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

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Summary

Background Limited options exist for patients with locally advanced or metastatic urothelial carcinoma (mUC) after progression on platinum-based chemotherapy. We evaluated atezolizumab (anti–programmed death-ligand 1 [PD-L1]) *vs* chemotherapy in this setting.

Methods In IMvigor211 (ClinicalTrials.gov, number NCT02302807, not recruiting), a global, open-label, randomised phase 3 trial, 931 patients with mUC who had progressed on platinum-based chemotherapy were randomly assigned (1:1) to atezolizumab 1200 mg or chemotherapy (physician's choice: vinflunine, paclitaxel, or docetaxel) intravenously every 3 weeks. The primary endpoint, overall survival, was tested hierarchically in patients with PD-L1 expression on ≥5% (IC2/3) and ≥1% (IC1/2/3) of immune cells and the intention-to-treat (ITT) population.

Findings Median overall survival in IC2/3 patients (n=234; 25%) was 11·1 months (95% confidence interval [CI], 8·6–15·5; n=116) in the atezolizumab arm *vs* 10·6 months (95% CI, 8·4–12·2; n=118) with chemotherapy (hazard ratio [HR], 0·87; 95% CI, 0·63–1·21; P=0·41). Objective response rates in IC2/3 patients were 23% with atezolizumab and 22% with chemotherapy, although duration of response appeared to favour atezolizumab (medians, 15.9 mo with atezolizumab *vs* 8.3 mo with chemotherapy; HR, 0·57; 95% CI, 0·26–1·26). ITT population patients receiving atezolizumab (n=459) experienced fewer grade 3-4 treatment-related adverse events (19·8% *vs* 42·7% for chemotherapy-treated patients [n=443]). Subsequent predefined exploratory analyses found ITT median overall survival was 8·6 months (95% CI, 7·8–9·6; n=467) for atezolizumab *vs* 8·0 months (95% CI, 7·2–8·6; n=464) with chemotherapy (HR, 0·85; 95% CI, 0·73–0·99; n=931). Exploratory biomarker analysis showed promising results for atezolizumab (n=123) *vs* chemotherapy (n=151) for patients with high tumour mutation burden in this setting (overall survival HR, 0·68; 95% CI, 0·51–0·90; n=274).

Interpretation Atezolizumab was not associated with significantly longer overall survival in platinum-refractory mUC patients overexpressing PD-L1 (IC2/3) compared with chemotherapy. Exploratory analysis of the ITT population showed well-tolerated, durable responses in line with previous phase 2 data for atezolizumab in this setting.

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Research in context

Evidence before this study

A survey of the existing literature on clinical trials in advanced or metastatic urothelial carcinoma (mUC) as of January, 2015 was undertaken. We focused on PubMed search results and international congress presentations pertaining to phase 3 studies in platinum-treated urothelial carcinoma within the previous 10 years. Prior to the conduct of this study, vinflunine was the only agent approved by a health authority (in Europe) for the treatment of advanced or metastatic urothelial carcinoma after progression on platinum-based chemotherapy based on phase 3 data. Vinflunine and taxanes were commonly used agents globally, but no standard appeared to predominate and these agents were associated with poor overall survival and toxicity. Since cancer immunotherapies had provided breakthroughs in numerous tumour types, and as urothelial carcinomas may be especially immunogenic due to high somatic mutation burden, checkpoint inhibitor agents targeting the PD-L1/PD-1 pathway warranted investigation in this setting. Single-arm Phase 1 and 2 data with atezolizumab from 2014-2017 have demonstrated safety and activity in this previously treated mUC setting.

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 mUC. In our study, atezolizumab did not prolong overall survival in the predefined PD-L1

IC2/3 population, precluding further statistical analysis. The PD-L1 biomarker enriched for responses in both the chemotherapy arm as well as atezolizumab which was unexpected and accounted in part for the negative result of the trial. Atezolizumab was associated with well-tolerated, durable remissions in both the PD-L1 positive and ITT populations. This was consistent with previous phase 2 data and is uncommon with chemotherapy. Exploratory analysis showed differential overall survival benefit within the control arm, based on chemotherapy choice, which may have accounted for some of the findings. They also showed promise for alternative biomarkers beyond PD-L1 expression such as tumour mutational burden. The data suggests that the risk:benefit profile for atezolizumab is acceptable in platinum-treated advanced urothelial carcinoma.

Implications of all the available evidence

Five immune checkpoint inhibitors have been approved in at least one country in platinum-treated mUC. Randomised phase 3 data exist for only atezolizumab and pembrolizumab. These checkpoint inhibitors appear attractive compared with chemotherapy in unselected patients in this setting, changing the standard of care.

Introduction

Advanced urothelial carcinoma carries a poor prognosis, with a minority of patients surviving more than 5 years.[1] First-line cisplatin-based chemotherapy can improve overall survival,[2,3] but most patients experience progression. Treatment patterns for locally advanced or metastatic urothelial carcinoma (mUC) following platinum vary globally. Vinflunine (approved only in the European Union) and taxanes are commonly used,[4,5] with prospective clinical data for these agents showing a modest median overall survival of 6 to 7 months in this setting.[6,7] Recently, checkpoint inhibitors have altered the treatment of mUC.[8] Pembrolizumab, an anti–programmed death-1 (PD-1) agent, demonstrated longer survival over chemotherapy in mUC in a randomised phase 3 trial.[9] 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 mUC.[11–16]

The US approval of atezolizumab in platinum-treated mUC was based on phase 1 and 2 studies demonstrating durable responses with long-term clinical benefit.[12,16] While atezolizumab has demonstrated activity in patients with all levels of PD-L1 expression, notably, response rates were higher in patients with higher PD-L1 expression on tumour-infiltrating immune cells.[12,16] Our aim was to confirm these findings by performing a large, randomised phase 3 study, IMvigor211, comparing overall survival with atezolizumab to that with chemotherapy by PD-L1 expression in platinum-treated mUC. To increase our understanding of the biology of mUC, we also explored the relevance of tumour mutation burden (TMB) to overall survival. Here, we report the primary analysis and exploratory endpoints from this global, open-label study.

Methods

Study design

This international, open-label, randomised phase 3 trial enrolled patients at 217 academic medical centres and community oncology practices globally. The study protocol, which is included in the appendix, was approved by each site's independent ethics committee.

Patients

Eligible patients aged ≥18 years with mUC had measurable disease at baseline 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 received no more than two prior lines of therapy and progressed during or following one or more platinum-containing regimen for mUC (or [neo]adjuvant therapy with progression within 12 months). A

predominance of transitional histology was required. Patients with prior autoimmune disease or who received CD137-, CTLA4-, or PD-L1/PD-1–targeted therapies were excluded as were those with symptomatic brain metastasis or inadequate renal or liver function. Additional criteria are in the appendix. IMvigor211 was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent.

Outcomes

The primary endpoint was overall survival. Secondary endpoints included investigator-assessed RECIST v1·1 objective response rate, progression-free survival, and duration of response. Confirmed objective response rates were exploratory. 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, further details in Methods S1) were also evaluated.

Randomisation and masking

Patients were assigned 1:1 to atezolizumab or chemotherapy using a permuted block randomisation via an interactive voice/web response system (IXRS). The study was open label. The primary endpoint of OS mitigates most potential biases associated with an open-labelled study. Patients, investigators, and the sponsor were also blinded to the PD-L1 expression status. Before randomisation, investigators selected a chemotherapy regimen (vinflunine, paclitaxel, or docetaxel) that the patient had not previously received. Stratification was by PD-L1 expression (IC0/1 *vs* IC2/3, described below), chemotherapy type (vinflunine *vs* taxanes), liver metastases (yes *vs* no), and number of prognostic factors (0 *vs* 1/2/3—defined as time from prior chemotherapy <3 months, ECOG performance status ≥1, and haemoglobin <10 g/dL). The Sponsor was not permitted to perform any population-level summaries on outcome data until the time of primary analysis.

Procedures

Archival or fresh tumour samples were centrally and prospectively evaluated using the VENTANA SP142 PD-L1 immunohistochemistry assay (Ventana Medical Systems, Inc., Tucson, AZ). Scoring criteria designated tumour samples as IC2/3 (PD-L1 expression on ≥5% of tumour-infiltrating immune cells), IC1 (PD-L1 expression on ≥1% and <5% of tumour-infiltrating immune cells), or IC0 (PD-L1 expression on <1% of tumour-infiltrating immune cells). Patients received atezolizumab (1200 mg) or chemotherapy (vinflunine, 320 mg/m^2; paclitaxel, 175 mg/m^2; docetaxel, 75 mg/m^2) intravenously every 3 weeks until unacceptable toxicity, RECIST v1·1 progression, or informed consent withdrawal. Tumour imaging was performed at baseline and every 9 weeks (every 12 weeks after 54 weeks). Atezolizumab treatment could continue beyond radiographic progression per investigator-deemed clinical benefit. 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 (NCI CTCAE) was used to assess adverse event frequency and severity.

Statistical analysis

This study was designed to enrol 931 patients, including ≥230 with PD-L1 expression on ≥5% of immune cells (IC2/3 status) and ≥537 with IC1/2/3 status. Comparisons of overall survival between treatment arms were tested using a hierarchical fixed-sequence procedure based on a stratified log-rank test at 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 ITT population. The ITT population included all randomised patients regardless of whether they received study treatment. The IC2/3 and IC1/2/3 populations included all ITT patients with IC2/3 and IC1/2/3 status, respectively. Statistical significance was required at each step prior to formally testing 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 arms 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 approximately 152, 403, and 652 deaths were observed in the IC2/3, IC1/2/3, and ITT populations, respectively, 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 based on the following assumptions: a two-sided significance level of 5%, 94% power in the IC2/3 subgroup analysis with a hazard ratio (HR) of 0·57 (corresponding to a median overall survival improvement from 7·5 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 to 11 months), 97% power for the ITT 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 randomization ratio, and a dropout rate of 5% per year over 24 months.

Overall survival was defined as the time between randomization and death, and 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 randomization day for those without post-baseline data). The Kaplan-Meier approach was used to estimate overall survival, progression-free survival, and duration of response, with Brookmeyer–Crowley methodology used to estimate 95% confidence intervals (CIs). Hazard ratios (HRs) were estimated using a stratified Cox regression analysis (stratification factors were the same used for randomization, unless otherwise indicated). RECIST v1·1 objective response rates and 95% CIs for each treatment group were calculated using the Clopper–Pearson method and were compared between arms using the Mantel–Haenszel test. Study drug exposure (treatment duration, number of doses, and dose intensity) were summarised for each treatment arm using descriptive statistics. 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 arm. Statistics were calculated using SAS v9·2. An independent data monitoring committee reviewed safety approximately every 6 months. The study, which is ongoing but not recruiting participants, is registered with ClinicalTrials.gov as number NCT02302807.

Tumour mutational burden analysis

Tumour DNA extraction and preparation were performed by HistoGeneX N.V. (Antwerp, Belgium). Foundation Medicine, Inc. (Cambridge, MA, USA) performed sequencing library construction, hybridization 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] Tumour mutation burden (TMB) was categorized as high (at or above the median) or low (less than the median).

Role of the funding source

F. Hoffmann-La Roche Ltd/Genentech, Inc. sponsored IMvigor211, provided study drugs, and collaborated with academic authors on study design, data collection, analysis, and interpretation. All authors verify that IMvigor211 was conducted per protocol, which was approved by each site's independent ethics committee. All authors had access to the study data and vouch for data accuracy and completeness. Manuscript medical writing assistance was provided by a sponsor-funded professional medical writer. The corresponding author had final responsibility for the decision to submit for publication.

Results

Screening and enrolment occurred at 217 sites from January 13, 2015 to February 15, 2016. A total of 931 patients were enrolled (ITT population) and randomised (Figure 1) at 198 sites including 712 (77%) from Europe, 71 (8%) from North America, 132 (14%) from Asia Pacific, and 16 (2%) from other regions (Table S1). A total of 467 patients were assigned to receive atezolizumab, and 464 were assigned to chemotherapy. The treated (safety-evaluable) population included 902 patients (atezolizumab arm, 459; chemotherapy arm, 443) (Figure 1). Two hundred forty-two patients received vinflunine, and 211 patients

received taxanes (paclitaxel, 148; docetaxel, 53). Baseline characteristics by treatment arm for both the IC2/3 and ITT population are shown in Table 1.

At data cutoff (March 13, 2017) in the ITT population, 133 of 467 patients in the atezolizumab arm (28·5%) and 89 of 464 in the chemotherapy arm (19·2%) remained on study. Treated patients received atezolizumab for a median of 2·8 months (range, 0–24 months) and vinflunine, paclitaxel, or docetaxel for medians of 2·1 months (range, 0–23 months), 2·1 months (range, 0–15 months), or 1·6 months (range, 0–10 months), respectively. Eighty-one patients who received atezolizumab (17·6%), 12 who received vinflunine (5·0%), and two who received paclitaxel (1·4%) were treated for ≥1 year. At data cutoff, 65 patients receiving atezolizumab (14·2%) and nine patients receiving chemotherapy (2·0%) remained on treatment. Reasons for treatment discontinuations, mostly disease progression, are detailed in Figure 1. After treatment discontinuation, 108 patients in the atezolizumab arm (23·1%) and 118 in the chemotherapy arm (25·4%) received at least one subsequent non-protocol therapy (Table S2), with 28 patients in the chemotherapy arm (6%) receiving post-protocol immunotherapy. The median follow-up duration for ITT patients was 17·3 months (range, 0–24·5 months). A total of 674 deaths occurred: 324 in the atezolizumab arm and 350 in the chemotherapy arm.

The efficacy analysis was first performed in the IC2/3 population. The characteristics of these patients are given in Table 1. Median overall survival in the IC2/3 population was 11·1 months (95% confidence interval [CI], 8·6–15·5) in the atezolizumab arm *vs* 10·6 months (95% CI, 8·4–12·2) in the chemotherapy arm (stratified HR, 0·87; 95% CI, 0·63–1·21; P=0·41) (Figure 2A), precluding further formal statistical comparisons and rendering subsequent analyses exploratory in nature. Exploratory forest plot analyses for overall survival were evaluated in subgroups based on baseline characteristics (Figure S1). Most efficacy differences between treatment arms were marginal. For patients receiving chemotherapy, vinflunine outperformed study expectations (unstratified HR, 0·95; 95% CI, 0·62–1·45; n=128), and variations in overall survival HRs were seen for upper-tract renal pelvis urothelial tumours.

Exploratory confirmed objective response rates were similar between treatment arms in the IC2/3 population (Table 2). Sixteen of 26 responders to atezolizumab (61·5%) and 5 of 25 responders to chemotherapy (20·0%) had ongoing responses; the median durations of response for atezolizumab and chemotherapy were 15·9 months (95% CI, 10·4 to not estimable) and 8·3 months (95% CI 5·6– 13·2), respectively (Figure 2C). The median progression-free survival was 2·4 months (95% CI, 2·1–4·2) with atezolizumab and 4·2 months (95% CI, 3·7–5·0) with chemotherapy (Table 2 and Figure 2B).

Adverse events for the IC2/3 and ITT populations are given in Table 3. Results for the two populations were similar although the ITT population was more robust due to higher numbers. In the IC2/3 population, treatment-related adverse events leading to treatment discontinuation occurred in 7 of 114 atezolizumab treated patients [6·1%] and 17 of 112 treated chemotherapy patients [15·2%]). There were 2 atezolizumab related deaths and 3 chemotherapy related deaths in this population. Treatment discontinuations and treatment-related deaths in the ITT population mirrored these results (3.5% and 0.7% respectively for atezolizumab; Tables S2-S3). Adverse events of any grade deemed treatment related by the investigator occurred in 85 atezolizumab-treated patients (74·6%) *vs* 99 chemotherapy-treated patients (88·42%) in the IC2/3 population (Figure 3). For both the IC2/3 and ITT populations, treatment-related adverse events occurring in >10% of patients in both arms were decreased appetite, asthenia, fatigue, and diarrhoea. For both IC2/3 and ITT patients, treatment-related nausea, constipation, and alopecia of any grade occurred in >25·0% of patients receiving chemotherapy but did not meet this threshold for atezolizumab. Conversely, treatment-related pruritus was more common in the atezolizumab arm in the IC2/3 population (12·3% [n=14] *vs* 2·7% [n=3] with chemotherapy) and the ITT population (12·0% [n=55] *vs* 3·2% for chemotherapy) (Table 3). In the IC2/3 population, treatment-related rash was also more common with atezolizumab (11·4% [n=13] *vs* 6·3% [n=7] with chemotherapy) (Table 3). In both IC2/3 and ITT populations, grade 3 or 4 treatment-related adverse events were less common with

atezolizumab (22·8% [n=26] in the IC2/3 and 19·8% [n-91] in the ITT populations) than chemotherapy (34·8% [n=39] in the IC2/3 and 42·7% [n=189] in the ITT population).

Subsequent overall survival analyses were performed on the ITT population for exploratory purposes only (Figure 4). This analysis was performed 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. The characteristics of the ITT population were similar to those of the IC2/3 population, although good prognostic factors were more prevalent in the ITT population. In the ITT population, median overall survival was 8·6 months (95% CI, 7·8–9·6) in the atezolizumab arm, *vs* 8·0 months (95% CI, 7·2–8·6) in the chemotherapy arm (HR, 0·85; 95% CI, 0·73–0·99); One-year overall survival rate in ITT patients was 39·2% (95% CI, 34·8–43·7) with atezolizumab and 32·4% (95% CI, 28·0–36·8) with chemotherapy (Figure 4A). Pre-specified subgroup analyses of overall survival in the ITT population by baseline and clinical characteristic are included in Figure 4B and results generally agreed with those from the IC2/3 population. In an exploratory analysis, overall survival was assessed in ITT patients by investigator-prespecified chemotherapy subgroup (taxane and vinflunine), as recorded in IXRS. Atezolizumab demonstrated better comparative results in those patients intended for treatment with taxanes (HR, 0·73; 95% CI, 0·58–0·92; n=429) as opposed to vinflunine (HR, 0·97; 95% CI, 0·78–1·19; n=502) (Figure S2).

Confirmed objective response rates for the ITT population appeared lower for both atezolizumab and chemotherapy compared with those seen for the PD-L1 IC2/3 population (Table 2); the ITT objective response rates with atezolizumab and chemotherapy were each 13·4% (95% CI, 10·5–16·9); median response durations appeared longer with atezolizumab than chemotherapy in this population (Table 2 and Figure 4C), mirroring the results in the IC2/3 population (Table 2 and Figure 2C). In the ITT population, 39 of 62 responders receiving atezolizumab (62·9%) had ongoing responses, while responses were

ongoing in 13 of 62 responders receiving chemotherapy (21·0%). The ITT median progression-free survival was 4·0 months (95% CI, 3·4–4·2) with chemotherapy *vs* 2·1 months (95% CI, 2·1–2·2) with atezolizumab. Key efficacy endpoints (overall survival, objective response rate and duration, and progression-free survival) were also analysed for the IC1/2/3 population for exploratory purpose only and are included in Figures S3-4 and Table S5.

In an exploratory biomarker analysis, tumour samples were evaluable for TMB measurements for a total of 544 of the 931 in the ITT population. Baseline characteristics of the overall biomarker-evaluable population (n=544), including PD-L1 status (Figure S5A), were generally balanced between treatment arms and representative of the ITT population. Median TMB in the overall biomarker-evaluable population was 9·65 mutations per megabase and was also similar between treatment arms (Figure S5A). The correlation observed between PD-L1 expression and TMB was minor (R=0·13). Overall survival was evaluated based on patients whose samples had high (at or above the median) or low (below the median) TMB values (Figure 4D and E). Results showed that for patients with high TMB samples (n=274), median overall survival durations were numerically longer for those treated with atezolizumab (11·3 months) *vs* chemotherapy (8·3 months; HR, 0·68; 95% CI, 0·51–0·90), whereas for those with low TMB samples (n=270), survival was similar between arms (medians, 8·3 and 8·1 months with atezolizumab and chemotherapy, respectively; HR, 1·00; 95% CI, 0·75–1·32). We next evaluated whether PD-L1 status conferred a survival advantage for patients with TMB-high tumours (Figure S5B-C). Patients with TMB-high and PD-L1 IC2/3 samples (n=96) had median survival of 17·8 months with atezolizumab and 10·6 months with chemotherapy (HR, 0·50; 95% CI, 0·29–0·86).

Prespecified patient-reported outcomes based on EORTC QLQ-C30 global health status, physical functioning, and fatigue scores were also evaluated (Figures S6 and S7), and baseline scores were measured in the ITT population (Table S6). Mean changes in these scores deteriorated initially, but returned to baseline after several cycles and remained stable thereafter for the atezolizumab arm; mean

scores changes were worse, particularly for fatigue, in the chemotherapy arm (Figure S7). Although deterioration event-to-patient rates remained low at time of analysis, median time to deterioration was similar between arms for global health status and prolonged with atezolizumab for physical function and fatigue (Figure S6).

Discussion

In this randomised phase 3 study, the primary endpoint of overall survival improvement with atezolizumab was not met in patients with mUC who had ≥5% PD-L1 expression (IC2/3) on tumour-infiltrating immune cells, precluding additional formal statistical analysis. Our hierarchical study design hypothesized that efficacy would be associated with PD-L1 expression based on phase 1 and 2 findings with atezolizumab[12,16,19] and other checkpoint inhibitors.[20,21] Unexpectedly, our study revealed that overexpression of PD-L1 (SP142 immunohistochemistry assay) indicated 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 prior positive phase 3 studies of both atezolizumab in advanced NSCLC[14] and pembrolizumab in mUC (KEYNOTE-045).[9] An explanation for these inverse results is not readily available, although PD-L1 assay disparities—widespread in this field[22]—may contribute to these differences. Indeed, the assay used in KEYNOTE-045 (22C3 antibody) measured PD-L1 expression on both immune and tumour cells, which 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 phenomenon 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 mUC and associated with impressive 12-month landmark analysis rates.

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

Due to lack of global consensus, the control arm 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 hypothesized based on previous studies,[6,9] potentially compromising the statistical assumptions. This finding was not exclusive to the PD-L1–selected subgroups but was also seen in the ITT population. While previous data suggested similar overall survival for vinflunine, paclitaxel, and docetaxel,[6,7] comparative randomised studies have not been performed, questioning the wisdom of a mixed control arm and potentially affecting our results. Further, improved clinical proficiency and post-approval patient selection in Western Europe,[26–29] where most patients enrolled, may 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 *vs* chemotherapy; however, comparisons between biomarker-selected and unselected trials are challenging due to intrinsic differences in patient populations.

Prespecified exploratory efficacy analyses of the ITT population were performed to better understand the results of the study and evaluate atezolizumab *vs* chemotherapy in a biomarker unselected comparison—

which, with over 900 patients treated in the ITT population, is to our knowledge the largest interventional study in mUC. Median survivals were shorter compared with the IC2/3 population, likely partially due to the enrichment of responders occurring in both arms in the IC2/3 cohort. Comparative efficacy signals (overall survival HR, 0·85; 95% CI, 0·73–0·99) were similar to those seen 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 ITT populations were similar. Exploratory analysis showed that impressive 1-year milestone survival rates were achieved with atezolizumab (39·2% *vs* 32·4% with chemotherapy) in the ITT population. Similar to the IC2/3 subgroup, delayed separation of the KM 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 the majority of patients. These data from the ITT 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 risk-benefit ratio for atezolizumab is attractive for previously platinum-treated patients with mUC. Atezolizumab is approved in this setting in the US. Recently, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has issued a positive opinion for atezolizumab in prior-platinum mUC based in part on this data.

An attempt was made to identify alternative biomarkers for atezolizumab in view of the lack of predictive values for the PD-L1 immunohistochemistry biomarker. TMB, which is high in bladder cancer, is thought to be a surrogate marker for neoantigen expression may be required for immune recognition of tumours. Previous exploratory studies have shown TMB to outperform PD-L1 expression as a biomarker for nivolumab in other tumour types.[30] Our study showed similar results. These consistent results across different tumour types suggest similar broad mechanisms of action for this group of agents. These results are currently hypothesis generating; if validated in future trials, TMB—alone or with other biomarkers—could improve the accuracy of selecting patients for monotherapy.

Contributors

TP, NC, XS, and CLD contributed to the design of the study. All authors contributed to data collection, analysis, and 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 Astra Zeneca as well as honoraria from Roche, BMS, and Merck. ID has received honoraria for consulting and/or advsory roles for Jansen, Roche, Amgen, and Novartis as well as other support for travel and accommodations expenses from Astellas. MvdH has received a research grant from Astellas, reimbursement for patient care and data management of study subjects from Roche/Genentech, and has received honoraria for advisory roles with Roche/Genentech, Astellas, and Astra Zeneca. YL has received honoraria from Roche, Sanofi, Astellas, Janssen, iPSEN, and BMS as well as a research grant from Sanofi. SO has received honoraria from Roche, Novartis, iPSEN, BMS, and Bayer. AB has received honoraria from Roche, Novartis, Pfizer, BMS and AstraZeneca, research grants and non-financial support from Novartis and Pfizer as well as investigator and institutional support from Roche AF has received honoraria from Janssen, Pfizer, Roche, Astra Zeneca, MSD, and Pierre Fabre as well as support for travel and accommodations 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 BMS 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, Inc. and own Roche stock. AR has received honoraria and support for travel and accommodations expenses from Pfizer, Novartis, BMS, AstraZeneca, Roche, MSD and iPSEN as well as a research grant from Pfizer. NV, UdG, MMR, DC, and GG have nothing to disclose.

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Tables

Characteristic	IC2/3 population		ITT population	
	Atezolizumab (n=116)	Chemotherapy (n=118)	Atezolizumab (n=467)	Chemotherapy (n=464)
Median age (years)	67 (43-88)	67 (36-84)	67 (33-88)	67 (31-84)
Male sex	81 (69·8)	95 (80·5)	357 (76·4)	361 (77·8)
Race				
White	86 (74·1)	88 (74·6)	335 (71·7)	336 (72·4)
Black or African American	0	1 (0·8)	1 (0·2)	2 (0·4)
Asian	16 (13·8)	12 (10·2)	63 (13·5)	55 (11·9)
Multiple	0	1 (0·8)	0	1 (0·2)
Unknown	14 (12·1)	16 (13·6)	68 (14·6)	70 (15·1)
Tobacco use*				
Current	12 (10·4)	18 (15·3)	60 (12·9)	60 (13·0)
Former	68 (59·1)	68 (57·6)	266 (57·1)	280 (60·6)
Never	35 (30·4)	32 (27·1)	140 (30)	122 (26·4)
Primary tumour site				
Bladder	85 (73·3)	88 (74·6)	324 (69·4)	338 (72·8)
Urethra	2 (1·7)	5 (4·2)	9 (1·9)	9 (1·9)
Renal pelvis	13 (11·2)	12 (10·2)	66 (14·1)	52 (11·2)
Ureter	15 (12·9)	11 (9·3)	60 (12·8)	58 (12·5)
Other	1 (0·9)	2 (1·7)	8 (1·7)	7 (1·5)
Metastatic disease	99 (85·3)	111 (94·1)	425 (91·0)	430 (92·7)
Site of metastases				
Lymph node only	18 (15·5)	27 (22·9)	54 (11·6)	66 (14·2)
Visceral sites†	78 (67·2)	82 (69·5)	361 (77·3)	355 (76·5)
Liver sites	28 (24·1)	30 (25·4)	138 (29·6)	130 (28·0)
ECOG PS				
0	61 (52·6)	57 (48·3)	218 (46·7)	207 (44·6)
1	55 (47·4)	61 (51·7)	249 (53·3)	257 (55·4)
Haemoglobin concentration <10 g/dL	17 (14·7)	19 (16·1)	65 (13·9)	73 (15·7)
No. of risk factors‡				
0	44 (37·9)	41 (34·7)	145 (31·0)	140 (30·2)
1	50 (43·1)	48 (40·7)	214 (45·8)	208 (44·8)
2	16 (13·8)	25 (21·2)	86 (18·4)	96 (20·7)
3	6 (5·2)	4 (3·4)	22 (4·7)	20 (4·3)
Prior cystectomy	57 (49·1)	58 (49·2)	199 (42·6)	200 (43·1)
Intravesical Bacillus Calmette-Guérin administered	2 (1·7)	4 (3·4)	15 (3·2)	14 (3·0)
Time since previous chemotherapy <3 months	35 (30·2)	43 (36·4)	160 (34·3)	160 (34·5)
Number of previous systemic regimens in the metastatic setting				
0	43 (37·1)	41 (34·7)	131 (28·1)	120 (25·9)
1	54 (46·6)	59 (50·0)	249 (53·3)	261 (56·3)
2	18 (15·5)	18 (15·3)	79 (16·9)	74 (15·9)
≥3	1 (0·9)	0	8 (1·7)	9 (1·9) §
Prior Systemic Regimen Setting				
Metastatic	73 (62·9)	77 (65·3)	336 (71·9)	344 (74·1)
Neoadjuvant or adjuvant chemotherapy with progression within ≤12 months	37 (31·9)	37 (31·4)	117 (25·1)	108 (23·3)
Other	6 (5·1)	4 (3·4)	14 (3·0)	12 (4·5)

Data are median (range) and n (%), unless otherwise indicated. ECOG PS= Eastern Cooperative Oncology Group Performance Status.
*In the atezolizumab arm, n=115 for IC2/3 and n=462 for ITT populations. In the chemotherapy arm, n=466 for the ITT population. † Visceral metastasis defined as liver, lung, bone, any non–lymph node or soft tissue metastasis. ‡ Refers to ECOG PS ≥1, the presence of baseline liver metastases, and haemoglobin <10 g/dL. § One patient in the chemotherapy arm (0·2%) received four prior 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 and prior therapy

Population	IC2/3 population		ITT population	
	Atezolizumab (n=116)	Chemotherapy (n=118)	Atezolizumab (n=467)	Chemotherapy (n=464)
Progression-free survival				
Patients with event (%)*	93 (80·2)	105 (89·0)	407 (87·2)	410 (88·4)
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†				
No. of objective response–evaluable patients	113	116	462	461
No. of patients with response	26	25	62	62
Percentage of patients (95% CI)	23·0 (15·6–31·9)	21·6 (14·5–30·2)	13·4 (10·5–16·9)	13·4 (10·5–16·9)
Best overall response — no. (%)†				
Complete response	8 (7·1)	8 (6·9)	16 (3·5)	16 (3·5)
Partial response	18 (15·9)	17 (14·7)	46 (10·0)	46 (10·0)
Stable disease	23 (20·4)	37 (31·9)	92 (19·9)	162 (35·1)
Progressive disease	47 (41·6)	30 (25·9)	240 (51·9)	150 (32·5)
Missing or unevaluable	17 (15·0)	24 (20·7)	68 (14·7)	87 (18·9)
Duration of response†				
Patients with event (%)*	10 (38·5)	20 (80·0)	23 (37·1)	49 (79·0)
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)

ITT=intention-to-treat. PD-L1=programmed death-ligand 1. * Refers to progressive disease or death. † Refers to confirmed, investigator-assessed objective responses.

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

	IC2/3 population		ITT population	
Adverse event	**Atezolizumab (n=114)**	**Chemotherapy (n=112)**	**Atezolizumab (n=459)**	**Chemotherapy (n=443)**
A Most common treatment-related adverse events of any grade*				
All	85 (74·6%)	99 (88·4%)	319 (69·5%)	395 (89·2%)
Fatigue	18 (15·8%)	27 (24·1%)	71 (15·5%)	116 (26·2%)
Pruritus	14 (12·3%)	3 (2·7%)	55 (12·0%)	14 (3·2%)
Asthenia	14 (12·3%)	23 (20·5%)	51 (11·1%)	79 (17·8%)
Rash	13 (11·4%)	7 (6·3%)	40 (8·7%)	21 (4·7%)
Pyrexia	12 (10·5%)	4 (3·6%)	40 (8·7%)	25 (5·6%)
Decreased appetite	11 (9·6%)	20 (17·9%)	56 (12·2%)	81 (18·3%)
Diarrhoea	11 (9·6%)	15 (13·4%)	50 (10·9%)	66 (14·9%)
Nausea	9 (7·9%)	25 (22·3%)	46 (10·0%)	117 (26·4%)
Dyspnoea	9 (7·9%)	3 (2·7%)	18 (3·9%)	19 (4·3%)
Anaemia	8 (7·0%)	18 (16·1%)	25 (5·4%)	84 (19·0%)
Constipation	5 (4·4%)	44 (39·3%)	29 (6·3%)	145 (32·7%)
Vomiting	5 (4·4%)	17 (15·2%)	16 (3·5%)	62 (14%)
Abdominal pain	5 (4·4%)	8 (7·1%)	9 (2·0%)	34 (7·7%)
Arthralgia	4 (3·5%)	13 (11·6%)	17 (3·7%)	40 (9·0%)
Myalgia	4 (3·5%)	9 (8·0%)	13 (2·8%)	48 (10·8%)
Neutropaenia	3 (2·6%)	13 (11·6%)	3 (0·7%)	64 (14·4%)
Mucosal inflammation	3 (2·6%)	9 (8·0%)	15 (3·3%)	44 (9·9%)
Peripheral neuropathy	2 (1·8%)	15 (13·4%)	3 (0·7%)	50 (11·3%)
Dysgeusia	2 (1·8%)	7 (6·3%)	6 (1·3%)	22 (5·0%)
Paraesthesia	1 (0·9%)	6 (5·4%)	7 (1·5%)	25 (5·6%)
Decreased weight	1 (0·9%)	5 (4·5%)	12 (2·6%)	26 (5·9%)
Alopecia	0	33 (29·5%)	0	120 (27·1%)
Peripheral sensory neuropathy	0	11 (9·8%)	3 (0·7%)	39 (8·8%)
Stomatitis	0	9 (8·0%)	10 (2·2%)	33 (7·4%)
Decreased neutrophil count	0	8 (7·1%)	0	28 (6·3%)
Febrile neutropaenia	0	5 (4·5%)	1 (0·2%)	25 (5·6%)
B Grade 3 or 4 treatment-related adverse events for IC2/3 and ITT populations†				
Fatigue	4 (3·5%)	2 (1·8%)	7 (1·5%)	18 (4·1%)
Anaemia	3 (2·6%)	3 (2·7%)	9 (2·0%)	21 (4·7%)
Neutropaenia	2 (1·8%)	9 (8·0%)	2 (0·4%)	49 (11·1%)
Peripheral neuropathy	1 (0·9%)	3 (2·7%)	1 (0·2%)	8 (1·8%)
Asthenia	1 (0·9%)	2 (1·8%)	8 (1·7%)	18 (4·1%)
Neutrophil count decreased	0	7 (6·3%)	0	26 (5·9%)
Febrile neutropaenia	0	5 (4·5%)	1 (0·2%)	25 (5·6%)
Constipation	0	4 (3·6%)	0	20 (4·5%)
Peripheral sensory neuropathy	0	3 (2·7%)	0	6 (1·4%)
Ileus	0	3 (2·7%)	0	4 (0·9%)
White blood cell count decreased	0	2 (1·8%)	0	11 (2·5%)

Data are n (%)· *****Listed are adverse events of all grades reported in ≥5·0% of patients in either arm of the treated populations.
†Listed are adverse events reported in ≥2·0% of patients in either arm of the treated populations.

Table 3: **Treatment-related adverse events for IC2/3 and ITT populations.**

Figures and figure legends

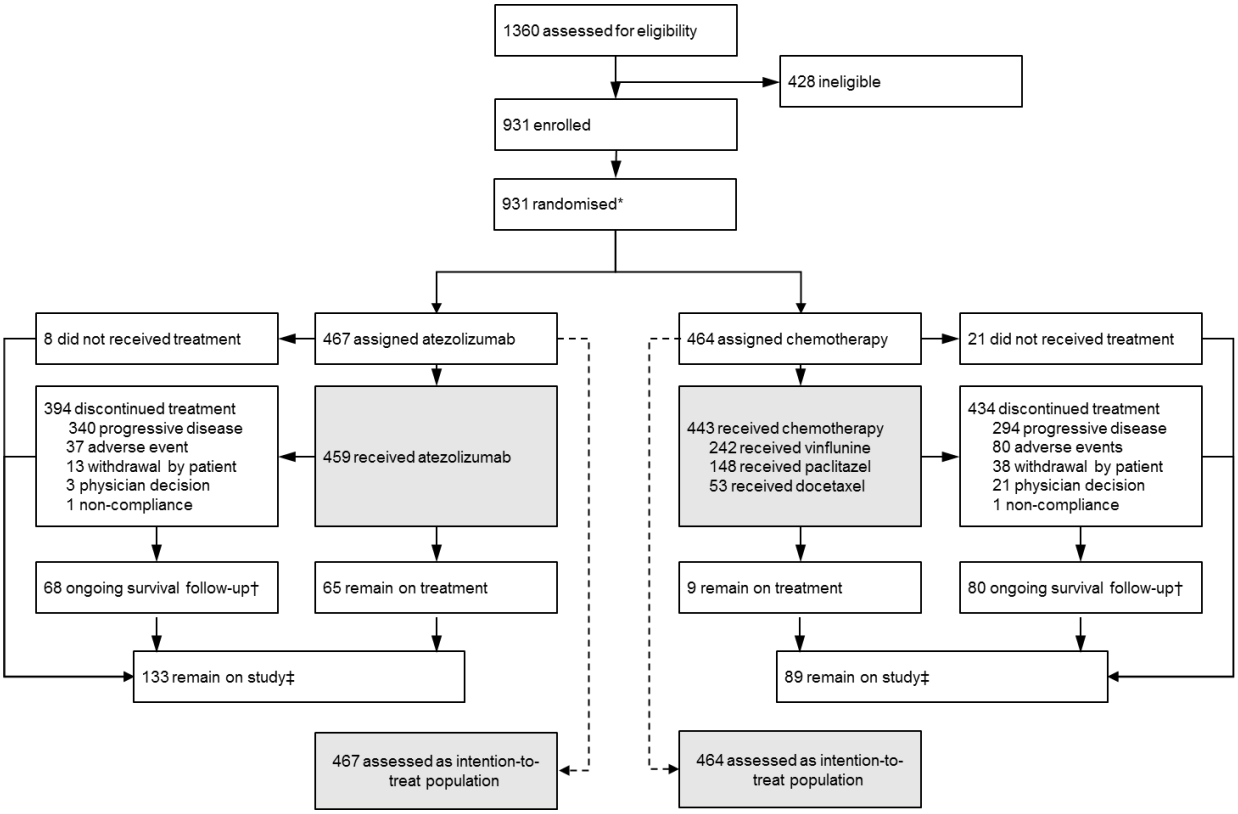
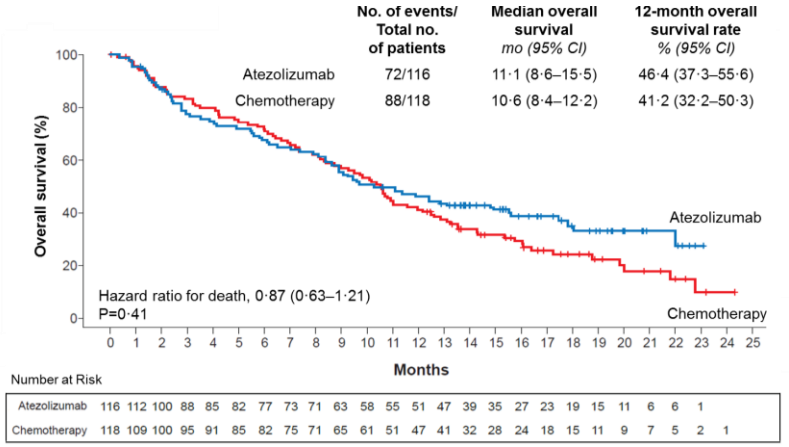
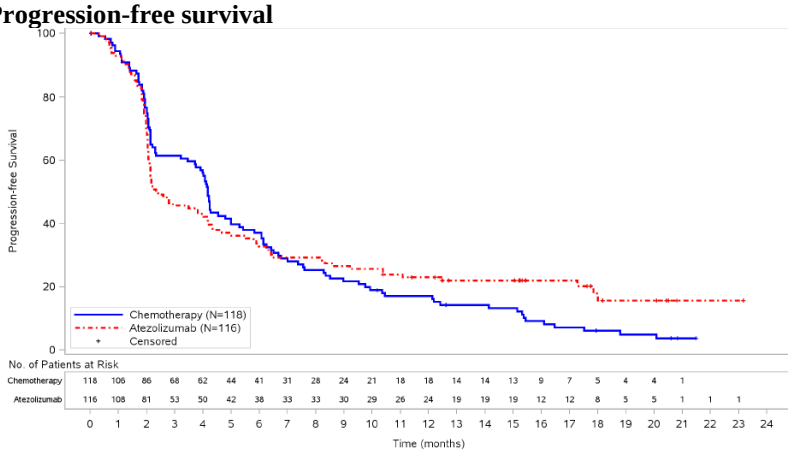


Figure 1: **Trial profile.** Screened, enrolled, and treated IMvigor211 patients and population definitions are depicted, as well as reasons for non-enrolment and discontinuation. Boxes in grey refer to the safety and intention-to-treat populations for each arm. *One patient was randomised to chemotherapy 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 (one in each treatment arm) 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 date. Of 334 patients who discontinued study in the atezolizumab arm, 322 were due to death, 9 were due to withdrawal by patient, and 3 due to loss to follow-up. Of 375 patients who discontinued study in the chemotherapy arm, 345 were due to death, 27 were due to withdrawal by patient, and 3 due to loss to follow-up. An additional five deaths (four in the chemotherapy arm, one in the atezolizumab arm) were collected from public records and are recorded under "withdrawal by patient" and included as uncensored deaths in the efficacy analyses.

A Overall survival



B Progression-free survival



C Duration of response

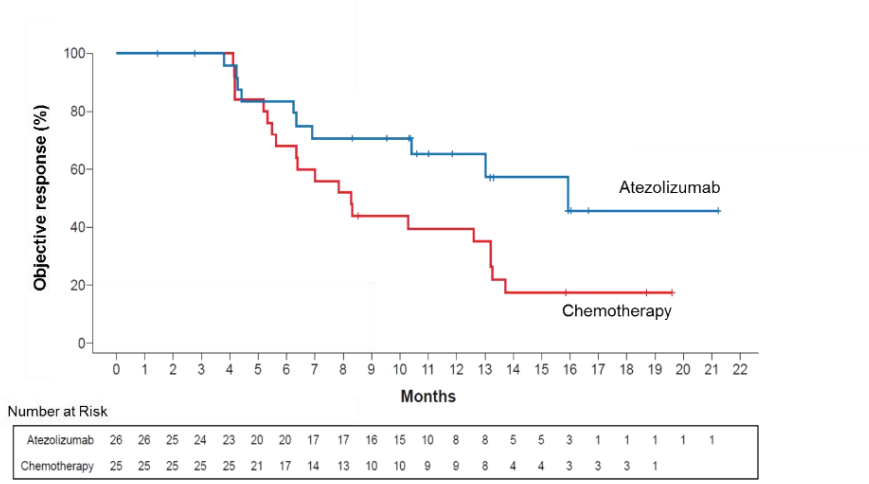
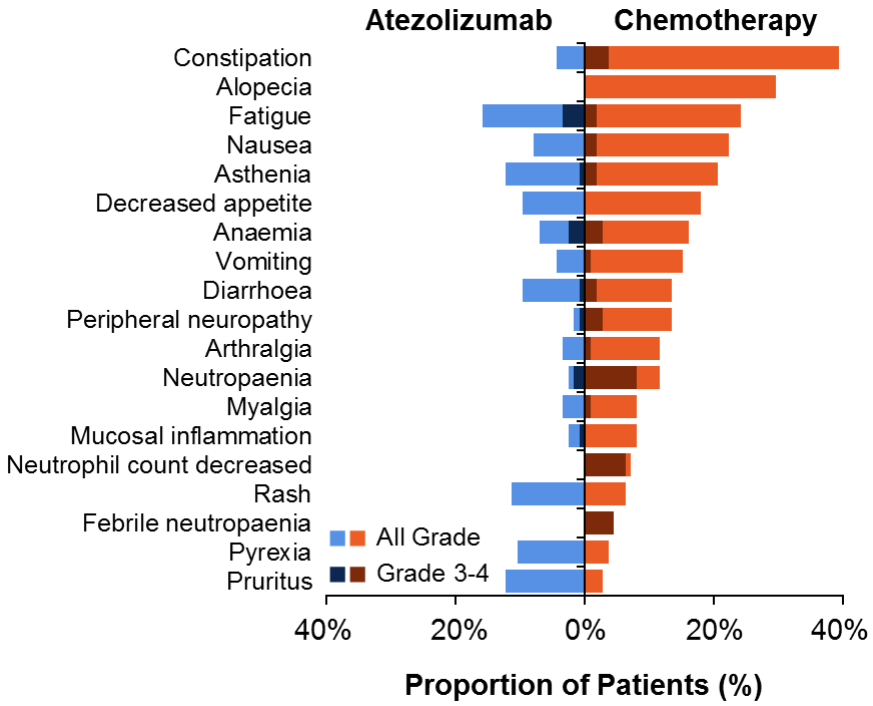


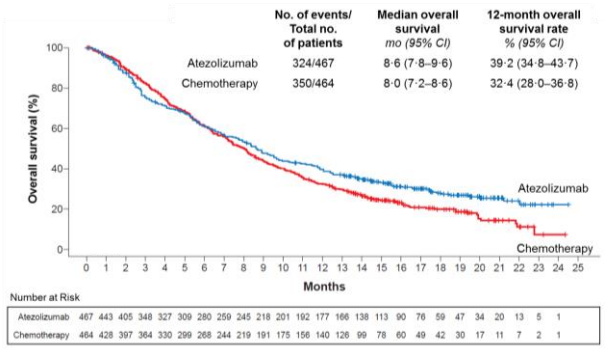
Figure 2: **Efficacy outcomes in the IC2/3 population.** Kaplan-Meier estimates of (A) overall survival, (B) progression-free survival and (C) duration of response for PD-L1 IC2/3 population (patients with ≥5% PD-L1 expression on tumour-infiltrating immune cells. Stratified hazard ratio for death is reported in part A. Censored events (death or progression) are indicated with a + symbol. ITT=intention-to-treat. PD-L1=programmed death-ligand 1.



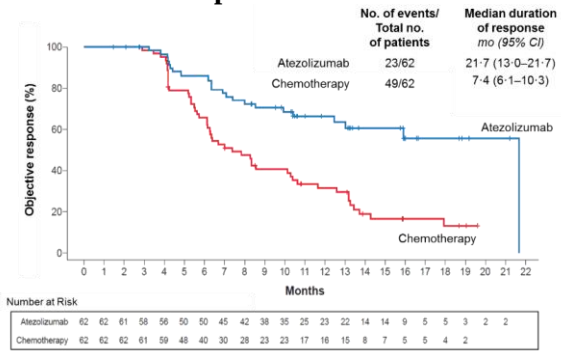
567

568 ***Figure 3:*** **Treatment-related AEs in the IC2/3 population.** Treatment-related adverse events of
569 frequency ≥ 10% (All Grade) and ≥ 4% (Grade 3-4) in either arm for the PD-L1 IC2/3. Adverse events
570 that occurred within 30 days from the last study treatment are reported for safety-evaluable patients.

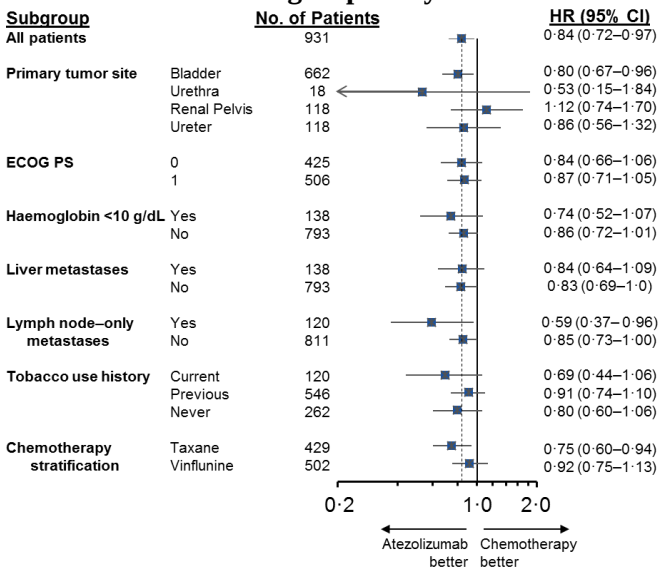
A Overall survival



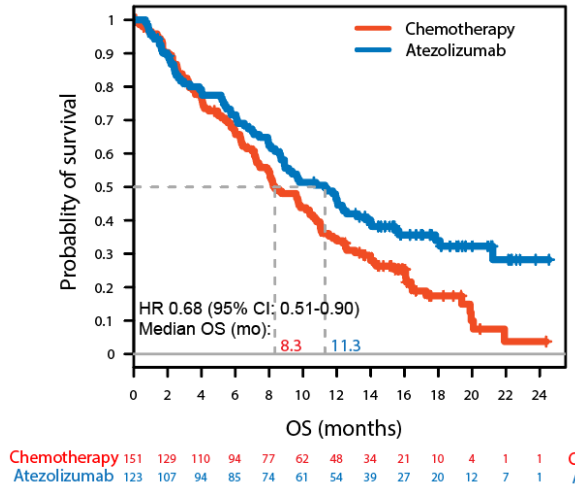
C Duration of response



B Overall survival subgroup analysis



D Overall survival in TMB-high biomarker-evaluable population



E Overall survival in TMB-low biomarker-evaluable population

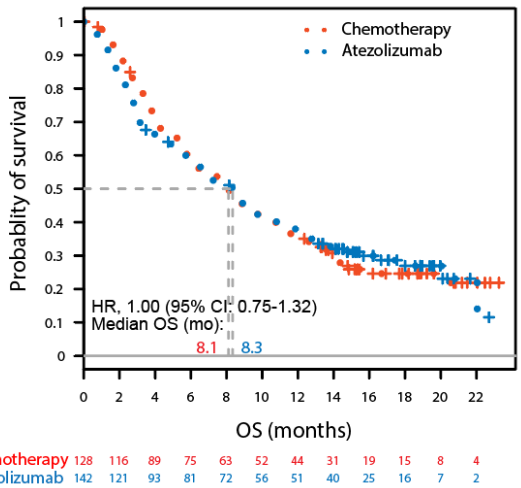


Figure 4: **Exploratory efficacy outcomes in the ITT population. (legend on next page).**

Kaplan-Meier estimates for (A) overall survival. (B) Forest plot of overall survival by baseline and clinical characteristics in the ITT populations. Hazard ratios for death with unstratified analyses in the intention-to-treat population relative to chemotherapy are displayed in the graph. Hazard ratios and 95% CIs estimated using Cox regression are displayed. The vertical dashed line indicates the hazard ratio for all patients. (C) Kaplan-Meier estimates for duration of response in the intention-to-treat population. Kaplan-Meier estimates of overall survival by treatment arm in the biomarker-evaluable population in patients with (D) high (at or above median value) TMB and (E) low (less than median) TMB tumours. Censored events (death or progression) are indicated with a + symbol. ECOG PS=Eastern Cooperative Oncology Group performance status. IC=tumour-infiltrating immune cells. ITT=intention-to-treat. NE=not estimable. TCC=transitional cell carcinoma. TMB=tumour mutation burden. PD=progressive disease. PD-L1=programmed death-ligand 1.