Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial

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Summary

Background PD-1 and PD-L1 inhibitors are active in metastatic urothelial carcinoma, but positive randomised data supporting their use as a first-line treatment are lacking. In this study we assessed outcomes with first-line pembrolizumab alone or combined with chemotherapy versus chemotherapy for patients with previously untreated advanced urothelial carcinoma.

Methods KEYNOTE-361 is a randomised, open-label, phase 3 trial of patients aged at least 18 years, with untreated, locally advanced, unresectable, or metastatic urothelial carcinoma, with an Eastern Cooperative Oncology Group performance status of up to 2. Eligible patients were enrolled from 201 medical centres in 21 countries and randomly allocated (1:1:1) via an interactive voice-web response system to intravenous pembrolizumab 200 mg every 3 weeks for a maximum of 35 cycles plus intravenous chemotherapy (gemcitabine [1000 mg/m²] on days 1 and 8 and investigator's choice of cisplatin [70 mg/m²] or carboplatin [area under the curve 5] on day 1 of every 3-week cycle) for a maximum of six cycles, pembrolizumab alone, or chemotherapy alone, stratified by choice of platinum therapy and PD-L1 combined positive score (CPS). Neither patients nor investigators were masked to the treatment assignment or CPS. At protocol-specified final analysis, sequential hypothesis testing began with superiority of pembrolizumab plus chemotherapy versus chemotherapy alone in the total population (all patients randomly allocated to a treatment) for the dual primary endpoints of progression-free survival (p value boundary 0·0019), assessed by masked, independent central review, and overall survival (p value boundary 0·0142), followed by non-inferiority and superiority of overall survival for pembrolizumab versus chemotherapy in the patient population with CPS of at least 10 and in the total population (also a primary endpoint). Safety was assessed in the as-treated population (all patients who received at least one dose of study treatment). This study is completed and is no longer enrolling patients, and is registered at ClinicalTrials.gov, number NCT02853305.

Findings Between Oct 19, 2016 and June 29, 2018, 1010 patients were enrolled and allocated to receive pembrolizumab plus chemotherapy (n=351), pembrolizumab monotherapy (n=307), or chemotherapy alone (n=352). Median follow-up was 31·7 months (IQR 27·7–36·0). Pembrolizumab plus chemotherapy versus chemotherapy did not significantly improve progression-free survival, with a median progression-free survival of 8·3 months (95% CI 7·5–8·5) in the pembrolizumab plus chemotherapy group versus 7·1 months (6·4–7·9) in the chemotherapy group (hazard ratio [HR] 0·78, 95% CI 0·65–0·93; p=0·0033), or overall survival, with a median overall survival of 17·0 months (14·5–19·5) in the pembrolizumab plus chemotherapy group versus 14·3 months (12·3–16·7) in the chemotherapy group (0·86, 0·72–1·02; p=0·0407). No further formal statistical hypothesis testing was done. In analyses of overall survival with pembrolizumab versus chemotherapy (now exploratory based on hierarchical statistical testing), overall survival was similar between these treatment groups, both in the total population (15·6 months [95% CI 12·1–17·9] with pembrolizumab *vs* 14·3 months [12·3–16·7] with chemotherapy; HR 0·92, 95% CI 0·77–1·11) and the population with CPS of at least 10 (16·1 months [13·6–19·9] with pembrolizumab *vs* 15·2 months [11·6–23·3] with chemotherapy; 1·01, 0·77–1·32). The most common grade 3 or 4 adverse event attributed to study treatment was anaemia with pembrolizumab plus chemotherapy (104 [30%] of 349 patients) or chemotherapy alone (112 [33%] of 342 patients), and diarrhoea, fatigue, and hyponatraemia (each affecting four [1%] of 302 patients) with pembrolizumab alone. Six (1%) of 1010 patients died due to an adverse event attributed to study treatment; two patients in each treatment group. One each occurred due to cardiac arrest and device-related sepsis in the pembrolizumab plus chemotherapy group, one each due to cardiac failure and malignant neoplasm progression in the pembrolizumab group, and one each due to myocardial infarction and ischaemic colitis in the chemotherapy group.

Interpretation The addition of pembrolizumab to first-line platinum-based chemotherapy did not significantly improve efficacy and should not be widely adopted for treatment of advanced urothelial carcinoma.

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See **Comment** page 894

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See Online for appendix

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Introduction

Platinum-based chemotherapy has formed the basis of standard-of-care systemic treatment for advanced urothelial carcinoma for more than 40 years.[1,2] In the past 5 years, PD-1 and PD-L1 inhibitors, such as atezolizumab, avelumab, nivolumab, and pembrolizumab, have become established treatments in the post-platinum disease setting, and, most recently, avelumab was recommended as maintenance therapy for the subgroup of patients who benefit from first-line platinum-based chemotherapy.[3–7]

There is increasing evidence to support the combination of immune checkpoint inhibitors with chemotherapy to treat cancer; for example, metastatic non-small-cell lung cancer is treated with pembrolizumab plus platinum-based chemotherapy as a standard of care.[8,9] Until 2020, there had been a paucity of data on combination treatment in patients with previously untreated, advanced urothelial carcinoma. IMvigor130 is a randomised, phase 3 trial comparing atezolizumab with or without platinum-based chemotherapy versus chemotherapy in patients with previously untreated, advanced urothelial carcinoma. The trial results showed a significant improvement in investigator-assessed progression-free survival with atezolizumab plus chemotherapy versus chemotherapy alone (hazard ratio [HR] 0·82; 95% CI 0·70–0·96), but has not yet shown a significant benefit in overall survival (interim analysis HR 0·83 [95% CI 0·69–1·00]; final analysis pending).[10]

Pembrolizumab and atezolizumab have both been approved by the US Food and Drug Administration and the European Medicines Agency for use as monotherapy in the first-line setting for cisplatin-ineligible patients with PD-L1-positive urothelial tumours, and—in the USA and Canada—for patients ineligible for any platinum-containing regimen irrespective of PD-L1 positivity, based on single-arm phase 2 studies.[11–14] At a minimum follow-up of 2 years, 52 (47%) of 110 cisplatin-ineligible patients

Research in context

Evidence before this study

We searched PubMed on Sept 29, 2020, with no date or language restrictions, using the search strings: "PD-1 OR PD-L1 OR pembrolizumab OR MK-3475 OR nivolumab OR BMS-936558 OR MPDL3280A OR atezolizumab OR BMS-936559 OR MEDI4736 OR durvalumab OR avelumab AND urothelial cancer" OR "PD-1 OR PD-L1 OR pembrolizumab OR MK-3475 OR nivolumab OR BMS-936558 OR MPDL3280A OR atezolizumab OR BMS-936559 OR MEDI4736 OR durvalumab OR avelumab AND bladder cancer". We identified reports of six phase 2 or 3 clinical studies describing results of PD-1 and PD-L1 inhibitors (including atezolizumab, durvalumab, nivolumab, and pembrolizumab) for patients with metastatic urothelial carcinoma that has progressed on a previous line of chemotherapy. Additionally, we identified two phase 3 studies in untreated, advanced urothelial carcinoma: one study investigated first-line anti-PD-L1 antibody atezolizumab alone or combined with chemotherapy versus chemotherapy, and one investigated first-line anti-PD-L1 antibody durvalumab alone or in combination with the anti-CTLA-4 antibody tremelimumab versus chemotherapy. We also found one phase 3 switch maintenance study of anti-PD-L1 antibody avelumab versus best supportive care as maintenance therapy for patients who achieve at least stable disease to first-line chemotherapy. Finally, we identified two phase 2 studies, of atezolizumab monotherapy and pembrolizumab monotherapy, in cisplatin-ineligible patients with untreated, advanced urothelial carcinoma.

Added value of this study

To our knowledge, this is the first randomised phase 3 study to report final overall survival data for the combination of chemotherapy and an immune checkpoint inhibitor as a first-line treatment for advanced urothelial carcinoma. The addition of pembrolizumab to first-line chemotherapy did not significantly prolong progression-free survival or overall survival versus chemotherapy alone in the total population. Overall survival with pembrolizumab monotherapy was not formally statistically tested due to the trial design; however, it did not appear different from chemotherapy. Pembrolizumab was associated with durable responses and lower rates of any-grade and grade 3 or worse adverse events of any cause versus chemotherapy. Outcomes with pembrolizumab in patients with PD-L1 CPS of at least 10 were in line with those observed for the total population, suggesting that PD-L1 CPS could not select for clinical benefit. Exploratory analyses suggested that some patients might benefit from pembrolizumab as a first-line treatment option, although selection criteria for these patients remain unclear.

Implications of all the available evidence

The final analysis of the KEYNOTE-361 study suggests that the addition of pembrolizumab to first-line platinum-based chemotherapy does not confer survival benefits for patients with advanced urothelial carcinoma. This trial adds to the growing body of evidence showing that the combination of immune checkpoint inhibitors and chemotherapy is not associated with superior survival in this disease setting. Based on our primary findings, platinum-based chemotherapy remains the current first-line standard of care for patients able to receive it, with avelumab maintenance therapy for those who achieve a clinical benefit.

with urothelial carcinoma and a PD-L1 combined positive score (CPS) of at least 10 in the KEYNOTE-052 study achieved an overall response to pembrolizumab, and median overall survival in these patients was 18·5 months (95% CI 12·2–28·5).[15] Randomised clinical trials that include a comparison of first-line, single-agent PD-L1 inhibitors (atezolizumab and durvalumab) to standard chemotherapy in patients with PD-L1-positive disease have not yet demonstrated a significant survival benefit for immune checkpoint inhibitor monotherapy over chemotherapy.[10,16]

KEYNOTE-361 is a randomised, phase 3 study investigating the efficacy of pembrolizumab plus platinum-based chemotherapy versus platinum-based chemotherapy for patients with previously untreated, advanced urothelial carcinoma. Furthermore, the trial investigated outcomes with pembrolizumab monotherapy versus platinum-based chemotherapy in patients with PD-L1 CPS of at least 10 and in all treated patients irrespective of CPS.

Methods

Study design and patients

The KEYNOTE-361 trial was a randomised, open-label, phase 3 trial done at 201 medical centres in 21 countries (appendix pp 2–8). Patients were recruited through hospitals and clinics. Eligible patients for enrolment had to be aged at least 18 years and have a histologically or cytologically confirmed diagnosis of locally advanced, unresectable or metastatic urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra, and no previous systemic treatment for advanced disease. Urothelial carcinoma was required to be the predominant histology (≥50%). Patients had to have an Eastern Cooperative Oncology Group performance status score of 0, 1 or 2; have at least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; and have an archival or newly obtained tissue sample from a lesion not previously irradiated, or from a metastasis originating from the original tumour, for PD-L1 assessment. Patients were excluded if they had disease suitable for local therapy with curative intent, had received previous PD-(L)1 inhibitor therapy, had active CNS metastases, had autoimmune disease, or had immunodeficiency or were receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days before randomisation. Patients were also excluded if they had a history of non-infectious pneumonitis requiring steroids, current pneumonitis, active tuberculosis, HIV, hepatitis C, or hepatitis B. Patients who had received perioperative chemotherapy for resectable urothelial carcinoma at least 1 year before the study entry were eligible. Finally, patients had to have adequate renal function, defined as serum creatinine levels of up to 1·5 times the upper limit of normal (or calculated creatinine clearance of at least 30 mL/min if serum creatinine levels are more than 1·5 times the upper limit of normal), to be eligible to receive at least carboplatin treatment. Full eligibility criteria are included in the trial protocol (appendix). The trial protocol and all amendments were approved by the appropriate ethics committee at each medical centre. The study was done in accordance with the standards of Good Clinical Practice. All patients provided written informed consent before enrolment. Patients could withdraw from the study at any time for any reason. Patients had to be withdrawn from the study if they, or a legally acceptable representative, withdrew consent, or if the patient was lost to follow-up.

Randomisation and masking

Patients were enrolled by delegated investigators. The funder generated a permuted block randomisation sequence using SAS version 9.4 (block size of 3). Randomisation was done using a centralised interactive voice-response and interactive web-response system (Almac Clinical Technologies, Souderton, PA, USA), and was stratified by PD-L1 CPS of at least 10 versus PD-L1 CPS of less than 10, and choice of platinum chemotherapy (cisplatin versus carboplatin) as selected by investigators; the stratification was done in both the interactive voice-response system and the interactive web-response system. Patients were randomly assigned (1:1:1) to receive pembrolizumab plus platinum-based chemotherapy (gemcitabine plus investigator's choice of either cisplatin or carboplatin), pembrolizumab monotherapy, or platinum-based chemotherapy. After Feb 21, 2018, on the basis of a recommendation from the external Data Monitoring Committee, a protocol amendment limited randomisation of patients with CPS of less than 10 to the pembrolizumab plus chemotherapy or chemotherapy alone groups only. This recommendation was on the basis of emerging survival data for PD-(L)1 inhibitor monotherapy in patients with CPS of less than 10 in the KEYNOTE-361 and IMvigor130 studies, which were of concern. There was no change to randomisation of patients with CPS of at least 10. Neither patients nor investigators were masked to the treatment assignment or CPS. Imaging data were centrally reviewed without knowledge of treatment allocation.

Procedures

Pembrolizumab was administered intravenously at a dose of 200 mg once every 3 weeks until disease progression according to RECIST version 1.1, intolerable toxicity, physician or patient decision to withdraw from the study, or a maximum of 35 cycles, whichever occurred first, in the pembrolizumab plus chemotherapy and pembrolizumab monotherapy treatment groups. Dose modifications for pembrolizumab were not permitted; dose interruptions were permitted to manage most grade 2 immune-mediated adverse events, and interruption or discontinuation for grade 3 or 4 immune-mediated adverse events. Patients in the pembrolizumab plus chemotherapy and chemotherapy alone groups

received gemcitabine (1000 mg/m²) on days 1 and 8 of each 3-week cycle, and either cisplatin (70 mg/m²) or carboplatin (area under the concentration curve [AUC] 5) on day 1 of every 3-week cycle, intravenously until disease progression, intolerable toxicity, physician or patient decision to withdraw from the study, or a maximum of six cycles, whichever occurred first. Dose modifications for cisplatin, carboplatin, and gemcitabine were implemented according to local guidelines and practices. Dose interruptions were also permitted for cisplatin, carboplatin, and gemcitabine, according to local guidelines. If one or all chemotherapy components in the pembrolizumab plus chemotherapy treatment group were discontinued, patients could continue to receive pembrolizumab for up to 35 total cycles. In the pembrolizumab plus chemotherapy and pembrolizumab groups, treatment discontinuation could be considered for patients who had a confirmed complete response and had received at least eight cycles of pembrolizumab (including two cycles beyond the date of initial response) and four cycles of chemotherapy (if applicable). Clinically stable patients with radiographic progression could receive up to 17 additional cycles of pembrolizumab at the investigator's discretion. Patients with a complete or partial response or stable disease who completed 35 cycles of pembrolizumab as part of study treatment could be considered for retreatment with pembrolizumab upon disease progression for up to 17 additional cycles.

PD-L1 status was centrally assessed by Quest Diagnostics (Secaucus, NJ, USA) and Q² Solutions (Morrisville, NC, USA) using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA), as previously described,[17] and measured using the CPS, defined as the number of PD-L1-staining cells (tumour cells, lymphocytes, and macrophages) divided by the total number of viable tumour cells, multiplied by 100. Predominant urothelial histology for enrolment eligibility was centrally assessed by Quest Diagnostics and Q² Solutions.

On-trial imaging assessments (CT was strongly preferred, although MRI was permitted if CT was contraindicated or for imaging of the brain) were done by investigators and site radiologists every 9 weeks from the date of randomisation for the first 54 weeks, and every 12 weeks thereafter. Responses and disease progression were assessed according to RECIST (version 1.1). Patients were contacted directly or virtually to assess survival every 12 weeks during follow-up until death, withdrawal of consent, or the end of the trial. Blood and urine samples for haematology (haematocrit, haemoglobin, platelet count, white or red blood cell count, and absolute neutrophil or lymphocyte counts), chemistry (albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, carbon dioxide, calcium, chloride, creatinine, glucose, magnesium, phosphorus, potassium, sodium, bilirubin, total protein, blood urea nitrogen, and uric acid), urinalysis (blood, glucose, protein, specific gravity, and microscopic examination) and other tests (pregnancy tests, coagulation factors, thyroid serology tests, and biomarker analyses) were analysed within 2 weeks before the first dose of study treatment, and up to 72 h before each dose thereafter. Thyroid serology could be done within 28 days before the first dose of study treatment. Adverse events and laboratory abnormalities were collected and recorded regularly by investigators throughout treatment and for 30 days thereafter or before the initiation of a new anticancer therapy, whichever occurred first. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). The European Organisation for Research and Treatment of Cancer Quality of Life (EORTC) Global Quality of Life Questionnaire (QLQ-C30)[18] and the EuroQol-5 Dimension (EuroQoL EQ-5D) questionnaire were administered electronically at cycles 1 to 4, every three cycles thereafter for up to 54 weeks, and every four cycles thereafter until treatment discontinuation and the 30-day post-treatment safety follow-up visit.

Outcomes

The dual primary endpoints were progression-free survival assessed by masked, independent central review, defined as the time from randomisation to radiographically confirmed disease progression or death from any cause (whichever occurred first), and overall survival, defined as the time from randomisation to death from any cause, for pembrolizumab plus chemotherapy versus chemotherapy alone for the total patient population. Overall survival was also a primary endpoint for pembrolizumab monotherapy versus chemotherapy for the patients with CPS of at least 10 and the total population irrespective of CPS, but was lower down in the hierarchical testing strategy than the dual primary endpoints.

Secondary endpoints were overall response rate (the proportion of patients with a radiographically confirmed complete response or partial response according to RECIST version 1.1), disease control rate (the proportion of patients with a radiographically confirmed complete response, partial response, or stable disease, according to RECIST version 1.1), and duration of response (defined as the time from first documented complete or partial response to radiographically confirmed disease progression or death from any cause, whichever occurred first) by masked central review; and safety and tolerability. Other secondary endpoints were progression-free survival at milestone timepoints (6 months, 12 months, 18 months, and 24 months) and time to deterioration of patient-reported outcomes. The protocol describes all endpoints in detail (appendix).

The following secondary and exploratory endpoints will be reported separately or as applicable with additional study follow-up: time to deterioration in global health status or quality of life score as measured by the EORTC QLQ-C30, change from baseline to week 18 in quality of

life as measured by the EORTC QLQ-C30, and exploratory biomarker analyses.

Statistical analysis

Planned enrolment was approximately 990 eligible patients, with approximately 330 patients allocated to each treatment group. The sample size was calculated to ensure at least 80% power for the overall survival superiority comparisons of pembrolizumab versus chemotherapy for the population with CPS of at least 10 and the total population. Thus, the trial would have 94% power to detect overall survival superiority for pembrolizumab plus chemotherapy versus chemotherapy alone at an initially assigned α of 0·02 (one-sided) at a hazard ratio of 0·70 for the total patient population, and 97% power to detect progression-free survival superiority of pembrolizumab plus chemotherapy versus chemotherapy at a hazard ratio of 0·68 at an initially assigned α of 0·005 (one-sided). The proportional hazards assumption was assessed via visual inspection of the Kaplan-Meier curves. Two interim analyses were planned: one after approximately 347 progression-free survival events and another after approximately 357 overall survival events, in the total population allocated to the pembrolizumab plus chemotherapy and chemotherapy treatment groups. The final analysis was to be done when at least 22 months had elapsed after the last patient was randomly assigned, and when approximately 616 overall survival events were observed in the three treatment groups, and approximately 208 overall survival events were observed in the pembrolizumab monotherapy and chemotherapy alone groups in the population with PD-L1 CPS of at least 10.

The type I error rate over the multiple treatment comparisons, multiple primary endpoints, and key secondary endpoints was controlled by the graphical approach of Maurer and Bretz.[19] A Bonferroni approach was used to control the type I error rate at α=0·025 (one-sided), with 0·005 allocated to progression-free survival and 0·02 allocated to overall survival. A sequential testing strategy was used, beginning with superiority testing of progression-free survival and overall survival for pembrolizumab plus chemotherapy versus chemotherapy alone in the total population, followed by non-inferiority and superiority testing of overall survival for pembrolizumab monotherapy versus chemotherapy in the population with CPS of at least 10 and the total population (appendix p 10). If neither of the dual primary endpoints were met, statistical significance for superiority or non-inferiority was not tested for subsequent primary endpoints and only descriptive analyses without p values were included. The type I error allocated to a set of hypotheses that is successfully tested was planned to be redistributed for the testing of hypotheses in another set. Actual α allocated at the interim analysis was based on the Pocock α-spending function for progression-free survival and the Hwang-Shih-DeCani α-spending function with γ parameter (–4) for overall survival. Cumulative α spent at the first interim, second interim, and final analysis was 0·0035, 0·0046, and 0·005, respectively for progression-free survival, with a p value boundary for significance of 0·0019 (one-sided) at final analysis. Cumulative α spent at the first interim, second interim, and final analysis was 0·0023, 0·0113, and 0·02, respectively, for overall survival with a p value boundary for significance of 0·0142 (one-sided) at final analysis. Here, we present the results of the protocol-specified final analysis of the KEYNOTE-361 trial.

Efficacy was assessed in the total population and the population with CPS of at least 10 in the intention-to-treat population, defined as all patients randomly assigned to a treatment group. Duration of response was assessed in all patients who had a confirmed complete or partial response. Safety was assessed in the as-treated population, defined as all patients who had received at least one dose of study treatment.

Progression-free survival, by masked, independent central review and by investigator assessment, overall survival, duration of response, and duration of disease control for each treatment group and any subgroups were estimated using a non-parametric Kaplan-Meier method. Censoring rules are outlined in the protocol (appendix). A stratified Cox proportional hazards model with Efron's method of tie handling was used to assess the hazard ratio (HR) and 95% CIs for progression-free survival and overall survival. Between-group differences were assessed using a stratified log-rank test. An exploratory, simplified two-stage approach was used to conduct a sensitivity analysis of the effect of subsequent anti-PD-(L)1 therapy on overall survival for the chemotherapy group. In the first stage, a lognormal parametric model was developed to estimate the effect, or acceleration factor, of subsequent anti-PD-(L)1 therapy on overall survival time starting at the study treatment discontinuation date. The acceleration factor was then used to adjust the overall survival of the patients who had received subsequent anti-PD-(L)1 therapy to estimate the survival time that would have been observed if the patient had not received subsequent anti-PD-(L)1 therapy. In the second stage, the adjusted survival times were analysed with a proportional hazards model, with inflated standard errors used to estimate 95% CIs of the HR. Exploratory post-hoc analyses included overall survival for patients who were chosen to recieve carboplatin-based chemotherapy, overall survival for all treatment groups and patients with CPS of at least 10 in the pembrolizumab and chemotherapy groups at a milestone of 12 months, and duration of disease control (eg, time from achievement of disease control to disease progression as defined by RECIST version 1.1) in the pembrolizumab and chemotherapy groups.

An independent, external data monitoring committee monitored safety and efficacy throughout the trial (appendix p 9). No formal treatment comparisons were

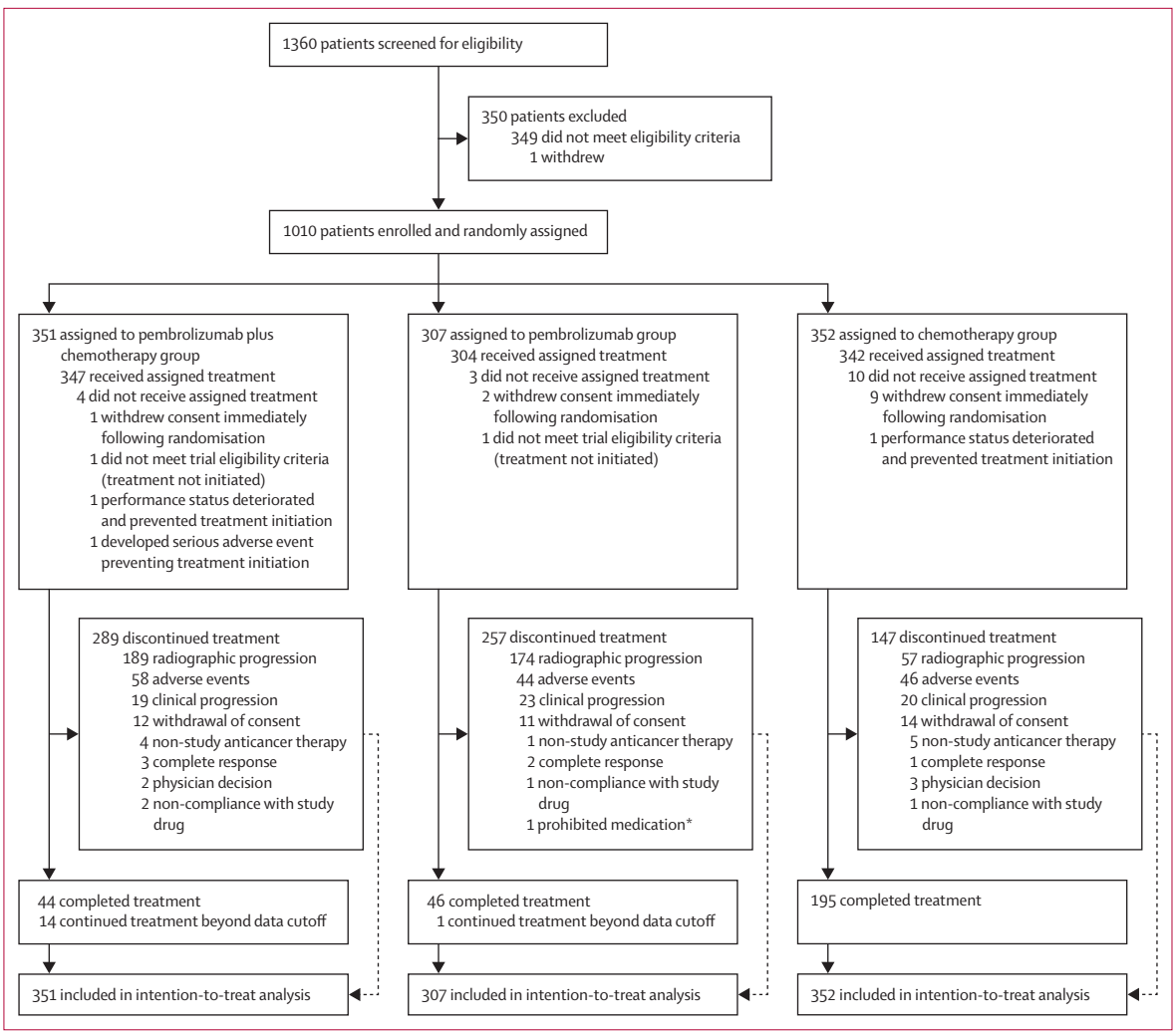

Figure 1: **Trial profile**
Two of 307 patients randomised to the pembrolizumab group received pembrolizumab plus chemotherapy in error. Therefore, they were considered in the safety population for pembrolizumab plus chemotherapy, and were removed from the safety population for pembrolizumab monotherapy. *Prohibited medications included antineoplastic systemic chemotherapy or biological therapy, immunotherapy or chemotherapy not specified in the protocol, investigational agents other than pembrolizumab, radiation therapy, live vaccine within 30 days before first pembrolizumab dose if randomised to a pembrolizumab-containing group, any chronic immunosuppressive treatment other than for the management of adverse events as outlined in the protocol, and any medication prohibited in combination with chemotherapy as outlined in the prescribing information for cisplatin, carboplatin, and gemcitabine.

planned with respect to safety results. Between-treatment CIs were calculated using the Miettinen and Nurminen method.[20]

We used SAS version 9.4 for all statistical analyses. This trial is registered with ClinicalTrials.gov, number NCT02853305.

Role of the funding source

The funder of the study participated in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

1360 patients were screened for this study, of whom 349 (26%) patients did not meet trial eligibility criteria and one patient withdrew from the trial. Between Oct 19, 2016 and June 29, 2018, 1010 patients (intention-to-treat population) were randomly allocated to receive pembrolizumab plus platinum-based chemotherapy (351 [35%]), pembrolizumab monotherapy (307 [30%]), or platinum-based chemotherapy (352 [35%]; figure 1). All 1010 patients were assessed for the dual primary endpoints of the trial. Before the protocol amendment on Feb 21, 2018, 823 (82%) of the 1010 patients had already been randomly assigned. Therefore, the proportion of the population with PD-L1 CPS of at least 10 was slightly higher in the pembrolizumab group (160 [52%] of 307) than in the pembrolizumab plus chemotherapy group (159 [45%] of 351) and the chemotherapy group (158 [45%] of 352). Per investigator's choice at randomisation, 156 (44%) of 351 patients in the

pembrolizumab plus chemotherapy group, 137 (45%) of 307 patients in the pembrolizumab group, and 156 (44%) of 352 patients in the chemotherapy group were eligible to receive cisplatin-based therapy if randomly assigned to a chemotherapy-containing group. Renal impairment was the most common reason why patients were chosen to receive carboplatin over cisplatin by investigators across all three groups (124 [35%] of 351 patients in the pembrolizumab plus chemotherapy group, 117 [38%] of 307 patients in the pembrolizumab group, and 127 [36%] of 352 patients in the chemotherapy group). Reasons for choosing carboplatin are outlined in detail in the appendix (p 21). Patient demographics and baseline disease characteristics were well balanced across the three treatment groups (table 1).

At final analysis, median follow-up, defined as time from randomisation to data cutoff on April 29, 2020, was 31·7 months (IQR 27·7–36·0). 283 (81%) of 349 patients in the pembrolizumab plus chemotherapy group received at least six cycles of therapy, with a median of 11 cycles (IQR 7–21) of pembrolizumab (appendix p 41). 169 (56%) of 302 patients in the pembrolizumab group received at least six cycles of therapy, with a median of seven cycles (IQR 3–17), and 231 (68%) of 342 patients in the chemotherapy group received the maximum planned six cycles of chemotherapy treatment, with a median of six cycles (5–6). Following treatment discontinuation, 124 (35%) of 351 patients in the pembrolizumab plus chemotherapy group, 126 (41%) of 307 patients in the pembrolizumab group, and 215 (61%) of 352 patients in the chemotherapy group received any subsequent systemic anticancer therapy (primarily chemotherapy or immune checkpoint inhibitors), including 23 (7%) of 351 patients in the pembrolizumab plus chemotherapy group, 14 (5%) of 307 patients in the pembrolizumab group, and 169 (48%) of 352 patients in the chemotherapy group receiving a subsequent anti-PD-1 or anti-PD-L1 antibody (appendix p 11).

At final analysis, 733 (73%) of all 1010 patients had progression-free survival events, including 260 (74%) of 351 patients in the pembrolizumab plus chemotherapy group, 240 (78%) of 307 patients in the pembrolizumab group, and 233 (66%) of 352 patients in the chemotherapy group. Median progression-free survival by central review was 8·3 months (95% CI 7·5–8·5) in the pembrolizumab plus chemotherapy group versus 7·1 months (6·4–7·9) in the chemotherapy group (HR 0·78, 95% CI 0·65–0·93; p=0·0033; figure 2A). The addition of pembrolizumab to first-line platinum-based chemotherapy did not significantly improve progression-free survival by central review in the total population per the prespecified p value boundary of 0·0019 for the final analysis at an initially assigned α=0·005 (one-sided). At 6, 12, 18, and 24 months, the estimated proportion of patients who were alive and progression-free was 74% (95% CI 69–78), 34% (29–39), 23% (18–8), and 20% (15–24) respectively, in the pembrolizumab plus chemotherapy group, and 70% (65–75), 21% (16–26), 14% (9–18), and 14% (9–18), respectively, in the chemotherapy group. In a prespecified exploratory analysis, median progression-free survival by investigator assessment was 8·3 months (95% CI 7·4–8·5) in the pembrolizumab plus chemotherapy group, and 6·5 months (6·2–7·4) in the chemotherapy group (HR 0·69, 95% CI 0·59–0·82; appendix p 14). A prespecified exploratory analysis of progression-free survival in patients chosen for cisplatin- or carboplatin-based chemotherapy is included in the appendix (p 14).

At final analysis, 717 (71%) of all 1010 patients had died, including 245 (70%) of 351 patients in the pembrolizumab plus chemotherapy group, 209 (68%) of 307 patients in the

	Pembrolizumab plus chemotherapy group (n=351)	Pembrolizumab group (n=307)	Chemotherapy group (n=352)
Age			
Median (IQR), years	69 (62–75)	68 (61–74)	69 (61–75)
<65 years	118 (34%)	109 (36%)	119 (34%)
Sex			
Male	272 (78%)	228 (74%)	262 (74%)
Female	79 (23%)	79 (26%)	90 (26%)
ECOG performance status score			
0	150 (43%)	134 (44%)	168 (48%)
1	178 (51%)	148 (48%)	162 (46%)
2	23 (7%)	25 (8%)	22 (6%)
Primary tumour site			
Upper tract	64 (18%)	65 (21%)	82 (23%)
Lower tract	287 (82%)	242 (79%)	270 (77%)
Metastatic staging			
M0	24 (7%)	16 (5%)	24 (7%)
M1	327 (93%)	291 (95%)	328 (93%)
Site of metastasis			
Lymph node only	81 (23%)	64 (21%)	94 (27%)
Visceral disease	259 (74%)	239 (78%)	252 (72%)
No lymph node or visceral metastasis	11 (3%)	4 (1%)	6 (2%)
Liver metastasis			
Present	78 (22%)	65 (21%)	74 (21%)
Absent	273 (78%)	242 (79%)	278 (79%)
Haemoglobin concentration			
≥10 g/dL	318 (91%)	273 (89%)	326 (93%)
<10 g/dL	33 (9%)	34 (11%)	26 (7%)
PD-L1 CPS			
≥10	159 (45%)	160 (52%)	158 (45%)
<10	192 (55%)	147 (48%)	194 (55%)
Prior adjuvant or neoadjuvant platinum-based chemotherapy	37 (11%)	29 (9%)	47 (13%)
Cisplatin or carboplatin chosen by investigator assessment			
Cisplatin	156 (44%)	137 (45%)	156 (44%)
Carboplatin	195 (56%)	170 (55%)	196 (56%)

Data are median (IQR) or n (%). CPS=combined positive score. ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline characteristics in the intention-to-treat population**

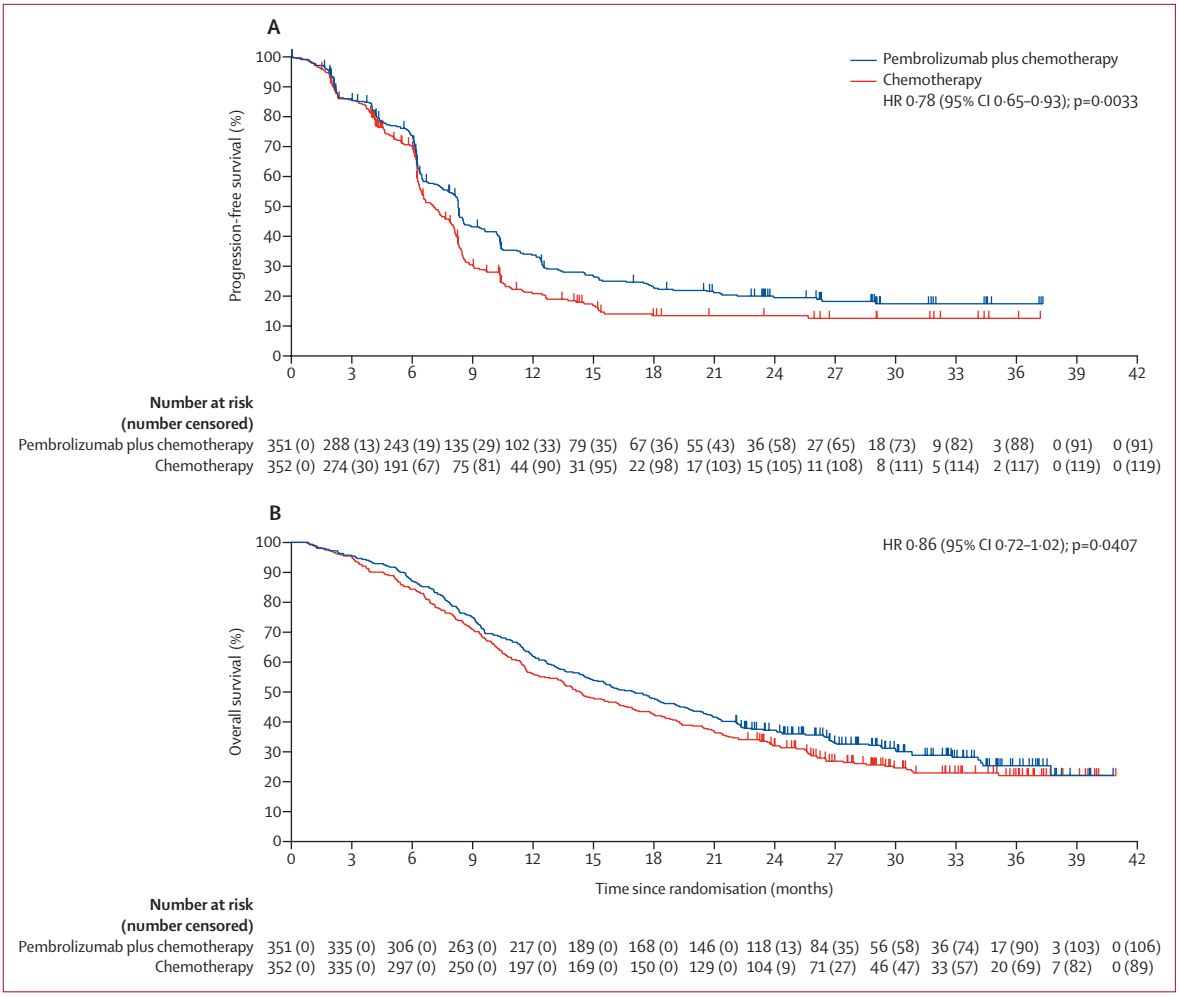

Figure 2: **Progression-free survival and overall survival (dual primary endpoints)**
Progression-free survival by masked central review (A) and overall survival, in patients treated with pembrolizumab plus chemotherapy versus chemotherapy alone in the total population (B). Tick marks represent censoring of the data at the last time the patient was known to be alive. HR=hazard ratio.

pembrolizumab group, and 263 (75%) of 352 patients in the chemotherapy group. Median overall survival was 17·0 months (95% CI 14·5–19·5) in the pembrolizumab plus chemotherapy group versus 14·3 months (12·3–16·7) in the chemotherapy group (HR 0·86 [95% CI 0·72–1·02], p=0·0407; figure 2B). The addition of pembrolizumab to first-line platinum-based chemotherapy did not significantly improve overall survival in the total population per the prespecified p-value boundary of 0·0142 for the final analysis at an initially assigned α=0·02 (one-sided). The proportional hazards assumption appeared to have been met based on visual inspection of the Kaplan-Meier curves. At 12 months, the estimated proportion of patients who were alive was 62% (95% CI 57–67) in the pembrolizumab plus chemotherapy group and 56% (51–61) in the chemotherapy group. Overall survival outcomes across key prespecified subgroups of patients were largely similar (appendix pp 12–13). An exploratory two-stage sensitivity analysis adjusting overall survival for subsequent anti-PD-(L)1 immune checkpoint inhibitor therapy in the chemotherapy treatment group yielded an HR of 0·71 (95% CI 0·48–1·04) for pembrolizumab plus chemotherapy versus chemotherapy alone in the total patient population (appendix p 18).

Per the trial design, the prespecified sequential statistical testing plan required that at least one of the dual primary endpoints of progression-free survival or overall survival for pembrolizumab plus chemotherapy versus chemotherapy alone in the total population be met before the testing of subsequent hypotheses (appendix p 10). Therefore, no formal statistical testing was done for any primary hypotheses for pembrolizumab versus chemotherapy.

In analyses of overall survival with pembrolizumab versus chemotherapy (which are now exploratory because the dual primary endpoints were not met), in the population with CPS of at least 10, median overall survival was 16·1 months (95% CI 13·6–19·9) with pembrolizumab

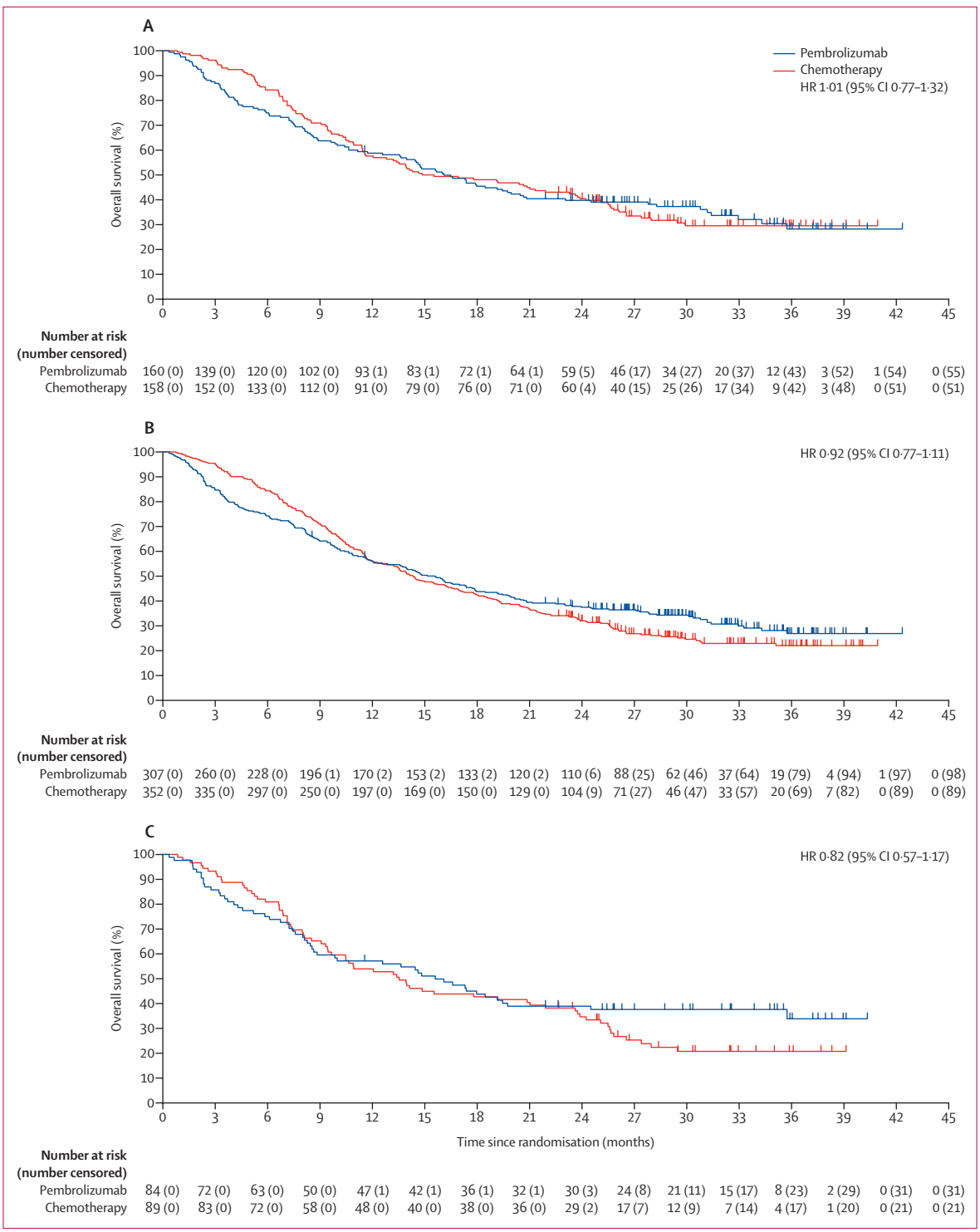

Figure 3: **Overall survival with pembrolizumab alone versus chemotherapy alone**

Overall survival in patients treated with pembrolizumab alone versus chemotherapy alone in patients with PD-L1 CPS of at least 10 (A), in the total population irrespective of PD-L1 CPS (B), and in patients with PD-L1 CPS of at least 10 who were chosen to receive carboplatin (C). Tick marks represent censoring of the data at the last time the patient was known to be alive. CPS=combined positive score. HR=hazard ratio.

	Total patient population (n=1010)			Patients with PD-L1 CPS ≥10 (n=477)		
	Pembrolizumab plus chemotherapy group (n=351)	Pembrolizumab group (n=307)	Chemotherapy group (n=352)	Pembrolizumab plus chemotherapy group (n=159)	Pembrolizumab group (n=160)	Chemotherapy group (n=158)
Proportion of patients with a complete or partial response	192 (54·7%, 49·3–60·0)	93 (30·3%, 25·2–35·8)	158 (44·9%, 39·6–50·2)	91 (57·2%, 49 ·2–65·0)	52 (32·5%, 25·3–40·3)	73 (46·2%, 38·2–54·3)
Chosen to receive cisplatin	100/156 (64·1%, 56·0–71·6)	46/137 (33·6%, 25·7–42·1)	76/156 (48·7%, 40·6–56·8)	48/72 (66·7%, 54·6–77·3)	27/76 (35·5%, 24·9–47·3)	32/69 (46·4%, 34·3–58·8)
Chosen to receive carboplatin	92/195 (47·2%, 40·0–54·4)	47/170 (27·6%, 21·1–35·0)	82/196 (41·8%, 34·8–49·1)	43/87 (49·4%, 38·5–60·4)	25/84 (29·8%, 20·3–40·7)	41/89 (46·1%, 35·4–57·0)
Best overall response						
Complete response	53 (15%)	34 (11%)	43 (12%)	25 (16%)	21 (13%)	26 (17%)
Partial response	139 (40%)	59 (19%)	115 (33%)	66 (42%)	31 (19%)	47 (30%)
Stable disease	90 (26%)	52 (17%)	109 (31%)	39 (25%)	30 (19%)	47 (30%)
Progressive disease	39 (11%)	118 (38%)	39 (11%)	16 (10%)	59 (37%)	14 (9%)
Non-complete response or non-progressive disease	10 (3%)	8 (3%)	16 (5%)	2 (1%)	3 (2%)	7 (4%)
Not evaluable or assessed*	20 (6%)	36 (12%)	30 (9%)	11 (7%)	16 (10%)	17 (11%)
Median duration of complete or partial response, months	8·5 (8·2–11·4)	28·2 (13·5–not evaluable)	6·2 (5·8–6·5)	13·0 (8·3–not evaluable)	35·0 (13·9–not evaluable)	7·3 (6·2–10·2)
Estimated ongoing responses at 12 months	42% (35–50)	65% (54–74)	24% (17–31)	52% (41–62)	70% (55–81)	34% (22–45)
Estimated ongoing responses at 18 months	33% (26–40)	54% (43–64)	19% (13–26)	42% (32–52)	59% (44–72)	26% (16–38)

Data are n (%), 95% CI), n/N (%, 95% CI), median (95% CI), or % (95% CI). Percentages may not total 100 because of rounding. CPS=combined positive score. *Not evaluable includes patients with insufficient data for assessment of response per RECIST version 1.1; not assessed includes patients without post-baseline assessment on the data cutoff date.

Table 2: **Summary of antitumour activity**

monotherapy versus 15·2 months (11·6–23·3) with chemotherapy alone (HR 1·01, 95% CI 0·77–1·32; figure 3A). At final analysis, 105 (66%) of 160 patients in the pembrolizumab group and 107 (68%) of 158 patients in the chemotherapy group had died. At 12 months, the estimated proportion of patients who were alive was 59% (95% CI 51–66) in the pembrolizumab group and 58% (50–65) in the chemotherapy group. In the total population (irrespective of CPS), median overall survival was 15·6 months (95% CI 12·1–17·9) with pembrolizumab monotherapy versus 14·3 months (12·3–16·7) with chemotherapy (HR 0·92, 95% CI 0·77–1·11; figure 3B). At 12 months, the estimated proportion of patients who were alive was 56% (95% CI 50–61) in the pembrolizumab group and 56% (51–61) in the chemotherapy group. An exploratory two-stage sensitivity analysis adjusting overall survival for subsequent anti-PD-(L)1 immune checkpoint inhibitor therapy in the chemotherapy treatment group yielded an HR of 0·80 (95% CI 0·48–1·32) for pembrolizumab versus chemotherapy in the total patient population (appendix p 18). Kaplan-Meier estimates of progression-free survival in both populations are included in the appendix (p 15).

A post-hoc exploratory analysis of overall survival in patients who were chosen to receive carboplatin and with CPS of at least 10 (in whom pembrolizumab monotherapy is an approved first-line treatment in the USA and Europe) is shown in figure 3C. For these patients, median overall survival was 15·6 months (95% CI 8·6–19·7) in 84 patients who received pembrolizumab versus 13·5 months (9·5–21·0) in 89 patients who received chemotherapy (HR 0·82, 95% CI 0·57–1·17). For patients chosen to receive carboplatin, irrespective of CPS, median overall survival was 14·6 months (95% CI 10·2–17·9) in 170 patients who received pembrolizumab versus 12·3 months (10·0–15·5) in 196 patients who received chemotherapy (HR 0·83, 95% CI 0·65–1·06; appendix p 16). These analyses are purely exploratory because of the hierarchical statistical testing strategy.

Responses and durations of response in the total population and in patients with a CPS of at least 10 in each treatment group are shown in table 2. Kaplan-Meier estimates of duration of response and duration of disease control for the total population treated with pembrolizumab versus chemotherapy are shown in the appendix (p 17). In patients who were chosen to receive carboplatin, with CPS of at least 10, 25 (30%) of 84 had a partial or complete response to pembrolizumab versus 41 (46%) of 89 to chemotherapy. In this group, median duration of response in the pembrolizumab group was not reached (95% CI 9·6 months–not evaluable) versus 8·3 months (5·9–12·2) with chemotherapy.

In the as-treated population, the median duration of treatment was 7·7 months (IQR 5·0–14·4) in the pembrolizumab plus chemotherapy group, 4·2 months (1·4–11·3) in the pembrolizumab group, and 3·7 months (3·0–4·2) in the chemotherapy group (appendix p 41).

At least one grade 3 or worse adverse event of any cause occurred in 305 (87%) of 349 patients in the pembrolizumab plus chemotherapy group, 190 (63%) of

	Pembrolizumab plus chemotherapy group (n=349)				Pembrolizumab group (n=302)				Chemotherapy group (n=342)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any adverse event	344 (99%)	297 (85%)	108 (31%)	32 (9%)	284 (94%)	173 (57%)	40 (13%)	26 (9%)	339 (99%)	270 (79%)	96 (28%)	9 (3%)
Any treatment-related adverse event	334 (96%)	254 (73%)	80 (23%)	2 (1%)	192 (64%)	46 (15%)	9 (3%)	2 (1%)	322 (94%)	233 (68%)	80 (23%)	2 (1%)
Any adverse event leading to discontinuation	37 (11%)	44 (13%)	27 (8%)	22 (6%)	7 (2%)	21 (7%)	2 (1%)	19 (6%)	36 (11%)	23 (7%)	10 (3%)	2 (1%)
Blood and lymphatic system disorders	208 (60%)	188 (54%)	50 (14%)	0	64 (21%)	33 (11%)	3 (1%)	0	194 (57%)	196 (57%)	49 (14%)	0
Anaemia	140 (40%)	118 (34%)	3 (1%)	0	54 (18%)	30 (10%)	1 (<1%)	0	119 (35%)	135 (40%)	3 (1%)	0
Neutropenia	80 (23%)	81 (23%)	23 (7%)	0	2 (1%)	0	0	0	84 (25%)	86 (25%)	22 (6%)	0
Thrombocytopenia	65 (19%)	31 (9%)	25 (7%)	0	0	1 (<1%)	1 (<1%)	0	65 (19%)	34 (10%)	34 (10%)	0
Cardiac disorders	22 (6%)	10 (3%)	3 (1%)	5 (1%)	15 (5%)	8 (3%)	1 (<1%)	5 (2%)	19 (6%)	5 (2%)	2 (1%)	3 (1%)
Endocrine disorders	45 (13%)	6 (2%)	1 (<1%)	0	38 (13%)	4 (1%)	0	0	2 (1%)	0	0	0
Hypothyroidism	34 (10%)	2 (1%)	0	0	30 (10%)	1 (<1%)	0	0	1 (<1%)	0	0	0
Gastrointestinal disorders	274 (79%)	37 (11%)	1 (<1%)	1 (<1%)	153 (51%)	31 (10%)	2 (1%)	1 (<1%)	257 (75%)	36 (11%)	0	1 (<1%)
Abdominal pain	40 (12%)	5 (1%)	0	0	27 (9%)	2 (1%)	0	0	28 (8%)	2 (1%)	0	0
Constipation	123 (35%)	3 (1%)	0	0	55 (18%)	5 (2%)	0	0	105 (31%)	5 (2%)	0	0
Diarrhoea	101 (29%)	8 (2%)	0	0	56 (19%)	9 (3%)	0	0	70 (21%)	7 (2%)	0	0
Nausea	178 (51%)	7 (2%)	0	0	42 (14%)	3 (1%)	0	0	152 (44%)	9 (3%)	0	0
Vomiting	88 (25%)	9 (3%)	0	0	32 (11%)	2 (1%)	0	0	69 (20%)	10 (3%)	0	0
General disorders and administration site conditions	269 (77%)	34 (10%)	3 (1%)	8 (2%)	168 (56%)	19 (6%)	0	5 (2%)	237 (69%)	29 (9%)	2 (1%)	0
Asthenia	75 (22%)	11 (3%)	0	0	34 (11%)	8 (3%)	0	0	77 (23%)	11 (3%)	1 (<1%)	0
Fatigue	138 (40%)	11 (3%)	0	0	73 (24%)	7 (2%)	0	0	112 (33%)	13 (4%)	0	0
Peripheral oedema	47 (14%)	1 (<1%)	0	0	26 (9%)	2 (1%)	0	0	43 (13%)	1 (<1%)	0	0
Pyrexia	77 (22%)	4 (1%)	1 (<1%)	0	45 (15%)	1 (<1%)	0	0	44 (13%)	1 (<1%)	0	0
Infections and infestations	179 (51%)	73 (21%)	19 (5%)	8 (2%)	116 (38%)	54 (18%)	10 (3%)	9 (3%)	118 (35%)	44 (13%)	9 (3%)	3 (1%)
Urinary tract infection	67 (19%)	35 (10%)	2 (1%)	1 (<1%)	55 (18%)	27 (9%)	1 (<1%)	0	45 (13%)	25 (7%)	0	0
Injury, poisoning, and procedural complications	46 (13%)	9 (3%)	0	0	22 (7%)	9 (3%)	0	0	26 (8%)	3 (1%)	0	0
Investigations	212 (61%)	102 (29%)	33 (10%)	0	114 (38%)	14 (5%)	8 (3%)	0	146 (43%)	91 (27%)	40 (12%)	0
Decreased neutrophil count	42 (12%)	51 (15%)	13 (4%)	0	2 (1%)	0	0	0	31 (9%)	49 (14%)	19 (6%)	0
Decreased platelet count	58 (17%)	28 (8%)	21 (6%)	0	3 (1%)	1 (<1%)	2 (1%)	0	57 (17%)	38 (11%)	29 (9%)	0
Decreased white blood cell count	45 (13%)	20 (6%)	2 (1%)	0	1 (<1%)	0	0	0	34 (10%)	25 (7%)	4 (1%)	0
Decreased weight	36 (10%)	2 (1%)	0	0	37 (12%)	2 (1%)	0	0	22 (6%)	0	0	0
Increased ALT	49 (14%)	6 (2%)	0	0	18 (6%)	2 (1%)	0	0	20 (6%)	2 (1%)	0	0
Increased AST	46 (13%)	6 (2%)	1 (<1%)	0	21 (7%)	0	0	0	19 (6%)	1 (<1%)	0	0
Increased blood creatinine	67 (19%)	3 (1%)	0	0	36 (12%)	2 (1%)	0	0	38 (11%)	1 (<1%)	0	0
Metabolism and nutrition disorders	200 (57%)	56 (16%)	13 (4%)	0	123 (41%)	48 (16%)	6 (2%)	0	144 (42%)	30 (9%)	1 (<1%)	0
Decreased appetite	119 (34%)	3 (1%)	0	0	67 (22%)	7 (2%)	0	0	93 (27%)	5 (2%)	0	0
Hypomagnesaemia	36 (10%)	4 (1%)	0	0	9 (3%)	0	0	0	22 (6%)	2 (1%)	0	0
Hyponatraemia	20 (6%)	12 (3%)	7 (2%)	0	15 (5%)	11 (4%)	1 (<1%)	0	11 (3%)	6 (2%)	0	0
Musculoskeletal and connective tissue disorders	136 (39%)	15 (4%)	1 (<1%)	0	108 (36%)	16 (5%)	0	0	78 (23%)	8 (2%)	0	0
Arthralgia	34 (10%)	4 (1%)	1 (<1%)	0	27 (9%)	4 (1%)	0	0	15 (4%)	1 (<1%)	0	0
Back pain	48 (14%)	3 (1%)	0	0	34 (11%)	4 (1%)	0	0	19 (6%)	0	0	0
Nervous system disorders	154 (44%)	14 (4%)	2 (1%)	3 (1%)	57 (19%)	10 (3%)	0	0	122 (36%)	10 (3%)	2 (1%)	0
Dizziness	45 (13%)	0	0	0	19 (6%)	0	0	0	36 (11%)	0	0	0
Headache	43 (12%)	0	0	0	16 (5%)	1 (<1%)	0	0	26 (8%)	1 (<1%)	0	0
Psychiatric disorders	68 (20%)	3 (1%)	0	1 (<1%)	41 (14%)	5 (2%)	0	0	42 (12%)	3 (1%)	1 (<1%)	0
Insomnia	35 (10%)	0	0	0	19 (6%)	0	0	0	15 (4%)	1 (<1%)	0	0

(Table 3 continues on next page)

	Pembrolizumab plus chemotherapy group (n=349)				Pembrolizumab group (n=302)				Chemotherapy group (n=342)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)												
Renal and urinary disorders	113 (32%)	42 (12%)	5 (1%)	2 (1%)	78 (26%)	42 (14%)	5 (2%)	0	63 (18%)	21 (6%)	1 (<1%)	0
Haematuria	52 (15%)	10 (3%)	0	0	30 (10%)	15 (5%)	0	0	15 (4%)	6 (2%)	0	0
Respiratory, thoracic, and mediastinal disorders	143 (41%)	22 (6%)	4 (1%)	4 (1%)	79 (26%)	16 (5%)	5 (2%)	1 (<1%)	106 (31%)	12 (4%)	3 (1%)	2 (1%)
Cough	55 (16%)	0	0	0	30 (10%)	0	0	0	28 (8%)	0	0	0
Dyspnoea	53 (15%)	3 (1%)	0	0	30 (10%)	5 (2%)	1 (<1%)	0	34 (10%)	2 (1%)	0	0
Skin and subcutaneous tissue disorders	190 (54%)	13 (4%)	0	0	122 (40%)	5 (2%)	0	0	88 (26%)	4 (1%)	0	0
Pruritus	78 (22%)	3 (1%)	0	0	66 (22%)	0	0	0	17 (5%)	0	0	0
Rash	78 (22%)	5 (1%)	0	0	40 (13%)	0	0	0	22 (6%)	2 (1%)	0	0
Vascular disorders*	73 (21%)	15 (4%)	1 (<1%)	0	27 (9%)	16 (5%)	2 (1%)	2 (1%)	47 (14%)	10 (3%)	0	0

Data are n (%). The table shows adverse events of any cause that occurred in at least 10% of patients in one or more treatment groups in the as-treated population at final analysis. Adverse events are presented according to the Medical Dictionary for Regulatory Affairs system organ class. Numbers represent total number of patients with each grade event, not limited to maximum grade (ie, each patient is counted only once in each cell). ALT=alanine aminotransferase. AST=aspartate aminotransferase. The as-treated population includes all patients who received at least one dose of trial treatment. *Most commonly deep vein thrombosis, hypertension, and hypotension, each occurring in less than 10% of patients.

Table 3: **Adverse events**

302 patients in the pembrolizumab group, and 280 (82%) of 342 patients in the chemotherapy group. Grade 3 or worse adverse events attributed to study treatment were reported in 262 (75%) of 349 patients in the pembrolizumab plus chemotherapy group, 51 (17%) of 302 patients in the pembrolizumab group, and 245 (72%) of 342 patients in the chemotherapy group. The most common grade 3 or 4 adverse event attributed to study treatment was anaemia with pembrolizumab plus chemotherapy (104 [30%] of 349 patients) or chemotherapy (112 [33%] of 342 patients), and diarrhoea, fatigue, and hyponatraemia (each affecting four [1%] of 302 patients) with pembrolizumab (appendix p 42).

Grade 3 or worse adverse events of any cause and all adverse events leading to death are provided in the appendix (pp 22–36). 108 (31%) of 349 patients in the pembrolizumab plus chemotherapy group, 48 (16%) of 302 patients in the pembrolizumab group, and 62 (18%) of 342 patients in the chemotherapy group discontinued any therapy due to an adverse event (appendix pp 37–40). 102 (29%) of 349 patients in the pembrolizumab plus chemotherapy group, 37 (12%) of 302 patients in the pembrolizumab group, and 90 (26%) of 342 patients in the chemotherapy group had serious adverse events attributed to study treatment (appendix pp 43–45). The most common serious adverse event attributed to study treatment was anaemia in the pembrolizumab plus chemotherapy group (11 [3%] of 349) and in the chemotherapy group (15 [4%] of 342), and pneumonitis in the pembrolizumab group (four [1%] of 302). Six (1%) of all 1010 patients died due to an adverse event attributed to study treatment; two patients in each treatment group. Of these deaths, one each occurred due to cardiac arrest and device-related sepsis in the pembrolizumab plus chemotherapy group, one each due to cardiac failure and malignant neoplasm progression in the pembrolizumab group, and one each due to myocardial infarction and ischaemic colitis in the chemotherapy group.

Anaemia was the most common any-grade adverse event of any cause (table 3) and the most common adverse event attributed to study treatment (appendix p 42) in patients treated either with pembrolizumab plus chemotherapy or chemotherapy. The most common adverse events of any cause with pembrolizumab monotherapy were anaemia and fatigue (table 3); the most common adverse events attributed to study treatment were pruritus and fatigue (appendix p 42). The addition of pembrolizumab to chemotherapy was associated with greater risk of select adverse events, such as pruritus, rash, and haematuria, among others. Pembrolizumab monotherapy was associated with a greater risk of pruritus, whereas chemotherapy was associated with a greater risk of anaemia, neutropenia, nausea, thrombocytopenia, and decreased neutrophil, platelet and white blood cell count, among others (appendix pp 19–20). Immune-mediated adverse events and infusion reactions are detailed in the appendix (p 46).

Discussion

The KEYNOTE-361 trial did not meet the primary endpoints of superior progression-free survival and overall survival with first-line pembrolizumab plus chemotherapy versus chemotherapy alone in patients with advanced urothelial carcinoma. Prespecified analyses indicated that neither PD-L1 CPS of at least 10 nor physician's choice of platinum chemotherapy seemed to be associated with improved benefit from the addition of pembrolizumab to chemotherapy. No new or unexpected safety signals were reported for pembrolizumab plus platinum-based chemotherapy, and this treatment had a similar safety

profile to chemotherapy alone. Taken together, the primary results of the study suggest that combining first-line pembrolizumab plus chemotherapy does not improve survival of unselected patients with advanced urothelial carcinoma, with no subgroups performing better than others. Alternative approaches might be more attractive, including treatment sequencing of chemotherapy with maintenance immune therapy, which has shown a significant survival advantage.[5,21] Other approaches, potentially including patient selection for first-line immune checkpoint inhibitor therapy on the basis of additional biomarkers, or new treatment combinations such as pembrolizumab plus antibody–drug conjugate enfortumab vedotin (NCT04223856), are warranted.

The progression-free survival by central review endpoint was not met in the KEYNOTE-361 study, whereas progression-free survival by investigator assessment with atezolizumab plus platinum-based chemotherapy versus chemotherapy alone was significantly better in the atezolizumab group in the IMvigor130 study (HR 0·82, 95% CI 0·70–0·96), leading to contrasting conclusions despite a similarity in hazard ratios.[10] Although no definitive statements on causality can be made, IMvigor130 used masked treatment, no central review in the primary analysis, different statistical assumptions, and a larger sample size, which might have accounted for the differences between study results. Sensitivity analyses of overall survival in the chemotherapy group in KEYNOTE-361 suggested that wide use of subsequent PD-1 or PD-L1 inhibitor therapy for patients progressing on chemotherapy might have also affected the observed overall survival results. Nevertheless, the observations reported here were not significant but seem to be broadly applicable to first-line combinations of an immune checkpoint inhibitor plus chemotherapy for advanced urothelial carcinoma. It remains unclear why these combination treatments have not shown superiority to chemotherapy alone as first-line therapy, although it could possibly be due to unfavourable chemotherapy interactions with immune therapy.

Although non-inferiority and superiority of the primary endpoint of overall survival with pembrolizumab monotherapy versus chemotherapy could not be formally statistically tested, our exploratory analyses suggested that survival outcomes seemed similar between pembrolizumab monotherapy versus chemotherapy, both in the population of patients with CPS of at least 10 and in the total patient population in the study. Chemotherapy was associated with a greater number of initial responses, whereas pembrolizumab was associated with longer durations of response. The proportions of patients with a complete or partial response to pembrolizumab monotherapy were also similar between the total population and the population with CPS of at least 10. The safety profile of pembrolizumab was in line with previous observations,[3,12] and had a lower rate of all-cause adverse events, grade 3 or worse all-cause adverse events, and adverse events leading to treatment discontinuation than chemotherapy. Overall, these results suggest that the PD-L1 CPS of at least 10 cutoff alone did not enrich for patients with urothelial carcinoma likely to gain a survival benefit with pembrolizumab monotherapy. Across published studies in urothelial carcinoma, different PD-L1 assays and cutoff points further complicate the applicability of PD-L1 positivity as a selection biomarker.[10,16] Indeed, in the final analysis of the DANUBE trial, overall survival was 14·4 months with durvalumab versus 12·1 months with platinum-based chemotherapy in patients with PD-L1-positive (by SP263) urothelial carcinoma (HR 0·89, 95% CI 0·71–1·11; p=0·30),[16] and an interim analysis of the IMvigor130 study suggested a possible survival benefit with atezolizumab versus platinum-based chemotherapy in patients with PD-L1-positive (by SP142) tumours (HR 0·68, 95% CI 0·43–1·08), although data are not yet mature and the 95% confidence interval crosses 1·0.[10] Therefore, additional investigation into biomarkers to identify particular patients likely to achieve highly durable responses and long survival with first-line immune checkpoint inhibitor therapy is warranted. Further biomarker analyses for KEYNOTE-361, including tumour mutational burden, will be presented when available.

Split-dose cisplatin does not have robust, randomised data supporting its use in metastatic urothelial carcinoma,[6,7] and was not included in the KEYNOTE-361 study design. 561 (56%) patients in the total study population were determined to be ineligible for standard cisplatin-based chemotherapy at baseline by participating investigators. This finding was in line with observations made in IMvigor130 study.[10] Taken together, these results suggest that more patients receive carboplatin-containing first-line chemotherapy rather than cisplatin-containing first-line chemotherapy than was expected during study planning. Future investigations should take this key learning into consideration.

We did an exploratory subgroup analysis of the patients for whom pembrolizumab is currently approved as a first-line therapy (namely, patients who had been chosen to receive carboplatin and with CPS of at least 10). Pembrolizumab had durable antitumour activity in these patients. Although overall survival with pembrolizumab was not markedly different to that with chemotherapy in this patient subgroup, pembrolizumab monotherapy could be an attractive treatment option for some patients.

A potential limitation of this study was the open-label design, which might have led to differences between progression-free survival results by masked central review versus investigator assessment. Additionally, because of the prespecified sequential statistical analysis strategy, formal statistical hypothesis testing could not be done for the pembrolizumab monotherapy versus chemotherapy treatment groups. Interpretability of the tumour response results might have been limited by the 6–12% of patients across treatment groups who were not evaluable or not assessed for response by RECIST version 1.1. Data on

mixed responses were not collected and could not be analysed further.

This trial adds to the growing body of evidence showing that immune checkpoint inhibitors given with chemotherapy are not associated with clear survival benefits for urothelial carcinoma. Based on the primary findings of the KEYNOTE-361 study, platinum-based chemotherapy remains the current first-line standard of care for patients able to receive it, with avelumab maintenance therapy for those who have a clinical benefit.

Contributors

TP, KN, KI, BHM, and AA conceived, designed, or planned the study. KN analysed the data. TP, TC, MO, NM, LG, SY-SC, YF, SO, CV, RMB, AF, SG, YL, AR-V, RM, EYY, and AA acquired the data. TP, TC, MO, NM, LG, SY-SC, YF, SO, CV, RMB, AF, SG, YL, AR-V, RM, EYY, KN, KI, BHM, and AA helped to interpret the results. TP, KN, KI, BHM, and AA drafted the manuscript. All authors revised and reviewed this work. All access had access to and verified the data, vouch for its accuracy and completeness, and approved the decision to submit for publication. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Declaration of interests

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Data sharing

Merck Sharp and Dohme, a subsidiary of Merck, Kenilworth, NJ, USA is committed to providing qualified scientific researchers access to anonymised data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. Merck Sharp and Dohme is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The Merck Sharp and Dohme data sharing website outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of Merck Sharp and Dohme subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with Merck Sharp and Dohme before data access is granted. Data will be made available for request after product approval in the USA and EU or after product development is discontinued. There are circumstances that could prevent Merck Sharp and Dohme from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and Merck Sharp and Dohme subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, Merck Sharp and Dohme will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

For the **data sharing website** http://engagezone.msd.com/ds_documentation.php

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