Clinical Study Report Synopsis	
Drug Substance	Gefitinib/Durvalumab
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A Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of Gefitinib in Combination With MEDI4736 (anti PD-L1) in Subjects with Non-Small Cell Lung Cancer (NSCLC)

Study dates: First subject enrolled: 24 March 2014
Data cut-off date: 11 June 2018

Phase of development: Clinical pharmacology (I)

Sponsor's Responsible Medical Officer: [redacted]
Global Clinical Lead
AstraZeneca, Global Medicine Development, Oncology, [redacted]
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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

This study was performed at 7 centres in 3 countries: Japan (2 centres), South Korea (2 centres) and United States (3 centres).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Refer to the Clinical Study Protocol for details.

Study design

This was a Phase I, open-label, multicentre study to assess the safety, tolerability, pharmacokinetics and preliminary anti-tumour activity of gefitinib in combination with durvalumab in subjects with NSCLC. The study design allowed for an escalation of dose with intensive safety monitoring, ensuring the safety of the subjects.

This study had 2 parts: Escalation Phase (Part A) and Expansion Phase (Part B).

Escalation Phase

Approximately 12 subjects who had either failed to respond to or relapsed following any line of standard treatment, were unable to tolerate, or were not eligible for standard treatment were enrolled in dose escalation/de-escalation cohorts.

Durvalumab and gefitinib were concurrently administered initially in sequential cohorts of 3 to 6 subjects. Each subject received durvalumab administered Q2W and gefitinib 250 mg once daily (QD). The first cohort was to enrol a minimum of 3 subjects, according to a standard 3+3 design. Subjects in the first cohort received a dose of 3 mg/kg durvalumab and 250 mg gefitinib. If 0 out of the first 3 subjects experienced dose limiting toxicity (DLT), then dose escalation was to continue as planned. If 1 out of the first 3 subjects experienced a DLT, then the cohort was to be expanded to a total of 6 subjects, and if no more than 1 out of 6 subjects experienced a DLT in a given dose cohort, dose escalation was to continue as planned. If $\geq$2 DLTs were observed in the first dose cohort, the dose was to be de-escalated to 1 mg/kg and a dose de-escalation cohort was to be enrolled.

Expansion Phase

Approximately 20 subjects with Epidermal Growth Factor Receptor (EGFR) mutation positive locally advanced or metastatic NSCLC who were naïve to EGFR-tyrosine kinase inhibitor (TKI) therapy were to be enrolled in 1 of 2 dose expansion cohorts (Arm 1 and Arm 2), in order to explore further the tolerability, PK and biological activity of the combination at the recommended dose.

Initiation of the Expansion Phase with the recommended dose of durvalumab in combination with gefitinib was to be based on an identified recommended dose with an adequate safety and tolerability profile (ie, a dose that did not exceed the maximum tolerated dose) from the Escalation Phase.

The Expansion Phase consisted of 2 arms:

- Arm 1 and 1(a): Approximately 30 subjects (10 in Arm 1 and 20 in Arm 1[a]) with EGFR mutation positive locally advanced or metastatic NSCLC who were naïve to EGFR-TKI therapy, were to receive concurrent gefitinib 250 mg QD and durvalumab Q2W beginning on Day 1 using the recommended dose from the Escalation Phase to further evaluate safety, tolerability, PK profiling, preliminary evaluation of clinical efficacy and overall survival.

Additional subjects were included as Arm 1(a) to further evaluate updated toxicity management guidelines that were implemented.

- Arm 2: Approximately 10 subjects with EGFR mutation positive locally advanced metastatic NSCLC who were naïve to EGFR-TKI therapy, were to receive 4 weeks of gefitinib 250 mg QD monotherapy followed by concurrent gefitinib 250 mg QD and durvalumab Q2W beginning on Day 29 using the recommended dose from the Escalation Phase to further evaluate safety, tolerability, PK profile and preliminary efficacy.

Target subject population and sample size

Escalation Phase

Male and female subjects aged 18 years and older with histologically or cytologically confirmed locally advanced or metastatic NSCLC. Subjects must have either failed to respond or relapsed following any line of standard treatment, must have been unable to tolerate, or not eligible for standard treatment.

Approximately 12 subjects were planned to be included in the Escalation Phase.

Expansion Phase

Male and female subjects aged 18 years and older with histologically or cytologically confirmed locally advanced or metastatic NSCLC who are naïve to EGFR-TKI therapy and have EGFR mutations (via local testing), which are sensitive to EGFR TKIs therapy; eg, exons 19 and 21 mutations (Arm 1, and Arm 2).

Approximately 40 subjects were planned to be included in the Expansion Phase (20 of whom were added as Arm 1a following a protocol amendment).

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Gefitinib 250 mg was to be administered as a single oral daily dose.

Durvalumab was to be administered as an initial dose of 3 mg/kg every 2 weeks (Q2W) single intravenous infusion given over approximately 60 mins (± 5 mins). The dose could have been escalated (eg, 10 mg/kg) or de-escalated (eg, 1 mg/kg) based on the tolerability profile.

Investigational product	Dosage form and strength	Manufacturer	Batch numbers
Gefitinib	250 mg tablet	AstraZeneca	[redacted]
Durvalumab	Lyophilised powder containing 200 mg durvalumab	AstraZeneca	

Duration of treatment

All subjects could receive a maximum of 12 months (13 cycles) of combination treatment with gefitinib and durvalumab, unless they were treated during the retreatment period. At the discretion of the Investigator, if the subject may have benefitted from continuing gefitinib monotherapy after the initial 12-month period, subjects were able to receive gefitinib until disease progression. Subjects were not allowed to be retreated with the durvalumab/gefitinib combination during the follow-up period.

Statistical methods

There was no formal statistical analysis required for this study. Demographic and other baseline disease characteristics, concomitant medication, dosing, exposure, safety, and tolerability data are listed and summarised as defined by the relevant Oncology Phase I study outputs described in the Oncology TA standard TFL templates (v2.0).

Quantitative variables are summarised using descriptive statistics, including n, arithmetic mean, standard deviation, median, minimum, and maximum values. Upper and lower quartiles may also have been used for some summaries.

Additionally, geometric means and CV% were reported for durvalumab PK variables (concentrations and all PK parameters) and durvalumab pharmacodynamic variables.

Subject population

Escalation Phase

A total of 16 subjects were enrolled and all were assigned to treatment: 3 subjects in Cohort 0 (3 mg/kg), 7 subjects in Cohort 1 (10 mg/kg) and 6 subjects in the Japan Cohort (10 mg/kg).

All 16 subjects received treatment in the combination treatment period. All except for 1 subject in [redacted] Cohort discontinued treatment, with the most common reason for discontinuation being due to adverse events (AEs; n=8). [redacted].

Expansion Phase

A total of 54 subjects were enrolled and 40 subjects were assigned to treatment: 11 subjects were considered screen failures, 2 subjects withdrew consent and 1 subject [redacted].

A total of 10 subjects were assigned to treatment in Arm 1, 20 subjects in Arm 1a and 10 subjects in Arm 2; all 40 subjects received treatment.

In Arm 1, 6 subjects completed combination treatment and all 6 subjects received post-combination gefitinib monotherapy. The 4 subjects who discontinued treatment did so due to worsening condition (n=3) or withdrawal by the subject (n=1).

In Arm 1a, 4 subjects completed combination treatment and all 4 subjects received post-combination gefitinib monotherapy. The 16 subjects who discontinued treatment did so due to adverse events (n=11) or worsening condition (n=5).

In Arm 2, 2 subjects completed combination treatment and both subjects received post-combination gefitinib monotherapy. The 8 subjects who discontinued treatment did so due to adverse events (n=6) or worsening condition (n=2).

Summary of efficacy results

Escalation Phase

No complete responses were observed. The objective response rate (ORR) for subjects receiving durvalumab (10 mg/kg) + gefitinib was 15.4%, with 2 subjects considered as having a partial response (PR). There were no responses in the 3 mg/kg cohort.

Expansion Phase

The majority of subjects had a response: 19/30 subjects in Arm 1+1a and 7/10 subjects in Arm 2. Of the remaining subjects, all except 1 (in Arm 2) had stable disease for at least 8 weeks.

The ORR for subjects in Arm 1+1a was 63.3%; this was similar to the ORR observed in Arm 2 of 70.0%.

Median progression free survival (PFS) was 10.1 months (95% CIs: 5.5, 15.2) for Arm 1+1a and 12.0 months (95% CIs: 2.7, 15.6) for Arm 2.

Summary of pharmacokinetic results

Durvalumab mean concentrations increased in a dose-related manner between 3 mg/kg and 10 mg/kg Q2W following combination therapy with gefitinib; durvalumab mean concentrations following 10 mg/kg Q2W were similar across different cohorts.

Gefitinib steady-state levels were within range of historical steady-state levels of gefitinib when given as a monotherapy.

Summary of pharmacodynamic results

Following intravenous administration of durvalumab in combination with gefitinib, complete soluble programmed death ligand 1 (PD-L1) suppression (surrogate for PD-L1 targeting) was observed in all treatment groups.

Summary of immunogenicity results

Escalation Phase

All subjects tested negative for anti-drug antibodies ADAs for the entire study duration.

Expansion Phase

A total of 3 subjects overall (of 40) tested positive for ADA during the study. Two subjects had positive ADA at the baseline assessment only. The one remaining subject tested negative for ADAs at baseline but tested positive at the 90-day follow-up assessment after discontinuation of study treatment. Therefore, no treatment-emergent ADA was observed.

Summary of safety results

Escalation Phase

No dose limiting toxicities were observed during the study; therefore, the dose of 10 mg/kg was recommended for the Expansion Phase.

The median (range) total combination treatment durations in the 3 mg/kg and 10 mg/kg cohorts were 5.9 (3 to 9) months and 1.8 (1 to 13) months, respectively.

All subjects (n=16) had at least 1 AE reported during the combination treatment period. The most commonly reported AEs by System Organ Class (SOC) were Gastrointestinal disorders (13 subjects), Skin and subcutaneous disorders and Investigations (12 subjects each), General

disorders and administration site conditions (11 subjects) and Metabolism and nutrition disorders (10 subjects). In the 3 mg/kg cohort, the most commonly reported AEs by Preferred Term were diarrhoea (3 subjects, 100%) and alanine aminotransferase (ALT) increased, amylase increased, aspartate aminotransferase (AST) increased, dry skin, fatigue and hyponatraemia (2 subjects each, 66.7%). In the 10 mg/kg cohort, the most commonly reported AEs by Preferred Term were diarrhoea (8 subjects, 61.5%), nausea (6 subjects, 46.2%) and ALT increased, dry skin and fatigue (5 subjects each, 38.5%).

Related AEs, as assessed by the Investigator, were reported for 15 subjects, the most common AEs considered causally related to study treatment were diarrhoea (8 subjects) and ALT increased and aspartate aminotransferase (AST) increased (6 subjects each). Half of subjects had AEs considered as related to durvalumab treatment only, however most subjects had AEs which were considered as related to gefitinib or the combination. The following AEs, reported in ≥2 subjects, were considered as solely related to durvalumab per the Investigator: hypothyroidism, myalgia and fatigue (2 subjects each).

Most subjects (11 of 16) had an AE of Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 3. While the majority of severe AEs were reported singularly, events of ALT increased (4 subjects) and dyspnoea (3 subjects) were the most common. Seven subjects had CTCAE Grade ≥ 3 AEs that were considered causally related to study treatment; ALT increased was reported for 2 subjects and was the most common related AE.

Adverse events leading to dose interruption were reported for 6 subjects; ALT and AST elevations were reported for 2 subjects each, all other AEs were reported singularly.

Most subjects had adverse events of special interest, with dermatitis/rash (10 subjects) and diarrhoea/colitis (11 subjects) being the most common.

Two subjects had AEs leading to death (pneumonia and suicide attempt) and both were considered by the Investigator as unrelated to study treatment. In addition, 3 subjects died during the study due to the disease under investigation.

Serious AEs (SAEs) were reported for 8 subjects overall, with dyspnoea (2 subjects) the only SAE reported in more than 1 subject. Events reported for 3 subjects (including dyspnoea, hypoxia, ALT increased, AST increased and myalgia) were considered by the Investigator as related to one or both study treatments.

A total of 8 subjects had AEs which led to discontinuation of one or both study treatments. Alanine aminotransferase increased (3 subjects) and dyspnoea (2 subjects) were the only preferred terms to be reported in more than 1 subject.

There were no clinically relevant differences between baseline and subsequent assessments for haematology, clinical chemistry, vital signs, ECG and left ventricular ejection fraction (LVEF) parameters. No pregnancies were reported during the study.

Expansion Phase

The median (range) total combination treatment duration in Arm 1 (12.0 months [5 to 13 months]) was higher than Arm 1a (5.7 months [1 to 12 months]) and Arm 2 (6.2 months [0 to 12 months]).

All subjects (n=40) had at least 1 AE reported during the combination treatment period. The most commonly reported AEs by SOC were Skin and subcutaneous disorders (38 subjects), Gastrointestinal disorders (37 subjects), Investigations (34 subjects) and General disorders and administration site conditions (24 subjects).

In Arm 1, the most commonly reported AEs by Preferred Term were diarrhoea (10 subjects, 100%), nausea (8 subjects, 80%), ALT increased and rash (7 subjects each, 70%) and fatigue (6 subjects, 60%). In Arm 1a, the most common were diarrhoea (15 subjects, 75%), ALT increased (11 subjects, 55%), AST increased and rash (9 subjects each, 45%), dermatitis acneiform (8 subjects, 40%), constipation and pruritus (7 subjects each, 35%). In Arm 2, the most common were ALT increased, diarrhoea and pruritus (6 subjects each; 60%) and AST increased, dry skin and rash (5 subjects each, 50%).

Causally related AEs, as assessed by the Investigator, were reported for all 40 subjects. In Arm 1, the most commonly reported causally related AEs by Preferred Term were diarrhoea (9 subjects, 90.0%), ALT increased (7 subjects, 70.0%) and nausea and rash (6 subjects each, 60.0%). In Arm 1a, the most commonly reported causally related AEs by Preferred Term were diarrhoea (12 subjects, 60.0%), ALT increased (10 subjects, 50.0%), rash (9 subjects, 45.0%) and AST increased (8 subjects, 40.0%). In Arm 2, the most commonly reported causally related AEs by Preferred Term were ALT increased, diarrhoea and pruritus (6 subjects each, 60.0%) and AST increased, rash and dry skin (5 subjects each, 50.0%).

Most subjects (28 of 40) had an AE of CTCAE Grade ≥ 3. The incidence of CTCAE Grade ≥3 AEs was higher in Arm 1a (75.0%) and Arm 2 (80.0%) compared with Arm 1 (50.0%).

In Arm 1, the most commonly reported CTCAE Grade ≥3 AE by Preferred Term was ALT increased (3 subjects, 30%). In Arm 1a, the most commonly reported CTCAE Grade ≥3 AEs by Preferred Term were ALT increased (6 subjects, 30%) and AST increased (5 subjects, 25%). In Arm 2, the most commonly reported CTCAE Grade ≥3 AEs by Preferred Term were ALT increased (5 subjects, 50%) and AST increased (3 subjects, 30%).

Overall, severe AEs relating to liver enzyme increases were most frequently reported: ALT increased (14 subjects) and AST increased (8 subjects).

A total of 22 subjects had CTCAE Grade ≥ 3 AE that was considered causally related to study treatment. The most commonly reported CTCAE Grade ≥3 causally related events were: ALT increased (13 subjects), AST increased (7 subjects) and diarrhoea (4 subjects).

Adverse events leading to dose interruption were reported for 28 subjects. Increases in ALT and AST were most frequently reported (16 subjects and 12 subjects, respectively).

Most subjects had adverse events of special interest, with dermatitis/rash (38 subjects), diarrhoea/colitis (31 subjects) and hepatic events (31 subjects) being the most common.

There were no AEs leading to death and 6 subjects died in the study, during follow-up. With the exception of 1 subject [redacted] all deaths were due to the disease under investigation.

The incidence of SAEs was higher in Arm 1a (65.0%) and Arm 2 (50.0%) compared with Arm 1 (30.0%). Serious AEs were reported for 21 subjects overall; ALT increased (4 subjects) and pneumothorax (3 subjects) were most commonly reported. Twelve subjects had SAEs which were considered by the Investigator as related to one or both study treatments; 6 subjects (of 12) had related SAEs of liver enzymes increased.

A total of 16 subjects had AEs which led to discontinuation of one or both study treatments. The incidence of AEs leading to study treatment discontinuation was higher in Arm 1a (55.0%) and Arm 2 (50.0%) compared with Arm 1 (0%). None of the subjects in Arm 1 discontinued treatment due to an AE, supporting the decision to further evaluate an additional 20 patients in Arm 1a. It was therefore not anticipated to see a high incidence of AEs leading to study treatment combination discontinuation in Arm 1a.

Adverse events leading to study treatment discontinuation included:

- ALT increased: 0 subjects in Arm 1, 5 subjects in Arm 1a (25.0%), 3 subjects in Arm 2 (30.0 %); all CTCAE Grade ≥3
- AST increased: 0 subjects in Arm 1, 3 subjects in Arm 1a (15.0%; all CTCAE Grade ≥3), 3 subjects in Arm 2 (30.0%; 2 subjects with Grade 3 AEs and 1 subject with a Grade 2 AE)
- Nephritis: 0 subjects in Arm 1, 1 subject in Arm 1a (5.0%), 1 subject in Arm 2 (10.0%); both CTCAE Grade 2
- Transaminases increased: 0 subjects in Arm 1, 2 subjects in Arm 1a (10.0%; both CTCAE Grade ≥3), 0 subjects in Arm 2
- Pneumonitis: 0 subjects in Arm 1 and Arm 1a and 1 subject in Arm 2 (CTCAE Grade 4)

- Drug-induced liver injury: 0 subjects in Arm 1, 1 subject in Arm 1a (CTCAE Grade 4) and 0 subjects in Arm 2

With the exception of increases in liver enzymes, there were no clinically relevant differences between baseline and subsequent assessments for haematology, clinical chemistry, vital signs, ECG and LVEF parameters. No pregnancies were reported during the study and one case of accidental overdose of gefitinib (500 mg) did not result in an AE.

Conclusions

- In the Escalation Phase, safety data showed that treatment with durvalumab at both dose levels (3 mg/kg and 10 mg/kg) was well tolerated with no DLT reported. This supported the use of durvalumab 10 mg/kg in combination with gefitinib (250 mg) in the Expansion Phase.
- In the Expansion Phase, AEs following treatment with durvalumab (10 mg/kg) in combination with gefitinib (250 mg) were managed, with reported toxicities related to liver enzyme increases that required discontinuation of durvalumab and/or gefitinib. A high discontinuation rate of durvalumab + gefitinib was reported due to AEs related to liver enzyme increased, being significantly higher than each drug individually historically reported.
- There is insufficient supporting evidence to conclude that the gefitinib + durvalumab higher rate of AEs leading to study treatment discontinuation in Arm 1a may have curtailed the efficacy and this could be a cohort random phenomenon.
- While this study was intended primarily as a safety study, efficacy data indicated that the combination of durvalumab and gefitinib did not appear to offer any additional clinical benefit to patients with EGFR mutation positive tumours when comparted with historical Phase III data for gefitinib monotherapy in terms of ORR and PFS.
- Due to the changing therapeutic landscape, in which osimertinib has been approved for first-line therapy of patients with EGFR positive mutation NSCLC due to a clinically significant improvement in efficacy and lower rates of serious adverse events, the benefit-risk profile of durvalumab in combination with gefitinib has changed.