

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <https://orca.cardiff.ac.uk/id/eprint/171498/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Sternberg, Cora N., Loriot, Yohann, Choy, Ernest, Castellano, Daniel, Lopez-Rios, Fernando, Banna, Giuseppe Luigi, Zengerling, Friedemann, De Giorgi, Ugo, Gedy, Craig, Masini, Cristina, Bamias, Aristotelis, Garcia del Muro, Xavier, Duran, Ignacio, Powles, Thomas, Retz, Margitta, Gamulin, Marija, Geczi, Lajos, Huddart, Robert A., Calabrò, Fabio, Kandula, Geetha, Skamnioti, Pari and Merseburger, Axel S. 2024. Final Results from SAUL, a single-arm international study of atezolizumab in unselected patients with pretreated locally advanced/metastatic urinary tract carcinoma. *European Urology Focus* 10 (6), pp. 938-946. 10.1016/j.euf.2024.05.007

Publishers page: <http://dx.doi.org/10.1016/j.euf.2024.05.007>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



Final Results from SAUL, a Single-Arm International Study of Atezolizumab in Unselected Patients with Pretreated Locally Advanced/Metastatic Urinary Tract Carcinoma

Cora N. Sternberg^{a,b,*}, Yohann Loriot^c, Ernest Choy^d, Daniel Castellano^e, Fernando Lopez-Rios^f, Giuseppe Luigi Banna^{g,†}, Friedemann Zengerling^h, Ugo De Giorgiⁱ, Craig Gedyel, Cristina Masini^k, Aristotelis Bamias^l, Xavier Garcia del Muro^m, Ignacio Duran^{n,‡}, Thomas Powles^o, Margitta Retz^p, Marija Gamulin^q, Lajos Geczi^r, Robert A. Huddart^s, Fabio Calabrò^{b,§}, Geetha Kandula^t, Pari Skamnioti^u, Axel S. Merseburger^v

^aEnglander Institute for Precision Medicine, Weill Cornell Medicine, Meyer Cancer Center, New York, NY, USA; ^bSan Camillo and Forlanini Hospitals, Rome, Italy (affiliation where patients were enrolled); ^cDepartment of Cancer Medicine and INSERM U981, Université Paris-Sud, Université Paris-Saclay, Gustave Roussy, Villejuif, France; ^dCREATE Centre, Section of Rheumatology, Division of Infection and Immunity, Cardiff University School of Medicine, Cardiff, UK; ^eMedical Oncology Service, Hospital Universitario 12 de Octubre, Madrid, Spain; ^fPathology Department, Hospital Universitario 12 de Octubre, Universidad Complutense de Madrid, Research Institute 12 de Octubre University Hospital (i+12), CIBERONC, Madrid, Spain; ^gCannizzaro Hospital, Catania, Italy; ^hDepartment of Urology, University Hospital Ulm, Ulm, Germany; ⁱIstituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Istituto Romagnolo per lo Studio dei Tumori (IRST) “Dino Amadori”, Meldola, Italy; ^jCalvary Mater Newcastle, Waratah, Australia; ^kMedical Oncology Unit, Azienda Unita Sanitaria Locale (AUSL)-IRCCS Reggio Emilia, Reggio Emilia, Italy; ^lAlexandra Hospital, National and Kapodistrian University of Athens, Athens, Greece; ^mInstitut Catala d’Oncologia, Institut d’Investigació Biomèdica de Bellvitge (IDIBELL), University of Barcelona, Barcelona, Spain; ⁿHospital Universitario Virgen del Rocio, Seville, Spain; ^oBarts Cancer Institute, Experimental Cancer Medicine Centre, Queen Mary University of London, St Bartholomew’s Hospital, London, UK; ^pDepartment of Urology, Technical University of Munich, Rechts der Isar Medical Center, Munich, Germany; ^qUniversity Hospital Centre

Zagreb and School of Medicine, University of Zagreb, Zagreb, Croatia; ^rNational Institute of Oncology, Budapest, Hungary; ^sInstitute of Cancer Research and Royal Marsden NHS Foundation Trust, Sutton, UK; ^tBiostatistics, Hoffmann-La Roche Ltd, Mississauga, Canada; ^uGlobal Product Development Medical Affairs Oncology, F. Hoffmann-La Roche Ltd, Basel, Switzerland; ^vDepartment of Urology, Campus Lübeck, University Hospital Schleswig-Holstein, Lübeck, Germany

[†]Current affiliation: Portsmouth Hospitals University NHS Trust and Faculty of Science and Health, School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, UK

[‡]Current affiliation: Hospital Universitario Marques de Valdecilla, IDIVAL, Santander, Spain

[§]Current affiliation: Oncologia Medica 1, IRCCS Istituto Nazionale Tumori Regina Elena, Rome, Italy

* Corresponding author: Englander Institute for Precision Medicine, Weill Cornell Medicine, Meyer Cancer Center, Belfer Research Building, 413 East 69th Street, New York, NY 10021, USA. Tel: +1 646 962 2072. E-mail address: cns9006@med.cornell.edu

Word count: 2733

Key words: Atezolizumab; overall survival; PD-L1; urothelial carcinoma

Abstract

Background and Objective: To determine the safety of atezolizumab in unselected patients (including understudied populations typically excluded from clinical trials) with pretreated urinary tract carcinoma (UTC). The prespecified final analysis updates previously reported safety and efficacy data.

Methods: The single-arm prospective SAUL study (NCT02928406) enrolled 1004 patients with locally advanced/metastatic urothelial/non-urothelial UTC that had progressed during/after 1–3 prior treatment lines for advanced UTC (or <12 months after [neo]adjuvant therapy). Broad eligibility criteria allowed patients with complex comorbidities approximating the real-world setting. Patients received atezolizumab 1200 mg every 3 weeks until disease progression/unacceptable toxicity. The primary endpoint was safety. Secondary endpoints included duration of response and overall survival (OS).

Key Findings and Limitations: Treated patients included 10% with poor performance status, 5% with creatinine clearance <30 mL/min, and 4% with autoimmune disease. At 55 months' median follow-up, median atezolizumab duration was 2.8 (range 0–62) months; 68 patients (7%) continued atezolizumab for >4 years. Treatment-related grade ≥3 adverse events occurred in 16% of patients (deaths in 1%); 8% discontinued atezolizumab for adverse events. Median OS was 8.6 (95% CI, 7.8, 9.7) months. OS was >4 years in 136 patients (14%). Limitations include the small sample sizes of some subgroups of special interest.

Conclusions and clinical implications: Long-term safety and efficacy data continue to show benefit of atezolizumab in unselected patients with UTC. Remarkably, 14% of patients lived for >4 years after starting atezolizumab. These results can inform multidisciplinary team discussions and treatment decision-making for patients with UTC with complex comorbidities.

Plain English summary: The SAUL study looked at how well tolerated a drug called 'atezolizumab' was in a group of people with urinary tract carcinoma who had already received up to three previous treatments for their cancer, including in people who are usually not included in clinical trials because of other medical conditions. The study also looked at how long people lived after starting treatment. Overall, this study showed that atezolizumab was well tolerated including in people with other medical conditions. People who had failed other therapies, lived for about 8.6 months on average after starting treatment; 14% of people were still alive after 4 years.

1. Introduction

The anti-PD-L1 agent atezolizumab is an established therapy in patients with locally advanced/metastatic urothelial carcinoma who have previously received platinum-containing therapy or are considered cisplatin-ineligible with tumors expressing PD-L1 on $\geq 5\%$ of immune cells (IC2/3).[1-5] The pivotal phase 3 IMvigor211 trial [3] excluded certain patient populations, including those with previous autoimmune disease, ongoing systemic corticosteroid treatment, symptomatic brain metastases, Eastern Cooperative Oncology Group performance status (ECOG PS) 2, inadequate renal or liver function, or HIV. However, these populations frequently present in routine oncology practice: for example, 25% of >1200 patients in a Spanish real-world dataset had ECOG PS 2 and 32% had creatinine clearance (CrCl) <60 mL/min.[6] Combination chemotherapy is not recommended in these patients and some receive no treatment.[7, 8] There are limited data on outcomes with cancer immunotherapy in these clinically challenging patient populations.

The multinational single-arm SAUL study provides first and critical insight into the tolerability and effectiveness of atezolizumab in a broad population of patients with pretreated urinary tract carcinoma (UTC), including understudied populations that are typically excluded from randomized clinical trials.[9-11] For example, patients with previous autoimmune disease were excluded from the IMvigor211 trial, as were those with inadequate renal function (creatinine clearance <30 mL/min) or positive HIV status,[3] but these patients were eligible for the SAUL study. Clinical outcomes at the primary analysis were similar to phase 3 results for anti-PD-(L)1 therapies in highly selected patients.[3, 12] We report the prespecified final analysis 4 years after completing enrollment, focusing on patients with particularly favorable long-term outcomes.

2. Patients and Methods

The design of the SAUL study (NCT02928406), including details of eligibility criteria, has been published previously.[9] In brief, eligible patients had locally advanced/metastatic urothelial or non-urothelial UTC that had progressed during/after one to three prior treatment lines for advanced UTC (or within 12 months of [neo]adjuvant therapy). Patients with autoimmune disease, ECOG PS 2, CrCl ≥ 15 –30 mL/min, and/or stable central nervous system (CNS) metastases were eligible. Atezolizumab 1200 mg was given once every 3 weeks until disease progression, unacceptable toxicity, loss of clinical benefit, or patient/physician decision.

The primary endpoint was safety. Adverse events of special interest (AESIs) for atezolizumab were defined based on the company-defined categories current at the time of the analysis. These included additional adverse events (AEs) since the primary analysis, reflecting increased experience with immunotherapy and surveillance over time. Post hoc analyses explored the time to onset and resolution of AESIs using summary statistics within the subset of patients experiencing each AESI.

Secondary efficacy endpoints included progression-free survival (reported previously[9]), overall response rate (ORR; assessed by Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1), disease control rate (DCR; complete or partial response [CR/PR], or stable disease for ≥ 4 weeks), overall survival (OS), duration of response (DoR), and patient-reported outcomes, assessed using the European Organisation for the Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30) on day 1 of the first three cycles, then at tumor assessment visits every three cycles. Changes from baseline of ≥ 10 points were considered to be clinically meaningful.[13] Compliance with questionnaire completion at each timepoint was calculated as a percentage of all patients remaining on treatment at that timepoint.

Subgroup analyses of key safety and/or efficacy parameters according to PD-L1 status, ECOG PS (0/1 vs 2), CNS metastases, renal impairment at study entry, history of autoimmune disease, and concomitant steroids were prespecified.[9] In further post hoc analyses according to baseline CrCl, patients were classified as chemotherapy ineligible (CrCl 15–<30 mL/min), cisplatin ineligible and carboplatin eligible (CrCl 30–<60 mL/min), or cisplatin eligible (CrCl ≥60 mL/min).

Additional post hoc exploratory analyses characterized patients with exceptional outcomes, defined (in non-mutually exclusive subgroups) as: CR/PR with OS >2 years; OS >4 years; or atezolizumab treatment for >4 years.

Baseline characteristics, treatment exposure, and safety were analyzed in all patients who received at least one atezolizumab dose. Efficacy was analyzed in the intention-to-treat (ITT) population (all enrolled patients). In each subgroup analysis, any patients with missing data for the parameter defining the specific subgroup were excluded.

The protocol and study-related materials were approved by each site's institutional review board or ethics committee before study initiation. All patients provided written informed consent before any study-specific procedures.

3. Results

3.1. Patient population

SAUL enrolled 1004 patients from 172 sites in 32 countries across Europe, Asia, South America, Australia, and Canada between November 30, 2016, and March 16, 2018. Among 997 treated patients, 10% had ECOG PS 2, 5% had CrCl <30 mL/min, 4% had a history of autoimmune disease, and 7% had received two to three prior treatment lines. Approximately two-thirds of patients (64%) had received ≥1 prior treatment for metastatic disease (Supplementary Table 1).

3.2 *Treatment exposure*

At the database lock (December 20, 2022; median follow-up 55 months) all patients had discontinued treatment in the study or transferred to a rollover study or commercial supply. The most common reason for discontinuing atezolizumab was disease progression (75% of patients). Median treatment duration was 2.8 months (Table 1). Atezolizumab was continued for >3 years in 96 patients (10%) and for >4 years in 68 patients (7%), including three patients receiving concomitant steroids, two with CrCl <30 mL/min, and two with ongoing autoimmune disease.

3.3 *Safety*

Grade ≥ 3 AEs occurred in 51% of patients and were considered treatment related in 16% (Table 1). The most common were urinary tract infection (6%), anemia (5%), fatigue (3%), hyponatremia (2%), and asthenia (2%). Atezolizumab was discontinued for AEs in 8% of patients, most frequently pneumonitis (0.5%), nephritis (0.4%), and acute kidney injury (0.3%; one patient also had nephritis and CrCl 30–<60 mL/min; the other two had CrCl ≥ 60 mL/min). Eight deaths were considered by the investigator to be treatment related (two from dyspnea, one each from respiratory failure, intestinal perforation, drug-induced liver injury, colitis, chronic kidney disease, and pericardial hemorrhage; Supplementary Table 2).

The most common AESIs typically occurred in early cycles, except for pneumonitis, cerebrovascular conditions, nephritis, pancreatitis, and diabetes mellitus (Table 2). The median duration of key AESIs was <2 months except for low-grade acute kidney injury, low-grade hyperthyroidism, and low-grade nephritis.

Generally, incidences of AEs in subgroups of special interest were consistent with the overall treated population. However, in patients with ECOG PS 2 (median treatment duration 0.7 months), treatment-related AEs and AESIs were less common than in the overall population (Table 1). Conversely, in patients with autoimmune disease (median treatment duration 5.7 months), treatment-related AEs (all grades and grade ≥ 3) were more

common than in the overall treated population (Table 1), although there was no increase in AEs leading to atezolizumab discontinuation.

Baseline CrCl was available for 995 patients, of whom 46 (5%) were classified as chemotherapy ineligible. Among chemotherapy-eligible patients, 529 (53%) were cisplatin eligible and 420 (42%) were cisplatin ineligible and carboplatin eligible. Subgroups with lower CrCl tended to be older, female, have never smoked, have worse ECOG PS, and have previously received treatment for metastatic disease (Supplementary Table 3). However, the median duration of atezolizumab was similar in chemotherapy-ineligible patients (3.0 months), the other two subgroups (2.8 months) and the overall population. There was no excess of AEs in the chemotherapy-ineligible or cisplatin-ineligible subgroups (Supplementary Table 4). Treatment-related AEs appeared to be slightly less common in patients with CrCl <30 mL/min. Compared with the other subgroups, chemotherapy-ineligible patients had a numerically higher incidence of grade 1/2 decreased appetite and lower incidence of grade 1/2 pyrexia (Supplementary Fig. 1). The only AESI categories in >10% of chemotherapy-ineligible patients were acute kidney injury and immune-mediated colitis/non-infectious diarrhea.

3.4 *Efficacy*

In the ITT population, 78% of patients had died and median OS was 8.6 months (95% confidence interval [CI] 7.8, 9.7 months) (Fig. 1A and Table 3). OS was >4 years in 136 patients (14%). Median DoR in 158 responding patients was 27.8 (95% CI, 18.9, 43.3) months (Fig. 1B).

3.5 *Long-term responders*

Among 158 responding patients, 132 (84%) lived for >2 years (median atezolizumab treatment duration: 38.7 months), 113 (72%) for >3 years (median atezolizumab duration: 45.3 months), and 90 (57%) for >4 years (median atezolizumab duration: 49.1 months). Of

234 patients alive 2 years after starting treatment in SAUL, 136 (58%; 14% of the ITT population) were still alive 2 years later (median treatment duration: 47.8 months).

Compared with the overall population, patients with exceptional long-term outcomes had less visceral disease, better ECOG PS, and higher PD-L1 expression score (Supplementary Table 1). Among 68 patients treated with atezolizumab for >4 years, 13 had stable disease and five had disease progression as best response; two patients had autoimmune disease (one with psoriasis, one with Hashimoto's disease). Patients treated for >4 years had higher incidences of all-grade treatment-related AEs (85% vs 54% in those treated for ≤4 years), grade ≥3 treatment-related AEs (22% vs 15%, respectively), all-grade AESIs (91% vs 50%), and grade ≥3 AESIs (26% vs 15%), but fewer discontinued treatment for AEs (4% vs 8%).

3.6 *Efficacy in subgroups of special interest*

Table 3 and Fig. 1C summarize efficacy in clinically relevant patient populations. In 268 patients (27%) with PD-L1 IC2/3 expression, median OS was 11.2 months, the 3-year OS rate was 30%, ORR was 24%, and median DoR was 35.2 months. In patients with no prior treatment for metastatic disease (36%), ORR was 16% and median DoR was 35.4 months. In patients with autoimmune disease, median OS and ORR were similar to the overall population but median DoR was shorter. Among patients with CrCl <30 mL/min (chemotherapy ineligible), median OS and OS rates were slightly lower than in the overall population (Supplementary Fig. 2), but ORR was similar and median DoR was 20.7 months. Outcomes were particularly poor in patients with ECOG PS 2 or CNS metastases, consistent with the primary analysis.[9, 10] In post hoc analyses, ORR and DCR were similar across subgroups defined by CrCl (Supplementary Table 5).

3.7 *Subsequent therapy*

Relatively few patients (23%) received further anticancer therapy, comprising chemotherapy in 18% and immunotherapy in 2% (Table 4). Paclitaxel (8%), vinflunine (6%), gemcitabine

(4%), and carboplatin (3%) were the most frequent. Among 90 patients with CR/PR and OS >4 years (9% of the overall population), only 14% received subsequent anticancer therapy.

3.8 *Patient-reported outcomes*

At baseline, 96% of patients answered ≥ 1 question of EORTC QLQ-C30. Mean baseline global health status/quality of life (GHS/QoL) was 59.0 (standard deviation 22.8).

Questionnaire completion rates remained >80% (of those still on treatment) up to and including cycle 16. However, consistent with the short treatment duration in many patients, fewer than 340 patients (34% of the ITT population) completed questionnaires beyond cycle 4.

During the first 4 cycles, there was no clinically meaningful change from baseline in QLQ-C30 GHS/QoL (Supplementary Fig. 3). Similarly, there was no meaningful change from baseline in physical, role, emotional, cognitive, or social functioning scales, fatigue, nausea/vomiting, pain symptom scales, nor dyspnea, insomnia, appetite loss, constipation, diarrhea, or financial difficulty items (data not shown).

4. Discussion

The population enrolled in SAUL approximated routine oncology practice across a broad international spectrum of healthcare systems, including important understudied subgroups: patients with autoimmune disease, CrCl <30 mL/min, CNS metastases, ECOG PS 2, or taking concomitant steroids. Two-thirds of patients were previously treated for metastatic disease. A detailed analysis of outcomes in patients with autoimmune disease has been published previously.[11] Long-term safety data provide further support for the tolerability of atezolizumab in patients with complex comorbidities. AEs were generally not increased in patients potentially at higher risk of immune-related AEs. Among 136 patients with OS >4 years (14%), median atezolizumab treatment duration was 47.8 months. Most AEs occurred in early cycles.

After 55 months' median follow-up, median OS of 8.6 months in the ITT population and 11.2 months in the PD-L1 IC2/3 subgroup is remarkably similar to trials enrolling highly selected populations (8.6 months in IMvigor211 [4] and CHECKMATE-275,[14] 10.1 months in KEYNOTE-045 [15] regardless of PD-L1 status; 11.1 months in the IMvigor211 PD-L1 IC2/3 population [4]), although cross-trial comparison is complicated by differing trial designs, patient populations, and follow-up.

Although ORRs with immune checkpoint inhibitors tend to be modest, responding patients often have sustained and durable responses. Of note, the median DoR in SAUL was 27.8 months. Furthermore, 132 responding patients had exceptional long-term outcomes, with OS >2 years. In exploratory analyses, the only notable characteristics over-represented in patients with exceptional outcomes were non-visceral disease, good performance status, and PD-L1 IC2/3. Among 90 responders with OS >4 years, only 14% received subsequent therapy, suggesting that multiple further treatment lines were unlikely to be the explanation for the favorable long-term outcome.

The subgroup of 68 patients (7%) treated for >4 years included five patients whose best RECIST assessment was disease progression. In routine clinical practice or a registrational trial these patients would discontinue immunotherapy, but they appeared to derive long-term benefit from continued atezolizumab in SAUL. Isolated cases showing similar benefit from atezolizumab after pseudoprogression have been reported in other tumor types.[16-19] The 68 patients treated for >4 years also included patients with ongoing autoimmune conditions, ongoing concomitant steroids, and renal impairment, populations typically denied atezolizumab because of perceived tolerability concerns. Adverse reactions to atezolizumab include renal effects, but relatively little was known about the impact of severe pre-existing renal impairment on the efficacy and safety of atezolizumab, as these patients were excluded from IMvigor211.[3] The SAUL dataset provides important new information on the feasibility of long-term atezolizumab treatment in patients who ordinarily are refused treatment, suggesting that, with guidance, patients with multiple conditions

previously excluded from immunotherapy trials can indeed receive treatment with immune checkpoint inhibitors. Implementing this new knowledge in clinical practice often requires a multidisciplinary approach. Physicians should consult with specialists in immunotherapy and the specific conditions of the patient to determine the potential risks and benefits of immune checkpoint inhibitor treatment. Individualized treatment plans for each patient should be developed, taking into account their unique conditions, disease severity, and other relevant factors. Regular monitoring protocols to closely follow patients for any adverse reactions or changes in their condition during treatment with immune checkpoint inhibitors should be implemented. Patients should be educated about the potential risks and benefits of immune checkpoint inhibitor therapy, as well as alternative treatment options, to allow them to make informed decisions about their care. Shared decision-making with patients and their families is essential, weighing the potential benefits of immune checkpoint inhibitors against the risks based on the available evidence and individual patient factors. Healthcare providers must use their clinical judgement and available evidence to make informed decisions about the use of immune checkpoint inhibitors in patients with multiple conditions. The SAUL study has shown that atezolizumab, with proper multidisciplinary monitoring, can be both tolerable and effective in populations that were not eligible for treatment during registration clinical trials.

SAUL sheds particular light on the potential role of atezolizumab in patients unable to receive cisplatin (or carboplatin). Although patients with lower CrCl were more likely to be older, female, with a worse performance status, and have received prior therapy for metastatic disease, there was no signal of increased AEs or AESIs in patients with CrCl <30 mL/min. This small subgroup had shorter median OS and lower OS rates than in patients with CrCl ≥30 mL/min, but ORR was similar and median DoR was 20.7 months. Considering the differences in baseline characteristics between the populations and the small sample size it is not possible to draw any conclusions about potential differences in OS. Of note, a retrospective study of 79 patients treated with PD-(L)1 inhibitors, including a population with

CrCl <30 mL/min, suggested similar efficacy to unselected populations with cisplatin-ineligible advanced urothelial carcinoma, although grade ≥ 3 toxicities were increased.[20] In a recent Japanese retrospective study of real-world data, the incidence of grade ≥ 2 treatment-related AEs with pembrolizumab was similar in patients with CrCl <30 versus ≥ 30 mL/min; ORR and OS were also similar.[21]

A real-world evidence analysis from the US healthcare system suggested median OS of 7.7 months with PD-(L)1 inhibitor monotherapy.[22] In the prospective STRONG phase 3b study of fixed-dose durvalumab in 867 patients with previously treated UTC, including patients with ECOG PS 2, median OS was 7.0 months (95% CI, 6.4, 8.2 months).[23] Patients with CrCl ≤ 40 mL/min were excluded, and median follow-up was only 13.8 (range 0–29) months.[23]

Although this is a large trial, the main limitations of this study are the single-arm design and the small numbers of patients with some of the clinically challenging conditions (eg, HIV positive, renal dialysis), despite being eligible. This may reflect investigator hesitancy to treat patients with certain comorbidities, perhaps because of a less favorable anticipated balance of benefit versus risk. Although the trial population was more representative of real-world practice than most trials of immunotherapy in this setting, there were nevertheless some exclusion criteria and possibly selection bias inherent in this type of trial design. An additional weakness is the lack of information on genomic or molecular markers, preventing exploration of multifaceted prognostic indices. A clinico-genomic analysis of real-world data showed that in patients treated with immunotherapy, high tumor mutational burden was associated with improved OS.[24] Prognostic indices potentially offer the opportunity to identify a priori those patients who may have exceptional long-term outcomes on atezolizumab therapy.

5. Conclusion

To our best knowledge, SAUL is the largest prospective international dataset of patients approximating routine practice, with remarkable long-term follow-up. It provides unique insight into outcomes in treatment scenarios frequently encountered in clinical practice but rarely studied in clinical trials, including patients ineligible for chemotherapy or with complex comorbidities. Safety and efficacy data build on reports from the primary analysis focusing on subgroups of special interest [10, 11] and provide reassurance that atezolizumab therapy is well tolerated, even in patients with comorbidities for whom chemotherapy may not be an option. A notable subset of patients had exceptional long-term outcomes, including OS >4 years. Compared with the overall population, these patients were characterized by less visceral disease, better ECOG PS, and higher PD-L1 expression score. These findings potentially go beyond urothelial carcinoma and could be extrapolated to immunotherapy in other populations with severe comorbidities.

Patient summary: The SAUL study was to see how well tolerated an immunotherapy drug called 'atezolizumab' was in a group of people with urothelial cancer who had already received up to three previous treatments for their cancer, including people who are usually not included in clinical trials because of other medical conditions. The study also looked at how long people lived after starting treatment. Overall, this study showed that atezolizumab was well tolerated including in people with medical conditions that may have prevented them from receiving immunotherapy. People who had failed prior therapy, lived for about 8.6 months on average after starting treatment; 14% of people were still alive after 4 years.

Author contributions: Cora N. Sternberg and Pari Skamnioti had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

Study concept and design: Sternberg, Lorient, Choy, Castellano, Lopez-Rios, Skamnioti, Merseburger

Acquisition of the data: Sternberg, Lorient, Castellano, Lopez-Rios, Banna, Zengerling, De Giorgi, Gedye, Masini, Bamias, Garcia del Muro, Duran, Powles, Retz, Gamulin, Geczi, Huddart, Calabrò, Merseburger

Analysis and interpretation of data: Kandula, Skamnioti

Draft of the manuscript: Sternberg, Kandula, Skamnioti

Critical revision of the manuscript for important intellectual content: All authors

Statistical analysis: Kandula

Administrative, technical, or material support: Kandula, Skamnioti

Supervision: Skamnioti

Financial disclosures: Cora N. Sternberg certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Dr Sternberg reported consulting/advisory roles for Amgen, Astellas Pharma, AstraZeneca, Bayer, Bristol-Myers Squibb, Foundation Medicine, Genzyme, Gilead Sciences, Janssen Oncology, Merck, MSD, Pfizer, Roche, Medscape, and UroToday. Dr Lorient reported consulting/advisory roles for Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, Immunomedics, Janssen, Janssen (Inst), Loxo/Lilly, MSD Oncology, MSD Oncology (Inst), Pfizer/EMD Serono, Roche, Seagen, Taiho Pharmaceutical; research funding to his institution from Astellas Pharma, AstraZeneca, Basilea, BMS, Exelixis, Gilead Sciences, Incyte, Janssen Oncology, Merck KGaA, MSD Oncology, Nektar, Pfizer, Roche, Sanofi, Seagen, and Taiho Pharmaceutical; and

travel/accommodation/expenses from Astellas Pharma, AstraZeneca, Janssen Oncology, MSD Oncology, Roche, and Seagen. Dr Choy reports honoraria from AbbVie, Amgen, Biogen, Chugai Pharma, Fresenius Kabi, Gilead Sciences, GlaxoSmithKline, Janssen, Lilly, R-Pharm, Sanofi, and UCB; consulting/advisory roles for AbbVie, Amgen, Biogen, Chugai Pharma, Fresenius Kabi, Gilead Sciences, GlaxoSmithKline, Janssen, Lilly, R-Pharm, Sanofi, and UCB; speaker bureau participation for AbbVie, Amgen, Chugai Pharma, Fresenius Kabi, Galapagos NV, Lilly, Novartis, Pfizer, and Sanofi; research funding to his institution from Bio-Cancer, Biogen, Pfizer, and Sanofi; and

travel/accommodations/expenses from Janssen and UCB. Dr Castellano reports consulting/advisory roles for Astellas Pharma, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Ipsen, Janssen Oncology, Lilly, MSD Oncology, Novartis, Pfizer, Pierre Fabre, Roche/Genentech, and Sanofi; research funding to his institution from Janssen Oncology; and travel/accommodation/expenses from AstraZeneca Spain, Bristol-Myers Squibb, Pfizer, and Roche. Dr Lopez-Rios reports honoraria from AbbVie, Astellas, AstraZeneca, Bayer, BMS, Daichii Sankyo, Janssen, Lilly, MSD, Merck, Pfizer, Roche, Sanofi, Takeda, and Thermo Fisher Scientific and research funding from AstraZeneca, Lilly, Pfizer, Roche, and Thermo Fisher Scientific. Dr Banna reports speaker bureaus for Astellas Pharma, AstraZeneca, and Amgen; coauthorship of four patents with STMicroelectronics; and travel/accommodation for scientific conferences from Merck and Janssen. Dr Zengerling reports honoraria from Astellas Pharma, Bayer/Vital, Ipsen, Janssen, Merck, and Pfizer; consulting/advisory roles for Apogepha, AstraZeneca, Bayer Health, Bristol-Myers Squibb, Ipsen, Janssen, Merck, Merck Sharp & Dohme, Pfizer, and Roche; and

travel/accommodation/expenses from Astellas Pharma, Ipsen, Janssen, and Pfizer. Dr De Giorgi reports consulting/advisory roles for Amgen, Astellas Pharma, AstraZeneca, Bayer, Bristol-Myers Squibb, Clovis Oncology, Dompé Farmaceutici, Eisai, Ipsen, Janssen, Merck KGaA, MSD, Novartis, Pfizer, and PharmaMar; research funding to his institution from AstraZeneca, Roche, and Sanofi; and travel/accommodation/expenses from Ipsen and Pfizer. Dr Gedye reports consulting/advisory roles with personal honoraria from BCAL

Diagnostics, Cadex Genomics, and Novotech and with honoraria to his institution from Bristol-Myers Squibb and Merck Sharp & Dohme; and speaker bureau participation (for his institution) for Limbic Oncology. Dr Masini reports consulting/advisory roles for Astellas Pharma, Bristol-Myers Squibb, Ipsen, Janssen, Merck Serono, and MSD. Dr Bamias reports honoraria from Astellas Pharma, Bristol-Myers Squibb, Debiopharm Group, MSD and Sanofi; consulting/advisory roles for AstraZeneca, Bristol-Myers Squibb, Ferring, Ipsen, MSD, Pfizer, and Roche; and research funding to his institution from AstraZeneca, Bristol-Myers Squibb, Ipsen, Pfizer, and Roche. Dr Garcia del Muro reports consulting/advisory roles for Bristol-Myers Squibb, Eisai, EUSA Pharma, GlaxoSmithKline, Ipsen, Lilly, Merck, Pfizer, PharmaMar, and Roche; speaker bureau membership for Astellas Pharma, Eisai, and Pfizer; research Funding from AstraZeneca; and travel/accommodation/expenses from Pfizer and Roche. Dr Duran reports honoraria from Astellas Pharma, Bayer/Onyx, Bristol-Myers Squibb, EUSA Pharma, Ipsen, Janssen Oncology, MSD Oncology, and Roche/Genentech; consulting/advisory roles for Bayer, Bristol-Myers Squibb, Immunomedics, Janssen Oncology, MSD Oncology, Novartis, Pfizer/EMD Serono, Pharmacyclics, Roche/Genentech, and Seagen; research funding to his institution from Astellas Pharma, AstraZeneca Spain, Bayer, Janssen Oncology, and Roche/Genentech; and travel/accommodation/expenses from Astellas Pharma, AstraZeneca Spain, Ipsen, Pfizer/EMD Serono, and Roche/Genentech. Dr Powles reports honoraria from Astellas Pharma, AstraZeneca, BMS, Eisai, Exelixis, Gilead Sciences, Incyte, Ipsen, Johnson & Johnson/Janssen, MashupMD, Merck, Merck Serono, Merck Sharp & Dohme LLC, Novartis, Pfizer, Roche, and Seagen; consulting/advisory roles for Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, Eisai, Exelixis, Incyte, Ipsen, Johnson & Johnson, MashupMD, Merck, Merck Serono, MSD, Novartis, Pfizer, Roche, and Seagen; research funding from Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, Eisai, Exelixis, Ipsen, Johnson & Johnson, Merck Serono, MSD, Novartis, Pfizer, Roche, and Seagen; and travel/accommodation/expenses from AstraZeneca, Ipsen, MSD, Pfizer, and Roche. Dr Gamulin reports consulting/advisory roles for BMS, Janssen Oncology, Pfizer/Astellas, and

Roche; drug provision for patients from Janssen; and travel/accommodation/expenses from Roche. Dr Huddart reports a leadership role at Cancer Clinic London LLP; consulting/advisory roles for Bayer, BioNTech, Gilead Sciences, Janssen Oncology, Merck Sharp & Dohme, Merck KGA, Nektar, and Roche; speakers' bureau for Bristol-Myers Squibb Foundation and Pfizer; research funding to his institution from Astellas Pharma, Basilea, Bristol-Myers Squibb, Immunomedics, Janssen, Merck Sharp & Dohme, Nektar, and Roche; royalties for drug discovery to his institution from Janssen; and travel/accommodation/expenses from Nektar and Roche/Genentech. Ms Kandula and Dr Skamnioti are Roche employees and shareholders. Dr Merseburger reports honoraria from Astellas Pharma, Bristol-Myers Squibb, Eisai, Ipsen, Janssen-Cilag, Novartis, Pfizer, Roche, and Takeda; consulting/advisory roles for Astellas Pharma, Bristol-Myers Squibb, Clovis Oncology, Ipsen, Janssen-Cilag, MSD Oncology, and Takeda; speakers' bureau for Ipsen; research funding to his institution from AstraZeneca, Bristol-Myers Squibb, Clovis Oncology, Janssen-Cilag, and Novartis; and travel/accommodation/expenses from Astellas Pharma, Ipsen, and Janssen-Cilag. The remaining authors report no disclosures.

Funding/Support and role of the sponsor: This trial was sponsored and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland. Medical writing assistance for this manuscript was provided by Jennifer Kelly, MA (Medi-Kelsey Ltd, Ashbourne, UK), funded by F. Hoffmann-La Roche Ltd. The sponsor was involved in the design and conduct of the study; data collection, management, analysis, and interpretation; and preparation, review, and approval of the manuscript.

Data sharing statement: Qualified researchers may request access to individual patient-level clinical data through a data request platform. At the time of writing, this request platform is Vivli (<https://vivli.org/ourmember/roche/>). For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see https://go.roche.com/data_sharing. Anonymized records for individual

patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient re-identification.

Acknowledgments

The authors would like to thank the patients participating in the trial and their families, the investigators and staff at participating centers, the independent Data Monitoring Committee (Maria De Santis [Chair], Jack Cuzick, Anja Lorch, and Arnulf Stenzl), Peiqing Yu, Kate Madden-Raja, and other members of the Core Study Management team at F. Hoffmann-La Roche Ltd. This trial was sponsored and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland.

Take home message

SAUL assessed atezolizumab in a broad population of 1004 patients with pretreated urinary tract carcinoma, including understudied populations of patients with complex comorbidities. Long-term safety and efficacy results (55 months' median follow-up) support the use of atezolizumab in pretreated UTC.

References

- [1] Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet*. 2016;387:1909-20.
- [2] Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. *Lancet*. 2017;389:67-76.
- [3] Powles T, Durán I, van der Heijden MS, Loriot Y, Vogelzang NJ, De Giorgi U, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. *Lancet*. 2018;391:748-57.
- [4] van der Heijden MS, Loriot Y, Durán I, Ravaud A, Retz M, Vogelzang NJ, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma: A long-term overall survival and safety update from the phase 3 IMvigor211 clinical trial. *Eur Urol*. 2021;80:7-11.
- [5] GmbH RR. 2023.
- [6] Fernandez R. EBANO study: Clinical characteristics, treatment patterns and survival results in patients with locally advanced/metastatic urothelial carcinoma (la/mUC) in northern Spain. European Society of Medical Oncology. Madrid, Spain: *Ann Oncol*; 2023. p. Abstract 2382P.
- [7] Dash A, Galsky MD, Vickers AJ, Serio AM, Koppie TM, Dalbagni G, et al. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. *Cancer*. 2006;107:506-13.
- [8] Balducci L. Evidence-based management of cancer in the elderly. *Cancer Control*. 2000;7:368-76.
- [9] Sternberg CN, Loriot Y, James N, Choy E, Castellano D, Lopez-Rios F, et al. Primary results from SAUL, a multinational single-arm safety study of atezolizumab therapy for locally advanced or metastatic urothelial or nonurothelial carcinoma of the urinary tract. *Eur Urol*. 2019;76:73-81.
- [10] Merseburger AS, Castellano D, Powles T, Loriot Y, Retz M, Voortman J, et al. Safety and efficacy of atezolizumab in understudied populations with pretreated urinary tract carcinoma: Subgroup analyses of the SAUL study in real-world practice. *J Urol*. 2021;206:240-51.
- [11] Loriot Y, Sternberg CN, Castellano D, Oosting SF, Dumez H, Huddart R, et al. Safety and efficacy of atezolizumab in patients with autoimmune disease: Subgroup analysis of the SAUL study in locally advanced/metastatic urinary tract carcinoma. *Eur J Cancer*. 2020;138:202-11.
- [12] Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med*. 2017;376:1015-26.
- [13] Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol*. 1998;16:139-44.
- [14] Ohyama C, Kojima T, Kondo T, Naya Y, Inoue T, Tomita Y, et al. Nivolumab in patients with unresectable locally advanced or metastatic urothelial carcinoma: CheckMate 275 2-year global and Japanese patient population analyses. *Int J Clin Oncol*. 2019;24:1089-98.

- [15] Balar AV, Castellano DE, Grivas P, Vaughn DJ, Powles T, Vuky J, et al. Efficacy and safety of pembrolizumab in metastatic urothelial carcinoma: results from KEYNOTE-045 and KEYNOTE-052 after up to 5 years of follow-up. *Ann Oncol*. 2023;34:289-99.
- [16] Odagiri N, Tamori A, Kotani K, Motoyama H, Kawamura E, Hagihara A, et al. A case of hepatocellular carcinoma with "pseudoprogression" followed by complete response to atezolizumab plus bevacizumab. *Clin J Gastroenterol*. 2023;16:392-6.
- [17] Nakashima K, Demura Y, Sato M, Fujii Y, Igarashi K, Ishizuka T. Successful re-administration of atezolizumab for a non-small-cell lung cancer patient after cardiac tamponade development as a manifestation of pseudo-progression induced by combination treatment with atezolizumab and cytotoxic chemotherapy. *Intern Med*. 2021;60:3009-13.
- [18] Won SE, Park HJ, Byun S, Pyo J, Kim JH, Choi CM, et al. Impact of pseudoprogression and treatment beyond progression on outcome in patients with non-small cell lung cancer treated with immune checkpoint inhibitors. *Oncoimmunology*. 2020;9:1776058.
- [19] Molinero L, Li Y, Chang CW, Maund S, Berg M, Harrison J, et al. Tumor immune microenvironment and genomic evolution in a patient with metastatic triple negative breast cancer and a complete response to atezolizumab. *J Immunother Cancer*. 2019;7:274.
- [20] Pond GR, Agarwal A, Ornstein M, Garcia J, Gupta R, Grivas P, et al. Clinical outcomes of platinum-ineligible patients with advanced urothelial carcinoma treated with first-line PD1/L1 inhibitors. *Clin Genitourin Cancer*. 2021;19:425-33.
- [21] Kita Y, Ito K, Kanda S, Joraku A, Yamaguchi R, Shimizu Y, et al. Tolerability and treatment outcome of pembrolizumab in patients with advanced urothelial carcinoma and severe renal dysfunction. *Urol Oncol*. 2022;40:410.e11-.e18.
- [22] Morgans AK, Galsky MD, Wright P, Hepp Z, Chang N, Willmon CL, et al. Real-world treatment patterns and clinical outcomes with first-line therapy in patients with locally advanced/metastatic urothelial carcinoma by cisplatin-eligibility. *Urol Oncol*. 2023;41:357.e11-.e21.
- [23] Sonpavde GP, Sternberg CN, Loriot Y, Marabelle A, Lee JL, Fléchon A, et al. Primary results of STRONG: An open-label, multicenter, phase 3b study of fixed-dose durvalumab monotherapy in previously treated patients with urinary tract carcinoma. *Eur J Cancer*. 2022;163:55-65.
- [24] Szabados B, Ponz-Sarvisé M, Machado R, Saldana D, Kadel EE, Banchereau R, et al. Clinico-genomic characterization of patients with metastatic urothelial carcinoma in real-world practice identifies a novel bladder immune performance index (BIPI). *Clin Cancer Res*. 2022;28:4083-91.

Figure Legend

Fig. 1 – Long-term efficacy. (A) OS in the ITT population, (B) DoR and (C) OS in subgroups of special interest.

CNS = central nervous system; CrCl = creatinine clearance; DoR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; IC2/3 = PD-L1 expression on $\geq 5\%$ of tumor-infiltrating immune cells; ITT = intention-to-treat; OS = overall survival; PD-L1 = programmed death-ligand 1.

Table 1 – Overview of safety overall and in subgroups of special interest (safety population, *N* = 997)

Parameter	All treated patients (<i>N</i> = 997)	Auto-immune disease (<i>N</i> = 36)	Concomitant steroids (<i>N</i> = 55)	CrCl <30 mL/min (<i>N</i> = 46)	ECOG PS 2 (<i>N</i> = 100)	CNS metastases (<i>N</i> = 14)	PD-L1 IC2/3 (<i>N</i> = 264)	0 prior treatment lines (<i>N</i> = 360)
Median atezolizumab duration, months (range)	2.8 (0–62.1)	5.7 (0–55.2)	1.4 (0–62.1)	3.0 (0–57.3)	0.7 (0–42.5)	1.4 (0–18.6)	3.7 (0–58.5)	2.3 (0–59.7)
Any grade AE, <i>N</i> (%)	900 (90)	33 (92)	50 (91)	40 (87)	77 (77)	11 (79)	243 (92)	328 (91)
Grade ≥3	507 (51)	21 (58)	33 (60)	23 (50)	55 (55)	6 (43)	143 (54)	190 (53)
Grade 5	50 (5)	4 (11)	4 (7)	5 (11)	7 (7)	0	13 (5)	11 (3)
Treatment-related AE, <i>N</i> (%)	562 (56)	26 (72)	33 (60)	21 (46)	36 (36)	6 (43)	168 (64)	203 (56)
Grade ≥3	155 (16)	11 (31)	8 (15)	4 (9)	14 (14)	2 (14)	52 (20)	56 (16)
Grade 5	8 (1)	0	0	0	3 (3)	0	2 (1)	2 (1)

AE of special interest, <i>N</i> (%)	525 (53)	21 (58)	27 (49)	23 (50)	40 (40)	6 (43)	168 (64)	198 (55)
Grade ≥3	156 (16)	7 (19)	9 (16)	7 (15)	11 (11)	0	56 (21)	57 (16)
AE leading to treatment discontinuation, <i>N</i> (%)	76 (8)	3 (8) ^a	3 (5) ^b	5 (11) ^c	3 (3) ^d	0	24 (9)	31 (9)

AE = adverse event; CrCl = creatinine clearance; CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance status; IC2/3 = PD-L1 expression on ≥5% of tumor-infiltrating immune cells; PD-L1 = programmed death-ligand 1.

AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. PD-L1 status was assessed on immune cells using the VENTANA SP142 assay, Ventana Medical Systems, Oro Valley, AZ, USA.

^a One case each of grade 4 sarcoidosis (considered related to atezolizumab and concurrent illness; recovered/resolved), grade 2 alkaline phosphatase increased (considered related to atezolizumab; not recovered/resolved) with grade 1 alanine aminotransferase increased (considered related to atezolizumab; recovered/resolved), and grade 2 psoriasis (considered related to atezolizumab; not recovered/resolved).

^b One case each of grade 4 worsening to grade 5 septic shock (considered unrelated to atezolizumab, related to other cause), grade 3 pneumonitis (considered related to treatment; recovered/resolved), and grade 2 arthralgia (considered related to atezolizumab; recovered/resolved).

^c One case each of grade 2 hepatic enzyme increased (considered related to atezolizumab; recovered/resolved), grade 3 cerebral atrophy (considered unrelated to atezolizumab, related to disease; not recovered/resolved), grade 1 pruritus (considered related to atezolizumab; not recovered/resolved), grade 3 worsening to grade 5 urosepsis (considered unrelated to atezolizumab; related to concurrent illness), and grade 3

blood creatinine increased (considered unrelated to atezolizumab, related to disease; not recovered/resolved) with grade 3 anemia (considered unrelated to atezolizumab, related to disease; recovered/resolved).

^d One case each of grade 3 pneumonitis (considered related to atezolizumab; recovered/resolved), grade 3 worsening to grade 5 dyspnea (considered related to atezolizumab, disease, and other cause), grade 3 worsening to grade 5 drug-induced liver injury (considered related to atezolizumab and disease).

Data in bold highlight durations >2 months longer or <2 months shorter than in the overall population, and AE incidences >10 percentage points higher or lower than in the overall population.

Table 2 – Frequency, time to onset, and duration of selected adverse events of special interest (N = 997)

Adverse event of special interest ^a	Frequency, N (%)		Median (range) time to first onset, months		Median (95% CI) duration, months	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Immune-mediated colitis and non-infectious diarrhea	175 (18)	22 (2)	2.2 (0–57)	3.0 (0–47)	0.3 (0.3, 0.6)	0.6 (0.4, 1.1)
Immune-mediated colitis	17 (2)	10 (1)	2.9 (0–12)	3.0 (1–12)	0.8 (0.4, 1.2)	0.6 (0.3, 1.5)
Non-infectious diarrhea	165 (17)	12 (1)	2.1 (0–57)	3.1 (0–47)	0.3 (0.2, 0.6)	0.6 (0.4, 1.7)
Acute kidney injury	148 (15)	41 (4)	2.5 (0–49)	1.8 (0–44)	10.6 (2.2, NE)	1.4 (0.8, NE)
Immune-mediated hepatitis (diagnosis and laboratory abnormalities)	105 (11)	36 (4)	2.1 (0–57)	1.8 (0–37)	1.8 (1.1, 6.7)	1.6 (1.1, 4.9)
Immune-mediated hepatitis (diagnosis)	25 (3)	13 (1)	3.5 (0–35)	2.8 (0–35)	1.8 (1.1, 7.9)	1.6 (0.5, 4.7)
Immune-mediated hepatitis (laboratory abnormality)	89 (9)	28 (3)	1.4 (0–57)	1.3 (0–37)	1.6 (1.0, 7.2)	1.6 (1.0, NE)
Immune-mediated pneumonitis	37 (4)	10 (1)	8.2 (0–45)	7.1 (0–27)	1.7 (1.1, 2.7)	1.4 (0.4, 3.1)
Immune-mediated rash	135 (14)	16 (2)	3.5 (0–57)	7.0 (0–46)	1.6 (1.1, 2.2)	2.4 (1.1, 7.8)
Immune-mediated hypothyroidism	91 (9)	1 (<1)	3.4 (0–56)	4.2 (4–4)	NE (NE, NE)	NE (NE, NE)

Immune-mediated hyperthyroidism	47 (5)	0	1.4 (0–20)	–	2.1 (1.5, 3.7)	–
Infusion-related reactions	19 (2)	2 (<1)	0.7 (0–13)	8.1 (2–14)	0.0	0.0
Ischemic cerebrovascular conditions	11 (1)	3 (<1)	12.0 (0–43)	12.4 (2–21)	1.9 (0.2, NE)	0.2 (0.1, 2.0)
Immune-mediated nephritis	11 (1)	3 (<1)	20.3 (1–39)	0.7 (1–13)	3.5 (0.5, NE)	0.5 (0.3, NE)
Immune-mediated thyroiditis	11 (1)	0	1.4 (1–48)	–	NE (NE, NE)	–
Immune-mediated pancreatitis	9 (1)	5 (1)	11.8 (1–43)	10.5 (1–24)	1.4 (0.2, 2.1)	1.5 (0.2, NE)
Immune-mediated diabetes mellitus	7 (1)	3 (<1)	10.4 (2–26)	10.4 (4–20)	NE (NE, NE)	NE (NE, NE)
Immune-mediated hypophysitis	7 (1)	1 (<1)	2.5 (0–4)	2.7 (3–3)	1.1 (0.1, 2.7)	2.7
Immune-mediated pericardial disorders	7 (1)	3 (<1)	2.1 (0–18)	1.3 (0–2)	1.1 (0.5, NE)	0.5 (0.1, 0.5)

NE = not estimable.

^a Adverse events of special interest for atezolizumab were defined based on the company-defined categories current at the time of the analysis, which included additional adverse events since the primary analysis reflecting increased experience and surveillance over time.

Table 3 – Efficacy overall and in subgroups of special interest (ITT population, *N* = 1004)

Endpoint	All patients (<i>N</i> = 1004)	Auto- immune disease (<i>N</i> = 36)	Concomit ant steroids (<i>N</i> = 55)	CrCl <30 mL/min (<i>N</i> = 46)	ECOG PS 2 (<i>N</i> = 100)	CNS metastases (<i>N</i> = 14)	PD-L1 IC2/3 (<i>N</i> = 268)	0 prior Tx lines (<i>N</i> = 362)
Median OS, months (95% CI)	8.6 (7.8, 9.7)	8.5 (7.3, 11.7)	6.1 (3.1, 10.1)	5.7 (3.4, 11.0)	2.1 (1.5, 2.4)	3.7 (1.5, 7.0)	11.2 (8.8, 16.1)	8.6 (7.3, 10.4)
OS rate, % (95% CI)								
1-year	41 (37, 44)	33 (18, 49)	33 (21, 45)	25 (14, 39)	11 (6, 19)	19 (4, 44)	48 (42, 54)	41 (35, 46)
2-year	27 (24, 30)	21 (9, 36)	25 (14, 37)	23 (12, 36)	8 (3, 14)	0 (NE, NE)	34 (28, 40)	27 (22, 32)
3-year	21 (19, 24)	18 (7, 32)	19 (10, 31)	13 (5, 25)	6 (2, 13)	0 (NE, NE)	30 (24, 36)	21 (17, 26)

ORR, % (95% CI)	16 (14, 18)	19 (8, 36)	18 (9, 31)	17 (8, 31)	5 (2, 11)	0 (0, 23)	24 (19, 29)	16 (12, 20)
Median DoR, months (95% CI)	27.8 (18.9, 43.3)	11.1 (4.4, 45.5)	10.7 (4.2, 42.0)	20.7 (4.2, NE)	6.4 (4.1, 41.2)	–	35.2 (15.2, NE)	35.4 (13.9, NE)

CrCl = creatinine clearance; CNS = central nervous system; DCR = disease control rate (complete or partial response, or stable disease for ≥4 weeks); DoR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; IC2/3 = PD-L1 expression on ≥5% of tumor-infiltrating immune cells; ITT = intention-to-treat; NE = not estimable; ORR = overall response rate; OS = overall survival; PD-L1 programmed death-ligand 1; Tx = treatment.

Data in bold highlight durations >2 months longer or <2 months shorter than in the overall population, and OS rates and ORRs >5 percentage points higher or lower than in the overall population.

Table 4 – Subsequent therapy

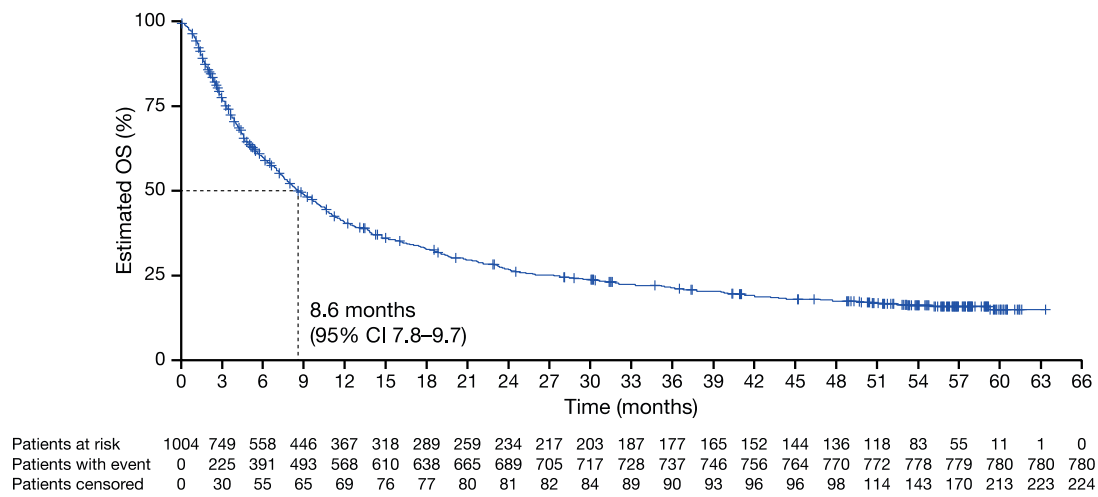
Treatment, <i>N</i> (%)	All treated patients (<i>N</i> = 997)	Patients with CR/PR and OS >4 years (<i>N</i> = 90)	Patients with OS >4 years (<i>N</i> = 136)
Any subsequent anticancer therapy ^a	224 (23)	13 (14)	30 (22)
Chemotherapy	181 (18)	7 (8)	20 (15)
Immunotherapy	23 (2)	4 (4)	9 (7)
Atezolizumab	6 (1)	3 (3)	4 (3)

CR/PR = complete or partial response; OS = overall survival.

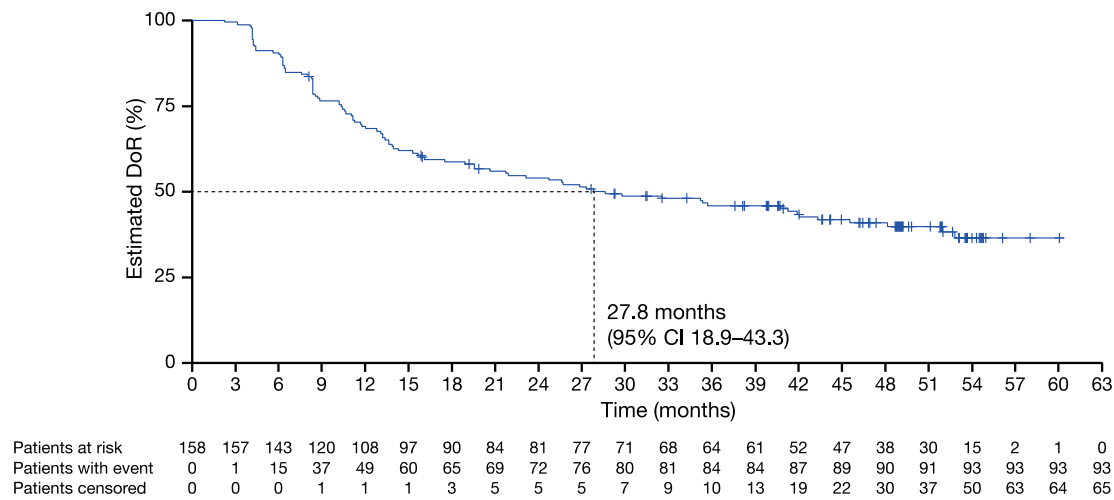
^a Including radiotherapy.

Figure 1.

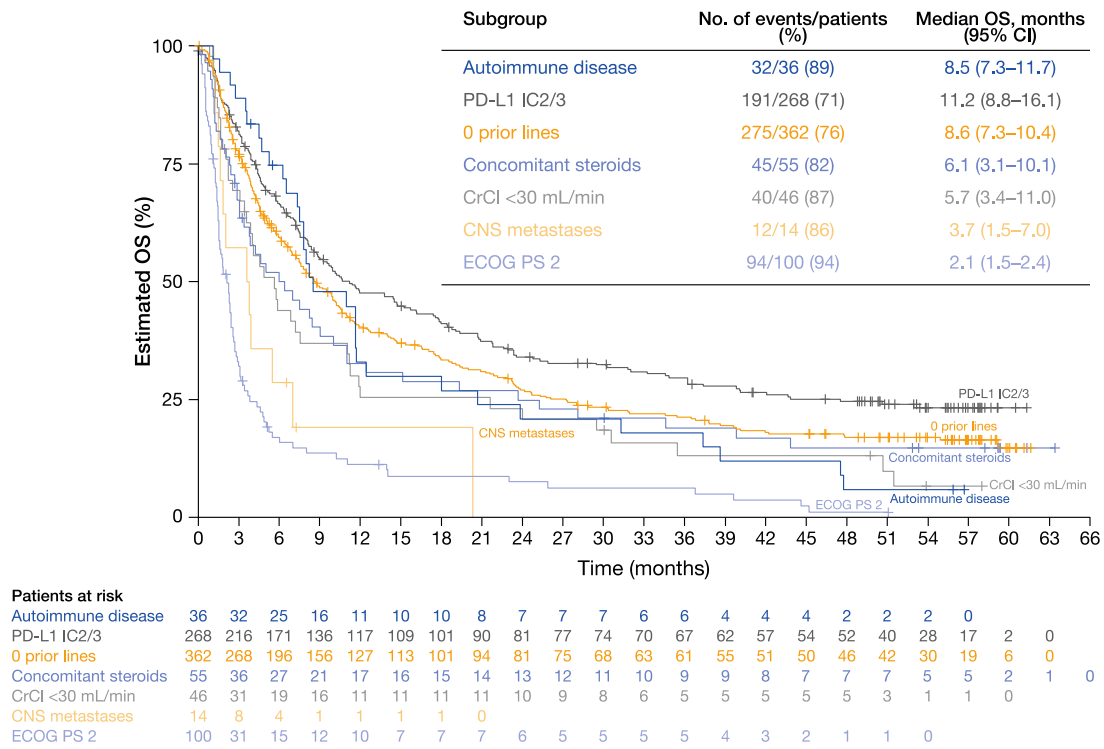
A



B



C



Supplementary Table 1 – Baseline characteristics overall and in patients with exceptional long-term outcomes

Characteristic		All treated patients (<i>N</i> = 997)	Patients with CR/PR and OS >2 years (<i>N</i> = 132)	Patients with OS >4 years (<i>N</i> = 136)	Patients treated with atezolizumab for >4 years (<i>N</i> = 68)
Median age, years (range)		68 (34–93)	68 (44–85)	67 (44–83)	67 (45–83)
Age ≥80 years, <i>N</i> (%)		78 (8)	6 (5)	7 (5)	1 (1)
Male, <i>N</i> (%)		772 (77)	106 (80)	109 (80)	57 (84)
Race, <i>N</i> (%)	White	920 (92)	125 (95)	128 (94)	64 (94)
	Asian	30 (3)	5 (4)	4 (3)	2 (3)
	Other	15 (2) ^a	0	0	0
	Unknown	32 (3)	2 (2)	4 (3)	2 (3)
	0	426 (43)	74 (56)	75 (55)	39 (57)
	1	471 (47)	54 (41)	60 (44)	29 (43)

Characteristic		All treated patients (<i>N</i> = 997)	Patients with CR/PR and OS >2 years (<i>N</i> = 132)	Patients with OS >4 years (<i>N</i> = 136)	Patients treated with atezolizumab for >4 years (<i>N</i> = 68)
ECOG PS at screening, <i>N</i> (%)	2	100 (10)	4 (3)	1 (1)	0
Smoking history, <i>N</i> (%)	Current smoker	167 (17)	20 (15)	19 (14)	7 (10)
	Former smoker	503 (50)	70 (53)	73 (54)	35 (51)
	Never smoked	327 (33)	42 (32)	44 (32)	26 (38)
No. of prior treatment lines for	0	360 (36)	47 (36)	46 (34)	24 (35)
	1	562 (56)	75 (57)	80 (59)	38 (56)
	2	54 (5)	6 (5)	7 (5)	4 (6)

Characteristic		All treated patients (<i>N</i> = 997)	Patients with CR/PR and OS >2 years (<i>N</i> = 132)	Patients with OS >4 years (<i>N</i> = 136)	Patients treated with atezolizumab for >4 years (<i>N</i> = 68)
metastatic disease, <i>N</i> (%)	3	20 (2)	3 (2)	2 (1)	1 (1)
	Missing	1 (<1)	1 (1)	1 (1)	1 (1)
Prior platinum, <i>N</i> (%)		972 (97)	127 (96)	132 (97)	65 (96)
PD-L1 expression score, <i>N</i> (%)	IC0/1	664 (67)	68 (52)	73 (54)	35 (51)
	IC2/3	264 (26)	54 (41)	52 (38)	26 (38)
	Missing	69 (7)	10 (8)	11 (8)	7 (10)
Urothelial histology, <i>N</i> (%)		950 (95)	129 (98)	134 (99)	66 (97)

Characteristic		All treated patients (<i>N</i> = 997)	Patients with CR/PR and OS >2 years (<i>N</i> = 132)	Patients with OS >4 years (<i>N</i> = 136)	Patients treated with atezolizumab for >4 years (<i>N</i> = 68)
Tumor location, <i>N</i> (%)	Bladder	743 (75)	105 (80)	96 (71)	47 (69)
	Renal pelvis	123 (12)	13 (10)	18 (13)	8 (12)
	Ureter	96 (10)	12 (9)	19 (14)	11 (16)
	Urethra	11 (1)	1 (1)	2 (1)	1 (1)
	Other	24 (2)	1 (1)	1 (1)	1 (1)
Visceral metastases, <i>N</i> (%)		374 (38)	29 (22)	26 (19)	12 (18)

CR/PR = complete or partial response; ECOG PS = Eastern Cooperative Oncology Group performance status; IC 0/1 = PD-L1 expression on <5% of tumor-infiltrating immune cells; IC2/3 = PD-L1 expression on ≥5% of tumor-infiltrating immune cells; OS = overall survival; PD-L1 = programmed death-ligand 1.

^a American Indian/Alaska Native (*N* = 11), Black or African American (*N* = 4).

Supplementary Table 2 – Details of treatment-related fatal adverse events (N = 8)

Preferred term	Age, years	Sex	ECOG PS	Prior chemotherapy	Pre-existing conditions	Smoking history	Onset day	Initial grade	Other suspected causes	Action taken with study drug	Study day of death
Dyspnea	77	Male	1	Carboplatin + gemcitabine (3 cycles) completed 27 days before first study dose		None	2	1	Other	Drug interrupted	24
Intestinal perforation	63	Female	1	Cisplatin + etoposide (4 cycles) with radiotherapy completed 176 days before first study dose	Hypertension, atrial fibrillation, increased liver enzymes	Past	5	4		Drug withdrawn	6
Respiratory failure	69	Male	2	Neoadjuvant gemcitabine + cisplatin (4 cycles)	Hypertension, dyspnea secondary to	Past	7	5	Disease under study	N/A	7

Preferred term	Age, years	Sex	ECOG PS	Prior chemotherapy	Pre-existing conditions	Smoking history	Onset day	Initial grade	Other suspected causes	Action taken with study drug	Study day of death
				completed 238 days before first study dose	lung metastases, asthenia						
Drug-induced liver injury	64	Male	2	Cisplatin + gemcitabine (6 cycles) completed 422 days before first study dose		None	16	3	Disease under study	Drug withdrawn	30
Dyspnea	77	Male	2	Carboplatin + gemcitabine (4 cycles) completed 112 days before first study dose	Hypertension, dyslipidemia, diabetes mellitus, myocardial	Past	32	3	Disease under study, other	Drug withdrawn	34

Preferred term	Age, years	Sex	ECOG PS	Prior chemotherapy	Pre-existing conditions	Smoking history	Onset day	Initial grade	Other suspected causes	Action taken with study drug	Study day of death
					ischemia, aortic stenosis						
Chronic kidney disease	74	Male	1	Carboplatin + gemcitabine (5 cycles) completed 423 days before first study dose	Chronic kidney disease, type 2 diabetes mellitus, anemia, hypertension	Past	40 (first episodes) and 75	3	Concurrent illness	Drug withdrawn	106
Colitis	63	Male	0	Adjuvant gemcitabine + cisplatin (3 cycles) completed 57 days before first study dose (after	Dyslipidemia, thromboangiitis obliterans, hyperuricemia, emphysema	Past	141	3	None	N/A	159

Preferred term	Age, years	Sex	ECOG PS	Prior chemotherapy	Pre-existing conditions	Smoking history	Onset day	Initial grade	Other suspected causes	Action taken with study drug	Study day of death
				curative radical cystectomy)							
Pericardial hemorrhage	67	Male	0	Gemcitabine + cisplatin (6 cycles) completed 197 days before first study dose		Current	244	3	None	N/A	247

AESI = adverse event of special interest; ECOG PS = Eastern Cooperative Oncology Group performance status; N/A = not applicable.

Supplementary Table 3 – Baseline characteristics according to creatinine clearance

Characteristic		Creatinine clearance, mL/min		
		15–<30 (<i>N</i> = 46)	30–<60 (<i>N</i> = 420)	≥60 (<i>N</i> = 529)
Median age, years (range)		75 (48–92)	72 (40–93)	63 (34–86)
Sex, <i>N</i> (%)	Male	31 (67)	308 (73)	432 (82)
	Female	15 (33)	112 (27)	97 (18)
Visceral metastases, <i>N</i> (%)		18 (39)	161 (38)	194 (37)
ECOG PS, <i>N</i> (%)	0	9 (20)	167 (40)	249 (47)
	1	35 (76)	204 (49)	232 (44)
	2	2 (4)	49 (12)	48 (9)
Prior lines for metastatic	0	12 (26)	137 (33)	210 (40)
urinary tract carcinoma, <i>N</i> (%)	1	28 (61)	250 (60)	283 (54)
	2	4 (9)	25 (6)	25 (5)
	3	2 (4)	8 (2)	10 (2)
	Missing	0	0	1 (<1)

Characteristic		Creatinine clearance, mL/min		
		15–<30 (<i>N</i> = 46)	30–<60 (<i>N</i> = 420)	≥60 (<i>N</i> = 529)
Prior platinum, <i>N</i> (%)		43 (93)	410 (98)	517 (98)
	Gemcitabine + carboplatin	26 (57)	216 (51)	173 (33)
	Gemcitabine + cisplatin	14 (30)	187 (45)	328 (62)
	MVAC	0	6 (1)	29 (5)
	MVEC	0	1 (<1)	0
	MVC	0	2 (<1)	0
Smoking history, <i>N</i> (%)	Current	5 (11)	73 (17)	89 (17)
	Former	19 (41)	217 (52)	266 (50)
	Never	22 (48)	130 (31)	174 (33)
PD-L1 status, <i>N</i> (%)	IC0	9 (20)	103 (25)	130 (25)
	IC1	22 (48)	173 (41)	226 (43)
	IC2/3	10 (22)	115 (27)	138 (26)
	Missing	5 (11)	29 (7)	35 (7)

ECOG PS = Eastern Cooperative Oncology Group performance status; IC0 = PD-L1 expression on <1% of tumor-infiltrating immune cells; IC1 = PD-L1 expression on $\geq 1\%$ but <5% of tumor-infiltrating immune cells; IC2/3 = PD-L1 expression on $\geq 5\%$ of tumor-infiltrating immune cells; MVAC = methotrexate + vinblastine + cisplatin + doxorubicin; MVEC = methotrexate + vinblastine + cisplatin + epirubicin; MVC, methotrexate + vinblastine + cisplatin; PD-L1 = programmed death-ligand 1.

Supplementary Table 4 – Overview of safety according to creatinine clearance

Parameter	Creatinine clearance, mL/min		
	15–<30 (<i>N</i> = 46)	30–<60 (<i>N</i> = 420)	≥60 (<i>N</i> = 529)
Median atezolizumab treatment duration, months (range)	3.0 (0.0–57.3)	2.8 (0.0–62.1)	2.8 (0.0–60.8)
Any grade AE, <i>N</i> (%)	40 (87)	373 (89)	485 (92)
Grade 3/4	22 (48)	209 (50)	255 (48)
Grade 5	5 (11)	23 (5)	22 (4)
Treatment-related AEs, <i>N</i> (%)	21 (46)	235 (56)	305 (58)
Grade ≥3	4 (9) ^a	68 (16)	83 (16)
Grade 5	0	4 (1)	4 (1)
AE of special interest, <i>N</i> (%)	23 (50)	221 (53)	279 (53)
Grade ≥3	7 (15)	69 (16)	79 (15)

AE leading to treatment discontinuation, <i>N</i>	5 (11) ^b	29 (7)	42 (8)
(%)			

AE = adverse event.

^a One case each of pruritus, musculoskeletal pain, and hypertension, and one patient with drug-induced liver injury, pruritus, and hypertension (all grade 3).

^b One case each of hepatic enzyme increased (two episodes), cerebral atrophy, pruritus, urosepsis, and blood creatinine increased with anemia.

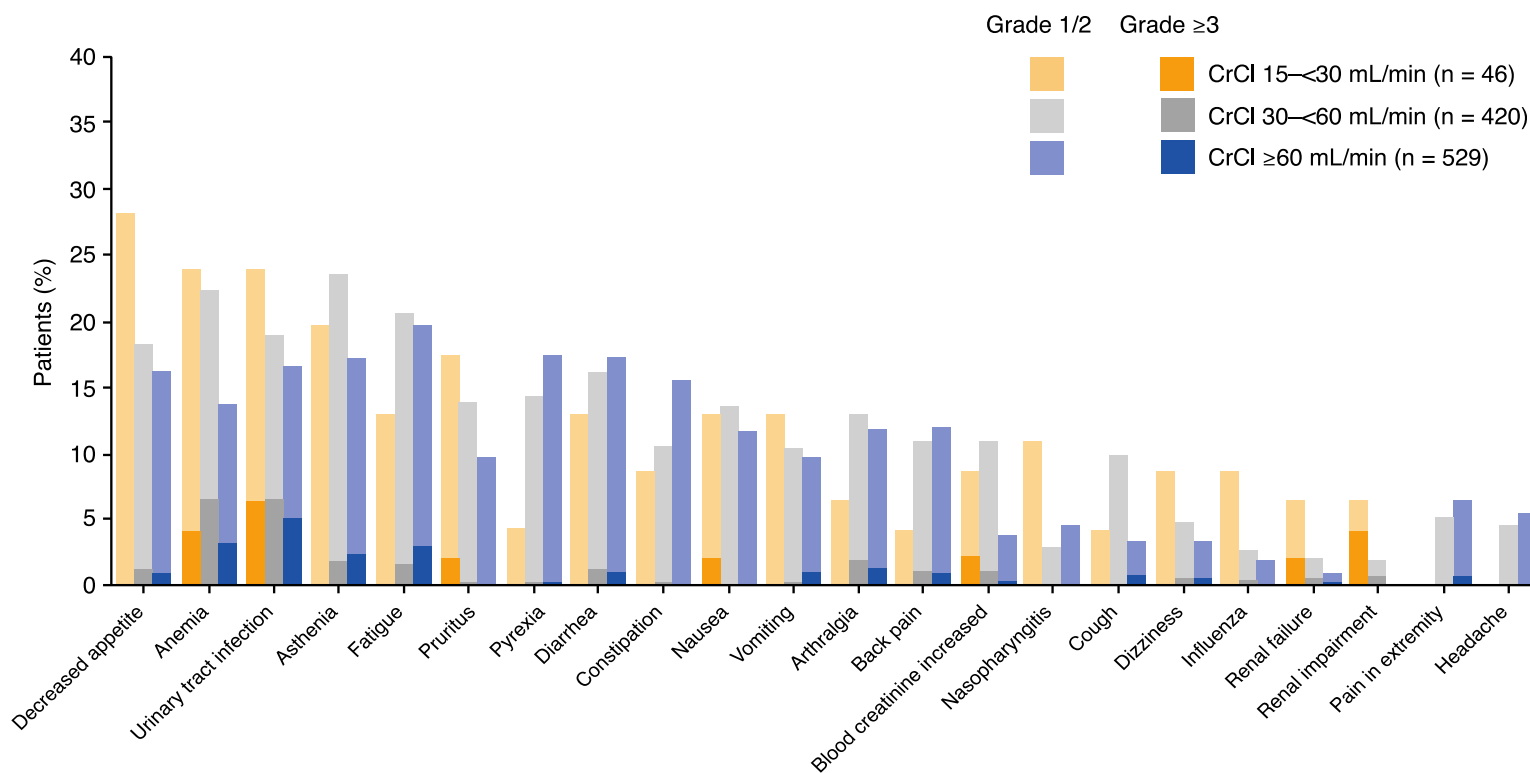
Supplementary Table 5 – Response rate according to creatinine clearance

Response, <i>N</i> (%) [95% CI]	Creatinine clearance, mL/min		
	15–<30 (<i>N</i> = 46)	30–<60 (<i>N</i> = 420)	≥60 (<i>N</i> = 529)
Overall response rate	8 (17) [8, 31%]	74 (18) [14, 22%]	76 (14) [12, 18%]
Complete response	0	24 (6)	26 (5)
Partial response	8 (17)	50 (12)	50 (9)
Stable disease	13 (28)	107 (25)	122 (23)
Disease control rate	21 (46) [31, 61%]	181 (43) [38, 48%]	198 (37) [33, 42%]
Disease progression	11 (24)	153 (36)	232 (44)
Missing	14 (30)	86 (20)	99 (19)

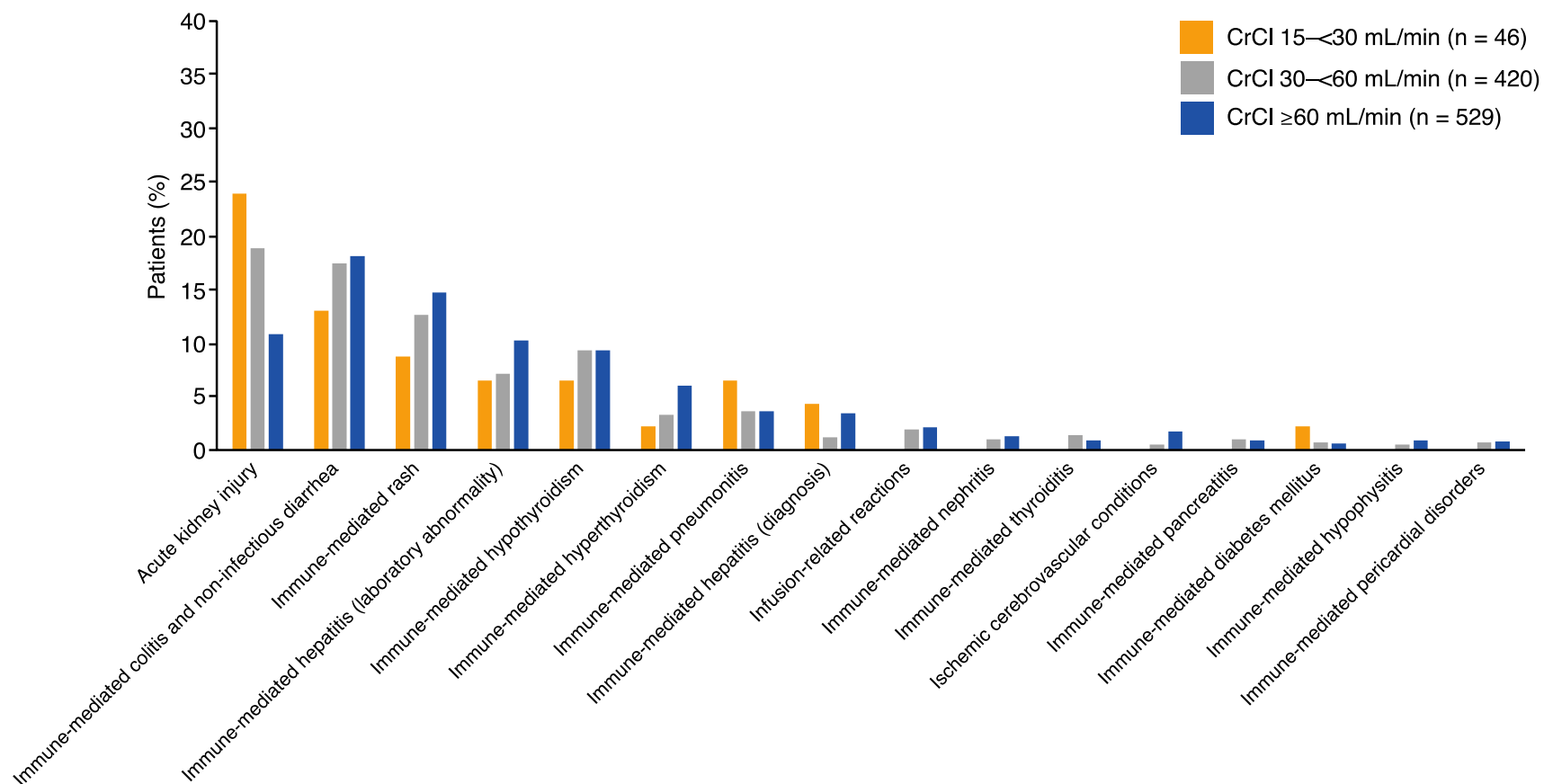
Supplementary Figure 1 – Safety according to creatinine clearance at baseline.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CrCl = creatinine clearance; GGT = gammaglutamyl transferase.

(A) Most common adverse events (occurring in >10% of patients overall or with >5% absolute difference between subgroups)

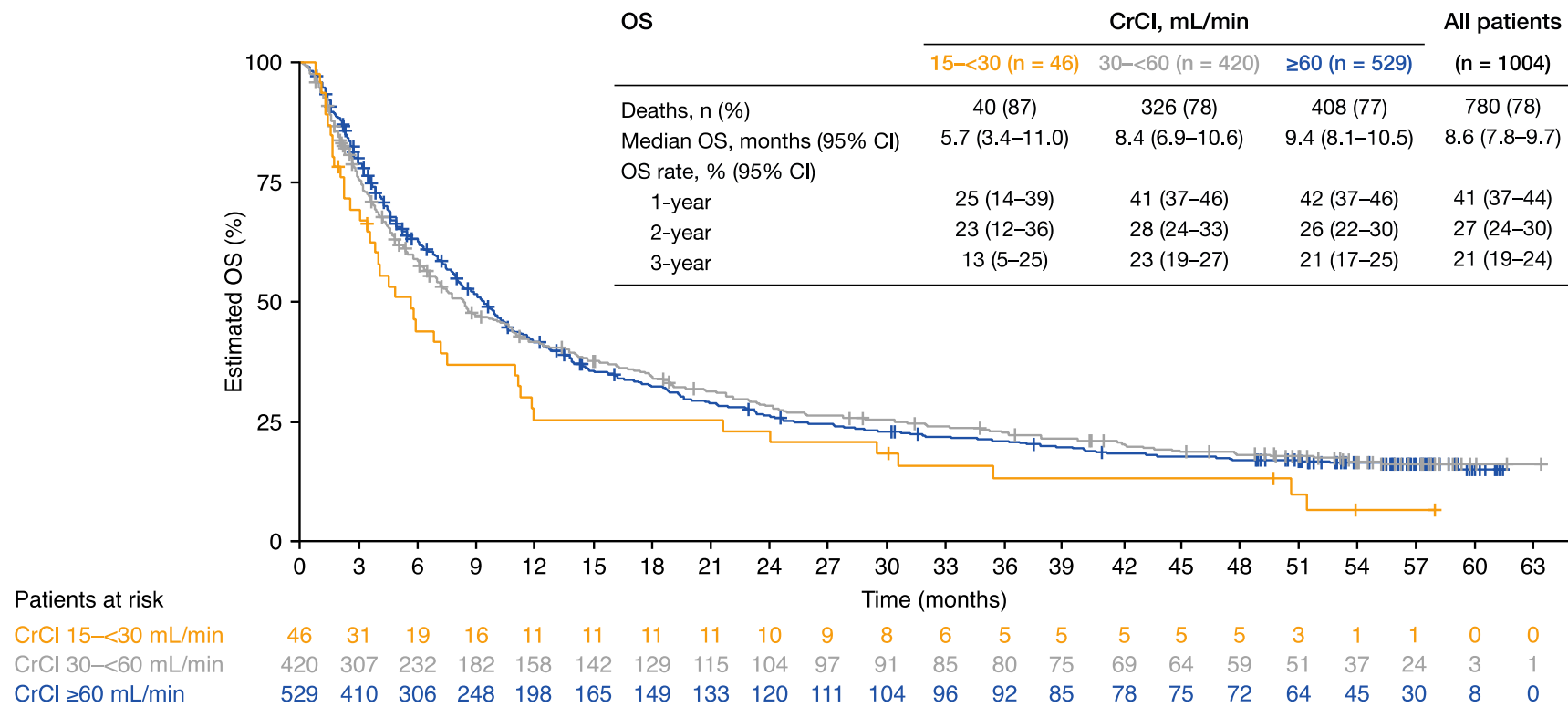


(B) Most common adverse events of special interest (occurring in >5 patients overall)



Supplementary Figure 2. OS according to creatinine clearance at baseline.

CrCl = creatinine clearance; OS = overall survival.



Supplementary Figure 3 – EORTC QLQ-C30 GHS/QoL change from baseline (95% CI) (ITT population).

Timepoints where <10 patients filled questionnaires are not shown.

C = cycle; D = day; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30;

GHS/QoL = global health status/quality of life; ITT = intention-to-treat.

