2 SYNOPSIS

Study centres

This study was conducted at 76 centres and patients were enrolled at 65 centres in 12 countries (3 in Belgium, 6 in Hungary, 8 in India, 8 in Japan, 6 in South Korea, 3 in Mexico, 3 in Netherlands, 4 in Poland, 8 in Russia, 5 in Ukraine, 2 in the United Kingdom, and 9 in the United States).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To assess the efficacy of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy in terms of PFS (Investigator-assessed)	PFS: Time from date of randomisation until the date of objective radiological disease progression according to Investigator assessment using RECIST 1.1 or death (by any cause in the absence of progression)
Secondary	Efficacy	To further assess the efficacy of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy in terms of OS, ORR, and DoR	OS: Time from date of randomisation until the date of death by any cause ORR: Percentage of patients with an Investigator-assessed response of CR or PR after randomisation DoR: Time from the date of first documented response following randomisation until the first date of documented progression or death in the absence of disease progression
Secondary	Efficacy	To further assess the efficacy of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy in terms of PFS (Investigator-assessed) in the HRRm population	PFS: Time from date of randomisation until the date of objective radiological disease progression according to Investigator assessment in HRRm population using RECIST 1.1 or death (by any cause in the absence of progression)
Secondary	PK	To assess the PK of durvalumab in combination with olaparib	Concentration of durvalumab

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	PRO	To assess disease-related symptoms and HRQoL in patients treated with durvalumab plus olaparib combination therapy compared with durvalumab monotherapy	Change from baseline and time to deterioration (for maintenance phase) in EORTC QLQ-C30 and EORTC QLQ-LC13
Secondary	Immunogenicity	To investigate the immunogenicity of durvalumab	Presence of ADAs for durvalumab
Safety	Safety	To assess the safety and tolerability profile of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy	AEs, physical examinations, laboratory findings, and vital signs
CCI			

ADA Anti-drug antibody; AE Adverse event; CR Complete response; CCI DoR Duration of response; EORTC European Organisation for Research and Treatment of Cancer; CCI HRQoL Health-related quality of life; CCI HRRm Homologous recombination repair-related gene mutation; CCI CCI ORR Objective response rate; OS Overall survival; CCI PFS Progression-free survival; CCI PK Pharmacokinetics; PR Partial response; PRO Patient reported outcome; QLQ-C30 30-item Core Quality of Life Questionnaire; QLQ-LC13 13-item Lung Cancer Quality of Life Questionnaire; RECIST 1.1 Response Evaluation Criteria in Solid Tumours version 1.1; CCI .

Study design

This was a Phase II randomised, multi-centre, double-blind, global study to determine the efficacy and safety of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy as maintenance therapy in patients whose disease had not progressed following standard of care (SoC) platinum-based chemotherapy with durvalumab in first-line Stage IV non-small cell lung cancer (NSCLC). During the initial therapy phase, patients received treatment with durvalumab, along with the Investigator's choice of platinum-based doublet therapy for squamous NSCLC (nanoparticle albumin-bound [nab]-paclitaxel plus carboplatin or gemcitabine plus carboplatin/cisplatin) and nonsquamous NSCLC (nab-paclitaxel plus carboplatin or pemetrexed plus carboplatin/cisplatin) for 4 cycles.

Patients who had complete response [CR], partial response [PR], or stable disease [SD] at Cycle 4 of the initial therapy phase according to Investigator-assessed RECIST 1.1 were randomised into the maintenance phase of the study. Patients were randomised 1:1 to receive either durvalumab plus placebo or durvalumab plus olaparib maintenance therapy. Randomisation was stratified by histologic subtype (squamous or nonsquamous) and objective response (CR/PR or SD; obtained at the last visit prior to randomisation [Cycle 4 scan]) during the initial therapy phase.

Confirmation of eligibility criteria for randomisation (eligibility scan and other specific criteria; see Sections 9.3.1 and 9.3.2) took place 14 to 28 days after Cycle 4 Day 1 of the initial therapy phase. Laboratory assessments for eligibility were taken after the last dose of chemotherapy in the initial therapy phase. If determined eligible, patients were randomised within 5 weeks after Cycle 4 Day 1 of the initial therapy phase with every effort made to minimise the time between confirmation of eligibility, randomisation, and starting maintenance treatment. Patients received maintenance treatment until specific discontinuation criteria were met, including clinical disease progression (as assessed by the Investigator) or RECIST 1.1-defined radiological PD, unacceptable toxicity, and withdrawal of consent.

An Independent Data Monitoring Committee (IDMC) was established to perform an assessment of the safety of durvalumab plus olaparib therapy combinations in this population on an ongoing basis. The IDMC was comprised of independent experts who reported to

AstraZeneca and who would recommend any changes in the conduct of the study following review of the unblinded safety data on an ongoing basis.

Target subject population and sample size

Approximately 350 to 400 patients were to be enrolled in the initial therapy phase of the study. Approximately 250 patients globally who had not progressed were to be randomised in a 1:1 ratio to either the durvalumab + olaparib group or the durvalumab + placebo group, approximately 125 patients per group.

Investigational product and comparators: dosage, mode of administration, and batch numbers

Durvalumab (initial therapy and maintenance phase): 50 mg/mL IV at a dose of 1500 mg every 3 weeks in the initial therapy phase and every 4 weeks in the maintenance phase, manufacturing batch-lot numbers CCI [redacted]

Olaparib (maintenance phase): 2 × 150-mg tablets for 300-mg dose twice daily, manufacturing batch-lot numbers CCI [redacted]

Placebo (maintenance phase): Matching placebo for oral tablet twice daily, manufacturing batch-lot numbers CCI [redacted] /1

SoC chemotherapy (initial therapy phase):

- Nab-paclitaxel: 100 mg/m^2 IV on Days 1, 8, and 15 of each 3-week cycle
- Carboplatin: Area under the concentration-time curve (AUC) 5 or 6 on Day 1 of each 3-week cycle
- Cisplatin: 75 mg/m^2 IV on Day 1 of each 3-week cycle
- Gemcitabine: 1000 or 1250 mg/m^2 IV on Days 1 and 8 of each 3-week cycle
- Pemetrexed: 500 mg/m^2 IV on Day 1 of each 3-week cycle

Duration of treatment

Unless specific treatment discontinuation criteria were met, treatment during the initial therapy phase continued for a maximum of 4 cycles of durvalumab plus chemotherapy. There was no maximum treatment duration for the maintenance phase; patients received maintenance treatment until specific discontinuation criteria were met, including clinical disease progression (as assessed by the Investigator) or RECIST 1.1-defined radiological PD, unacceptable toxicity, and withdrawal of consent.

Patients with clinical disease progression (as assessed by the Investigator), in the initial therapy or maintenance phase of the study, were not eligible for treatment through progression. Patients who were clinically stable with RECIST 1.1-defined radiological PD at Cycle 2 of the initial therapy phase could continue to receive study treatment at the discretion of the Investigator and patient; however, if the patient continued to show a RECIST 1.1-defined radiological PD at Cycle 4, the patient was not eligible for the maintenance phase of the study. Patients completing the initial therapy phase who were not randomised could not continue durvalumab.

Patients with PD in the maintenance phase who continued to receive study treatment had tumour assessments on their regular imaging schedule for the duration of treatment. However, patients were not permitted to continue immunotherapy or olaparib/placebo if progression occurred after confirmed response (CR or PR as defined by RECIST 1.1) in the target lesions to either the initial therapy (durvalumab plus chemotherapy) or maintenance treatment (durvalumab or olaparib/placebo) of the study regardless of the appearance of new lesions. Patients who had discontinued durvalumab were not permitted to be treated with olaparib/placebo monotherapy after progression.

Statistical methods

The primary objective of this study was to assess the efficacy of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy during the maintenance phase in terms of PFS as determined by Investigator assessment according to RECIST 1.1 in all randomised patients. A key secondary objective was to assess the efficacy of durvalumab plus olaparib compared with durvalumab monotherapy in terms of OS. In order to provide strong control of the type I error rate α=5% (2-sided), the testing procedure for PFS (the primary endpoint) and OS (key secondary endpoint) was hierarchical.

Additional, secondary efficacy variables included objective response rate (ORR) and duration of response (DoR) in the full analysis set (FAS), and PFS as determined by Investigator assessment according to RECIST 1.1 in the homologous recombination repair related gene mutation (HRRm) subgroup. Sensitivity analyses for the primary endpoint were performed, including analysing PFS according to blinded independent central review (BICR) in the FAS.

The effect of durvalumab + olaparib versus durvalumab + placebo was estimated by the hazard ratio (HR) together with its 95% confidence interval (CI) from a stratified Cox model (an HR less than 1 favoured durvalumab in combination with olaparib). The CI was calculated using a profile likelihood approach. Interactions between treatment and stratification factors were also tested to rule out any qualitative interaction using the approach of Gail and Simon.

The primary analyses were based on Investigator-recorded assessment of disease progression using RECIST 1.1 criteria. The primary analysis of PFS and interim OS analysis was to occur when approximately 163 PFS events had occurred across the durvalumab plus olaparib and durvalumab monotherapy treatment arms. CCI

The final OS analysis will occur when approximately 163 death events have occurred across the durvalumab plus olaparib and durvalumab monotherapy treatment arms.

Subject population

A total of 594 patients were enrolled in 65 study centres across 12 countries, including sites in Belgium, Hungary, India, Japan, Mexico, Netherlands, Poland, South Korea, Russia, Ukraine, the United Kingdom, and the United States. Of the enrolled patients, 401 (67.5%) received treatment in the initial therapy phase, with all 401 patients receiving durvalumab and all 401 patients receiving chemotherapy. Following the initial therapy phase, 269 patients were randomised in the maintenance phase in a 1:1 ratio to receive either durvalumab + olaparib (134 patients) or durvalumab + placebo (135 patients). At the time of the data cut-off date of 11 January 2021, 92 patients (51 [38.1%] patients in the durvalumab + olaparib group and 41 [30.6%] patients in the durvalumab + placebo group) were ongoing on treatment, and 155 patients (77 [57.5%] patients in the durvalumab + olaparib group and 78 [57.8%] patients in the durvalumab + placebo group) were ongoing in the study.

- The demographics were representative of the intended patient population and were generally balanced between randomised treatment groups, though there was a higher frequency of patients ≥75 years of age in the durvalumab + olaparib group (17.9%) compared to the durvalumab + placebo group (8.9%) and a lower frequency of patients <50 years of age in the durvalumab + olaparib group (5.2%) compared to the durvalumab + placebo group (10.4%). There was also a higher frequency of patients of Asian race in the durvalumab + placebo group (33.3%) compared to the durvalumab + olaparib group (27.6%). Overall, patients had a median age of 65.0 years, 72.5% were male, and, in terms of Race, 68.8% were White.
- The disease characteristics were also representative of the intended patient population and were generally balanced between the durvalumab + olaparib and durvalumab + placebo groups: baseline WHO performance status of 0 (38.8% and 40.0%, respectively), squamous histology (43.3% and 43.7%, respectively), and Stage IVA at initial diagnosis (56.7% and 57.0%, respectively). The majority of patients were former and current smokers, of which 24.5% were current smokers (26.1% in the durvalumab + olaparib group and 23.0% in the durvalumab + placebo group), 54.3% were former smokers (55.2% and 53.3%, respectively), and 21.2% were never smokers (18.7% and 23.7%, respectively).

- HRRm status was unknown for 32.7% of all patients and PD-L1 status was unknown for 30.5% of patients.
  - Five (3.7%) patients in the durvalumab + olaparib group and 9 (6.7%) of patients in the durvalumab + placebo group had a positive HRRm status result.
  - A total of 85 (31.6%) patients had a PD-L1 status result <1% and 43 (16.0%) patients had a PD-L1 status result ≥50%.
- The medical and surgical history, as well as the types of concomitant medication used, is typical for this population.
- The incidence of important protocol deviations was low (7.8% of the randomised population) and those observed do not raise any concerns regarding the overall conduct or quality of the study.
- In the durvalumab + olaparib group, 32.1% of patients received any post-discontinuation disease-related anticancer therapy compared to 36.3% of patients in the durvalumab + placebo group; cytotoxic chemotherapy was the most common subsequent therapy (25.4% and 28.9% of patients, respectively), followed by targeted therapy (9.7% and 13.3%, respectively), palliative radiotherapy (8.2% and 11.9%, respectively), and immunotherapy (3.7% and 5.2%, respectively).

Summary of efficacy results

- Durvalumab + olaparib treatment showed a numerical improvement in PFS (according to Investigator assessment of RECIST 1.1) over durvalumab + placebo in patients whose disease has not progressed following SoC platinum-based chemotherapy with durvalumab in first-line metastatic NSCLC, however this difference was not statistically significant (HR: 0.76; 95% CI: 0.57, 1.02; p-value=0.074).
  - The Kaplan-Meier estimate of median PFS was 7.2 months in the durvalumab + olaparib group (95% CI: 5.3, 7.9), compared to 5.3 months (95% CI: 3.7, 5.8) in the durvalumab + placebo group.
  - The median duration of follow-up in censored patients was 10.92 months in the durvalumab + olaparib group and 9.12 months in the durvalumab + placebo group.
- The PFS was not different between the treatment groups across all pre-specified sensitivity analyses, including the PFS analysis based on BICR assessment.
- PFS observations were generally consistent across subgroups defined by demographics and disease characteristics, with the exception of a numerical difference observed for the gemcitabine doublet chemotherapy subgroup (HR: 1.12, 95% CI: 0.68, 1.86).
- Median OS was 17.4 months in the durvalumab + olaparib group and was not reached in the durvalumab + placebo group (HR 0.90, 95% CI: 0.59, 1.36; p-value=0.604). However, the OS endpoint was immature (89 events, 33%).
- Treatment with durvalumab + olaparib resulted in a numerical improvement in ORR based on Investigator assessments according to RECIST 1.1 compared to durvalumab + placebo; however, this difference was not significant (22 [17.1%] patients in the durvalumab + olaparib group vs 18 [13.7%] patients in the durvalumab + placebo group; p-value=0.458).

- The median DoR was not reached in either the durvalumab + olaparib or durvalumab + placebo group. Based on Kaplan-Meier estimates, 79.1% and 65.7% of patients in the durvalumab + olaparib and durvalumab + placebo groups, respectively, were estimated to remain in response at 6 months, and 69.2% and 65.7%, respectively, were estimated to remain in response at 12 months.
- Patient reported outcomes data showed high level of compliance (greater than 80%) for both groups. Overall, durvalumab + olaparib treatment maintained the patient-reported symptoms, functioning and global health status/QoL.

Summary of safety results

- At the time of PFS analysis, the extent of exposure and follow-up was adequate to characterise the safety profile of durvalumab + olaparib in comparison with durvalumab + placebo treatment groups in the maintenance phase of the study. The median total duration of durvalumab treatment was 210.5 days (range: 28 to 582 days) for durvalumab + olaparib and 168.0 days (range: 11 to 615 days) for durvalumab + placebo.
- Overall, following 4 cycles of durvalumab plus chemotherapy, the durvalumab plus olaparib combination therapy was generally tolerated with no new safety signals identified.
- The most frequently reported AEs, by MedDRA preferred term (PT), regardless of causality (≥5% in any treatment group and occurring at a >5% higher frequency in the durvalumab + olaparib group than patients in the durvalumab + placebo group) were anaemia (26.1% and 8.2%, for durvalumab + olaparib and durvalumab + placebo, respectively), nausea (14.2% and 7.5%, respectively), decreased appetite (11.9% and 6.7%, respectively), and vomiting (11.2% and 2.2%, respectively).
- AEs of CTCAE Grade 3 or 4 were reported in 34.3% of patients in the durvalumab + olaparib group and 17.9% of patients in the durvalumab + placebo group. The most frequently reported AEs (≥2% in any treatment group and occurring at a >2% higher frequency in the durvalumab + olaparib group than patients in the durvalumab + placebo group) were anaemia (12.7% and 2.2%, for durvalumab + olaparib and durvalumab + placebo, respectively), fatigue (3.7% and 1.5%, respectively), and gamma-glutamyltransferase increased, nausea, and pneumonia (each in 2.2% and 0%, respectively).
- SAEs were reported in 18.7% of patients in the durvalumab + olaparib group and 14.2% of patients in the durvalumab + placebo group. The most frequently reported SAEs (at a frequency >1% in either treatment group and a >1.0% difference) were anaemia (5 [3.7%] patients and no patients in the durvalumab + olaparib and durvalumab + placebo groups, respectively), atrial fibrillation (2 [1.5%] patients and no patients, respectively), haemoptysis (no patients and 2 [1.5%] patients, respectively), and disease progression (no patients and 2 [1.5%] patients, respectively).
- AEs leading to discontinuation of either study treatment were reported in 10.4% of patients in the durvalumab + olaparib group and 4.5% of patients in the durvalumab + placebo group.
  - The most frequently (>1% in either treatment group and a >1.0% difference) reported AEs leading to discontinuation of either study medication were anaemia (3 [2.2%]

patients in the durvalumab + olaparib group and no patients in the durvalumab + placebo group) and dyspnoea (2 [1.5%] patients in the durvalumab + olaparib group and no patients in the durvalumab + placebo group).

  - Three (2.2%) patients in the durvalumab + olaparib group and 3 (2.2%) patients in the durvalumab + placebo group had AEs leading to discontinuation of durvalumab only. All PT events were reported in only 1 patient total for each.
  - Seven (5.2%) patients in the durvalumab + olaparib group and 2 (1.5%) patients in the durvalumab + placebo group had AEs leading to discontinuation of olaparib/placebo only. All PT events were reported in only 1 patient total for each, with the exception of anaemia which was reported in 2 (1.5%) patients in the durvalumab + olaparib group and no patients in the durvalumab + placebo group.

- AEs with an outcome of death were comparable between treatment groups (3.7% and 5.2% of patients in the durvalumab + olaparib and durvalumab + placebo groups, respectively). For the patients who experienced a fatal AE, there was no pattern to the types of events and all events were experienced by a single patient with the exception of events of disease progression (reported for 2 patients in the durvalumab + placebo group) and pneumonia (reported for 1 patient in each treatment group).
- AESIs/AEPIs associated with durvalumab were reported in 41.0% of patients in the durvalumab + olaparib group and 41.0% of patients in the durvalumab + placebo group.
  - In the durvalumab + olaparib group, 5 (9.1%) patients had CTCAE Grade 3 or 4 events. A total of 44 (80.0%) patients had AEs categorised as AESIs or AEPIs that were considered possibly related to treatment by the Investigator. A total of 18 (13.4%) patients had AEs categorised as AESIs or AEPIs that were adjudicated to be imAEs. The majority of imAEs were CTCAE Grade 1 or 2. CTCAE Grade 3 or 4 imAEs were reported in 3 (5.5%) patients.
  - In the durvalumab + placebo group, 5 (9.1%) patients had CTCAE Grade 3 or 4 events. A total of 36 (65.5%) patients had AEs categorised as AESIs or AEPIs considered possibly related to treatment by the Investigator. A total of 20 (14.9%) patients had AEs categorised as AESIs or AEPIs that were adjudicated to be imAEs. All but 1 of the imAEs were CTCAE Grade 1 or 2.
  - Only 1 patient in the durvalumab + placebo group reported an AEPI with an outcome of death (myocarditis event of cardiac failure acute).
- AESIs associated with olaparib were reported in 3.7% of patients in both treatment groups. With the exception of 1 patient in the durvalumab + olaparib group who reported an event of basal cell carcinoma, AESIs were all pneumonitis-type events which are also events of interest for durvalumab. There was one CTCAE Grade 3 event of pneumonitis; all other olaparib AESIs were CTCAE Grade 1 or 2.

- With regard to clinical laboratory evaluations:
  - The changes from baseline or trends in haematology observed over time were not different than what would be expected from the known toxicities of durvalumab and olaparib.
  - One (0.7%) patient in the durvalumab + olaparib group met the criteria for Potential Hy's Law based on clinical chemistry laboratory results (ALT or AST ≥3 × upper limit of normal [ULN] and total bilirubin ≥2 × ULN), though this was not a confirmed Hy's Law case. Disease progression in the liver provides an alternate cause for the elevation of the liver laboratory parameters in this patient.
  - A total of 28 (21.4%) patients in the durvalumab + olaparib group and 27 (21.6%) patients in the durvalumab + placebo group had on-treatment elevated TSH > ULN with TSH ≤ ULN at baseline. A total of 12 (9.2%) patients in the durvalumab + olaparib group and 20 (16.0%) patients in the durvalumab + placebo group had on-treatment TSH < LLN with TSH ≥ LLN at baseline.
- No notable changes from baseline in vital signs were observed in either treatment group.
- There was no clear evidence of any potential impact of ADA for durvalumab on patient safety.

Summary of durvalumab pharmacokinetic results

The PK concentration of durvalumab in this patient population was consistent with PK observations from previous studies.

Summary of immunogenicity results

ADA incidence was similar between the treatment groups: 5 (3.8%) patients in the durvalumab + olaparib group and 4 (3.1%) patients in the durvalumab + placebo group. Of the ADA positive patients in the durvalumab + olaparib and durvalumab + placebo groups, no patients and 3 (2.3%) patients were persistently positive for the presence of ADA, including 2 patients classified as such because the last ADA assessment was positive.

Conclusions

- Progression-free survival (Investigator-assessed according to RECIST 1.1) did not show statistically significant improvement with durvalumab plus olaparib combination therapy compared to durvalumab monotherapy (HR: 0.76; 95% CI: 0.57, 1.02; p-value=0.074).
- PFS observations were generally consistent across subgroups defined by demographics and disease characteristics, with the exception of a numerical difference observed for the gemcitabine doublet chemotherapy subgroup (HR: 1.12, 95% CI: 0.68, 1.86).
- The OS endpoint was immature (89 events, 33%), with results at the data cutoff showing no statistically significant improvement with durvalumab plus olaparib combination therapy compared to durvalumab monotherapy (HR: 0.90; 95% CI: 0.59, 1.36; p-value=0.604).

- Following 4 cycles of durvalumab plus chemotherapy, the durvalumab plus olaparib combination therapy was generally tolerated with no new safety signals identified.