Clinical Study Report Synopsis	
Drug Substance	AZD9833
Study Code	D8530C00006
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EudraCT Number	Not applicable
NCT Number	NCT04541433

A Phase 1, Open-label Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti- tumor Activity of AZD9833 in Japanese Women with ER Positive, HER2 Negative Advanced Breast Cancer

Study dates: First patient enrolled: 29 September 2020
Last subject last visit: 14 December 2021
The analyses presented in this report are based on a clinical data cut-off date of 15 June 2022 and a clinical data lock date of 29 July 2022

Phase of development: Clinical pharmacology (I)

Principal Investigators: PPD

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

Study centers

The study was performed at 3 sites in Japan.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Objective	Endpoints/variables
Primary/safety objective	
• To investigate the safety and tolerability of AZD9833 in Japanese women with eER+ HER2- advanced breast cancer	• Dose-limiting toxicities (only Cohort 1) • Adverse events/serious adverse events • Vital signs • Clinical chemistry/hematology/urinalysis parameters • Triplicate electrocardiograms/echocardiogram
Secondary Objective	
• To assess the anti-tumor activity and efficacy of AZD9833	According to the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 by Investigator assessment: • Objective response rate • Duration of response • Clinical benefit rate at 24 weeks • Percentage change in tumor size • Progression-free survival
• To characterize the first- and multiple-dose pharmacokinetics of AZD9833	Plasma AZD9833 concentrations and derived pharmacokinetic parameters
Exploratory objectives [a]	
CCI [redacted]	

Objective	Endpoints/variables
CCI	

[a] Exploratory endpoints are not reported in this CSR.

CSR, clinical study report; CCI ; ER+, estrogen receptor positive; HER2, human epidermal growth factor receptor 2; RECIST, response evaluation criteria in solid tumors; CCI

Study design

This was a Phase I, open-label study designed to evaluate the safety, tolerability, pharmacokinetics (PK), and anti-tumor activity of AZD9833 in Japanese women with endocrine-related estrogen receptor positive (ER+) human epidermal growth factor receptor 2 negative (HER2-) breast cancer that was not amenable to treatment with curative intent.

The study was conducted in the following phases: enrolment, screening, treatment, and follow-up.

In Cohort 1, patients received AZD9833 150 mg monotherapy orally once daily (QD). Each patient underwent a 28-day evaluation period to determine the dose limiting toxicity (DLT) of AZD9833. Patients continued with treatment until disease progression or withdrawal from the study.

In Cohort 2, patients received AZD9833 75 mg monotherapy orally QD. Patients continued with treatment until disease progression or withdrawal from the study.

Patients were followed up for 28 days (plus 7 days) after the last dose of study treatment for any new reports of adverse events (AEs). Seven-day and 14-day post discontinuation visits to provide information on recovery were performed. Tumor assessments were continued until objective disease progression as designed by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1), even if a patient discontinued treatment prior to progression. If a

patient commenced an alternative cancer therapy prior to objective progression, follow-up tumor assessments ceased.

Target subject population and sample size

The number of patients planned for this study was based on the desire to obtain adequate tolerability, safety, and PK data while exposing as few patients as possible to the study treatments and procedures. At least 3 evaluable patients of the target population were to be enrolled in Cohort 1; patients not evaluable for DLT were to be replaced. Hence, the total number of patients depended on the available data in each cohort and the decision by the Safety Review Committee. In Cohort 2, at least 6 to a maximum of 12 patients with ER+ HER2- advanced breast cancer were to be enrolled for exploratory biomarker evaluation.

Investigational product: dosage, mode of administration and batch numbers

Patients in Cohort 1 received 150 mg AZD9833 orally QD, CCI [redacted]

Patients in Cohort 2 received 75 mg AZD9833 orally QD, CCI [redacted]

Duration of treatment

There was no maximum duration of treatment, and patients could continue to receive study treatment as long as they continued to show clinical benefit, as judged by the Investigator.

Statistical methods

Descriptive statistics were used for all variables, as appropriate. Continuous variables were summarized by the number of observations, mean, standard deviation, median, upper and lower quartiles (as applicable), minimum, and maximum. For log transformed data it was more appropriate to present geometric mean, coefficient of variation (CV), median, minimum, and maximum. Categorical variables were summarized by frequency counts and percentages for each category.

Study population

A total of 17 patients were enrolled; 7 (41.2%) patients were screen failures, and 10 (58.8%) patients were assigned to treatment. Of the 10 patients who were assigned to treatment, 3 patients were assigned to Cohort 1 and received treatment with AZD9833 150 mg QD, and 7 patients were assigned to Cohort 2 and received treatment with AZD9833 75 mg QD.

The study population was representative of the intended target population of Japanese women with ER+ HER2- advanced breast cancer; all patients were female and Asian. The mean age

of study patients was 66.6 years; the majority of patients were ≥ 65 years old (7 [70.0%] patients) and postmenopausal (9 [90.0%] patients). The mean body mass index (standard deviation) of the study patients was 23.7 (3.24) kg/m^2.

At the time of data cut-off, 5 (50.0%) patients were ongoing in the study, 3 (30%) patients were ongoing with study treatment, and 2 (20.0%) patients were in the 28-day follow-up period. Overall, 7 (70.0%) patients had discontinued study treatment. Six (60.0%) patients had discontinued due to a worsening of the condition under investigation, and 1 (10.0%) patient had discontinued due to other reasons.

No patient experienced an important protocol deviation during the study.

Summary of efficacy results

In Cohort 1, 1 (33.3%) patient (95% confidence interval [CI]: 0.84, 90.57) had a response (partial response) and 2 (66.7%) patients had no response. Both patients with no response had a best objective response of stable disease for ≥ 7 weeks. The 1 (33.3%) patient responder was still responding at the time of data cut-off. All 3 (100.0%) patients (95% CI: 29.24, 100.0) in Cohort 1 had clinical benefit at 24 weeks. The median best percentage change from baseline in target lesion size was -5.30% (range: -52.4% to 0.0%); 2 (66.7%) patients had a reduction in target lesion size and 1 (33.3%) patient had a reduction in target lesion size of > 10%. At the time of data cut-off, 1 (33.3%) patient was progression-free; 2 (66.7%) patients had RECIST progression; 1 (33.3%) patient had RECIST progression in a non-target lesion, and 1 (33.3%) patient had RECIST progression due to the appearance of new lesions.

In Cohort 2, in the evaluable for response set, 0 patients (95% CI: 0.00, 40.96) had a response; 6 (85.7%) patients had a best objective response of stable disease for ≥ 7 weeks, and 1 (14.3%) patient had a best objective response of RECIST progression. In the evaluable for response set, patients with measurable disease at baseline, 0 patients (95% CI: 0.00, 52.18) had a response; 4 (80.0%) patients had a best objective response of stable disease for ≥ 7 weeks, and 1 (20.0%) patient had a best objective response of RECIST progression. The median best percentage change from baseline in target lesion size was -9.90% (range: -13.6% to 76.6%); 3 (60.0%) patients had a reduction in target lesion size and 2 (40.0%) patients had a reduction in target lesion size of > 10%.

In Cohort 2, 2 (28.6%) patients (95% CI: 3.67, 70.96) had clinical benefit at 24 weeks. At the time of data cut-off, 2 (28.6%) patients were progression-free and 5 (71.4%) patients had RECIST progression; 2 (28.6%) patients had progression in target lesions, 2 (28.6%) patients had progression in non-target lesions, and 3 (42.9%) patients had progression due to the appearance of new lesions (not mutually exclusive).

Summary of pharmacokinetic results

After a single dose of AZD9833, median t_{max} values ranged from 2.883 to 3.617 hours. After reaching C_{max}, the plasma concentration of AZD9833 declined with similar geometric mean $t_{1/2\lambda z}$ values ranging from 11.13 to 11.85 hours. However, as the majority of $t_{1/2\lambda z}$ values were calculated over a time period spanning less than 3 half-lives, the reported estimates should be considered with caution. The inter-patient variability in C_{max} and AUC values was moderate, with geometric CV values ranging from 13.5% to 36.1%. The increase in systemic exposure was approximately dose-proportional between the cohorts.

After multiple QD doses of AZD9833, median t_{max} values ranged from 2.083 to 5.717 hours. Accumulation of AZD9833 was observed in plasma, with mean geometric Rac(C_{max}) values ranging from 1.239 to 1.598 and geometric mean Rac(AUC) values ranging from 1.550 to 1.816. The inter-patient variability in C_{max} and AUC values was moderate, with geometric CV values ranging from 13.2% to 22.4%. The increase in systemic exposure was approximately dose proportional between the cohorts.

Summary of safety results

The total and actual treatment durations were the same in each cohort; the median treatment duration was 13.860 months in Cohort 1 (range: 4.60 to 18.89 months) and 5.390 months in Cohort 2 (range: 1.81 to 12.02 months).

All patients experienced at least 1 AE, and 9 (90.0%) patients experienced AEs that were assessed as related to the study treatment by the Investigator. No patients experienced AEs of Common Terminology Criteria for Adverse Events (CTCAE) Grade 4; 2 (20.0%) patients experienced 2 AEs of CTCAE Grade 3, neither of which were considered related to study treatment. One (10.0%) patient experienced a serious adverse event (SAE) not considered related to the study treatment. No patient experienced an AE with the outcome of death, or an AE that led to discontinuation, interruption, or dose reduction of study treatment. There were no dose limiting toxicities reported during the study.

There were no trends observed in hematology, clinical chemistry, or urinalysis parameters in either cohort. In Cohort 2, 1 (14.3%) patient experienced a change from baseline to Grade 3 in lymphocytes. No patients met the criteria for a potential Hy's Law case.

There were no trends observed in the vital sign parameters of body temperature, body weight, and blood pressure; there was a decrease in pulse rate noted in patients at all time points during Cycle 1 Day 15. Five (50.0%) patients experienced clinically important abnormalities related to vital signs; these were reported under the preferred terms (PTs) of bradycardia (Grade 1), sinus bradycardia (Grade 1), and hypertension (Grade 2).

Trends of heart rate reductions from baseline (sinus bradycardia) and QTcF increase were observed in electrocardiogram (ECG) data during the study. In Cohort 1, 1 (33.3%) patient had a QTcF increase of more than 30 ms; in Cohort 2, 2 (28.6%) patients had a QTcF value above 450 ms and 1 (14.3%) patient had a QTcF increase of more than 30 ms. Three (30.0%) patients experienced clinically important abnormalities related to ECG; these were reported under the PT of Grade 1 Electrocardiogram QT prolonged.

There were no trends observed in echocardiogram data and no clinically significant changes to patient's eyes were documented based on ophthalmological examination.

Conclusions

- AZD9833 at doses of 75 and 150 mg QD was safe and well tolerated in female patients with ER+ HER2- advanced breast cancer.
- Anti-tumor activity was observed, however definitive conclusions could not be stated due to the small number of patients in each cohort.
- After administration of single and multiple doses of AZD9833, the increase in systemic exposure was approximately dose-proportional between the 75 mg and the 150 mg doses.