1. SYNOPSIS

Study Centre(s)

A total of 84 patients were enrolled in 17 study centres across 7 countries worldwide (Canada, France, Italy, Portugal, Spain, Switzerland, and the United States of America).

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints

Objectives	Outcome variable/description
Primary (efficacy)	
• Assess the antitumor activity of durvalumab alone and/or in combination with novel agents	• MPR rate
Secondary (safety)	
• Assess the feasibility of receiving the planned surgical resection	• Feasibility, defined as having the planned surgical resection within Day 29 to Day 42 after Week 1, Day 1
• Assess the safety and tolerability of durvalumab alone and/or in combination with novel agents	• Presence of AEs, SAEs, laboratory abnormalities, and vital signs
Secondary (efficacy)	
• Assess the antitumor activity of durvalumab alone and/or in combination with novel agents	• pCR rate
Secondary (PK)	
• To describe the PK of durvalumab alone and/or in combination with novel agents [a]	• Concentration of durvalumab or novel agents in plasma or serum
Secondary (immunogenicity)	
• a) To assess the immunogenicity of durvalumab alone or in combination with novel agents [a] • b) To assess the immunogenicity of novel biologic agents in combination with durvalumab [a]	• ADA incidence of durvalumab or novel biologic agents

[a] These data will be reported in a CSR Addendum.

ADA = Anti-drug antibody; AE = Adverse event; BOR = Best objective response; CD = Cluster of differentiation; CT = Computed tomography; ctDNA = Circulating tumour DNA; mRNA = Messenger RNA; MPR = Major pathological response; MRI = Magnetic resonance imaging; NKp36 = Natural cytotoxicity triggering receptor 1; ORR = Objective response rate; pCR = pathological complete response; PD-L1 = Programmed death-ligand 1; PK = Pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumours; SAE = Serious adverse event; TMB = Tumour mutational burden.

Study Design

Study D9108C00002 (NeoCOAST) was a Phase II, open-label, multi-centre, randomised, multidrug platform study of neoadjuvant durvalumab alone or in combination with novel agents in patients with resectable, early-stage (Stage I [> 2 cm] to IIIA) non-small cell lung cancer (NSCLC).

Target Population and Sample Size

This study allowed patients with resectable, early-stage (Stage I [> 2 cm] to IIIA) NSCLC to receive durvalumab alone or in combination with novel therapies.

To be included in this study, patients must have provided informed consent, been ≥ 18 years old and ≥ 35 kg in body weight, must have had early-stage resectable cytologically and/or histologically-documented NSCLC without prior therapy for this condition, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate organ and marrow function.

A total of up to 40 patients per arm may have been enrolled (overall 160 patients).

Investigational Product and Comparator(s): Dosage, Mode of Administration and Batch Numbers

Durvalumab (MEDI4736) was supplied as a vialed liquid solution containing 50 mg/mL durvalumab with 500 mg (nominal) durvalumab per vial. The durvalumab solution was manufactured by Cook Pharmacia, Bloomington, United States of America (USA). A fixed single dose of durvalumab 1500 mg intravenous (IV) was used in both the monotherapy and combination arms of the study. The durvalumab batch number used in the study was CCI

Oleclumab (MEDI9447) was supplied as a vialed liquid solution containing 50 mg/mL oleclumab with 500 mg (nominal) oleclumab per vial. the oleclumab solution was manufactured by MedImmune Nijmegen, Netherlands. A dosing regimen of 3000 mg oleclumab IV every 2 weeks was used in the durvalumab + oleclumab arm (patients received durvalumab + oleclumab on Day 1 and oleclumab on Day 15). The oleclumab batch number used in the study was CCI

Monalizumab (IPH2201) was supplied as a vialed lyophilised powder containing 375 mg (nominal) monalizumab per vial. The powder was to be reconstituted with 7.4 mL water for injection. After reconstitution, the vial contained 50 mg/mL monalizumab. The monalizumab was manufactured by MedImmune Nijmegen, Netherlands. A dosing regimen of 750 mg monalizumab IV every 2 weeks was used in the durvalumab + monalizumab arm (patients received durvalumab + monalizumab on Day 1 and monalizumab on Day 15). The monalizumab batch numbers used in the study were CCI and CCI

Danvatirsen (AZD9150) was supplied as a 100 mg (nominal) per vial concentrate for solution for infusion. The solution contained 50 mg/mL AZD9150. The Danvatirsen was manufactured by Pyramid Labs Inc, Costa Mesa, USA. A dosing regimen of 200 mg danvatirsen IV every week was used in the durvalumab + danvatirsen arm (patients received durvalumab + danvatirsen on Day 1, and danvatirsen on Day 8, Day 15 and Day 22). The 28-day dosing period was also preceded by a 7-day danvatirsen lead-in period with dosing on Week 0, Days 1, 3, and 5), The danvatirsen batch number used in the study was CCI [redacted] Note that on 15 April 2020, a decision was made to terminate the danvatirsen (AZD9150) programme due to an overall lack of efficacy (no new safety signals were observed).

Duration of Treatment

Patients were treated with durvalumab alone or in combination with novel agents for up to 28 days, followed by surgical resection. After surgical resection, patients were to be followed up to Day 105. Note: for patients randomised to the durvalumab + danvatirsen arm, there was also a 7-day danvatirsen lead-in period which preceded the 28-day dosing period.

Statistical Methods

Data analyses were conducted using the SAS® System (SAS Institute, Inc., Cary, NC, USA) Version 9.3 or above, unless otherwise specified.

The primary endpoint of major pathological response (MPR) rate was defined as proportion of patients with ≤ 10% residual viable tumour cells in the surgical specimen. Local review of the resected specimens was used for assessment of MPR. The MPR rate and the corresponding 95% confidence interval (CI) were reported for each arm. In addition, an estimate of the difference in MPR rate as well as its 2-sided 95% exact CI between each combination therapy arm and monotherapy arm was reported. The rates between any durvalumab combination therapy arm and the durvalumab monotherapy arm were evaluated and compared from the Cochran-Mantel-Haenszel (CMH) test stratified by the baseline lymph node involvement (yes or no). Secondary efficacy endpoint, pathological complete response (pCR) (defined as proportion of patients with no viable tumour cells in the surgical specimen; local review of the resected specimens was used for assessment of pCR), was analysed similarly to MPR rate. Safety evaluations included treatment-emergent adverse events, serious adverse events (SAEs), adverse events of special interest (AESIs), adverse events of possible interest (AEPIs), immune-mediated adverse events (imAEs), clinical laboratory values, vital signs, and ECOG performance status.

Study Population

A total of 84 patients were enrolled in 17 study centres across 7 countries (Canada, France, Italy, Portugal, Spain, Switzerland, and the USA). These 84 patients were randomised to receive either durvalumab monotherapy 1500 mg every 4 weeks (Q4W) (27 patients); durvalumab 1500 mg Q4W plus oleclumab 3000 mg every 2 weeks (Q2W) (21 patients);

durvalumab 1500 mg Q4W plus 750 mg monalizumab Q2W (20 patients); or durvalumab 1500 mg Q4W plus danvatirsen 200 mg every week (including a lead-in period of danvatirsen 200 mg on Days 1, 3, and 5 [Week 0]) (16 patients). The database lock date for the study was 15 September 2021.

Of the 84 patients, 83 patients received study treatment; one patient (1/27 [3.7%]) in the durvalumab monotherapy arm was randomised but did not receive any study treatment (Exclusion Criterion 15 {uncontrolled intercurrent illness} was met]). At the time of the database lock date of 15 September 2021 for this report, of those patients randomised and treated across all arms, 82 patients/83 patients completed durvalumab treatment. In the durvalumab + oleclumab arm 20 patients (95.2%) completed treatment with oleclumab; oleclumab was discontinued in one patient (4.8%) due to patient decision and this patient did not receive durvalumab. In the durvalumab + monalizumab arm 19 patients (95.0%) completed treatment with monalizumab, one patient (5.0%) discontinued monalizumab due to an adverse event (AE) of Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 coronavirus disease 2019 (COVID-19). In the durvalumab + danvatirsen arm 15 patients (93.8%) completed treatment with danvatirsen, one patient (6.3%) discontinued treatment with danvatirsen due to an AE of CTCAE Grade 2 hepatic enzyme increased. The number and reasons for discontinuations from treatment did not raise any concerns about the conduct of the study. Overall, 6 patients did not complete the study, of these 6 patients; 2 patients withdrew from the study, one patient died, 2 patients were lost to follow-up, and one patient had an ‘other’ reason of progressive disease for not completing the study.

The intent-to-treat (ITT) Population comprised all 84 randomised patients: 27 patients in the durvalumab monotherapy arm, 21 patients in the durvalumab + oleclumab arm, 20 patients in the durvalumab + monalizumab arm, and 16 patients in the durvalumab + danvatirsen arm. The ITT Population included patients who were randomised, and patients were analysed according to their randomised treatment arm. The ITT Population was used for all baseline and efficacy parameters as the primary analysis. The As-treated Population was used for all safety parameters and included all patients who received any investigational product. Patients were analysed according to the treatment they actually received. The As-treated Population comprised all patients randomised except for one patient in the durvalumab monotherapy arm who did not receive any study treatment. The Efficacy Evaluable Population was a supportive population used for efficacy analyses and comprised 78 patients: 24 patients in the durvalumab monotherapy arm, 20 patients in the durvalumab + oleclumab arm, 19 patients in the durvalumab + monalizumab arm, and 15 patients in the durvalumab + danvatirsen arm. The Efficacy Evaluable Population included patients from the As-treated Population who had the opportunity to be followed for the planned surgery by the time of the data cut-off, and either had pathological tumour response data post-surgery, or did not undergo surgical resection due to death or disease progression.

The patient population was representative of the intended population to be treated and the current unmet need relative to available therapies (ie, patients with resectable early-stage [Stage I (> 2 cm) to IIIA] NSCLC). The demographics were generally well balanced between the 4 treatment arms. Overall, in all 4 treatment arms of the study, patients had a median age of 67.5 years (range: 51 to 87 years) and 40.5% were female. A total of 89.3% of patients were White, 6.0% were Black or African American and 2.4% were Asian. It is however worth noting that patients randomised to the durvalumab + danvatirsen arm had a slightly higher median age at screening (71.5 years) compared with the other 3 arms (64.5 to 67.0 years).

Disease characteristics were representative of the intended patient population, and were generally balanced across the 4 treatment arms although the durvalumab + monalizumab arm included a higher proportion of patients with Stage IA3 disease at study entry (30.0%) and a lower proportion of patients with Stage IIIA disease (15.0%) compared with the overall study population (14.3% and 17.9%, respectively). Overall, at baseline, 63.9% of patients had an ECOG performance status of 0. Overall, the most common tumour histologies for patients were adenocarcinoma (60.7% of patients) and squamous cell carcinoma (31.0% of patients).

Summary of Efficacy Results

The primary analysis of MPR rate was conducted in concurrently enrolled durvalumab monotherapy patients; these are patients randomised to the monotherapy arm who also had the opportunity to be randomised to the respective combination therapy arm. All efficacy parameters were summarised based on the ITT population as primary analysis. Local review of the resected specimens was used for assessment of MPR.

In durvalumab monotherapy patients, overall, 3 of 27 patients (11.1%; 95% CI: 2.4%, 29.2%) had a MPR.

In durvalumab monotherapy patients who were enrolled concurrently with the durvalumab + oleclumab arm, 3 of 20 patients (15.0%; 95% CI: 3.2%, 37.9%) had a MPR. In the durvalumab + oleclumab arm, 4 of 21 patients (19.0%; 95% CI: 5.4%, 41.9%) had a MPR. The rate difference between these 2 groups of patients was 4.0% (95% CI: -18.9%, 27.0%); p-values for the Stratified CMH Test and the Fisher's Exact Test were 0.7445 and 1.0000, respectively.

In durvalumab monotherapy patients who were enrolled concurrently with the durvalumab + monalizumab arm, none of the 20 patients (0%; 95% CI: 0.0%, 16.8%) had a MPR. In the durvalumab + monalizumab arm, 6 of 20 patients (30.0%; 95% CI: 11.9%, 54.3%) had a MPR. The rate difference between these 2 groups of patients was 30.0% (95% CI: 9.9%, 50.1%); p-values for the Stratified CMH Test and the Fisher's Exact Test were 0.0098 and 0.0202, respectively.

In durvalumab monotherapy patients who were enrolled concurrently with the durvalumab + danvatirsen arm, 3 of 19 patients (15.8%; 95% CI: 3.4%, 39.6%) had a MPR. In the durvalumab + danvatirsen arm, 5 of 16 patients (31.3%; 95% CI: 11.0%, 58.7%) had a MPR. The rate difference between these 2 groups of patients was 15.5% (95% CI: -12.6%, 43.5%); p-values for the Stratified CMH Test and the Fisher's Exact Test were 0.2752 and 0.4236, respectively.

The secondary endpoint analysis of pCR was conducted in concurrently enrolled durvalumab monotherapy patients; these are patients randomised to the monotherapy arm who also had the opportunity to be randomised to the respective combination therapy arm.

In the durvalumab monotherapy arm overall, one of 27 patients (3.7%; 95% CI: 0.1%, 19.0%) had a pCR.

In durvalumab monotherapy patients who were enrolled concurrently with the durvalumab + oleclumab arm, 1 of 20 patients (5.0%; 95% CI: 0.1%, 24.9%) had a pCR. In the durvalumab + oleclumab arm, 2 of 21 patients (9.5%; 95% CI: 1.2%, 30.4%) had a pCR. The rate difference between these 2 groups of patients was 4.5% (95% CI: -11.3%, 20.3%); p-values for the Stratified CMH Test and the Fisher's Exact Test were 0.5706 and 1.0000, respectively.

In durvalumab monotherapy patients who were enrolled concurrently with the durvalumab + monalizumab arm, none of the 20 patients (0%; 95% CI: 0.0%, 16.8%) had a pCR. In the durvalumab + monalizumab arm, 2 of 20 patients (10.0%; 95% CI: 1.2%, 31.7%) had a pCR. The rate difference between these 2 groups of patients was 10.0% (95% CI: -3.1%, 23.1%); p-values for the Stratified CMH Test and the Fisher's Exact Test were 0.1652 and 0.4872, respectively.

In durvalumab monotherapy patients who were enrolled concurrently with the durvalumab + danvatirsen arm, one of 19 patients (5.3%; 95% CI: 0.1%, 26.0%) had a pCR. In the durvalumab + danvatirsen arm, 2 of 16 patients (12.5%; 95% CI: 1.6%, 38.3%) had a pCR. The rate difference between these 2 groups of patients was 7.2% (95% CI: -11.8%, 26.3%); p-values for the Stratified CMH Test and the Fisher's Exact Test were 0.4261 and 0.5820, respectively.

In the durvalumab monotherapy arm, no patients were reported with a complete response (CR) (by investigator assessment of Response Evaluation Criteria for Solid Tumours version 1.1 [RECIST v1.1] criteria) and 2 of 27 patients (7.4%) were reported with a partial response (PR). In the durvalumab + oleclumab arm, no patients were reported with a CR and 1 patient (4.8%) was reported with a PR.

In the durvalumab + monalizumab arm, no patients were reported with a CR (by investigator assessment of RECIST v1.1 criteria) and 3 of 20 patients (15.0%) were reported with a PR.

In the durvalumab + danvatirsen arm, no patients were reported with a CR (by investigator assessment of RECIST v1.1 criteria), one of 16 patients (6.3%) was reported with a PR.

Summary of Pharmacokinetic Results

Pharmacokinetic results will be presented in an Addendum to this Clinical Study Report.

Summary of Safety Results

Safety parameters were summarized based on the As-treated Population as primary analysis.

All doses of durvalumab (monotherapy and combination) were administered fully (1500 mg) and relative dose intensity was 100% in all arms. One patient in the durvalumab + oleclumab arm stopped treatment during the first oleclumab infusion due to an AE and did not receive durvalumab. One patient in each of the combination arms received less than the intended dose of their novel therapy.

There were no remarkable differences between the treatment arms for feasibility of surgery with a mean time to surgical resection from Week 1 Day 1 of 36.8 days (standard deviation 6.8 days) in the durvalumab + danvatirsen arm, 37.8 days (standard deviation 4.0 days) in the durvalumab + monalizumab arm, 38.7 days (standard deviation 6.6 days) in the durvalumab monotherapy arm, and 39.2 days (standard deviation 10.5 days) in the durvalumab + oleclumab arm. Overall, 4 patients (5.3%) had their surgical resection on Day 44 or after (2 patients in the durvalumab monotherapy arm [reason for delay was a scheduling delay in one patient and a lung infection in the second], and one patient in each of the durvalumab + oleclumab [reason for delay was the patient was no longer a candidate for surgery and this was confirmed by a second opinion] and durvalumab + danvatirsen [reason for delay was due to insurance constraints] arms).

In the durvalumab monotherapy arm, the majority of patients (18/26 patients [69.2%]) experienced an AE. The most frequently reported AEs regardless of causality (≥ 10%) were fatigue, procedural pain, asthenia, decreased appetite, and dyspnoea. The majority of AEs were CTCAE Grade 1 or 2; CTCAE Grade 3 or 4 AEs were reported in 19.2% of patients. No patients were reported with treatment-related CTCAE Grade 3 or 4 AEs. Nine patients (34.6%) had AEs that were considered treatment-related; treatment-related AEs occurring in 2 or more patients were fatigue, asthenia, and musculoskeletal pain. Three patients (11.5%) had SAEs (immune-mediated arthritis [considered to be treatment-related], pericarditis and pneumonia). No patients discontinued treatment in the durvalumab monotherapy arm due to an AE. No patients had an AE with an outcome of death. A total of 7 patients (26.9%) in the durvalumab monotherapy arm experienced at least one AESI/AEPI during the study. One patient (3.8%) in the durvalumab monotherapy arm had imAEs (CTCAE Grade 2 immune-mediated arthritis and CTCAE Grade 2 musculoskeletal pain). Two patients (7.7%)

experienced CTCAE Grade 3 or 4 AESIs/AEPIs and no patients experienced CTCAE Grade 3 or 4 imAEs.

In the durvalumab + oleclumab arm, the majority of patients (19/21 patients [90.5%]) experienced an AE. The most frequently reported AEs regardless of causality (≥ 10%) were fatigue, asthenia, cough, and nausea. The majority of AEs were CTCAE Grade 1 or 2; CTCAE Grade ≥ 3 AEs were reported in 3 patients (14.3%). Treatment-related CTCAE AEs of Grade ≥ 3 (diabetic ketoacidosis) were reported in one patient. Those considered to be durvalumab-related AEs occurring in 2 or more patients were asthenia, arthralgia, fatigue, nausea, pruritus, and pyrexia. The oleclumab-related AEs experienced by more than 2 or more patients were asthenia, arthralgia, fatigue, nausea, pruritus, and pyrexia. Twelve patients (57.1%) had AEs that were considered treatment-related. Two patients (9.5%) experienced SAEs (pneumonia and pulmonary air leakage in the same patient, and diabetic ketoacidosis [considered treatment-related]). One patient discontinued durvalumab treatment due to an AE of transient ischaemic attack, which occurred during dosing with oleclumab. No patients had an AE with an outcome of death. A total of 11 patients (52.4%) experienced at least one AESI/AEPI during the study and one patient (4.8%) had an imAE (CTCAE Grade ≥ 3 imAE [diabetic ketoacidosis]). One patient (4.8%) experienced CTCAE Grade 3 or 4 AEPIs. One patient (4.8%) in the durvalumab + oleclumab arm had a Grade 1 AESI of transient ischaemic attack that was considered not related to durvalumab (this patient did not receive their dose of durvalumab) and considered related to oleclumab.

In the durvalumab + monalizumab arm, the majority of patients (15/20 patients [75.0%]) experienced an AE. The most frequently reported AEs regardless of causality (≥ 10%) were constipation, fatigue, pruritus, and upper respiratory tract infection. The majority of AEs were CTCAE Grade 1 or 2; CTCAE Grade ≥ 3 AEs were reported in 10.0% of patients. No patient reported treatment-related CTCAE AEs of Grade ≥ 3. Ten patients (50.0%) had AEs that were considered treatment-related. Pruritus was the only event considered to be durvalumab-related and experienced by 2 or more patients. The monalizumab-related AEs experienced by 2 or more patients were fatigue and pruritus. One patient (5.0%) experienced an SAE (pneumothorax [not considered to be treatment-related]), one patient discontinued treatment due to an AE, and no patients had an AE with an outcome of death. A total of 6 patients (30.0%) experienced at least one AESI/AEPI during the study, one patient (5.0%) had an imAE (rash maculo-papular), and no patients experienced CTCAE Grade 3 or 4 AESIs/AEPI or imAEs.

In the durvalumab + danvatirsen arm, the majority of patients (13/16 patients [81.3%]) experienced an AE. The most frequently reported AEs regardless of causality (≥ 10%) were dyspnoea, fatigue, alanine aminotransferase increased, cough, gastrooesophageal reflux disease, paraesthesia, and pruritus. The majority of AEs were CTCAE Grade 1 or 2; CTCAE Grade ≥ 3 AEs were reported in 31.3% of patients. One patient (6.3%) reported a

treatment-related CTCAE AE of Grade 3 or 4 (procedural haemorrhage). Seven patients (43.8%) had AEs that were considered treatment-related. No durvalumab-related AEs were reported by more than one patient. The only danvatirsen-related AE experienced by 2 or more patients was fatigue. Five patients (31.3%) experienced SAEs (pneumonia, bronchial anastomosis complication, COVID-19, haemothorax, pleural effusion, renal infarct, and wound infection [all not considered to be treatment-related] and procedural haemorrhage [considered treatment-related]). One patient (6.3%) discontinued treatment due to an AE of hepatic enzyme increased that was considered related to danvatirsen and one patient (6.3%) had an AE with an outcome of death (bronchial anastomosis complication). A total of 7 patients (43.8%) experienced at least one AESI/AEPI during the study. No patients had an imAE. One patient (6.3%) experienced a CTCAE Grade 3 or 4 AEPI.

No unexpected results were obtained for haematology, clinical chemistry, urinalysis, coagulation, or thyroid function in any of the treatment arms. No unexpected results were obtained for vital signs or electrocardiograms in any of the treatment arms.

Durvalumab monotherapy and in combination with oleclumab, monalizumab, or danvatirsen appeared relatively well tolerated in this patient population with resectable, early-stage (Stage I [> 2 cm] to IIIA) NSCLC.

Conclusion(s)

- Durvalumab monotherapy and in combination with oleclumab, monalizumab, or danvatirsen demonstrated antitumor activity in patients with resectable, early-stage (Stage I [> 2 cm] to IIIA) NSCLC where an MPR rate showed a rate difference versus concurrent durvalumab monotherapy of 4.0%, 30.0%, and 15.5% for oleclumab, monalizumab, or danvatirsen, respectively. However, due to the small sample size, and local determination of the pathological response, these results are to be considered preliminary. Moreover, no statistically significant differences between the treatment arms could be determined.
- There was no clinically significant impact on the feasibility for surgery in the durvalumab monotherapy or combination arms, with ~95% of patients having their surgical resection before Day 44. No remarkable differences were observed between the treatment arms for feasibility of surgery.
- Durvalumab monotherapy and in combination with oleclumab, monalizumab or danvatirsen appeared relatively well tolerated with no unexpected safety findings in this patient population with resectable, early-stage (Stage I [> 2 cm] to IIIA) NSCLC.