Clinical Study Report Synopsis	
Drug Substance	AZD9150 and durvalumab
Study Code	PPD
Edition Number	1.0
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A Phase Ib/II, Open-Label, Multicentre Study to Assess Safety, Tolerability, Pharmacokinetics, and Preliminary Anti-tumour Activity of AZD9150 plus Durvalumab alone or in Combination with Chemotherapy in Patients with Advanced, Solid Tumours and Subsequently in Patients with Non-Small-Cell Lung Cancer

Study dates:	First subject enrolled: 12 February 2018 Last subject enrolled: 13 March 2019 The analyses presented in this report are based on a database lock date of 06 May 2020
Phase of development:	Clinical pharmacology (Ib) / Therapeutic exploratory (II)
Co-ordinating Investigator:	PPD, MD PPD PPD PPD PPD
Sponsor's Responsible Medical Officer:	PPD PPD PPD

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

SYNOPSIS

Study centres

This study was conducted at 6 clinical sites in the United States.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Outcome Variables

Outcome Variable		
Priority	**Objective**	**Endpoint/variable**
Primary (Part A)	In patients with advanced solid malignancies: Safety, tolerability, MTD, or RP2D of AZD9150 CCI + durvalumab CCI Safety, tolerability, MTD and RP2D of AZD9150 + durvalumab in combination with standard chemotherapy regimens	Incidence of DLTs DLT period without chemotherapy: 5 weeks DLT period with chemotherapy: 3 weeks Incidence and severity of AEs/SAEs; Incidence of change from baseline in vital signs, clinical chemistry, haematology, and urinalysis parameters; ECGs
Primary (Part D)	Compare the single and steady state PK of AZD9150 CCI relative to AZD9150 CCI in combination with durvalumab CCI	AZD9150 $C_{troughss}$, AUC_{ss}
Secondary (Part A)	Evaluate anti-tumour activity of AZD9150 and durvalumab with or without chemotherapy	Efficacy parameters as defined by RECIST v1.1 for each combination (with or without chemotherapy) and schedule: disease control rate at 12 weeks; duration of overall response; progression-free survival
Secondary (Part A)	Characterise the PK of AZD9150 and durvalumab when given at 2 different dosing schedules in combination with or without chemotherapy	Single dose and steady state PK parameters (eg, C_{max}, AUC for AZD9150, and peak and trough concentration for durvalumab)
Secondary (Part A)	Characterise the immunogenicity of: durvalumab and AZD9150	ADA against AZD9150 and durvalumab
Secondary (Part A)	Evaluate baseline tumour PD-L1 expression for potential correlation with drug activity or the ability to prospectively identify patients likely to respond to treatment	IHC for PD-L1 was carried out using a tumour sample from a biopsy either archival or one taken at screening
Secondary (Part A)	Pharmacodynamics: Assess STAT3 knockdown in tumour biopsies taken on-treatment at W3D1	Baseline and on-treatment biopsies were used to measure STAT3 expression levels by IHC
Secondary (Part D)	Evaluate the safety, tolerability, and immunogenicity of AZD9150 CCI	Injection site tolerability (SC only)

	CCI relative to AZD9150 CCI in combination with durvalumab CCI	Incidence and severity of adverse events/serious adverse events Incidence of change from baseline in vital signs, clinical chemistry, haematology, and urinalysis parameters ECGs
Secondary (Part D)	Characterise the PK of AZD9150 after single dosing and at steady state after multiple doses when given as AZD9150 CCI relative to AZD9150 CCI in combination with durvalumab CCI	Single dose: C_{max}, t_{max}, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}48h}$, CL or CL/F, V_z/F, MRT, $t_{1/2}$ Multiple dose: AUC_{ss}, $C_{ss\ max}$, CL_{ss}

Note: Exploratory objectives are not listed. Pharmacodynamics and exploratory objectives are reported separately from the aCSR.

Abbreviations: ADA, anti-drug antibody; AUC, area under the plasma concentration-time curve; $AUC_{0\text{-}inf}$, AUC from 0 to infinity; $AUC_{0\text{-}t}$, AUC from time 0 to time of last quantifiable concentration; $AUC_{0\text{-}48h}$, AUC from 0 to 48 h; AUC_{ss}, AUC at steady state; CL, clearance; CL/F, apparent plasma clearance after non-IV administration; CL_{ss}, systemic clearance at steady state; C_{max}, peak plasma concentration; $C_{ss\ max}$, maximum concentration at steady state; C_{trough}, trough plasma concentration; $C_{troughss}$; C_{trough} at steady state; DLT, dose-limiting toxicity; ECG, electrocardiogram; IHC, immunohistochemistry; IV, intravenous; MRT, mean residence time; MTD, maximum-tolerated dose; PK, pharmacokinetics; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; PD-L1, programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, Recommended Phase 2 dose; SC, subcutaneous; STAT3; signal transducer and activator of transcription 3; $t_{1/2}$, half-life; t_{max}, time of peak plasma concentration; V_z/F, apparent volume of distribution; W3D1, Week 3 Day 1.

Study design

This was a Phase Ib/II, open-label, multicentre study to assess the safety, tolerability, pharmacokinetics (PK), and preliminary anti-tumour activity of AZD9150 plus durvalumab alone or in combination with chemotherapy.

The study was originally designed to be conducted in 3 parts at approximately 40 clinical sites across multiple countries. With the implementation of Clinical Study Protocol (CSP) Amendment number 3, Part D was added to compare the relative bioavailability and safety of AZD9150 intravenous (IV) versus subcutaneous (SC) formulations administered every week (QW) in patients with treatment-refractory solid malignancies. Parts B and C were intended to evaluate patients with locally advanced or metastatic Stage IV non-small-cell lung cancer (NSCLC); however, due to changes in the AstraZeneca programme strategy for NSCLC, the study did not move forward with Part B and Part C and subjects were not enrolled (CSP Amendment number 4).

AstraZeneca presented the results of the interim analysis of the Part D PK and safety data to study investigators on 07 June 2019, and it was agreed by all parties that it would be appropriate to proceed to the next dose level. However, as a result of AstraZeneca's strategic

review across the AZD9150 programme, AstraZeneca ultimately decided not to further expand Part D and to close enrolment.

The study was conducted in 2 parts:

Part A was non-randomised and focused on testing weekly and alternate week dosing schedules of AZD9150 in combination with fixed dose durvalumab, and testing the administration of AZD9150 plus durvalumab in combination with various chemotherapy regimens in patients with advanced solid tumours.

Part A consisted of 5 arms (A1 through A5). The following chemotherapy agents were administered in Arms A2-A5: cisplatin + 5-fluorouracil (5-FU) (A2 and A3), gemcitabine + cisplatin or carboplatin (A4), and carboplatin + nab-paclitaxel (A5).

After enrolment in Arm A2 was completed, enrolment in Arm A3 could be opened based on Safety Review Committee (SRC) recommendations; the SRC would determine the starting dose.

Part D was randomised and compared the single-dose and multiple-dose (steady state) PK of AZD9150 CCI to AZD9150 CCI in combination with durvalumab CCI

Target subject population and sample size

The study included patients who had histological confirmation of a solid malignancy (other than hepatocellular carcinoma) that was refractory to standard therapy or for which no standard-of-care regimen currently existed. Patients had to have at least 1 measurable lesion as defined by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1).

For Part A, approximately 30 to 78 dose-limiting toxicity (DLT)-evaluable patients were expected to be enrolled.

For Part D, approximately 50 to 62 PK-evaluable patients were expected to be enrolled.

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

AZD9150 was administered as an IV infusion over approximately 1 hour (± 10 minutes) at doses of CCI or as a CCI in the abdomen or thigh over no more than 60 seconds at a dose of CCI. During the 7-day lead-in period, AZD9150 was administered as a loading dose of CCI on Days 1, 3, and 5. Durvalumab was administered as an IV infusion over 1 hour at a dose of CCI.

Additionally, when applicable in Part A, the following chemotherapy agents were administered approximately 1 hour after the end of the AZD9150 or durvalumab infusion: cisplatin, 5-FU, gemcitabine, carboplatin, and nab-paclitaxel. Details for administration of these agents were per the approved label of each agent and each was sourced locally. Batch numbers for AZD9150 and durvalumab are provided in the abbreviated clinical study report (aCSR).

Duration of treatment

Patients continued to receive AZD9150 until disease progression or when discontinuation criteria were met. Toxicity, PK, and pharmacodynamics were assessed throughout the study.

Statistical methods

Descriptive statistics were used for all variables, as appropriate. Continuous variables were summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. For log-transformed data, geometric mean, coefficient of variation (CV), arithmetic mean, standard deviation, median, minimum, and maximum were presented. Categorical variables were summarised by frequency counts and percentages for each category.

If data were available for fewer than 3 patients, no summary statistics other than minimum, maximum, and number of observations were presented. The remaining summary statistics were presented as 'Not Calculable' (NC).

Subject population

Thirty-two patients received AZD9150 in Part A and 40 patients received AZD9150 in Part D of the study. Twenty-six patients participated in the combination arms of the study (Arms A2 to A5) and received chemotherapy treatments in addition to AZD9150 and durvalumab. Thirty (93.8%) patients in Part A and 40 (100.0%) patients in Part D received durvalumab. Twelve (37.5%) patients in Part A completed the study and 18 (45.0%) patients in Part D completed the study. As of the data lock date (06 May 2020), 2 patients (both in Part A) remained on the study.

The patient demographics and disease history were typical for a population with refractory solid tumours.

In Part A, most patients were white (29 patients, 90.6%) and the majority were female (18 patients, 56.3%). The median age was 57 (PPD) years, with 62.5% of patients being between PPD years of age.

In Part D, most patients were white (35 patients, 87.5%) and female (27 patients, 67.5%). The median age was 58.5 (PPD) years with 45% of patients being between PPD years of age, and 37.5% of patients PPD .

All patients enrolled in the study had previously treated advanced solid tumours.

Summary of efficacy results

Preliminary efficacy and anti-tumour activity of AZD9150 were investigated in this study as a secondary objective.

There were no patients who achieved a complete response during this study, per RECIST v1.1.

In Part A, 6 patients (18.8%) had a partial response (PR) per RECIST v1.1, with the majority occurring in Arm A4 (4 patients, 36.4%) which included AZD9150 and durvalumab in combination with gemcitabine and cisplatin/carboplatin. Thirteen patients (40.6%) had a best overall response of stable disease (SD), with most occurring in Arm A2 (6 patients, 66.7%) which included AZD9150 and durvalumab in combination with cisplatin and 5-FU. Twelve patients (37.5%) had disease progression (PD), and 1 patient (3.1%) was not evaluable due to death > 14 weeks after first dosing and no post-baseline tumour assessment. In Part D, 2 patients (5.0%) had PR per RECIST v1.1 (1 patient each [4.8% and 5.3%] in Arm D1 and Arm D2, respectively), and 15 patients (37.5%) had a best overall response of SD; the majority occurred in Arm D1 (9 patients, 42.9%). Twenty-three patients (57.5%) had PD (of which 3 patients [7.5%] died).

Summary of pharmacokinetic results

Under the treatment regimens and combinations evaluated, IV administration of AZD9150 at single or multiple doses of CCI resulted in geometric mean peak plasma concentration (C_{max}) of 22100 to 40180 ng/mL, with trough plasma concentration (C_{trough}) of 9.576 to 30.26 ng/mL. There was no evidence of accumulation following weekly dosing.

Subcutaneous administration of AZD9150 resulted in lower exposure compared to IV infusion, most notably in terms of C_{max} at steady state. Based on geometric least squares (GLS) mean ratios, AUC_{0-48h} and C_{trough} at steady state for the SC route were approximately 74% and 83% of that observed following weekly IV infusions, with lower bounds for the 90% confidence interval (CI) that were below 0.8.

Geometric mean durvalumab serum concentrations ranged from 389.4 to 469.2 µg/mL at the end of infusion, and from 100.5 to 198.5 µg/mL in samples collected prior to dosing. C_{trough} tended to be slightly higher on Week 17 compared to Week 4 for Arms D1 and D2 (dosed Q4W).

Summary of safety results

The investigator's assessment of a causal relationship for AEs to AZD9150 and durvalumab is reported. Although the details of the dosing and administration of the chemotherapy regimens are provided for individual patients in the aCSR, an AE causality assessment to chemotherapy was not collected in the study's clinical database, and is therefore not reported in the body of the aCSR. However, in cases in which such information was included in the serious adverse event (SAE) Report Form submitted to the Sponsor, the SAE causality assessment to chemotherapy has been included in patient narratives.

In all, there were 24 deaths during the study; 11 occurred in Part A and 13 occurred in Part D. Seventeen deaths were related to the disease under investigation, 2 patients died due to unrelated SAEs, and 5 deaths were attributed to 'other', cause unknown.

Of the 22 patients reported with SAEs, 2 had a fatal outcome (Grade 5 sepsis and Grade 5 acute cardiac failure); neither was considered related to either AZD9150 or durvalumab. Two patients (6.3%) experienced an SAE assessed as related to AZD9150 (thrombocytopenia, neutropenia, and haemolysis) and 2 patients (6.3%) experienced an SAE assessed as related to durvalumab (haemolysis and anaemia) in Part A. In Part D, 2 patients (5.0%) experienced an SAE assessed as related to AZD9150 (febrile neutropenia, alanine aminotransferase [ALT] increased, and aspartate aminotransferase [AST] increased) and 2 patients (5.0%) experienced an SAE assessed as related to durvalumab (adrenal insufficiency, drug-induced liver injury, ALT increased, and AST increased).

In both parts of the study, the most frequently reported AZD9150-related AEs occurred in the system organ class (SOC) of Blood and lymphatic disorders. Thrombocytopenia was the most frequently reported AZD9150-related AE, occurring in 17 patients (53.1%) in Part A and 15 patients (37.5%) in Part D.

In both parts of the study, the most frequently reported durvalumab-related AEs occurred in the SOC of Investigations. Alanine aminotransferase increased was the most frequently reported durvalumab-related AE, occurring in 6 patients (18.8%) in Part A and 12 patients (30.0%) in Part D.

Dose-limiting toxicities were experienced by 3 patients. One patient in Arm A2 experienced Grade 4 neutropenia, one patient in Arm A4 experienced Grade 3 ALT increased, and one patient in Arm A5 experienced Grade 4 thrombocytopenia.

In Part A, 4 patients (12.5%) had an AE that led to discontinuation of AZD9150 and one patient (3.1%) had an AE that led to discontinuation of durvalumab. In Part D, 8 patients (20.0%) had an AE that led to discontinuation of AZD9150 and 4 patients (10.0%) had an AE that led to discontinuation of durvalumab.

No trends or clinically important changes in vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, or electrocardiograms were observed.

Conclusions

AZD9150 and durvalumab were relatively well tolerated by this patient population with advanced solid tumours. In addition to AZD9150 and durvalumab, patients also received various combinations of chemotherapy, which included cisplatin + 5-FU, gemcitabine + cisplatin or carboplatin, and carboplatin + nab-paclitaxel. The addition of AZD9150 and durvalumab to the chemotherapy treatments appeared to be well tolerated for doses up to CCI of AZD9150 and CCI of durvalumab; however, no additional clinically relevant efficacy benefit was observed compared to chemotherapy alone.

There were no deaths related to either AZD9150 or durvalumab on study. In Part A, 4 patients (12.5%) had an AE that led to discontinuation of AZD9150 and 1 patient (3.1%) had an AE that led to discontinuation of durvalumab. In Part D, 8 patients (20.0%) had an AE that led to discontinuation of AZD9150 and 4 patients (10.0%) had an AE that led to discontinuation of durvalumab.

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No patients achieved a complete response per RECIST v1.1 during this study. In Part A, 6 patients (18.8%) had a PR and 13 patients (40.6%) had a best overall response of SD. In Part D, 2 patients (5.0%) had PR and 15 patients (37.5%) had a best overall response of SD.

Under the treatment regimens and combinations evaluated, IV administration of AZD9150 at single or multiple doses of CCI resulted in geometric mean C_{max} of 22100 to 40180 ng/mL, with C_{trough} of 9.576 to 30.26 ng/mL. There was no evidence of AZD9150 accumulation following weekly dosing. Subcutaneous administration of AZD9150 resulted in lower exposure compared to IV infusion, with GLS mean ratios of 74% and 83% for $AUC_{0\text{-}48h}$ and C_{trough} at steady state, respectively, with lower bounds for the 90% CI that were below 0.8.

Geometric mean durvalumab concentrations in serum ranged from 100.5 to 198.5 µg/mL in samples collected prior to dosing CCI every 3 or 4 weeks.