Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial

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Summary

Background Few options exist for patients with locally advanced or metastatic urothelial carcinoma after progression with platinum-based chemotherapy. We aimed to assess the safety and efficacy of atezolizumab (anti-programmed death-ligand 1 [PD-L1]) versus chemotherapy in this patient population.

Methods We conducted this multicentre, open-label, phase 3 randomised controlled trial (IMvigor211) at 217 academic medical centres and community oncology practices mainly in Europe, North America, and the Asia-Pacific region. Patients (aged ≥18 years) with metastatic urothelial carcinoma who had progressed after platinum-based chemotherapy were randomly assigned (1:1), via an interactive voice and web response system with a permuted block design (block size of four), to receive atezolizumab 1200 mg or chemotherapy (physician's choice: vinflunine 320 mg/m², paclitaxel 175 mg/m², or 75 mg/m² docetaxel) intravenously every 3 weeks. Randomisation was stratified by PD-L1 expression (expression on <1% [IC0] or 1% to <5% [IC1] of tumour-infiltrating immune cells *vs* ≥5% of tumour-infiltrating immune cells [IC2/3]), chemotherapy type (vinflunine *vs* taxanes), liver metastases (yes *vs* no), and number of prognostic factors (none *vs* one, two, or three). Patients and investigators were aware of group allocation. Patients, investigators, and the sponsor were masked to PD-L1 expression status. The primary endpoint of overall survival was tested hierarchically in prespecified populations: IC2/3, followed by IC1/2/3, followed by the intention-to-treat population. This study, which is ongoing but not recruiting participants, is registered with ClinicalTrials.gov, number NCT02302807.

Findings Between Jan 13, 2015, and Feb 15, 2016, we randomly assigned 931 patients from 198 sites to receive atezolizumab (n=467) or chemotherapy (n=464). In the IC2/3 population (n=234), overall survival did not differ significantly between patients in the atezolizumab group and those in the chemotherapy group (median 11·1 months [95% CI 8·6–15·5; n=116] *vs* 10·6 months [8·4–12·2; n=118]; stratified hazard ratio [HR] 0·87, 95% CI 0·63–1·21; p=0·41), thus precluding further formal statistical analysis. Confirmed objective response rates were similar between treatment groups in the IC2/3 population: 26 (23%) of 113 evaluable patients had an objective response in the atezolizumab group compared with 25 (22%) of 116 patients in the chemotherapy group. Duration of response was numerically longer in the atezolizumab group than in the chemotherapy group (median 15·9 months [95% CI 10·4 to not estimable] *vs* 8·3 months [5·6–13·2]; HR 0·57, 95% CI 0·26–1·26). In the intention-to-treat population, patients receiving atezolizumab had fewer grade 3–4 treatment-related adverse events than did those receiving chemotherapy (91 [20%] of 459 *vs* 189 [43%] of 443 patients), and fewer adverse events leading to treatment discontinuation (34 [7%] *vs* 78 [18%] patients).

Interpretation Atezolizumab was not associated with significantly longer overall survival than chemotherapy in patients with platinum-refractory metastatic urothelial carcinoma overexpressing PD-L1 (IC2/3). However, the safety profile for atezolizumab was favourable compared with chemotherapy, Exploratory analysis of the intention-to-treat population showed well-tolerated, durable responses in line with previous phase 2 data for atezolizumab in this setting.

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Introduction

Advanced urothelial carcinoma has a poor prognosis, with few patients surviving more than 5 years after diagnosis.[1] First-line cisplatin-based chemotherapy can improve overall survival,[2,3] but most patients have disease progression. Treatment patterns for locally advanced or metastatic urothelial carcinoma following platinum-containing chemotherapy vary globally. Vinflunine (approved only in the European Union [EU]) and taxanes are commonly used,[4,5] with prospective clinical data for these drugs showing a modest median overall survival of 6–7 months in this setting.[6,7] In the past few years,

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Research in context

Evidence before this study

Between Jan 1, 2005, and Sep 5, 2014, we searched PubMed and international congress presentations pertaining to phase 3 studies of platinum-treated urothelial carcinoma. We searched PubMed for articles published in English with medical subject heading search terms "advanced" AND "bladder cancer", "urothelial carcinoma", "transitional cell carcinoma". Before the present study (IMvigor211), vinflunine was the only drug approved by a health authority (in Europe) for the treatment of advanced or metastatic urothelial carcinoma after progression with platinum-based chemotherapy based on phase 3 data. Vinflunine and taxanes were commonly used drugs globally, but no standard appeared to predominate, and these drugs were associated with poor overall survival and toxicity. Because cancer immunotherapies had provided breakthroughs in numerous tumour types, and because urothelial carcinomas might be especially immunogenic on the basis of high somatic mutation burden, checkpoint inhibitor drugs targeting the programmed death-ligand 1 (PD-L1)–anti-programmed death-1 pathway warranted investigation in this setting. Single-arm phase 1 and 2 data with atezolizumab from 2014–17 have demonstrated safety and activity in this setting of previously treated metastatic urothelial carcinoma.

Added value of this study

To our knowledge, IMvigor211 is the first phase 3 randomised trial to report results for an anti-PD-L1 antibody in patients with metastatic urothelial carcinoma. Atezolizumab did not prolong overall survival in the predefined population of patients with PD-L1 expression on 5% or more of tumour-infiltrating immune cells, which precluded further statistical analysis. The PD-L1 biomarker enriched for responses in both the chemotherapy and the atezolizumab groups, which was unexpected and partly accounted for the negative result of the trial. Atezolizumab was associated with well tolerated, durable remissions in both the PD-L1-selected and intention-to-treat populations—a finding that was consistent with previous phase 2 data and that is uncommon with chemotherapy. Exploratory analysis showed differential overall survival benefit within the control group, based on chemotherapy choice, which could have accounted for some of the findings. Our results additionally show promise for alternative biomarkers beyond PD-L1 expression, such as tumour mutation burden. The data suggest that the risk–benefit profile for atezolizumab could be acceptable in patients with platinum-treated advanced urothelial carcinoma.

Implications of all the available evidence

Five immune checkpoint inhibitors have been approved in at least one country for patients with platinum-treated metastatic urothelial carcinoma. Data from randomised phase 3 trials exist for only atezolizumab and pembrolizumab. These checkpoint inhibitors appear attractive compared with chemotherapy in unselected patients in this setting and have potential to change the standard of care.

checkpoint inhibitors have changed the treatment of metastatic urothelial carcinoma.[8] In a randomised phase 3 trial,[9] patients with metastatic urothelial carcinoma given pembrolizumab, an anti-programmed death-1 (PD-1) drug, had longer survival than did those given chemotherapy. Additionally, atezolizumab—a monoclonal antibody that inhibits programmed death-ligand 1 (PD-L1) while leaving the PD-L2–PD-1 interaction intact[10,11]—is active and well tolerated across multiple cancers, including metastatic urothelial carcinoma.[11–16]

See Online for appendix

US approval of atezolizumab in patients with platinum-treated metastatic urothelial carcinoma was based on findings from phase 1 and 2 studies showing durable responses with long-term clinical benefit.[12,16] Although atezolizumab has shown activity in patients with all levels of PD-L1 expression, response rates were notably higher in patients with higher PD-L1 expression on tumour-infiltrating immune cells.[12,16] We therefore designed the IMvigor211 study to compare overall survival with atezolizumab to that with chemotherapy by PD-L1 expression in patients with platinum-treated metastatic urothelial carcinoma. To increase our understanding of the biology of metastatic urothelial carcinoma, we also explored the relevance of tumour mutation burden to overall survival. Here, we report results of the primary and exploratory analyses.

Methods

Study design and patients

We conducted this multicentre, open-label, phase 3 randomised controlled trial at 217 academic medical centres and community oncology practices mainly in Europe, North America, and the Asia-Pacific region (appendix pp 9–12). The study protocol (appendix pp 26–185) was approved by the independent ethics committee of each study site.

Eligible patients were aged 18 years or older with metastatic urothelial carcinoma, had measurable disease at baseline as per Response Evaluation Criteria In Solid Tumors version 1·1 (RECIST v1.1), an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and an evaluable sample for PD-L1 testing (regardless of PD-L1 status). Patients had received no more than two previous lines of therapy and had progressed during or following one or more platinum-containing regimens for metastatic urothelial carcinoma (or neoadjuvant or adjuvant therapy with progression within 12 months). A predominance of transitional histology was required. We excluded patients with previous autoimmune disease or those who

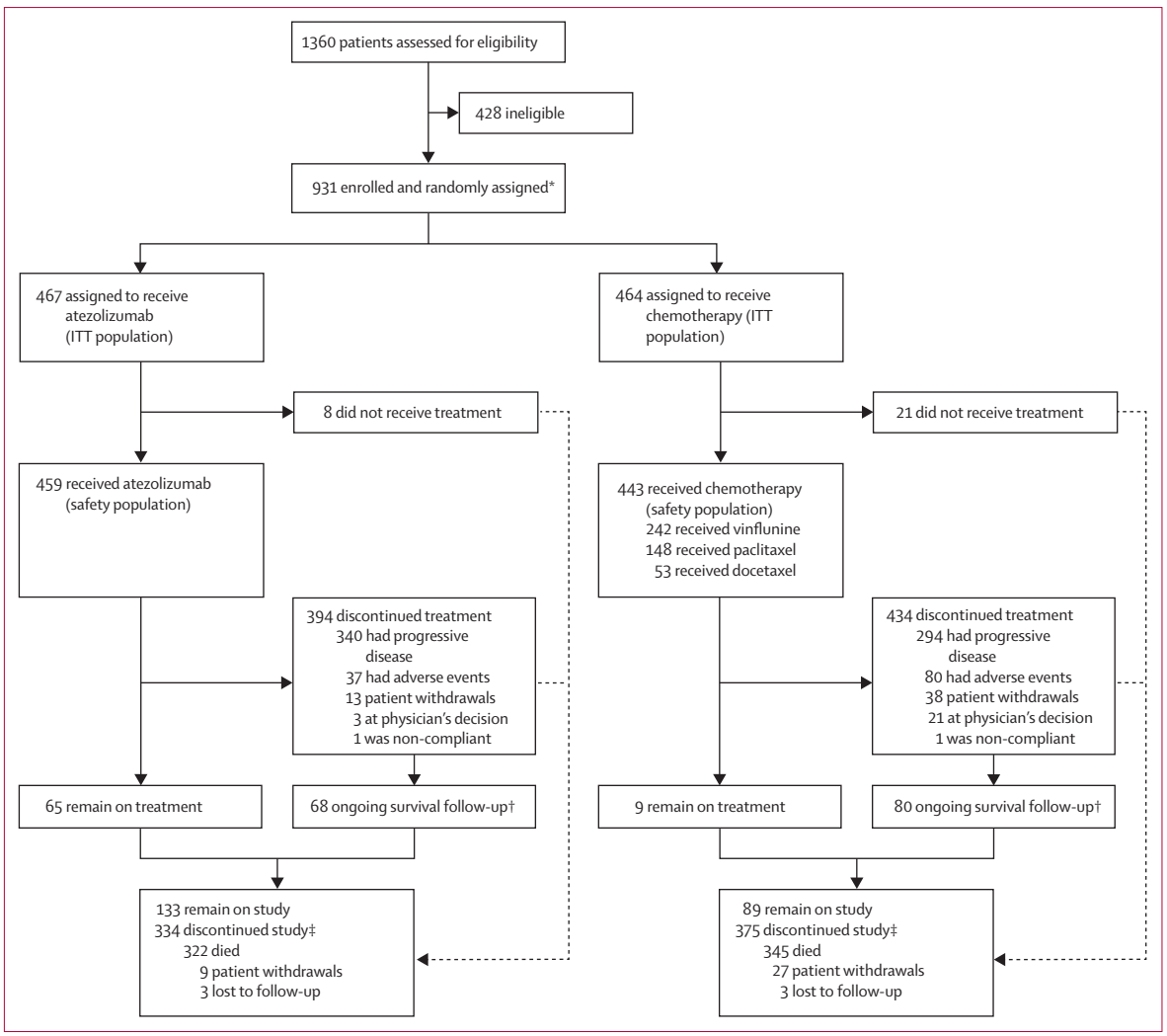

Figure 1: **Trial profile**
ITT=intention-to-treat. *One patient was assigned to chemotherapy twice (first to docetaxel, then to vinflunine) due to a randomisation error. This patient was counted only once in this report. †An additional two deaths (n=1 per group) were collected from public records and were not recorded under study discontinuation, but were included as uncensored deaths in the efficacy analyses. ‡As of data cutoff (March 13, 2017). An additional five deaths (n=4 in the chemotherapy group, n=1 in the atezolizumab group) were collected from public records and are recorded under "patient withdrawals" and included as uncensored deaths in the efficacy analyses.

had received therapies targeting CD137, CTLA4, or PD-L1–PD-1, and patients with symptomatic brain metastasis or inadequate renal or liver function. The appendix (pp 3–8) provides a full list of inclusion and exclusion criteria. This study was done in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1), via an interactive voice and web response system (IXRS) with a permuted block design (block size of four) to receive atezolizumab or chemotherapy. Randomisation was stratified by PD-L1 expression (expression on <1% [IC0] or 1% to <5% [IC1] of tumour-infiltrating immune cells *vs* ≥5% of tumour-infiltrating immune cells [IC2/3]), chemotherapy type (vinflunine *vs* taxanes), liver metastases (yes *vs* no), and number of prognostic factors (none *vs* one, two, or three—defined as time from previous chemotherapy <3 months, ECOG performance status ≥1, and haemoglobin <10 g/dL). Investigators and participants were aware of treatment allocation. The primary endpoint of overall survival mitigates most potential biases associated with an open-label study. Patients, investigators, and the sponsor were masked to PD-L1 expression status. Before randomisation, investigators selected a chemotherapy regimen (vinflunine, paclitaxel, or docetaxel) that the patient had not previously received. The sponsor was not permitted to do any population-level summaries of outcome data until the time of

	IC2/3 population		ITT population	
	Atezolizumab group (n=116)	Chemotherapy group (n=118)	Atezolizumab group (n=467)	Chemotherapy group (n=464)
Median age (years)	67 (43–88)	67 (36–84)	67 (33–88)	67 (31–84)
Sex				
Female	35 (30%)	23 (19%)	110 (24%)	103 (22%)
Male	81 (70%)	95 (81%)	357 (76%)	361 (78%)
Race				
White	86 (74%)	88 (75%)	335 (72%)	336 (72%)
Black or African American	0	1 (1%)	1 (<1%)	2 (<1%)
Asian	16 (14%)	12 (10%)	63 (13%)	55 (12%)
Multiracial	0	1 (1%)	0	1 (<1%)
Unknown	14 (12%)	16 (14%)	68 (15%)	70 (15%)
Tobacco use				
Current	12/115 (10%)	18/118 (15%)	60/466 (13%)	60/462 (13%)
Former	68/115 (59%)	68/118 (58%)	266/466 (57%)	280/462 (61%)
Never	35/115 (30%)	32/118 (27%)	140/466 (30%)	122/462 (26%)
Primary tumour site				
Bladder	85 (73%)	88 (75%)	324 (69%)	338 (73%)
Urethra	2 (2%)	5 (4%)	9 (2%)	9 (2%)
Renal pelvis	13 (11%)	12 (10%)	66 (14%)	52 (11%)
Ureter	15 (13%)	11 (9%)	60 (13%)	58 (13%)
Other	1 (1%)	2 (2%)	8 (2%)	7 (2%)
Metastatic disease	99 (85%)	111 (94%)	425 (91%)	430 (93%)
Site of metastases				
Lymph node only	18 (16%)	27 (23%)	54 (12%)	66 (14%)
Visceral*	78 (67%)	82 (69%)	361 (77%)	355 (77%)
Liver	28 (24%)	30 (25%)	138 (30%)	130 (28%)
ECOG performance status				
0	61 (53%)	57 (48%)	218 (47%)	207 (45%)
1	55 (47%)	61 (52%)	249 (53%)	257 (55%)
Haemoglobin concentration <10 g/dL	17 (15%)	19 (16%)	65 (14%)	73 (16%)
Number of risk factors†				
0	44 (38%)	41 (35%)	145 (31%)	140 (30%)
1	50 (43%)	48 (41%)	214 (46%)	208 (45%)
2	16 (14%)	25 (21%)	86 (18%)	96 (21%)
3	6 (5%)	4 (3%)	22 (5%)	20 (4%)

(Table 1 continues on next page)

primary analysis.

Procedures

Archival or fresh tumour samples were centrally and prospectively evaluated with the VENTANA SP142 PD-L1 immunohistochemistry assay (Ventana Medical Systems, Tucson, AZ, USA). Scoring criteria designated tumour samples as IC2/3, IC1, or IC0. Patients received atezolizumab 1200 mg or chemotherapy (vinflunine 320 mg/m², paclitaxel 175 mg/m², or docetaxel 75 mg/m²) intravenously every 3 weeks until unacceptable toxicity, RECIST v1.1 progression, or informed consent withdrawal. Tumour imaging was done at baseline and every 9 weeks (every 12 weeks after week 54). Atezolizumab treatment could continue beyond radiographic progression if deemed of clinical benefit by the investigator. No prespecified crossover was planned per protocol. Survival follow-up occurred every 3 months after treatment discontinuation. National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 was used to assess adverse event frequency and severity.

For analysis of tumour mutation burden, tumour DNA extraction and preparation were done with HistoGeneX NV (Antwerp, Belgium). Foundation Medicine (Cambridge, MA, USA) did sequencing library construction, hybridisation capture, DNA sequencing, and genomic alteration detection.[17] In addition to sample processing, Foundation Medicine estimated the mutation burden for each sample using an algorithm that leverages genomic alterations detected by the targeted FoundationOne test to extrapolate to the whole exome or genome.[18] We categorised tumour mutation burden as high (at or above the median) or low (less than the median).

Outcomes

The primary endpoint was overall survival, defined as the time from randomisation to death. Secondary efficacy endpoints were investigator-assessed RECIST v1.1 objective response rate, progression-free survival, and duration of response. Confirmed objective response rates were exploratory. We additionally assessed safety and prespecified patient-reported outcomes (European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 [EORTC QLQ-C30] health-related quality of life, physical functioning, and fatigue; appendix p 8).

Statistical analysis

This study was designed to enrol 931 patients, including at least 230 patients with IC2/3 status and at least 537 with IC1/2/3 status. Comparisons of overall survival between treatment groups were tested with a hierarchical fixed-sequence procedure based on a stratified log-rank test at a two-sided level of 5% significance (similar to that used for objective response rate)[15,16] in prespecified populations: IC2/3, followed by IC1/2/3, followed by the intention-to-treat population. The intention-to-treat population included all randomly assigned patients regardless of whether they received study treatment. The IC2/3 and IC1/2/3 populations included all patients in the intention-to-treat population with IC2/3 and IC1/2/3 status, respectively. Statistical significance was required at each step before formal testing of the subsequent population. If overall survival benefit with atezolizumab was statistically significant in all three populations, the null hypothesis of no difference in overall survival between the two groups was rejected, and key secondary efficacy endpoints could then be tested in the same order (ie, objective response rate followed by progression-free survival). The primary efficacy analysis was planned when

roughly 152 deaths were observed in the IC2/3 population, 403 deaths were observed in the IC1/2/3 population, and 652 deaths were observed in the intention-to-treat population, whichever occurred last. There was no planned maximum follow-up period or interim analysis based on the event-driven endpoints per protocol. The number of events required to demonstrate overall survival benefit with atezolizumab versus chemotherapy were estimated on the basis of a two-sided significance level of 5%, 94% power in the IC2/3 subgroup analysis with an hazard ratio (HR) of 0·57 (corresponding to a median overall survival improvement from 7·5 months to 13·2 months), 98% power in the IC1/2/3 analysis with an HR of 0·68 (corresponding to a median overall survival improvement from 7·5 months to 11 months), 97% power for the intention-to-treat population with an HR of 0·74 (corresponding to a median overall survival improvement from 7·5 months to 10·1 months), a 1:1 randomisation ratio, and a dropout rate of 5% per year over 24 months.

In analysis of overall survival, patients who were not reported to have died by the data cutoff date were censored at the last date they were known to be alive (or at randomisation day for those with no post-baseline data). We used the Kaplan–Meier approach to estimate overall survival, progression-free survival, and duration of response, with Brookmeyer–Crowley methodology used to estimate 95% CIs. HRs were estimated with a stratified Cox regression analysis (stratification factors were the same as those used for randomisation, unless otherwise indicated). RECIST v1.1 objective response rates and 95% CIs for each treatment group were calculated with the Clopper–Pearson method and were compared between groups with the Mantel–Haenszel test. We used descriptive statistics to summarise study drug exposure (treatment duration, number of doses, and dose intensity) for each treatment group. Safety-evaluable patients included randomised patients who received any amount of study treatment. Deaths were reported during the study or follow-up period and summarised by treatment group.

We did statistical analysis with SAS (version 9.2). An independent data monitoring committee reviewed safety roughly every 6 months. This study, which is ongoing but not recruiting participants, is registered with ClinicalTrials.gov, number NCT02302807.

Role of the funding source

The sponsor of the study had a role in study design, data collection, data analysis, and data interpretation. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between Jan 13, 2015, and Feb 15, 2016, we randomly assigned 931 patients (intention-to-treat population) from 198 sites (appendix pp 9–12) to receive atezolizumab (n=467) or chemotherapy (n=464; figure 1). The treated (safety-evaluable) population included 902 patients (figure 1). Of 443 patients who received chemotherapy, 242 (55%) received vinflunine, 148 (33%) received paclitaxel, and 53 (12%) received docetaxel (figure 1). Baseline characteristics between groups were similar in both the IC2/3 and intention-to-treat populations (table 1).

	IC2/3 population		ITT population	
	Atezolizumab group (n=116)	Chemotherapy group (n=118)	Atezolizumab group (n=467)	Chemotherapy group (n=464)
(Continued from previous page)				
Previous cystectomy	57 (49%)	58 (49%)	199 (43%)	200 (43%)
Time since previous chemotherapy <3 months	35 (30%)	43 (36%)	160 (34%)	160 (34%)
Number of previous systemic regimens in the metastatic setting				
0	43 (37%)	41 (35%)	131 (28%)	120 (26%)
1	54 (47%)	59 (50%)	249 (53%)	261 (56%)
2	18 (16%)	18 (15%)	79 (17%)	74 (16%)
≥3	1 (1%)	0	8 (2%)	9 (2%)‡
Previous systemic regimen setting				
Metastatic	73 (63%)	77 (65%)	336 (72%)	344 (74%)
Neoadjuvant or adjuvant chemotherapy with progression within ≤12 months	37 (32%)	37 (31%)	117 (25%)	108 (23%)
Other§	6 (5%)	4 (3%)	14 (3%)	12 (3%)

Data are median (range), n (%), or n/N (%), unless otherwise specified. IC2/3=patients with programmed death-ligand-1 expression on 5% or more of tumour-infiltrating immune cells. ITT=intention-to-treat. ECOG=Eastern Cooperative Oncology Group. *Defined as liver, lung, bone, any non-lymph-node, or soft tissue metastasis. †Refers to an ECOG performance status of 1 or more, presence of baseline liver metastases, and a haemoglobin concentration of less than 10 g/dL. ‡One (<1%) patient in the chemotherapy group received four previous systemic regimens for metastatic disease. §Refers to neoadjuvant or adjuvant chemotherapy with progression after 12 months, neoadjuvant or adjuvant chemotherapy with progression time unknown, and other treatment settings.

Table 1: **Baseline characteristics**

At data cutoff (March 13, 2017) in the intention-to-treat population, 133 (28%) of 467 patients remained in the study in the atezolizumab group, and 89 (19%) of 464 patients remained in the study in the chemotherapy group (figure 1). Treated patients received atezolizumab for a median of 2·8 months (range 0–24), vinflunine for a median of 2·1 months (0–15), paclitaxel for a median of 2·1 months (0–23), and docetaxel for a median of 1·6 months (0–10). 81 (18%) patients who received atezolizumab, 12 (5%) who received vinflunine, and two (1%) who received paclitaxel were treated for 1 year or more. At data cutoff, 65 (14%) patients receiving atezolizumab and nine (2%) patients receiving chemotherapy remained on treatment (figure 1). After treatment discontinuation, 108 (23%) patients in the atezolizumab group and 118 (25%) patients in the chemotherapy group received at least one subsequent non-protocol treatment (appendix p 13), with 28 (6%) patients in the chemotherapy group receiving post-protocol immunotherapy. The median follow-up duration in the intention-to-treat population was 17·3 months (range 0–24·5). A total of 674 (72%) deaths occurred: 324 in the atezolizumab group and 350 in the chemotherapy group.

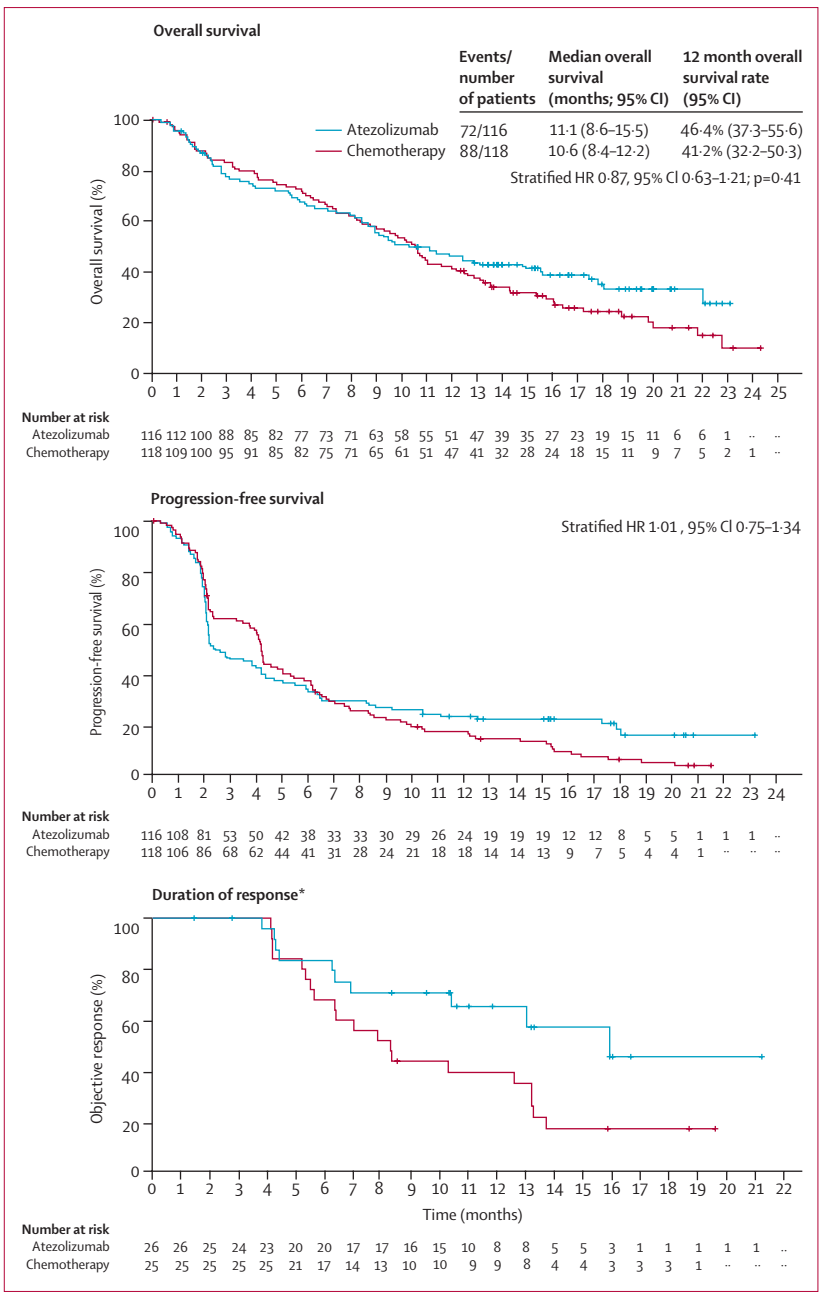

Figure 2: **Efficacy outcomes in patients with programmed death-ligand-1 expression on 5% or more of tumour-infiltrating immune cells (IC2/3 population)**
Complete data for progression-free survival and duration of response are shown in table 2. Vertical lines indicate censored events (death or progression). HR=hazard ratio. *In the subset of patients with objective response.

The efficacy analysis was first done in the IC2/3 population. Overall survival did not differ significantly between the atezolizumab group and the chemotherapy group (median 11·1 months [95% CI 8·6–15·5] *vs* 10·6 months [8·4–12·2]; stratified HR 0·87, 95% CI 0·63–1·21; p=0·41; figure 2), precluding further formal statistical comparisons and rendering subsequent analyses exploratory in nature. Exploratory forest plot analyses for overall survival were evaluated in subgroups on the basis of baseline characteristics (appendix p 18). Most efficacy differences between treatment groups were marginal (appendix p 18). For patients receiving chemotherapy, vinflunine outperformed study expectations; unstratified HRs were 0·95 (95% CI 0·62–1·45) and 0·69 (0·44–1·10) in subgroups based on chemotherapy stratification with vinflunine (n=106) and taxanes (n=128), respectively. We also recorded variations in overall survival HRs for upper-tract renal pelvis urothelial tumours (appendix p 18).

Confirmed objective response rates were similar between treatment groups in the IC2/3 population (table 2). 16 (62%) of 26 responders to atezolizumab and five (20%) of 25 responders to chemotherapy had ongoing responses; the duration of response was numerically longer in the atezolizumab group (table 2, figure 2). Progression-free survival was numerically longer in patients given chemotherapy; however, patients given atezolizumab had fewer progression-free survival events (table 2, figure 2).

The proportion of patients with adverse events was similar between groups in the IC2/3 and intention-to-treat populations, although results for the intention-to-treat population were more robust in view of the higher number of patients (table 3). In the IC2/3 population, treatment-related adverse events leading to treatment discontinuation occurred in seven (6%) of 114 patients in the atezolizumab group and 17 (15%) of 112 patients in the chemotherapy group (appendix p 14). We recorded two (2%) atezolizumab-related deaths and two (2%) chemotherapy-related deaths in the IC2/3 population. These safety results were mirrored in the intention-to-treat population, in which treatment discontinuations due to adverse events occurred in 16 (3%) of 459 patients in the atezolizumab group and 63 (14%) of 443 patients in the chemotherapy group; treatment-related deaths occurred in four (1%) and nine (2%) patients, respectively (appendix pp 14, 15). Adverse events of any grade deemed treatment related by the investigator occurred in 85 (75%) atezolizumab-treated patients versus 99 (88%) chemotherapy-treated patients in the IC2/3 population (table 3). For both the IC2/3 and intention-to-treat populations, treatment-related adverse events occurring in 10% or more of patients in both groups were fatigue, asthenia, decreased appetite, and diarrhoea (table 3). For both populations, treatment-related fatigue, nausea, constipation, and alopecia of any grade occurred in 22% or more of patients receiving chemotherapy, but did not meet this threshold for patients receiving atezolizumab (table 3). Conversely, treatment-related pruritus was more common in the atezolizumab group of the IC2/3 and the intention-to-treat populations (table 3). In the IC2/3 population, treatment-related rash was likewise more common with atezolizumab then chemotherapy (table 3). In both the IC2/3 and intention-to-treat populations, grade 3 or 4 treatment-related adverse events were less common with atezolizumab than chemotherapy (table 3).

Subsequent overall survival analyses were done in the intention-to-treat population for exploratory purposes only (figure 3, appendix p 19). We did this analysis for two primary reasons: to explore potential reasons for the negative primary endpoint in the IC2/3 population and to inform understanding around the hypothesis that atezolizumab would provide benefit regardless of PD-L1 expression, but would perform better in the IC2/3 subgroup. Overall survival in the intention-to-treat population was numerically improved in the atezolizumab group compared with the chemotherapy group (figure 3). At 12 months, the overall survival rate was 39·2% (95% CI 34·8–43·7) with atezolizumab and 32·4% (28·0–36·8) with chemotherapy (figure 3). Results from prespecified subgroup analyses of overall survival in the intention-to-treat population by baseline and clinical characteristics generally agreed with those from the IC2/3 population (figure 3). In exploratory analyses we additionally assessed overall survival in the intention-to-treat population by investigator-prespecified chemotherapy subgroup (taxane and vinflunine). Atezolizumab demonstrated better comparative overall survival in patients intended for treatment with taxanes (median 8·3 months [95% CI 6·6–9·8; n=215] *vs* 7·5 months [6·7–8·6; n=214]; HR 0·73, 95% CI 0·58–0·92), but not in those given vinflunine (median 9·2 months [7·9–10·4; n=252] *vs* 8·3 months [6·9–9·6; n=250]; 0·97, 0·78–1·19; appendix p 21).

Confirmed objective response rates were lower for both atezolizumab-treated and chemotherapy-treated patients in the intention-to-treat population than for those in the IC2/3 population (table 2). Median response durations were longer with atezolizumab than chemotherapy in the intention-to-treat population (table 2, figure 3), mirroring the results in the IC2/3 population (table 2, figure 2). In the intention-to-treat population, 39 (63%) of 62 responders receiving atezolizumab had ongoing responses compared with 13 (21%) of 62 responders receiving chemotherapy. Progression-free survival in this population was longer in patients given chemotherapy than in those given atezolizumab (table 2, figure 2). The appendix (pp 16, 20, 22) shows results for additional exploratory analyses of key efficacy endpoints (overall survival, objective response rate and duration, and progression-free survival) for the IC1/2/3 population.

In an exploratory biomarker analysis, 544 (58%) of 931 patients in the intention-to-treat population had tumour samples evaluable for measurement of tumour mutation burden. Baseline characteristics of the overall biomarker-evaluable population, including PD-L1 status (appendix p 23), were generally balanced between treatment groups and representative of the intention-to-treat population. Median tumour mutation burden in the biomarker-evaluable population was 9·65 mutations per megabase (IQR 8·78) and was also similar between groups (appendix p 23). The correlation observed between PD-L1 expression and tumour mutation burden was modest (r=0·13). We assessed overall survival based on patients whose samples had high (at or above the median) or low (below the median) values for tumour mutation burden (appendix p 23). For patients with samples with high tumour mutation burden (n=274), overall survival was numerically longer for those treated with atezolizumab than for those treated with chemotherapy (median 11·3 months [95% CI 8·7–13·2] *vs* 8·3 months [7·2–10·4]; HR 0·68, 95% CI 0·51–0·90), whereas for those with samples with low tumour mutation burden (n=270), survival was similar between groups (median 8·3 months [6·4–9·8] *vs* 8·1 months [6·2–10·4]; 1·00, 0·75–1·32; appendix p 23). We next evaluated whether PD-L1 status conferred a survival advantage for patients with samples with high tumour mutation burden (appendix p 23). In patients with samples with high tumour mutation burden and PD-L1 IC2/3 samples (n=96), median survival for patients given atezolizumab was 17·8 months (95% CI 9·7–not estimable) versus 10·6 months (8·2–14·3) for those given chemotherapy (HR 0·50, 95% CI 0·29–0·86; appendix p 23).

In a further analysis, we evaluated prespecified patient-reported outcomes based on EORTC QLQ-C30 global health status, physical functioning, and fatigue scores (appendix pp 24, 25), and measured baseline scores in the intention-to-treat population (appendix p 17). Mean changes in these scores initially deteriorated, but returned to baseline after several cycles and re-

	IC2/3 population		ITT population	
	Atezolizumab group (n=116)	Chemotherapy group (n=118)	Atezolizumab group (n=467)	Chemotherapy group (n=464)
Progression-free survival				
Patients with event (%)*	93 (80%)	105 (89%)	407 (87%)	410 (88%)
Median (months; 95% CI)	2·4 (2·1–4·2)	4·2 (3·7–5·0)	2·1 (2·1–2·2)	4·0 (3·4–4·2)
Objective response†				
Number of evaluable patients	113	116	462	461
Number of patients with response (%, 95% CI)	26 (23·0%, 15·6–31·9)	25 (21·6%, 14·5–30·2)	62 (13·4%, 10·5–16·9)	62 (13·4%, 10·5–16·9)
Best overall response†				
Complete response	8 (7%)	8 (7%)	16 (3%)	16 (3%)
Partial response	18 (16%)	17 (15%)	46 (10%)	46 (10%)
Stable disease	23 (20%)	37 (32%)	92 (20%)	162 (35%)
Progressive disease	47 (42%)	30 (26%)	240 (52%)	150 (32%)
Missing or unevaluable	17 (15%)	24 (21%)	68 (15%)	87 (19%)
Duration of response†				
Patients with event (%)*	10/26 (38%)	20/25 (80%)	23/62 (37%)	49/62 (79%)
Median (months; 95% CI)	15·9 (10·4–NE)	8·3 (5·6–13·2)	21·7 (13·0–21·7)	7·4 (6·1–10·3)

Data are n (%) or n/N (%), unless otherwise specified. IC2/3=patients with programmed death-ligand-1 expression on 5% or more of tumour-infiltrating immune cells. ITT=intention-to-treat. NE=not estimable. *Progressive disease or death. †Confirmed investigator-assessed objective responses.

Table 2: **Secondary and exploratory efficacy outcomes**

	IC2/3 population		ITT population	
	Atezolizumab group (n=114)	Chemotherapy group (n=112)	Atezolizumab group (n=459)	Chemotherapy group (n=443)
Most common treatment-related adverse events of any grade*				
All	85 (75%)	99 (88%)	319 (69%)	395 (89%)
Fatigue	18 (16%)	27 (24%)	71 (15%)	116 (26%)
Pruritus	14 (12%)	3 (3%)	55 (12%)	14 (3%)
Asthenia	14 (12%)	23 (21%)	51 (11%)	79 (18%)
Rash	13 (11%)	7 (6%)	40 (9%)	21 (5%)
Pyrexia	12 (11%)	4 (4%)	40 (9%)	25 (6%)
Decreased appetite	11 (10%)	20 (18%)	56 (12%)	81 (18%)
Diarrhoea	11 (10%)	15 (13%)	50 (11%)	66 (15%)
Nausea	9 (8%)	25 (22%)	46 (10%)	117 (26%)
Dyspnoea	9 (8%)	3 (3%)	18 (4%)	19 (4%)
Anaemia	8 (7%)	18 (16%)	25 (5%)	84 (19%)
Constipation	5 (4%)	44 (39%)	29 (6%)	145 (33%)
Vomiting	5 (4%)	17 (15%)	16 (3%)	62 (14%)
Abdominal pain	5 (4%)	8 (7%)	9 (2%)	34 (8%)
Arthralgia	4 (4%)	13 (12%)	17 (4%)	40 (9%)
Myalgia	4 (4%)	9 (8%)	13 (3%)	48 (11%)
Neutropenia	3 (3%)	13 (12%)	3 (1%)	64 (14%)
Mucosal inflammation	3 (3%)	9 (8%)	15 (3%)	44 (10%)
Peripheral neuropathy	2 (2%)	15 (13%)	3 (1%)	50 (11%)
Dysgeusia	2 (2%)	7 (6%)	6 (1%)	22 (5%)
Paraesthesia	1 (1%)	6 (5%)	7 (2%)	25 (6%)
Decreased weight	1 (1%)	5 (4%)	12 (3%)	26 (6%)
Alopecia	0	33 (29%)	0	120 (27%)
Peripheral sensory neuropathy	0	11 (10%)	3 (1%)	39 (9%)
Stomatitis	0	9 (8%)	10 (2%)	33 (7%)
Decreased neutrophil count	0	8 (7%)	0	28 (6%)
Febrile neutropenia	0	5 (4%)	1 (<1%)	25 (6%)
Grade 3 or 4 treatment-related adverse events†				
Fatigue	4 (4%)	2 (2%)	7 (2%)	18 (4%)
Anaemia	3 (3%)	3 (3%)	9 (2%)	21 (5%)
Neutropaenia	2 (2%)	9 (8%)	2 (<1%)	49 (11%)
Peripheral neuropathy	1 (1%)	3 (3%)	1 (<1%%)	8 (2%)
Asthenia	1 (1%)	2 (2%)	8 (2%)	18 (4%)
Neutrophil count decreased	0	7 (6%)	0	26 (6%)
Febrile neutropenia	0	5 (4%)	1 (<1%)	25 (6%)
Constipation	0	4 (4%)	0	20 (5%)
Peripheral sensory neuropathy	0	3 (3%)	0	6 (1%)
Ileus	0	3 (3%)	0	4 (1%)
White blood cell count decreased	0	2 (2%)	0	11 (2%)

Data are n (%). IC2/3=patients with programmed death-ligand-1 expression on 5% or more of tumour-infiltrating immune cells. ITT=intention-to-treat. *Adverse events of all grades reported in at least 5% of patients in either group. †Adverse events reported in at least 2% of patients in either group.

Table 3: **Treatment-related adverse events**

mained stable thereafter for the atezolizumab group; mean scores changes were worse, particularly for fatigue, in the chemotherapy group (appendix p 25). Although event-to-patient deterioration rates remained low at time of analysis, median time to deterioration was similar between groups for global health status, and prolonged with atezolizumab for physical function and fatigue (appendix p 24).

Discussion

In this randomised phase 3 study, the primary endpoint of overall survival improvement with atezolizumab was not met in patients with metastatic urothelial carcinoma with at least 5% PD-L1 expression on tumour-infiltrating immune cells, precluding additional formal statistical analysis. Our hierarchical study design hypothesised that efficacy would be associated with PD-L1 expression on the basis of phase 1 and 2 findings with atezolizumab[12,16,19] and other checkpoint inhibitors.[20,21] Unexpectedly, in our study, overexpression of PD-L1 (SP142 immunohistochemistry assay) resulted in a more favourable outcome (longer overall survival and increased response rates) with both chemotherapy and atezolizumab, negating its potentially predictive effects. The reasons for these results remain unclear and differ from previous positive phase 3 studies of atezolizumab in patients with advanced non-small-cell lung cancer[14] and pembrolizumab in patients with metastatic urothelial carcinoma (KEYNOTE-045).[9] An explanation for these inverse results is not readily available, although PD-L1 assay disparities—widespread in this field[22]—might contribute to these differences. Indeed, the assay used in KEYNOTE-045 (22C3 antibody) measured PD-L1 expression on both immune and tumour cells, which, unlike SP142, was associated with a poor prognosis.[9] These results underscore the risks of biomarker-focused statistical designs without supportive randomised data, and highlight the need for improved predictive biomarkers for cancer immunotherapy.[23,24] Kaplan–Meier analysis also revealed non-proportional hazards, with curve separation and inflection occurring relatively late. This outcome is common with immune checkpoint inhibitors,[9,25] but appears more pronounced here, partially accounting for the statistical findings of the study. Atezolizumab was associated with a longer duration of response, consistent with other immune checkpoint inhibitors in metastatic urothelial carcinoma and associated with notable 12 month landmark overall survival rates.

The adverse event profile for atezolizumab was favourable compared with chemotherapy for both the IC2/3 and intention-to-treat populations. Patients receiving atezolizumab had lower rates of adverse events leading to treatment discontinuation and fewer treatment-related adverse events than did those receiving chemotherapy. The safety profiles for cancer immunotherapies and chemotherapy are distinct; rates for grade 3 or 4 adverse events of special interest were less than 10% for atezolizumab in IC2/3 and intention-to-treat patients, with immune-mediated events generally consistent with previous atezolizumab studies.[16] These data further translated to sustained health-related quality of life with atezolizumab.

Because of an absence of global consensus, the control group permitted different chemotherapy regimens; however, our results revealed numerical differences when efficacy was evaluated by chemotherapy type. Survival with vinflunine was better than the protocol hypothesised on the basis of previous studies,[6,9] potentially compromising the statistical assumptions. This finding was not exclusive to the PD-L1-selected subgroups, but was also noted in the intention-to-treat population. Although previous data suggested similar overall survival rates for vinflunine, paclitaxel, and docetaxel,[6,7] comparative randomised studies with these drugs have not been done, which calls into question the suitability of a mixed control group and potentially affects our results. Furthermore, improved clinical proficiency and post-approval patient selection in western Europe,[26–29] where most patients were enrolled, might have also contributed to these findings. The primary analysis of KEYNOTE-045 did not pursue a hierarchical PD-L1 biomarker-driven approach and demonstrated positive survival results for pembrolizumab versus chemotherapy; however, comparisons between biomarker-selected and unselected trials are challenging because of intrinsic differences in patient populations.

We did prespecified exploratory efficacy analyses of the intention-to-treat population to better understand the results of the study and evaluate atezolizumab versus chemotherapy in a biomarker-unselected comparison, which, with more than 900 patients treated in that population, is to our knowledge the largest interventional study of metastatic urothelial carcinoma. Median survival rates were shorter in the intention-to-treat population than in the IC2/3 population, potentially due to the enrichment of responders occurring in both groups in the IC2/3 cohort. Comparative efficacy signals (overall survival HR 0·85, 95% CI 0·73–0·99) were similar to those in the IC2/3 population, underlining the problem with our biomarker enrichment hypothesis for the primary endpoint. Toxicity and duration of response for the IC2/3 and intention-to-treat populations were similar. Exploratory analysis showed that notable 1 year milestone survival rates were achieved with atezolizumab compared with chemotherapy in the intention-to-treat population (39·2% *vs* 32·4%). Similar to the IC2/3 subgroup, delayed separation of the Kaplan–Meier curves was observed when indirectly compared with KEYNOTE-045. Median progression-free survival is short for all immune checkpoint inhibitors in this setting, irrespective of biomarker selection. Different strategies will be required to achieve disease control in most patients. These data from the intention-to-treat population were not formally tested for statistical significance. However, in view of the high unmet need in this population, the well tolerated, durable remissions observed with atezolizumab, and the complications associated with chemotherapy, the benefit–risk ratio for atezolizumab can be considered favourable for patients with metastatic urothelial carcinoma previously treated with platinum-containing regimens. Atezolizumab is approved in this setting in the US.[30] EU approval of atezolizumab was granted in patients with platinum-treated metastatic urothelial carcinoma partly on the basis of these data.[31]

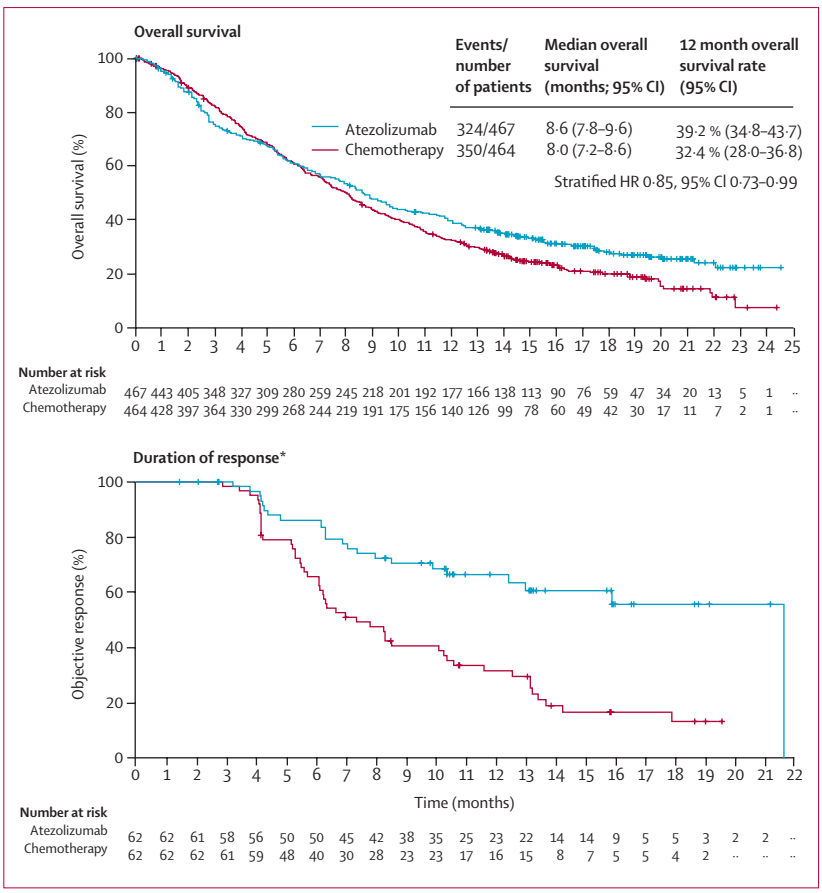

Figure 3: **Exploratory efficacy outcomes in the intention-to-treat population**
HR=hazard ratio. *In the subset of patients with objective response.

We attempted to identify alternative biomarkers for atezolizumab in view of the absence of predictive values for the PD-L1 immunohistochemistry biomarker. Tumour mutation burden, which is high in bladder cancer, is thought to be a surrogate marker for neoantigen expression and might be required for immune recognition of tumours. Previous exploratory studies have shown that tumour mutation burden outperforms PD-L1 expression as a biomarker for nivolumab in other tumour types.[32] Our study showed similar results. These consistent results across different tumour types suggest similar broad mechanisms of action for this group of drugs. These results are hypothesis generating; if validated in future trials, tumour mutation burden—alone or with other biomarkers—could improve the accuracy of selection of patients for monotherapy.

Contributors

TP, NC, XS, and CLD contributed to the design of the study.

All authors contributed to data collection, data analysis, and data interpretation. All authors contributed to writing of the manuscript, approved the final version, and agree to be accountable for all aspects of the report.

Declaration of interests

TP has received research funding from Roche and AstraZeneca, and honoraria from Roche, Bristol-Myers Squibb, and Merck. ID has received honoraria for consulting or advisory roles from Jansen, Roche, Amgen, and Novartis, and travel support and accommodation expenses from Astellas. MSvdH has received a research grant from Astellas, reimbursement for patient care and data management of study participants from Roche–Genentech, and honoraria for advisory roles from Roche–Genentech, Astellas, and AstraZeneca. YL has received honoraria from Roche, Sanofi, Astellas, Janssen, iPSEN, and Bristol-Myers Squibb, and a research grant from Sanofi. SO has received honoraria from Roche, Novartis, iPSEN, Bristol-Myers Squibb, and Bayer. AB has received honoraria from Roche, Novartis, Pfizer, Bristol-Myers Squibb, and AstraZeneca; research grants and non-financial support from Novartis and Pfizer; and investigator and institutional support from Roche. AF has received honoraria from Janssen, Pfizer, Roche, AstraZeneca, MSD, and Pierre Fabre, and travel support and accommodation expenses from Janssen, Pfizer, MSD, Roche, AstraZeneca, and Pierre Fabre. SH has served in advisory roles for Roche, Merck, AstraZeneca, Pierre Fabre, Bayer, Janssen, and Bristol-Myers Squib, and has received educational grants and institutional funding from Cancer Research UK, Boehringer Ingelheim, Janssen, and Eli Lilly. TT has received honoraria from Daiichi-Sankyo. NL, EEK, RB, PSH, SM, NC, XS, CLD, and MCG are employees of Genentech and own Roche stock. AR has received honoraria, travel support, and accommodation expenses from Pfizer, Novartis, Bristol-Myers Squib, AstraZeneca, Roche, MSD, and iPSEN and a research grant from Pfizer. NJV, UDG, MMR, DC, and GG declare no competing interests.

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