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Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): a randomised, open-label, multicentre, phase 3 trial

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Summary

Background Survival outcomes are poor for patients with metastatic urothelial carcinoma who receive standard, first-line, platinum-based chemotherapy. We assessed the overall su=rvival of patients who received durvalumab (a PD-L1 inhibitor), with or without tremelimumab (a CTLA-4 inhibitor), as a first-line treatment for metastatic urothelial carcinoma.

Methods DANUBE is an open-label, randomised, controlled, phase 3 trial in patients with untreated, unresectable, locally advanced or metastatic urothelial carcinoma, conducted at 224 academic research centres, hospitals, and oncology clinics in 23 countries. Eligible patients were aged 18 years or older with an Eastern Cooperative Oncology Group performance status of 0 or 1. We randomly assigned patients (1:1:1) to receive durvalumab monotherapy (1500 mg) administered intravenously every 4 weeks; durvalumab (1500 mg) plus tremelimumab (75 mg) administered intravenously every 4 weeks for up to four doses, followed by durvalumab maintenance (1500 mg) every 4 weeks; or standard-of-care chemotherapy (gemcitabine plus cisplatin or gemcitabine plus carboplatin, depending on cisplatin eligibility) administered intravenously for up to six cycles. Randomisation was done through an interactive voice–web response system, with stratification by cisplatin eligibility, PD-L1 status, and presence or absence of liver metastases, lung metastases, or both. The coprimary endpoints were overall survival compared between the durvalumab monotherapy versus chemotherapy groups in the population of patients with high PD-L1 expression (the high PD-L1 population) and between the durvalumab plus tremelimumab versus chemotherapy groups in the intention-to-treat population (all randomly assigned patients). The study has completed enrolment and the final analysis of overall survival is reported. The trial is registered with ClinicalTrials.gov, NCT02516241, and the EU Clinical Trials Register, EudraCT number 2015-001633-24.

Findings Between Nov 24, 2015, and March 21, 2017, we randomly assigned 1032 patients to receive durvalumab (n=346), durvalumab plus tremelimumab (n=342), or chemotherapy (n=344). At data cutoff (Jan 27, 2020), median follow-up for survival was 41·2 months (IQR 37·9–43·2) for all patients. In the high PD-L1 population, median overall survival was 14·4 months (95% CI 10·4–17·3) in the durvalumab monotherapy group (n=209) versus 12·1 months (10·4–15·0) in the chemotherapy group (n=207; hazard ratio 0·89, 95% CI 0·71–1·11; p=0·30). In the intention-to-treat population, median overall survival was 15·1 months (13·1–18·0) in the durvalumab plus tremelimumab group versus 12·1 months (10·9–14·0) in the chemotherapy group (0·85, 95% CI 0·72–1·02; p=0·075). In the safety population, grade 3 or 4 treatment-related adverse events occurred in 47 (14%) of 345 patients in the durvalumab group, 93 (27%) of 340 patients in the durvalumab plus tremelimumab group, and in 188 (60%) of 313 patients in the chemotherapy group. The most common grade 3 or 4 treatment-related adverse event was increased lipase in the durvalumab group (seven [2%] of 345 patients) and in the durvalumab plus tremelimumab group (16 [5%] of 340 patients), and neutropenia in the chemotherapy group (66 [21%] of 313 patients). Serious treatment-related adverse events occurred in 30 (9%) of 345 patients in the durvalumab group, 78 (23%) of 340 patients in the durvalumab plus tremelimumab group, and 50 (16%) of 313 patients in the chemotherapy group. Deaths due to study drug toxicity were reported in two (1%) patients in the durvalumab group (acute hepatic failure and hepatitis), two (1%) patients in the durvalumab plus tremelimumab group (septic shock and pneumonitis), and one (<1%) patient in the chemotherapy group (acute kidney injury).

Interpretation This study did not meet either of its coprimary endpoints. Further research to identify the patients with previously untreated metastatic urothelial carcinoma who benefit from treatment with immune checkpoint inhibitors, either alone or in combination regimens, is warranted.

Funding AstraZeneca.

Introduction

The prognosis for patients with advanced bladder cancer remains poor, with a 5-year survival rate of less than 5% for those with distant metastases.[1] Urothelial carcinoma accounts for approximately 90% of all bladder cancers.[2] The current standard of care for the first-line treatment of locally advanced or metastatic urothelial carcinoma is platinum-based chemotherapy, typically gemcitabine plus cisplatin or, for patients ineligible to receive cisplatin-based chemotherapy, gemcitabine plus carboplatin.[3–5] Although platinum-based chemotherapy yields high response rates, survival outcomes with these regimens remain poor. In 2017, first-line treatment options for cisplatin-ineligible patients with metastatic urothelial carcinoma expanded to include two immune checkpoint inhibitors: atezolizumab (anti-PD-L1) and pembrolizumab (anti-PD-1).[6] The approvals of both agents were based on the results of single-arm, phase 2 trials in which the primary endpoint was objective response rate,[7,8] and were later restricted to patients whose tumours express high levels of PD-L1.

The results of two randomised, controlled, phase 3 trials, which evaluated anti-PD-L1 agents as first-line treatments for metastatic urothelial carcinoma, have

Research in context

Evidence before this study

Platinum-based chemotherapy has long been established as a standard of care for the first-line treatment of metastatic urothelial carcinoma. Eligible patients can receive cisplatin-based regimens, most commonly gemcitabine plus cisplatin. However, approximately 40% of patients are ineligible to receive cisplatin due to medical comorbidities, including impaired renal function and hearing loss, and these patients often receive carboplatin in combination with gemcitabine. Although response rates are high with standard-of-care chemotherapy, most patients with metastatic urothelial carcinoma will progress and median overall survival is approximately 14 months. We searched PubMed and major international oncology congresses for articles and abstracts pertaining to metastatic urothelial carcinoma between July 1, 2010, and July 1, 2020, with no language restrictions. We used the terms "metastatic urothelial carcinoma" OR "metastatic bladder cancer" AND "immuno-oncology", "immune checkpoint inhibitor", "immunogenic", "programmed cell death 1", "programmed cell death ligand-1", "cytotoxic T-lymphocyte antigen-4", "PD-1", "PD-L1", and "CTLA-4". Urothelial carcinoma is a highly immunogenic tumour. In advanced disease, improved overall survival has been shown with pembrolizumab in the platinum-refractory setting and with avelumab as first-line maintenance therapy in patients whose disease had not progressed on or after platinum-based chemotherapy.

Added value of this study

DANUBE is a robust, mature, and randomised study of immune checkpoint inhibitors alone or in combination for previously untreated, advanced urothelial carcinoma. To our knowledge, it is the first of a number of trials exploring this approach to report final overall survival data. The hypothesis that overall survival would be superior with durvalumab alone versus platinum-based chemotherapy in the PD-L1-positive population, and that the combination of durvalumab and tremelimumab would be superior to platinum-based chemotherapy in the intention-to-treat population, was not shown. Both experimental groups revealed that chemotherapy was efficacious in terms of initial control of disease, and long-term durable outcomes were observed with durvalumab and durvalumab plus tremelimumab. Data for durvalumab alone showed activity consistent with that of other single-agent immune checkpoint inhibitors in this setting, including in the intention-to-treat population. Secondary analyses suggested that tremelimumab resulted in increased antitumour activity, albeit with greater toxicity, when given in combination with durvalumab.

Implications of all the available evidence

For several years, overall survival outcomes for patients with metastatic urothelial carcinoma had reached a plateau with chemotherapy. Immune checkpoint inhibitors, such as pembrolizumab, became the standard of care in platinum-refractory disease based on randomised trials. More recently, atezolizumab and pembrolizumab were approved as first-line treatments for cisplatin-ineligible patients with metastatic urothelial carcinoma whose tumours express high levels of PD-L1. The regulatory approvals were based on the results of single-arm, phase 2 studies. The JAVELIN Bladder 100 study was the first randomised controlled trial of an immune checkpoint inhibitor to show a significant improvement in overall survival in previously untreated, metastatic urothelial carcinoma. However, that study was conducted in a selected patient population, because only those who achieved an objective response or stable disease with platinum-based chemotherapy received maintenance avelumab. The results of the DANUBE trial, which, to our knowledge, are the most robust so far for an immune checkpoint inhibitor in this setting, do not show that durvalumab is superior to chemotherapy as a first-line treatment, questioning the approach of immune checkpoint inhibitor monotherapy in this setting, including in cisplatin-ineligible patients. Secondary analyses suggested that the addition of tremelimumab might increase the efficacy, as well as toxicity, of durvalumab in previously untreated metastatic urothelial carcinoma. Further research with CTLA-4 inhibitors in metastatic urothelial carcinoma is warranted, especially in the PD-L1 biomarker-positive population.

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See Online for appendix

recently been reported. In the IMvigor130 study,[9] progression-free survival was significantly improved with atezolizumab plus platinum-based chemotherapy versus placebo plus platinum-based chemotherapy, although differences in overall survival did not reach statistical significance at the time of the first interim analysis. In the JAVELIN Bladder 100 study,[10] overall survival was significantly improved with maintenance avelumab plus best supportive care versus best supportive care alone in patients who had achieved an objective response or stable disease after platinum-based chemotherapy. Both studies enrolled cisplatin-eligible and cisplatin-ineligible patients. Currently, a chemotherapy-free option for cisplatin-eligible patients with metastatic urothelial carcinoma does not exist.

Durvalumab, a human IgG1 monoclonal antibody that selectively binds to PD-L1, is approved for the treatment of platinum-refractory, advanced urothelial carcinoma, based on evidence of antitumour activity in a phase 1–2 open-label study.[11] Updated results from this study showed higher objective response rates and improved overall survival in patients whose tumours expressed high levels of PD-L1 compared with patients whose tumours expressed low levels of PD-L1.[12] Tremelimumab, which blocks CTLA-4, has shown single-agent activity in metastatic urothelial carcinoma after progression on platinum-based chemotherapy.[13] Although durvalumab combined with tremelimumab has shown activity in other tumour types, such as non-small-cell lung cancer,[14] and in the second-line setting for metastatic urothelial carcinoma,[15] the combination has not been evaluated in previously untreated, metastatic urothelial carcinoma.

We did a randomised phase 3 study (DANUBE) to evaluate durvalumab compared with standard of care chemotherapy as a first-line treatment for advanced urothelial carcinoma in cisplatin-eligible and cisplatin-ineligible patients whose tumours express high levels of PD-L1. Based on the evidence that durvalumab and tremelimumab, alone and in combination, have activity in platinum-refractory urothelial carcinoma, we also evaluated the efficacy and safety of the combination in the first-line setting in all randomly assigned patients, irrespective of PD-L1 expression level.

Methods

Study design and participants

DANUBE is an open-label, multicentre, randomised, controlled, phase 3 study done at 224 academic research centres, hospitals, and oncology clinics in 23 countries (appendix pp 2–6). After global enrolment, recruitment into an expansion cohort was done at 19 additional academic research centres and hospitals in China (the results of this cohort will be reported separately). Patients were eligible for enrolment if they were aged 18 years or older; had histologically or cytologically confirmed, unresectable, locally advanced or metastatic transitional cell carcinoma of the urothelium (including renal pelvis, ureters, urinary bladder, and urethra); had not been previously treated with first-line chemotherapy for advanced disease; had at least one measurable lesion, according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), that had not been previously irradiated; had a life expectancy of at least 12 weeks (as judged by the investigator); and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Eligible patients were also required to provide tumour tissue for the assessment of PD-L1 expression, and to have adequate bone marrow, liver, and kidney function (ie, haemoglobin concentration of ≥9 g/dL, serum bilirubin ≤1·5-times the upper limit of normal, alanine aminotransferase and aspartate aminotransferase levels ≤2·5-times the upper limit of normal, and creatinine clearance ≥30 mL per min).

Patients were excluded if they had received previous systemic immunotherapy (including anti-CTLA-4, anti-PD-1, and anti-PD-L1 agents); radiotherapy within 28 days of the first dose of study drug; active or previous autoimmune or inflammatory disorders; active infection with hepatitis B or C virus; HIV; uncontrolled intercurrent illness (eg, uncontrolled hypertension); or symptomatic and untreated brain metastases. Patients who had received adjuvant or neoadjuvant treatment for locally advanced disease and had progressed within 6 months of their last therapy or surgery were also excluded.

The trial was conducted in accordance with Good Clinical Practice guidelines, as defined by the International Conference on Harmonisation, and with provisions of the Declaration of Helsinki. The trial was overseen by an independent data monitoring committee and a steering committee. Before enrolment, all patients (or their legal representatives) provided written, informed consent to participate in the trial. The study protocol was approved by independent review boards or independent ethics committees at each study site. The complete study protocol is provided in the appendix (p 28).

Randomisation and masking

Patients were randomly assigned to the three treatment groups using an interactive voice–web response system. At randomisation, the investigators determined which chemotherapy treatment (gemcitabine with cisplatin or gemcitabine with carboplatin) the patient would have received in the absence of randomised therapy (based on cisplatin eligibility[4]) and entered this information into the interactive voice–web response system. Randomisation was done using a blocked randomisation method (block size of three) and stratified according to cisplatin eligibility (yes *vs* no), PD-L1 status (high *vs* low or negative), and presence or absence of liver or lung metastases or both (either or both *vs* neither). As an open-label study, none of the investigators, the trial coordination staff, or the patients were masked to treatment allocation. Sponsor staff were masked to treatment allocation.

Procedures

We randomly assigned patients (1:1:1) to receive durvalumab monotherapy (at a fixed dose of 1500 mg, administered intravenously every 4 weeks); the combination of durvalumab (1500 mg) and tremelimumab (75 mg), both administered intravenously every 4 weeks for up to four doses, followed by durvalumab maintenance monotherapy (1500 mg, administered intravenously every 4 weeks); or standard-of-care chemotherapy (gemcitabine plus cisplatin or gemcitabine plus carboplatin). In the chemotherapy group, patients eligible for cisplatin had one of two treatment options: intravenous infusions of cisplatin at a dose of 70 mg/m² on day 2 of each 28-day cycle plus gemcitabine at 1000 mg/m² on days 1, 8, and 15 of each 28-day cycle, for up to six cycles; or intravenous infusions of cisplatin at 70 mg/m² on day 1 of each 21-day cycle plus gemcitabine at 1000–1250 mg/m² on days 1 and 8 of each 21-day cycle, for up to six cycles. Patients ineligible for cisplatin received intravenous infusions of carboplatin with an area under the curve of 4·5–5·0 on day 1 of each 21-day cycle plus gemcitabine 1000 mg/m² on days 1 and 8 of each 21-day cycle, for up to six cycles.

Dose reductions were not permitted for durvalumab or durvalumab plus tremelimumab. However, dose interruptions were permitted for the management of immune-mediated reactions or non-immune-mediated reactions. No dose interruptions were required for adverse events of grade 1. For adverse events of grade 2, dose interruptions were recommended until resolution to grade 1 or baseline. Depending on the specific grade 3 adverse event, study drug treatment could either be permanently discontinued or interrupted until resolution to grade 1 or baseline within a certain time period. For example, toxicity management guidelines recommended permanent discontinuation for grade 3 pneumonitis, but for grade 3 diarrhoea or colitis, study drug treatment could be resumed if the toxicity resolved to grade 1 or baseline within 14 days. Study drug treatment was permanently discontinued for grade 4 immune-mediated adverse events. Dose reductions and dose interruptions were permitted for chemotherapy according to local standard clinical practice.

Treatment was continued until the occurrence of disease progression, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion. For discontinuation of durvalumab or durvalumab plus tremelimumab due to disease progression, as assessed by the investigators according to RECIST v1.1 or by clinical deterioration, a confirmatory scan was required; treatment with chemotherapy was discontinued at the first identified progression as assessed by the investigators according to RECIST v1.1 or by clinical deterioration (ie, no confirmatory scan was required). The criteria for confirmation of progression can be found in the study protocol. Per protocol, crossover from the chemotherapy group to either the durvalumab or durvalumab plus tremelimumab groups was not allowed. Patients in the durvalumab and durvalumab plus tremelimumab groups could be treated beyond confirmed disease progression if the study investigator determined that the patient continued to derive clinical benefit. In the combination group, patients who completed the four dosing cycles of durvalumab plus tremelimumab, but who subsequently had disease progression on durvalumab monotherapy, could restart combination treatment if the investigator judged that the patient was deriving clinical benefit.

Recently acquired tumour samples or archival (<3 years old) formalin-fixed, paraffin-embedded tissue was used for PD-L1 immunohistochemical staining. PD-L1 expression was assessed at a central laboratory using the VENTANA PD-L1 (SP263) Assay (Ventana Medical Systems, Tucson, AZ, USA).[16] High PD-L1 expression was defined as at least 25% of tumour cells with membrane staining or at least 25% of immune cells staining for PD-L1 at any intensity if more than 1% of the tumour area contained immune cells, or 100% of immune cells staining for PD-L1 at any intensity if 1% of the tumour area contained immune cells.[17] Tumour cells with PD-L1 membrane staining were scored as a proportion of the total tumour cells, and tumour-associated immune cells expressing PD-L1 were scored as a proportion of immune cells present.[18] Low PD-L1 expression was defined as not meeting any of the criteria for high PD-L1.[17]

Tumour imaging using CT (preferred) or MRI imaging of the chest, abdomen, and pelvis was done at baseline and every 8 weeks from the date of randomisation until disease progression (confirmation required for durvalumab and durvalumab plus tremelimumab but not for chemotherapy). Required confirmatory scans were done no less than 4 weeks after the initial assessment of response or disease progression. After baseline assessment, if any of the target lesions were not assessed or not evaluable or had a lesion intervention (and scaling up could not be done for lesions with interventions), then the patient was considered not evaluable for response. Information regarding the first and subsequent therapies for cancer, after discontinuation of treatment, were collected. Blood and urine samples were taken for clinical chemistry and haematology assessments. For durvalumab and durvalumab plus tremelimumab, laboratory monitoring included serum or plasma chemistry (complete clinical chemistry panel) and haematology (on day 1 and every 4 weeks), thyroid function tests (on day 1 and every 4 weeks), human chorionic gonadotropin measurements, and coagulation parameters (as clinically indicated throughout the study). In the chemotherapy group, laboratory monitoring included serum or plasma chemistry (complete clinical chemistry panel) and haematology (days 1, 8, and 15 for each of the six cycles of a 28-day cycle treatment period; days 1 and 8 for each of the six cycles of a 21-day cycle treatment period), thyroid function tests (on day 1 of cycles 1–5 for a 28-day cycle treatment period; on day 1 of cycle 5 for a 21-day cycle treatment period), human chorionic gonadotropin measurements, and coagulation

parameters (as clinically indicated throughout the study). Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Data on adverse events and serious adverse events were collected from the time the informed consent was signed up to 90 days after the last dose of study treatment.

Outcomes

The coprimary endpoints were to compare overall survival between the durvalumab monotherapy and chemotherapy groups among patients whose tumours had high PD-L1 expression; and to compare overall survival between the durvalumab plus tremelimumab and chemotherapy groups in the intention-to-treat population. Overall survival was defined as the time from the date of randomisation until death due to any cause.

Secondary endpoints were overall survival in the durvalumab monotherapy versus chemotherapy groups in the intention-to-treat population; overall survival in the durvalumab and tremelimumab versus chemotherapy groups in the low PD-L1 population; progression-free survival (time from randomisation to disease progression or death; investigator-assessed according to RECIST v1.1), the proportion of patients alive and progression free at 12 months from randomisation, time from randomisation to second progression, overall survival at 24 months, objective response rate (investigator-assessed complete or partial responses according to RECIST 1.1), duration of response (time from date of first response to progression or death), and disease control rate at 6 months and 12 months (defined as the proportion of patients who achieved a complete or partial response in the first 6 months or 12 months and who had stable disease for a minimum of 24 weeks or 48 weeks, respectively, from the start of treatment) in the durvalumab versus chemotherapy groups in the high PD-L1 and intention-to-treat populations; objective response rate, duration of response, time to response, disease control rate, progression-free survival (by blinded independent central review according to RECIST v1.1), and overall survival in the durvalumab versus chemotherapy groups in cisplatin-ineligible patients; overall survival in the durvalumab plus tremelimumab versus chemotherapy groups in the high PD-L1 population; progression-free survival, proportion of patients alive and progression-free at 12 months from randomisation, time from randomisation to second progression, overall survival at 24 months, objective response rate, duration of response, and disease control rate in the durvalumab plus tremelimumab versus chemotherapy groups in the intention-to-treat and high PD-L1 populations; overall survival at 24 months, progression-free survival, proportion of patients alive and progression free at 12 months from randomisation, time from randomisation to second progression, objective response rate, duration of response, and disease control rate in the durvalumab plus tremelimumab versus chemotherapy groups in the low PD-L1 population; overall survival, overall survival at 24 months, progression-free survival, proportion of patients alive and progression free at 12 months from randomisation, time from randomisation to second progression, objective response rate, duration of response, and disease control rate in the durvalumab plus tremelimumab versus durvalumab groups in the low PD-L1 population; health-related quality of life in the durvalumab and durvalumab plus tremelimumab groups; and pharmacodynamics and immunogenicity of durvalumab and durvalumab plus tremelimumab. Additional secondary analyses (health-related quality of life, pharmacodynamics, and immunogenicity) are ongoing and will be reported separately elsewhere. Other secondary endpoints, as described in the study protocol (duration of response, time to response, and disease control rate in cisplatin-ineligible patients; time from randomisation to second progression; and proportion of patients alive and progression free at 12 months in the intention-to-treat, high PD-L1 high, and low or negative PD-L1 populations), were analysed but will be reported elsewhere.

We also assessed adverse events of special interest, which include, but are not limited to, events with a potential inflammatory or immune-mediated mechanism that might require more frequent monitoring and interventions such as steroids or immunosuppressants. We additionally assessed adverse events associated with study drug exposure that were consistent with an immune-mediated mechanism of action and which had no clear alternative cause. Serological, immunological, and histological (biopsy) data, as appropriate, were used to support the diagnosis of an immune-mediated adverse event. The full list of study endpoints is provided in the protocol.

Statistical analysis

We planned to randomly allocate approximately 1005 patients in a 1:1:1 ratio to each of the three treatment groups. It was expected that approximately 60% of patients would have high tumour PD-L1 expression, as defined per protocol. To test our hypotheses, we used a multiple testing procedure with an α-exhaustive recycling strategy, in which we tested hypotheses in a predefined order to strongly control type I error at 5% (two-sided), among all key hypotheses. In this approach, the overall α of 5% was split for the two coprimary statistical comparisons: overall survival for durvalumab monotherapy versus chemotherapy (3·5%) in the high PD-L1 population and durvalumab plus tremelimumab versus chemotherapy (1·5%) in the intention-to-treat population. The α from either rejected hypothesis was then recycled to the second level of hypothesis testing, overall survival for durvalumab monotherapy versus chemotherapy in the intention-to-treat population. If the second level of hypothesis was also rejected, then the available α was recycled to the third level of testing, overall survival for

durvalumab plus tremelimumab versus chemotherapy in the low PD-L1 population.[19] Other secondary endpoints were not planned for formal statistical analyses and are considered exploratory.

Two interim analyses were performed. The first interim analysis assessed the objective response rate and duration of response in all cisplatin-ineligible patients who received durvalumab monotherapy and who had a minimum follow-up of 24 weeks. The second interim analysis of overall survival was planned at approximately 80% information fraction for the comparison of durvalumab monotherapy versus chemotherapy in the high PD-L1 population. The O'Brien-Fleming spending function was used to adjust multiplicity for the interim and final analyses. By the time of the final analysis of overall survival in the high PD-L1 population, it was expected that there would be approximately 327 overall survival events for patients treated in the durvalumab monotherapy and chemotherapy groups (150 events and 177 events, respectively), from a total of 402 patients with high PD-L1 (81% maturity). This provides 84% power to show a statistically significant difference in overall survival at a two-sided α level of 3·03% at the final analysis (the difference between groups was considered statistically significant if p<0·0301). Assuming that the survival curves of the two treatment groups did not separate for 6 months (hazard ratio [HR] of 1), then the HR will be 0·57 after 6 months, which yields an anticipated overall average HR of 0·71.[20]

For the comparison of durvalumab plus tremelimumab and chemotherapy groups in the intention-to-treat population, an interim analysis was planned at approximately 80% information fraction and the final analysis of overall survival based on 550 events (from 670 patients; 82% maturity; 255 events for durvalumab plus tremelimumab and 295 events for chemotherapy) was expected to occur around 46 months after the first patient was randomly assigned. This provides approximately 87% power to show a statistically significant difference in overall survival at a two-sided α level of 1·33% (with overall α for overall survival of 1·5%) at the final analysis (the difference between groups was considered statistically significant if p<0·0134). Assuming that the survival curves of the two treatment groups did not separate for 6 months (HR=1), then the HR will be 0·61 after 6 months, which yields an anticipated overall average HR of 0·73. Overall survival was estimated using the Kaplan-Meier method. Surviving patients were censored at the cutoff date, or last contact date if lost to follow-up, or upon withdrawal of consent. Differences in overall survival between groups were determined with the use of a stratified log-rank test, with the stratification factors of cisplatin eligibility, PD-L1 status, and presence or absence of liver metastases, lung metastases, or both, according to randomisation. A sensitivity analysis was planned to do the stratified overall survival analysis using the stratification factors at baseline per the electronic case report form. HRs and 95% CIs were calculated with the use of a stratified Cox proportional hazards model. The overall survival landmarks at 1 year and 2 years were estimated according to the Kaplan-Meier method. These analyses are considered exploratory only and are not included in formal statistical inference.

An interim analysis was done on Oct 11, 2018, in which 265 overall survival events (81% information fraction) were confirmed for the durvalumab and chemotherapy groups; and 435 overall survival events (79% information fraction) were confirmed for the durvalumab plus tremelimumab and chemotherapy groups. The independent data and monitoring committee recommended continuing the study without change. The adjusted significance level was 0·0301 for the final analysis of durvalumab versus chemotherapy and 0·0134 for the final analysis of durvalumab plus tremelimumab versus chemotherapy.

The proportional hazards assumption was visually checked using log-log survival plots. To evaluate the potentially non-proportional hazard of immunotherapy regimens, the max-combo test[21] was prespecified as a sensitivity analysis for the two coprimary endpoints. The max-combo analysis is based on adaptive procedure-optimising test statistics among the log-rank test ($G_{0,0}$) and the Fleming-Harrington test ($G_{0,1}$, $G_{1,0}$, and $G_{1,1}$) with α correction, and is recommended by the Cross-Pharma Non-proportional Hazard Working Group in the presence of non-proportional hazards.[22]

Prespecified subgroup analyses for overall survival included all stratification factors (cisplatin eligibility, PD-L1 status, and presence or absence of liver metastases, lung metastases, or both), sex, age at randomisation, race, geographical region, smoking status, haemoglobin levels, visceral metastasis or lymph node only involvement, ECOG performance status, previous adjuvant or neo-adjuvant systemic chemotherapy, primary tumour site, previous BCG therapy, histology type, Bellmunt risk factors, and Bajorin risk factors.

For the secondary endpoints, analyses of progression-free survival were done using the same methods as for the primary endpoint. Patients who missed at least two assessments were censored at their last evaluable assessment before the missed visits. Objective response rate was compared between groups using logistic regression, adjusting for the stratification factors, and summarised with an odds ratio with a 95% CI calculated by profile likelihood. Median duration of response was calculated using the Kaplan-Meier method. Other secondary endpoints (disease control rate, time to second progression, time to response, quality of life, pharmacokinetics, and immunogenicity) were not formally compared.

The intention-to-treat population included all patients who were randomly assigned to the three treatment groups, whether or not the assigned study treatment was received. Safety was assessed in all patients who received at least one dose of study drug in each of the three treatment groups.

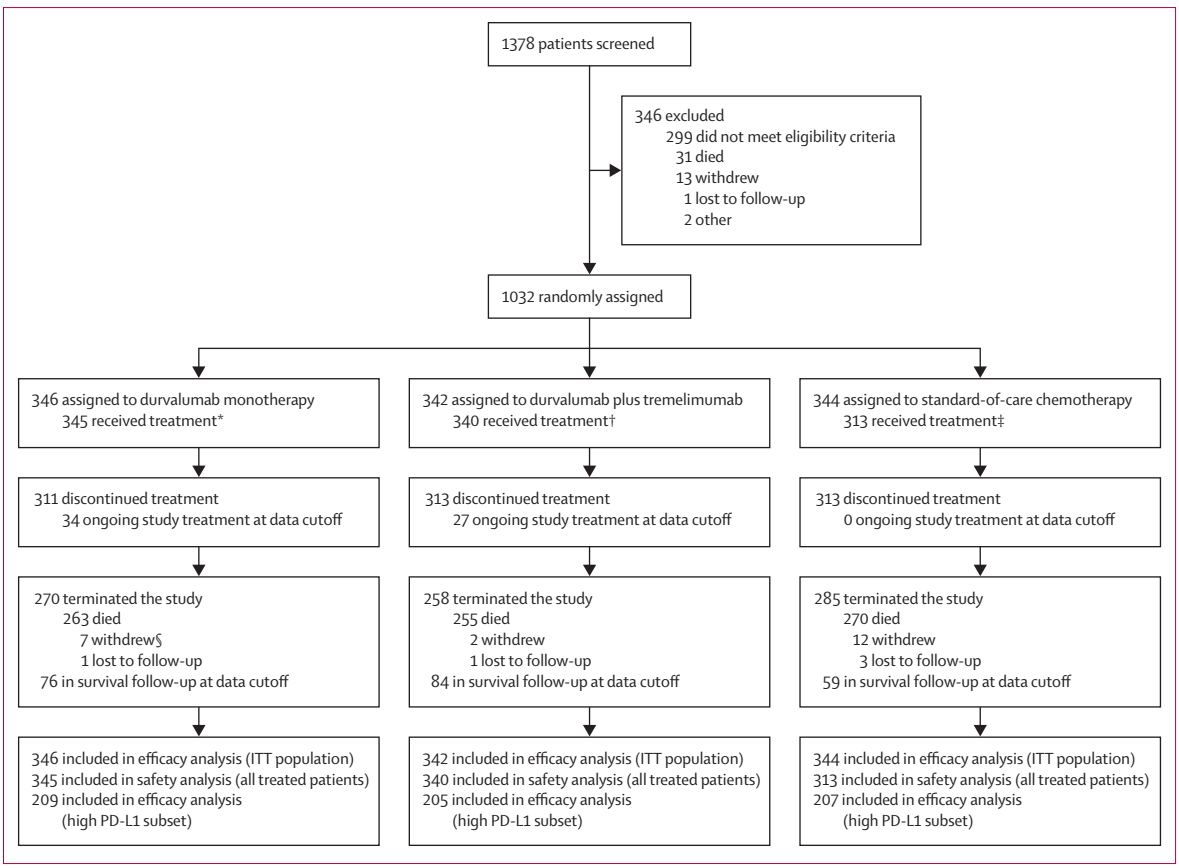

Figure 1: **Trial profile**
ITT=intention-to-treat. *One patient withdrew before starting treatment. †Two patients had disease progression before starting treatment. ‡23 patients withdrew, two patients experienced adverse events, five patients had disease progression, and one patient developed study discontinuation criteria before starting treatment. §One patient died after withdrawing consent for all study procedures except the collection of survival data and is therefore included in both the patients who died and the patients who withdrew.

Statistical analyses were done with SAS, version 9.4. This trial is registered with ClinicalTrials.gov, NCT02516241, and the EU Clinical Trials Register, EudraCT number 2015-001633-24.

Role of the funding source

The sponsor (AstraZeneca) designed the study in collaboration with members of the trial steering committee. Data were collected by each study site and submitted to the sponsor for analysis. The sponsor collaborated with the academic authors regarding data interpretation and writing of the report. All authors had access to study data. The corresponding author had final responsibility for the decision to submit for publication.

Results

1378 patients were initially screened, of whom 346 were excluded (figure 1). Between Nov 24, 2015, and March 21, 2017, we randomly assigned 1032 patients (intention-to-treat population) to durvalumab monotherapy (n=346), durvalumab in combination with tremelimumab (n=342), or standard-of-care chemotherapy (n=344). At data cutoff on Jan 27, 2020, median follow-up for survival was 41·2 months (IQR 37·9–43·2) for all patients, based on the reverse Kaplan-Meier method,[23] and the minimum follow-up was 34 months from the date that the last patient underwent randomisation. Baseline characteristics of the patients were well balanced across the three treatment groups in the intention-to-treat population (table 1) and in the population of patients with high PD-L1 expression (appendix p 7). Baseline characteristics in the low or negative PD-L1 population were similar to those in the high PD-L1 population (data not shown). 209 (60%) of 346 patients in the durvalumab group, 205 (60%) of 342 in the durvalumab plus tremelimumab group, and 207 (60%) of 344 in the chemotherapy group had high PD-L1 expression. In the intention-to-treat population, 197 (57%) of 346 patients in the durvalumab group, 194 (57%) of 342 in the durvalumab plus tremelimumab group, and 193 (56%) of 344 in the chemotherapy group were eligible for cisplatin. During randomisation, there was a mis-stratification that resulted in an approximate difference of 10% between the interactive voice–web response system and the electronic

case report form for cisplatin eligibility; however, a preplanned sensitivity analysis revealed no impact on the primary outcome (data not shown).

Among patients who underwent randomisation, 345 of 346 in the durvalumab group, 340 of 342 in the durvalumab plus tremelimumab group, and 313 of 344 in the chemotherapy group received study treatment (figure 1). Among treated patients, the median treatment duration (including dose interruptions and dose delays) was 16·3 weeks (IQR 8·1–42·9) for durvalumab monotherapy; 19·9 weeks (8·6–57·3) for durvalumab and 15·9 weeks (8·2–16·1) for tremelimumab in the combination group; and 18·9 weeks (13·0–20·4) in the chemotherapy group. The median number of doses or cycles was four (2–10) in the durvalumab monotherapy group; four (2–14) for durvalumab and four (2–4) for tremelimumab in the combination group; and six (4–6) in the chemotherapy group (and five patients received more than six cycles of chemotherapy). At data cutoff, 34 patients (10%) in the durvalumab group and 27 patients (8%) in the durvalumab plus tremelimumab group were still receiving the study intervention, but no patients in the chemotherapy group were still receiving treatment at data cutoff. Subsequent anticancer therapy was received by 164 (47%) of 346 patients in the durvalumab group, 153 (45%) of 342 patients in the durvalumab plus tremelimumab group, and 187 (54%) of 344 patients in the chemotherapy group (appendix p 9). 106 (31%) of 344 patients in the chemotherapy group, nine (3%) of 346 patients in the durvalumab monotherapy group, and 18 (5%) of 342 patients in the durvalumab plus tremelimumab group received subsequent immunotherapy; 146 (42%) of 346 patients in the durvalumab group, 135 (39%) of 342 patients in the durvalumab plus tremelimumab group, and 105 (31%) of 344 patients in the chemotherapy group received subsequent chemotherapy. In the high PD-L1 population, subsequent anticancer therapy was received by 94 (45%) of 209 patients in the durvalumab group, 87 (42%) of 205 patients in the durvalumab plus tremelimumab group, and 116 (56%) of 207 patients in the chemotherapy group (appendix p 11).

At the time of the data cutoff for the final analysis (Jan 27, 2020), 263 (76%) of 346 patients in the durvalumab group, 255 (75%) of 342 patients in the durvalumab plus tremelimumab group, and 270 (78%) of 344 patients in the chemotherapy group had died; in the high PD-L1 population, 151 (72%) of 209 patients in the durvalumab group, 143 (70%) of 205 patients in the durvalumab plus tremelimumab group, and 161 (78%) of 207 patients in the chemotherapy group had died.

For the analysis of the coprimary endpoints, in the high PD-L1 population, median overall survival was 14·4 months (95% CI 10·4–17·3) in the durvalumab group and 12·1 months (10·4–15·0) in the chemotherapy group (HR 0·89, 95% CI 0·71–1·11; two-sided p=0·30; figure 2A). Overall survival results for the comparison of durvalumab versus chemotherapy in patients with high PD-L1 expression were consistent across most prespecified subgroups (appendix p 22). In the intention-to-treat population, median overall survival was 15·1 months (13·1–18·0) in the durvalumab plus tremelimumab group and 12·1 months (10·9–14·0) in the chemotherapy group (HR 0·85, 95% CI 0·72–1·02; two-sided p=0·075; figure 2B). Overall survival results across most prespecified subgroups were consistent with those observed in the intention-to-treat population (appendix p 23). For each treatment group within the intention-to-treat and high PD-L1 populations, overall survival was similar between cisplatin-eligible and cisplatin-ineligible patients (appendix pp 13, 23).

The proportional hazards assumption was checked using log-log survival plots and was found to be violated for both coprimary endpoints. The prespecified sensitivity analysis using the max-combo method produced a p value

	Durvalumab monotherapy group (n=346)	Durvalumab plus tremelimumab group (n=342)	Chemotherapy group (n=344)
Age, years	67 (60–73)	68 (60–73)	68 (60–73)
Age group, years			
<65	137 (40%)	137 (40%)	133 (39%)
≥65	209 (60%)	205 (60%)	211 (61%)
Sex			
Female	97 (28%)	86 (25%)	70 (20%)
Male	249 (72%)	256 (75%)	274 (80%)
Race			
White	278 (80%)	253 (74%)	260 (76%)
Black or African–American	3 (1%)	3 (1%)	0
Asian	60 (17%)	72 (21%)	76 (22%)
Other	4 (1%)	13 (4%)	8 (2%)
Missing	1 (<1%)	1 (<1%)	0
Smoking status			
Never	125 (36%)	98 (29%)	101 (29%)
Current	60 (17%)	66 (19%)	61 (18%)
Former	159 (46%)	176 (51%)	178 (52%)
Missing	2 (1%)	2 (1%)	4 (1%)
Histology type: pure transitional cell carcinoma	305 (88%)	310 (91%)	298 (87%)
Primary tumour site			
Bladder	282 (82%)	264 (77%)	255 (74%)
Renal pelvis	40 (12%)	47 (14%)	55 (16%)
Ureter	22 (6%)	27 (8%)	30 (9%)
Urethra	2 (1%)	4 (1%)	3 (1%)
Other	0	0	1 (<1%)
Disease status			
Locally advanced	12 (3%)	13 (4%)	21 (6%)
Metastatic	334 (97%)	329 (96%)	323 (94%)
Site of metastatic disease			
Lymph node only	61 (18%)	73 (21%)	77 (22%)
Liver metastases, lung metastases, or both	189 (55%)	186 (54%)	178 (52%)
Visceral metastases*	285 (82%)	268 (78%)	266 (77%)

(Table 1 continues on next page)

	Durvalumab monotherapy group (n=346)	Durvalumab plus tremelimumab group (n=342)	Chemotherapy group (n=344)
(Continued from previous page)			
ECOG performance status			
0	170 (49%)	189 (55%)	189 (55%)
1	176 (51%)	152 (44%)	154 (45%)
2	0	1 (<1%)	0
Missing	0	0	1 (<1%)
Haemoglobin concentration <10 g/dL	33 (10%)	33 (10%)	42 (12%)
Bajorin risk factors†			
0	121 (35%)	129 (38%)	130 (38%)
1	225 (65%)	212 (62%)	213 (62%)
2	0	1 (<1%)	0
Missing	0	0	1 (<1%)
Previous adjuvant or neoadjuvant chemotherapy	72 (21%)	71 (21%)	70 (20%)
PD-L1 expression			
High	209 (60%)	205 (60%)	207 (60%)
Low	137 (40%)	137 (40%)	137 (40%)
Cisplatin eligible‡			
Yes	197 (57%)	194 (57%)	193 (56%)
No	149 (43%)	148 (43%)	151 (44%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. *Includes liver, lung, bone, and soft tissue. †The two risk factors are ECOG performance status of 2 or higher and the presence of Bajorin-defined visceral metastasis (liver, lung, or bone). ‡Patients were not eligible for cisplatin if they met one of the following criteria: creatinine clearance of less than 60 mL per min calculated by the Cockcroft-Gault equation or by measured 24-h urine collection; National Cancer Institute Common Terminology Criteria for Adverse Events grade 2 or worse audiometric hearing loss or grade 2 or worse peripheral neuropathy; New York Heart Association class III or higher heart failure.

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

of 0·036 for durvalumab versus chemotherapy and 0·0025 for durvalumab plus tremelimumab versus chemotherapy.

In secondary analyses, median overall survival was 13·2 months (95% CI 10·3–15·0) in the durvalumab group in the intention-to-treat population (HR *vs* chemotherapy 0·99, 95% CI 0·83–1·17; figure 3A). Median overall survival was 17·9 months (95% CI 14·8–24·2) in the durvalumab plus tremelimumab group in the high PD-L1 population (HR *vs* chemotherapy 0·74, 95% CI 0·59–0·93; figure 3B). Overall survival outcomes in the low PD-L1 population are shown in the appendix (pp 24–25).

255 (74%) of 346 patients in the durvalumab group, 254 (74%) of 342 in the durvalumab plus tremelimumab group, and 241 (70%) of 344 in the chemotherapy group had experienced progression or death at the data cutoff. In the intention-to-treat population, median progression-free survival was 2·3 months (95% CI 1·9–3·5) in the durvalumab group, 3·7 months (3·4–3·8) in the durvalumab plus tremelimumab group, and 6·7 months (5·7–7·3) in the chemotherapy group (appendix p 26). In the high PD-L1 population, 177 (85%) of 209 patients in the durvalumab group, 168 (82%) of 205 in the durvalumab plus tremelimumab group, and 169 (82%) of 207 in the chemotherapy group had experienced progression or died at the data cutoff, with median progression-free survival of 2·4 months (1·9–3·7) in the durvalumab group, 4·1 months (3·6–5·7) in the durvalumab plus tremelimumab group, and 5·8 months (5·6–7·2) in the chemotherapy group (appendix p 27).

In the intention-to-treat population, 89 (26%) of 346 patients in the durvalumab group, 124 (36%) of 342 patients in the durvalumab plus tremelimumab group, and 169 (49%) of 344 patients in the chemotherapy group had an investigator-assessed objective response (table 2). In the high PD-L1 population, 58 (28%) of 209 patients in the durvalumab group, 96 (47%) of 205 patients in the durvalumab plus tremelimumab group, and 100 (48%) of 207 patients in the chemotherapy group had an investigator-assessed objective response (table 2). In both the intention-to-treat and high PD-L1 populations, objective response rates were similar between cisplatin-eligible and cisplatin-ineligible patients across the treatment groups (table 2; appendix p 13). Results for duration of response and disease control rate at 6 and 12 months in each treatment group in the intention-to-treat and high PD-L1 populations are shown in table 2. Objective response rates in the low PD-L1 population are provided in the appendix (p 13).

In the safety population, treatment-related adverse events of any grade occurred in 193 (56%) of 345 patients in the durvalumab group, 255 (75%) of 340 patients in the durvalumab plus tremelimumab group, and 283 (90%) of 313 patients in the chemotherapy group (one patient in the durvalumab group and one patient in the durvalumab plus tremelimumab group had an adverse event of unkown grade), with grade 3 or 4 adverse events in 47 (14%), 93 (27%), and 188 (60%) patients, respectively (table 3; appendix p 14). The most common grade 3 or 4 treatment-related adverse event was increased lipase in both the durvalumab monotherapy and durvalumab plus tremelimumab groups (table 3; appendix p 15). In the chemotherapy group, the most common grade 3 or 4 treatment-related adverse events in the chemotherapy group were neutropenia and anaemia (table 3; appendix p 15). Drug interruptions were required in 95 (28%) of 345 patients in the durvalumab group and in 122 (36%) of 340 patients in the durvalumab plus tremelimumab group; dose reductions or drug interruptions were required in 217 (69%) of 313 patients in the chemotherapy group. Adverse events leading to discontinuation of study treatment occurred in 41 (12%) of 345 patients in the durvalumab group, 80 (24%) of 340 patients in the durvalumab plus tremelimumab group, and 53 (17%) of 313 patients in the chemotherapy group. Serious treatment-related adverse events occurred in 30 (9%) of 345 patients in the durvalumab group, 78 (23%) of 340 patients in the durvalumab plus tremelimumab group, and 50 (16%) of 313 patients in the chemotherapy group (appendix p 14). The most common serious treatment-related adverse event was pneumonia in the durvalumab group (three [1%] of 345 patients), diarrhoea in the durvalumab plus tremelimumab group (14 [4%] of

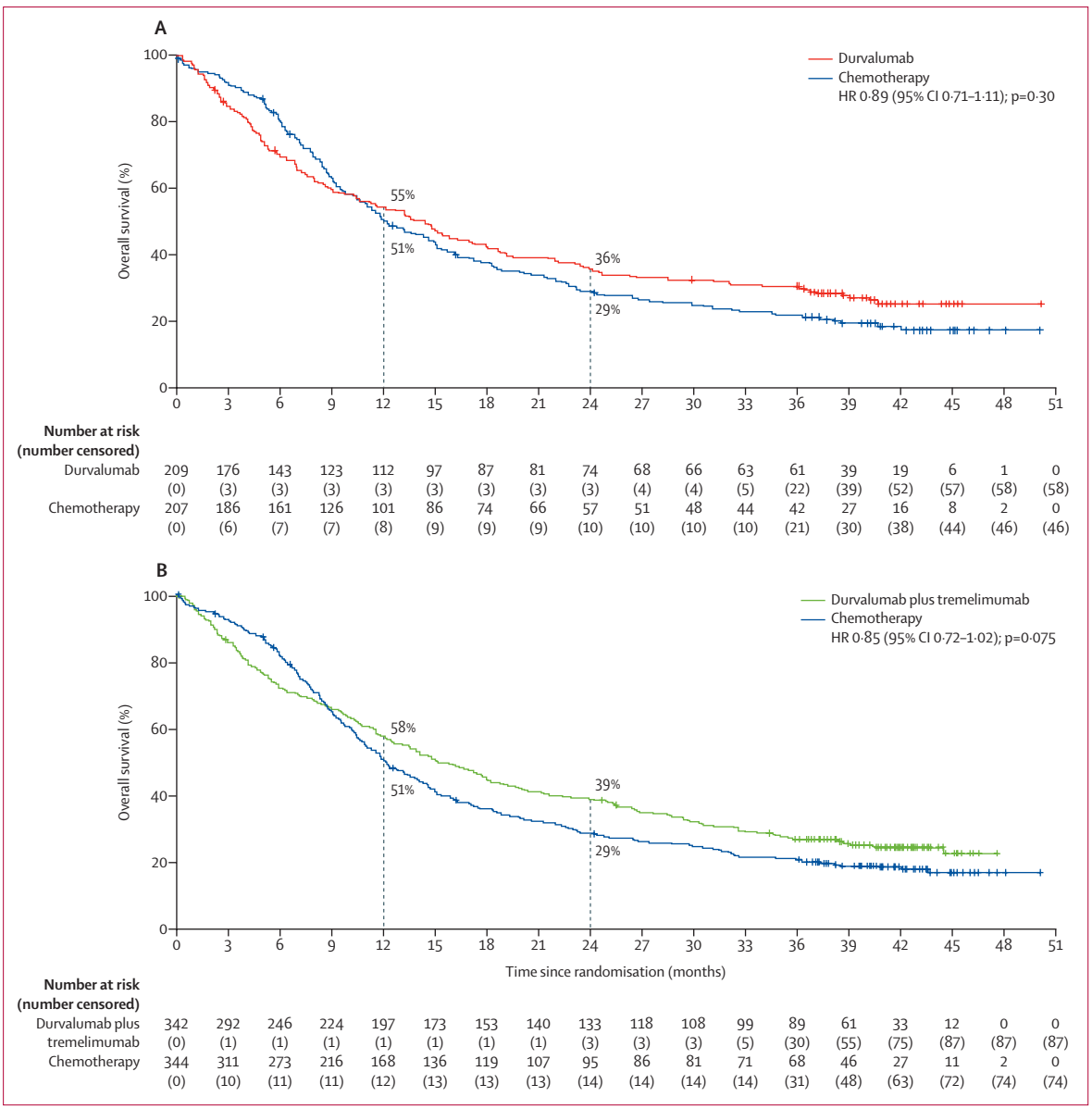

Figure 2: **Overall survival (coprimary endpoints)**
Kaplan-Meier estimates of overall survival for durvalumab monotherapy versus chemotherapy in the high PD-L1 population (A) and for durvalumab plus tremelimumab versus chemotherapy in the intention-to-treat population (B). Tick marks on the Kaplan-Meier plots indicate censored data. HR=hazard ratio.

340 patients), and anaemia in the chemotherapy group (seven [2%] of 313 patients).

Deaths on treatment or within 90 days of the last dose of study treatment occurred in 106 (31%) of 345 patients in the durvalumab group, 103 (30%) of 340 patients in the durvalumab plus tremelimumab group, and 47 (15%) of 313 patients in the chemotherapy group; 86 (25%), 80 (24%), and 38 (12%) deaths, respectively, were related to disease. Deaths due to study drug toxicity were reported in two patients in the durvalumab group (acute hepatic failure and hepatitis), two patients in the durvalumab plus tremelimumab group (septic shock and pneumonitis), and one patient in the chemotherapy group (acute kidney injury). Treatment-related adverse events of special interest are reported in the appendix (pp 14, 20). 37 (11%) patients in the durvalumab group, 90 (26%) in the durvalumab plus tremelimumab group, and four (1%) in the chemotherapy group required the use of systemic corticosteroids for an adverse event of special interest. Immune-mediated adverse events are reported in the appendix (p 14).

Discussion

The DANUBE study did not show a survival advantage for durvalumab compared with effective standard-of-care

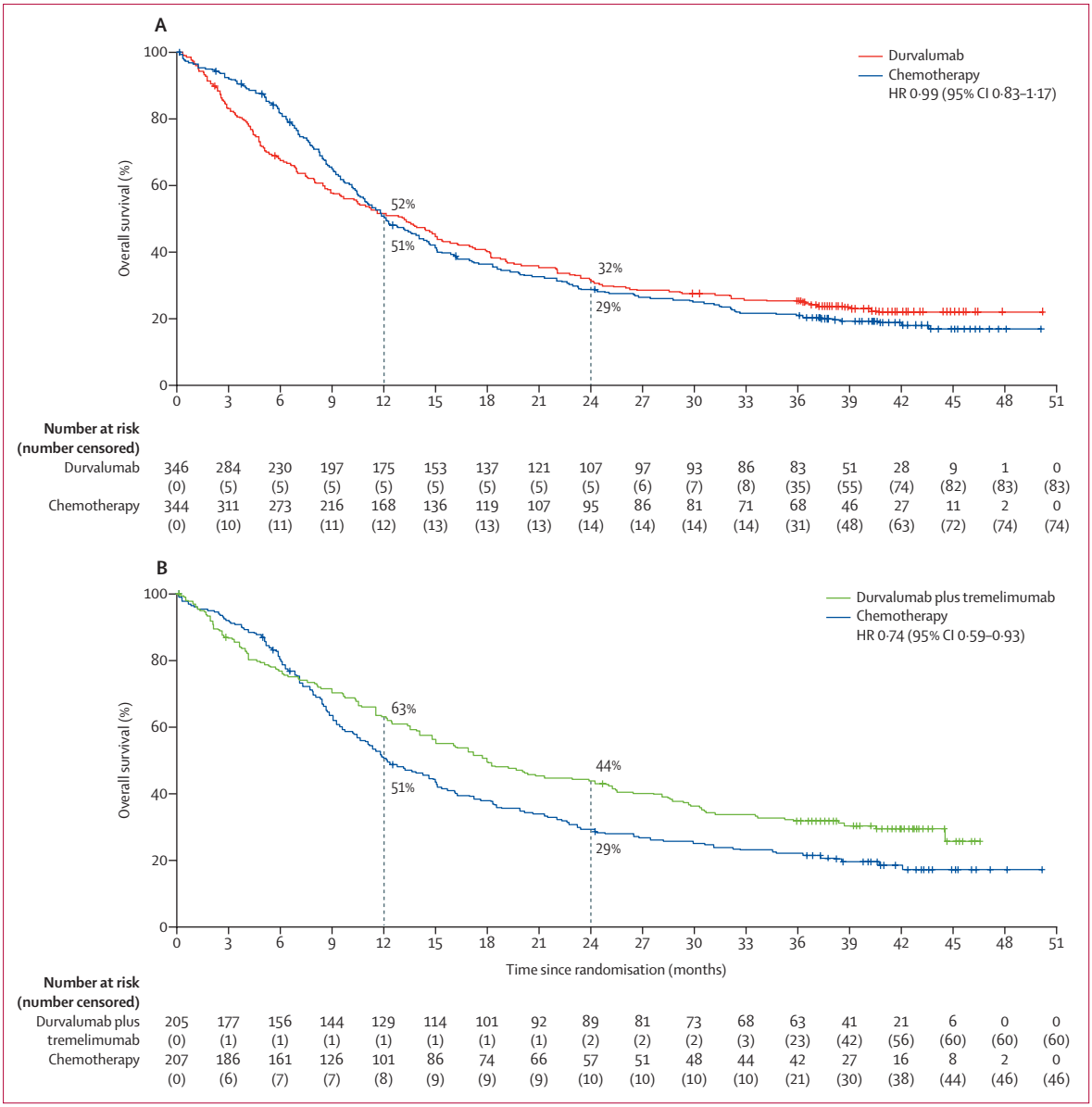

Figure 3: **Overall survival (secondary endpoints)**
Kaplan-Meier estimates of overall survival for durvalumab monotherapy versus chemotherapy in the intention-to-treat population (A) and durvalumab plus tremelimumab versus chemotherapy in the high PD-L1 population (B). Tick marks on the Kaplan-Meier plots indicate censored data. HR=hazard ratio.

platinum-based chemotherapy in previously untreated, PD-L1-positive patients with metastatic urothelial carcinoma, or for durvalumab plus tremelimumab versus chemotherapy in all previously untreated patients with metastatic urothelial carcinoma irrespective of PD-L1 expression.

Survival outcomes in the chemotherapy group were consistent with historical survival data for platinum-based chemotherapy in metastatic urothelial carcinoma (for gemcitabine plus cisplatin, median overall survival is around 14 months).[3] The PD-L1 biomarker-positive population was chosen for analysis of one of the coprimary endpoints in DANUBE because of encouraging single-arm, phase 1–2 data for durvalumab in PD-L1-positive patients with platinum-refractory disease.[12] However, in our study, chemotherapy appeared better than durvalumab at achieving initial control of disease, showing higher response rates and longer progression-free survival. This pattern, in which immunotherapy is inferior to chemotherapy during the initial period of treatment, has previously been described with other immune checkpoint inhibitors (eg, atezolizumab),[9] and it might account for the negative result of the study. Of note, the HRs tended to be smaller with increasing time from randomisation,

	Intention-to-treat population			High PD-L1 population		
	Durvalumab monotherapy group (n=346)	Durvalumab plus tremelimumab group (n=342)	Chemotherapy group (n=344)	Durvalumab monotherapy group (n=209)	Durvalumab plus tremelimumab group (n=205)	Chemotherapy group (n=207)
Objective response	89 (26%)	124 (36%)	169 (49%)	58 (28%)	96 (47%)	100 (48%)
Cisplatin eligible	53/197 (27%)	71/194 (37%)	99/193 (51%)	34/117 (29%)	54/115 (47%)	56/113 (50%)
Cisplatin ineligible	36/149 (24%)	53/148 (36%)	70/151 (46%)	24/92 (26%)	42/90 (47%)	44/94 (47%)
Best objective response						
Complete response	27 (8%)	27 (8%)	22 (6%)	21 (10%)	24 (12%)	15 (7%)
Partial response	62 (18%)	97 (28%)	147 (43%)	37 (18%)	72 (35%)	85 (41%)
Stable disease ≥8 weeks	70 (20%)	66 (19%)	80 (23%)	43 (21%)	36 (18%)	47 (23%)
Progressive disease	182 (53%)	145 (42%)	63 (18%)	107 (51%)	70 (34%)	41 (20%)
Not evaluable	5 (1%)	7 (2%)	32 (9%)	1 (<1%)	3 (1%)	19 (9%)
Duration of response						
Responders who subsequently progressed or died	55/89 (62%)	83/124 (67%)	139/169 (82%)	34/58 (59%)	64/96 (67%)	84/100 (84%)
Duration, months	9·3 (5·8–20·5)	11·1 (7·9–18·5)	5·7 (5·6–6·2)	18·5 (7·6–NE)	10·0 (7·4–18·7)	5·8 (5·1–7·0)
Disease control at 6 months	110 (32%)	142 (42%)	191 (56%)	72 (34%)	102 (50%)	110 (53%)
Disease control at 12 months	97 (28%)	130 (38%)	174 (51%)	64 (31%)	97 (47%)	101 (49%)

Data are n (%), n/N (%), or median (95% CI). Response was assessed by the investigators according to Response Evaluation Criteria in Solid Tumors version 1.1. NE=not estimable.

Table 2: **Antitumour activity**

which suggests a larger treatment benefit at the tail of the Kaplan-Meier curves. In patients with previously untreated metastatic urothelial carcinoma, the JAVELIN Bladder 100 study evaluated platinum-based chemotherapy followed by maintenance PD-L1 inhibition (avelumab) plus best supportive care and showed improved overall survival compared with best supportive care alone;[10] this approach has become a standard of care.

Approximately 60% of patients in the DANUBE trial had PD-L1-positive tumours. Although efficacy across treatment groups was enhanced in the biomarker-selected populations, PD-L1 expression alone might not be sufficient to identify patients who benefit from PD-1 or PD-L1 inhibitors. More specific patient selection might be required for biomarker-targeted monotherapy to outperform effective chemotherapy, considering the response rate of 26% for durvalumab in the intention-to-treat population compared with 49% for chemotherapy. Results for atezolizumab and pembrolizumab in this setting, using other biomarkers, are awaited (NCT02853305).[9]

Similarly, in our comparison of durvalumab and tremelimumab versus chemotherapy in the intention-to-treat population, responses (and specifically partial responses) occurred at a higher rate with chemotherapy than with durvalumab plus tremelimumab, whereas durable remissions were more apparent with durvalumab plus tremelimumab as shown by the longer duration of response in this treatment group than in the chemotherapy group. Secondary analyses suggested that the activity of durvalumab plus tremelimumab (as assessed by overall survival and objective response rate) was higher than durvalumab alone, supporting previous evidence that tremelimumab monotherapy has activity in metastatic urothelial carcinoma.[13] Of note, we do not have data on the treatment duration or median number of doses or cycles for patients who achieved an objective response with durvalumab monotherapy or durvalumab plus tremelimumab (followed by durvalumab maintenance therapy). This is an analysis worth exploring and could be the focus of future research. The combination treatment was associated with a higher frequency of adverse events than durvalumab monotherapy and a higher proportion of patients had to discontinue therapy due to toxicity (24% *vs* 12%). This is an important consideration for tumours such as urothelial carcinoma for which comorbidities are common.

At the time the DANUBE trial was designed, we hypothesised that the combination of PD-L1 and CTLA-4 inhibitors would be effective irrespective of PD-L1 status. Data from a single-arm, phase 1 study with durvalumab plus tremelimumab in metastatic urothelial carcinoma showed encouraging antitumour activity and promising survival rates irrespective of PD-L1 expression, albeit with numerically higher objective response rate and 6-month overall survival in the high PD-L1 population.[15] Therefore, the choice of an intention-to-treat population rather than a biomarker-selected population appeared logical for the combination treatment group. More recent biomarker and clinical data suggest that CTLA-4 inhibition could be more active in PD-L1-positive tumours.[24] Predefined secondary analyses for the combination supported the hypothesis that tremelimumab might have increased activity when combined with durvalumab versus duravalumab alone, especially in the biomarker-positive population. Although

	Durvalumab monotherapy group (n=345)				Durvalumab plus tremelimumab group* (n=340)				Chemotherapy group* (n=313)			
	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 treatment-related adverse event	144 (42%)	36 (10%)	11 (3%)	2 (1%)	159 (47%)	81 (24%)	12 (4%)	2 (1%)	93 (30%)	144 (46%)	44 (14%)	1 (<1%)
Blood and lymphatic system disorders												
Anaemia	2 (1%)	4 (1%)	0	0	5 (1%)	2 (1%)	0	0	69 (22%)	62 (20%)	0	0
Leucopenia	0	0	0	0	1 (<1%)	0	0	0	13 (4%)	12 (4%)	0	0
Neutropenia	1 (<1%)	0	0	0	0	0	0	0	17 (5%)	54 (17%)	12 (4%)	0
Thrombocytopenia	2 (1%)	0	0	0	0	0	0	0	24 (8%)	17 (5%)	7 (2%)	0
Gastrointestinal disorders												
Constipation	5 (1%)	0	0	0	9 (3%)	1 (<1%)	0	0	39 (12%)	0	0	0
Diarrhoea	21 (6%)	2 (1%)	0	0	63 (19%)	9 (3%)	0	0	28 (9%)	5 (2%)	0	0
Nausea	27 (8%)	0	0	0	15 (4%)	1 (<1%)	0	0	120 (38%)	8 (3%)	0	0
Vomiting	6 (2%)	0	0	0	16 (5%)	2 (1%)	0	0	36 (12%)	5 (2%)	0	0
General disorders and administrative-site conditions												
Asthenia	18 (5%)	1 (<1%)	1 (<1%)	0	21 (6%)	5 (1%)	0	0	41 (13%)	7 (2%)	0	0
Fatigue	40 (12%)	1 (<1%)	0	0	43 (13%)	6 (2%)	0	0	77 (25%)	8 (3%)	0	0
Hepatobiliary disorders												
Acute hepatic failure	0	0	0	1 (<1%)	0	0	0	0	0	0	0	0
Cholestatic hepatitis	0	0	0	1 (<1%)	0	0	0	0	0	0	0	0
Infections and infestations												
Septic shock	0	0	0	0	0	0	0	1 (<1%)	0	0	0	0
Investigations												
Increased amylase	6 (2%)	3 (1%)	0	0	4 (1%)	8 (2%)	0	0	1 (<1%)	0	0	0
Increased lipase	4 (1%)	4 (1%)	3 (1%)	0	4 (1%)	13 (4%)	3 (1%)	0	1 (<1%)	1 (<1%)	0	0
Decreased neutrophil count	1 (<1%)	0	0	0	0	0	0	0	10 (3%)	28 (9%)	18 (6%)	0
Decreased platelet count	1 (<1%)	0	0	0	0	0	0	0	26 (8%)	14 (4%)	17 (5%)	0
Decreased white blood cell count	0	0	0	0	0	0	0	0	17 (5%)	11 (4%)	1 (<1%)	0
Metabolism and nutrition disorders												
Decreased appetite	20 (6%)	3 (1%)	0	0	22 (6%)	3 (1%)	0	0	56 (18%)	4 (1%)	0	0
Renal and urinary disorders												
Acute kidney injury	2 (1%)	0	0	0	1 (<1%)	2 (1%)	1 (<1%)	0	6 (2%)	1 (<1%)	0	1 (<1%)
Respiratory, thoracic, and mediastinal disorders												
Pneumonitis	4 (1%)	2 (1%)	0	0	9 (3%)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	0	0	0
Skin and subcutaneous tissue disorders												
Alopecia	2 (1%)	1 (<1%)	0	0	4 (1%)	0	0	0	33 (11%)	0	0	0
Pruritus	35 (10%)	1 (<1%)	0	0	76 (22%)	2 (1%)	0	0	11 (4%)	0	0	0
Rash	20 (6%)	2 (1%)	0	0	47 (14%)	4 (1%)	0	0	12 (4%)	0	0	0

Data are n (%). Treatment-related adverse events of grade 1–2 occurring in at least 10% of patients in any group, treatment-related adverse events of grade 3 or 4 occurring in at least 2% of patients in any group, and all treatment-related adverse events of grade 5 are reported. *One patient in the durvalumab plus tremelimumab group and one patient in the chemotherapy group had an adverse event of unknown grade.

Table 3: **Treatment-related adverse events**

not conclusive, this observation is of interest and requires further evaluation. Ongoing, first-line phase 3 trials, including durvalumab and tremelimumab in combination with chemotherapy (NCT03682068) and nivolumab in combination with ipilimumab or standard-of-care chemotherapy (NCT03036098), will further explore this hypothesis.

A substantial proportion of patients in all three groups in the DANUBE trial received subsequent therapy upon disease progression, reflecting the aggressive nature of metastatic urothelial carcinoma. 31% of patients randomly assigned to the chemotherapy group received subsequent systemic immunotherapy, which could have affected survival outcomes. Additionally, 31 patients (9%) in the chemotherapy group were randomly assigned but did not start chemotherapy, which was higher than in the other treatment groups. The reasons for this difference are not available, but these patients might have pursued alternative avenues of treatment. We do not know whether or not this difference affected our results.

Of note, the durvalumab monotherapy and combination groups appeared to have similar efficacy outcomes in the cisplatin-eligible and cisplatin-ineligible populations. Thus, we can extrapolate indirectly from these

data that the activity of gemcitabine plus cisplatin and gemcitabine plus carboplatin appeared to be similar across the overall response and overall survival endpoints. The generally perceived superiority of cisplatin over carboplatin as first-line therapy for metastatic urothelial carcinoma is largely driven by a randomised phase 2 study of 47 patients from the 1990s[25] and indirect comparisons between trials.[3,5] Thus, re-exploration of this issue is warranted.

Across the treatment groups, adverse events were consistent with those reported for the individual agents, with no new safety signals observed. As expected, a higher incidence of adverse events and a higher rate of discontinuations due to treatment-related adverse events were observed with the combination of durvalumab and tremelimumab than with durvalumab alone. However, in both groups, the incidence of treatment-related adverse events of any grade and of grade 3 or 4 was lower than with chemotherapy. Durvalumab monotherapy and the combination of durvalumab and tremelimumab had a manageable safety profile. Health-related quality-of-life assessments and patient-reported outcome data, which are also clinically relevant in this disease setting, will be reported separately in the future.

This robust and mature randomised study did not show a survival advantage compared with standard of care chemotherapy in either experimental treatment group. These findings could add to our understanding of immune checkpoint inhibitors in urothelial carcinoma and dampen enthusiasm for this approach in light of the recent positive study that sequenced chemotherapy and avelumab.[10] Secondary endpoint results for the combination treatment suggest that tremelimumab has activity in this disease when given in combination with durvalumab, but it also increases toxicity. Further studies and analyses are needed to identify the potential role of immune checkpoint inhibitors, alone or in combination, as first-line treatments for metastatic urothelial carcinoma.

Contributors

TP, MSvdH, AKG, WL, and JB conceived and designed the study. SW, PH, and AKG developed the methods. TP, MSvdH, DC, MDG, YL, DPP, OO, SHP, J-LL, UDG, MB, AB, BJE, HG, SDM, YF, IS, MT, ANo, CS, APF, ID, ANe, SW, NA, WL, and JB collected the data. TP, MSvdH, MDG, SW, PH, NA, AKG, WL, and JB analysed and interpreted the data. PH did the statistical analysis. TP, MSvdH, DC, MDG, YL, DPP, OO, and JB were members of the steering committee. TP, WL, and JB conducted the literature search. TP, MSvdH, NA, and WL provided administrative, technical, or material support. TP, SW, PH, NA, and WL prepared the original draft of the manuscript. All authors critically revised the manuscript for intellectual content. All authors contributed to drafts of the manuscript, approved the final version of the submitted report and agree to be accountable for all aspects. All authors verify that this study was done per protocol and vouch for data accuracy and completeness.

Declaration of interests

TP has received honoraria from AstraZeneca, Bristol-Myers Squibb (BMS), Merck Sharp & Dohme (MSD), Novartis, Pfizer, and Roche/Genentech; has served as a consultant or adviser for AstraZeneca, BMS, Genentech/Roche, Incyte, Ipsen, MSD, Novartis, Pfizer, and Seattle Genetics; has received research funding from AstraZeneca/MedImmune and Roche/Genentech; and has received travel expenses from AstraZeneca, BMS, MSD, Novartis/Ipsen, Pfizer, and Roche/Genentech. MSvdH has served as a consultant or adviser for Astellas Pharma, AstraZeneca/MedImmune, BMS, MSD Oncology, Roche/Genentech, and Seattle Genetics; has received research funding from Astellas Pharma, BMS, and Roche; and has received travel expenses from Astellas Pharma, MSD Oncology, Novartis, and Roche. 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Data sharing

Data reported in this Article may be obtained in accordance with AstraZeneca's data sharing policy.

For **AstraZeneca's data sharing policy** see https://astrazenecagrouptrials.pharmacm.com/ST?Submission/Disclosure

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