## Title

Atezolizumab monotherapy for metastatic urothelial carcinoma: final analysis from the phase II IMvigor210 trial.



## Journal

ESMO Open, 9(12)

## Authors

Rosenberg, J
Galsky, M
Powles, T
et al.

## Publication Date

2024-12-01

## DOI

10.1016/j.esmoop.2024.103972

Peer reviewed

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

ORIGINAL ARTICLE

# Atezolizumab monotherapy for metastatic urothelial carcinoma: final analysis from the phase II IMvigor210 trial

J. E. Rosenberg[1*], M. D. Galsky[2], T. Powles[3], D. P. Petrylak[4], J. Bellmunt[5], Y. Loriot[6], A. Necchi[7], J. Hoffman-Censits[8], J. L. Perez-Gracia[9], M. S. van der Heijden[10], R. Dreicer[11], I. Durán[12†], D. Castellano[13], A. Drakaki[14], M. Retz[15], S. S. Sridhar[16], P. Grivas[17‡], E. Y. Yu[18], P. H. O'Donnell[19], H. A. Burris[20], S. Mariathasan[21], Y. Shi[21], E. Goluboff[21] & D. Bajorin[1]

[1]Memorial Sloan Kettering Cancer Center, New York; [2]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, USA; [3]Barts Cancer Institute, Queen Mary University of London ECMC, Barts Health, London, UK; [4]Yale Cancer Center, New Haven; [5]Dana-Farber Cancer Institute, PSMAR-IMIM Lab, Harvard Medical School, Boston, USA; [6]Université Paris-Sud, Université Paris-Saclay, Gustave Roussy, Villejuif, France; [7]Vita-Salute San Raffaele University and IRCCS San Raffaele Hospital, Milan, Italy; [8]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, USA; [9]Department of Oncology, Clinica Universidad de Navarra, Pamplona, Spain; [10]Netherlands Cancer Institute, Amsterdam, Netherlands; [11]University of Virginia Cancer Center, Charlottesville, USA; [12]Hospital Universitario Virgen del Rocio, Seville; [13]Hospital 12 de Octubre, Madrid, Spain; [14]University of California Los Angeles, Los Angeles, USA; [15]Technical University Munich, Munich, Germany; [16]Department of Medical Oncology and Hematology, Princess Margaret Cancer Center, Toronto, Canada; [17]Taussig Cancer Institute, Cleveland Clinic, Cleveland; [18]University of Washington and Fred Hutchinson Cancer Center, Seattle; [19]University of Chicago, Chicago; [20]Sarah Cannon Research Institute, Nashville; [21]Genentech, Inc., South San Francisco, CA, USA

Available online xxx

**Background:** The IMvigor210 trial demonstrated clinical benefit and manageable toxicity with atezolizumab monotherapy [anti-programmed death-ligand 1 (PD-L1)] in patients with metastatic urothelial carcinoma (UC) in primary analyses. Final efficacy and safety results after long-term follow-up are reported.

**Patients and methods:** This phase II single-arm trial of atezolizumab monotherapy in patients with advanced UC included two cohorts: untreated patients ineligible for cisplatin-based chemotherapy (cohort 1; $n = 119$) and those previously treated with platinum-based chemotherapy (cohort 2; $n = 310$). Atezolizumab was administered i.v. (1200 mg every 21 days) until progression or unacceptable toxicity. Primary endpoints were independent review facility-assessed confirmed objective response rate (ORR) per RECIST 1.1 in cohort 1 and independent review facility-assessed ORR per RECIST 1.1 and investigator-assessed modified (m)RECIST in cohort 2. Overall survival (OS), efficacy by PD-L1 status, and safety were also assessed.

**Results:** At data cut-off (1 June 2023), the median survival follow-up was 96.4 months (range, 0.2-103.4 months) in cohort 1 and 46.2 months [0.2 (censored)-54.9 months] in cohort 2. In cohort 1, the ORR [95% confidence interval (CI)] was 23.5% (16.2% to 32.2%) in all patients and 28.1% (13.8% to 46.8%) in the PD-L1 tumor-infiltrating immune cell (IC)2/3 subgroup. Median OS (95% CI) was 16.3 months (10.4-24.5 months) overall and 12.3 months (6.0-49.8 months) in the PD-L1 IC2/3 subgroup. In cohort 2, the ORR (95% CI) was 16.5% (12.5% to 21.1%) per RECIST 1.1 and 19.7% (95% CI 15.4% to 24.6%) per mRECIST in all patients and 27.0% (18.6% to 36.8%) and 28.0% (19.5% to 37.9%), respectively, in the PD-L1 IC2/3 subgroup. Median OS (95% CI) was 7.9 months (6.7-9.3 months) in all patients and 11.9 months (9.0-22.8 months) in the IC2/3 subgroup. Treatment-related grade 3/4 adverse events occurred in 21.8% (cohort 1) and 18.7% (cohort 2); one treatment-related death occurred in cohort 1.

**Conclusions:** With long-term follow-up, atezolizumab monotherapy demonstrated clinically meaningful efficacy with durable responses in a subset of patients with metastatic UC; there were no new safety signals.

**Key words:** metastatic urothelial carcinoma, checkpoint inhibitor, long-term survival, PD-L1-high, cisplatin-ineligible, platinum-refractory

## INTRODUCTION

Historically, platinum-based chemotherapy was the mainstay treatment of urothelial carcinoma (UC), predominantly bladder cancer, which is estimated to cause >220 000 deaths globally.[1] Cisplatin- and carboplatin-containing regimens remain an important cornerstone of treatment, including for metastatic UC (mUC).[2,3] The introduction of anti-programmed death-ligand 1 (PD-L1)/programmed cell

*Correspondence to: Dr Jonathan E. Rosenberg, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA. Tel: +1-646-422-4461

E-mail: rosenbj1@mskcc.org (J. E. Rosenberg).

†Present address: Hospital Universitario Marques de Valdecilla, IDIVAL, Santander, Spain.

‡Present address: University of Washington and Fred Hutchinson Cancer Center, Seattle, WA, USA.

death protein 1 (PD-1) immune checkpoint inhibitors (CPIs), however, provided new monotherapy treatment options for patients with advanced UC who would otherwise have been ineligible for cisplatin or any platinum-based chemotherapy and resulted in improved duration of response (DOR) and quality of life for many patients.[2,3]

For eligible patients, CPI monotherapy is an approved treatment option for bacillus Calmette—Guerin (BCG)-unresponsive non-muscle-invasive bladder cancer, as adjuvant therapy in high-risk muscle-invasive UC after radical surgery, and for metastatic disease in the first-line (1L) (up front in platinum-ineligible patients or as switch maintenance in patients without progression on induction chemotherapy) and second-line and beyond (2L+) settings.[4-6] Combination therapy approaches of CPI plus enfortumab vedotin, an antibody—drug conjugate, or CPI plus cisplatin/gemcitabine chemotherapy have recently emerged as new 1L treatment options for patients with advanced UC.[7-9] The PD-L1-directed antibody atezolizumab demonstrated safety and clinical activity in the previously treated mUC cohort from a first-in-human phase I trial,[10,11] which led to its evaluation in the pivotal phase II IMvigor210 trial.

IMvigor210 was a single-arm trial of atezolizumab monotherapy for patients with mUC. The trial included two cohorts: patients ineligible for standard 1L cisplatin-based chemotherapy and those who were previously treated with platinum-based chemotherapy.[12,13] IMvigor210 cohort 1 demonstrated a higher objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors v1.1 (RECIST 1.1) in the PD-L1-high subgroup [tumor-infiltrating immune cells (IC)2/3] relative to a 10% benchmark (22%; non-significant $P = 0.07$) and in the IC1/2/3 and all-comer populations (19% each; not tested).[12,14] IMvigor210 cohort 2 met its co-primary ORR endpoints, demonstrating higher ORRs relative to the 10% benchmark in both PD-L1-expressing subgroups and all patients [ORRs of 17% (PD-L1 IC2/3), 18% (IC1/2/3), and 15% (all patients)].[13] Following the primary analyses, additional responses were seen over time in both cohorts as the data matured.[15] Here, we report the final efficacy and safety data from cohorts 1 and 2 of the IMvigor210 trial of atezolizumab in patients with mUC.

## METHODS

### Study design and patients

The global, single-arm, phase II IMvigor210 study (ClinicalTrials.gov ID: cohort 1, NCT02951767; cohort 2, NCT02108652) was conducted to evaluate the efficacy and safety of atezolizumab in patients with inoperable locally advanced or metastatic UC.[12,13] The study was conducted in accordance with the Declaration of Helsinki and International Conference of Harmonization Good Clinical Practice guidelines. The protocol[12] was approved by each study site's institutional review board or independent ethics committee. All patients provided written informed consent before study entry.

The study design and patient eligibility criteria have been previously described.[12,13] Briefly, eligible patients had UC of renal pelvis, ureters, bladder, or urethra; measurable disease per RECIST 1.1; and a tumor tissue sample for PD-L1 testing. Patients in cohort 1 had no previous treatment of mUC, although neoadjuvant or adjuvant platinum-based chemotherapy was allowed for patients with recurrence after 12 months of completing this treatment. Patients had to be ineligible for cisplatin-based chemotherapy based on one or more of the following criteria: glomerular filtration rate >30 to <60 ml/min, grade ≥2 hearing loss or peripheral neuropathy, or Eastern Cooperative Oncology Group performance status 2. Patients in cohort 2 had to have received prior platinum-based chemotherapy for inoperable locally advanced or metastatic UC or its recurrence, with progression during or after this treatment. Patients who received prior platinum-containing neoadjuvant or adjuvant chemotherapy and progressed within 12 months of such treatment were considered to be treated in the 2L setting.

### Treatment and assessments

In both cohorts, atezolizumab was given i.v. (1200 mg every 21 days) until investigator-assessed radiographic progression (cohort 1), loss of clinical benefit by the investigator (cohort 2), or unacceptable toxicity. Dose reductions were not permitted. Patients underwent tumor assessments at baseline, every 9 weeks for the first 12 months, and every 12 weeks thereafter. Tumor samples were prospectively assessed for PD-L1 expression at a central site (HistoGeneX, Brussels, Belgium) using the VENTANA SP142 immunohistochemistry assay. The PD-L1 status on tumor-infiltrating IC was defined as follows: IC2/3, PD-L1-stained immune cells covering ≥5% of the tumor area; IC1, ≥1% but <5%; IC0, <1%.[16]

### Study endpoints

In cohort 1, the primary endpoint was confirmed ORR per RECIST 1.1 [centrally reviewed by an independent review facility (IRF)]. In cohort 2, the co-primary endpoints were confirmed ORR per IRF-assessed RECIST 1.1 and per investigator-assessed modified (m)RECIST.[13] Key secondary endpoints included RECIST 1.1 ORR per investigator, DOR per IRF and per investigator, progression-free survival (PFS) per IRF and per investigator, overall survival (OS), and safety assessed per National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Exploratory analyses of DOR, PFS, and OS by PD-L1 status were carried out without statistical testing. IRF-assessed time to onset of RECIST 1.1 response (TTOR) was evaluated in a *post hoc* analysis.

### Statistical analysis

Details on sample size and statistical testing associated with the primary endpoints have been previously reported.[12,13] This exploratory analysis was carried out to evaluate the long-term consistency of efficacy and safety data with that of the earlier data, including the primary analyses.

ORR and corresponding 95% confidence intervals (CIs) were calculated using the Clopper—Pearson method. DOR [time from first response to disease progression (per IRF or investigator) or death due to any cause], PFS (time from first dose of atezolizumab to disease progression per IRF or investigator or death due to any cause), and OS (time from first dose of atezolizumab to death from any cause on study) were estimated by the Kaplan—Meier method. The 95% CIs for median durations were computed using the Brookmeyer—Crowley method, and those for OS estimated at 4 and 5 years using the Greenwood formula. TTOR was defined as the time from the date of the first dose of atezolizumab to the date of the first occurrence of a documented partial response (PR) or complete response (CR), whichever occurred first, per IRF and was analyzed in the same way as PFS. For DOR and PFS analyses, patients who had not had cancer progression or died at the time of analysis were censored at the last tumor assessment date. For PFS, patients with no post-baseline tumor assessment were censored at the time of first dose plus 1 day. For OS analyses, patients who were alive at the time of analysis were censored at the last study assessment date for on-study patients, or at the last date known to be alive for patients in follow-up.

## RESULTS

### *Patients and treatment*

In cohort 1, 167 patients were screened and 123 were enrolled from 9 June 2014 to 30 March 2015 (Figure 1). The last patient's last visit was 28 February 2023. In cohort 2, 494 patients were screened and 315 were enrolled from 13 May 2014 to 19 November 2014 (Figure 1). The last patient's last visit was 25 February 2019. Baseline characteristics were previously reported.[12,13] Briefly, in cohorts 1 (treated, $n = 119$) and 2 ($n = 310$), respectively, 80.7% and 77.7% of patients were male, 26.9% and 32.3% had PD-L1 IC2/3 status, and 71.4% and 75.8% had bladder (or urethra) cancer as their primary tumor site. In cohort 1, 69.7% were ineligible for cisplatin due to renal impairment, and in cohort 2, 81.0% had one or more prior systemic regimens in the inoperable/metastatic setting.

The median treatment duration was 3.4 months (range, 0-59.4 months) in cohort 1, with 21.0% of patients receiving atezolizumab for >1 year. Patients received a median of 6 doses (range, 1-83 doses), with 32.8% having received ≥10 doses. The median treatment duration was 2.8 months (range, 0-52.9 months) in cohort 2, with 20.0% of patients receiving atezolizumab for >1 year. Patients received a median of 5 doses (range, 1-76 doses), with 31.6% having received ≥10 doses. At the time of data cut-off (1 June 2023), the median survival follow-up duration was 96.4 months (range, 0.2-103.4 months) in cohort 1 and 46.2 months [range, 0.2 (censored)-54.9 months] in cohort 2.

### *Efficacy in cohort 1*

In objective response-evaluable patients in cohort 1, IRF-assessed RECIST 1.1 ORR was 23.5% (95% CI 16.2% to 32.2%) in all patients, with 10.1% achieving a best overall response of CR. ORR was 20.5% (95% CI 9.3% to 36.5%), 22.9% (95% CI 12.0% to 37.3%), and 28.1% (95% CI 13.8% to

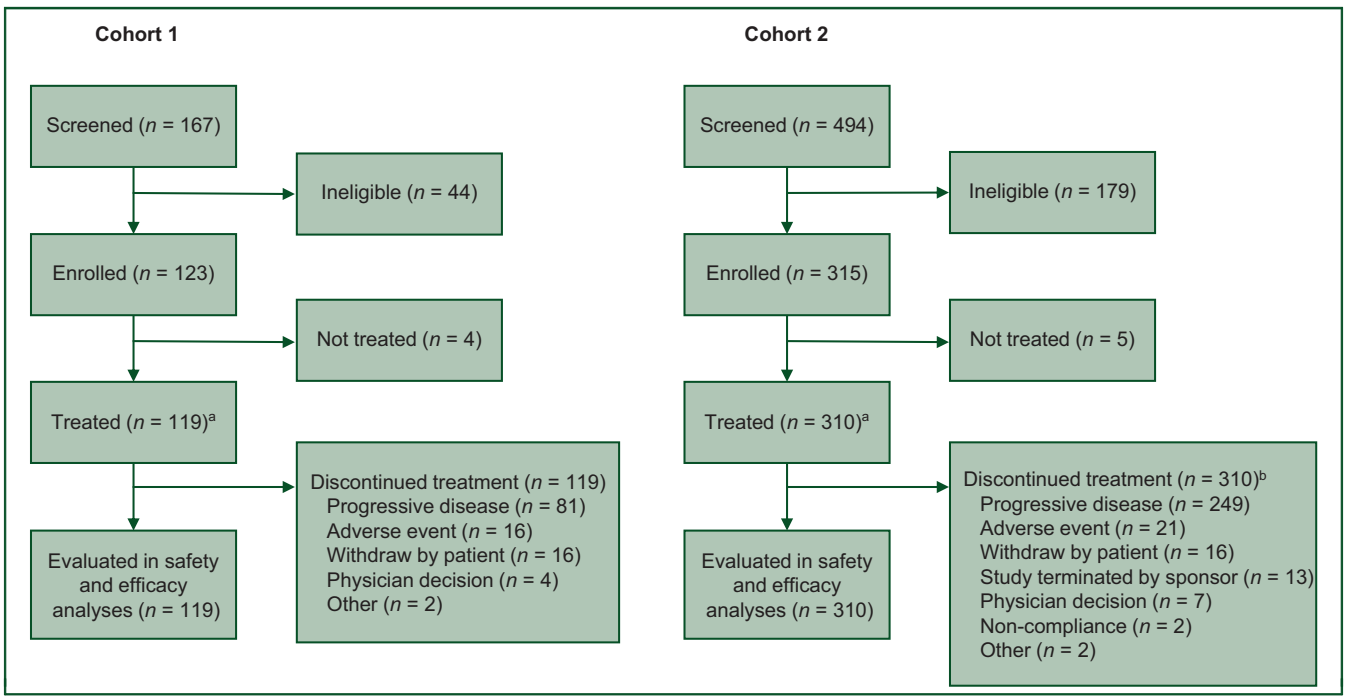


**Figure 1. Patient flow diagram.** Patients enrolled and treated in IMvigor210 are shown for both cohorts 1 and 2.
[a]Based on the 1 June 2023 data cut. Two patients initially assigned to cohort 1 and one patient initially assigned to cohort 2 were reassigned to the other cohort as a result of reassessment of eligibility criteria.
[b]At the time of study termination, 13 patients in cohort 2 who were still receiving atezolizumab continued treatment in an alternative clinical rollover study (BO39633) or via a commercially available source.

**Table 1. Efficacy analyses**

| | Cohort 1 | | | | Cohort 2 | | | |
|---|---|---|---|---|---|---|---|---|
| | IC0 | IC1 | IC2/3 | All patients | IC0 | IC1 | IC2/3 | All patients |
| Primary efficacy endpoint | | | | | | | | |
| ORR [central review (IRF)], *n*[a] | *n* = 39 | *n* = 48 | *n* = 32 | *n* = 119 | *n* = 103 | *n* = 107 | *n* = 100 | *n* = 310 |
| Responders, *n* (%) | 8 (20.5) | 11 (22.9) | 9 (28.1) | 28 (23.5) | 9 (8.7) | 15 (14.0) | 27 (27.0) | 51 (16.5) |
| 95% CI | (9.3-36.5) | (12.0-37.3) | (13.8-46.8) | (16.2-32.2) | (4.1-15.9) | (8.1-22.1) | (18.6-36.8) | (12.5-21.1) |
| Secondary efficacy endpoints | | | | | | | | |
| ORR (per investigator), *n*[a] | *n* = 39 | *n* = 48 | *n* = 32 | *n* = 119 | *n* = 103 | *n* = 107 | *n* = 100 | *n* = 310 |
| Responders, *n* (%) | 11 (28.2) | 11 (22.9) | 10 (31.3) | 32 (26.9) | 12 (11.7) | 15 (14.0) | 25 (25.0) | 52 (16.8) |
| 95% CI | (15.0-44.9) | (12.0-37.3) | (16.1-50.0) | (19.2-35.8) | (6.2-19.5) | (8.1-22.1) | (16.9-34.7) | (12.8-21.4) |
| DOR (central review), *n*[a] | *n* = 8 | *n* = 11 | *n* = 9 | *n* = 28 | *n* = 9 | *n* = 15 | *n* = 27 | *n* = 51 |
| Events, *n* (%) | 6 (75.0) | 6 (54.5) | 4 (44.4) | 16 (57.1) | 6 (66.7) | 9 (60.0) | 15 (55.6) | 30 (58.8) |
| Median (95% CI), months | 40.8 (12.8-53.5) | 66.3 (30.4-NE) | 93.8 (11.1-NE) | 59.1 (37.5-93.8) | 18.6 (8.3-NE) | 24.8 (8.1-30.5) | 29.7 (13.8-NE) | 24.8 (13.8-30.4) |
| DOR (per investigator), *n*[a] | *n* = 11 | *n* = 11 | *n* = 10 | *n* = 32 | *n* = 12 | *n* = 15 | *n* = 25 | *n* = 52 |
| Events (%) | 9 (81.8) | 6 (54.5) | 5 (50.0) | 20 (62.5) | 11 (91.7) | 8 (53.3) | 9 (36.0) | 28 (53.8) |
| Median (95% CI), months | 16.8 (10.7-84.8) | 53.2 (34.5-NE) | 76.0 (18.4-NE) | 53.2 (18.4-84.8) | 13.0 (8.3-17.1) | 20.5 (10.7-NE) | NE (16.6-NE) | 27.7 (13.1-NE) |
| PFS (central review), *n*[b] | *n* = 39 | *n* = 48 | *n* = 32 | *n* = 119 | *n* = 103 | *n* = 107 | *n* = 100 | *n* = 310 |
| Events (%) | 36 (92.3) | 41 (85.4) | 26 (81.3) | 103 (86.6) | 97 (94.2) | 97 (90.7) | 80 (80.0) | 274 (88.4) |
| Median (95% CI), months | 3.4 (2.1-6.1) | 2.1 (2.1-5.4) | 4.1 (2.1-12.3) | 4.0 (2.1-4.3) | 2.1 (2.0-2.4) | 2.1 (2.0-2.1) | 2.1 (2.1-4.2) | 2.1 (2.1-2.1) |
| PFS (per investigator), *n* | *n* = 39 | *n* = 48 | *n* = 32 | *n* = 119 | *n* = 103 | *n* = 107 | *n* = 100 | *n* = 310 |
| Events (%) | 35 (89.7) | 41 (85.4) | 25 (78.1) | 101 (84.9) | 98 (95.1) | 98 (91.6) | 82 (82.0) | 278 (89.7) |
| Median (95% CI), months | 4.1 (2.0-6.2) | 4.1 (2.1-8.7) | 4.2 (2.1-15.1) | 4.2 (2.3-5.8) | 2.1 (2.0-2.5) | 2.0 (2.0-2.1) | 2.3 (2.1-4.2) | 2.1 (2.1-2.1) |
| OS, *n* | *n* = 39 | *n* = 48 | *n* = 32 | *n* = 119 | *n* = 103 | *n* = 107 | *n* = 100 | *n* = 310 |
| Events (%) | 33 (84.6) | 38 (79.2) | 25 (78.1) | 96 (80.7) | 91 (88.3) | 95 (88.8) | 67 (67.0) | 253 (81.6) |
| Median (95% CI), months | 20.2 (6.7-28.7) | 16.3 (9.2-33.6) | 12.3 (6.0-49.8) | 16.3 (10.4-24.5) | 6.5 (4.4-8.3) | 6.7 (5.4-9.2) | 11.9 (9.0-22.8) | 7.9 (6.7-9.3) |
| 1-year OS rate (95% CI), % | 62.2 (46.6-77.8) | 58.5 (44.2-72.8) | 52.4 (34.9-69.9) | 58.1 (49.1-67.2) | 30.0 (20.9-39.1) | 31.3 (22.5-40.2) | 49.9 (40.0-59.9) | 36.9 (31.5-42.4) |
| 4-year OS rate (95% CI), % | 21.6 (8.4-34.9) | 30.8 (17.1-44.5) | 36.0 (19.1-52.9) | 29.0 (20.5-37.5) | 7.3 (2.1-12.4) | 9.4 (3.6-15.2) | 30.3 (20.6-40.0) | 15.3 (11.1-19.6) |
| 5-year OS rate (95% CI), % | 15.8 (3.8-27.7) | 22.6 (9.7-35.4) | 27.0 (10.3-43.7) | 21.6 (13.7-29.5) | — | — | — | — |

Data cut-off is 1 June 2023, unless otherwise stated.

CI, confidence interval; DOR, duration of response; IC, tumor-infiltrating immune cells; IRF, independent review facility; NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

[a]Data cut-off for cohort 2 ORR and DOR data is 12 July 2017.

[b]Data cut-off for cohort 2 PFS data is 4 July 2016. ORR and DOR were evaluated per Response Evaluation Criteria in Solid Tumors 1.1.

46.8%) in the IC0, IC1, and IC2/3 subgroups, respectively (Table 1). Corresponding CR rates were 7.7%, 8.3%, and 15.6%.

Median TTOR per IRF was 2.1 months (95% CI 2.1-3.9 months) in all responding patients and 2.1 months (95% CI 2.0-4.0 months), 2.5 months (95% CI 2.0-4.1 months), and 2.1 months (95% CI 2.0-2.2 months) in the IC0, IC1, and IC2/3 subgroups, respectively. IRF median DOR was 59.1 months (95% CI 37.5-93.8 months) in all patients, 40.8 months (95% CI 12.8-53.5 months) in the IC0 subgroup, 66.3 months [95% CI 30.4 months-not evaluable (NE)] in the IC1 subgroup, and 93.8 months (95% CI 11.1 months-NE) in the IC2/3 subgroup (Table 1).

Overall, 96 of the 119 patients (80.7%) had died at the final analysis. Median OS was 16.3 months (95% CI 10.4-24.5 months) in all patients, 20.2 months (95% CI 6.7-28.7 months) in the IC0 subgroup, 16.3 months (95% CI 9.2-33.6 months) in the IC1 subgroup, and 12.3 months (95% CI 6.0-49.8 months) in the IC2/3 subgroup (Table 1). The 5-year OS rate was 21.6% (95% CI 13.7% to 29.5%) in all patients, 15.8% (95% CI 3.8% to 27.7%) in the IC0 subgroup, 22.6% (95% CI 9.7% to 35.4%) in the IC1 subgroup, and 27.0% (10.3% to 43.7%) in the IC2/3 subgroup. Kaplan—Meier curves for OS, including results by PD-L1 status, are shown in Figure 2A and B. Additional efficacy results, including PFS, as well as ORR and DOR assessed by the treating investigator by PD-L1 status are shown in Table 1.

### *Efficacy in cohort 2*

In evaluable patients in cohort 2, the IRF-assessed RECIST 1.1 ORR was 16.5% (95% CI 12.5% to 21.1%) in all patients, with a 7.1% CR rate. The ORRs in the IC0, IC1, and IC2/3 subgroups were 8.7% (95% CI 4.1% to 15.9%), 14.0% (95% CI 8.1% to 22.1%), and 27.0% (95% CI 18.6% to 36.8%), respectively, with CR rates of 1.9%, 5.6%, and 14.0%. When evaluated by mRECIST 1.1, the ORR was 19.7% (95% CI 15.4% to 24.6%) in all patients and 28.0% (95% CI 19.5% to 37.9%) in the IC2/3 subgroup.

The median TTOR in all patients was previously reported as 2.1 months (95% CI 2.0-2.2 months).[13] The median DOR per IRF-assessed RECIST 1.1 was 24.8 months (95% CI 13.8-30.4 months) in the all-comer population and 29.7 months (95% CI 13.8 months-NE) in the IC2/3 subgroup.

At the time of final analysis, 253 of 310 patients (81.6%) had died. Median OS was 7.9 months (95% CI 6.7-9.3 months) in all patients, 6.5 months (95% CI 4.4-8.3 months) in the IC0 subgroup, 6.7 months (95% CI 22.5-39.1 months) in the IC1 subgroup, and 11.9 months (95% CI 9.0-22.8 months) in the IC2/3 subgroup (Table 1). The 4-year OS rate was 15.3% (95% CI 11.1% to 19.6%) in all patients, 7.3%

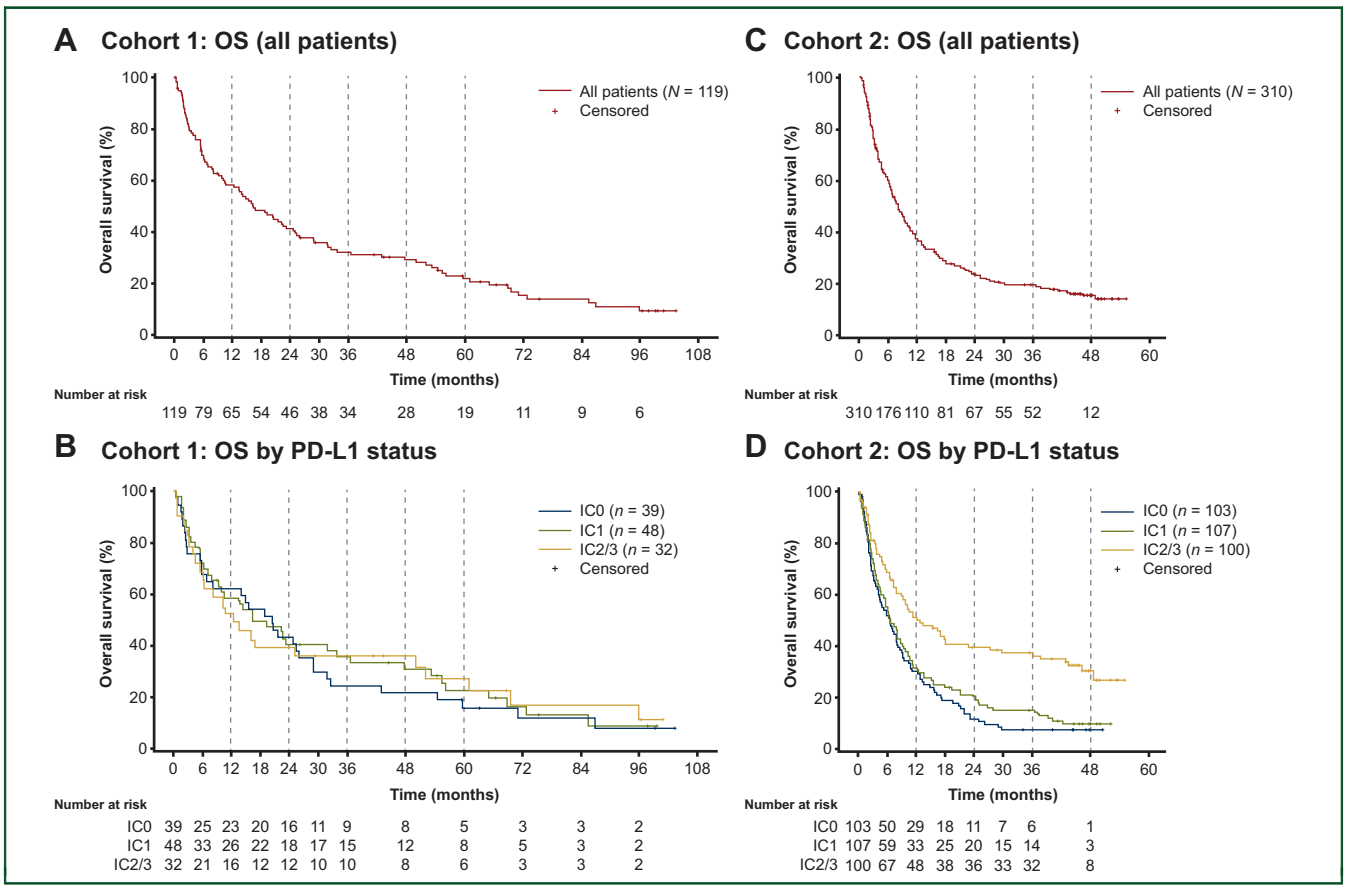


**Figure 2. Overall survival.** Kaplan—Meier analysis of overall survival in cohort 1 (A) in all patients and (B) by PD-L1 status and in cohort 2 (C) in all patients and (D) by PD-L1 status. IC status refers to the percentage of tumor area covered by PD-L1-expressing tumor-infiltrating immune cells (IC0, <1%; IC1, ≥1% and <5%; IC2/3, ≥5% per VENTANA SP142 assay).
IC, tumor-infiltrating immune cell; OS, overall survival; PD-L1, programmed death-ligand 1.

(95% CI 2.1% to 12.4%) in the IC0 subgroup, 9.4% (95% CI 3.6% to 15.2%) in the IC1 subgroup, and 30.3% (95% CI 20.6% to 40.0%) in the IC2/3 subgroup. Kaplan–Meier curves for OS, including results by PD-L1 status, are shown in Figure 2C and D. Additional efficacy results are shown in Table 1.

### *Safety*

A summary of safety is reported in Table 2. Treatment-related adverse events (AEs) occurred at frequencies of 74.8% and 71.3% in cohorts 1 and 2, respectively. Treatment-related grade 3/4 AEs occurred in 21.8% of patients in cohort 1 and 18.7% in cohort 2. The most common treatment-related AE (Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.esmoop.2024.103972) was fatigue, occurring in 33.6% and 31.0% of patients, respectively, in cohorts 1 and 2. Pruritus (in 13.4% and 13.2%), diarrhea (in 12.6% and 8.7%), decreased appetite (in 10.1% and 11.0%), and nausea (in 6.7% and 13.9%) were also among the most commonly reported treatment-related events in cohorts 1 and 2, respectively. One treatment-related death (sepsis) occurred in cohort 1 in a patient who had an unidentified source of infection. Overall AEs of any cause leading to discontinuation of atezolizumab occurred in 13.4% of patients from cohort 1 and 6.8% in cohort 2.

Immune-mediated AEs of special interest (AESIs) are reported in Table 3. AESIs of any grade occurred in 41.2% and 33.5% of patients in cohorts 1 and 2, respectively. The most common AESI was immune-mediated rash, occurring in 25.2% and 21.6% of patients; 10.9% of patients in cohort 1 and 7.4% of patients in cohort 2 had a grade 3/4 AESI.

## DISCUSSION

With a median follow-up of 96.4 months in cohort 1 and 46.2 months in cohort 2, the final analysis of IMvigor210 provides one of the longest datasets for atezolizumab and the longest follow-up of 1L CPI monotherapy for mUC. In both cohorts, clinically meaningful efficacy was observed, including durability of response and notable 4- and 5-year OS rates in a small proportion of patients. Atezolizumab was generally well tolerated with manageable toxicity. The tolerability profile remains consistent with that of previous analyses, with no new safety signals observed with longer follow-up, including in patients treated with atezolizumab beyond 1 year.

Efficacy results of the final analysis of IMvigor210 are generally in line with results from the previous analyses. Cohort 2 data were also consistent with both the phase I results and the confirmatory phase III IMvigor211 trial.[10,17] IMvigor211, however, which was designed with a similar hierarchical testing approach to evaluate OS in PD-L1 IC2/3, then IC1/2/3, then all intention-to-treat patients, did not meet its OS primary endpoint.[17] The treatment approach in cohort 1 was later evaluated in the larger phase III IMvigor130 trial (atezolizumab monotherapy arm analysis population, $n = 360$), which reported a median OS of 15.2 months at the final analysis.[18] Due to differences in the patient populations between studies (for example, IMvigor130 also enrolled patients who were eligible for cisplatin), however, direct comparisons cannot be made with IMvigor210. Early IMvigor210 cohort 1 data suggested that efficacy might be seen regardless of PD-L1 status, evidenced in part by the median OS duration, which did not appear to be associated with higher PD-L1 expression. With extended follow-up, however, PD-L1 positivity appeared to associate more notably with landmark OS rates, as evidenced by the higher OS rates at 4 and 5 years in the IC2/3

**Table 2. Safety summary**

| Patients with AEs, *n* (%)[a] | Cohort 1 (*n* = 119) | Cohort 2 (*n* = 310) |
|---|---|---|
| Any AE | 115 (96.6) | 304 (98.1) |
| Treatment-related AE | 89 (74.8) | 221 (71.3) |
| Grade 3/4 AE | 64 (53.8) | 193 (62.3) |
| Grade 3/4 treatment-related AE | 26 (21.8) | 58 (18.7) |
| Grade 5 AE | 5 (4.2) | 3 (1.0) |
| Grade 5 treatment-related AE | 1 (0.8) | 0 |
| Serious AE | 49 (41.2) | 155 (50.0) |
| Treatment-related serious AE | 12 (10.1) | 41 (13.2) |
| AE leading to discontinuation of atezolizumab | 16 (13.4) | 21 (6.8) |
| AE leading to dose modification/interruption | 44 (37.0) | 108 (34.8) |

AE, adverse event.
[a]Refers to patients who had one or more AE. Multiple occurrences of the same AE in one individual were counted once.

**Table 3. Adverse events of special interest**

| *n* (%) | Cohort 1 (*n* = 119) | Cohort 2 (*n* = 310) |
|---|---|---|
| **Any AESI** | 49 (41.2) | 104 (33.5) |
| Grade 3/4 | 13 (10.9) | 23 (7.4) |
| Serious AESI | 7 (5.9) | 16 (5.2) |
| AESI leading to atezolizumab withdrawal | 2 (1.7) | 4 (1.3) |
| AESI leading to dose interruption | 9 (7.6) | 24 (7.7) |
| AESI requiring systemic corticosteroid[a] | 13 (10.9) | 25 (8.1) |
| **AESI medical concept** | | |
| Immune-mediated rash | 30 (25.2) | 67 (21.6) |
| Immune-mediated hepatitis | | |
| Diagnosis and laboratory abnormalities | 17 (14.3) | 31 (10.0) |
| Laboratory abnormalities | 16 (13.4) | 31 (10.0) |
| Diagnosis | 3 (2.5) | 4 (1.3) |
| Immune-mediated hypothyroidism | 11 (9.2) | 13 (4.2) |
| Infusion-related reactions[b] | 5 (4.2) | 3 (1.0) |
| Immune-mediated colitis | 4 (3.4) | 4 (1.3) |
| Immune-mediated pneumonitis | 3 (2.5) | 11 (3.5) |
| Immune-mediated hyperthyroidism | 2 (1.7) | 3 (1.0) |
| Immune-mediated myositis + rhabdomyolysis | 2 (1.7) | 2 (0.6) |
| Immune-mediated rhabdomyolysis | 2 (1.7) | 0 |
| Immune-mediated diabetes | 1 (0.8) | 0 |
| Immune-mediated nephritis | 1 (0.8) | 0 |
| Immune-mediated adrenal insufficiency | 0 | 2 (0.6) |
| Immune-mediated myositis | 0 | 2 (0.6) |
| Immune-mediated pericardial disorders | 0 | 1 (0.3) |
| Immune-mediated severe cutaneous reaction | 0 | 1 (0.3) |

The medical concepts for identified risks associated with atezolizumab are included. No deaths occurred in either cohort. AESIs specified as potential risks associated with atezolizumab included immune-mediated ocular inflammatory toxicity [$n = 1$ (0.8%)] in cohort 1 and immune-mediated vasculitis [$n = 1$ (0.3%)] in cohort 2.
AESI, adverse event of special interest.
[a]Within 30 days of AESI onset.
[b]AEs that occurred during or within 1 day after study treatment administration.

subgroup relative to IC0 and IC1. This observation is in line with data from IMvigor130, which suggested that the clinical benefit seen in patients with PD-L1-high tumors was enhanced in cisplatin-ineligible patients, although these results could not be formally statistically tested based on the hierarchical study design.[18]

The tolerability profile of atezolizumab was generally similar between the cohorts of IMvigor210. AEs were manageable, and only one treatment-related death occurred (due to sepsis). The frequency of AEs leading to discontinuation was slightly higher in cohort 1 than in cohort 2 (13.4% versus 6.8%). In IMvigor130 and IMvigor211, the rates of AEs leading to atezolizumab discontinuation were 9% and 7%, respectively.[17,18] Comparison of IMvigor210 safety data with those with other CPIs is challenging given differences in study designs, patient populations, duration of therapy and follow-up, and reporting details. The final safety data from IMvigor210, however, were consistent with prior analyses.

A limitation of IMvigor210 was that it was a single-arm trial that evaluated ORR (not PFS or OS) as a primary endpoint, which limited data extrapolation. As described previously,[12] cohort 1 was also initially designed as an exploratory subgroup of 30 patients, before the protocol was amended to allow accrual of a larger population of around 100 patients. Thus, despite consistency with aspects of larger datasets, these findings nonetheless represent data from a small, non-randomized phase II trial.

Since IMvigor210 was designed, several new CPI therapy approaches, including 1L combination regimens, have become available for mUC treatment, and the landscape will likely evolve further as new paradigms are evaluated. For example, 1L switch maintenance treatment with avelumab was approved in several countries for patients with locally advanced or metastatic UC who have not progressed on 1L induction platinum-containing chemotherapy based on the JAVELIN Bladder 100 trial (NCT02603432).[6,19] Enfortumab vedotin plus pembrolizumab received Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval for patients with locally advanced or metastatic UC based on the EV-302/KN-A39 trial (NCT04223856).[8] The combination of nivolumab plus cisplatin/gemcitabine in advanced UC was also approved by the FDA and EMA following results from the CheckMate 901 trial (NCT03036098).[7]

In the early bladder cancer setting, a biomarker-informed approach is being evaluated in the phase III IMvigor011 trial of atezolizumab versus placebo in patients with high-risk muscle-invasive UC who are circulating tumor DNA positive after cystectomy.[20] Ongoing trials of perioperative CPI approaches include the following in patients with UC who are cisplatin eligible [e.g. NIAGARA (cisplatin/gemcitabine ± durvalumab), which recently met its event-free survival co-primary endpoint as well as its OS secondary endpoint,[21] NCT03661320 (cisplatin/gemcitabine ± nivolumab), KEYNOTE-866 (cisplatin/gemcitabine ± pembrolizumab), and KEYNOTE-B15/EV-304 (pembrolizumab + enfortumab vedotin)] and cisplatin ineligible [KEYNOTE-905/EV-303 (pembrolizumab ± enfortumab vedotin), and VOLGA (durvalumab ± tremelimumab + enfortumab vedotin)].[22] Atezolizumab is also being evaluated in the phase III ALBAN trial in combination with BCG in patients with high-risk BCG-naive non-muscle-invasive bladder cancer[23] and in the phase III S1806 trial of concurrent chemoradiotherapy ± atezolizumab for patients with localized muscle-invasive bladder cancer (NCT03775265). Additional CPI combination approaches to 1L treatment are also underway, including a phase II trial of tobemstomig (a bispecific anti-PD-1 anti-LAG3 antibody) with or without tiragolumab (anti-TIGIT antibody) versus atezolizumab in patients with platinum-ineligible mUC.[24]

In conclusion, the final long-term data from this trial indicate that atezolizumab monotherapy may provide durable clinical benefit to a subset of patients with mUC. This trial—which led to the first approvals of CPI monotherapy with atezolizumab in both the 1L cisplatin-ineligible and 2L settings—provides data from one of the longest median follow-up durations of 1L CPI monotherapy in mUC. The findings also demonstrated that the tolerability profile of atezolizumab remained consistent with longer follow-up, likely supporting the potential use of combination CPI-based systemic therapy approaches in the 1L setting and beyond. Furthermore, the data suggest that well-selected patients with ultimately non-curable disease treated in the 1L setting might benefit from CPI monotherapy—if a suitable validated biomarker is found in the future to identify them before initiating therapy—because it can offer better tolerability than conventional cytotoxic chemotherapy.

## ACKNOWLEDGEMENTS

We thank the patients who participated in this study, their family members, as well as the study investigators and staff at participating sites. Medical writing assistance for this manuscript was provided by Ashley J. Pratt, PhD, and Samantha Santangelo, PhD, of Nucleus Global, an Inizio Company, and funded by F. Hoffmann-La Roche Ltd.

## FUNDING

This study was sponsored by F. Hoffmann-La Roche Ltd (no grant number), who provided financial support for the conduct of study and were involved in the study design; in the collection, analysis, and interpretation of data; in the writing of the clinical study report; in the decision to submit the article for publication; and in the funding of the third-party medical writing assistance. This work was also supported in part by National Cancer Institute Cancer Center Support Grant [grant number P30 CA008748].

## DISCLOSURE

JER reports grants or contracts from Acrivon, Astellas, AstraZeneca, Bayer, Lilly Oncology, and Seagen/Pfizer; and consulting fees from Aktis, Astellas, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb (BMS), Century Therapeutics, EMD Serono, Gilead, Janssen, Lilly, Merck,

Pfizer, Roche/Genentech, Seagen, Tyra Biosciences, Aadi Bioscience, Alligator Bioscience, Imvax Inc., and Hengrui. MDG reports consulting fees (to self) from Astellas, BMS, Merck, Genentech, AstraZeneca, Pfizer, EMD Serono, Seagen, Janssen, Numab, Dragonfly, GlaxoSmithKline, Basilea, UroGen, Rappta Therapeutics, Alligator, Silverback, Fujifilm, Curis, Gilead, Bicycle, Asieris, AbbVie, Analog Devices, Veracyte, Daiichi, and Aktis. TP reports grants or contracts from AstraZeneca, Roche, BMS, Exelixis, Ipsen, Merck Sharp & Dohme (MSD), Novartis, Pfizer, Seagen, Merck Serono (EMD), Astellas, Johnson & Johnson, and Eisai; consulting fees and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AstraZeneca, BMS, Exelixis, Incyte, Ipsen, MSD, Novartis, Pfizer, Seagen, Merck Serono (EMD), Astellas, Johnson & Johnson, Eisai, Roche, and Mashup; support for attending meetings and/or travel from Roche, Pfizer, MSD, AstraZeneca, and Ipsen; and patents planned, issued, or pending from AstraZeneca, Roche, BMS, Exelixis, MSD, Novartis, Pfizer, Seagen, Merck Serono (EMD), Astellas, Johnson & Johnson, and Eisai. DP reports support for the present manuscript from Genentech Inc.; grants or contracts from Arvinas, Astellas, AstraZeneca, Merck, Pfizer, and Seagen; consulting fees from Amgen, AstraZeneca, Exelixis, Flare, Janssen, Merck, Pfizer, and Seagen; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Aptitude, Carden Jennings, Clinical Care Options, Dava, PER, and Research to Practice; and receipt of equipment, materials, drugs, medical writing, gifts, or other services (to self) from Genentech Inc. and Pfizer. JB reports the following financial interests: advisory board participation with AstraZeneca, BMS, Merck, and Pfizer; participation as an invited speaker or lecturer by Merck and MSD; stocks and/or shares from Bicycle; and royalties from UpToDate. JB also reports the following non-financial interests: coordinating principal investigator for MSD and Pfizer; and steering committee member of IMvigor011 and member of ASCO. YL reports receipt of grants/research from Janssen, MSD, Roche, and Sanofi; and receipt of honoraria or consultation fees from AstraZeneca, Astellas, BMS, Gilead, Janssen, Merck KGaA, MSD, Pfizer, Roche, and Tahio. AN reports grants or contracts (to institution) from BMS, Gilead, and Merck; consulting fees (to self) from AstraZeneca, BMS, CatalYm, Gilead, Johnson & Johnson, and Samsung Bioepis; and support for attending meetings and/or travel (to self) from AstraZeneca, Gilead, and Merck. JHC reports research support from Astellas Pharma, Daiichi Sankyo, EMD Serono, Ikena Oncology, and Seagen; grant support from Roche/Genentech; support for the present manuscript from Roche/Genentech; and consulting fees from Gilead Sciences. JLPG reports research grants and support from Astellas, Amgen, BMS, Novartis, Roche, and Seagen; speakers bureau and advisory board participation with Astellas, MSD, and Roche; and travel support from BMS, MSD, Roche, and Merck. MSvdH reports grants or contracts (to institute) from BMS, 4SC, AstraZeneca, Roche, and MSD/Merck; consulting fees (to institute) from and participation on an advisory board with BMS, Janssen, AstraZeneca, MSD/Merck, Astellas, Seagen, Roche, and Pfizer; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from PeerView and Onco Today; support for attending meetings and/or travel from BMS; and membership on the ESMO Bladder Cancer Guideline Committee and the EAU/ASCO Penile Cancer Guideline Committee. RD reports grants or contracts from Exelixis and Arvinas; consulting fees from Bayer, Pfizer, Astellas, Seagen, and MacroGenics; and participation on a data safety monitoring board or advisory board with Aveo and Merck. ID reports research grants from Roche/Genentech and AstraZeneca; compensated consulting fees (to self) from Samsung Bioepis; honoraria for lectures and presentations (to self) from Astellas, MSD, Merck, AstraZeneca, Pfizer, Janssen, and BMS; support for attending EAU and ASCO meetings from Bayer; support for attending ASCO GU and/or ASCO from AstraZeneca, Ipsen, and Gilead; paid participation (to self) on an advisory board from Astellas, MSD, Merck, AstraZeneca, Pfizer, Janssen, and Gilead; a role as co-founder and president with GO NORTE (Spanish GU cooperative group) (unpaid); membership on the board of directors for ASEICA (Spanish Society for Cancer Research) (unpaid); co-founder and member of the board of directors for CANVES (bladder cancer patient advocacy group) (unpaid); co-founder and member of the board of directors for GUARD (Spanish GU cooperative group) (unpaid); and medical writing support (publication plan; paid to institution) from Roche Genentech Spain. DC reports payment or honoraria (for lectures, presentations, speakers bureaus, manuscript writing, or educational events) as well as support for attending meetings and/or travel from Astellas, AstraZeneca, BMS, Exelixis, Ipsen, Janssen, Lilly, MSD, Merck, Novartis, Pfizer, and Roche. AD reports grants or contracts from Acrivon Therapeutics, Adcentrx, AstraZeneca, Infinity, Loxo/Lilly, Merck, Roche/Genentech, and Seagen; consulting or advisory board participation from AstraZeneca, BMS, Daiichi Sankyo, and Seagen; and stock from Athos Therapeutics. MR reports support for the present manuscript (medical writing and analysis) from Roche. SSS reports grants or contracts from EMD Serono (project on split-dose cisplatin); payment or honoraria for consulting from Astellas, AstraZeneca, Bayer, Bicycle Therapeutics, BMS, Eisai, EMD Serono, F.Hoffmann-La Roche, Gilead, Ipsen, Janssen, Merck, Pfizer, and Seagen; and participation on a data safety monitoring board (PMCC DSMB Co-Chair). PG reports support for the present manuscript from Roche/Genentech; grants or contracts from Acrivon Therapeutics, ALX Oncology, BMS, EMD Serono, G1 Therapeutics, Genentech, Gilead Sciences, GlaxoSmithKline, Mirati Therapeutics, MSD, Pfizer, and QED Therapeutics; consulting fees from AbbVie, Aadi Bioscience, Asieris Pharmaceuticals, Astellas Pharma, AstraZeneca, Bicycle Therapeutics, BostonGene, BMS, CG Oncology, EMD Serono, Fresenius Kabi, G1 Therapeutics, Gilead Sciences, ImmunityBio, Janssen, Lucence Health, MSD, Pfizer, PureTech, Replimune, Roche, Silverback Therapeutics, and Strata Oncology; and participation on a data safety monitoring board or advisory board

for BMS and Strata Oncology. EYY reports research funding (to institution) from Dendreon, Merck, Seagen, Blue Earth, Bayer, Lantheus, Tyra, and Oncternal; and consulting for Janssen, Merck, AAA, Novartis, Bayer, Aadi Bioscience, Oncternal, BMS, Loxo, and Lantheus. PHOD reports research funding (to institution) from Acerta Pharma, Astellas Pharma, AstraZeneca/MedImmune, Boehringer Ingelheim, BMS, Genentech/Roche, Janssen, Loxo/Lilly, Merck, Pfizer, and Seagen; honoraria from AbbVie, Adept Field Solutions, Advarra, Amerisource Bergen, Astellas, Curio Science, Custom Learning Designs, Axiom Healthcare Strategies, EMD Serono, FirstWord, Gilead, Great Debates and Updates, Health Advances, Institute for Enquiring Minds, IntrinsiQ, ImmunityBio, ISMIE, Loxo/Lilly, Med Learning Group, Merck, MJH Life Sciences, NAMCP, Parexel Intl Corp, PeerView, Pfizer, PharmaVision UK, PRIME Education LLC, Research to Practice, Seagen, Vaniam Group, and Vida Ventures LLC; expert testimony for Hart Wagner LLP and O'Brien and Ryan LLP; travel, accommodations, and expenses from Astellas, Curio Science, and Seagen; and the following other relationships: Dragonfly Therapeutics, G1 Therapeutics, Janssen, the National Institutes of Health (via Duke University), and Nektar. HAB reports support for the present manuscript from Roche (to institution); grants or contracts (to institution) from AbbVie, Agios, Arch Oncology, ARMO Biosciences, Array BioPharma, Arvinas, AstraZeneca, BioAtla, BMS, CALGB, Celgene, Coordination Pharmaceuticals, CytomX, Lilly, EMD Serono, Roche/Genentech, Gossamer Bio, Harpoon Therapeutics, Hengrui Therapeutics, Incyte, Jounce Therapeutics, Kymab, MacroGenics, MedImmune, Merck, Millennium/Takeda, Moderna, Novartis, Pfizer, Revolution Medicines, Ryvu Therapeutics, Foundation Medicine, Seagen, Tesaro, TG Therapeutics, Verastem, Vertex Pharmaceuticals, XBiotech, and Zymeworks; uncompensated consulting with BMS; consulting fees (to institution) from AstraZeneca, Bicycle, GRAIL, Incyte, Roche, and Vincerx Pharma; and stock or stock options (to self) from HCA Healthcare. SM is an employee of Genentech Inc. and Roche stockholder. YS reports paid employment with and stock and stock options from Roche/Genentech. EG is an employee of Genentech Inc. and Roche stockholder. DB has received grants or contracts and consulting fees from BMS and Merck; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from BMS; and reports participation on a data safety monitoring board or advisory board with Merck.

## DATA SHARING

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 because of a potential increase in risk of patient reidentification.

## REFERENCES


1. International Agency for Research on Cancer. Global cancer observatory: cancer today. Available at https://gco.iarc.fr/today. Accessed February 8, 2024.
2. Powles T, Bellmunt J, Comperat E, et al. Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2022;33(3):244-258.
3. Witjes JA, Bruins HM, Carrión A, et al. EAU guidelines on muscle-invasive and metastatic bladder cancer. Available at https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Muscle-Invasive-And-Metastatic-Bladder-Cancer-2022.pdf. Accessed February 24, 2023.
4. Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. *N Engl J Med*. 2021;384(22):2102-2114.
5. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med*. 2017;376(11):1015-1026.
6. Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. *N Engl J Med*. 2020;383(13):1218-1230.
7. van der Heijden MS, Sonpavde G, Powles T, et al. Nivolumab plus gemcitabine-cisplatin in advanced urothelial carcinoma. *N Engl J Med*. 2023;389(19):1778-1789.
8. Powles T, Valderrama BP, Gupta S, et al. Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. *N Engl J Med*. 2024;390(10):875-888.
9. Grivas P, Pouessel D, Park CH, et al. Sacituzumab govitecan in combination with pembrolizumab for patients with metastatic urothelial cancer that progressed after platinum-based chemotherapy: TROPHY-U-01 cohort 3. *J Clin Oncol*. 2024;42(12):1415-1425.
10. Petrylak DP, Powles T, Bellmunt J, et al. Atezolizumab (MPDL3280A) monotherapy for patients with metastatic urothelial cancer: long-term outcomes from a phase 1 study. *JAMA Oncol*. 2018;4(4):537-544.
11. Powles T, Eder JP, Fine GD, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. *Nature*. 2014;515(7528):558-562.
12. Balar AV, Galsky MD, Rosenberg JE, 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(10064):67-76.
13. Rosenberg JE, Hoffman-Censits J, Powles T, 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(10031):1909-1920.
14. Balar AV, Galsky MD, Loriot Y, et al. Atezolizumab (atezo) as first-line (1L) therapy in cisplatin-ineligible locally advanced/metastatic urothelial carcinoma (mUC): primary analysis of IMvigor210 cohort 1. *J Clin Oncol*. 2016;34(suppl 18):LBA4500.
15. Duran I, Dreicer R, Loriot Y, et al. Atezolizumab as first-line therapy in patients with cisplatin-ineligible locally advanced or metastatic urothelial cancer: efficacy by PD-L1 status over time from IMvigor210 Cohort 1. Paper presented at the Global Congress on Bladder Cancer 2018. September 20-21, 2018; Madrid, Spain.
16. Vennapusa B, Baker B, Kowanetz M, et al. Development of a PD-L1 complementary diagnostic immunohistochemistry assay (SP142) for atezolizumab. *Appl Immunohistochem Mol Morphol*. 2019;27(2):92-100.
17. Powles T, Duran I, van der Heijden MS, 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(10122):748-757.

18. Bamias A, Davis ID, Galsky MD, et al. Atezolizumab monotherapy versus chemotherapy in untreated locally advanced or metastatic urothelial carcinoma (IMvigor130): final overall survival analysis from a randomised, controlled, phase 3 study. *Lancet Oncol*. 2024;25(1):46-61.
19. Powles T, Park SH, Caserta C, et al. Avelumab first-line maintenance for advanced urothelial carcinoma: results from the JAVELIN bladder 100 trial after ≥2 years of follow-up. *J Clin Oncol*. 2023;41(19):3486-3492.
20. Jackson-Spence F, Toms C, O'Mahony LF, et al. IMvigor011: a study of adjuvant atezolizumab in patients with high-risk MIBC who are ctDNA+ post-surgery. *Future Oncol*. 2023;19(7):509-515.
21. Powles T, Catto JWF, Galsky MD, et al. Perioperative durvalumab with neoadjuvant chemotherapy in operable bladder cancer. *N Engl J Med*. 2024;391(19):1773-1786. https://doi.org/10.1056/NEJMoa2408154.
22. Sridhar SS. Interpretation of current peri-operative trial designs and endpoints. Paper presented at the ESMO Congress 2023. October 22, 2023; Madrid, Spain.
23. Roupret M, Neuzillet Y, Bertaut A, et al. ALBAN: An open label, randomized, phase III trial, evaluating efficacy of atezolizumab in addition to one year BCG (bacillus Calmette-Guerin) bladder instillation in BCG-naive patients with high-risk nonmuscle invasive bladder cancer (AFU-GETUG 37). *J Clin Oncol*. 2019;37(suppl 15):TPS4589.
24. Gupta S, Alhalabi O, Bamias A, et al. 2409TiP A global, multicentre, open-label, randomised phase II trial of tobemstomig (tobe) with or without tiragolumab (tira) vs atezolizumab (atezo) in patients (pts) with untreated metastatic urothelial cancer (mUC) ineligible for platinum-based chemotherapy (chemo). *Ann Oncol*. 2023;34:S1225.