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Adjuvant atezolizumab vs placebo for patients with renal cell carcinoma at increased risk of recurrence following resection (IMmotion010): a multicentre, randomised, double-blind, phase 3 trial

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Abstract

Background The standard-of-care for loco-regional renal cell carcinoma (RCC) is surgery, but many patients experience recurrence. The objective of the current study was to determine if adjuvant atezolizumab (versus placebo) delayed recurrence in patients with an increased risk of recurrence after resection.

Methods We conducted a randomised, double-blind, phase 3 trial (NCT03024996) enrolling patients ≥ 18 years with RCC with a clear cell or sarcomatoid component and increased risk of recurrence. After nephrectomy with or without metastasectomy, patients were randomly assigned 1:1 to receive atezolizumab (1200 mg) or placebo (both intravenous) once every 3 weeks for 16 cycles or 1 year. Stratification factors were disease stage (T2/T3a vs T3b/c/T4/N+ vs M1 NED), region (North America [excluding Mexico] vs rest of world) and PD-L1 status on tumour-infiltrating immune cells ($<1\%$ vs $\geq 1\%$ expression). The primary endpoint was investigator-assessed disease-free survival in the intention-to-treat population. Overall survival and safety were secondary endpoints.

Findings Between 03 Jan 2017 and 15 Feb 2019, 778 patients were enrolled; 390 (50%) were assigned to the atezolizumab group and 388 (50%) to the placebo group. At data cutoff (03 May 2022), the median follow-up duration was 44·7 months (range 0–62). Median investigator-assessed disease-free survival was 57·2 months (95% CI 44·6–not evaluable) with atezolizumab and 49·5 months (95% CI 47·4–not evaluable) with placebo (hazard ratio (HR) 0·93, 95% CI 0·75–1·15, $p=0·50$). A survival benefit from atezolizumab was not observed (HR 0·97, 95% CI 0·67–1·42). Grade 3/4 adverse events occurred in 27% (106/390) and 21% (81/383) of patients who received atezolizumab and placebo, respectively; adverse events leading to death occurred in one ($<1\%$) and three (1%), respectively, with none related to treatment.

80 **Interpretation** Atezolizumab as adjuvant therapy after resection for patients with RCC with
81 increased risk of recurrence showed no evidence of improved clinical outcomes vs placebo.
82 These study results do not support adjuvant atezolizumab for treatment of RCC.

83 **Funding** F. Hoffmann-La Roche and Genentech, Inc, a member of the Roche group.

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Research in Context

Evidence before this study

We searched PubMed and major international oncology conferences for articles published in the 5 years prior to initiation of the study (between 01 Jan 2012 and 01 Jan 2017) pertaining to adjuvant treatment of renal cell carcinoma (RCC) with the terms (“renal cell carcinoma” OR “RCC”) AND (“adjuvant” OR “after resection”). At the time of initiation of this study, the standard of care for patients with intermediate- to high-risk RCC was partial or radical nephrectomy without any adjuvant therapy. In the S-TRAC study, patients with locoregional RCC with high risk of recurrence, the anti-VEGF tyrosine kinase inhibitor sunitinib demonstrated a disease-free survival benefit over placebo (hazard ratio [HR] 0·76, 95% confidence interval [CI] 0·59–0·98, $p=0\cdot03$). In contrast, in the ASSURE trial, a disease-free survival benefit over placebo was not observed with sunitinib (HR 1·02, 95% CI 0·85–1·23; $p=0\cdot80$) or with another anti-angiogenic agent, sorafenib (HR 0·97, 95% CI 0·80–1·17, $p=0\cdot72$). After initiation of our trial, the PROTECT trial evaluated the anti-angiogenic agent pazopanib and did not demonstrate a disease-free survival benefit over placebo (HR 0·86, 95% CI 0·70–1·06, $p=0\cdot17$). In November 2017, sunitinib received approval from the United States Food and Drug Administration as an adjuvant therapy for patients with RCC with high risk of recurrence, yet sunitinib was not approved by the European Medicines Agency. Due to the conflicting efficacy data and toxicity concerns, sunitinib was not widely adopted as adjuvant therapy in the United States. At time of initiation of this study, additional adjuvant therapy strategies, including immunotherapies, were beginning to be investigated.

Added value of this study

The IMmotion010 study was the first initiated phase 3 randomised trial assessing an anti-programmed death ligand 1 (PD-L1) immune checkpoint inhibitor as adjuvant therapy in RCC. This study did not meet the primary endpoint, as there was no disease-free survival benefit seen

with atezolizumab versus placebo. Similarly, an overall survival benefit was not observed. Recently, the KEYNOTE-564 trial met its primary endpoint, demonstrating that adjuvant treatment with the programmed death-1 (PD-1) antibody pembrolizumab improved investigator-assessed disease-free survival versus placebo in patients with RCC who have an intermediate to high risk of recurrence (HR 0·63, 95% CI 0·50–0·80, nominal $p < 0·0001$). At the primary analysis and a follow-up analysis with an additional 6 months of follow-up, a statistically significant overall survival benefit has not been observed as the data remained immature. In addition to IMmotion010, CheckMate 914 did not show a disease-free survival benefit with nivolumab and ipilimumab as adjuvant therapy for locally advanced RCC and the PROSPER RCC trial evaluating perioperative nivolumab did not meet its primary endpoint. Other studies in this space, such as the RAMPART trial, are ongoing and will readout in the near future.

Implications of all the available evidence

Our results show that adjuvant therapy with atezolizumab did not provide a clinical benefit in patients with RCC who have an increased risk of recurrence. Emerging data from other studies in this setting may help clarify adjuvant therapy in RCC.

INTRODUCTION

Globally, renal cell carcinoma (RCC) is the twelfth most common cancer.¹ Approximately 80% of patients are diagnosed with locoregional disease²; however, many patients will experience recurrence after surgery, with 5-year rates ranging from 10% in low-risk patients to 68% in high-risk patients.³ The standard of care for patients with locoregional RCC is partial or radical nephrectomy.^{4,5} Despite multiple advances in the treatment of advanced disease in past decades, the role of adjuvant therapy following surgery with curative intent for patients with intermediate- to high-risk non-metastatic RCC and complete resection of metastatic sites in patients with limited metastasis remains unsettled. The anti-vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor agent sunitinib was approved in the United States as adjuvant treatment for patients with high risk of recurrence based on improved disease-free survival versus placebo in the S-TRAC trial.⁶ However, an overall survival benefit was not observed in this study and furthermore, sunitinib showed a non-significant detriment to quality of life.^{7,8} Other trials of anti-VEGF agents (pazopanib, axitinib and sorafenib) have not met their primary efficacy endpoints, including a large phase III trial (ASSURE) comparing sunitinib, sorafenib and placebo in the adjuvant setting.⁹⁻¹² Given these mixed results, utilization of adjuvant targeted therapy in RCC remains infrequent. The mTOR inhibitor everolimus as adjuvant therapy after nephrectomy did not demonstrate a significant disease-free survival or overall survival benefit vs placebo, although a trend towards a greater benefit from everolimus on disease-free survival was observed in very high-risk patients.¹³

Recently, the anti-programmed death-1 (PD-1) antibody pembrolizumab was approved in the United States and European Union as adjuvant therapy based on results of the KEYNOTE-564 trial.^{14,15} Adjuvant immunotherapy with pembrolizumab is considered optional for patients with intermediate- or high-risk operable clear cell RCC per European Society for Medical Oncology and European Association of Urology guidelines,^{4,16} due to the lack of confirmed overall survival

benefit as well as toxicity-related considerations associated with immunotherapy.¹⁷ These factors must be considered in the adjuvant setting as following nephrectomy, patients are cancer free and may be cured by surgery alone. As such, additional trials are needed to clarify the role of adjuvant immunotherapy in this disease space. Two factors support the investigation of atezolizumab, an anti-programmed death-ligand 1 (PD-L1) antibody, in this setting. First, immunotherapy with PD-1 and PD-L1 antibodies in combination with CTLA-4- or VEGF-targeting agents has demonstrated clinical activity as first-line treatment for patients with metastatic RCC.¹⁸ Secondly, atezolizumab is approved for multiple tumour types.¹⁹ With data supporting the clinical activity of immunotherapy in RCC and atezolizumab demonstrating utility in other tumour types, investigating the role of atezolizumab as an adjuvant treatment in patients with resected increased risk RCC is appropriate.

We conducted the IMmotion010 trial to evaluate the efficacy and safety of atezolizumab versus placebo after resection in patients with renal cell carcinoma that had a component of either clear cell or sarcomatoid histology with an increased risk of recurrence. Here we report efficacy and safety results from the primary analysis of IMmotion010 (NCT03024996).

METHODS

Participants

Eligible patients were 18 years of age or older with histologically confirmed RCC with a component of either clear cell histology or sarcomatoid histology (sarcomatoid dedifferentiation regardless of the primary epithelial subtype) and had increased risk of recurrence following nephrectomy or following nephrectomy and metastasectomy (M1 resected with no evidence of disease [NED]) in patients with metastatic disease. Increased risk was defined as T2 Fuhrman Grade 4, T3a Grade 3/4, T3b/c any Grade, T4 any Grade or TxN+ any Grade. The M1 NED category included patients with synchronous metastatic disease to the adrenal gland or lung, or

metachronous metastatic disease to the lung, lymph node or soft tissue with recurrence occurring more than 12 months following initial nephrectomy. All patients must have undergone nephrectomy with or without metastasectomy within 12 weeks of randomisation with NED at screening. Disease-free status at screening was assessed by investigators and confirmed by central radiology review. Patients could not have received prior anticancer therapy for RCC. Patients had an Eastern Cooperative Oncology Group performance status score of 0 or 1 (scores range from 0 to 5, with higher scores indicating greater disability). Additional eligibility criteria are described in the protocol in the Supplemental Appendix.

Randomisation and masking

Participants were randomly assigned (1:1) using a permuted block method with a block size of 4. Patients were stratified according to disease stage (T2/T3a vs T3b/c/T4/N+ vs M1 NED), region (North America [excluding Mexico] vs rest of world) and PD-L1 status on tumour-infiltrating immune cells (PD-L1 immune cell [IC] expression <1% vs ≥1%, as assessed by immunohistochemistry using SP142 assay). Notably, although PD-L1 was not included as a stratification factor in the original version of the protocol, it was included ahead of enrolment of the first patient. Patients, investigators and the study sponsor were masked to the treatment allocation.

Trial Design and Procedures

In this phase 3, randomised, double-blind, international trial, patients were randomly assigned in a 1:1 ratio to receive adjuvant atezolizumab or placebo after nephrectomy with or without metastasectomy.

Atezolizumab (at a dose of 1200 mg intravenous) or placebo (intravenous) was administered once every 3 weeks for 16 cycles or 1 year (whichever occurred first) or until disease recurrence, unacceptable toxicity, intercurrent illness that may impact patient safety with

continued treatment, pregnancy, withdrawal of consent or study termination by the sponsor. No dose modification was allowed. Interruption or discontinuation of atezolizumab was allowed per study guidelines, which are outlined in the protocol.

Endpoints

The primary endpoint was investigator-assessed disease-free survival, defined as the time from randomisation to the first documented recurrence event (local recurrence, new primary RCC, distant metastasis) or death from any cause. Secondary endpoints were overall survival, independent review facility-assessed disease-free survival, independent review facility- and investigator-assessed disease-free survival in patients with PD-L1 immune cell expression $\geq 1\%$, independent review facility–assessed event-free survival (defined as time from randomisation to death from any cause, first recurrence in patients without baseline disease or first disease progression in patients with baseline disease), disease-specific survival (defined as time from randomisation to death from RCC), distant metastasis-free survival (defined as time from randomisation to death from any cause or the date of diagnosis of distant metastases) and the 1-, 2- and 3-year rates of investigator-assessed disease-free survival and independent review facility–assessed disease-free survival. Assessments for RCC recurrence were performed every 3 months following randomisation in the first 3 years and every 6 months thereafter until death, disease recurrence, loss to follow-up, or withdrawal of consent. Safety was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

During the conduct of the study, the primary endpoint was changed from assessment of disease-free survival by independent review facility to assessment by investigator. This change was made at the recommendation of the study Steering Committee in advance of the primary analysis. Independent review facility–assessed disease-free survival was continued as a secondary endpoint to support the primary endpoint in the event of potential investigator bias despite the double-blind nature of the trial. Independent review facility–assessed event-free

survival was also added as an endpoint during this protocol amendment. Full details and rationale are available in the Methods section of the Appendix (p 7).

Efficacy was assessed in the intention-to-treat population, defined as all patients who were randomised, regardless of whether study treatment was received. The safety-evaluable population included all patients who received any dose of atezolizumab or placebo.

Oversight

The trial was designed by academic advisors and employees of the sponsor (F. Hoffmann–La Roche). The trial protocol was approved by independent review boards or ethics committees at each of the 215 study sites in 28 countries. The trial sponsor provided all investigational medicinal products (atezolizumab and placebo). The trial was conducted according to Good Clinical Practice guidelines of the International Conference on Harmonisation and the principles of the Declaration of Helsinki. All patients provided written informed consent. The trial protocol is available in the Appendix.

Role of the funding source

The sponsor conducted the data analyses and provided the data to the authors. All authors had full access to the data. The authors vouched for the accuracy and completeness of the data and verified that the trial was conducted according to the protocol. All drafts of the manuscript were prepared by the authors, with the assistance of professional medical writers funded by the sponsor.

Statistical Analysis

The study was designed to enrol approximately 764 patients with a 1:1 randomisation of 382 patients per treatment arm. The primary analysis of investigator-assessed disease-free survival was performed when the prespecified 334 disease-free survival events (44% of 764 patients) occurred in the intention-to-treat population with 90% power (two-sided α level of 0.05),

assuming an HR of 0.70 (corresponding to median disease-free survival of 67 months in the atezolizumab group and 47 months in the placebo group) and 5% loss to follow-up over 24 months. An interim analysis of overall survival was performed, but overall survival was not formally tested as the primary endpoint was not met. Other secondary endpoints were not statistically tested and results are presented with point estimates and corresponding 95% CIs. Investigator-assessed disease-free survival and overall survival were compared between treatment arms using the stratified log-rank test. The HR was estimated using a stratified Cox proportional hazards model, and the 95% confidence interval (CI) for the HR was provided. Schoenfeld test was used to assess the proportional hazards assumption. Kaplan-Meier methodology was used to estimate the median survival time (Brookmeyer-Crowley methodology was used to construct the 95% CI) and the survival rate at specific timepoints (Greenwood's formula was used to construct the 95% CIs) for each treatment arm. All analyses were performed in the intention-to-treat population other than safety analyses, which were performed in all patients who received at least one dose of study treatment. SAS version 9.4 was used for statistical analyses. The full statistical analysis plan is available in the Appendix.

RESULTS

Patients and Trial Interventions

From 03 January 2017 to 15 February 2019, a total of 1399 patients at 182 sites in 28 countries were screened for trial eligibility (Appendix p 8). There were 621 patients excluded at screening, with the most common reasons being not meeting inclusion criteria (n=416) and withdrawal of consent (n=99).

A total of 778 patients were randomised, with 390 assigned to the atezolizumab group and 388 to the placebo group. There were 390 patients who received at least one dose of atezolizumab and 383 who received at least one dose of placebo. The data cutoff date was 03 May 2022, and

the median time from randomisation to date of death, last known alive date or data cutoff date was 44·7 months (interquartile range 39·1–51·0) for the intention-to-treat population, 45·1 months (interquartile range 39·4–51·6) for the atezolizumab group and 44·2 months (interquartile range 38·6–50·8) for the placebo group. In the atezolizumab group, 135 (35%) patients discontinued study treatment, most commonly due to disease relapse (n=51; 13%) or adverse event (n=45; 12%); in the placebo group, 109 (28%) patients discontinued study treatment, most commonly due to disease relapse (n=60; 16%) or other reasons (n=25; 7%) (Appendix p 8).

The most frequent subsequent anti-cancer therapy in both treatment arms was a tyrosine kinase inhibitor, received by 86 (22%) and 72 (19%) patients in the atezolizumab and placebo groups, respectively (Appendix p 13). Overall, 86 (11%) patients received immune therapies as subsequent therapy, 40 (10%) in the atezolizumab group and 46 (12%) in the placebo group. The median time from randomisation to subsequent anticancer therapy was 13·2 months (interquartile range 6·4–24·5) months in the atezolizumab group and 8·9 months (interquartile range 5·2–16·4) in the placebo group. Baseline characteristics were balanced between treatment arms (Table 1 and Appendix p 14).

Efficacy

As of the data cutoff date, 332 events of investigator-assessed disease-free survival had occurred (164 [42%] events in the atezolizumab group and 168 [43%] in the placebo group; figure 1A). Patients who were alive and disease-free at the time of data cutoff were censored. The risk of disease recurrence or death was not statistically significantly reduced with adjuvant atezolizumab vs placebo (hazard ratio [HR] for recurrence or death 0·93, 95% CI 0·75–1·15, p=0·50). The estimated percentage of patients who remained alive and recurrence free at 36 months was 59·4% (95% CI, 54·4–64·5) in the atezolizumab group and 59·0% (95% CI, 54·0–

64·0) in the placebo group; the corresponding percentages were 67·3% (95% CI 62·6–72·1) and 65·0% (95% CI 60·2–69·9) at 24 month, and 77·4% (95% CI 73·2–81·6) and 74·1% (95% CI 69·7–78·5) at 12 months. Among 157 patients with investigator-assessed recurrence in the atezolizumab arm, 143 (91%) had metastatic recurrence, nine (6%) had local recurrence and five (3%) had a new primary tumour. Among 159 patients with investigator-assessed recurrence in the placebo arm, 145 (91%) had metastatic recurrence, 13 (8%) had local recurrence, and one (1%) had a new primary tumour. Investigator-assessed disease-free survival across key subgroups is shown in figure 1B.

At data cutoff, the overall survival event ratio was immature and patients alive were censored. There were 107 deaths, 54 (14%) in the atezolizumab group and 53 (14%) in the placebo group. There was no evidence of a reduced risk of death from any cause with adjuvant atezolizumab vs placebo (HR for death 0·97, 95% CI 0·67–1·42) (figure 2). The estimated percentage of patients who remained alive at 36 months was 90·3% (95% CI 87·3–93·3) in the atezolizumab group and 89·8% (95% CI 86·6–92·9) in the placebo group.

In addition to investigator-assessed disease-free survival, independent review facility–assessed disease-free survival was also analysed. In total, 263 events of independent review facility–assessed disease recurrence or death had occurred (125 events in the atezolizumab group and 138 in the placebo group (table 2 and Appendix p 9). The risk of disease recurrence or death was 13% lower with adjuvant atezolizumab vs placebo (HR for recurrence or death 0·87, 95% CI 0·69–1·12).

The estimated percentage of patients who remained alive and recurrence free as assessed by the independent review facility at 36 months was 65·0% (95% CI 59·9–70·2) in the atezolizumab group and 62·7% (95% CI 57·5–67·9) in the placebo group; the corresponding percentages at 24 months were 70·4% (95% CI 65·5–75·3) and 68·2% (95% CI 63·3–73·2), and at 12 months were 81·0% (95% CI 76·9–85·2) and 76·4% (95% CI 72·0–80·9).

In the subgroup of patients with PD-L1 immune cell expression $\geq 1\%$ (IC1/2/3), the risk of investigator-assessed disease recurrence or death was 17% lower with adjuvant atezolizumab versus placebo (HR for recurrence or death 0·83, 95% CI 0·63–1·10). A similar result was observed per independent review facility assessment in patients with PD-L1 immune cell expression $\geq 1\%$ (table 2). In an exploratory analysis of PD-L1 expression level, among the 103 patients with high PD-L1 expression (IC2/3 [$\geq 5\%$ expression]), the risk of investigator-assessed disease recurrence or death was 43% lower with adjuvant atezolizumab vs placebo (HR for recurrence or death 0·57, 95% CI 0·29–1·15) (Appendix pp 10-11). Among the 364 patients with low PD-L1 expression (IC1 [$1-\lt 5\%$ expression]), the risk of investigator-assessed disease recurrence or death was 8% lower (HR for recurrence or death 0·92, 95% CI 0·68–1·25). The risk of independent review facility–assessed event-free survival was 16% lower with adjuvant atezolizumab (HR 0·84, 95% CI 0·67–1·06) (table 2). The risk of investigator–assessed disease-specific survival was 15% lower with adjuvant atezolizumab vs placebo (HR 0·85, 95% CI 0·55–1·33) and the risk of distant metastases free survival was 7% lower (HR 0·93, 95% CI 0·74–1·16) (table 2).

Safety

Overall, 773 patients received study treatment and were included in the safety analysis population, including 390 in the atezolizumab group and 383 in the placebo group. In the atezolizumab group, 255 (65%) of the patients completed the full 16 cycles or 1 year of trial treatment; 135 (35%) patients discontinued treatment due to disease relapse (13%), adverse event (12%), withdrawal by patient (5%), other reasons (4%), physician decision (1%) or death ($<1\%$). In the placebo group, 274 (72%) of the patients completed the full 16 cycles or 1 year of trial treatment; 109 (28%) patients discontinued treatment due to disease relapse (16%), other reasons (7%), withdrawal by patient (3%), adverse event (3%), physician decision ($<1\%$) or

348 death (<1%). The median duration of the trial regimen was 10·4 months (interquartile range
349 5.6–10.6) in the atezolizumab group and 10·4 months (interquartile range 8.9–10.5) in the
350 placebo group.

351 Adverse events of any grade were reported in 373 (96%) patients who received atezolizumab
352 and 341 (89%) patients who received placebo (table 3). Adverse events that occurred in >15%
353 of patients who received atezolizumab were fatigue, diarrhoea, arthralgia and pruritus, while
354 those occurring in >15% of patients who received placebo were fatigue and diarrhoea
355 (Appendix p 15). The adverse events with a $\geq 5\%$ incidence difference between patients who
356 received atezolizumab and those who received placebo were arthralgia, pruritus,
357 hypothyroidism, rash, pyrexia, and dry mouth (Appendix p 12).

358 A total of 296 patients (76%) who received atezolizumab and 203 (53%) who received placebo
359 experienced at least one adverse event deemed by investigators as related to atezolizumab or
360 placebo (table 3). Adverse events related to treatment that occurred in >10% of patients in the
361 atezolizumab group were fatigue, pruritus, hypothyroidism and diarrhoea; those occurring in
362 >10% of patients in the placebo group were fatigue, pruritus and diarrhoea (Appendix p 16).
363 Grade 3/4 adverse events occurred in 106 (27%) patients who received atezolizumab and 81
364 (21%) patients who received placebo. Grade 3/4 adverse events related to treatment occurred
365 in 55 (14%) patients who received atezolizumab and 18 (5%) who received placebo.

366 There were four deaths due to adverse events in the study, one among patients who received
367 atezolizumab and three among patients who received placebo. One patient who received
368 atezolizumab died due to acute myeloid leukaemia. Among patients who received placebo,
369 deaths due to adverse events resulted from respiratory failure, sepsis and unknown cause.
370 There were no deaths attributed to treatment.

371 In total, 69 (18%) patients who received atezolizumab experienced a serious adverse event,
372 versus 46 (12%) patients who received placebo. Serious adverse events that occurred in $\geq 1\%$

of patients in the atezolizumab arm were hyperglycaemia in 1% of patients (vs 1% in the placebo arm) and urinary tract infection in 1% (vs 1% in the placebo arm) (Appendix p 17). Serious adverse events related to treatment occurred in 34 (9%) patients who received atezolizumab and three (1%) who received placebo.

Adverse events that led to treatment discontinuation were reported in 45 (12%) patients in the atezolizumab group and ten (3%) in the placebo group (table 3). Among the patients who received atezolizumab, pneumonitis, hepatitis, colitis, ALT increased, AST increased, myositis and dermatitis led to treatment discontinuation in more than one patient (Appendix pp 18-19). Adverse events that led to dose interruption were reported in 90 (23%) patients in the atezolizumab group and 49 (13%) in the placebo group (table 3).

Immune-mediated adverse events of any grade occurred in 212 (54%) of the patients who received atezolizumab and 106 (28%) who received placebo. Grade 3/4 immune-mediated adverse events occurred in 30 (8%) patients who received atezolizumab and in ten (3%) who received placebo. Immune-mediated adverse events that occurred in $\geq 15\%$ of patients who received atezolizumab were rash and hypothyroidism (appendix p 20). A total of 40 (10%) patients who received atezolizumab and four (1%) who received placebo experienced an immune-mediated adverse event requiring corticosteroids (Appendix p 21).

DISCUSSION

At the prespecified primary analysis, this trial did not meet its primary endpoint. Treatment with adjuvant atezolizumab did not result in a statistically significant improvement in disease-free survival as assessed by investigators versus placebo in patients with RCC with a clear cell or sarcomatoid component who were at increased risk for recurrence. Strengths of this study include the large population and long median follow-up time of 45 months, as this was the primary analysis of the first initiated adjuvant PD-L1 trial and not an interim analysis. Our study was enriched for patients with increased risk of recurrence by enrolling locally advanced

intermediate and high risk M1 NED. The control arm in our study performed per the expectation of these patients,²⁰ suggesting that the trial enrolled the intended patient population. The median duration of treatment in this study was 10 months, excluding the possibility that undertreatment could have led to the lack of benefit seen.

The safety of atezolizumab was consistent with the known safety profile of the drug. There were no treatment-related deaths in the study. A new potential adverse drug reaction of dry mouth was identified. All adverse events of dry mouth were Grade 1 or 2 and did not impact the risk-benefit profile of atezolizumab.

The results of our study are also of interest as they contrast with those of the KEYNOTE-564 study, which observed a disease-free survival benefit with the PD-1 inhibitor pembrolizumab in this setting at 24 months (HR 0·68, 95% CI 0·53–0·87) and in an updated analysis conducted at 30 months (HR 0·63, 95% CI 0·50–0·80).^{14,15} There were differences between our study and KEYNOTE-564 that warrant further analysis. In KEYNOTE-564, M1 NED patients constituted only 6% of the enrolled population and only patients with synchronous metastases or metastases resected within 1 year of nephrectomy were eligible. In our study, M1 NED patients constituted 14% of the enrolled population, and included both synchronous and metachronous (recurrence no less than 12 months following primary nephrectomy) disease. The impact of this is challenging to infer – while our study had a higher proportion of M1 NED patients, those enrolled into KEYNOTE-564 were ostensibly at higher risk for recurrence. Additionally, our study restricted eligibility of pT3a to only include those with tumour Fuhrman Grade 3/4. Our studies also ultimately enrolled different proportions of patients with lymph node involvement (6% in KEYNOTE-564 versus 11% in our trial), although other factors, such as the aforementioned differences in the M1 NED population, may have counterbalanced these variations. Despite these differences, the outcomes in the placebo groups of the two studies appear to be similar (disease-free survival rates in the respective placebo groups at 24 months were 65% in

IMmotion010 and 68% in KEYNOTE-564). Subgroup analysis of KEYNOTE-564 suggested that the small number of patients with M1 NED derived a greater disease-free survival benefit from pembrolizumab (HR 0·29, 95% CI 0·12–0·69); such a benefit was not seen in IMmotion010, despite having a larger proportion of patients with M1 NED, including synchronous and metachronous subtypes. In our study, a trend towards improved disease-free survival was seen in patients with a sarcomatoid component, consistent with prior trials of checkpoint inhibitors,^{21,22} and in the subgroup of patients with higher PD-L1 expression (IC2/3).

The investigative community may look to several other studies to clarify the role of adjuvant checkpoint inhibition. The ALLIANCE cooperative group has led the phase III PROSPER trial, a study comparing perioperative nivolumab (1 or 2 doses preoperatively, continuing up to approximately 9 months post-operatively) to observation in a similar setting.²³ Although full results have not yet been published, it has been reported that the study failed to meet its primary endpoint.²⁴ In advanced disease and in the front-line setting, the activity of checkpoint inhibitor monotherapy appears to be lower than that with doublet therapy.^{21,25} Other unique strategies have also been applied in the adjuvant setting. The ongoing RAMPART trial explores doublet immunotherapy, comparing observation with durvalumab and with durvalumab/tremelimumab following surgery.²⁶ The CheckMate 914 trial, which has completed accrual, has a similar premise, comparing adjuvant placebo with nivolumab and with nivolumab/ipilimumab in patients with resected, high-risk RCC.²⁷ An initial report from CheckMate 914 indicates that the study did not meet the primary endpoint of improvement in disease-free survival.²⁸ Given differences in trial design, it is possible that sample size, perioperative versus adjuvant treatment, duration of therapy and use of placebo versus observation control arm may have driven the varied outcomes across these trials. Specific drug properties and mechanism of action must also be considered – atezolizumab is directed at PD-L1, whereas pembrolizumab antagonizes PD-1. With emerging data around the combined

448 impact of CTLA4 and PD-1 inhibition in the adjuvant setting from CheckMate-914, there will
449 hopefully be opportunities to understand the biological impact of these strategies, possibly
450 through exploration of circulating biomarkers and peripheral immunophenotyping.

451 Limitations of the study results include the screen failure rate in our study of 44%, considerably
452 higher than the 29% screen failure rate observed in KEYNOTE-564.¹⁴ Reasons for screen
453 failure are not detailed in available publications for KEYNOTE-564. However, on detailed
454 comparison of both study protocols, KEYNOTE-564 did not require central confirmation of
455 absent metastases on baseline scans, whereas our study did. Combining categories and
456 removing stratification variables due to small number of events is also a limitation in the
457 analysis. An additional limitation is the inherent potential bias in the HRs common across
458 oncology studies. Lastly, there is difficulty in interpretation of any secondary and exploratory
459 analyses in a study that does not meet its primary endpoint.

460 Taken together, our results add to an emerging body of literature around the role of adjuvant
461 immunotherapy for RCC. With the longest duration of follow-up to date, we observed no
462 evidence of clinical benefit in disease-free survival or overall survival with adjuvant atezolizumab
463 in patients with high-risk localised or fully resected RCC. Biomarker work is underway to
464 determine whether tumour genomic characteristics or circulating biomarkers may identify patient
465 populations who derive benefit from adjuvant atezolizumab. There is precedent for tissue-based
466 adjuvant therapy selection in other diseases, such as HER2- and endocrine receptor-based
467 approaches in breast cancer and *EGFR* mutation directed therapy in lung cancer. The
468 IMvigor010 study showed no significant benefit in disease-free survival with adjuvant
469 atezolizumab in muscle-invasive bladder cancer, but a benefit in disease-free survival was
470 observed in patients positive for circulating tumour DNA identified using a bespoke assay,²⁹
471 which led to the prospective evaluation of a circulating tumour DNA positive population with

472 muscle invasive bladder cancer.³⁰ Similar biomarker-based clinical trial designs may advance
473 development of personalized adjuvant treatment regimens in RCC.

474

Contributors

SKP, RU, CS, LA, BR, MH, DB, BC, WL, OK, SD, AB **conceived and designed** the study. All authors were involved in the **collection of the data**. BC provided the **statistical analysis**. All authors **analyzed and interpreted the data, drafted and critically revised the manuscript for intellectual content and approved the final version** of the submitted manuscript.

Declaration of interests

Sumanta Kumar Pal: Has received advisory/consulting fees from Pfizer, Novartis, Aveo, Myriad Pharmaceuticals, Genentech, Exelixis, Bristol Myers Squibb, Astellas Pharma, Ipsen and Eisai. Has received travel support from CRISPR Therapeutics and Roche.

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533

534 **Data sharing**

535 For eligible studies qualified researchers may request access to individual patient level clinical

536 data through a data request platform. At the time of writing this request platform is Vivli.

537 <https://vivli.org/ourmember/roche/>. For up-to-date details on Roche's Global Policy on the

538 Sharing of Clinical Information and how to request access to related clinical study documents,

539 see here: https://go.roche.com/data_sharing.

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640

641 **Table 1: Patient characteristics at baseline (intention-to-treat population)**

	Atezolizumab (n=390)	Placebo (n=388)
Age		
Median (IQR), y	60·5 (52·0–69·0)	60·0 (52·8–68·0)
≥65 y	142 (36)	140 (36)
Male sex	287 (74)	278 (72)
Race		
White	324 (83)	304 (78)
Asian	43 (11)	51 (13)
Black/African American	8 (2)	9 (2)
Other/unknown	15 (4)	24 (6)
ECOG performance status score		
0	311 (80)	304 (78)
1	79 (20)	84 (22)
Geographic location		
North America*	143 (37)	139 (36)
Rest of World	247 (63)	249 (64)
Predominant histology		
Clear cell	364 (93)	356 (92)
Papillary	6 (2)	11 (3)
Chromophobe	3 (1)	5 (1)
Other	17 (4)	16 (4)
Component of sarcomatoid dedifferentiation	37 (9)	67 (17)
Pathological disease stage		
T2/T3a	252 (65)	248 (64)
T3b/c/T4/N+	82 (21)	88 (23)

M1 no evidence of disease [†]	56 (14)	52 (13)
Synchronous metastasis resected	11 (3)	13 (3)
Metachronous metastasis resected	45 (12)	39 (10)
PD-L1 immune cell expression		
<1%	158 (41)	153 (39)
≥1%	232 (59)	235 (61)

Data are n (%) unless otherwise stated.

ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; PD-L1, programmed death ligand 1.

*Excluding Mexico.

[†]Among the M1 NED patients with synchronous metastasectomy (n=24), the most common site of metastasis resected was the adrenal gland (n=17; 71%). Among the patients with metachronous metastasectomy (n=84), the most common sites of metastasis resected were lung (n=46; 55%), lymph node (n=8; 10%) and soft tissue (n=6; 7%).

652 **Table 2: Secondary outcomes**

	Atezolizumab	Placebo	HR (95% CI)
ITT population, n	390	388	
IRF-assessed disease-free survival			
Patients with event	125 (32)	138 (36)	
Median time to event (95% CI), mo	NE (54·1–NE)	NE (49·4–NE)	0·87 (0·69–1·12)
IRF-assessed event-free survival			
Patients with event	145 (37)	161 (41)	
Median time to event (95% CI), mo	NE (54·1–NE)	NE (45·4–NE)	0·84 (0·67–1·06)
Disease-specific survival			
Patients with event	37 (9)	41 (11)	
Median time to event (95% CI), mo	NE (NE–NE)	NE (NE–NE)	0·85 (0·55–1·33)
Distant metastasis-free survival			
Patients with event	155 (40)	158 (41)	
Median time to event (95% CI), mo	NE (48·4–NE)	52·9 (47·9–NE)	0·93 (0·74–1·16)
Patients with ≥1% PD-L1 expression on immune cells, n	232	235	
IRF-assessed disease-free survival in patients with ≥1% PD-L1 immune cells			
Patients with event	71 (31)	92 (39)	

Median time to event (95% CI), mo	NE (NE–NE)	NE (41·4–NE)	0·75 (0·55–1·03)
Investigator-assessed disease-free survival in patients with ≥ 1% PD-L1 immune cells			
Patients with event	93 (40)	105 (45)	
Median time to event (95% CI), mo	57·2 (44·6–NE)	47·9 (38·6–NE)	0·83 (0·63–1·10)

653 Data are n (%) unless otherwise stated.

654 CI, confidence interval; IRF, independent review facility; ITT, intention to treat; NE, not evaluable; PD-L1,
655 programmed death ligand 1.

656

657 **Table 3: Adverse events**

	Atezolizumab (n=390)	Placebo (n=383)
Any grade adverse event	373 (96)	341 (89)
Any-cause adverse event related to treatment	296 (76)	203 (53)
Grade 3 or 4 adverse event	106 (27)	81 (21)
Grade 3 or 4 adverse event related to treatment	55 (14)	18 (5)
Death due to adverse event	1 (<1)	3 (1)
Death due to adverse event related to treatment	0	0
Serious adverse event	69 (18)	46 (12)
Serious adverse event related to treatment	34 (9)	3 (1)
Adverse event leading to discontinuation of atezolizumab or placebo	45 (12)	10 (3)
Adverse event leading to dose interruption of atezolizumab or placebo	90 (23)	49 (13)

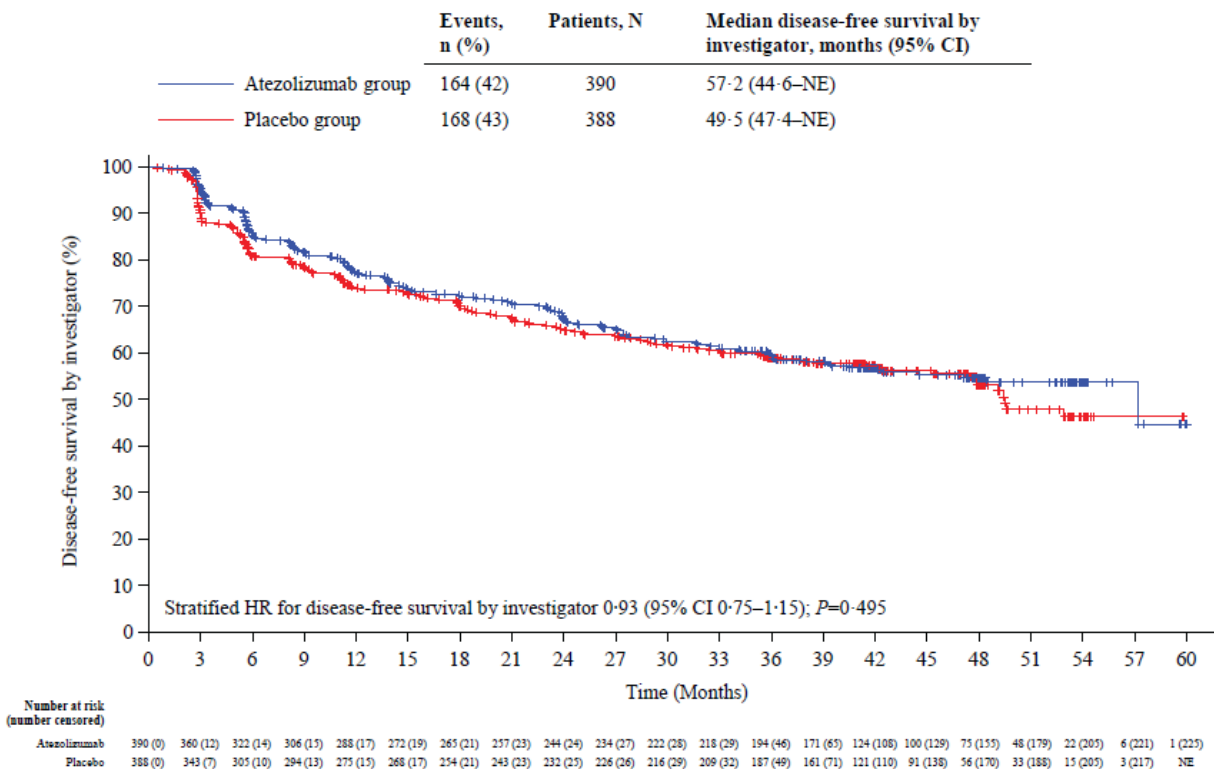
658 Data are n (%).

659

Figure 1: Kaplan-Meier estimate of disease-free survival as assessed by investigators and subgroup analysis

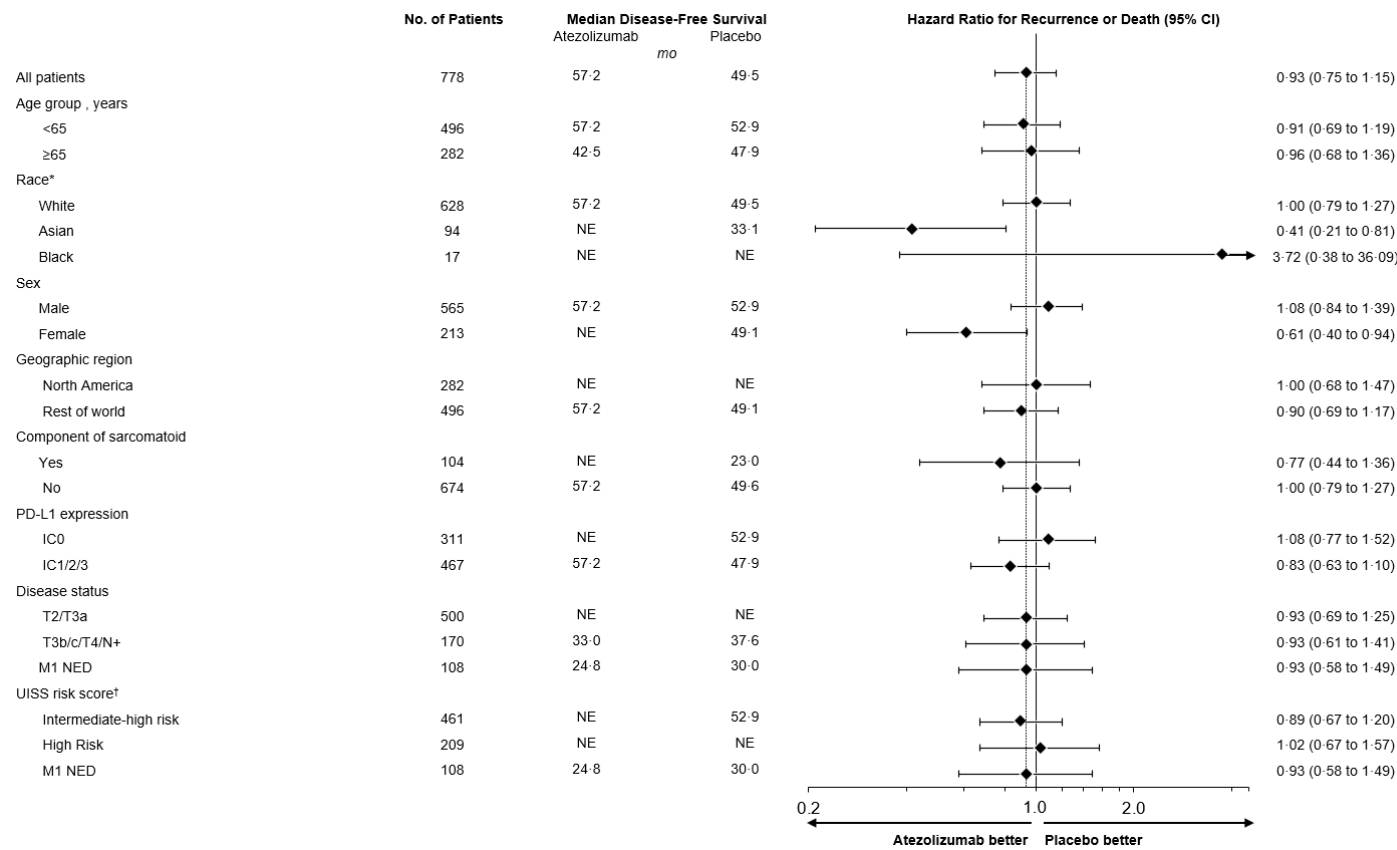
Kaplan-Meier estimates of disease-free survival as assessed by investigators, in the intention-to-treat population (A) and disease-free survival as assessed by investigators in key subgroups (B). The dashed line represents the HR for the overall population. *39 patients are not shown (race unknown [n=36], American Indian or Alaskan Native [n=2], multiple race [n=1]). [†]UISS risk score was a derived outcome. CI, confidence interval; HR, hazard ratio; NE, not evaluable; NED, no evidence of disease; UISS, UCLA Integrated Staging System.

A



672 **B**

673

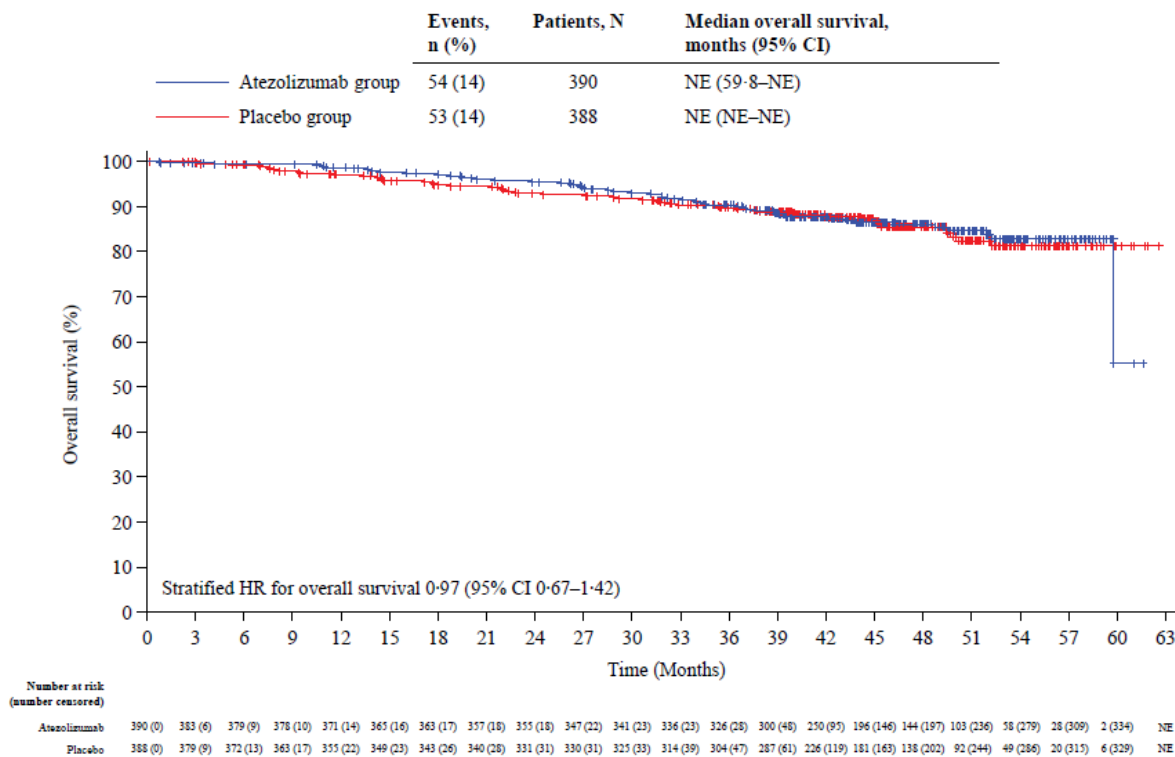


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Figure 2: Kaplan-Meier estimate of overall survival

Kaplan-Meier estimate of overall survival, in the intention-to-treat population. CI, confidence interval; HR, hazard ratio; NE, not evaluable.



681 **Supplementary appendix**

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682

683

684

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	Hansen, Aaron	Princess Margaret Cancer Center
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	Escudier, Bernard	Institut Gustave Roussy
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	Bigot, Pierre	CHU d'Angers
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	Hatakeyama, Shingo	Hirosaki University Hospital
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	Alekseev, Boris	P.A. Herzen Oncological Institution
	Atduev, Vagif	Privolzhsk Regional Medical Center
	Stroyakovskii, Daniil	City Clinical Oncology Hospital
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	Vats, Anna	City Clinical Oncology Dispensary
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	Puente Vazquez, Javier	Hospital Universitario Clínico San Carlos
	Gajate Borau, Pablo	Hospital Ramon y Cajal
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	Ou, Yen-Chuan	Taichung Veterans General Hospital
	Chuang, Cheng-Keng	Chang Gung Medical Foundation-Linkou
	Huang, Kuo-How	National Taiwan University Hospital
	Lin, Tzu-Ping	Taipei Veterans General Hospital
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	Chang, Chao-Hsiang	China Medical University Hospital
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	Hussain, Syed	Weston Park Hospital
	Powles, Thomas	Royal Free Hospital
	Faust, Guy	Leicester Royal Infirmary
	Allison, Jennifer	Christie Hospital
	Hawkins, Robert	Christie Hospital
	Pillai, Manon	Christie Hospital
	Mohamed, Wael	Singleton Hospital
	Shaheen, Ahmed	Singleton Hospital
	Wagstaff, John	Singleton Hospital
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	Spiess, Philippe	Moffitt Cancer Center
	Bratslavsky, Gennady	SUNY Upstate Medical University
	Lam, Elaine	University of Colorado Cancer Center
	Pal, Sumanta	City of Hope National Medical Center
	Leibovich, Bradley	Mayo Clinic - Rochester
	Karam, Jose Antonio	MD Anderson Cancer Center
	Matin, Surena	MD Anderson Cancer Center
	Master, Viraj	Emory University – Winship Cancer Center
	Barata, Pedro	Tulane University Health Sciences Center
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	Matrana, Marc	Ochsner Clinic Foundation
	Canter, Daniel	Ochsner Clinic Foundation
	Luchey, Adam	West Virginia University Hospitals Inc
	Ho, Thai	Mayo Clinic- Scottsdale
	Stadler, Walter	The University of Chicago Biological Sciences
	Hurwitz, Michael	Yale School of Medicine
	Shuch, Brian	Yale School of Medicine
	Pantuck, Allan	UCLA Urology
	Crispen, Paul	University of Florida
	Dang, Long	University of Florida
	Sumey, Christopher	Sanford Cancer Center Oncology Clinic
	Rose, Tracy	University of North Carolina at Chapel Hill
	Milowsky, Matthew	University of North Carolina at Chapel Hill
	Burgess, Earle	Levine Cancer Institute
	Gaston, Kris	Levine Cancer Institute
	Sanchez, Alejandro	University of Utah; Huntsman Cancer Hospital
	Lowrance, Will	University of Utah; Huntsman Cancer Hospital
	Adorno-Febles, Victor	Laura and ISAAC Perlmutter Cancer Center at NYU Langone
	Cho, Daniel	Laura and ISAAC Perlmutter Cancer Center at NYU Langone
	Stratton, Kelly	University of Oklahoma; Stephenson Oklahoma Cancer Center
	Merchan, Jaime	University of Miami, School of Med
	Rini, Brian	Vanderbilt University Medical Center; Vanderbilt University
	Chism, David	Vanderbilt University Medical Center; Vanderbilt University
	Rathmell, Wendy	Vanderbilt University Medical Center; Vanderbilt University
	Uchio, Edward	University of California Irvine Medical Center
	Tsao, Che-kai	Mount Sinai Medical Center
	Sahasrabudhe, Deepak	University of Rochester Medical Center
	Guancial, Elizabeth	University of Rochester Medical Center
	Kingsley, Clint Daniel	Erlanger Health Systems
	Singh, Amar	Erlanger Health Systems
	Ornstein, Moshe	Cleveland Clinic Foundation
	Kaufman Jr., Ronald	New York Oncology Hematology at Albany Medical Center
	Shipstone, Asheesh	Urology Associates of Kingsport
	DaSilva, Marco	Urology Associates of Kingsport
	Herman, James	Urology Associates of Kingsport
	Prasad, Sandip	Garden State Urology
	Clark, Joseph	Loyola University Medical Center, Cardinal Bernardin Cancer Center
	Rubenstein, Jonathan	Chesapeake Urology Research Associates
	Brugarolas, James	University of Texas Southwestern Medical Center
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Supplementary Methods

There was a protocol amendment where the primary endpoint was changed from assessment of disease-free survival by independent review facility to assessment by investigator. In a double blinded trial design, investigator assessment was acceptable for the determination of recurrence in the adjuvant setting and better approximated clinical practice.¹ However, in clinical trials, central radiology review has traditionally been considered a method that decreases the risks of bias, and that was the intention at the onset of this study. Since then, challenges associated with radiographic assessments at times of screening and recurrence in genitourinary adjuvant trials have been identified.^{2,3} Certain radiographic assessment methodologies of backdating recurrence do not reflect real-world practice, where patients and their associated radiographic assessments are managed prospectively and may lead to challenges in interpretation and clinical applicability of the results. In light of these challenges, the study Steering Committee recommended reverting the primary endpoint back to investigator-based disease-free survival. It is important to note that during this process the Sponsor remained blinded to the data and the endpoint was changed in advance of the primary analysis. Independent review facility–assessed disease-free survival was continued as a secondary endpoint to support the primary endpoint in the event of potential investigator bias despite the double-blind nature of the trial.

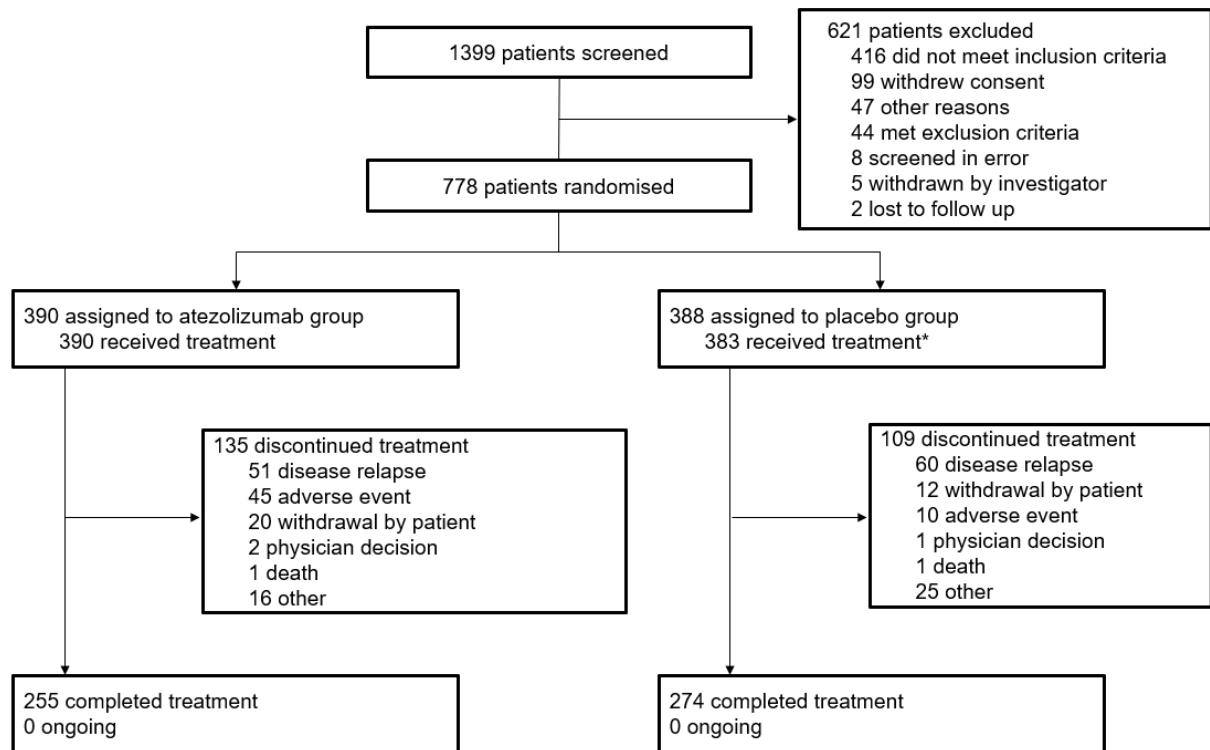
Event-free survival was also added as an endpoint during this protocol amendment. Independent review facility–assessed event-free survival allowed for the assessment of patients with baseline radiographic indeterminate lesions. In the absence of confirmed evidence of malignant disease, such patients are potentially at high risk, are likely to benefit from adjuvant therapies and are recommended to not be excluded from adjuvant clinical trials.²

As a separate amendment, during the conduct of the study, the assumption of the median survival time of the control arm was increased from 36 to 47 months based on emerging data from adjuvant trials. Hence sample size was increased by 100 to approximately 764.

Supplemental references

1. McKay RR. The promise of adjuvant immunotherapy in renal-cell carcinoma. *N Engl J Med* 2021; **385**: 756–8.
2. Agrawal S, Haas NB, Bagheri M, Lane BR, Coleman J, Hammers H, et al. Eligibility and radiological assessment for adjuvant clinical trials in kidney cancer. *JAMA Oncol* 2020; **6**: 133–41.
3. Apolo AB, Milowsky MI, Kim L, et al. Eligibility and radiological assessment in adjuvant clinical trials in bladder cancer. *JAMA Oncol* 2019; **5**: 1790–8.

Figure S1: Trial flowchart



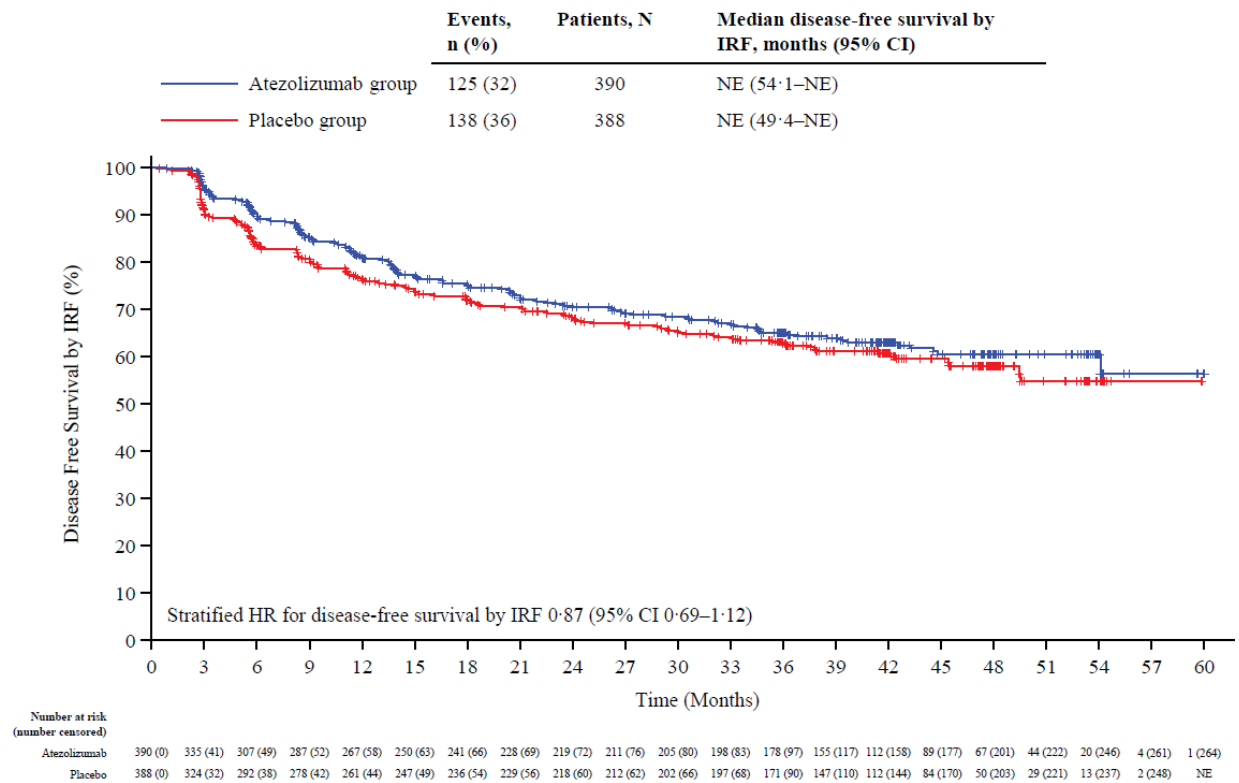
*Five patients in the placebo group did not receive treatment (due to withdrawal by patient [n=2], lost to follow up [n=1], disease relapse [n=1] and other [n=1]).

All efficacy analyses were performed in the intention-to-treat population (all patients who were randomized; N=778) and all safety analyses were performed in patients who received at least one dose of atezolizumab or placebo.

Further details of patient disposition are in supplemental Table S9 (appendix p 22).

Figure S2: Kaplan-Meier estimate of disease-free survival as assessed by IRF

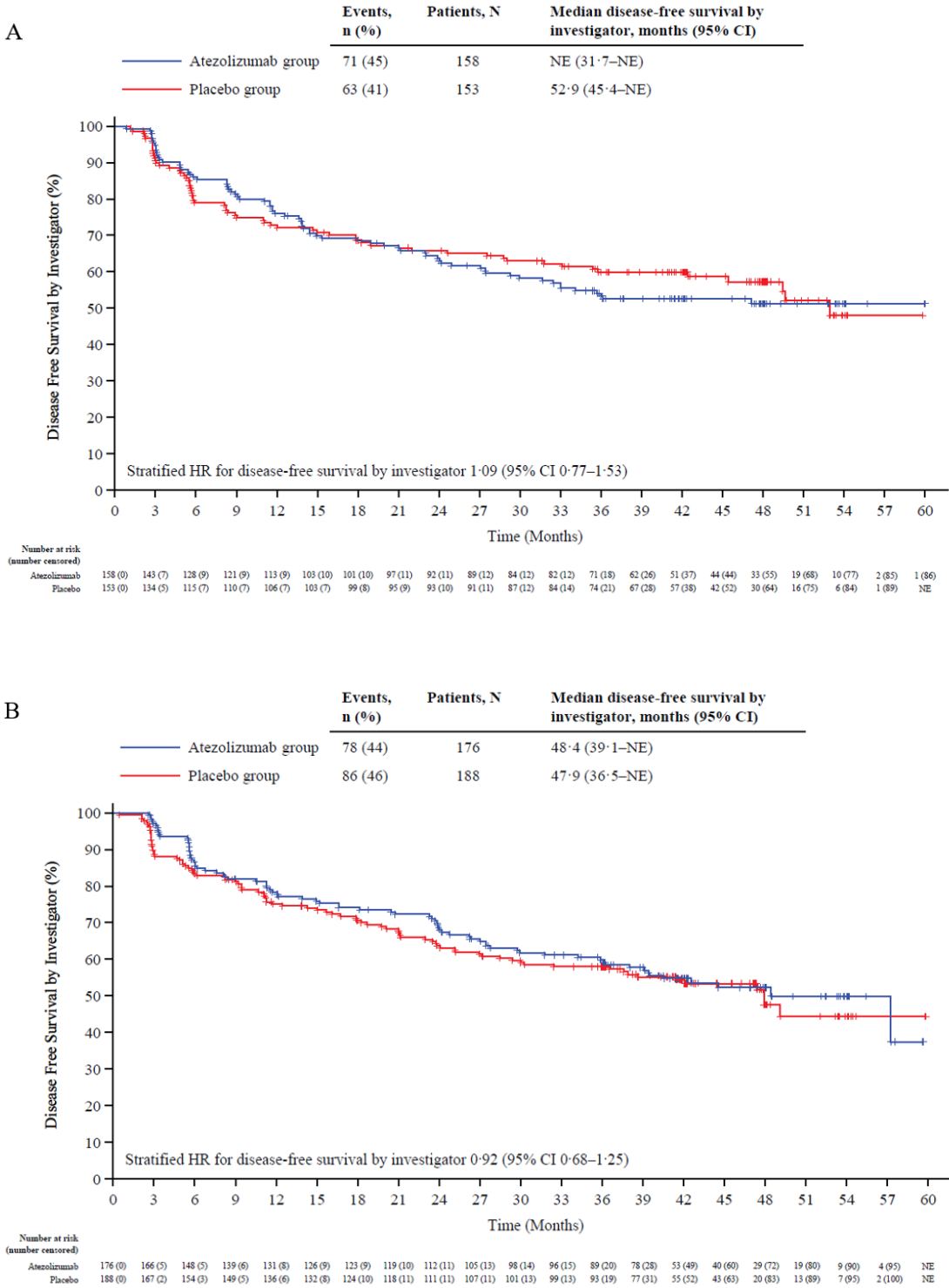
Kaplan-Meier estimates of disease-free survival as assessed by IRF, in the intention-to-treat population.



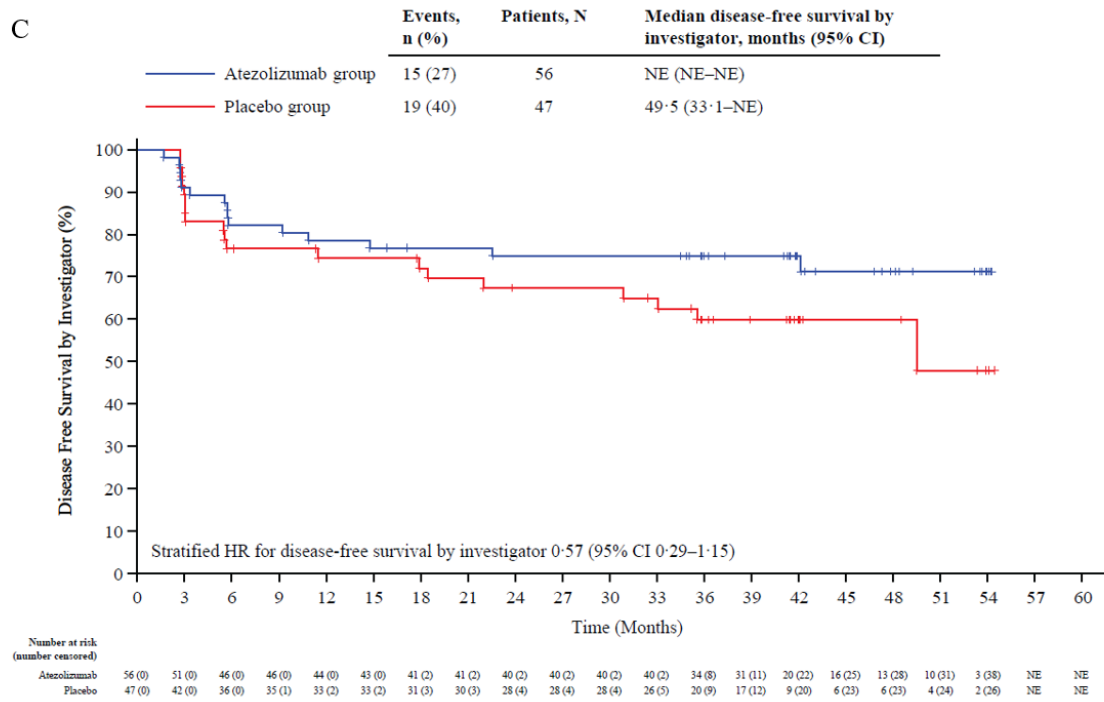
CI, confidence interval; HR, hazard ratio; IRF, independent review facility; ITT, intention to treat; NE, not evaluable.

Figure S3: Kaplan-Meier estimate of disease-free survival as assessed by investigators by PD-L1 expression status

Kaplan-Meier estimates of disease-free survival as assessed by investigators, in patients with PD-L1 IC0 (A) PD-L1 IC1 (B) and PD-L1 IC2/3 (C).



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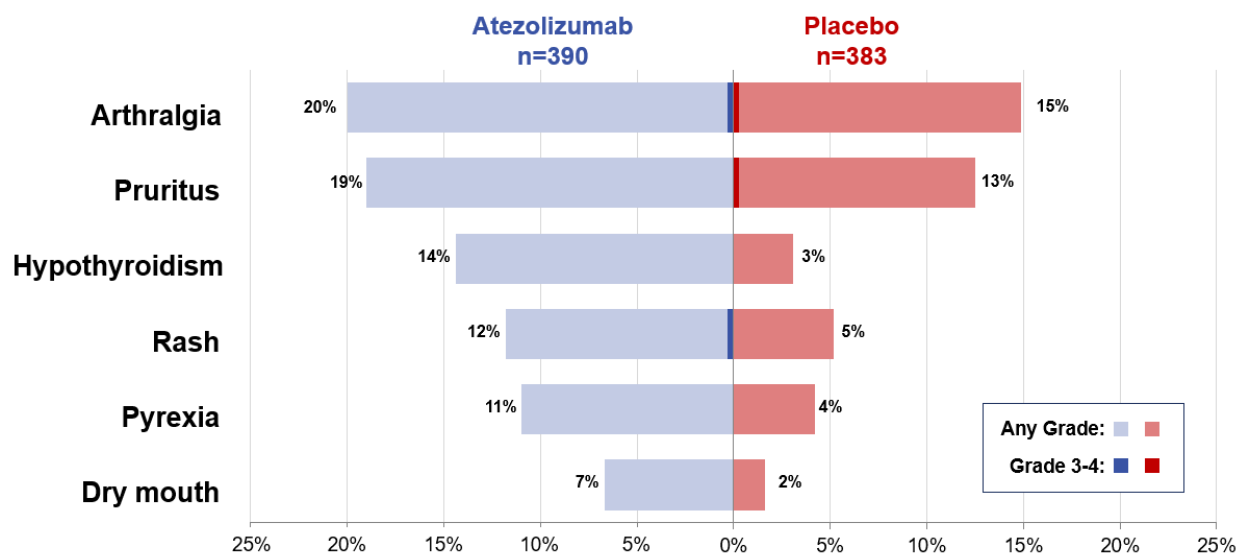


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746 CI, confidence interval; HR, hazard ratio; ITT, intention to treat; NE, not evaluable; PD-L1, programmed death
 747 ligand 1.

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749 **Figure S4: Adverse events with an incidence difference $\geq 5\%$ between patients who received atezolizumab and**
750 **those who received placebo**



752 **Table S1: Subsequent therapies**
753

	Atezolizumab (n=390)	Placebo (n=383)
TKI/VEGF inhibitor	86 (22)	72 (19)
Cabozantinib	28 (7)	23 (6)
Sunitinib	21 (5)	25 (6)
Axitinib	19 (5)	18 (5)
Pazopanib	14 (4)	11 (3)
Sunitinib malate	12 (3)	6 (2)
Lenvatinib	7 (2)	5 (1)
Pazopanib hydrochloride	4 (1)	6 (2)
Cabozantinib S-malate	6 (2)	3 (1)
Tivozanib	2 (1)	3 (1)
Sorafenib tosylate	0	2 (1)
Bevacizumab	0	1 (<1)
Erlotinib hydrochloride	0	1 (<1)
Tivozanib hydrochloride monohydrate	1 (<1)	0
Immunotherapy	40 (10)	46 (12)
Nivolumab	21 (5)	35 (9)
Ipilimumab	9 (2)	19 (5)
Pembrolizumab	16 (4)	10 (3)
Atezolizumab	1 (<1)	1 (<1)
Avelumab	1 (<1)	1 (<1)
Bempegaldesleuken	0	2 (1)
Quavonlimab	2 (1)	0
Rituximab	1 (<1)	1 (<1)
BMS 813160	1 (<1)	0
Durvalumab	0	1 (<1)
MTOR	8 (2)	5 (1)
Everolimus	8 (2)	5 (1)
Other/investigational agent	7 (2)	5 (1)
Belzutifan	4 (1)	4 (1)
Buserelin	1 (<1)	0
Ciforadenant	1 (<1)	0
CPI 006	1 (<1)	0
Other	0	1 (<1)
Telaglenastat	0	1 (<1)
Trastuzumab	1 (<1)	0
Chemotherapy	4 (1)	0
Capecitabine	2 (1)	0
Carboplatin	1 (<1)	0
Cyclophosphamide	1 (<1)	0
Doxorubicin	1 (<1)	0
Epirubicin	1 (<1)	0
Methotrexate	1 (<1)	0
Oxaliplatin	1 (<1)	0
Vincristine	1 (<1)	0

Data are n (%) unless otherwise stated.

Table S2: Additional baseline characteristics

	Atezolizumab (n=390)	Placebo (n=388)
Component of clear cell	381 (98)	370 (95)
Prior surgery in patients without metastasectomy, n	334	336
Partial nephrectomy	34 (10)	22 (7)
Radical nephrectomy	300 (90)	314 (93)
Prior surgery in patients with metastasectomy, n	56	52
Partial nephrectomy	9 (16)	7 (13)
Radical nephrectomy	47 (84)	45 (87)
Stage at diagnosis		
Stage I	12 (3)	18 (5)
Stage II	31 (8)	19 (5)
Stage III	329 (84)	330 (85)
Stage IV	18 (5)	21 (5)
Primary tumour status (pathologic T stage)		
pT1a	6 (2)	9 (2)
pT1b	12 (3)	14 (4)
pT2a	26 (7)	18 (5)
pT2b	11 (3)	10 (3)
pT3a	284 (73)	278 (72)
pT3b	39 (10)	41 (11)
pT3c	2 (1)	8 (2)
pT4	10 (2)	10 (3)
Lymphadectomy performed	132 (34)	132 (34)
Fuhrman nuclear grade*		
1	6 (2)	3 (1)
2	53 (14)	39 (10)
3	223 (57)	210 (54)
4	106 (27)	135 (35)
Regional lymph node status (N stage)[†]		
pN0	183 (47)	178 (46)
pN1	42 (11)	41 (11)
pNx	165 (42)	169 (44)
Leibovich score		
Low risk (0-2)	1 (<1)	0
Intermediate risk (3-5)	94 (24)	97 (25)
High risk (≥6)	239 (61)	239 (62)
M1 NED	56 (14)	52 (13)
UISS score		
Intermediate-high risk	240 (62)	221 (57)
High risk	94 (24)	115 (30)
M1 NED	56 (14)	52 (13)

Data are n (%) unless otherwise stated.

NED, no evidence of disease; UISS, UCLA Integrated Staging System.

*Fuhrman grade data were missing for 2 patients in the atezolizumab group and 1 patient in the placebo group.

[†]264 patients (34%) received lymph node dissection (132 [34%] from the atezolizumab group and 132 [34%] from the placebo group).

Table S3: Adverse events with an incidence rate of $\geq 5\%$ in either treatment arm

	Atezolizumab (n=390)	Placebo (n=383)
General disorders and administration site conditions		
Fatigue	109 (28)	93 (24)
Asthenia	38 (10)	25 (7)
Pyrexia	43 (11)	16 (4)
Influenza-like illness	31 (8)	18 (5)
Peripheral oedema	20 (5)	17 (4)
Gastrointestinal disorders		
Diarrhoea	87 (22)	79 (21)
Nausea	46 (12)	54 (14)
Constipation	26 (7)	26 (7)
Abdominal pain	26 (7)	22 (6)
Vomiting	20 (5)	28 (7)
Dry mouth	26 (7)	6 (2)
Musculoskeletal and connective tissue disorders		
Arthralgia	78 (20)	57 (15)
Back pain	43 (11)	45 (12)
Myalgia	35 (9)	25 (7)
Pain in extremity	18 (5)	20 (5)
Skin and subcutaneous tissue disorders		
Pruritus	74 (19)	48 (13)
Rash	46 (12)	20 (5)
Rash maculopapular	25 (6)	14 (4)
Infections and infestations		
Upper respiratory tract infection	33 (8)	27 (7)
Nasopharyngitis	23 (6)	26 (7)
Urinary tract infection	22 (6)	18 (5)
Nervous system disorders		
Headache	51 (13)	49 (13)
Dizziness	30 (8)	29 (8)
Respiratory, thoracic and mediastinal disorders		
Cough	51 (13)	48 (13)
Dyspnoea	27 (7)	16 (4)
Investigations		
Blood creatinine increased	29 (7)	29 (8)
Alanine aminotransferase increased	27 (7)	12 (3)
Aspartate aminotransferase increased	20 (5)	13 (3)
Weight increased	11 (3)	21 (5)
Metabolism and nutrition disorders		
Hyperglycaemia	23 (6)	17 (4)
Decreased appetite	21 (5)	16 (4)
Endocrine disorders		
Hypothyroidism	56 (14)	12 (3)
Hyperthyroidism	20 (5)	4 (1)
Vascular disorders		
Hypertension	19 (5)	36 (9)
Blood and lymphatic system disorders		
Anaemia	26 (7)	14 (4)

Data are n (%).

768 **Table S4: Adverse events related to treatment with an incidence rate of $\geq 5\%$ in either treatment arm**
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	Atezolizumab (n=390)	Placebo (n=383)
General disorders and administration site conditions		
Fatigue	77 (20)	69 (18)
Asthenia	24 (6)	12 (3)
Skin and subcutaneous tissue disorders		
Pruritus	56 (14)	40 (10)
Rash	29 (7)	14 (4)
Gastrointestinal disorders		
Diarrhoea	45 (12)	39 (10)
Nausea	21 (5)	25 (7)
Dry mouth	20 (5)	6 (2)
Musculoskeletal and connective tissue disorders		
Arthralgia	35 (9)	30 (8)
Myalgia	25 (6)	11 (3)
Investigations		
Alanine aminotransferase increased	20 (5)	7 (2)
Nervous system disorders		
Headache	17 (4)	20 (5)
Endocrine disorders		
Hypothyroidism	52 (13)	8 (2)

Data are n (%).

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Table S5: Serious adverse events occurring in >1 patient in either treatment arm

	Atezolizumab (n=390)	Placebo (n=383)
Infections and infestations		
Urinary tract infection	4 (1)	3 (1)
Pneumonia	3 (1)	2 (1)
Sepsis	1 (<1)	2 (1)
Nervous system disorders		
Headache	1 (<1)	2 (1)
Syncope	2 (1)	1 (<1)
Cerebrovascular accident	0	2 (1)
Presyncope	0	2 (1)
Gastrointestinal disorders		
Diarrhoea	3 (1)	1 (<1)
Colitis	3 (1)	0
Acute pancreatitis	0	2 (1)
Vomiting	2 (1)	0
General disorders and administrative site conditions		
Pyrexia	3 (1)	0
Asthenia	2 (1)	0
Influenza-like illness	2 (1)	0
Respiratory, thoracic and mediastinal disorders		
Pulmonary embolism	3 (1)	1 (<1)
Metabolism and nutrition disorders		
Hyperglycaemia	5 (1)	2 (1)
Cardiac disorders		
Atrial fibrillation	2 (1)	0
Hepatobiliary disorders		
Cholecystitis	0	3 (1)
Renal and urinary disorders		
Acute kidney injury	0	3 (1)
Blood and lymphatic system disorders		
Anaemia	2 (1)	0

Data are n (%).

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Table S6: Adverse events leading to discontinuation of atezolizumab or placebo

	Atezolizumab (n=390)	Placebo (n=383)
Gastrointestinal disorders		
Colitis	3 (1)	0
Autoimmune colitis	1 (<1)	0
Diarrhoea	1 (<1)	0
Dry mouth	1 (<1)	0
Eosinophilic colitis	1 (<1)	0
Intestinal obstruction	1 (<1)	0
Pancreatitis	0	1 (<1)
Salivary duct inflammation	1 (<1)	0
Terminal ileitis	0	1 (<1)
Musculoskeletal and connective tissue disorders		
Myositis	2 (1)	1 (<1)
Arthralgia	1 (<1)	0
Musculoskeletal pain	1 (<1)	0
Myalgia	1 (<1)	0
Polymyalgia rheumatica	1 (<1)	0
Polymyositis	1 (<1)	0
Investigations		
Alanine aminotransferase increased	3 (1)	0
Aspartate aminotransferase increased	2 (1)	0
Blood alkaline phosphatase increased	1 (<1)	0
Blood creatinine increased	1 (<1)	0
Hepatic enzyme increased	0	1 (<1)
Transaminase increased	1 (<1)	0
Skin and subcutaneous disorders		
Dermatitis	2 (1)	0
Psoriasis	1 (<1)	0
Rash erythematous	0	1 (<1)
Rash maculopapular	1 (<1)	0
Skin ulcer	1 (<1)	0
Vitiligo	1 (<1)	0
Infections and infestations		
Cellulitis	1 (<1)	0
Gingivitis	1 (<1)	0
Hepatitis C	1 (<1)	0
Urinary tract infection	0	1 (<1)
Urosepsis	1 (<1)	0
Endocrine disorders		
Hyperthyroidism	1 (<1)	1 (<1)
Hypothyroidism	1 (<1)	0
Silent thyroiditis	1 (<1)	0
Respiratory, thoracic and mediastinal disorders		
Pneumonitis	3 (1)	0
Dyspnoea	1 (<1)	0
Cardiac disorders		
Cardiac failure	1 (<1)	0
Myocarditis	1 (<1)	0
Ventricular arrhythmia	1 (<1)	0
Hepatobiliary disorders		
Hepatitis	3 (1)	0
Nervous system disorders		
Aphasia	1 (<1)	0
Axonal neuropathy	1 (<1)	0
Cerebrovascular accident	0	1 (<1)
Blood and lymphatic system disorders		
Leukopenia	1 (<1)	0
General disorders and administration site conditions		
Fatigue	0	1 (<1)
Immune system disorders		
Sarcoidosis	1 (<1)	0
Metabolism and nutrition disorders		
Hyperglycaemia	1 (<1)	0

Neoplasms benign, malignant and unspecified		
Gallbladder cancer	0	1 (<1)
Vascular disorders		
Vasculitis	0	1 (<1)

Data are n (%).

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783 **Table S7: Immune-mediated adverse events**
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	Atezolizumab (n=390)		Placebo (n=383)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Rash	108 (28)	4 (1)	53 (14)	1 (<1)
Hypothyroidism	69 (18)	0	16 (4)	0
Hepatitis (diagnosis and laboratory abnormalities)	43 (11)	10 (3)	25 (7)	2 (1)
Hepatitis (laboratory abnormalities)	39 (10)	9 (2)	25 (7)	2 (1)
Infusion-related reactions	19 (5)	0	10 (3)	0
Hyperthyroidism	21 (5)	1 (<1)	4 (1)	0
Myositis (myositis + rhabdomyolysis)	12 (3)	5 (1)	3 (1)	1 (<1)
Myositis	10 (3)	4 (1)	3 (1)	1 (<1)
Colitis	9 (2)	6 (2)	2 (1)	1 (<1)
Pancreatitis	5 (1)	2 (1)	5 (1)	4 (1)
Pneumonitis	8 (2)	0	2 (1)	0
Diabetes mellitus	6 (2)	2 (1)	1 (<1)	0
Hepatitis (diagnosis)	6 (2)	2 (1)	1 (<1)	0
Meningitis	4 (1)	1 (<1)	1 (<1)	0
Meningoencephalitis	4 (1)	1 (<1)	1 (<1)	0
Ocular inflammatory toxicity	3 (1)	0	1 (<1)	0
Severe cutaneous reaction	2 (1)	0	2 (1)	0
Vasculitis	2 (1)	1 (<1)	1 (<1)	1 (<1)
Adrenal insufficiency	2 (1)	0	0	0
Rhabdomyolysis	2 (1)	1 (<1)	0	0
Hypophysitis	1 (<1)	0	0	0
Myocarditis	1 (<1)	1 (<1)	0	0
Nephritis	1 (<1)	0	0	0

Data are n (%).

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Table S8: Immune-mediated adverse events requiring the use of systemic corticosteroids

	Atezolizumab (N=390)	Placebo (N=383) [†]
Any grade*	40 (10)	4 (1)
Grade 1	12 (3)	1 (<1)
Grade 2	15 (4)	1 (<1)
Grade 3	13 (3)	2 (1)

Data are n (%) unless otherwise stated.
*There were no grade 4 or 5 adverse events.
[†]Grade percentages do not add up to any grade value due to rounding.

Table S9: Patient disposition in the intention-to-treat population

	Atezolizumab (N=390)	Placebo (N=388)	All Patients (N=778)
Received Treatment	390 (100)	383 (99)	773 (99)
Ongoing on study	309 (79)	290 (75)	599 (77)
Tumour surveillance	199 (51)	187 (48)	386 (50)
Survival follow-up	110 (28)	103 (26.5)	213 (27)
Discontinued Study	81 (21)	98 (25)	179 (23)
Death	52 (13)	52 (13)	104 (13)
Disease relapse	1 (<1)	0 (0)	1 (<1)
Lost to follow-up	4 (1)	10 (3)	14 (2)
Other	3 (<1)	3 (1)	6 (1)
Physician decision	0 (0)	1 (<1)	1 (<1)
Withdrawal by patient	21 (5)	32 (8)	53 (7)