AstraZeneca

Synopsis-format Clinical Study Report Synopsis	
Drug Substance	AZD2171
Study Code	D8480C00040
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A Two-part Study in Japanese Patients with Advanced or Metastatic Non-Small Cell Lung Cancer Consisting of an Open-label Phase I Part to assess the Safety and Tolerability of AZD2171 in combination with Paclitaxel/Carboplatin, followed by a Phase II, Multicentre, Randomised, Double-blind Study to assess the Efficacy of Paclitaxel/Carboplatin in Combination with AZD2171 Compared to Paclitaxel/Carboplatin alone

Study dates: First patient enrolled: 28 September 2007
Last patient out: 19 September 2008

Phase of development: Therapeutic exploratory (II)

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

Premature termination of the study

The study was terminated prematurely in the course of Part A as a consequence of the lack of progression into Phase III of the corresponding Western study (Study BR24) in combination with paclitaxel/carboplatin in patients with NSCLC (non-small cell lung cancer). As a result, only 6 patients participated in Part A of the study, whereas Part B of the study was not conducted. Therefore, a synopsis-format CSR was applied to this study.

Study centre(s)

The study was conducted at three centers in Japan

Publications

None at the time of writing this report.

Objectives (Part A [Phase I Part])

The primary objective of this part of the study was to assess the safety and tolerability of AZD2171 in combination with paclitaxel/carboplatin in patients with advanced or metastatic NSCLC.

Secondary objectives:

1. To examine the effect of AZD2171 on the PK of carboplatin and paclitaxel

2. To determine the steady-state PK of AZD2171 when given in combination with carboplatin and paclitaxel.

Exploratory objectives:

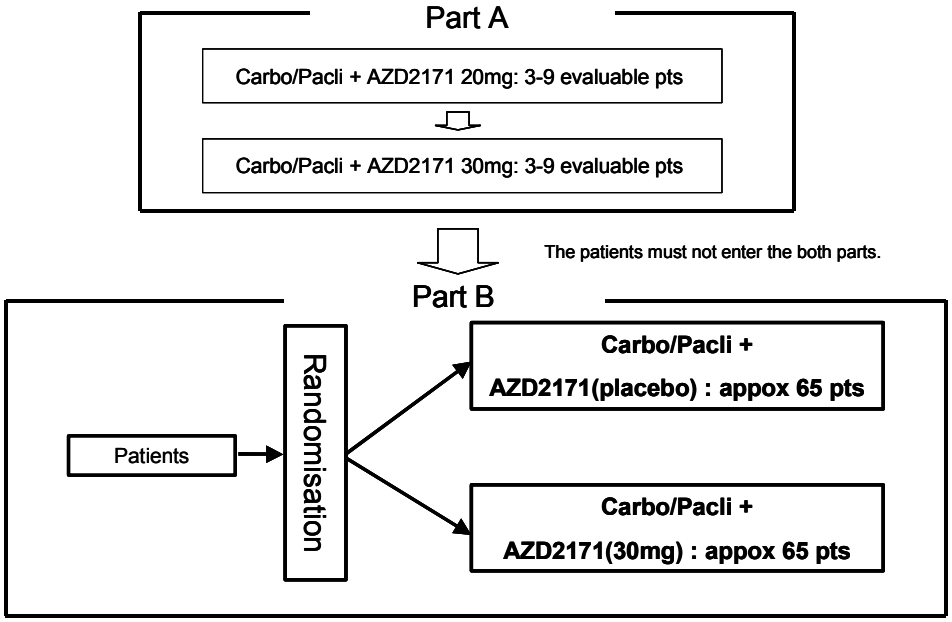
1. To explore the efficacy of AZD2171 in combination with paclitaxel/carboplatin in patients with advanced or metastatic NSCLC measured by RECIST and change in tumour size.

2. To perform retrospective pharmacogenetic analysis of the activity of AZD2171 in combination with paclitaxel/carboplatin from DNA extracted from an optional blood sample.

Study design

The study was a two part study in Japanese patients with advanced or metastatic NSCLC, consisting of an open-label phase I part to assess the safety and tolerability of AZD2171 in combination with paclitaxel and carboplatin followed by a phase II, randomised, double-blind, parallel group study to assess the efficacy of AZD2171 in combination with paclitaxel/carboplatin, comparing that for treatment with paclitaxel/carboplatin alone (see Figure S 1).

Figure S 1 Study Design Summary



Note) Evaluable patient was defined as those who had completed at least 21 days of continuous daily AZD2171 treatment or experienced an intolerant toxicity prior to completing 21 days continuous treatment.

Target patient population and sample size

The study was involved Japanese patients at age 18 or over with advanced or metastatic NSCLC. A maximum of 18 (a minimum of 6) evaluable patients were to be recruited in Part A of the study.

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

The patients received once daily oral AZD2171 20 mg or AZD2171 30 mg in combination with paclitaxel/carboplatin in Part A of the study. Carboplatin AUC 6 was administered on Day 1 of each treatment cycle at intervals of 3 weeks. Paclitaxel 200 mg/m^2 was administered on Day 1 of each treatment cycle at intervals of 3 weeks.

Duration of treatment

AZD2171 treatment was to continue until observation of objective disease progression defined by RECIST, occurrence of toxicity, death, withdrawal of patient's consent or other discontinuation criterion is met. For paclitaxel/carboplatin treatment, 8 cycles were to be at maximum, 6 cycles were to be recommended.

Variables (Part A)

Pharmacokinetic

- PK variables for paclitaxel and carboplatin (C_{max}, t_{max}, AUC, $AUC_{(0-t)}$, CL, $t_{½\lambda z}$ and MRT)
- AZD2171 Steady-state PK parameters ($C_{ss,max}$, $C_{ss,min}$, t_{max} and AUC_{ss})

Efficacy

- ORR (CR + PR)
- Change in tumour size

Genetics

- Retrospective analysis of host genes involved in the absorption, distribution, metabolism and excretion (ADME) and response to AZD2171 in combination with paclitaxel/carboplatin as well genes in the pathways targeted by AZD2171, in DNA obtained from an optional blood sample

Safety (primary variables)

- Adverse events (AEs)
- Laboratory findings (clinical chemistry, haematology, urinalysis)
- Vital signs
- Weight
- Electrocardiogram (ECG)

Statistical methods

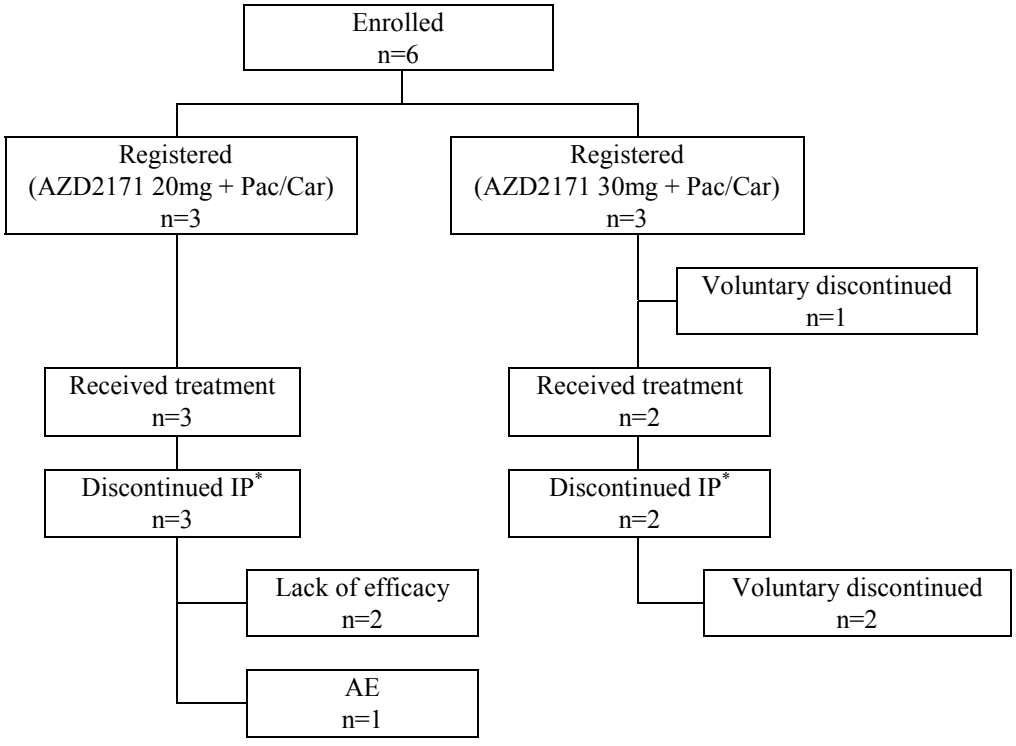
For data from Part A, only descriptive statistics for each dose level were summarised. The number of patients required in Part A was based on the desire to gain adequate safety information on the combination whilst exposing as few subjects as possible to the study medication and procedures (a minimum of 3 evaluable patients were to be required for assessment by the safety review committee).

Subject population

Patient disposition is illustrated in Figure S 2. Patient demography and baseline characteristics are given in Table 11.1.5, 11.1.6 and 11.1.7, Section 11.1. A total of 6 patients participated in Part A of the study (3 patients each in AZD2171 20 mg + paclitaxel/carboplatin group and AZD2171 30 mg + paclitaxel/carboplatin group). Six patients registered had a mean age of 56.5 years (range 42 to 73 years) and were considered to be representative of the broad population of Japanese patients with advanced or metastatic NSCLC. Three patients in AZD2171 20 mg + paclitaxel/carboplatin group and 2 patients in AZD2171 30 mg + paclitaxel/carboplatin group received treatment.

Analysis set is summarised in Table S 1. The data were basically calculated and listed based on the analysis set.

Figure S 2 Patient disposition



*: Investigational product

Table S 1 Analysis set

Analysis Set	20 mg + paclitaxel/carboplatin (N=3)	30 mg + paclitaxel/carboplatin (N=3)
Safety analysis set	3	2[†]
PK analysis set	3	1[‡]
Efficacy analysis set	2[*]	3

[*]: Patient E0003101 was excluded from efficacy analysis set because of no baseline RECIST data.
[†]: Patient E0001102 was excluded from safety analysis set because of no exposure to AZD2171.
[‡]: Patient E0001102 was excluded from PK analysis set because of no exposure to AZD2171.
Patient E0002102 was excluded from PK analysis set because of no PK sample of AZD2171.

Summary of pharmacokinetic results

Regarding the exposure of paclitaxel, 3 patients with evaluable PK data, AUC and C_{max} appeared higher (generally less than 2-fold) when given in combination with AZD2171 than given alone. Particularly, the plasma paclitaxel concentrations around intravenous infusion were higher when given in combination with AZD2171 compared with given alone. However, the half-life of paclitaxel was similar (ratio: 0.9 – 1.1) between combination with and without AZD2171.

Regarding the exposure of carboplatin, there wasn't apparent change in AUC and C_{max} when given alone or in combination with AZD2171.

The exposure after multiple dosing of AZD2171 at 20 mg was consistent with the PK data from Japanese Phase I study (Study D8480C00023).

Overall, it is a very limited data set but it is reasonably consistent with the PK data from western study (Study D8480C00009).

Summary of efficacy results

Objective response and % change in tumour size for each patient were given in Table S 2. Reductions in tumour size from baseline were observed in 2 patients each in AZD2171 20 mg + paclitaxel/carboplatin group and AZD2171 30 mg + paclitaxel/carboplatin group during the study.

Two confirmed partial responses (PR) were observed in AZD2171 30 mg + paclitaxel/carboplatin group and two confirmed stable diseases (SD) were seen in AZD2171 20 mg + paclitaxel/carboplatin group out of 5 patients with baseline RECIST data. However length of treatment on 30 mg AZD2171 was limited due to the termination of the study.

Table S 2 Objective response and % change in tumour size for each patient

Patient No.	Dose group	Objective response	%change in tumour size		Exposure to AZD2171 (days)
			to 1st visit	Best change	
E0001101	20 mg + paclitaxel/carboplatin	SD	–28.1%	–42.7%	123
E0002101	20 mg + paclitaxel/carboplatin	SD	–17.0%	–18.9%	31
E0003101*	20 mg + paclitaxel/carboplatin	(SD)	---	---	230
E0001102†	30 mg + paclitaxel/carboplatin	NE	---	---	0
E0002102	30 mg + paclitaxel/carboplatin	PR	–40.3%	–66.7%	18
E0003102	30 mg + paclitaxel/carboplatin	PR	–36.0%	–94.0%	41

*: Patient E0003101 did not have baseline RECIST data.
†: Patient E0001102 did not have any target legion post dosing.

Summary of safety results

Three patients in AZD2171 20 mg + paclitaxel/carboplatin group had a mean duration of exposure to AZD2171 of 128.0 days (range 31 to 230 days), whereas the 2 patients in AZD2171 30 mg + paclitaxel/carboplatin group had only 18 and 41 days of AZD2171 since the two patients discontinued AZD2171 in consideration of new information about study BR24. There were 2 patients who had dose pauses in AZD2171 20 mg + paclitaxel/carboplatin group (for three days and nine days, respectively). A total of 2 patients had a dose reduction of AZD2171 to 15 mg/day during the study in AZD2171 20 mg + paclitaxel/carboplatin group.

No intolerant toxicities (defined as any toxicities that may be causally related to AZD2171 and occurs in the first 21 days of continuous dosing with AZD2171) were found in this study. For further detailed definition of the intolerant toxicity, see Section 3.1.1.3 in the clinical study protocol.

Number (%) of patients who had at least one adverse event is summarised in Table S 3. One patient (Patient E0003102) in AZD2171 30 mg + paclitaxel/carboplatin group developed SAEs (serious adverse events) with fatal outcome. One patient (Patient E0002101) in AZD2171 20 mg + paclitaxel/carboplatin group experienced a SAE other than death. The same patient (Patient E0002101) also had DAEs (adverse events leading to permanent discontinuation of AZD2171).

Table S 3 Number (%) of patients who had at least one adverse event

	AZD2171 + paclitaxel/carboplatin		
	20 mg (N=3)	**30 mg (N=2)**	**Total (N=5)**
Any AE	3 (100.0)	2 (100.0)	5 (100.0)
Any causally related AE	3	2	5
Any AE of CTC grade 3 or higher	3	2	5
Any causally related AE of CTC grade 3 or higher	3	1	4
Any SAE with outcome = death	0	1	1
Any causally related SAE with outcome = death	0	1	1
Any SAE (including death)	1	1	2
Any SAE other than death	1	0	1
Any causally related SAE	0	1	1
Discontinuation of AZD2171due to AE	1	0	1
Discontinuation of AZD2171 due to causally related AE	1	0	1

Patients with multiple events in the same category are counted only once in that category.
Patients with events in more than one category are counted once in each of those categories.

Most common adverse events (≥ 4 patients in total) are given in Table S 4. Most common adverse events were neutropenia, constipation, anorexia, proteinuria, and alopecia (5 patients reported), thrombocytopenia, diarrhoea, hypertension, blood TSH increased, arthralgia, and fatigue (4 in 5 patients reported).

Table S 4 Most common adverse events

Adverse event	**AZD2171 + paclitaxel/carboplatin**		
(MedDRA preferred term)	**20 mg (N=3)**	**30 mg (N=2)**	**Total (N=5)**
NEUTROPENIA	3	2	5
CONSTIPATION	3	2	5
ANOREXIA	3	2	5
PROTEINURIA	3	2	5
ALOPECIA	3	2	5
THROMBOCYTOPENIA	3	1	4
DIARRHOEA	3	1	4
HYPERTENSION	3	1	4
BLOOD TSH INCREASED	3	1	4
ARTHRALGIA	3	1	4
FATIGUE	2	2	4

Cut-off frequency is ≥ 4 patients in total.
MedDRA version 11.0 used

Adverse events with CTC grade 3 or higher were listed in Table 11.3.2.5.2, Section 11.3. A total of 29 AEs with CTC grade 3 or higher were experienced by individual patients in the study but only neutropenia was experienced by more than one patient. Neutropenia with CTC grade 3 or higher was commonly reported (5 patients reported), but none of the cases were developed to SAE or DAE during the study. There were no cases of hypertension of CTC grade 3 or higher in this study.

Five SAEs in 2 patients occurred during the study, but all the SAEs were reported following discontinuation of AZD2171 (i.e., all the SAEs occurred during the period of single therapy with paclitaxel/carboplatin in the study). Key information for SAEs are given in Table 11.3.4.2.1, Section 11.3. One of these patients had SAEs (ileus, shock, intestinal perforation, and peritonitis) with fatal outcome which is described below:

- Patient E0003102 was a 73 year-old male who participated in the 30 mg group. The patient discontinued AZD2171 at Day 41 in consideration of new information about study BR24, but still continued paclitaxel/carboplatin in the study. The patient developed ileus and shock (CTC grade 3) at Day 74 during the 4th cycle of paclitaxel/carboplatin and hospitalised on the same day. The patient also developed intestinal perforation and peritonitis (CTC grade 3) at Day 84. Fourteen days later, the patient died at Day 98. The four SAEs were considered related to AZD2171 as well as paclitaxel/carboplatin by the investigators.

Four DAEs in 1 patient occurred during the study. Key information for DAEs are given in Table 11.3.5.2.1, Section 11.3.

- Patient E0002101 in AZD2171 20 mg + paclitaxel/carboplatin group developed nausea, fatigue, anorexia and hyponatraemia (CTC grade 3) at Day 34, which were considered related to AZD2171 as well as paclitaxel/carboplatin by the investigators. The four DAEs recovered to CTC grade 2 or lower 2 days after discontinuation of AZD2171.

Laboratory data showed nothing of note in laboratory values during the study. There were occasional isolated values outside reference range in platelet counts and, liver function tests which are part of AZD2171 emerging safety profile. Increased TSH was reported in four patients (E0001101, E0002101, E0003101 and E0003102), of whom none had any accompanying abnormalities in free T3 or T4. All patients developed mild proteinuria during the study. No ECG abnormalities were recorded during the study. One patient developed readings of moderate hypertension and the others had normal hypertension. No patients recorded readings of severe hypertension during the study.