infiltrating ICs) or IC 2/3 (PD-L1 expression on ≥5% of tumor-infiltrating ICs). 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.

Subgroup analyses according to PD-L1 status, ECOG PS and renal impairment were prespecified in the protocol. Post hoc analyses according to age categorized the population into nonoverlapping subgroups aged 65–74, 75–79, and ≥80 years.

Analyses according to ECOG PS (2 vs 0/1) compared baseline factors, adverse events and efficacy. AE incidences were restricted to the first 45 days of atezolizumab to adjust for differing treatment exposure between the 2 subgroups.

In SAUL, patients with a history of renal failure and/or renal impairment were eligible if creatinine clearance

(calculated using the Cockroft–Gault formula) was ≥15 ml/minute. Patients with a significant renal disorder indicating a need for renal transplant were ineligible. Patients were classified as: chemotherapy ineligible (CrCl 15–<30 ml/minute); cisplatin ineligible and carboplatin eligible (CrCl 30–<60 ml/minute); or cisplatin eligible (CrCl ≥60 ml/minute).

Finally, in post hoc analyses according to tumor location, patients were categorized as having upper tract (subdivided into renal pelvis vs ureter) or bladder urinary carcinoma. Analyses of the subgroup with Bellini collecting duct tumors were descriptive.

Baseline characteristics, treatment exposure, and safety were analyzed in patients who received at least 1 dose of atezolizumab using SAS® 9.4. Efficacy was analyzed in the intent-to-treat population, comprising all enrolled patients. In all subgroup analyses, patients with missing data for the parameter distinguishing the subgroup were excluded.

RESULTS

Between November 30, 2016 and March 16, 2018, 1,004 patients were enrolled from 32 countries. Of these, 997 received atezolizumab. Data cut-off for the prespecified primary analysis was September 16, 2018 (median followup 12.7 months). Table 1 summarizes baseline characteristics by subgroup.

PD-L1 Status

Subgroup analyses according to PD-L1 status excluded 69 patients (7%) with missing PD-L1 status. Baseline characteristics were similar between subgroups (supplementary table 1, https://www.jurology.com).

There were no obvious differences in safety according to PD-L1 status, especially when considering the longer treatment exposure in patients with IC 2/3 than IC 0/1 (median 3.7 vs 2.4 months, respectively; table 2). Reasons for treatment discontinuation were similar between subgroups, except that a slightly lower proportion of patients in the IC 2/3 than the IC 0/1 subgroup discontinued therapy because of disease progression (59% vs 69%, respectively).

OS, ORR, and DCR were more favorable in patients with IC 2/3 than IC 0/1 (see figure and table 3). The supplementary figure (https://www.jurology.com) shows further subgroup analyses by PD-L1 status and prior treatment lines for metastatic disease.

Age

Incidences of AEs, treatment-related AEs, and AEs of special interest were similar across age groups beyond what might be explained by differences in treatment duration (shortest in patients aged ≥80 years). Among the 78 patients aged ≥80 years, 7 (9%) experienced grade 3 treatment-related AEs, comprising fatigue, erysipelas/hypophosphatemia, diarrhea, colitis, increased aspartate aminotransferase/myocardial necrosis marker, hypertension, and atrial flutter/

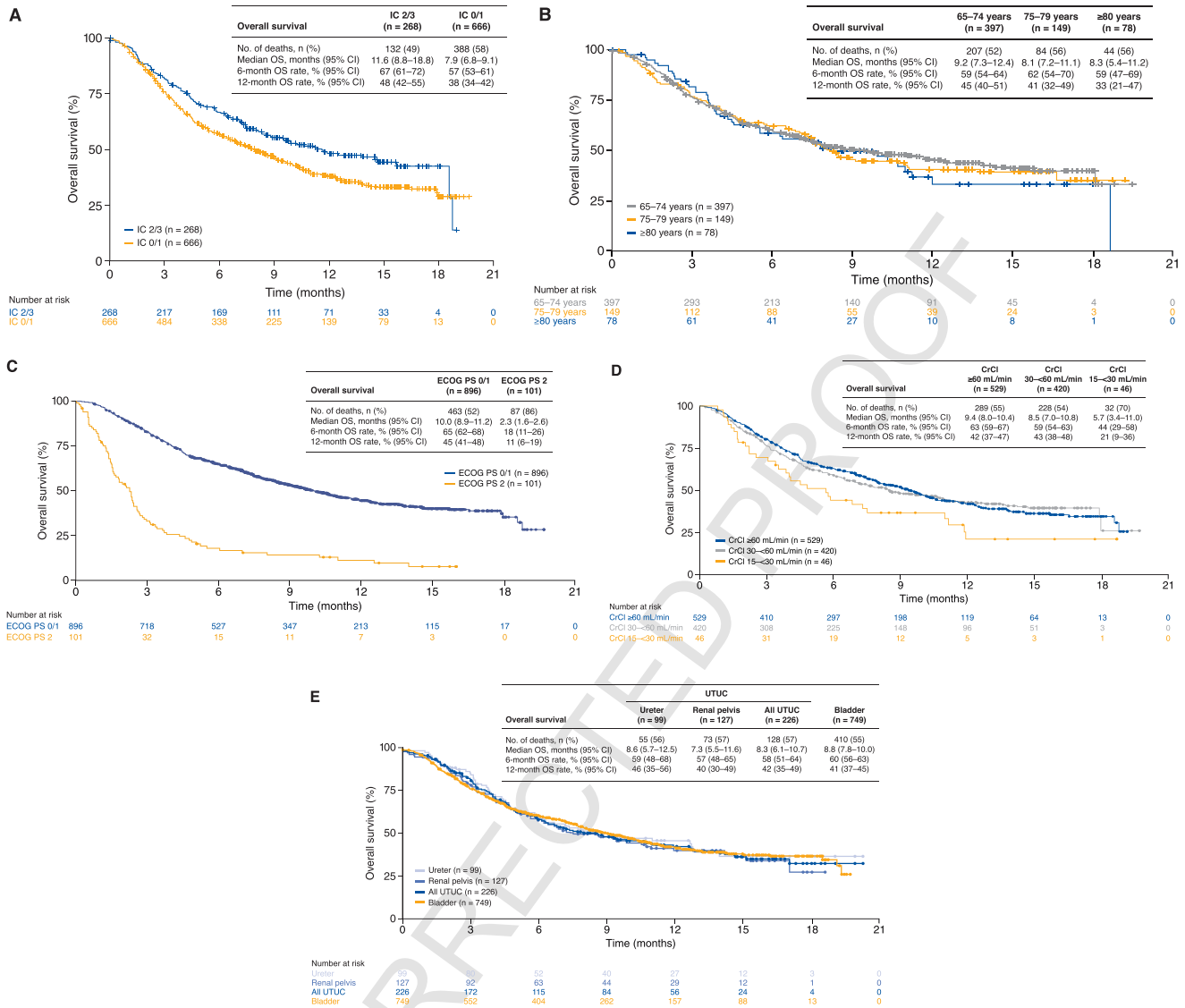
Table 1. *Baseline characteristics in subgroups of clinical interest*

		Age (yrs)			ECOG PS			Creatine Clearance (ml/min)				Tumor Location				
												UTUC				
		65–74	75–79	≥80	2	0/1	15–<30	30–<60	≥60	Ureter	Renal Pelvis	All UTUC	Bladder
No. pts	393	149	78	101	896	46	420	529	98	126	224	744	
Median yrs age (range)	70 (65–74)	77 (75–79)	82 (80–93)	69 (43–93)	68 (34–92)	75 (48–92)	72 (40–93)	63 (34–86)	68 (38–93)	70 (36–92)	69 (36–93)	68 (34–88)	
No. female (%)	89 (23)	30 (20)	21 (27)	23 (23)	202 (23)	15 (33)	112 (27)	97 (18)	24 (24)	43 (34)	67 (30)	153 (21)	
No. current/former smoker (%)	274 (70)	91 (61)	42 (54)	65 (64)	605 (68)	24 (52)	290 (69)	355 (67)	54 (55)	78 (62)	132 (59)	521 (70)	
No. ECOG PS (%):													
0	185 (47)	42 (28)	26 (33)	0	427 (48)	10 (22)	167 (40)	249 (47)	40 (41)	59 (47)	99 (44)	314 (42)	
1	173 (44)	85 (57)	42 (54)	0	469 (52)	34 (74)	203 (48)	232 (44)	48 (49)	51 (40)	99 (44)	356 (48)	
2	35 (9)	22 (15)	10 (13)	101 (100)	0	2 (4)	50 (12)	48 (9)	10 (10)	16 (13)	26 (12)	74 (10)	
No. PD-L1 expression (%):													
IC 0/1	267 (68)	93 (62)	51 (65)	70 (69)	594 (66)	31 (67)	276 (66)	356 (67)	65 (66)	83 (66)	148 (66)	494 (66)	
IC 2/3	99 (25)	43 (29)	22 (28)	21 (21)	243 (27)	10 (22)	115 (27)	138 (26)	21 (21)	33 (26)	54 (24)	205 (28)	
Missing	27 (7)	13 (9)	5 (6)	10 (10)	59 (7)	5 (11)	29 (7)	35 (7)	12 (12)	10 (8)	22 (10)	45 (6)	
No prior chemotherapy for metastatic urinary tract carcinoma	147 (37)	42 (28)	16 (21)	27 (27)	355 (40)	13 (28)	145 (35)	223 (42)	33 (34)	34 (27)	67 (30)	308 (41)	

Table 2. *Overview of safety*

	PD-L1 Status				Age (yrs)					Creatine Clearance (ml/min)						Tumor Location								
																UTUC								
	IC 0/1		IC 2/3		65–74		75–79		≥80	15–<30		30–<60		≥60		Ureter		Renal Pelvis		All UTUC		Bladder		
No. pts	664		264		363		149		78	46		420		529		98		126		224		744		
Median mos treatment duration (range)	2.4 (0.0–18.9)		3.7 (0.0–19.0)		2.8 (0.0–18.9)		3.8 (0.0–18.7)		2.5 (0.0–16.3)	3.0 (0.0–18.7)		2.8 (0.0–18.9)		2.8 (0.0–19.0)		2.7 (0.0–18.9)		2.0 (0.0–17.3)		2.1 (0.0–18.9)		2.9 (0.0–19.0)		
No. ongoing treatment at data cut-off (%)	128	(19)	76	(29)	92	(23)	37	(25)	15	(19)	8	(17)	102	(24)	110	(21)	25	(26)	22	(17)	47	(21)	167	(22)
No. AEs (%):																								
Any	584	(88)	235	(89)	339	(86)	135	(91)	69	(88)	37	(80)	365	(87)	476	(90)	85	(87)	111	(88)	196	(88)	656	(88)
Treatment related	332	(50)	161	(61)	210	(53)	91	(61)	38	(49)	18	(39)	220	(52)	291	(55)	49	(50)	70	(56)	119	(53)	391	(53)
Special interest	187	(28)	99	(38)	125	(32)	43	(29)	18	(23)	7	(15)	116	(28)	180	(34)	25	(26)	44	(35)	69	(31)	227	(31)
No. grade ≥3 AEs (%):																								
Any	299	(45)	119	(45)	179	(46)	81	(54)	29	(37)	21	(46)	188	(45)	239	(45)	42	(43)	53	(42)	95	(42)	339	(46)
Treatment related	75	(11)	41	(16)	56	(14)	19	(13)	8	(10)	3	(7)	51	(12)	73	(14)	11	(11)	20	(16)	31	(14)	93	(13)
Special interest	37	(6)	24	(9)	34	(9)	8	(5)	3	(4)	1	(2)	23	(5)	43	(8)	6	(6)	9	(7)	15	(7)	49	(7)
No. AE leading to atezolizumab withdrawal (%)	38	(6)	17	(6)	27	(7)	8	(5)	3	(4)	3	(7)	22	(5)	32	(6)	5	(5)	8	(6)	13	(6)	42	(6)

Safety analyses according to ECOG PS are provided in supplementary table 2 (https://www.jurology.com).



OS according to PD-L1 status (*A*), age (*B*), ECOG PS (*C*), CrCl (*D*) and tumor location (*E*). IC 0/1=PD-L1 expression on <5% of tumor-infiltrating immune cells; IC 2/3=PD-L1 expression on ≥5% of tumor-infiltrating immune cells.

tachycardia. There was 1 grade 4 treatment-related AE (neutropenia) but no treatment-related deaths. Three patients aged ≥80 years experienced grade 3 AEs of special interest (1 case each of aspartate aminotransferase increased, γ-glutamyltransferase increased and colitis). There was no excess of treatment discontinuations because of AEs in patients aged ≥80 years (table 2).

Subgroup analyses by age showed similar OS in patients aged 65−74, 75−79, and ≥80 years (see figure and table 3); ORR and DCR were numerically lower in the oldest patients but 95% CIs overlapped.

Eastern Cooperative Oncology Group Performance Status

There were notable differences in baseline characteristics between subgroups defined by ECOG PS (table 1). Patients with ECOG PS 2 were more likely to have visceral metastases (51% vs 36% of patients with ECOG PS 0/1), prior chemotherapy for metastatic disease (73% vs 60%, respectively), serum hemoglobin <10 g/dL (32% vs 13%), low albumin (≤lower limit of normal; 47% vs 21%) and high alkaline phosphatase (≥upper limit of normal; 45% vs 23%).

Treatment exposure (representing perceived duration of benefit) was considerably shorter in patients with ECOG PS 2 vs ECOG PS 0/1 (median 0.7 vs 3.5 months, respectively; 2 vs 6 cycles). In analyses restricting AE incidences to the first 45 days, safety appeared similar between the 2 subgroups, except for more (treatment-unrelated) grade ≥3 AEs in the ECOG PS 2 subgroup and fewer treatment-related grade 1/2 AEs (supplementary

Table 3. *Summary of efficacy*

	PD-L1 Status				Age (yrs)						ECOG PS				Creatine Clearance (ml/min)						Tumor Location							
																					UTUC							
	IC 0/1		IC 2/3		65–74		75–79		≥80		2		0/1		15–<30		30–<60		≥60		Ureter		Renal Pelvis		All UTUC		Bladder	
No. pts	666		268		397		149		78		101		896		46		420		529		99		127		226		749	
No. deaths (%)	388	(58)	132	(49)	207	(52)	84	(56)	44	(56)	87	(86)	463	(52)	32	(70)	228	(54)	289	(55)	55	(56)	73	(57)	128	(57)	410	(55)
Median mos OS (95% CI)	7.9	(6.8–9.1)	11.6	(8.8–18.8)	9.2	(7.3–12.4)	8.1	(7.2–11.1)	8.3	(5.4–11.2)	2.3	(1.6–2.6)	10.0	(8.9–11.2)	5.7	(3.4–11.0)	8.5	(7.0–10.8)	9.4	(8.0–10.4)	8.6	(5.7–12.5)	7.3	(5.5–11.6)	8.3	(6.1–10.7)	8.8	(7.8–10.0)
% 6-mo OS rate (95% CI)	57	(53–61)	67	(61–72)	59	(54–64)	62	(54–70)	59	(47–69)	18	(11–26)	65	(62–68)	44	(29–58)	59	(54–63)	63	(59–67)	59	(48–68)	57	(48–65)	58	(51–64)	60	(56–63)
% 12-mo OS rate (95% CI)	38	(34–42)	48	(42–55)	45	(40–51)	41	(32–49)	33	(21–47)	11	(6–19)	45	(41–48)	21	(9–36)	43	(38–48)	42	(37–47)	46	(35–56)	40	(30–49)	42	(35–49)	41	(37–45)
No. PFS events (%)	388	(58)	132	(49)	317	(80)	115	(77)	62	(79)	93	(92)	704	(79)	35	(76)	329	(78)	432	(82)	73	(74)	104	(82)	177	(78)	595	(79)
Median mos PFS (95% CI)	2.2	(2.1–2.3)	2.6	(2.1–4.1)	2.3	(2.1–3.4)	2.5	(2.1–4.2)	2.2	(2.1–2.9)	1.6	(1.4–1.9)	2.4	(2.2–2.9)	3.3	(2.1–5.9)	2.3	(2.1–2.9)	2.2	(2.1–2.4)	3.2	(2.1–4.2)	2.1	(2.1–2.6)	2.2	(2.1–3.3)	2.2	(2.1–2.5)
No. objective response rate (%), [95% CI]*	69	(10), [8–13]	55	(21), [16–26]	59	(15), [12–19]	23	(15), [10–22]	6	(8), [3–16]	5	(5), [2–11]	130	(15), [12–17]	6	(13), [5–26]	62	(15), [12–19]	67	(13), [10–16]	12	(12), [6–20]	14	(11), [6–18]	26	(12), [8–16]	107	(14), [12–17]
No. complete response (%), [95% CI]	14	(2), [1–4]	12	(4), [2–8]	12	(3), [2–5]	5	(3), [1–8]	1	(1), [0–7]	0	[0–4]	29	(3), [2–5]	0	[0–8]	15	(4), [2–6]	14	(3), [1–4]	3	(3), [1–9]	4	(3), [1–8]	7	(3), [1–6]	21	(3), [2–4]
No. DCR (%), [95% CI]†	250	(38), [34–41]	121	(45), [39–51]	172	(43), [38–48]	66	(44), [36–53]	27	(35), [24–46]	14	(14), [8–22]	384	(43), [40–46]	21	(46), [31–61]	179	(43), [38–48]	197	(37), [33–42]	42	(42), [33–53]	45	(35), [27–44]	87	(39), [32–45]	301	(40), [37–44]

IC 2/3 = PD-L1 expression on ≥5% of tumor-infiltrating immune cells.
* Patients with nonmeasurable disease are reported with overall responses (complete response/partial response/stable disease/progressive disease) according to investigator's overall assessment.
† Complete or partial response, or stable disease for ≥4 weeks.

table 2, https://www.jurology.com). There were no major qualitative differences in AEs according to ECOG PS, except for numerically more all-grade anemia (13% vs 8%) and vomiting (10% vs 5%) in the ECOG PS 2 vs 0/1 subgroup.

All efficacy parameters were notably worse in patients with ECOG PS 2 vs 0/1 (see figure and table 3). Among 101 patients with ECOG PS 2, none of the baseline factors explored was significantly associated with worse OS or DCR (supplementary table 3, https://www.jurology.com). However, patients with ECOG PS 2 and either visceral metastases or high alkaline phosphatase at baseline appeared to have particularly poor outcomes.

Renal Impairment

The SAUL study included 46 patients (5%) classified as chemotherapy ineligible, 420 (42%) as cisplatin ineligible and carboplatin eligible, and 529 (53%) as cisplatin eligible. Patients with lower CrCl were more likely to be older, female, have a worse ECOG PS and have received prior therapy for metastatic disease (table 1). However, these differences were not statistically significant after adjustment for multiplicity in the setting of this post hoc subgroup analysis.

Atezolizumab exposure was similar in the 3 CrCl subgroups and there was no difference in the proportion of patients discontinuing atezolizumab because of AEs (table 2), nor was there any excess of AEs in the chemotherapy-ineligible or cisplatin-ineligible subgroups. There was no evidence of an increase in treatment-related AEs, or any specific AE or AE of special interest in patients with CrCl 15−<30 ml/minute. Among patients with CrCl 15−<30 ml/minute, 3 experienced treatment-related grade 3 AEs (1 case each of pruritus, musculoskeletal pain and hypertension) but there were no grade 4 or 5 treatment-related AEs. There was 1 grade ≥3 AE of special interest (ascites, which had recovered/resolved by data cut-off).

OS appeared to be slightly worse in patients with CrCl 15−<30 ml/minute than in other subgroups (see figure and table 3). However, PFS, ORR and DCR were consistent across subgroups regardless of CrCl (table 3).

Upper Tract Urothelial Carcinoma

The UTUC subgroup included 226 patients (of whom 99 had ureteral carcinoma and 127 had renal pelvis carcinoma). Baseline characteristics in the subgroups and subcategories were generally similar (supplementary table 4, https://www.jurology.com), except that the UTUC subgroup included a numerically smaller proportion of patients with no prior therapy for metastatic disease compared with the bladder subgroup (30% vs 41%, respectively) and a numerically smaller proportion of patients reporting as current or former smokers (59% vs 70%, respectively). Supplementary table 5 shows outcomes in the 8 patients with Bellini collecting duct tumors (https://www.jurology.com).

Overall, the incidences of AEs, grade ≥3 AEs, treatment-related AEs, and AEs leading to treatment discontinuation were similar between the subgroups (table 2). Urinary tract infection was slightly more common in patients with bladder carcinoma than UTUC (17% vs 11%, respectively) and arthralgia was more common in patients with ureter than renal pelvis carcinoma (12% vs 6%, respectively). There were no relevant differences between subgroups in the incidences of the most common AEs of special interest (hypothyroidism, rash and hyperthyroidism).

Efficacy was very similar in the 4 subgroups (median OS: 8.3 months in the UTUC subgroup and 8.8 months in the bladder subgroup; 1-year OS rate: 42% vs 41%, respectively; see figure and table 3).

DISCUSSION

These analyses provide real-world context that is relevant for physicians treating urinary tract carcinoma with immunotherapy in routine clinical practice. These findings help address concerns about the gap between efficacy and effectiveness[9,10] and are important when discussing expectations with patients with comorbidities and/or older age. By including patients more representative of routine practice, who tend to be older, frailer, and with additional medical problems, and thus at higher risk of AEs, the SAUL study was designed to provide evidence that is often lacking from randomized controlled trials in highly selected patient populations treated in specialized centers.[10]

Older patients may be more likely to experience AEs because of biological changes to the immune system associated with aging[11] but there is limited understanding of the generalizability of immunotherapy efficacy and safety in older patients.[12] The SAUL study, which included 78 atezolizumab-treated patients aged ≥80 years, offers important new information in this setting, showing no evidence of increased toxicity or reduced OS in older patients. Outcomes did not differ substantially between patients aged 65−74 and 75−79 years, although 1-year OS, ORR, and DCR were numerically lower in patients aged ≥80 years.

In patients with ECOG PS 2, median OS was only 2.3 months, compared with 10.0 months in those with ECOG PS 0/1. This dismal prognosis is consistent with clinical experience and outcomes reported in the literature for chemotherapy.[13,14] The poor efficacy may potentially be explained by

differences in patient characteristics and prognostic variables, and subgroup differences in the prognostic effect of those variables. In SAUL, patients with ECOG PS 2 were more likely to have characteristics often associated with more aggressive disease. The higher proportion of patients with poor prognostic factors despite similar age in the ECOG PS 2 subgroup compared with the ECOG PS 0/1 subgroup may suggest that poor ECOG PS was related to disease rather than comorbidities. Safety analyses showed increased incidences of anemia and hypoalbuminemia, commonly observed in patients with ECOG PS 2. Although there was no substantial increase in treatment-related toxicities with ECOG PS 2, this should be interpreted cautiously given the short treatment duration.

These post hoc analyses suggest that immune checkpoint inhibitors may not overcome the negative prognostic impact of ECOG PS 2, consistent with reports in the literature.[15,16] Possible explanations include insufficient treatment duration for immune mediation, or a rapidly progressive disease that is unresponsive to immune-mediated control. Risk vs benefit should be considered especially carefully when treating patients with ECOG PS 2 due to high disease burden and/or visceral disease.

Little is known about the impact of severe preexisting renal impairment on the efficacy and safety of atezolizumab. Post hoc analyses according to CrCl suggest that patients typically considered ineligible for cisplatin or other chemotherapy are candidates for atezolizumab. Patients with renal impairment achieved similar ORR and DCR to patients with CrCl $\geq$60 ml/minute, without increased toxicity. Imbalances in patient characteristics may explain numerical differences in OS. Despite their post hoc nature, these analyses provide important new information on the potential role of atezolizumab in patients unable to receive platinum-based chemotherapy (cisplatin or carboplatin).

Owing to the rarity of UTUC, high-level evidence on outcomes is lacking,[17,18] but typically UTUC responds poorly to standard chemotherapy.[19] Analysis of 220 biomarker-evaluable atezolizumab-treated patients in phase II/III trials suggested worse outcomes in UTUC than lower tract urothelial carcinoma.[20] Exploratory analyses of the SAUL study showed very similar efficacy and safety in patients with UTUC versus bladder carcinoma, providing reassurance that atezolizumab is a reasonable treatment in such patients.

More generally, the relevance of PD-L1 as a predictive (and prognostic) factor appears to vary between settings. In the first line treatment setting for urothelial carcinoma, eligibility for atezolizumab (and pembrolizumab) is dependent on PD-L1 expression, whereas in the second line setting, immunotherapy may be used irrespective of PD-L1 status.[21] In exploratory subgroup analyses of SAUL, atezolizumab was effective and well tolerated across both subgroups defined by PD-L1 status. OS and ORR appear enhanced in the PD-L1 IC 2/3 subgroup, consistent with IMvigor210[4] and IMvigor211.[5] However, in this single-arm study, no conclusions can be drawn on predictive vs prognostic effects.

A limitation of all of these analyses is the lack of a control arm, preventing assessment of the contribution of atezolizumab to efficacy and safety outcomes, and the post hoc nature of most of the subgroup analyses. However, the homogeneous treatment, monitoring, and data collection in this prospective study provides some of the best available insights into safety and efficacy in these populations, for which experience and evidence are very limited. Another limitation in safety comparisons is the differing duration of treatment between subgroups. After adjusting for treatment duration, apparent differences favoring the ECOG PS 2 subgroup disappeared.

CONCLUSIONS

In conclusion, these results suggest that clinical characteristics traditionally associated with worse outcome do not necessarily preclude use of atezolizumab therapy for urothelial carcinoma. In more difficult-to-treat populations, such as those with low CrCl or old age, immunotherapy may be a reasonable approach. The exception to this is the patient with poor performance status, where careful consideration is needed before deciding to treat. The benefit:risk profile of atezolizumab observed in the SAUL study should be considered during treatment decision making.

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EDITORIAL COMMENTS

The application of data derived from well-selected phase III trial patients to real-world patients is unclear. In this context, inclusive studies of patients who are typically under represented in phase II or III registration trials play a major role in informing clinical practice and bridging the gulf between efficacy and utility. The SAUL trial is a large (1,004 patients) multinational, single-arm study to primarily assess the safety of atezolizumab in patients with progressive advanced urothelial or nonurothelial carcinoma of the urinary tract following prior platinum or nonplatinum therapy, many of whom were ineligible for preceding phase II and III trials. Previously, sub-analyses of SAUL have reported that atezolizumab was safe in those with preexisting controlled autoimmune disease (references 6 and 7 in article). This subgroup analysis in *The Journal of Urology®* reports outcomes based on age, impaired renal function, location of primary (upper vs lower tract), PD-L1 status and performance status (PS) of 2.

Overall, atezolizumab appeared safe and active regardless of age, renal function, and primary tumor location, although clinical outcomes appeared worse in those with PS 2 and low tumor tissue immune cell PD-L1 protein expression. Imbalances in patient characteristics did confound some observations. Notably, the survival was numerically lower in patients aged $\geq$80 years and those with CrCl 15 to <30 ml/minute. Atezolizumab was voluntarily withdrawn from the United States market in March 2021 for post-platinum patients by the manufacturer based on absence of corroborating phase III data. Atezolizumab remains an option for first line cisplatin-ineligible patients with high PD-L1 expression or platinum-ineligible patients.

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There is no doubt that checkpoint inhibitor (CPI) therapy represents the greatest forward stride in advanced bladder cancer therapy to date. The initial data for 5 CPIs (pembrolizumab, atezolizumab, durvalumab, avelumab, and nivolumab) following platinum-based chemotherapy offered the potential promise of long-term disease control, albeit in a minority of patients—each of these early data sets led to U.S. Food and Drug Administration approval. It has therefore been somewhat sobering to begin to see the U.S. Food and Drug Administration retract some of these approvals, most recently for atezolizumab and durvalumab.[1,2] These retractions have led to fierce debate—in the context of atezolizumab, for instance, the phase III IMvigor 211 trial was thought to have failed on account of a unique biomarker-based endpoint (reference 5 in article). Had IMvigor 211 instead followed the straightforward design used to evaluate pembrolizumab in KEYNOTE-045, the study may have been similarly positive.[3] Irrespective of the circumstances, the investigative community is now left with the challenge of how to interpret data sets like the SAUL trial. This rich experience with prospective examination of 1,004 patients with advanced bladder cancer treated with atezolizumab still bears significant fruit. Even if atezolizumab itself cannot be applied in clinical practice, the data support use of other CPIs in the context of mild renal dysfunction and older age. Similarly, the data suggest caution in using CPIs in patients with poor performance status. Although the purist might suggest that these principles would need to be reassessed in emerging settings for CPIs (eg maintenance therapy or adjuvant treatment), these data will suffice in the interim.

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