Partial Response and Stable Disease Correlate with Positive Outcomes in Atezolizumab-treated Patients with Advanced Urinary Tract Carcinoma

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Abstract

Background: The value of a complete response to immune checkpoint inhibitor treatment for urothelial cancer is well recognised, but less is known about long-term outcomes in patients with a partial response or the benefit of achieving disease stabilisation.

Objective: To determine clinical outcomes in patients with a partial response or stable disease on atezolizumab therapy for advanced urinary tract carcinoma (UTC). Design, setting, and participants: Data were extracted from three prospective trials (IMvigor210 cohort 2, SAUL, and IMvigor211) evaluating single-agent atezolizumab therapy for platinum-pretreated advanced UTC. The analysis population included 604 atezolizumab-treated and 208 chemotherapy-treated patients (229 achieving a partial response and 583 achieving stable disease).

Intervention: Atezolizumab 1200 mg every 3 wk until progression or unacceptable toxicity or single-agent chemotherapy for patients in the control arm of IMvigor211.

Outcome measurements and statistical analysis: Baseline characteristics, treatment exposure, overall survival, duration of disease control. Partial response and stable disease populations were analysed separately.

Results and limitations: The population of patients with a partial response included more patients with programmed cell death ligand 1 (PD-L1) expression on 5% of tumour-infiltrating immune cells than the stable disease population. The median time to best response was 2.1 mo across trials and treatments, regardless of the type of response. Atezolizumab-treated patients with a partial response had sustained disease control (median overall survival not reached); durations of disease control and overall survival were longer with atezolizumab than with chemotherapy. In patients with stable disease, median overall survival was numerically longer with atezolizumab (exceeding 1 yr) than with chemotherapy. Irrespective of treatment, durations of disease control and survival were shorter in patients with stable disease than in those achieving a partial response. These analyses are limited by their post hoc exploratory nature and relatively short follow-up.

Conclusions: Stable disease and partial response are meaningful clinical outcomes in atezolizumab-treated patients with advanced UTC.

Patient summary: In this report, we looked at the outcomes in patients whose tumours responded to treatment to some extent, but the tumour did not disappear completely.

We aimed to understand whether a modest response to treatment was associated with meaningful long-term outcomes for patients. We found that on average, life expectancy was >1 yr in patients whose disease was stabilised and even longer in those whose tumours showed some shrinkage in response to treatment.

1. Introduction

Since 2017, immune checkpoint blockade has become a standard-of-care treatment for advanced urothelial carcinoma. Five agents that inhibit either programmed cell death ligand 1 (PD-L1) or programmed cell death 1 (PD-1) are approved as treatment for advanced urothelial carcinoma that has progressed during or within 12 mo of receiving platinum-based chemo- therapy. These approvals are supported by results from large single-arm studies and randomised phase 3 trials. Long-term data suggest that responses to these treatments are durable [1– 7]. However, response rates are generally quite low (13–24% in single-arm studies and in the KEYNOTE 045 and IMvigor211 randomised phase 3 trials) and rates of complete response are typically around 5% [8]. The value of a complete response to immunotherapy is well recognised, but there is little information about long-term outcomes in patients achieving a partial response (PR), and even less is known about the benefit of achieving stable disease (SD). We sought to explore outcomes in patients with a PR or SD in prospective clinical trials of the immune checkpoint inhibitor atezolizumab, which targets PD- L1, for platinum-pretreated urothelial carcinoma.

2. Patients and methods

The analysis population included patients with metastatic urothelial carcinoma who achieved a PR or SD on study treatment in the single-arm IMvigor210 study (cohort 2 [patients previously treated with platinum for metastatic disease]; Clinicaltrials.gov: NCT02108652) [4], the IMvi- gor211 randomised phase 3 trial (Clinicaltrials.gov: NCT02302807) [7], and the single-arm phase 3B SAUL study (Clinicaltrials.gov: NCT02928406) of a broader population of patients with urothelial or nonurothelial carcinoma of the urinary tract [9]. The designs of all three trials have been described in

detail in the respective primary publications [4,7,9]. Except in the control arm of IMvigor211 (single-agent chemotherapy), all patients received atezolizumab 1200 mg intravenously every 3 wk until loss of clinical benefit or unacceptable toxicity. In the control arm of IMvigor211, patients received the investigator's choice of chemotherapy (vinflunine 320 mg/m2, paclitaxel 175 mg/ m2, or docetaxel 75 mg/m2 every 3 wk) until (but not beyond) progression according to Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1), unacceptable toxicity, or consent withdrawal. Key differences in patient eligibility between studies included disease measurability, inclusion of nonurothelial carcinomas, and Eastern Cooperative Oncology Group (ECOG) performance status eligibility criteria. In IMvigor210 and IMvigor211, all patients had to have measurable disease defined by RECIST (version 1.1) and the patient population was limited to patients with urothelial carcinoma (transitional cell carcinoma). Patients with autoimmune disease or renal impairment, and those receiving concomitant steroids were excluded. In SAUL, patients with non measurable disease, ECOG performance status 2, nonurothelial carcinoma, autoimmune disease, renal impairment, treated asymptomatic central nervous system metastases, and/or concomitant steroids were also eligible.

In all three studies, the best overall response (with confirmation of a complete response or PR) was assessed according to RECIST (version 1.1), and tumours were assessed every 9 wk for the first 12 mo. SD had to be sustained for at least three cycles. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) in all three trials.

In the present analysis, baseline characteristics, time to best response, treatment exposure, duration of disease control, overall survival (OS), and safety were analysed separately in the PR and SD populations of each trial, with the atezolizumab and chemotherapy arms of IMvigor211 analysed separately. OS was calculated as the interval between randomisation (IMvigor211) or the first dose of Results and limitations: The population of patients with a partial response included more patients with programmed cell death ligand 1 (PD-L1) expression on 5% of tumour-infiltrating immune cells than the stable disease population. The median time to best response was 2.1 mo across trials and treatments, regardless of the type of response. Atezolizumab-treated patients with a partial response had sustained disease control (median overall survival not reached); durations of disease control and overall survival were longer with atezolizumab than with chemotherapy.

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Conclusions: Stable disease and partial response are meaningful clinical outcomes in atezolizumab-treated patients with advanced UTC. Patient summary: In this report, we looked at the outcomes in patients whose tumours responded to treatment to some extent, but the tumour did not disappear completely.

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separately. OS was calculated as the interval between randomisation (IMvigor211) or the first dose study drug (IMvigor210 and SAUL) and death from any cause. Duration of disease control was defined as the interval between the first PR/SD and first disease progression or death, censoring at the last tumour assessment for patients alive without progression at data cut-off. Time-to-event data are summarised using Kaplan-Meier estimates; medians are reported with corresponding 95% confidence intervals (CIs). All results are exploratory due to the post hoc nature of this analysis.

In further subgroup analyses, Bellmunt risk factors (base-line ECOG performance status 1, liver metastases, and haemoglobin <10 g/dl) were assessed in each patient using baseline data. OS was assessed in subgroups according to the number of Bellmunt risk factors present and in subgroups according to PD-L1 status (IC 0/1 [PD-L1 expression on <5% of tumour-infiltrating immune cells] vs IC 2/3 [PD-L1 expression on 5% of tumour-infiltrating immune cells]), determined using VENTANA SP142 PD-L1 immunohistochemistry assay (VENTANA Medical Systems, Tucson, AZ, USA).

The data cut-offs used in this analysis represent those reported from the primary analysis of each trial, namely, May 5, 2015, for IMvigor210; March 13, 2017, for IMvigor211; and September 16, 2018, for SAUL [4,7,9].

Table 1 – Baseline characteristics (partial response population, *n* = 229).

	Atezolizumab			Chemotherapy
Characteristic	IMvigor210 (*n* = 31)	IMvigor211 (*n* = 46)	SAUL (*n* = 106)	IMvigor211 (*n* = 46)
Age (yr), median (range)	68 (49–82)	68 (41–84)	68 (44–84)	68 (48–80)
Age >75 yr, *n* (%)	7 (23)	11 (24)	23 (22)	7 (15)
Male, *n* (%)	28 (90)	40 (87)	92 (87)	38 (83)
Smoking history, *n* (%)				
Current	3 (10)	5 (11)	21 (20)	9 (20)
Former	23 (74)	29 (63)	58 (55)	28 (61)
Never	5 (16)	12 (26)	27 (25)	9 (20)
<3 mo since previous chemotherapy, *n* (%)	13 (42)	13 (28)	28 (26)	10 (22)
Creatinine clearance <60 ml/min, *n* (%)	9 (29)	16 (35)	53 (50)	12 (26)
ECOG PS at screening, *n* (%)				
0	18 (58)	25 (54)	54 (51)	26 (57)
1	13 (42)	21 (46)	47 (44)	20 (43)
2	0	0	5 (5)	0
Liver metastases, *n* (%)	7 (23)	10 (22)	18 (17)	6 (13)
Lymph node–only disease, *n* (%)	3 (10)	8 (17)	24 (23)	10 (22)
Number of Bellmunt risk factors, *n* (%)				
0	15 (48)	21 (46)	40 (38)	24 (52)
1	9 (29)	14 (30)	49 (46)	16 (35)
2	7 (23)	9 (20)	17 (16)	5 (11)
3	0	2 (4)	0	1 (2)
PD-L1 expression score, *n* (%)				
IC 0/1	17 (55)	28 (61)	55 (52)	29 (63)
IC 2/3	14 (45)	18 (39)	43 (41)	17 (37)
Missing	0	0	8 (8)	0

ECOG PS = Eastern Cooperative Oncology Group performance status; IC 0/1 = expression on <1–<5% of tumour-infiltrating immune cells; IC 2/3 = expression on >5% of tumour-infiltrating immune cells; PD-L1 = programmed death ligand 1.

3. Results

3.1. Patient population

The analysis population included 229 patients with a PR and583 with SD, of whom 183 (80%) and 421 (72%), respectively, were treated with atezolizumab; the remaining patients received single-agent chemotherapy. Baseline characteristics were generally similar between trials, except for a slightly higher proportion with renal impairment in SAUL, consistent with the less restrictive eligibility criteria in this study (Tables 1 and 2). Sixteen patients (three in the PR subgroup and 13 in the SD subgroup) had nonurothelial or mixed histology. Overall, approximately 40% of patients had no Bellmunt risk factors. PD-L1 IC 2/3 was more common in patients achieving a PR than in those

with SD. Of atezolizumab-treated patients, 41% with a PR versus 26% with SD had PD-L1 IC 2/3. In chemotherapy-treated patients in IMvigor211, 37% with a PR versus 23% with SD had PD-L1 IC 2/3. Compared with the SD population, the population of patients achieving aPR included a slightly higher proportion of males.

3.2. Efficacy

Treatment exposure and efficacy results are presented for the PR and SD populations in Table 3. The median time to best response was 2.1 mo across trials and treatments, irrespective of whether patients achieved a PR or SD as the best response.

In the PR population, there were marked differences in treatment exposure between atezolizumab-treated patients (median 11–20 mo) and patients treated with chemotherapy in the IMvigor211 control arm (median 7 mo). Atezolizumab was also associated with a longer duration of disease control and OS than was observed with chemotherapy. Median disease control was approximately 16 mo with atezolizumab versus 8 mo with chemotherapy alone in patients with a PR. Median OS was not reached in the atezolizumab arm in any of the trials and was 20 mo with chemotherapy alone in IMvigor211 (Fig. 1A).

In patients achieving SD, there was a more modest difference between atezolizumab and chemotherapy in the duration of treatment exposure (median 6–7 vs 4 mo). There was no clear difference in the duration of disease control (median 3–4 mo across trials and treatments) between atezolizumab and chemotherapy. However, OS was numerically longer with atezolizumab (median13–18 vs 11 mo with chemotherapy alone; Fig. 1B)

Table 2 – Baseline characteristics (stable disease population, *n* = 583).

	Atezolizumab			Chemotherapy
Characteristic	IMvigor210 (*n* = 66)	IMvigor211 (*n* = 92)	SAUL (*n* = 263)	IMvigor211 (*n* = 162)
Age (yr), median (range)	68 (42–83)	68 (43–83)	69 (40–88)	68 (31–84)
Age >75 yr, *n* (%)	13 (20)	18 (20)	64 (24)	33 (20)
Male, *n* (%)	45 (68)	71 (77)	202 (77)	121 (75)
Smoking history, *n* (%)				
Current	10 (15)	12 (13)	50 (19)	18 (11)
Former	33 (50)	57 (62)	131 (50)	98 (60)
Never	23 (35)	23 (25)	82 (31)	45 (28)
Missing	0	0	0	1 (1)
<3 mo since previous chemotherapy, *n* (%)	18 (27)	32 (35)	83 (32)	57 (35)
Creatinine clearance <60 ml/min, *n* (%)	29 (44)	35 (38)	132 (50)	73 (45)
ECOG PS at screening, *n* (%)				
0	30 (45)	46 (50)	140 (53)	68 (42)
1	36 (55)	46 (50)	114 (43)	94 (58)
2	0	0	9 (3)	0
Liver metastases, *n* (%)	14 (21)	7 (8)	43 (16)	27 (17)
Lymph node–only disease, *n* (%)	6 (9)	20 (22)	45 (17)	25 (15)
Number of Bellmunt risk factors, *n* (%)				
0	22 (33)	38 (41)	113 (43)	54 (33)
1	31 (47)	48 (52)	106 (40)	83 (51)
2	12 (18)	6 (7)	40 (15)	22 (14)
3	1 (2)	0	4 (2)	3 (2)
PD-L1 expression score, *n* (%)				
IC 0/1	45 (68)	69 (75)	181 (69)	125 (77)
IC 2/3	21 (32)	23 (25)	66 (25)	37 (23)
Missing	0	0	16 (6)	0

ECOG PS = Eastern Cooperative Oncology Group performance status; IC 0/1 = expression on <1–<5% of tumour-infiltrating immune cells; IC 2/3 = expression on >5% of tumour-infiltrating immune cells; PD-L1 = programmed death ligand 1.

Table 3 – Treatment exposure and clinical outcomes.

Median (mo)	Atezolizumab			Chemotherapy
	IMvigor210	IMvigor211	SAUL	IMvigor211
PR population (*n* = 229)	*n* = 31	*n* = 46	*n* = 106	*n* = 46
Time to best response (range)	2.1 (1.6–15.8)	2.1 (1.8–15.8)	2.1 (1.4–8.3)	2.1 (1.4–5.6)
Duration of treatment exposure (range)	20.2 (6.5–24.0)	14.5 (4.2–22.8)	11.4 (4.0–19.0)	6.5 (0–21.2)
Duration of progression-free survival (95% CI)	18.6 (13.1–24.5)	NE (11.1–NE)	NE (13.6–NE)	9.8 (7.7–11.0)
Duration of disease control (95% CI)	16.6 (11.0–NE)	15.9 (8.8–NE)	NE (11.7–NE)	7.8 (5.7–9.7)
Overall survival (95% CI)	NE (NE–NE)	NE (NE–NE)	NE (NE–NE)	19.9 (14.3–21.9)
SD population (*n* = 583)	*n* = 66	*n* = 92	*n* = 263	*n* = 162
Time to best response (range)	2.1 (1.6–2.3)	2.1 (1.4–3.3)	2.1 (1.1–8.5)	2.1 (1.4–3.5)
Duration of treatment exposure (range)	5.6 (1.4–23.7)	6.2 (0–23.8)	7.0 (0–18.9)	3.7 (0–15.0)
Duration of progression-free survival (95% CI)	4.4 (4.2–6.2)	6.3 (5.5–8.1)	6.1 (5.8–6.2)	5.5 (4.5–6.1)
Duration of disease control (95% CI)	2.7 (2.1–4.2)	4.3 (3.5–6.1)	4.1 (3.8–4.2)	3.7 (2.6–4.2)
Overall survival (95% CI)	12.7 (9.2–17.0)	16.6 (12.4–NE)	17.9 (14.7–NE)	11.3 (9.9–12.7)

CI = confidence interval; NE = not estimable, PR = partial response; SD = stable disease.

Irrespective of treatment, durations of disease control and OS were shorter in patients achieving SD than in those achieving a PR.

In Figs. 1 and 2, OS is shown for each trial, both overall and according to PD-L1 status. Of note, in each of the atezolizumab-treated subgroups achieving SD, at least twice as many patients had PD-L1 status IC 0/1 compared with IC 2/3, whereas PD-L1 status was more evenly distributed in atezolizumab-treated patients in the PR population.

Subgroup analyses by PD-L1 status in the PR population are difficult to interpret because of the small sample sizes, low event rates, and extensive censoring. In the SD population, median OS was consistently more favourable in the IC 2/3 subgroup than in the IC 0/1 subgroup, although 95% CIs are overlapping and the Kaplan-Meier curves show no major differences according to PD-L1 status. This finding was observed in both atezolizumab- and chemotherapy-treated patients.

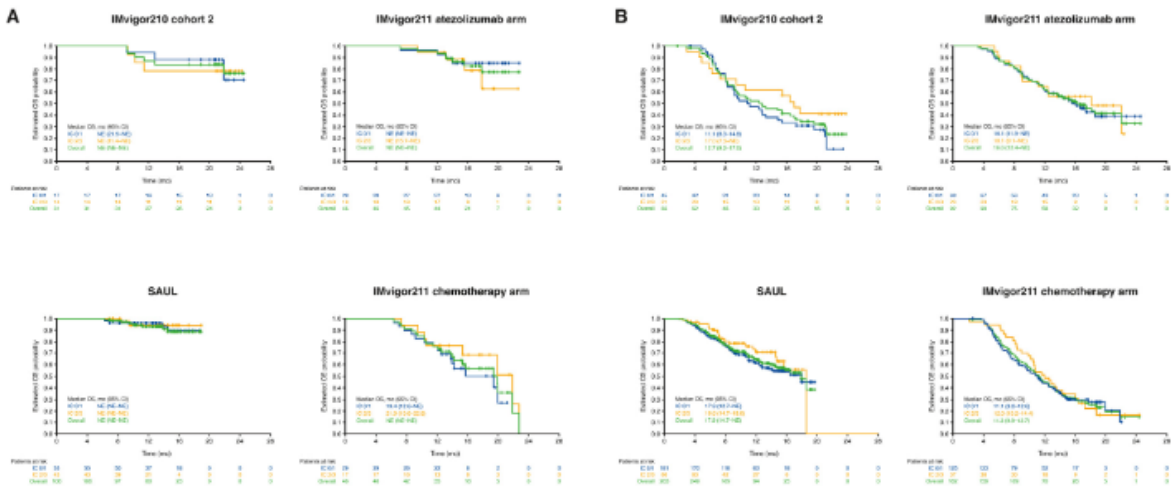

Fig. 1 – OS in patients achieving (A) partial response and (B) stable disease. CI = confidence interval; IC 0/1 = expression on <1–<5% of tumour-infiltrating immune cells; IC 2/3 = expression on ≥5% of tumour-infiltrating immune cells; NE = not estimable; OS = overall survival.

Generally, the presence of more Bellmunt risk factors was associated with marginally worse OS in patients treated with chemotherapy or atezolizumab (Fig. 2). In further exploratory subgroup analyses within the SD population, OS was generally similar in patients with versus without liver metastases (Supplementary Fig. 1).

3.3. Safety

Adverse events are summarised in Table 4. In general, adverse events were less frequent with atezolizumab than with chemotherapy. Adverse events rarely led to atezolizumab treatment discontinuation (5–10% of patients) or treatment-related death (two patients). The most common adverse events (any grade, irrespective of relationship to treatment) with atezolizumab were fatigue, diarrhoea, urinary tract infection, pyrexia, and decreased appetite (Supplementary Table 1).

4. Discussion

This analysis of >600 atezolizumab-treated patients provides insight into the value of SD or PR in patients receiving therapy for metastatic urinary tract carcinoma. Patients achieving a PR or SD with atezolizumab have meaningful OS expectancy, with median OS exceeding 1 yr in those showing disease stabilisation. Among patients with a PR to atezolizumab, median OS was not reached and disease control was sustained.

It is important to temper excitement about remarkable outcomes with immunotherapy in urothelial carcinoma with realism; patients should be counselled and should understand that cure or a durable complete response is a relatively unlikely outcome [10]. However, this can be balanced with realistic information about likely outcomes if patients achieve a PR or SD, as demonstrated in the present analysis. These outcomes were seen in approximately one-third of patients treated in the IMvigor210, IMvigor211, and SAUL trials [4,7,9].

The higher proportion of male patients in the PR population compared with the SD population is consistent with the previously reported numerically higher overall response rate to atezolizumab in men versus women [11]. Similarly, the prevalence of IC 2/3 PD-L1 status was higher in patients with a PR than in those with SD. Interestingly, these imbalances were seen in the chemotherapy arm of IMvigor211 as well as in atezolizumab-treated patients, demonstrating the potential role of PD-L1 positivity as a biomarker not only for immune checkpoint inhibition, but also for systemic treatment of patients with urothelial carcinoma in general.

Bellmunt risk factors appeared to provide no better prognostic information in patients who achieved a PR or SD with atezolizumab treatment than in those receiving conventional chemotherapy. Efforts to identify factors better predictive of efficacy in patients treated with atezolizumab have so far been unsuccessful. Furthermore, differentiating between prognostic and predictive effects is not possible in single-arm studies such as IMvigor210 and SAUL, and is therefore beyond the scope of this analysis. Nevertheless, the similar OS irrespective of PD-L1 status seen in patients achieving a PR is intriguing.

Limitations of these analyses include their exploratory, post hoc nature; small sample sizes in some of the sub-groups; relatively short duration of follow-up, particularly in the SAUL study; and the lack of information on poststudy treatment when interpreting OS. In atezolizumab-treated patients, treatment exposure can be considered as a measure of efficacy, because all patients were treated until the loss of clinical benefit, but the differences may be artificially exaggerated when compared with patients receiving chemotherapy in IMvigor211, as chemotherapy was not continued beyond progression. No information on molecular markers (other than PD-L1 status) was analysed. Finally, restricting this analysis to a single checkpoint inhibitor may be considered a weakness with respect to generalisability of immune checkpoint inhibition, but could also be viewed as a strength as it allows analysis of a more heterogeneous patient population treated in a uniform manner.

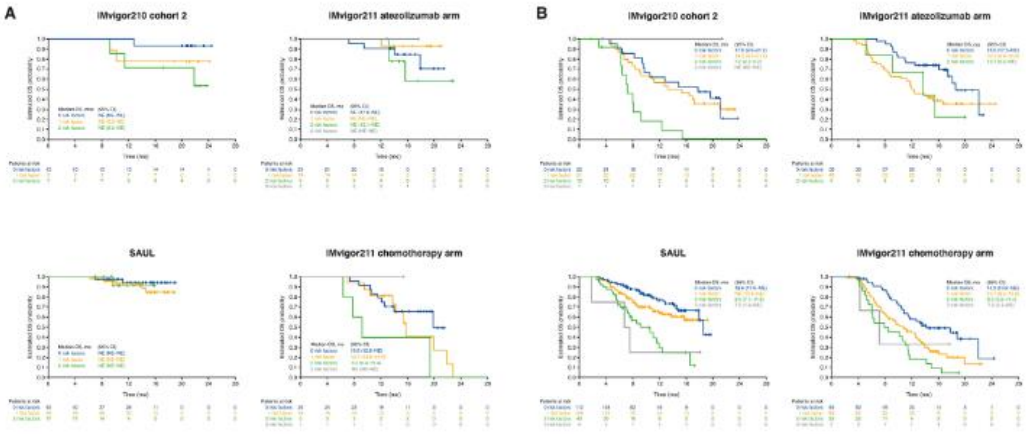

Fig. 2 – OS according to Bellmunt risk factors in patients achieving (A) partial response and (B) stable disease. CI = confidence interval; NE = not estimable; OS = overall survival.

Table 4 – Overview of safety.

	Atezolizumab			Chemotherapy
AE, *n* (%)	IMvigor210	IMvigor211	SAUL	IMvigor211
PR population (*n* = 229)	*n* = 31	*n* = 46	*n* = 106	*n* = 46
Any grade AE	31 (100)	46 (100)	99 (93)	46 (100)
Grade 3/4	18 (58)	23 (50)	44 (42)	27 (59)
Grade 5	1 (3)	0	1 (1)	0
Any treatment-related AE	27 (87)	43 (93)	79 (75)	44 (96)
Grade 3/4	8 (26)	15 (33)	19 (18)	21 (46)
Grade 5	0	0	0	0
AE leading to treatment discontinuation	4 (13)	3 (7)	6 (6)	12 (26)
SD population (*n* = 583)	*n* = 66	*n* = 92	*n* = 263	*n* = 162
Any grade AE	66 (100)	92 (100)	247 (94)	161 (99)
Grade 3/4	40 (61)	51 (55)	111 (42)	97 (60)
Grade 5	0	2 (2)	13 (5)	4 (2)
Any treatment-related AE	56 (85)	76 (83)	160 (61)	150 (93)
Grade 3/4	13 (20)	21 (23)	34 (13)	76 (47)
Grade 5	0	0	2 (1)	0
AE leading to treatment discontinuation	0	11 (12)	13 (5)	30 (19)

AE = adverse event; PR = partial response; SD = stable disease.

5. Conclusions

Achieving SD or a PR seems to be a meaningful clinical outcome in patients treated with atezolizumab for metastatic urothelial carcinoma. This effect was seen consistently across all three trials. Although on-going efforts to identify molecular markers for predicting a response are important [12], RECIST response outcomes less robust less than a complete response provide an indication of longer term expectations for patients treated with atezolizumab.

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