Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial

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Summary

Background First-line chemotherapy for patients with cisplatin-ineligible locally advanced or metastatic urothelial carcinoma is associated with short response duration, poor survival, and high toxicity. This study assessed atezolizumab (anti-programmed death-ligand 1 [PD-L1]) as treatment for metastatic urothelial cancer in cisplatin-ineligible patients.

Methods For this single-arm, multicentre, phase 2 study, in 47 academic medical centres and community oncology practices in seven countries in North America and Europe, we recruited previously untreated patients with locally advanced or metastatic urothelial cancer who were cisplatin ineligible. Patients were given 1200 mg intravenous atezolizumab every 21 days until progression. The primary endpoint was independently confirmed objective response rate per Response Evaluation Criteria in Solid Tumors version 1.1 (central review), assessed in prespecified subgroups based on PD-L1 expression and in all patients. All participants who received one or more doses of atezolizumab were included in the primary and safety analyses. This study was registered with ClinicalTrials.gov, number NCT02108652.

Findings Between June 9, 2014, and March 30, 2015, we enrolled 123 patients, of whom 119 received one or more doses of atezolizumab. At 17·2 months' median follow-up, the objective response rate was 23% (95% CI 16 to 31), the complete response rate was 9% (n=11), and 19 of 27 responses were ongoing. Median response duration was not reached. Responses occurred across all PD-L1 and poor prognostic factor subgroups. Median progression-free survival was 2·7 months (2·1 to 4·2). Median overall survival was 15·9 months (10·4 to not estimable). Tumour mutation load was associated with response. Treatment-related adverse events that occurred in 10% or more of patients were fatigue (36 [30%] patients), diarrhoea (14 [12%] patients), and pruritus (13 [11%] patients). One treatment-related death (sepsis) occurred. Nine (8%) patients had an adverse event leading to treatment discontinuation. Immune-mediated events occurred in 14 (12%) patients.

Interpretation Atezolizumab showed encouraging durable response rates, survival, and tolerability, supporting its therapeutic use in untreated metastatic urothelial cancer.

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See **Comment** page 6

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Introduction

Urothelial cancer is an aggressive malignancy associated with about 165 084 of global deaths annually and a 5 year survival of about 5% in the metastatic setting.[1,2] Cisplatin-based chemotherapy, a first-line treatment standard, provides overall survival benefit;[3] however, up to two-thirds of patients are ineligible[4] due to impaired performance status or comorbidities (eg, renal dysfunction). Treatment alternatives include carboplatin-based combinations and single-drug chemotherapy[5–8] but are associated with shorter overall survival.[9] In clinical practice, many patients do not receive systemic chemotherapy and are offered supportive care,[5,6,10] further underscoring the need for more efficacious and tolerable treatments in cisplatin-ineligible patients.[10,11]

Atezolizumab is a humanised engineered immunoglobulin G1 monoclonal antibody that inhibits binding of programmed death-ligand 1 (PD-L1) to receptors programmed death-1 (PD-1) and B7-1, thereby restoring anti-cancer T-cell activity and reinvigorating suppressed immune cells.[12,13] Atezolizumab has shown efficacy and a tolerable safety profile in a range of cancers, including locally advanced or metastatic urothelial cancer.[12–16] In the IMvigor210 cohort of patients who progressed during or following platinum-based treatment, atezolizumab conferred significant clinical benefit,[16] leading to accelerated regulatory approval, and several biomarkers associated with response were identified.[16] In this Article, we present clinical data from the first-line cisplatin-ineligible IMvigor210 cohort—the first report of an anti-PD-L1/PD-1 checkpoint inhibitor in this setting—along

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Research in context

Evidence before this study

We searched PubMed for phase 3 clinical trials on advanced urothelial carcinoma published in English between Jan 1, 2005, and Jan 1, 2014, using the MeSH search terms "advanced" AND "bladder cancer", "urothelial carcinoma", "transitional cell carcinoma". We identified 17 articles. We examined the articles specific to treatment of patients in the first-line setting, along with international congress presentations during the time period. We identified an unmet clinical need for effective and tolerable approaches to the treatment of patients with baseline characteristics that rendered them ineligible for cisplatin-based chemotherapy. No such treatments seemed to exist or be approved by the US Food and Drug Administration, European Medicines Agency, or related agencies, and the cytotoxic drugs commonly used in this population were consistently associated with toxicity and poor overall survival despite treatment.

Added value of this study

In this study, the humanised monoclonal anti-programmed death-ligand 1 antibody atezolizumab was assessed in patients with previously untreated, locally advanced or metastatic urothelial cancer who were ineligible for cisplatin-based chemotherapy. The original trial design for this study was focused on patients with disease progression during or after platinum-based chemotherapy and an exploratory cohort of first-line cisplatin-ineligible patients; however, in view of the potential for benefit in the first-line setting, the exploratory cohort was expanded to about 100 patients, using similar statistical assumptions. Objective responses by independent assessment according to Response Evaluation Criteria In Solid Tumors version 1.1 were durable, with 70% of patients continuing to respond after a median follow-up duration of almost 1·5 years. Overall survival also seemed to surpass historical rates, although differences in patient populations between studies, among other factors, complicate comparison. Atezolizumab also generally seemed to be safe and well tolerated in a patient population heavily dominated by renal insufficiency. Exploratory analyses to improve the understanding of the immune biology of atezolizumab efficacy identified correlates of response and survival including The Cancer Genome Atlas subtype and mutation load, which warrant further study as potential biomarkers for this drug in metastatic urothelial cancer.

Implications of all the available evidence

Cisplatin-based chemotherapy is the preferred first-line treatment for metastatic urothelial cancer and the only treatment shown to improve survival in patients with previously untreated disease. However, only a minority of patients with metastatic urothelial cancer receive first-line treatment with cisplatin-based chemotherapy. The population of patients who are ineligible for cisplatin has been under-represented in clinical studies in the past 30 years and as a result, these patients have poor outcomes. Atezolizumab shows potential as a first-line treatment option for these patients. Furthermore, biomarker data validate reports of this drug in the platinum-treated setting that linked intrinsic The Cancer Genome Atlas subtypes and mutation load with immunotherapy response.

with exploratory analyses to validate biomarker correlates of clinical outcomes.

Methods

Study design and patients

IMvigor210 was a multicentre, single-arm, phase 2 trial that investigated efficacy and safety of atezolizumab in metastatic urothelial cancer. This trial was done in 47 academic medical centres and community oncology practices across seven countries in North America and Europe. The protocol (appendix) was approved by the institutional review boards or independent ethics committees at each participating centre. All patients provided written informed consent before study entry. The study was done in accordance with the Declaration of Helsinki and International Conference of Harmonization Good Clinical Practice guidelines.

Cohort 1 enrolled patients without previous treatment for metastatic urothelial cancer. Eligible patients had inoperable, locally advanced or metastatic urothelial cancer (renal pelvis, ureters, bladder, or urethra), measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 2 or less, and a tumour sample available for PD-L1 testing. Neo-adjuvant or adjuvant chemotherapy or radiation was permitted if more than 12 months had elapsed between treatment and recurrence. Patients were required to be cisplatin ineligible per one or more of the following: glomerular filtration rate more than 30 mL/min and less than 60 mL/min (Cockcroft-Gault formula), grade 2 or higher hearing loss or peripheral neuropathy, or an ECOG PS of 2.[17] Complete inclusion and exclusion criteria are listed in the protocol (with statistical analysis plan; appendix). Cohort 2 (described previously)[16] enrolled patients previously treated with platinum-based chemotherapy.

Procedures

Patients received 1200 mg intravenous atezolizumab every 21 days until unacceptable toxicity or investigator-assessed radiographic progression. Dose interruptions, but not reductions, were permitted. Patients underwent response assessments at baseline, every 9 weeks for 12 months, and then every 12 weeks until disease progression, withdrawal of consent, or death; local investigators did the assessments, which were reviewed by a central independent facility

(BioClinica, Princeton, NJ, USA). These assessments included measurement of tumour burden, including change over time in sum of longest diameters. Additionally, the investigators and the sponsor assessed the objective response rate estimates in key subgroups defined by demographic and baseline characteristics. Safety was assessed per National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. We collected archival tumour tissue for biomarker assessments. We used the VENTANA SP142 immunohistochemistry assay (Ventana Medical Systems, Tucson, AZ, USA) to prospectively assess PD-L1 expression on tumour-infiltrating immune cells (IC) via a central laboratory (HistoGeneX, Brussels, Belgium). Scoring criteria designated tumours as IC0 (PD-L1 expression on <1% of IC), IC1 (PD-L1 expression on ≥1% and <5% of IC), or IC2/3 (PD-L1 expression on ≥5% of IC).[16] Patients, investigators, and sponsor were blinded to PD-L1 status. We assessed somatic mutation and tumour mutation load using a FoundationOne DNA-based panel (Foundation Medicine, Cambridge, MA, USA). Microsatellite status was centrally confirmed by next-generation sequencing-based scoring (Foundation Medicine, Cambridge, MA, USA). Gene expression was quantified for a T-effector gene signature (consisting of *CD8A, GZMA, GZMB, PRF1, INFG,* and *TBX21*) and for subtyping using The Cancer Genome Atlas[18] (TCGA) categories.[16]

Outcomes

The primary endpoint was independently confirmed objective response rate per RECIST version 1.1 (central review), assessed in prespecified subgroups based on PD-L1 expression and in all patients. Secondary endpoints included investigator-assessed objective response rate; duration of response, and progression-free survival, both assessed by independent review and investigator (RECIST version 1.1); and overall survival. Unless otherwise specified, RECIST results reported are per independent review. Exploratory analyses included biomarker correlates of response and survival.

Statistical analysis

The cisplatin-ineligible patient cohort of IMvigor210 was initially planned as an exploratory subgroup of 30 patients. Subsequently, a protocol amendment increased the sample size to about 100 patients to provide a better estimate of the objective response rate (RECIST version 1.1) in patients with urothelial cancer who were cisplatin ineligible, assessed by independent central review. Determination of sample size was based on the assumption of 30% IC2/3 prevalence. The 95% CI (calculated using the Clopper-Pearson method) for an objective response rate of 40·0% would be 22·7–59·4, resulting in 98% power to detect a 30% increase in the objective response rate from 10% to 40%.

We did the primary efficacy analysis of the cisplatin-ineligible IMvigor210 cohort (data cutoff: Sept 14, 2015) when the last patient enrolled had a minimum of 6 months of follow-up. We also did an interim efficacy analysis only for patients who had 24 or more weeks of follow-up at data cutoff (May 5, 2015; appendix). A hierarchical fixed-sequence testing procedure (previously described;[16] appendix) to compare the observed primary endpoint for three prespecified subgroups (PD-L1 IC2/3, followed by IC1/2/3, and followed by all patients) versus a control objective response rate of 10%. We did the hypothesis tests sequentially using Independent Review Facility-assessed RECIST version 1.1 at a specific two-sided α level of 0·05 for each test. If no statistical significance was detected at a specific level of the hierarchy, then no further testing was done. We expected the study to attract patients who would not be candidates for combination chemotherapy, including those not eligible for any cytotoxic chemotherapy—reflective of the heterogeneous cisplatin-ineligible population.[10] Therefore, we approximated the 10% objective response rate with a composite mean of 75% of patients enrolled who would

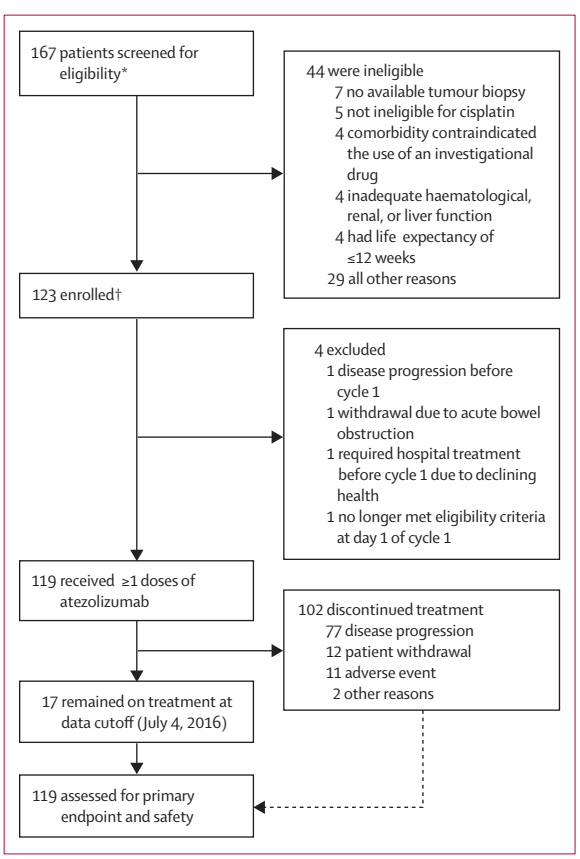

Figure 1: **Trial profile**
Displayed are the screened, enrolled, and treated IMvigor210 cohort 1 patients, including reasons for non-enrolment and discontinuation. *176 screening events by 167 patients; nine patients were re-screened. †Based on March 14, 2016, data cutoff. One cohort 1 patient was re-assigned to the platinum-treated cohort (IMvigor210 cohort 2) on the basis of eligibility reassessments between the May 5, 2015, and Sept 14, 2015, data cutoffs.

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See **Online** for appendix

	All patients* (n=119)
Age (years)	73 (51–92)
Aged ≥80 years	25 (21%)
Sex	
Male	96 (81%)
Female	23 (19%)
PD-L1 status on immune cells	
IC2/3	32 (27%)
IC1	48 (40%)
IC0	39 (33%)
Primary tumour site†	
Bladder or urethra	85 (71%)
Renal pelvis or ureter	33 (28%)
Metastatic disease	110 (92%)
Lymph node only	31 (26%)
Visceral sites‡	78 (66%)
Liver sites	25 (21%)
Prior tobacco use	
Current	7 (6%)
Former	77 (65%)
Never	35 (29%)
Previous treatment	
Radiotherapy	12 (10%)
Perioperative chemotherapy§	22 (18%)
Cisplatin ineligibility criteria	
Renal impairment¶	83 (70%)
Hearing loss of ≥25 dB‖	17 (14%)
Peripheral neuropathy, grade ≥2	7 (6%)
ECOG PS 2	24 (20%)
Renal impairment and ECOG PS 2	8 (7%)

Data are median (range) and n (%). PD-L1=programmed death-ligand 1. IC=tumour-infiltrating immune cell. ECOG PS=Eastern Cooperative Oncology Group performance status. *Intention-to-treat (efficacy-assessable and safety-assessable) patient population. †One patient with prostatic urethra primary site not included. ‡Visceral metastasis defined as liver, lung, bone, any non-lymph node, or soft tissue metastasis. §Adjuvant or neoadjuvant treatment with first disease progression beyond 12 months. ¶Glomerular filtration rate less than 60 mL/min and more than 30 mL/min. ‖At two contiguous frequencies.

Table 1: **Baseline characteristics and previous treatment**

	Patients	Complete response	Partial response	Objective response, n (% [95% CI])*	Median duration of response (95% CI)
	119	11	16	27 (23% [16–31])	NE (14·1–NE)
IC2/3	32	4	5	9 (28% [14–47])	NE (11·1–NE)
IC1/2/3	80	8	11	19 (24% [15–35])	NE (NE–NE)
IC1	48	4	6	10 (21% [10–35])	NE (NE–NE)
IC0	39	3	5	8 (21% [9–36])	NE (12·8–NE)

Data cutoff was July 4, 2016. PD-L1=programmed death-ligand 1. IC=tumour-infiltrating immune cell. NE=not estimable. *Includes objective response rate per Response Evaluation Criteria in Solid Tumors version 1.1 (independent review facility).

Table 2: **Objective response by PD-L1 status on tumour-infiltrating immune cells**

otherwise not be candidates for any cytotoxic chemotherapy (expected objective response rate 0%) and 25% of patients enrolled who would be candidates for carboplatin-based combination chemotherapy (expected objective response rate 36%).[9] The exact binomial test assessed whether atezolizumab treatment results in a significant difference between the observed and control response rates in the prespecified subgroups. We did the tests in a sequential order such that the subsequent hypothesis would not be done if the preceding test was not rejected (appendix). We assessed clinical significance in an ongoing manner, and subsequent analyses did not use hypothesis testing as described for the primary analysis. This report uses a later cutoff (July 4, 2016) to provide updated efficacy and safety data. An independent data monitoring committee assessed safety about every 6 months, in addition to a prespecified futility analysis of efficacy data. All participants who received one or more doses of atezolizumab were included in the primary and safety analyses. We used SAS version 9.4 for the analyses.

This study was registered with ClinicalTrials.gov, number NCT02108652.

Role of the funding source

The protocol was developed by the sponsor (F Hoffmann-La Roche Ltd.) and advisors. Data were collected, analysed, and interpreted in collaboration between the sponsor and the clinical investigators. All authors had full access to all the data in the study, contributed to the writing and review of the manuscript (with editorial assistance from a sponsor-funded professional medical writer), approved submission, verified the study conduct in accordance with the protocol, and attested for data accuracy and completeness. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between June 9, 2014, and March 30, 2015, we screened 167 patients and enrolled 123 of them; four of the enrolled patients subsequently did not meet eligibility criteria and did not receive the study drug atezolizumab (figure 1). 119 patients received one or more doses of atezolizumab. 102 (86%) patients discontinued treatment, either because of disease progression (n=77), patient withdrawal (n=12), an adverse event (n=11), or other reasons (n=2). At time of data cutoff (median follow-up was 17·2 months [range 0·2–23·5]), 25 (21%) patients had been treated for more than 52 weeks, and 17 (14%) remained on treatment. The median treatment duration was 15 weeks (range 0–102). 83 (70%) of the 119 patients who received atezolizumab were cisplatin ineligible because of renal impairment (table 1). Poor performance status and visceral metastatic disease are independent prognostic factors (Bajorin risk factors) that predict survival in metastatic urothelial cancer.[19] 66 (55%) of 119 patients in

this study had one Bajorin risk factor and 18 (15%) had both Bajorin risk factors. 104 (87%) patients had comorbidities. The distribution of PD-L1 subgroups matched previous study populations.[16]

The primary efficacy analysis was designed to be done when patients had a minimum of 6 months' follow-up. In that analysis (with a median follow-up duration of 8·5 months [range 0·2–14·3]), hierarchal testing did not reach significance in the IC2/3 patient subgroup (objective response rate 22% [95% CI 9–40]), compared with the prespecified 10% objective response rate, precluding further statistical tests. However, after a 17·2 month median follow-up duration, the objective response rate was 23% (95% CI 16–31; table 2) in all patients, with the lower bound of the 95% CI exceeding 10%. Furthermore, the updated objective response rate by PD-L1 subgroup rose to 28% (14–47) in the IC2/3 subgroup, 24% (15–35) in the IC1/2/3 subgroup, 21% (95% CI 10–35) in the IC1 subgroup, and 21% (95% CI 9–36) in the IC0 subgroup. Complete responses were seen in 11 (9%) patients (table 2). Concordance between responses assessed by investigators versus independent review was higher than 90% (appendix).

Median time to onset of first response was 2·1 months (range 1·8–10·5), but late responses were also seen (after 6 months in two patients; figure 2, appendix). Median response duration had not been reached in all patients or in predefined PD-L1 subgroups (range 3·7–21·0+), and 19 (70%) of 27 responses were ongoing. Median progression-free survival was 2·7 months (95% CI 2·1–4·2) in all patients, 4·1 months (2·3–11·8) in IC2/3 patients, 2·1 months (2·1–5·4) in IC1 patients, and 2·6 months (2·1–5·7) in IC0 patients. The clinical benefit rate in all patients was 30% (22–39; appendix).

The median overall survival was 15·9 months (95% CI 10·4 to not estimable) in all patients, 12·3 months (6·0 to not estimable) in IC2/3 patients, and 19·1 months (9·8 to not estimable) in IC0/1 patients (figure 3). The 12 month landmark survival was 57% (95% CI 48–66) in all patients.

Responses to atezolizumab occurred in all clinical subgroups assessed (table 3). Notably, 13 (39% [95% CI 23–58]) of 33 patients with upper-tract primary tumours (renal pelvis or ureter) had an objective response. Patient subgroups with lower response rates (eg, two [8%] of 25 patients with liver metastases) still had durable responses, with median response duration also not reached in any of these subgroups. Bajorin risk factors also seem to maintain prognostic utility.[19] Median survival was not reached in patients with no risk factors (appendix), was

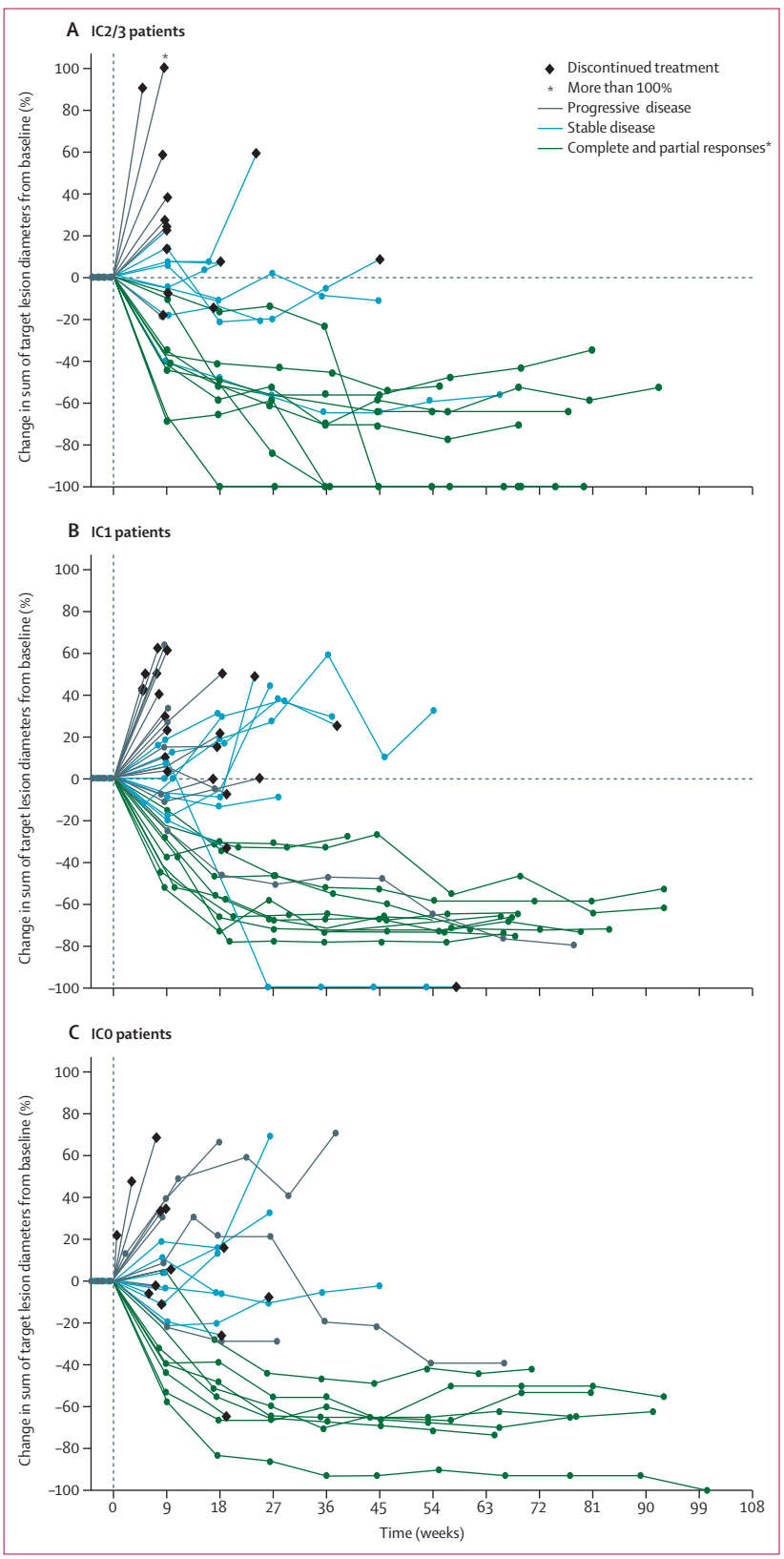

Figure 2: **Change from baseline tumour burden by PD-L1 status**
Change from baseline tumour burden is defined as the sum of target lesion diameters, in patients who received atezolizumab, based on baseline PD-L1 status on immune cells of (A) IC2/3, (B) IC1, and (C) IC0. Data cutoff was July 4, 2016. PD-L1=programmed death-ligand 1. IC=tumour-infiltrating immune cell. *Complete and partial responses per Response Evaluation Criteria in Solid Tumors version 1.1.

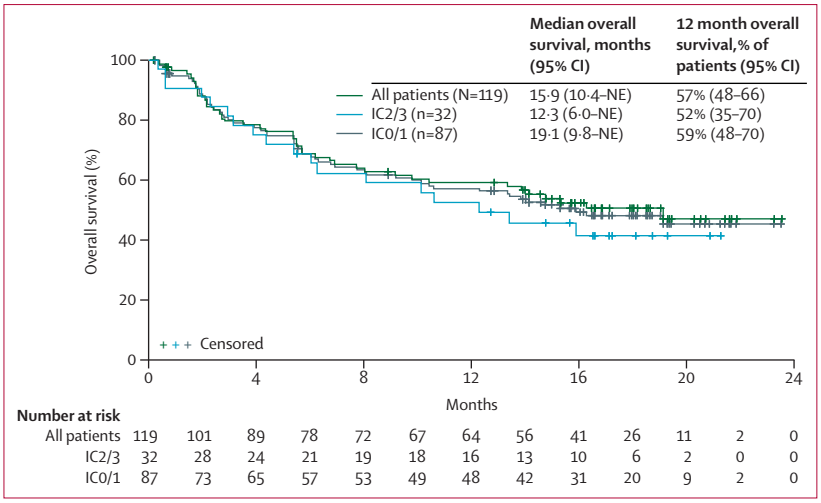

***Figure 3*: Overall survival in patients given atezolizumab according to PD-L1 status on immune cells**
A total of 59 events occurred in all patients by the data cutoff date (July 4, 2016; 18 in patients with IC2/3; 41 in patients with IC0/1). PD-L1=programmed death-ligand 1. NE=not estimable. IC=tumour-infiltrating immune cell.

13·4 months in patients with one risk factor (either visceral metastases or ECOG PS 2), and was 6·2 months in patients with two risk factors. Patients with liver metastases had a median survival of 5·5 months. Furthermore, patients aged 80 years or older (n=25) had median survival durations of 14·8 months and patients with renal dysfunction (n=83) had median survival durations of 14·1 months. Patients who achieved stable disease (n=29) had a median survival of 19·1 months (appendix).

Median survival in patients with upper-tract primary tumours had not been reached. To investigate a possible basis for improved outcomes in these patients, we assessed baseline covariates, including anatomic sites of metastases, tumour mutation load, T-effector gene expression, TCGA subtype, and baseline tumour burden; however, we found no significant differences in these factors between patients with upper-tract and lower-tract disease (appendix). Microsatellite instability was seen only in two patients with upper-tract primary tumours (and two with lower-tract primary tumours), suggesting that this factor was not a primary determinant.

Exploratory biomarker assessments that were not prespecified included expression of individual genes and gene sets, subtyping according to TCGA (appendix), and quantification of mutation load.[16] Overall, 72 (61%) of 119 samples obtained for these analyses were from primary tumour samples and 47 (39%) were from metastatic tumours. Responses were seen across all subtypes and were most frequent with the luminal II subtype (figure 4). Tumour mutation load was significantly higher in responding patients than in non-responders, and this association was consistent across TCGA subtypes and PD-L1 subgroups (figure 4). Mutation load was also associated with overall survival; patients with the highest mutation load (quartile 4) had significantly longer survival compared with patients in quartiles 1–3 (figure 4).

	Patients	Objective response, n (% [95% CI])*
All patients	119	27 (23% [16–31])
Demographics and previous treatment		
Age ≥80 years	25	7 (28% [12–49])
Perioperative chemotherapy†	22	8 (36% [17–59])
Primary tumour sites‡		
Bladder or urethra	85	14 (17% [9–26])
Upper tract	33	13 (39% [23–58])
Metastatic sites at baseline		
Lymph node only	31	10 (32% [17–51])
Visceral§	78	11 (14% [7–24])
Liver	25	2 (8% [1–26])
Cisplatin ineligibility criteria		
Impaired renal function	83	21 (25% [16–36])
ECOG PS 2	24	6 (25% [10–47])
Hearing loss of ≥25 dB¶	17	2 (12% [2–36])
Peripheral neuropathy, grade ≥2	7	1 (14% [0–58])
Renal impairment and ECOG PS 2	8	2 (25% [3–65])
Bajorin risk factors‖		
0	35	12 (34% [19–52])
1	66	13 (20% [11–31])
2	18	2 (11% [1–35])

Data cutoff was July 4, 2016. ECOG PS=Eastern Cooperative Oncology Group performance status. *Includes objective response rate per Response Evaluation Criteria in Solid Tumors version 1.1 (independent review facility). †Includes adjuvant or neoadjuvant treatment with disease progression occurring beyond 12 months. ‡One patient with prostatic urethra primary site not included. §Visceral metastasis defined as liver, lung, bone, or any non-lymph node or soft tissue metastasis. ¶At two contiguous frequencies. ‖Risk factors include baseline ECOG PS of more than 1 and baseline visceral metastasis.

***Table 3*: Objective response by baseline subgroups**

114 (96%) patients had an adverse event (appendix), and 79 (66%) patients had a treatment-related event (table 4). No major safety differences were seen across PD-L1 subgroups. Treatment-related adverse events reported in 10% or more of patients (any grade) were fatigue, diarrhoea, and pruritus. Grade 3 or 4 treatment-related events occurred in 19 (16%) patients, most frequently fatigue (four patients [3%]), increased alanine aminotransferase (four patients [3%]), and increased aspartate aminotransferase (three patients [3%]). Four patients had grade 5 adverse events; the investigator deemed one grade 5 adverse events to be treatment related (sepsis, in a patient with an unidentified source of infection; appendix).

Overall, 41 (34%) patients had an adverse event leading to dose interruption, with no single adverse event predominating, and nine (8%) patients had an event leading to treatment withdrawal. Most treatment discontinuations (77 of 102) and deaths (52 of 59) were due to progression. Immune-mediated all grade adverse events were reported in 14 (12%) patients and grade 3 or adverse events were

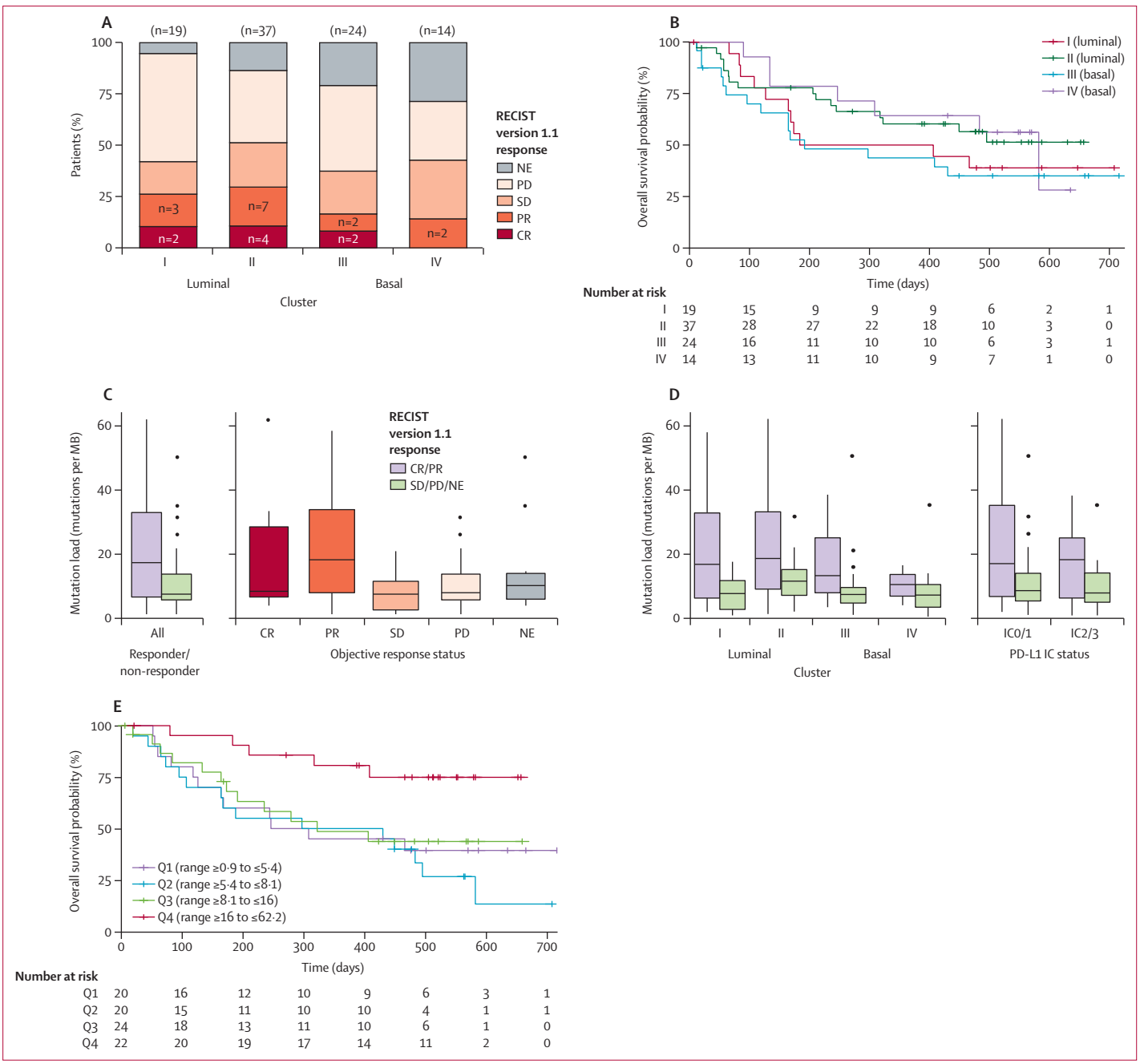

Figure 4: **Associations among TCGA subtype, mutation load, and clinical activity**
(A) Response as a function of TCGA subtype. (B) Kaplan-Meier plot of overall survival by subtype (luminal I, papillary-like; luminal II; basal III, squamous-like; and basal IV). (C) Mutation load as a function of response (Wilcoxon rank sum p=0·0180 for responding *vs* non-responding patients). (D) Mutation load versus response disaggregated by subtype or PD-L1 IC score. (E) Kaplan-Meier estimate of overall survival according to estimated mutation load (per MB), binned into quartiles (log-rank p=0·0041 for a difference in overall survival between quartiles 1–3 and quartile 4). p values are for descriptive purposes only. Data cutoff was July 4, 2016. TCGA=The Cancer Genome Atlas. PD-L1=programmed death-ligand 1. IC=tumour-infiltrating immune cell. RECIST=Response Evaluation Criteria in Solid Tumors. NE=not estimable. PD=progressive disease. SD=stable disease. PR=partial response. CR=complete response. MB=megabase. Q1–4=quartile 1–4.

reported in eight (7%) patients (appendix), most commonly rash (four [3%] all grade; one [1%] grade 3 or 4). No patients received systemic non-corticosteroid immunomodulatory drugs (eg, infliximab, tocilizumab) for immune-mediated events. 36 patients received corticosteroids.

Post-protocol treatment, defined as any treatment administered after progression on atezolizumab before study discontinuation, was reported for 25 patients (nine patients with IC0, 12 with IC1, and four with IC2/3) during follow-up. The most common treatment was

	Any grade (n=119)	Grade 3–4 (n=119)
Overall	79 (66%)	19 (16%)
Fatigue	36 (30%)	4 (3%)
Diarrhoea	14 (12%)	2 (2%)
Pruritus	13 (11%)	1 (1%)
Decreased appetite	11 (9%)	1 (1%)
Hypothyroidism	8 (7%)	0
Anaemia	6 (5%)	1 (1%)
Chills	6 (5%)	0
Nausea	6 (5%)	0
Pyrexia	6 (5%)	0
Rash	6 (5%)	1 (1%)
Vomiting	6 (5%)	0
Rash, maculopapular	5 (4%)	0
Alanine aminotransferase increased	5 (4%)	4 (3%)
Arthralgia	5 (4%)	0
Aspartate aminotransferase increased	4 (3%)	3 (3%)
Blood alkaline phosphatase increased	4 (3%)	1 (1%)
Blood bilirubin increased	4 (3%)	2 (2%)
Dyspnoea	4 (3%)	0
Infusion-related reaction	4 (3%)	0
Lymphocyte count decreased	4 (3%)	0
Asthenia	3 (3%)	0
Back pain	3 (3%)	0
Dermatitis acneiform	3 (3%)	0
Dry mouth	3 (3%)	0
Headache	3 (3%)	0
Hypophosphataemia	3 (3%)	2 (2%)
Hypotension	3 (3%)	1 (1%)
Influenza-like illness	3 (3%)	0
Muscle spasms	3 (3%)	0
Thrombocytopenia	3 (3%)	0
Renal failure	2 (2%)	2 (2%)
Autoimmune colitis	1 (1%)	1 (1%)
Liver disorder	1 (1%)	1 (1%)
Hypersensitivity	1 (1%)	1 (1%)
Multiple organ dysfunction syndrome	1 (1%)	1 (1%)
Portal vein thrombosis	1 (1%)	1 (1%)

Tables shows events deemed to be related to treatment by the investigator reported in three or more patients (any grade) or in one or more patients (grade 3 or 4). Multiple occurrences of the same event are counted once at maximum severity. Treatment-emergent adverse events include events occurring on or after the first dose of study drug until either 30 days after the last administration of the study drug, initiation of subsequent non-protocol anti-cancer treatment, or clinical cutoff date, whichever came first. Data cutoff was July 4, 2016.

Table 4: **Treatment-related adverse events**

gemcitabine-carboplatin (14 of 25 patients); other regimens given are listed in the appendix.

Discussion

In this single-arm, phase 2 study, atezolizumab is the first anti-PD-L1/PD-1 drug to show durable responses with a tolerable safety profile in untreated, cisplatin-ineligible, metastatic, urothelial cancer. Objective responses occurred across all PD-L1 subgroups and identified prognostic subgroups, with high complete response rates relative to previous chemotherapy trials.[9] With 17·2 months of median follow-up, median response duration had not been reached in all patients or in any of these subgroups. Although this is a single-arm study, the observed median overall survival of 15·9 months is still noteworthy when compared with first-line gemcitabine-carboplatin (9·3 months)[9] or cisplatin-based regimens in eligible patients (15·2–15·8 months).[20,21] Larger, randomised studies will be valuable in supporting these phase 2 findings.

Atezolizumab was well tolerated. Most treatment-related adverse events were of maximum grade 1 or 2, and immune-mediated events were manageable with systemic corticosteroids alone. The safety profile was consistent with previous atezolizumab trials across a range of cancers[12–16] and compared favourably with cytotoxic chemotherapy; whereas a study[9] of patients treated with gemcitabine-carboplatin, the most appropriate comparator in this population, reported 21% treatment discontinuation and high proportions of patients with haematological toxicity (eg, neutropenia),[9] only 8% of patients in this study discontinued treatment because of an adverse event, and no neutropenia was reported. Furthermore, no loss in median glomerular filtration rate was reported in this cohort (which mostly consisted of patients with baseline renal impairment) through 27 or more treatment cycles (data not shown)—a finding pertinent to patients with reduced kidney function or a solitary kidney, common with upper-tract disease.

Evolution of responses over time was noteworthy in this study, suggesting response rates and other historical surrogates of efficacy in trials of metastatic urothelial cancer chemotherapy (eg, progression-free survival) assessed at early timepoints might not fully capture the benefit of modern-day immunotherapy. Responses to immune checkpoint inhibitors can be delayed and show atypical kinetics. For example, in the primary analysis, objective response rates were numerically but not statistically higher than the prespecified response rate in the PD-L1-selected subgroup; however, with longer follow-up, several patients had further tumour shrinkage, leading to new complete and partial responses and the lower bound of the objective response rate 95% CI to now exceed 10%. Furthermore, durable benefit was seen even in the absence of RECIST response (19·1 month median overall survival reported in the stable disease subgroup), an observation common to immunotherapy[14,22] but not chemotherapy trials, which could have profound effects on standards of care for metastatic urothelial cancer. Cumulative toxicity often limits chemotherapy treatment to six to eight cycles with platinum-based treatment,[6, 8–10] even in responding patients; however, early treatment discontinuation can compromise benefit in patients

receiving immunotherapy. Future trials will be challenged to identify appropriate surrogates of long-term benefit and optimum timing for alternative treatments.

IMvigor210 was designed to test the association of PD-L1 expression with atezolizumab efficacy. By contrast with previous reports,[13,16] no significant enrichment of response by PD-L1 expression was seen. Differences in baseline characteristics (eg, tumour burden or nodal only *vs* visceral metastases) between populations or statistical assumptions underpowered to detect precise differences between IC subgroups for this initially exploratory cohort might have contributed to these findings. Such factors will be analysed in phase 3 studies IMvigor211 (platinum-treated patients; NCT02302807) and IMvigor130 (treatment-naive patients; NCT02807636).

TGCA subtypes have previously been associated with prognostic differences in survival, with basal tumours tending to be associated with decreased survival durations.[23,24] Nonetheless, outcomes reported in patients with luminal II samples are consistent with the IMvigor210 platinum-treated cohort;[16] however, with regard to PD-L1 status, the sample size was not sufficient to establish statistical significance in the present study cohort. The observation that patients with the highest tumour mutation load[25] derived the longest survival from atezolizumab suggests that a threshold for tumour mutation load might need to be surpassed before generation of neo-antigens most suited for recognition by tumour-specific T cells can occur. However, in view of the stochastic relation between total mutation load and generation of neo-antigens, anti-tumour responses seen in some patients with low mutation load are not unexpected—as seen in this study. These observations validate results from the platinum-treated population[16] and additional cancer immunotherapy studies in other tumour types.[26,27] As previously suggested, tumour mutation load, PD-L1 expression on immune cells, and tumour TCGA subtypes might be independent predictors of response,[16] and further analyses in larger studies of metastatic urothelial cancer that incorporate multiple biomarkers could help patient selection for optimum efficacy and guide appropriate combination treatments in the future.

Several populations enrolled in this trial warrant further study. Good outcomes were reported in patients with upper-tract disease—a group historically associated with a poor prognosis.[28] However, microsatellite instability, common in this population and associated with response to checkpoint inhibitors in some cancers,[29] was reported in only a few patients in our trial, precluding further study. Additionally, elderly patients tend to have poor outcomes[30] and chemotherapy intolerance; the single-arm design of this trial might have attracted such patients who would otherwise not participate in trials with a chemotherapy control group. Patients aged 80 years or older (21% of the study population) had outcomes similar to the intention-to-treat population, with good tolerability.

Overall, atezolizumab showed promising response durability and survival, coupled with a low incidence of clinically relevant toxicities despite numerous comorbidities in this population. The observations in this phase 2 study are remarkable in this area of high unmet need, and highlight the role of atezolizumab as an attractive first-line option for cisplatin-ineligible metastatic urothelial cancer. These results warrant further study in the phase 3 setting in this population (IMvigor130, NCT02807636), and suggest the future potential of atezolizumab for all patients in the first-line setting.

Contributors

ACT, OOA, and GDF contributed to the conception and design of the study. AVB, MDG, JER, TP, DPP, JB, YL, AN, JH-C, JLP-G, NAD, MSvdH, RD, SS, MMR, RWJ, AD, UNV, SSS, DIQ, ID, DRS, BJE, PDG, EYY, RB, SM, and DFB contributed to data collection. EEK III, RB, PSH, and SM contributed to analysis of data related to exploratory gene expression and mutation load biomarkers. OOA was the medical monitor for the study and responsible for the database lock, data analysis, and interpretation. AVB, ACT, OOA, GDF, and DFB revised the manuscript critically for intellectual content and oversaw author review of the report. AVB, SL, RB, SM, and ACT contributed to the design of the figures. All authors were involved in data interpretation, drafting, review, and approval of the report, and the decision to submit for publication.

Declaration of interests

AVB, MDG, JER, DPP, JB, YL, MSvdH, SL, EEK III, ZB, RB, PSH, SM, ACT, OOA, GDF, and DFB received personal fees from Roche/Genentech outside the submitted work. MDG reports personal fees from Merck, Astellas, BioMotiv, and Novartis, and grants from Novartis, Bristol-Myers Squibb, and Celgene. JER received non-financial support and other support from Roche/Genentech during the conduct of the study, and personal fees from Agensys, Eli Lilly, Merck, Bayer, AstraZeneca, Sanofi, and Oncogenex outside the submitted work. TP received other support from Roche/Genentech, AstraZeneca, Bristol-Myers Squibb, and Merck during the conduct of the study. DPP received grants from Roche/Genentech during the conduct of the study, and grants and personal fees from Merck, AstraZeneca, Novartis, Pfizer, and Agenysis outside the submitted work. YL received grants and personal fees from Sanofi, and personal fees from Astellas, Janssen, iPSEN, and Bristol-Myers Squibb outside the submitted work. AN received personal fees from Roche/Genentech, and grants and personal fees from Merck Sharp & Dohme during the conduct of the study. JH-C received other support from Roche/Genentech, outside the submitted work. JLP-G and EYY received grants from Roche/Genentech during the conduct of the study. MSvdH received other support from Roche/Genentech, personal fees and grants from Astellas, and personal fees from AstraZeneca outside the submitted work. RD received personal fees from Roche/Genentech and Merck outside the submitted work. SS and SSS received personal fees from Roche/Genentech outside the submitted work. RWJ received personal fees from Bristol-Myers Squibb, Merck, Nektar, Eisai, Novartis, and Cerulean outside the submitted work. UNV received other support from Roche/Genentech during the conduct of the study, and honoraria and consulting fees from Roche/Genentech. DIQ received personal fees from Bristol-Myers Squibb, Merck, AstraZeneca, Novartis, Roche/Genentech, Pfizer, and EMD Serono outside the submitted work. ID received personal fees from Janssen, Roche/Genentech, Amgen, Novartis, and Resrefabre, and other support from Astellas outside the submitted work. DRS received support for advisory board and speaker participation from Roche/Genentech. BJE received grants and personal fees from Roche/Genentech outside the submitted work. PDG received other support from Roche/Genentech during the conduct of the study; in addition, PDG received personal fees from Roche/Genentech, Dendreon, Bayer, Merck, Bristol-Myers Squibb, Exelixis, and AstraZeneca, other support from Bayer, Merck, Mirati, Oncogenex, and Pfizer, and grants from Genmab outside the submitted work. EYY received grants and personal fees from Eli Lilly, Roche/Genentech,

Merck, Agensys, Janssen, Dendreon, Medivation, Astellas, Sanofi, and Bayer, and personal fees from Tolmar, Seattle Genetics, Tokai, Ferring, and AstraZeneca outside the submitted work. NAD, MMR, and AD declare no competing interests.

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