AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD4547
Study Code	D2610C00002
Edition Number	1
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A Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of Ascending Doses of AZD4547 in Japanese patients with Advanced Solid Malignancies

Study dates: First patient enrolled: 5 November 2010
Last patient enrolled: 22 November 2012

Phase of development: Clinical pharmacology (I)

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

Study centres

The study was conducted at 3 centres in Japan.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The objectives of the study and outcome variables are summarised in Table S1.

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To investigate the safety and tolerability of AZD4547 when given orally to Japanese patients with advanced solid malignancies	Adverse events, deaths, assessment of CTCAE grade, clinical chemistry, haematology, urinalysis, vital signs, electrocardiogram parameters (including left ventricular ejection fraction), physical examination, and ophthalmic assessments
Secondary	Safety	To define the maximum tolerated dose and/or a continuous, tolerable recommended dose if possible or biological effective dose in Japanese patients with advanced solid malignancies	Dose-limiting toxicities
	PK	To characterise the PK of AZD4547 following a single administration and at steady state after multiple dosing when given orally to Japanese patients with advanced solid malignancies	Single dose : C_{max}, t_{max}, λ_z, $t_{½}$ AUC, $AUC_{(0-12)}$, $AUC_{(0-t)}$, CL/F, V_{ss}/F, MRT Multiple dose: AUC_{ss}, $C_{ss\ max}$, $C_{ss\ min}$, $t_{ss\ max}$,CL_{ss}/F, Urine PK: CL_R, R_{AC}, Ae;% dose excreted, time dependency
	Efficacy	To obtain a preliminary assessment of the anti-tumour activity of AZD4547 by evaluation of tumour response using Response Evaluation Criteria in Solid Tumours version 1.1 in Japanese patients with advanced solid malignancies	Tumour response, percentage of patients without progression at 10 weeks (Part B only)
Exploratory	Biomarkers/ Pharmaco dynamic[a]	To measure exploratory biomarkers from blood samples and examine the relationship of these biomarkers with clinical outcome. Markers to be assessed are eg, cell death markers (M30, M65, Cyfra21-1), basic fibroblast growth factor (bFGF), and fibroblast growth factor-23(FGF23)	Fluorescence in situ hybridisation (FISH) ratio, bFGF and FGF23

[a] Apart from FISH ratio, bFGF and FGF23, other exploratory variables were reported separate from the CSR.

Ae Cumulative amount of unchanged drug excreted into urine; AUC Area under plasma concentration-time curve from zero to infinity; $AUC_{(0-12)}$ Area under plasma concentration-time curve from zero to 12 hour post dose; $AUC_{(0-t)}$ Area under plasma concentration-time curve from zero to time t; AUC_{ss} Area under plasma concentration-time curve during any dosing interval at steady state; bFGF Basic fibroblast growth factor; C_{max} Maximum plasma (peak) drug concentration after single dose administration; $C_{ss\ max}$ Maximum (peak) steady state drug concentration in plasma during dosing interval; $C_{ss\ min}$ Minimum (trough) steady state drug concentration in plasma during dosing interval; CL/F Total body clearance of drug from plasma after an oral dose; CL_{ss}/F Total body clearance of drug from plasma after an oral dose at steady state; CL_R Renal clearance of drug from plasma; CTCAE Common Terminology Criteria for Adverse Events; FGF23 Fibroblast growth factor-23; MRT Mean residence time; PK Pharmacokinetics; R_{AC} Accumulation ratio; t_{max} Time to reach peak or maximum concentration following drug administration; V_{ss}/F Volume of distribution (apparent) at steady state after an oral dose; λ_z Smallest (slowest) disposition rate constant.

Study design

This was a Phase I, open-label, multicentre study of AZD4547 administered orally in Japanese patients with advanced solid malignancies. The study consisted of 2 parts; Part A: dose escalation and Part B: dose expansion. Patients received a single dose on Day 1, then after a 5 to 10-day washout period, multiple dosing was initiated. Two different dosing schedules were initiated in Part A: Schedule 1 (twice daily [bd] regimen; starting dose: 40 mg) and Schedule 2 (once daily [od] regimen; starting dose: 160 mg). Schedule 2 was initiated after completion of Cohort 3 of Schedule 1. The dose-limiting toxicity (DLT) assessment period consisted of Cycle 0 (single dose and washout period) and Cycle 1 (21-day cycle).

Part B was started independent of Part A, as decided by the safety review committee. Part B investigated the safety, tolerability, pharmacokinetics (PK), and preliminary anti-tumour activity in a minimum of 6 and up to approximately 12 evaluable patients with advanced breast cancer, gastric cancer, or squamous non-small cell lung cancer (NSCLC) with fibroblast growth factor receptor (FGFR)1 and/or FGFR2 gene amplified tumours, at the recommended dose (RD) from the Study D2610C00001 (80 mg [regimen: bd]). The dose administration (ie, single dosing, washout period, and continuous multiple dosing) and dose assessment criteria were similar to that for Part A.

Target subject population and sample size

Male and female patients aged ≥25 years, with a histological or cytological confirmation of solid malignant tumour, including malignant lymphoma (for Part B: Advanced breast cancer, gastric cancer, or squamous NSCLC patients with tumours that have amplification of FGFR1 and/or FGFR2 by fluorescence in situ hybridisation [FISH] testing [FISH score=6]), with at least 1 measurable lesion that could be assessed accurately at baseline and was suitable for repeated assessments, and with a World Health Organisation (WHO) performance status of 0 to 1, were enrolled in the study.

Three to 6 evaluable patients were required for each cohort in Part A of the study. Six patients were required to confirm a dose as the maximum tolerated dose (MTD) and/or RD. For Part B, it was expected that approximately 8 to 20 patients were needed to be recruited in order to obtain a minimum of 6 and up to approximately 12 evaluable patients.

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

AZD4547 was administered orally as tablets of 20 mg and 100 mg in strength. AZD4547 was manufactured by AstraZeneca, UK. The batch numbers used were 10-004102AZ, P/5254/39, P/5275/15, P/5254/39-1, 11-001624AZ, 11-002720AZ, 11-001712AZ, 10-006327AZ, 10-006562AZ, and 12-001326AZ for 20 mg tablets and 10-006327AZ, 10-006561AZ, and 12-001666AZ for 100 mg tablets.

Duration of treatment

Each dosing cohort consisted of a single dose, followed by a 5 to 10-day washout period prior to multiple dosing. All evaluations during the multiple dosing were conducted as 21-day assessment cycles. Patients received AZD4547 as long as they continued to show clinical benefit, as judged by the investigator, and in the absence of discontinuation criteria.

Statistical methods

The data cut-off was defined as the earlier of 6 months after the last patient recruited into Part B started study treatment or 28 days after the final Part B patient discontinued study treatment. Data analysis on all data was to be performed after the data cut-off and the clinical study report written based on this data set.

No formal statistical analysis was done. Data was summarised using descriptive statistics.

Data from Part B was summarised along with Part A and all cohorts were presented separately. For Part B only, the percentage of patients without progression at 10 weeks was also reported.

Subject population

Part A: A total of 36 patients were enrolled from 3 centres and 30 patients received treatment. At the time of data cut-off (16 August 2013), all 30 patients had discontinued the treatment and were terminated from the study. The most common reasons for discontinuation of the treatment were condition under investigation worsened (14 [46.7%] patients) and adverse events (AEs) (9 [30.0%] patients).

The mean age of the patients was 62.3 years (range: 30 years to 78 years). There were 16 (53.3%) male and 14 (46.7%) female patients.

Majority of the patients (28 [93.3%] patients) had metastatic tumour while 2 (6.7%) patients had only locally advanced sites of disease.

Nine (30.0%) patients had locally advanced tumour with the commonly reported site of disease in the respiratory system (5 [16.7%] patients). Twenty-eight (93.3%) patients had metastatic tumour with the commonly reported site of disease in respiratory system (15 [50.0%] patients) and lymph nodes (10 [33.3%] patients).

Part B: A total of 4 patients were enrolled and received treatment. At the time of data cut-off (16 August 2013), all 4 patients had discontinued the study treatment due to worsening of the condition under investigation and all 4 (100%) patients were terminated from the study due to progression of disease.

The mean age of the patients in the study was 70.8 years (range: 64 years to 76 years). There were 3 male (75.0%) and 1 female (25.0%) patients.

The primary tumour location was stomach (2 patients), lung (1 patient), and breast (1 patient).

All 4 (100%) patients had metastatic tumour of which 1 (25%) patient had locally advanced gastrointestinal tumour. The commonly reported metastatic sites of disease were respiratory system (3 [75%] patients) and lymph nodes (3 [75%] patients).

The disease characteristics reflected the expected target population for this study.

Summary of efficacy results

Part A: All patients were non-responders. Among those with non-response, 21 (70.0%) patients had stable disease ≥4 weeks, 8 (26.7%) patients had disease progression (Response Evaluation Criteria In Solid Tumours [RECIST] 1.1) and 1 (3.3%) patient had non-evaluable response due to no post-baseline assessments.

The best percentage change in tumour size was a minimum increase of 5.9% in the median tumour size from baseline. The maximum reduction of 2.7% in tumour size was observed in the 120 mg cohort.

Part B: All 4 patients were non-responders. Among those with non-response, 1 (25.0%) patient had stable disease ≥4 weeks and 3 (75.5%) patients had disease progression (RECIST 1.1). A prolonged stable disease (≥10 weeks) was observed in 1 patient out of 4 patients in total.

The median best percentage change from baseline in target lesion size was similar between the 2 subgroups by FISH score of 6 in FGFR1 (N=2) and FGFR2 (N=2). The median of FGFR1 was an increase of 3.6% whilst that of FGFR2 was 3.0%.

Summary of pharmacokinetic results

PK parameters at the dose level of 80 mg were primarily evaluated with combined data of Part A and B because it was unlikely that FGFR gene amplified tumours made an impact on PK of AZD4547.

AZD4547 had a moderate rate of absorption, with a median t_{max} of 3 hours to 5 hours post-dose across all of the dose levels following single doses and at steady state. Following the maximum plasma (peak) drug concentration after single dose administration (C_{max}), plasma concentrations of AZD4547 declined biphasically with the mean terminal half-life ($t_{1/2\lambda z}$) ranging 22.4 hours to 33.5 hours.

Following multiple dosing, the steady state appeared to have been achieved by Day 8 as the pre-dose plasma concentrations appeared to be generally unchanged on Day 8, 15, and 21.

It was difficult to conclude the dose proportionality of AZD4547 exposures due to the limited number of patients and high variability of PK data.

In general for single dosing, absorption of AZD4547 was variable across the dose of 40 mg to 160 mg with individual t_{max} ranging from 0.5 hours to 7.98 hours, except for the t_{max} (49.0 hours) in Patient E0003056, and the percentage coefficient of variation (CV%) of C_{max} ranged from 54.07% to 141.5%. The total body clearance of drug from plasma after an oral dose (CL/F) of AZD4547 was moderate to high in comparison to human liver blood flow (approximately 80 L/h) although the variability of CL/F was relatively high with 7 of the 32 patients who had low CL/F less than 30 L/h. The mean oral steady state clearance (CL_{ss}/F) ranged from 37.90 L/h to 87.93 L/h, and were slightly lower than the corresponding mean CL/F following a single dose (mean: 57.76 L/h to 116.0 L/h).

The mean oral volume of distribution at steady state (V_{ss}/F) values ranged from 1920 L to 3892 L, and were independent of dose from 40 mg to 160 mg. The V_{ss}/F values were high, indicating that AZD4547 was likely to be well-distributed in the body.

The variability in the maximum (peak) steady state drug concentration in plasma during dosing interval [$C_{ss, max}$] and area under plasma concentration-time curve during any dosing interval at steady state [AUC_{ss}] at each dose level was relatively low in comparison with single dosing data, and the CV% of $C_{ss, max}$ and AUC_{ss} ranged from 23.00% to 65.89% and 10.46% to 61.04%, respectively, across the dose levels of 40 mg to 160 mg.

The mean values of temporal change (Tc; the ratio of multiple dose AUC_{ss} to single dose area under plasma concentration-time curve from zero to infinity [AUC]) were 1.4, 1.9, 1.6, and 1.4 , respectively for 40 mg, 80 mg, 120 mg bd and 160 mg od dosing. Since the Tc tended to be close to unity or slightly higher than unity, there would be no notable time-dependency in the AZD4547 PK, regardless of od or bd dosing.

Urine PK: Although a relatively small proportion of AZD4547 (mean ≤4.1%) is excreted in the urine unchanged, the apparent unbound renal clearance is high compared to glomerular filtration rate.

Summary of pharmacodynamic results

Part A: There was no evidence of association found between percentage change in tumour size and percentage change in fibroblast growth factor-23 (FGF23) and basic fibroblast growth factor (bFGF) for both parts of the study. Calculating FISH ratio for Part A was not possible as adequate data was not captured, thus any analysis involving FISH ratio was only performed using Part B.

Part B: There were no evidence of association found with respect to FGFR gene copy number, against FGFR FISH ratio for best objective response and change in tumour size at

Week 4. However, the small number of patients in the cohort precludes a meaningful interpretation of this observation.

Summary of safety results

Part A: AZD4547 has been investigated at doses from 40 mg to 120 mg bd and 160 mg od continuous dosing. There were no DLTs reported in the study.

The median total and actual duration of exposure to the study treatment was 42.5 days and 30.5 days, respectively. The mean relative dose intensity was 87.0. Out of 30 patients in the safety analysis set, 29 (96.7%) patients experienced at least 1 AE, of which 26 (86.7%) patients reported AEs casually related to the study treatment as judged by the investigator. The most commonly reported AEs by PT were dysgeusia, diarrhoea, stomatitis, hyperphosphataemia, dry month, dry skin, nausea, detachment of retinal pigment epithelium, vomiting, malaise, nail discolouration, and pruritus. Two patients (6.7%) experienced 3 SAEs of which one patient had SAEs that were considered causally related to the study treatment by the investigator (decrease appetite and nausea). There were 3 patients who had an AE of CTCAE Grade ≥3; most frequently reported AEs of CTCAE grade 3 or more in severity were neutropenia (2 [6.7%] patients) and nausea (2 [6.7%] patients). Nine (30.0%) patients had AEs leading to discontinuation of the study treatment and these AEs were considered causally related to the study treatment by the investigator. None of the patients in any cohort had an AE with an outcome of death. However, 1 patient in the 160 mg od cohort died during the follow-up period due to progression of disease under investigation.

Twenty eight (93.3%) patients had at least 1 AE of specific interest. Most commonly reported AEs of specific interest were seen in the following categories: Gastrointestinal (19 [63.3%] patients) and dryness (17 [56.7%] patients) type AEs.

Part B: AZD4547 has been investigated at a dose of 80 mg bd continuous dosing. The median total and actual duration of exposure to the study treatment was same, 24.5 days. The mean relative dose intensity was 83.5. All 4 patients experienced at least 1 AE and had AEs casually related to the study treatment. The most commonly reported AEs by PT were dysgeusia, stomatitis, hyperphosphataemia, dry month, nausea, and decreased appetite. One (25.0%) patient experienced an SAE (stomatitis) that was not considered causally related to the study treatment by the investigator. There were 3 patients with an AE of CTCAE Grade ≥3, which were not causally related to the study treatment. The most common AE of CTCAE Grade ≥3 was decreased appetite (2 [50.0%] patients). None of the patients in Part B had an AE leading to discontinuation of the study treatment. None of the patients in Part B had an AE with an outcome of death.

AEs in the 80 mg bd cohort tended to be more severe than in the160 mg od cohort (no AEs of CTCAE Grade ≥3 were reported). The laboratory findings (ALT, AST, bilirubin, creatinine, phosphate, and neutrophils) were comparable between the cohorts. No patient in the 80 mg bd cohort discontinued the study treatment due to AEs compared to 6 patients in the 160 mg od cohort.

All 4 patients in Part B had at least 1 AE of specific interest. The most commonly reported grouped AEs of specific interest were gastrointestinal (3 [75.0%] patients) type AEs.

Overall, the laboratory findings in the Japanese population are comparable to those reported in the Western population. No clinically relevant changes in the vital signs were observed.