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

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Summary

Background—First-line chemotherapy for patients with cisplatin-ineligible locally-advanced or metastatic urothelial carcinoma (mUC) is associated with short response duration, poor survival, and high toxicity. This multicenter, 2-cohort phase 2 study evaluated atezolizumab (anti–programmed death-ligand 1 [PD-L1]) as treatment for mUC in this setting, as well as in later lines.

Methods—In a cohort of previously untreated patients who were cisplatin ineligible, atezolizumab was given 1200 mg every 3 weeks until progression. The primary endpoint was independently confirmed objective response rate per Response Evaluation Criteria In Solid Tumors v1.1 (central review), evaluated in pre-specified subgroups based on PD-L1 expression and in all patients. Secondary endpoints included response duration, progression-free survival, overall survival, and safety. Exploratory analyses included biomarker correlates of response and survival. This study is registered with ClinicalTrials.gov, number NCT02108652.

Findings—Of 119 patients who received atezolizumab in the first-line setting, 83 (70%) had baseline renal impairment, and 24 (20%) had Eastern Cooperative Oncology Group performance status 2. At 17·2 months' median follow-up, the objective response rate was 23% (95% CI 16–31), the complete response rate was 9%, and 19 of 27 responses were ongoing. Median response duration was not reached. Responses occurred across all PD-L1 and poor prognostic factor subgroups. Median progression-free survival was 2·7 months. Median overall survival was 15·9 months. Tumour mutation load was associated with response. Treatment-related adverse events 10% were fatigue, diarrhoea, and pruritus. One treatment-related death (sepsis) occurred. Nine patients (8%) had an adverse event leading to treatment discontinuation. Immune-mediated events occurred in 14 (12%) patients.

Interpretation—Atezolizumab demonstrated encouraging durable response rates, survival, and tolerability, supporting its therapeutic use in untreated mUC.

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Introduction

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

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

Methods

Study design

IMvigor210 was a multicentre, single-arm, 2-cohort phase 2 trial that investigated efficacy and safety of atezolizumab in mUC. This trial was conducted in 47 academic medical centres and community oncology practices across 7 countries, in North America and Europe. Cohort 1 enrolled patients without prior treatment for mUC. Eligible patients had inoperable, locally advanced or metastatic UC (renal pelvis, ureters, bladder, or urethra), measurable disease per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1, Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2, and tumour sample for PD-L1 testing. (Neo)adjuvant chemotherapy or radiation was permitted if >12 months had elapsed between treatment and recurrence. Patients were required to be cisplatin ineligible per ≥1 of the following: glomerular filtration rate >30 and <60 mL/min (Cockcroft-Gault formula), grade ≥2 hearing loss or peripheral neuropathy, or ECOG PS 2.[17] Complete inclusion and exclusion criteria are listed in the protocol (with statistical analysis plan) at thelancet.com. Patients received 1200 mg intravenous atezolizumab every 21 days until unacceptable toxicity or investigator-assessed radiographic progression. Dose interruptions, but not reductions, were permitted. Cohort 2 (described previously)[16] enrolled patients previously treated with platinum-based chemotherapy. This study is registered with ClinicalTrials.gov, number NCT02108652.

Study assessments

Patients underwent response assessments at baseline, every 9 weeks for 12 months, and then every 12 weeks until disease progression, withdrawal of consent, or death; assessments were performed by local investigators and reviewed by a central independent facility (BioClinica; Princeton, NJ, USA). These assessments included measurement of tumor burden, including change over time in sum of longest diameters. Additionally, the ORR estimates in key subgroups defined by demographic and baseline characteristics were assessed. Safety was assessed per National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Archival tumour tissue was collected for biomarker assessments. The VENTANA SP142 immunohistochemistry assay (Ventana Medical Systems, Inc.; Tucson, AZ, USA) was used to prospectively evaluate PD-L1 expression on tumour-infiltrating immune cells (IC) via a central laboratory (HistoGeneX; Brussels, Belgium). Scoring criteria designated tumours as IC0, IC1, or IC2/3 (PD-L1 expression on <1%; 1% and <5%; or 5% of IC, respectively).[16] Patients, investigators, and sponsor were blinded to PD-L1 status. Somatic mutation and tumour mutation load assessments were made using a FoundationOne DNA-based panel (Foundation Medicine, Cambridge, MA, USA). Microsatellite status was centrally confirmed by next-generation sequencing-based scoring (Foundation Medicine, Cambridge, MA, USA). Gene expression was quantified for a T-effector gene signature (consisting of *CD8A, GZMA, GZMB, PRF1, INFG*, and *TBX21*) and for subtyping using The Cancer Genome Atlas[18] (TCGA) categories.[16]

Statistical analysis

The cisplatin-ineligible patient cohort of IMvigor210 was initially planned as an exploratory subgroup of 30 patients. Subsequently, a protocol amendment increased sample size to ≈100 patients to provide a better estimate of the response rate (RECIST v1.1) in UC patients who were cisplatin ineligible, assessed by independent central review. Determination of sample size was based on the assumption of 30% IC2/3 prevalence. The 95% CI (calculated using the Clopper-Pearson method) for an overall response rate of 40% would be 22·7% to 59·4%, resulting in 98% power to detect a 30% increase in the overall response rate from 10% to 40%.

The primary efficacy analysis of the cisplatin-ineligible IMvigor210 cohort (data cutoff: September 14, 2015) was performed when the last patient enrolled had a minimum of 6 months of follow-up. An interim efficacy analysis was also performed when patients had 24 weeks of follow-up (see appendix for details). A hierarchical fixed-sequence testing procedure (previously described and details in appendix)[16] to compare the observed primary endpoint for three pre-specified subgroups (PD-L1 IC2/3, followed by IC1/2/3, and followed by all patients) versus a control response rate of 10%. The hypothesis tests were conducted sequentially using IRF-assessed RECIST v1.1 at a specific two-sided α level of 0·05 for each test. If no statistical significance was detected at a specific level of the hierarchy, then no further testing was done. The study was expected to attract patients who would not be candidates for combination chemotherapy, including those not eligible for any cytotoxic chemotherapy, reflective of the heterogeneous cisplatin-ineligible population.[10] Therefore, the 10% rate was approximated by a composite average of 75% of patients enrolled who would otherwise not be candidates for any cytotoxic chemotherapy (expected ORR 0%) and

25% who would be candidates for carboplatin-based combination chemotherapy (expected ORR 36%).[9] The exact binomial test evaluated whether atezolizumab treatment results in a statistically significant difference between the observed and control response rates in the pre-specified subgroups. The tests were performed in a sequential order such that the subsequent hypothesis would not be performed if the preceding test was rejected (further described and presented in supplementary Methods S1). Clinical significance was assessed in an ongoing manner, and subsequent analyses did not use hypothesis testing as described for the primary analysis. This report uses a later cutoff (July 4, 2016) to provide updated efficacy and safety data.

Secondary endpoints included investigator-assessed objective response rate; duration of response and progression-free survival, both assessed by independent review and investigator (RECIST v1.1); and overall survival. Unless otherwise specified, RECIST results reported herein are per independent review.

Role of the funding source

The protocol, developed by the sponsor (F. Hoffmann-La Roche Ltd.) and advisors, was approved by the institutional review boards or independent ethics committees at each participating centre. All patients provided written informed consent before study entry. The study was conducted in accordance with the Declaration of Helsinki and International Conference of Harmonization Good Clinical Practice guidelines. Data were collected and analysed in collaboration between sponsor and clinical investigators. An independent data monitoring committee evaluated safety approximately every 6 months, in addition to a pre-specified futility analysis of efficacy data. All authors had access to the data, contributed to development and review of the manuscript (with editorial assistance from a sponsor-funded professional medical writer), approved submission, verified the study conduct in accordance with the protocol, and attested for data accuracy and completeness.

Results

Patients and treatment

Between June 9, 2014, and March 30, 2015, 167 patients were screened, and 123 patients were enrolled (supplementary figure S1), 4 of whom subsequently did not meet eligibility criteria and did not receive study drug. One-hundred nineteen patients received ≥1 dose of atezolizumab. One-hundred two patients (86%) discontinued treatment, either due to disease progression (n=77), patient withdrawal (n=12), an adverse event (n=11), or other reasons (n=2). The median treatment duration was 15 weeks (range 0–102), and 25 patients (21%) had been treated for >52 weeks at time of data cutoff (median follow-up 17·2 months [range 0·2–23·5]). Table 1 summarises baseline characteristics of the safety and efficacy population. Seventy percent were cisplatin ineligible due to renal impairment. Poor performance status and visceral metastatic disease are independent prognostic factors (Bajorin risk factors) that predict survival in metastatic UC.[19] Fifty-six percent of patients in this study had 1 Bajorin risk factor and 15% had both Bajorin risk factors. Most patients (87%) had comorbidities. The distribution of PD-L1 subgroups matched prior study populations.[16]

Efficacy

The primary efficacy analysis (Methods S1) was designed to be performed when patients had a minimum of 6 months' follow-up. In that analysis (with a median follow-up duration of 8·5 months [range 0·2–14·3]), hierarchal testing did not reach significance in the IC2/3 patient subgroup (objective response rate 22% 95% CI (9–40%), compared with the pre-specified 10% response rate, precluding further statistical tests (Methods S1). However, after a 17·2-month median follow-up duration, the objective response rate was 23% (95% confidence interval [CI] 16–31; table 2) in all patients, with the lower bound of the 95% CI exceeding 10%. Furthermore, the updated objective response rate by PD-L1 subgroup rose to 28% (95% CI 14–47) in IC2/3, 24% (95% CI 15–35) in IC1/2/3, 21% (95% CI 10–35) in IC1, and 21% (95% CI 9–36) in IC0 patients. Complete responses were seen in 11 patients (9%). Concordance between responses assessed by investigators *vs* independent review was >90% (supplementary table S2).

Median time to onset of first response was 2·1 months (range 1·8–10·5), but late responses were also observed (after 6 months in 2 patients; figure 1 and supplementary figure S2). Median response duration had not been reached in all patients or in pre-defined PD-L1 subgroups (range 3·7 to 21·0+), and 19 of 27 responses (70%) were ongoing. Median progression-free survival was 2·7 months (95% CI 2·1–4·2) in all patients, 4·1 months (95% CI 2·3–11·8) in IC2/3 patients, 2·1 months (95% CI 2·1–5·4) in IC1 patients, and 2·6 months (95% CI 2·1–5·7) in IC0 patients. The clinical benefit rate in all patients was 30% (95% CI 22–39; supplementary table S3).

The median overall survival was 15·9 months (95% CI 10·4 to not estimable; figure 2) in all patients, 12·3 months (95% CI 6·0 to not estimable) in IC2/3 patients, and 19·1 months (95% CI 9·8 to not estimable) in IC0/1 patients. The 12-month landmark survival rate was 57% (95% CI 48–66) in all patients.

Subgroup analyses

Responses to atezolizumab occurred in all clinical subgroups evaluated (table 3). Notably, 39% of patients with upper-tract primary tumours (renal pelvis/ureter; n=33) had an objective response. Patient subgroups with lower response rates (e.g., those with liver metastases [n=25]; 8%) still had durable responses, with median response duration also not reached in any of these subgroups. Bajorin risk factors also appeared to maintain prognostic utility.[19] Median survival was not reached in patients with no risk factors (supplementary table S4), was 13·4 months in those with 1 risk factor (either visceral metastases or ECOG PS 2), and was 6·2 months in those with 2 risk factors. Patients with liver metastases had a 5·5-month median survival. Furthermore, patients aged 80 years (n=25) and those with renal dysfunction (n=83) had median survival durations of 14·8 and 14·1 months, respectively. Patients who achieved stable disease (n=29) had a median survival of 19·1 months (supplementary table S5).

Median survival in patients with upper-tract primary tumours had not been reached. To investigate a possible basis for improved outcomes in these patients, we assessed baseline covariates, including anatomic sites of metastases, tumour mutation load, T-effector gene

expression, TCGA subtype, and baseline tumour burden; however, we found no significant differences in these factors between patients with upper- and lower-tract disease (supplementary figure S3). Microsatellite instability was observed only in two patients with upper-tract primary tumours (and two with lower-tract primary tumours), suggesting that this factor was not a primary determinant.

Exploratory analyses of biomarkers of efficacy

Exploratory biomarker assessments that were not pre-specified included expression of individual genes and gene sets, subtyping according to TCGA (supplementary figure S4), and quantification of mutation load.[16] Overall, 72 (61%) of samples obtained for these analyses were from primary tumor samples and 47 (39%) were from metastatic tumors. Responses were seen across all subtypes and were more frequent with the luminal II subtype (figure 3A). Survival by TCGA subtype is presented in figure 3B. Tumour mutation load was significantly higher in responding patients than in non-responders, and this relationship was consistent across TCGA subtypes and PD-L1 subgroups (figures 3C and 3D). Mutation load was also associated with overall survival (figure 3E); patients with the highest mutation load (quartile 4) had significantly longer survival compared with those in quartiles 1 to 3.

Safety

One hundred fourteen patients (96%) experienced an adverse event (see supplementary table S6 for list of adverse events regardless of attribution), and 79 patients (66%) experienced a treatment-related event (table 4). No major safety differences were observed across PD-L1 subgroups. Treatment-related adverse events observed in   10% of patients (any grade) were fatigue, diarrhoea, and pruritus. Grade 3 or 4 treatment-related events occurred in 19 patients (16%), most frequently fatigue (3·4%, n=4), increased alanine aminotransferase (3·4%, n=4), and increased aspartate aminotransferase (2·5%, n=3). Only 1 of 4 reported grade 5 adverse events (supplementary table S6) was considered treatment related by the investigator (sepsis, in a patient with an unidentified source of infection).

Overall, 41 patients (35%) had an adverse event leading to dose interruption, with no single adverse event predominating, and 9 patients (8%) had an event leading to treatment withdrawal. The majority of treatment discontinuations (77 of 102) and deaths (52 of 59) were due to progression. Immune-mediated all grade adverse events were reported in 14 patients (12%) and grade 3 or adverse events were reported in 8 patients (7%; supplementary table S7), most commonly rash (3% all grade [n=4]; 1% grade 3 or 4 [n=1]). No patients received systemic non-corticosteroid immunomodulatory agents (e.g., infliximab, tocilizumab) for immune-mediated events. 36 patients received corticosteroids.

Post-protocol therapies

Post-protocol therapy, defined as any therapy administered after progression on atezolizumab before study discontinuation, was reported for 25 patients (9 IC0, 12 IC1, 4 IC2/3) during follow-up. The most common therapy was gemcitabine-carboplatin (14 of 25 patients); other regimens given are listed in supplementary table S8.

Discussion

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

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

Evolution of responses over time was noteworthy in this study, suggesting response rates and other historical surrogates of efficacy in mUC chemotherapy trials (e.g., progression-free survival) assessed at early time points may not fully capture benefit of modern-day immunotherapy. Responses to immune checkpoint inhibitors can be delayed and display atypical kinetics. For example, in the primary analysis, response rates were numerically but not statistically higher than the pre-specified response rate in the PD-L1–selected subgroup; however, with longer follow-up, several patients experienced further tumour shrinkage, leading to new complete and partial responses and the lower bound of the objective response rate 95% CI to now exceed 10%. Furthermore, durable benefit was seen even in the absence of RECIST response (19·1-month median overall survival observed in the stable disease subgroup), an observation common to immunotherapy[14,22] but not chemotherapy trials, which could have profound impacts on standards of mUC care. Cumulative toxicity often limits chemotherapy treatment to up to 6 to 8 cycles with platinum-based therapy,[6, 8–10] even in responding patients, however discontinuing treatment may compromise benefit in patients receiving immunotherapy. Future trials will be challenged to identify appropriate surrogates of long-term benefit as well as optimal timing for alternative treatments.

IMvigor210 was designed to test the association of PD-L1 expression with atezolizumab efficacy. In contrast with previous reports,[13,16] no statistically significant enrichment of response by PD-L1 expression was observed. Differences in baseline characteristics (e.g., tumour burden or nodal only *vs* visceral metastases) between populations or statistical

assumptions underpowered to detect precise differences between IC subgroups for this initially exploratory cohort might have contributed to these findings. Such factors will be analysed in phase 3 studies IMvigor211 (platinum-treated patients) and IMvigor130 (treatment-naive patients; ClinicalTrials.gov numbers NCT02302807 and NCT02807636, respectively).

TGCA subtypes have previously been associated with prognostic differences in survival, with basal tumours tending to exhibit shorter survival durations.[23,24] Still, outcomes observed in patients with luminal II samples are consistent with the IMvigor210 platinum-treated cohort,[16] although, as for PD-L1 status, sample size was not sufficient to establish statistical significance in the current study cohort. The observation that patients with the highest tumour mutation load[25] derived the longest survival from atezolizumab suggests that a threshold for tumour mutation load may need to be surpassed for generation of neo-antigens most suited for recognition by tumour-specific T cells. However, given the stochastic relationship between total mutation load and generation of neo-antigens, anti-tumour responses observed in some patients with lower mutation load are not unexpected— as seen in this study. These observations validate results from the platinum-treated population[16] and additional cancer immunotherapy studies in other tumour types.[26,27] As previously suggested, tumor mutation load, PD-L1 expression on immune cells and tumor TCGA subtypes may be independent predictors of response,[16] and further analyses in larger mUC studies that incorporates multiple biomarkers may help patient selection for optimal efficacy.

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

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Declaration of Interests

AVB, MDG, JER, DPP, JB, YL, MSvdH, SL, EEKIII, ZB, RB, PH, SM, ACT, OOA, GDF, and DJB received personal fees from Roche/Genentech outside the submitted work. MDG reports personal fees from Merck, Astellas, BioMotiv, and Novartis, as well as grants from Novartis, BMS, and Celgene. JER received non-financial support and other support from Roche/Genentech during the conduct of the study, as well as personal fees from Agensys, Eli Lilly, Merck, Bayer, AstraZeneca, Sanofi, and Oncogenex outside the submitted work. TP received other support from Roche/Genentech, AstraZeneca, BMS, and Merck during the conduct of the study. DPP received grants from Roche/Genentech during the conduct of the study, as well as grants and personal fees from Merck, Astra Zeneca, Novartis, Pfizer, and Agenysis outside the submitted work. YL received grants and personal fees from Sanofi, personal fees from Astellas, Janssen, iPSEN, and BMS outside the submitted work. AN received personal fees from Roche/Genentech, and grants and personal fees from Merck Sharp & Dohme during the conduct of the study. JH-C received other support from Roche/Genentech, outside the submitted work. JLP-G and EYY received grants from Roche/Genentech during the conduct of the study. NAD, MR, and AD declare no competing interests. MSvdH received other support from Roche/Genentech as well as personal fees and grants from Astellas and personal fees from Astra Zeneca outside the submitted work. RD received personal fees from Roche/Genentech and Merck outside the submitted work. SS and SSS received personal fees from Roche/Genentech outside the submitted work. RWJ received personal fees from BMS, Merck, Nektar, Eisai, Novartis, and Cerulean outside the submitted work. UNV received other support from Roche/Genentech during the conduct of the study, as well as honoraria and Consulting fees from Roche/Genentech. DIQ received personal fees from BMS, Merck, AstraZeneca, Novartis, Roche/Genentech, Pfizer, and EMD Serono outside the submitted work. ID received personal fees from Janssen, Roche/Genentech, Amgen, Novartis, and Resrefabre, as well as other support from Astellas outside the submitted work. DRS received support for advisory board and speaker participation from Roche/Genentech. BJE received grants and personal fees from Roche/Genentech outside the submitted work. PDG received other support from Roche/Genentech during the conduct of the study; in addition, PDG received personal fees from Genentech, Dendreon, Bayer, and Myriad Genetics, as well as other support from Bayer, Merck, Mirati, and Oncogenex and grants from Genmab outside the submitted work. EYY received grants and personal fees from Eli Lilly, Roche/Genentech, Merck, Agensys, Janssen, Dendreon, Medivation, Astellas, Sanofi, and Bayer, as well as personal fees from Tolmar, Seattle Genetics, Tokai, Ferring, and AstraZeneca, outside the submitted work.

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Research in context

Evidence before this study

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

Added value of this study

In this study, the humanised monoclonal anti-programmed death ligand 1 (PD-L1) antibody atezolizumab was evaluated in patients with previously untreated, locally advanced or metastatic urothelial cancer (mUC) who were ineligible for cisplatin-based chemotherapy. The original trial design for this study was focused on patients with disease progression during or following platinum-based chemotherapy and an exploratory cohort of first-line cisplatin ineligible patients; however, given the potential for benefit in the first-line setting, the exploratory cohort was expanded to approximately 100 patients, utilizing similar statistical assumptions. Objective responses by independent assessment according to Response Evaluation Criteria In Solid Tumors version 1.1 were durable, with 70% of patients continuing to respond after a median follow-up duration of almost 1·5 years. Overall survival also appeared to surpass historical rates, although differences in patient populations between studies, among other factors, complicate comparison. Atezolizumab also generally appeared to be safe and well tolerated in a patient population heavily dominated by renal insufficiency. Exploratory analyses to improve our understanding of the immune biology of atezolizumab efficacy identified correlates of response and survival including The Cancer Genome Atlas (TCGA) subtype and mutation load, which warrant further study as potential biomarkers for this agent in mUC.

Implications of all the available evidence

Cisplatin-based chemotherapy is the preferred first-line therapy for mUC and the only treatment shown to improve survival in patients with previously untreated disease. However, only a minority of patients with mUC receive first-line treatment with cisplatin-based chemotherapy. The population of patients who are ineligible for cisplatin has been underrepresented in recent clinical studies and as a result, these patients have poor outcomes. Atezolizumab shows potential as a first-line treatment option for these patients. Furthermore, biomarker data validates reports of this agent in the platinum-treated setting that linked intrinsic TCGA subtypes and mutation load with immunotherapy response.

A IC2/3 patients
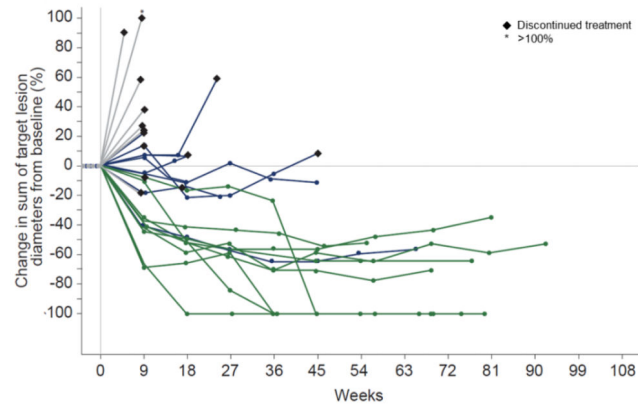
B IC1 patients
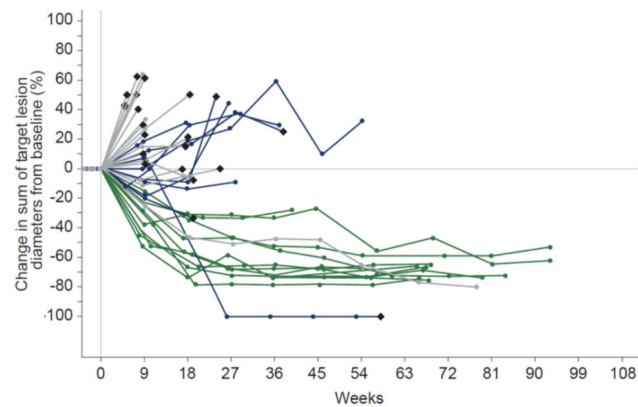
C IC0 patients
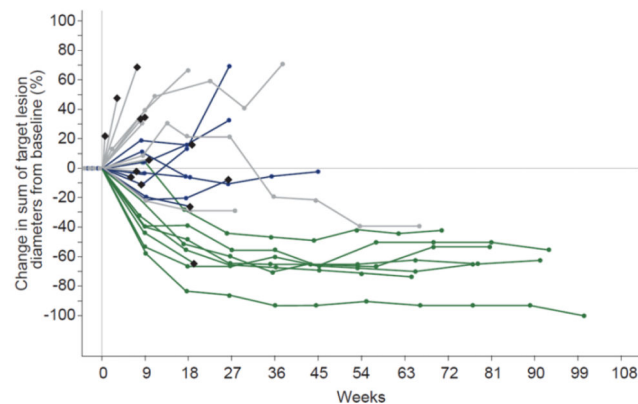
Figure 1. Change from baseline tumour burden by PD-L1 status

Spider plots depict changes from baseline tumour burden, defined as the sum of target lesion diameters, in patients who received atezolizumab, based on baseline PD-L1 status on immune cells of (A) IC2/3, (B) IC1, and (C) IC0. Grey colour denotes progressive disease; blue denotes stable disease; green denotes complete and partial responses (per RECIST v1.1). Data cutoff: July 4, 2016. PD-L1=programmed death-ligand 1. IC=tumour-infiltrating immune cell.
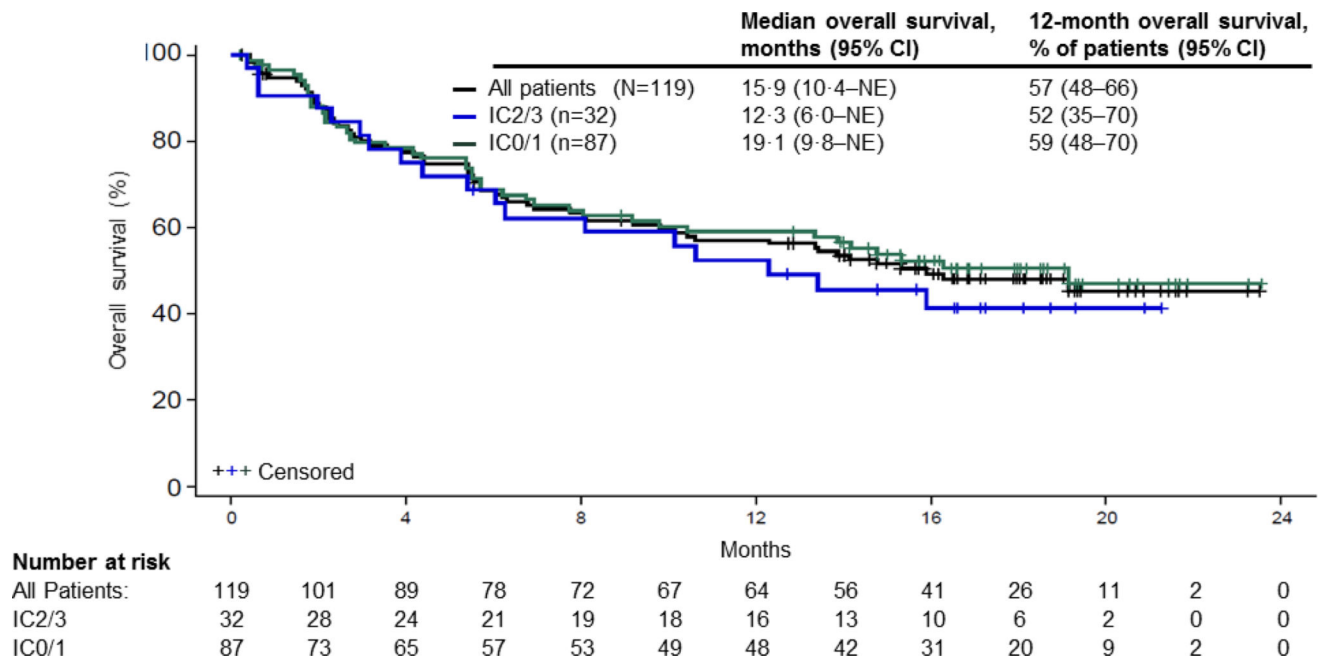
Figure 2. Overall survival in patients treated with atezolizumab

Kaplan-Meier estimates of overall survival according to PD-L1 status on immune cells. A total of 59 events occurred in all patients by the data cutoff date (18 in IC2/3 patients; 41 in IC0/1 patients). Data cutoff: July 4, 2016. PD-L1=programmed death-ligand 1. NE=not estimable. IC=tumour-infiltrating immune cell.
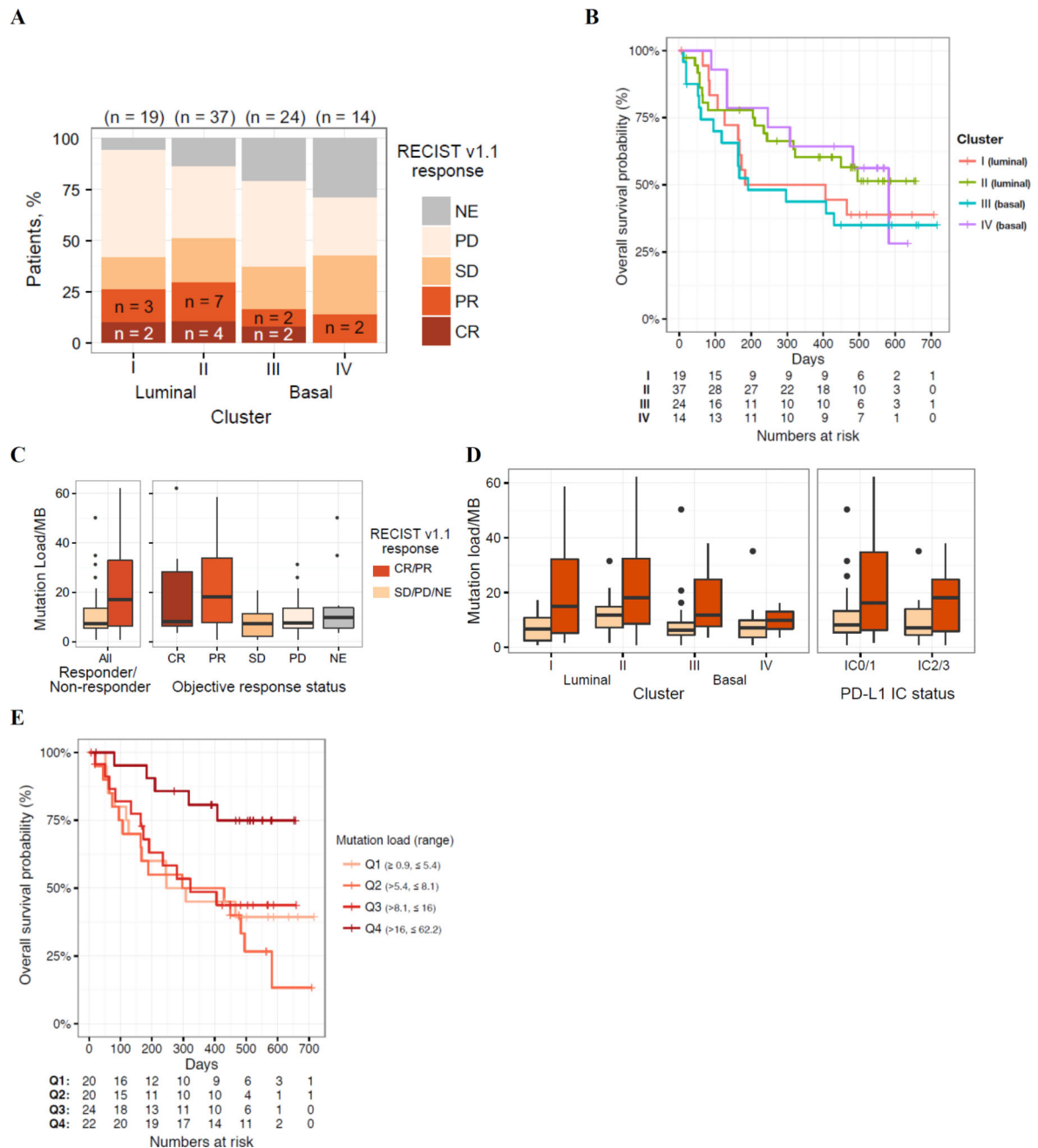
Figure 3. Associations among TCGA subtype, mutation load, and clinical activity

(A) Response as a function of The Cancer Genome Atlas subtype. (B) Kaplan-Meier plot of overall survival by subtype (luminal I, papillary-like; luminal II; basal III, squamous-like; and basal IV). (C) Mutation load as a function of response (Wilcoxon rank sum p=0·0180 for responding *vs* non-responding patients). (D) Mutation load versus response disaggregated by subtype or PD-L1 IC score. (E) Kaplan-Meier estimate of overall survival according to estimated mutation load (per megabase), binned into quartiles (log-rank p=0·0041 for a difference in overall survival between quartiles 1 to 3 and quartile 4). P values are for descriptive purposes only. TCGA=The Cancer Genome Atlas. PD-

L1=programmed death-ligand 1. Data cutoff: July 4, 2016. IC=tumour-infiltrating immune cell. Lum=luminal. Bas=basal. RECIST=Response Evaluation Criteria In Solid Tumors. NE=not estimable. PD=progressive disease. SD=stable disease. PR=partial response. CR=complete response. MB=megabase.

Table 1

Baseline characteristics and prior therapy

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

PD-L1= programmed death-ligand 1. IC= tumour-infiltrating immune cell. ECOG PS=Eastern Cooperative Oncology Group performance status. GFR=glomerular filtration rate.

[*] Intention-to-treat (efficacy- and safety-evaluable) patient population.

[†] One patient with prostatic urethra primary site not included.

[‡] Visceral metastasis defined as liver, lung, bone, any non–lymph node or soft tissue metastasis.

§Adjuvant or neoadjuvant therapy with first disease progression beyond 12 months.

∥GFR <60 and >30 mL/min.

¶At 2 contiguous frequencies.

Table 2

Objective response rate by PD-L1 status on tumour-infiltrating immune cells

	Patients	Complete response	Partial response	Objective response rate, n (% [95% CI])*	Median duration of response (95% CI),
All patients	119	11	16	27 (23% (16–31)	NE (14·1–NE)
IC2/3	32	4	5	9 (28% (14–47])	NE (11·1–NE)
IC1/2/3	80	8	11	19 (24% [15–35])	NE (NE)
IC1	48	4	6	10 (21% ([11–35])	NE (NE)
IC0	39	3	5	8 (21% [9–37])	NE (12·8–NE)

PD-L1=programmed death-ligand 1. ECOG PS=Eastern Cooperative Oncology Group performance status. IC=tumour-infiltrating immune cell. NE=not estimable.

*
Includes objective response rate per Response Evaluation Criteria In Solid Tumors version 1.1 (independent review facility). Data cutoff: July 4, 2016.

Table 3

Objective response rates by baseline subgroups

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

ECOG PS=Eastern Cooperative Oncology Group performance status. NE=not estimable.

[*] Includes objective response rate per Response Evaluation Criteria In Solid Tumors version 1.1 (independent review facility).

[†] Includes adjuvant or neoadjuvant treatment with disease progression experienced beyond 12 months.

[‡] One patient with prostatic urethra primary site not included.

[§] Visceral metastasis defined as liver, lung, bone, or any non–lymph node or soft tissue metastasis.

[‖] Risk factors include baseline ECOG PS >1 and baseline visceral metastasis. Data cutoff: July 4, 2016.

Table 4

Treatment-related adverse events

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

Events considered to be related to treatment by the investigator reported in 3 patients (any grade) or in 1 patient (grade 3 or 4). Multiple occurrences of the same event are counted once at maximum severity. Treatment-emergent adverse events include events occurring on or after the first dose of study drug until either 30 days after the last administration of study drug, initiation of subsequent non-protocol anti-cancer therapy or clinical cutoff date, whichever came first. Data cutoff: July 4, 2016.