AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Selumetinib (AZD6244; ARRY-142886)
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A Phase II, Double-Blind, Randomised, Placebo-Controlled Study to Assess the Efficacy and Safety of Selumetinib (AZD6244; ARRY-142886) (Hyd-Sulfate) in Combination with Docetaxel, Compared with Placebo in Combination with Docetaxel, in Patients Receiving Second-Line Treatment for Locally Advanced or Metastatic Non-Small Cell Lung Cancer (Stage IIIB-IV) (SELECT - 2)

Study dates: First patient enrolled: 18 December 2012
Last patient enrolled: 06 November 2015

Phase of development: Therapeutic exploratory (II)

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

Study centres

This study was conducted at 55 centres in 8 countries. Patients were randomised in 46 centres in these 8 countries: Bulgaria (5 centres), Brazil (6 centres), France (6 centres), Germany (8 centres), Hungary (9 centres), the Netherlands (4 centres), Poland (2 centres) and the USA (6 centres).

Publications

There were no publications at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Type	Objective	Variable
Primary		
Efficacy	To assess the efficacy in terms of PFS for each comparison of selumetinib in combination with docetaxel, compared to placebo in combination with docetaxel	PFS using investigator site assessments according to RECIST 1.1
Secondary		
Efficacy	To further assess the efficacy of each comparison of selumetinib in combination with docetaxel, compared to placebo in combination with docetaxel, in terms of OS	OS
Efficacy	To further assess the efficacy of each comparison of selumetinib in combination with docetaxel, compared to placebo in combination with docetaxel, in terms of ORR	ORR using investigator site assessments according to RECIST 1.1
Efficacy	To further assess the efficacy of each comparison of selumetinib in combination with docetaxel, compared to placebo in combination with docetaxel, in terms of DoR	DoR using investigator site assessments according to RECIST 1.1
Efficacy	To further assess the efficacy of each comparison of selumetinib in combination with docetaxel, compared to placebo in combination with docetaxel, in terms of change in tumour size at Week 6	Change in tumour size at Week 6
Safety	To assess the safety and tolerability profile for each treatment group	AEs, clinical chemistry, haematology, urinalysis, vital signs, ECG, echocardiogram/MUGA, and ophthalmologic examination
Efficacy	To explore whether *KRAS* mutation status is predictive of efficacy of selumetinib in combination with docetaxel, compared with docetaxel alone	Efficacy was assessed within *KRAS* mutation subgroups (*KRAS*m, *KRAS* NMD, *KRAS* mutation status unknown) in terms of, PFS, OS, ORR, and change in tumour size at Week 6
PRO	To assess the effect on NSCLC symptoms for each comparison	ASBI was used to assess the following: • Symptom improvement rate • Time to symptom progression
PRO	To assess the effect on HRQoL for each comparison	Assessment using LCSS and SF-36v2

Table S1 Objectives and outcome variables

Type	Objective	Variable
PK	To investigate the PK of selumetinib and N-desmethyl selumetinib when administered in combination with docetaxel	Where the data allowed, derived PK parameters for selumetinib, N-desmethyl selumetinib were produced which could include, but were not be restricted to, C_{max} and AUC
Exploratory[a]		
Biomarker research	To explore gene expression signatures/profiles or *KRAS* codon subtypes in tumour and/or tumour derived material that may influence response	Correlation of gene expression signature with efficacy Within *KRAS* mutation subgroup, looking at *KRAS* codon subtypes for correlation with efficacy
PK/PD	To investigate the relationship between selumetinib and/or N-desmethyl selumetinib plasma concentrations/exposure and clinical outcomes, efficacy, AEs, and/or safety parameters if deemed appropriate	Output from both graphical and/or appropriate PK/PD modelling techniques
Biomarker research	To investigate the use of plasma as a potential source of cfDNA for the analysis of *KRAS* mutation status at randomisation and at treatment discontinuation visit	Correlation of *KRAS* mutation status derived from plasma and tumour material at randomisation and treatment discontinuation
Biomarker research	To explore the correlation between plasma cfDNA levels and efficacy	Correlation of plasma cfDNA levels and efficacy (PFS, OS) at randomisation and treatment discontinuation
Biomarker research	To collect a serum sample to explore biomarker analysis at randomisation and at treatment discontinuation visit	Biomarker analysis of serum to assess exploratory markers, eg cytokines
Biomarker research	To collect a tumour biopsy at treatment discontinuation visit to allow an assessment of the biology of resistance (optional)	By comparing (eg) relevant tumour genetics or signal transduction pathways between the baseline and discontinuation tumour biopsy, the evolution of the tumour biology in response to treatment with selumetinib in combination with docetaxel can be explored
Host genetics research	To collect and store DNA, derived from a blood sample, for future exploratory research into genes/genetic factors that may influence response, eg, distribution, safety, tolerability and efficacy of selumetinib and/or agents used in combination and/or as comparators (optional)	Correlation of polymorphisms with variation in PK, PD, safety, or response parameters observed in patients treated with selumetinib (and/or agents used in combination or as comparators)
Biomarker research	To explore potential biomarkers in residual biological samples (eg, biopsy [tissue/cytology], plasma, and/or serum), which may influence development of cancer (and associated clinical characteristics) and/or response	Correlation of biomarkers to response and/or development of cancer

[a] The analyses for all exploratory objectives are reported separately from this CSR.

Abbreviations: AE, adverse event; ASBI, Average Symptom Burden Index; AUC, area under plasma concentration-time curve from zero to infinity; C_{max}, maximum plasma concentration; CSR, clinical study report; DoR, duration of response; cfDNA, circulating free-tumour deoxyribonucleic acid; DNA, deoxyribonucleic acid; ECG, electrocardiogram; HRQoL, health-related quality of life; *KRAS*, v Ki ras2 Kirsten rat sarcoma viral oncogene homolog; *KRAS*m, *KRAS*-mutant; LCSS, Lung Cancer Symptom Scale; MUGA, multi-gated acquisition scan; NMD, no mutation detected; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumours; SF-36v2, Short Form Health Survey-36 items (Version 2)

Study design

This was a Phase II, double-blind, randomised, placebo-controlled study that assessed the efficacy and safety of selumetinib (75 mg, orally uninterrupted twice daily [bd]) in combination with 2 different doses of docetaxel (intravenously [iv] 60 mg/m^2 or 75 mg/m^2, on Day 1 of every 21-day cycle), each compared to placebo in combination with docetaxel iv 75 mg/m^2, in patients receiving second-line treatment for locally advanced or metastatic non-small cell lung cancer (NSCLC) (Stage IIIB to IV).

Eligible patients were randomised using an interactive voice response system/interactive web response system in a 2:2:1 ratio to 1 of the following 3 treatment groups:

- Selumetinib 75 mg bd in combination with docetaxel 75 mg/m^2 (hereafter referred to as Sel 75 mg + Doc 75 mg/m^2)
- Selumetinib 75 mg bd in combination with docetaxel 60 mg/m^2 (hereafter referred to as Sel 75 mg + Doc 60 mg/m^2)
- Placebo in combination with docetaxel 75 mg/m^2 (hereafter referred to as Doc 75 mg/m^2 alone).

Target subject population and sample size

The target patient population was male and female patients aged ≥18 years with locally advanced or metastatic NSCLC who had failed first-line anti-cancer therapy due to radiological documentation of disease progression in advanced disease or subsequent relapse of disease following first-line therapy. Patients were eligible for second-line treatment and had no prior treatment with docetaxel or a mitogen-activated protein kinase (MEK) inhibitor. Patients had to have measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines, confirmation of histological or cytological locally advanced or metastatic NSCLC (IIIB to IV) and a World Health Organisation Performance Status of 0 to 1.

Initially the study protocol did not specify any selection of patients based on v-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue (*KRAS*) mutation status. Therefore, patients with *KRAS*-mutant (*KRAS*m), *KRAS* no mutation detected (NMD) and *KRAS* mutation status unknown were included in the study. Recruitment to the study was put on hold after the 77th patient was randomised in September 2013, to allow a protocol amendment to include only patients with centrally confirmed *KRAS* NMD NSCLC to be enrolled. Following clinical study protocol Amendment 2, prospective confirmation of *KRAS* mutation status was mandatory for all patients and only patients with *KRAS* NMD status were recruited. The first patient with approval of this amendment (after the recruitment stop) was randomised in March 2014. Confirmation of *KRAS* mutation status must have been determined prior to randomization by a central laboratory using the cobas® *KRAS* Mutation test (Roche Molecular Systems). If the patient had already been tested as a part of a screening process for D1532C00079 (SELECT-1) and the results were *KRAS* NMD, which made the patient

ineligible for SELECT-1, this test result could be used for the determination of eligibility for SELECT-2. No other form of *KRAS* testing could be used for this purpose.

Progression-free survival (PFS) was the primary endpoint. Approximately 225 patients were to be randomised between the 3 treatment groups (approximately 90 patients per selumetinib treatment groups and 45 patients in the placebo treatment group) to obtain approximately 107 progression events for each treatment comparison (approximately 174 events across the 3 treatment groups, approximately 77% overall maturity). If the true hazards ratio (HR) was 0.6, then 174 events provided 80% power to demonstrate a statistically significant difference for PFS, at a 10% 2-sided significance level. A 40% reduction in risk progression was regarded as clinically meaningful.

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

Selumetinib (AZD6244; ARRY-142886)/placebo, manufactured by AstraZeneca, were supplied in bottles of 60 capsules of 25 mg strength. Patients had to swallow 3 selumetinib/placebo 25 mg capsules twice daily, on an empty stomach, commencing on Day 1 of a 21-day cycle.

Commercially available docetaxel 60 mg/m^2 or 75 mg/m^2 was administered iv on Day 1 of every 21-day cycle.

Individual batch numbers and further information are included in Section 5.4.1 of the clinical study report (CSR).

Duration of treatment

Treatment with selumetinib or matching placebo commenced following randomisation and continued until objective disease progression, intolerable toxicity, or the occurrence of another discontinuation criterion. Patients were expected to receive up to 6 cycles of docetaxel although this could be increased at investigator discretion or decreased if significant toxicity developed. Per clinical study protocol (CSP) Amendment 2, pegylated granulocyte colony stimulating factor (G-CSF) was mandated a minimum of 24 hours after the administration of every docetaxel dose and not within 14 days prior to the next docetaxel administration.

Statistical methods

There were 3 treatment groups in this study and the following 2 treatment comparisons were made: selumetinib 75 mg bd in combination with docetaxel 75 mg/m^2 (Sel 75 mg + Doc 75 mg/m^2), selumetinib 75 mg bd in combination with docetaxel 60 mg/m^2 (Sel + Doc 60 mg/m^2) versus placebo in combination with docetaxel 75 mg/m^2 (Doc 75 mg/m^2 alone). Because this was a Phase II study, no multiplicity correction was performed, but this was considered when interpreting results.

All efficacy endpoints were analysed using the full analysis set (FAS) and by *KRAS* mutation status subgroup (*KRAS* NMD, *KRAS* NMD excluding patients in the interim analysis set, and *KRAS*m only) unless otherwise stated in the Statistical Analysis Plan. The analysis in the

KRAS NMD subgroup was considered of primary interest. Statistical analyses for the *KRAS* mutation status unknown subgroup were not performed.

The primary statistical analysis for the primary outcome variable of PFS was performed using the Cox proportional hazards model based on the FAS, and included terms for treatments and pre-defined covariates. It was based on the programmatically derived PFS. Results were presented in terms of HR for each treatment comparison with 90% confidence intervals (CIs) and 2-sided p-value. In addition, 95% CIs were presented for the primary statistical analysis. The assumption of proportionality was assessed. Sensitivity and subgroup analyses were also performed and the consistency of effect between subgroups was tested.

Overall survival was analysed using the same Cox proportional hazards model described for PFS. Objective response rate (ORR) treatment comparisons were performed using a logistic regression model. The duration of response for all patients in the FAS who had an objective response was summarised using descriptive statistics (formal statistical testing was not performed). Percentage change in tumour size at 6 weeks compared to baseline was analysed using an analysis of covariance model. Efficacy was also assessed within the *KRAS* mutation subgroups (*KRAS*m, *KRAS* NMD, and *KRAS* NMD excluding patients in the interim analysis set) in terms of PFS, OS, ORR, and change in tumour size at Week 6 (statistical analyses were performed for PFS, OS, and ORR and change in tumour size at Week 6). Average Symptom Burden Index was analysed and presented as described for ORR. Time to symptom progression was analysed as described for PFS.

Subject population

The first patient in this study was enrolled on 18 December 2012 and the last patient was enrolled on 06 November 2015. The data cut-off (DCO) date was 27 January 2016.

A total of 337 patients were enrolled at 55 centres in 8 countries and 212 were randomised: 23 patients in France, 42 patients in Germany, 50 patients in Hungary, 39 patients in Brazil, 19 patients in the USA, 14 patients in the Netherlands, 22 patients in Bulgaria, and 3 patients in Poland.

Of the 212 randomised patients, 85 patients were randomised to the Sel 75 mg + Doc 60 mg/m^2 group, 84 patients were randomised to the Sel 75 mg + Doc 75 mg/m^2 group, and 43 patients were randomised to the Doc 75 mg/m^2 alone group. A total of 211 patients (99.5%, 211/212) received treatment, all of whom received either selumetinib in combination with docetaxel or docetaxel alone.

At the DCO, a total of 189 patients (89.2%, 189/212) had discontinued selumetinib/placebo and 204 patients (96.2%, 204/212) had discontinued docetaxel.

At the DCO, 23 patients (10.8%, 23/212) were continuing to receive treatment. Twenty-two patients (10.4%, 22/212) were continuing to receive selumetinib/placebo, of which 16 patients (7.5%, 16/212) were continuing to receive selumetinib/placebo after discontinuing docetaxel. Seven patients (3.3%, 7/212) were continuing to receive docetaxel,

of which 1 patient (0.5%, 1/212) continued to receive docetaxel after discontinuing selumetinib/placebo.

At the DCO, 63 patients (29.7%, 63/212) were ongoing in the study, and 149 patients (70.3%, 149/212) had terminated the study.

The majority of patients (146 patients [68.9%, 146/212]) were *KRAS* NMD. Of the remaining patients, 44 patients (20.8%, 44/212) were *KRAS*m and 22 patients (10.4%, 22/212) were *KRAS* mutation unknown.

The demographic and baseline characteristics of the patients enrolled in this study were as expected for the population under study.

Overall, patients were predominantly White (199 patients [93.9%, 199/212) and male (151 patients [71.2%, 151/212]).

All but 2 patients had received previous chemotherapy (210 patients [99.1%, 210/212]), with 188 patients (88.7%, 188/212) having received exactly 1 previous chemotherapy regimen and 187 patients (89.0%, 187/212) having received platinum doublet therapy.

The most common relevant surgical history Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) for patients in this study were lung lobectomy (20 patients [9.4%, 20/212]), biopsy lung investigations (15 patients [7.1%, 15/212]), and cholecystectomy (12 patients [5.7%, 12/212]).

The use of concomitant medications was, with one exception, in compliance with the CSP and was as expected for the population under study.

Summary of efficacy results

The primary endpoint (improvement in PFS in the overall population) in SELECT-2 was not met and there is no evidence of efficacy benefit with the selumetinib combinations in the *KRAS* NMD population (compared to Doc 75 mg/m^2 alone).

For the Sel 75 mg + Doc 75 mg/m^2 versus Doc 75 mg/m^2 alone comparisons, no clinically meaningful improvements in PFS were observed in the FAS or *KRAS* NMD subgroup. A higher number of deaths in the absence of documented progression contributed to the PFS events in the combination arms compared to Doc 75 mg/m^2 alone group. There was an imbalance in the number of patients with new lesion sites, with more patients in the treatment combination groups having new lesions than patients in the Doc 75 mg/m^2 alone group.

No statistically significant difference in OS was observed in the FAS or *KRAS* NMD, with HRs numerically favouring the Doc 75 mg/m^2 alone compared with the Sel 75 mg + Doc 75 mg/m^2 group.

Patients who received Sel 75 mg + Doc 75 mg/m^2 among all FAS patients had a 33% response rate was and among patients in the *KRAS* NMD subgroup (vs. ~14%); however, responses were not maintained (median duration of response [DoR]: 4.5 months).

Although tumour shrinkage was greater in the Sel 75 mg + Doc 75 mg/m^2 group versus Doc 75 mg/m^2 alone group at Week 6, these differences were not maintained over time and, therefore, did not translate to PFS and OS benefit. Similar results were observed in the *KRAS* NMD population.

Reverse separation was observed in both PFS and OS curves, along with no clinically meaningful improvements in response rates suggest that patients receiving the lower docetaxel 60mg/m^2 dose may derive less efficacy compared to the standard 75 mg/m^2 docetaxel dose.

Summary of pharmacokinetic results

No formal pharmacokinetic analysis was performed. Population PK analysis will be reported outside of this CSR.

Summary of pharmacogenetic results

Results of the exploratory pharmacogenetic and biomarker research analyses are reported separately from this CSR.

Summary of safety results

The combination treatment has a safety profile consistent with the current knowledge based on historical data.

The mean (standard deviation [SD]) percentage intended dose of selumetinib/placebo was higher overall in the Doc 75 mg/m^2 alone group (94.2% [48.25]) versus the Sel 75 mg + Doc 60 mg/m^2 group (68.7% [31.51]) and the Sel 75 mg + Doc 75 mg/m^2 group (74.6% [29.32]) in alignment with the higher number of discontinuations, interruptions, and reductions due to adverse events (AEs).

No unexpected safety concerns were reported in the study and the safety profile appears consistent with historical data for docetaxel and emerging safety data for selumetinib as reported in the Investigator's Brochure.

The proportion of patients with at least 1 AE was comparable between the Sel 75 mg + Doc 60 mg/m^2 (81 patients [96.4%, 81/84]) and Sel 75 mg + Doc 75 mg/m^2 groups (83 patients [98.8%, 83/84]), but lower than in the Doc 75 mg/m^2 alone group (39 patients [90.7%, 39/43]). The most commonly reported AEs (diarrhoea, rash, and oedema peripheral) had a higher incidence in patients in the combination groups versus the patients on Doc 75 mg/m^2 alone.

The majority of AEs in each treatment group were classified as moderate to severe in severity (Common Terminology Criteria for Adverse Events [CTCAE] grade 2 or 3). The number of patients with at least 1 AE of CTCAE grade ≥3 was higher in patients in the combination

groups versus patients on Doc 75 mg/m^2 alone. All the AE of CTCAE grade ≥3 PTs were reported by <5% of patients in any treatment group with the exception of neutropenia, fatigue, diarrhoea, dyspnoea, anaemia and pneumonia.

Thirteen patients had CTCAE grade 5 or fatal AEs; 9 deaths were related to both NSCLC and AEs and 4 deaths were due to AEs only (ischaemic stroke, peritonitis, and 2 sepsis events). The number of patients with AEs with outcome of death was comparable among the treatment groups. The number of patients with at least 1 serious adverse event (SAE) was higher in patients in the combination groups versus patients on Doc 75 mg/m^2 alone. All the SAE PTs were reported by <5% of patients with the exception of pneumonia in the Sel 75 mg + Doc 60 mg/m^2 group and neutropenia in the Doc 75 mg/m^2 alone group.

The majority of patients overall had primary prophylaxis with G-CSF; 63 patients (75.0%, 63/84) in the Sel 75 mg + Doc 60 mg/m^2 group, 58 patients (69.0%, 58/84) in the Sel 75 mg + Doc 75 mg/m^2 group, and 29 patients (67.4%, 29/43) in the Doc 75 mg/m^2 alone group.

The incidence of CTCAE grade ≥3 neutropenia was higher in the groups containing docetaxel 75 mg/m^2 versus patients on Sel 75 mg + Doc 60 mg/m^2 group. However, the incidence in these groups was lower than the incidence observed in previous studies. The incidence of febrile neutropenia of grade ≥3 was <5%.

The number of patients with at least 1 AE leading to hospitalisation was higher in patients in the two selumetinib groups versus patients in the Doc 75 mg/m^2 alone group. These AEs leading to hospitalisation were most commonly reported within the infections and infestations system organ class (SOC) and the respiratory, thoracic, and mediastinal disorders SOC.

The incidence of infections (grouped term) was higher in the Sel 75 mg + Doc 75 mg/m^2 group (45 patients [53.6%, 43/84, 71 events]) versus the Sel 75 mg + Doc 60 mg/m^2 group (32 patients [38.1%, 32/84, 68 events]) and in the Doc 75 mg/m^2 alone group (17 patients [39.5%, 17/43, 29 events]).

The number of patients with at least 1 discontinuation of investigational product due to an adverse event (DAE) of selumetinib/placebo or docetaxel was higher in patients on selumetinib versus patients on Doc 75 mg/m^2 alone. All DAE PTs of selumetinib/placebo and docetaxel were reported by <5% of the patients.

No safety concerns were observed in haematology, electrolytes, liver and renal biochemistry, vital signs, electrocardiograms (ECGs), echocardiography, and World Health Organization (WHO) performance status (PS).

Conclusions

- The primary endpoint of improvement in PFS in the overall population for each comparison of selumatinib-docetaxel combination compared to docetaxel in SELECT-2 was not met; and the hypothesis of selumetinib plus docetaxel activity in *KRAS* NMD could not be confirmed

- No statistically significant difference in OS was observed for neither selumetinib-docetaxel combination with docetaxel versus docetaxel alone

- Higher response rates and differences in tumour shrinkage were observed between the high-dose selumetinib and placebo, but responses were not maintained and thus not translating to PFS and OS benefits

- No unexpected safety concerns were reported in the study and the safety profile appears consistent with historical data for docetaxel and emerging safety data for selumetinib in the Investigator Brochure (Version 16)

- The proportion of patients with at least 1 AE was comparable between the treatment groups, although SAEs and CTCAE grade ≥3 AEs occurred in a higher proportion of patients receiving selumetinib in combination with docetaxel compared to docetaxel alone

- The administration of prophylactic G-CSF resulted in a lower incidence of neutropenic events (including febrile neutropenia) compared to previous studies

- Combination of selumetinib with a lower 60 mg/m^2 dose of docetaxel did not improve the tolerability of the combination substantially compared to the higher 75 mg/m^2 docetaxel dose, however, data suggest that patients receiving the lower docetaxel dose derive less efficacy