AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD5363
Study Code	D3610C00002
Edition Number	1
Date	18 December 2017
EudraCT Number	2011-006312-31

A Phase I/II, Multicentre Study Comprising a Safety Run-In of AZD5363 when Combined with Paclitaxel in Patients with Advanced or Metastatic Breast Cancer; Followed by a Randomised Expansion of AZD5363 when Combined with Paclitaxel vs. Paclitaxel plus Placebo in Patients with ER-Positive Advanced or Metastatic Breast Cancer, Stratified by *PIK3CA* Mutation Status (BEECH)

Study dates:

Part A:

First patient enrolled: 03 October 2012
Last patient enrolled: 01 December 2014
Data cut-off: 23 February 2015

Part B:

No mutation detected

First patient enrolled: 06 February 2014
Last patient enrolled: 25 September 2015

Mutation detected

First patient enrolled: 24 March 2014
Last patient enrolled: 01 March 2016
Data cut-off: 28 January 2017

Phase of development:

Part A:

Clinical Pharmacology (I)/Therapeutic exploratory (IIa)

Part B:

Therapeutic exploratory (IIb)

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

Study centres

Part A was conducted at 9 centres: 3 centres in the United Kingdom, 3 centres in France and 3 centres in Spain.

Part B was conducted at 40 centres: 6 centres in Japan, 6 centres in Spain, 6 centres in the United Kingdom, 4 centres in Canada, 4 centres in Mexico, 4 centres in Peru, 4 centres in South Korea, 2 centres in Bulgaria, 2 centres in France, 1 centre in Czech Republic and 1 centre in Singapore.

Publications

Turner N, Oliveira M, Armstrong A, Sablin MP, Perez-Fidalgo JA, Herebien S, et al. "BEECH", a phase I/II study of the AKT inhibitor AZD5363 combined with paclitaxel in patients with advanced or metastatic breast cancer: results from the dose-finding study, including quantitative assessment of circulating tumor DNA as a surrogate for response/resistance. AACR. Cancer Res 2015;75(15 Suppl): Abstract nr CT331.

Turner N, Alarcón E, Armstrong A, Philco M, Chuken YA, Sablin MP, et al. BEECH: A randomised Phase II study assessing the efficacy of AKT inhibitor AZD5363 combined with paclitaxel in patients with ER+/HER2– advanced or metastatic breast cancer, and in a *PIK3CA* mutant sub-population. ESMO 2017, Annals of Oncology (2017) 28 (suppl_5): v74-v108. Manuscript in preparation.

Carr H, Kozarewa I, Hrebien S, Hanson R, McEwen R, Ahdesmaki M, et al. Broad and sensitive genomic profiling of plasma ctDNA from ER+ve metastatic breast cancer patients enrolled in the BEECH study (paclitaxel in combination with AZD5363/placebo), including a *PIK3CA* mutant sub-population. Third AstraZeneca MedImmune Cancer Research UK Cambridge Centre Symposium, 25-26 September 2017. Manuscript in preparation.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	Part A: To assess the safety and tolerability of 2 intermittent dosing schedules of AZD5363 when combined with weekly paclitaxel in patients with advanced or metastatic breast cancer, and to recommend, by assessment of DLTs and other safety, tolerability, PK and PDc data, a dose and schedule of AZD5363 for further study when combined with weekly paclitaxel.	AEs, ECG, laboratory safety assessment, physical examination, vital signs and LVEF.
Primary	Efficacy	Part B: To assess the relative efficacy of AZD5363 when combined with weekly paclitaxel compared with weekly paclitaxel plus placebo by assessment of PFS in the overall advanced or metastatic ER-positive breast cancer population and in the *PIK3CA* mutation-positive sub-population.	PFS
Secondary	Efficacy	Part A: To make a preliminary assessment of the anti-tumour activity of AZD5363 when combined with paclitaxel by assessment of ORR and the percentage of patients without PD, at 12 weeks.	ORR, BOR (CR, PR, SD, PD and NE), proportion of patients without PD at 12 weeks and change in tumour size.
Secondary	Efficacy	Part B: To assess the relative efficacy of AZD5363 when combined with weekly paclitaxel compared with weekly paclitaxel plus placebo by assessment of ORR at 12 weeks, BOR, DoR and DRR.	ORR at 12 weeks, BOR, DoR and DRR.
Secondary	Efficacy	Part B: To assess the relative anti-tumour activity of AZD5363 when combined with weekly paclitaxel versus weekly paclitaxel plus placebo by comparison of change in tumour size at 12 weeks (TL assessment using RECIST 1.1).	Change in tumour size at Week 12.
Secondary	Efficacy	Part B: To compare OS in patients treated with AZD5363 in combination with weekly paclitaxel compared with weekly paclitaxel plus placebo by assessment of time to death.	OS
Secondary	Safety	Part B: To further assess the safety and tolerability of AZD5363 when combined with weekly paclitaxel compared with paclitaxel plus placebo.	AEs, laboratory data; vital signs, physical and cardiac examination.

Table S1 Objectives and outcome variables

Objective			Variable
Priority	**Type**	**Description**	**Description**
Secondary	Efficacy	Part B: To investigate the effect on patients' QoL of AZD5363 when combined with weekly paclitaxel, compared with weekly paclitaxel alone by changes from baseline, utilising a patient-completed QoL questionnaire.	QoL: EORTC QLQ-C30 and BR-23.
Secondary[a]	PK	Part A and Part B: To assess the PK of AZD5363 when combined with paclitaxel. To assess the PK of paclitaxel alone and when combined with AZD5363.	Plasma concentrations of AZD5363 and paclitaxel were summarised and listed.
Secondary	PK/PDc	Part A and Part B: To assess the PK/PDc relationship between plasma AZD5363 exposure and plasma concentrations of biomarkers (including phosphorylated PRAS40, tPRAS40, pAKT and pGSK3β) anti-tumour activity (assessed by RECIST 1.1).	Phosphorylated PRAS40, tPRAS40, pAKT and pGSK3β.
Secondary	Safety	Part A and Part B: To assess the toxicity burden associated with diarrhoea in relation to the number of episodes, duration of episodes and variations in intensity within episodes of the event's occurrence.	AE collection including additional variables specifically for diarrhoea.
Exploratory[b]	PDc	Part A and Part B: To investigate the relationship between plasma AZD5363 exposure and plasma concentrations of exploratory biomarkers and efficacy. Biomarkers may include, but were not restricted to, somatic mutation or amplification of genes on the PI3K and related pathways in cfDNA.	Not applicable
Exploratory	PDc	Part B: To obtain a preliminary assessment of AZD5363 treatment effect by quantitative change in and/or characterisation of CTCs.	CTCs
Exploratory	PDc	Part A and Part B: To investigate the concordance of *PIK3CA* mutation status between per-patient analyses of blood and archival tumour tissue samples.	*PIK3CA* mutation status (detected/not detected)
Exploratory[b]	PDc	Part A and Part B: To explore changes in WHO PS in patients treated with AZD5363 in combination with weekly paclitaxel compared with weekly paclitaxel plus placebo.	WHO PS

Table S1 Objectives and outcome variables

Objective			Variable
Priority	**Type**	**Description**	**Description**
Exploratory[b]	PDc	Part A and Part B: To collect optional matched pre-and post-treatment tumour biopsy samples to conduct assessment of the PDc effect of therapy compared to baseline.	Not applicable
Exploratory[b]	Pharmacogenetic	Part A and Part B: To collect and store archival tumour samples and analyse surplus blood or tissue, for potential future exploratory research into factors that may influence development of cancer and/or response to AZD5363 (where response is defined broadly to include efficacy, tolerability, or safety). Biomarkers may include, but are not restricted to, somatic mutation or amplification of genes on the PI3 kinase and related pathways, PTEN protein expression and AKT protein expression.	Not applicable
Exploratory[b]	Pharmacogenetic	Part A and Part B: To obtain blood samples for DNA extraction for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD5363 treatment and/or susceptibility to cancer.	Not applicable

[a] Pharmacokinetics will be evaluated by population PK modelling and reported separately from the CSR.
[b] This exploratory research will be reported separately from the CSR.
This table has been modified according to CSP Amendment 2 and CSP Amendment 3.
Abbreviations: AE, adverse event; AKT, protein kinase B; BOR, best objective response; cfDNA, circulating free plasma DNA; CL/F, oral clearance of drug from plasma; CR, complete response; CSP, Clinical Study Protocol; CSR, Clinical Study Report; CTCs, circulating tumour cells; DLT, dose-limiting toxicity; DoR, duration of response; DRR, durable response rate; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; EORTC QLQ-C30; European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 is a core questionnaire); EORTC QLQ-BR-23, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-BR23 assesses disease symptoms, side effects of treatment, body image, sexual functioning and future perspective); NE, not evaluable; ORR, objective response rate; PD, progression of disease; PDc, pharmacodynamic(s); PI3K, phosphoinositide 3-kinase; *PIK3CA*, phosphoinositide 3-kinase, catalytic, alpha polypeptide; PFS, progression-free survival; PK, pharmacokinetic(s); PR, partial response; PRAS40, proline-rich AKT substrate of 40 kDaltons; PTEN, phosphatase and tensin homolog; QoL, quality of life; RECIST 1.1, Response Evaluation Criteria In Solid Tumours version 1.1; SD, stable disease; TL, target lesion; tPRAS40, total proline-rich AKT substrate of 40 kDaltons; WHO PS, World Health Organization performance status.

Study design

This was an international, multicentre study comprising a safety run-in phase (Part A) of AZD5363 in combination with paclitaxel in patients with advanced or metastatic breast cancer; followed by a randomised expansion phase (Part B) of AZD5363 in combination with paclitaxel versus paclitaxel plus placebo in patients with oestrogen receptor (ER)-positive and human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, stratified by phosphoinositide-3-kinase, catalytic, alpha polypeptide (*PIK3CA*) mutation status. The results from Part A were used to recommend a dose and schedule for AZD5363, when combined with weekly paclitaxel, for use in Part B of the study. Part B

assessed the relative efficacy of AZD5363, when combined with weekly paclitaxel, compared with weekly paclitaxel plus placebo, by assessment of progression-free survival (PFS) in the overall advanced or metastatic ER-positive and HER2-negative breast cancer population and in a *PIK3CA* mutation-positive sub-population. Patients were allocated to the *PIK3CA* mutation-positive stratum if a mutation was identified either in tissue or circulating tumour DNA (ctDNA) using the validated cobas® *PIK3CA* Mutation Test (research use only), as per manufacturing instructions, covering 17 hotspot mutations.

Target subject population and sample size

Patients in this study were female, aged ≥18 years, with a World Health Organization performance status of 0 to 1, with no deterioration over the previous 2 weeks and minimum life expectancy of 12 weeks.

Part A

For inclusion in Part A of the study, patients were required to have histological or cytological confirmation of breast cancer with evidence of advanced or metastatic disease. Patients were required to have at least 1 lesion (measurable and/or non-measurable) that could be accurately assessed at baseline by computed tomography or magnetic resonance imaging, and was suitable for repeated assessment. Patients could not have received >2 prior courses of chemotherapy (including taxanes) for breast cancer in the advanced or metastatic setting.

For Part A of the study, the planned number of patients was based on the desire to obtain adequate tolerability, safety, pharmacokinetic (PK) and pharmacodynamics (PDc) data. Cohorts of 3 to 6 evaluable patients were required. The total number of patients required was dependent upon the number of dose escalations necessary to fulfil the primary objective.

A total of 44 patients were enrolled, and 38 patients were assigned to treatment. Twenty patients were assigned to Schedule 1 (a weekly intermittent AZD5363 dosing schedule of 2 days on-treatment followed by 5 days off-treatment) and 18 patients were assigned to Schedule 2 (a weekly intermittent AZD5363 dosing schedule of 4 days on-treatment followed by 3 days off-treatment).

Part B

For inclusion in Part B of the study, patients were required to have histological or cytologic diagnosis of ER-positive and HER2-negative breast cancer with evidence of advanced or metastatic disease. Lesions should not have been amenable to surgery or radiation of curative intent and must have been considered unlikely to be rendered eligible for surgery by treatment with paclitaxel in this study. Patients were also required to provide an archival tumour sample and a baseline plasma sample for *PIK3CA* mutation testing. Patients could not have received any prior chemotherapy for breast cancer in the advanced or metastatic setting. Prior (neo) adjuvant chemotherapy was allowed (if the [neo] adjuvant therapy contained a taxane and there was a minimum of 12 months from completion of therapy to relapse).

For Part B, a sample size of 50 patients in each of the paclitaxel + placebo and the AZD5363 + paclitaxel groups (100 patients in total) was required to detect a hazard ratio (HR) of 0.61, corresponding to median improvements in PFS from 5 to 8.2 months; this sample size would therefore also allow the detection of an improvement in PFS from 9.0 months to 14.8 months (in case of superior performance of the control group in this study). A total of at least 76 PFS events were required to ensure power was at least 80%; the type 1 error assumed was a 1-sided 10% alpha level. For the *PIK3CA* mutation-positive subgroup, a sample size of 50 patients (25 patients in each of the paclitaxel + placebo and AZD5363 + paclitaxel groups) was required to detect a HR of 0.50, corresponding to median improvements in PFS from 5 to 10 months. A total of at least 38 PFS events were required to ensure power is at least 80%.

A total of 194 patients were enrolled and 110 patients were randomised; 54 patients were randomised to the paclitaxel plus AZD5363 treatment group (AZD5363 group) and 56 patients were randomised to the paclitaxel plus placebo treatment group (placebo group).

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

During both Part A and Part B of the study, patients received AZD5363 as capsules or as dose-equivalent tablets (40 mg to 200 mg). During Part B of the study, the placebo was also given as a capsule or as dose-equivalent tablets (40 mg to 200 mg). Paclitaxel was given weekly via an intravenous (IV) infusion of 90 mg/m^2.

Part A

In Part A, patients received 3 consecutive weekly paclitaxel infusions (given on Day 1 of Weeks 1, 2 and 3), followed by 1 week off-treatment within each 28-day treatment cycle. AZD5363 was taken orally, twice-daily (bd) on each week that paclitaxel was received. AZD5363 was given on Day 2 of Week 1 and the weekly regimens continued to start on the day after receipt of paclitaxel, according to the following dosing schedules:

- Schedule 1, a weekly intermittent AZD5363 dosing schedule of 2 days on-treatment followed by 5 days off-treatment. The starting dose for Cohort 1 was 560 mg bd (1120 mg daily);
- Schedule 2, a weekly intermittent AZD5363 dosing schedule of 4 days on-treatment followed by 3 days off-treatment. The starting dose for Cohort 1 was 360 mg bd (720 mg daily).

AZD5363 could have been taken each week following withdrawal of paclitaxel, at the discretion of the investigator, throughout a patient's participation in the study.

The AZD5363 maximum tolerated dose (MTD) was determined to be 560 mg bd for Schedule 1 (weekly intermittent AZD5363 dosing of 2 days on-treatment followed by 5 days off-treatment) and 400 mg bd for Schedule 2 (weekly intermittent AZD5363 dosing schedule

of 4 days on-treatment followed by 3 days off-treatment) in combination with 90 mg/m^2 paclitaxel.

Twenty-one batches of AZD5363 were used in Part A of the study: 11-002964AZ, 11-003083AZ, 12-001149AZ, 12-001150AZ, 12-001976AZ, 12-002803AZ, 13-000431AZ, 13-000532AZ, 13-001093AZ, 13-001178AZ, 13-001580AZ, 13-001764AZ, 13-001942AZ, 13-002263AZ, 13-002525AZ, 14-000082AZ, 14-000393AZ, 14-000620AZ, 14-000814AZ, 15-000718AZ and 15-000719AZ.

Part B

Part B was conducted at the dose and schedule of AZD5363 selected from Part A (400 mg bd dosing of 4 days on-treatment followed by 3 days off-treatment on each week that paclitaxel was received), in combination with paclitaxel administered in 4 weekly cycles (3 weeks on-treatment and 1 week off-treatment). Patients were randomised to receive paclitaxel 90 mg/m^2 IV once weekly plus AZD5363 capsules or tablets taken orally, bd, or paclitaxel 90 mg/m^2 IV once weekly plus AZD5363-matching placebo capsules or tablets taken orally, bd.

Fifteen batches of AZD5363 were used in Part B of the study: 006573, 007264, 007355, 007784, 008047, 008561, 008695, 14-002115AZ, 14-002269AZ, 14-002755AZ, 14-002756AZ, 15-000718AZ, 15-000719AZ, L004102 and L004103.

Four batches of placebo were used in Part B of the study: 12-001915AZ, 13-002164AZ, 14-002209AZ and 15-000738AZ.

Further details on the batches of the investigational product used in this study are included in Appendix 12.1.6.

Duration of treatment

Patients were to continue on treatment with AZD5363 and paclitaxel until Response Evaluation Criteria In Solid Tumours Version 1.1 (RECIST 1.1)-defined objective progression or until a treatment discontinuation criterion was met.

Statistical methods

Part A

The primary endpoints for Part A, safety and tolerability, were assessed using adverse events (AEs), physical examination, electrocardiogram (ECG), left ventricular ejection fraction, laboratory data and vital sign data as recorded in the case record form. The safety analysis set was used to present all safety data.

The efficacy endpoints were: objective response rate (ORR) at 12 weeks, the percentage of patients without progressive disease (PD) at 12 weeks and change in tumour size at 12 weeks. To assess anti-tumour activity, the tumour response was calculated using RECIST 1.1.

Part B

The primary endpoint for Part B of the study was PFS, defined as the time from the date of randomisation until the date of objective disease progression (defined by RECIST 1.1) or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomised therapy or received another anti-cancer therapy prior to progression, for the overall study population and *PIK3CA* mutation-positive subgroup. Progression-free survival in the *PIK3CA* mutation not detected subgroup was also assessed.

The primary analysis of PFS was performed for the intention to treat (ITT) analysis set using the Cox proportional hazard model. Progression-free survival was analysed for the overall study population and the *PIK3CA* mutation detected and not detected subgroups using separate Cox proportional-hazards models, allowing for the effect of treatment and including a term for *PIK3CA* mutation status in the overall analysis (ie, *PIK3CA* mutation detected or not detected). Sensitivity analyses were performed on PFS data using the ITT analysis set.

For Part B, the secondary efficacy endpoints included: change in tumour size at 12 weeks, ORR, duration of response, durable response rate, overall survival and health-related quality of life.

Part A and Part B

The plasma concentrations, determined using a sparse PK sampling scheme at sampling time points, were summarised and listed. All other PK results are reported separately from the CSR.

All biomarker analysis was performed on the ITT analysis set of patients for whom data were available. These included: phosphorylated proline-rich protein kinase B (AKT) substrate of 40 kDaltons (pPRAS40), total PRAS40 (tPRAS40, Part A only), phosphorylated AKT (pAKT) and phosphorylated glycogen synthase kinase 3 beta (pGSK3β).

Subject population

Part A

A total of 44 patients were enrolled in the study at 9 study centres in 3 countries. Of these, patients, 20 patients in Schedule 1 and 18 patients in Schedule 2 received the study treatment. The baseline demographic and disease characteristics of the patients recruited in Part A were consistent with the target patient population. The most common sites of metastatic breast cancer were the bone and liver (including gall bladder). The majority of patients (94.7%) had received at least 1 chemotherapy regimen prior to study entry. The most common prior chemotherapy agent was cyclophosphamide (17 [85.0%] patients in Schedule 1 and 15 [83.3%] patients in Schedule 2). At the data cut off (DCO), 23 February 2015, 5 (41.7%) patients were continuing on 560 mg bd AZD5363 and 3 (37.5%) patients were continuing on 640 mg bd AZD5363 (all in Schedule 1); there were no ongoing patients in Schedule 2. All 18 patients discontinued treatment in Schedule 2 (5 [100%], 7 [100%] and 6 [100%] patients in the 360 mg bd, 400 mg bd, 480 mg bd cohorts, respectively).

Twelve patients discontinued treatment in Schedule 1 (7 and 5 patients in the 560 mg bd and 640 mg bd cohorts, respectively).

Part B

A total of 194 patients were enrolled in the study at 40 study centres in 11 countries. Of these patients, 110 patients were randomised: 54 patients were randomised to the paclitaxel plus AZD5363 treatment group (AZD5363 group) and 56 patients were randomised to the paclitaxel plus placebo treatment group (placebo group). All 110 patients received paclitaxel and 109 (99.1%) patients received either AZD5363 or placebo treatment. Patient recruitment in Part B met the target population and the treatment groups were largely balanced with respect to baseline demographic characteristics. A total of 35 (31.8%) patients had locally advanced disease at baseline and 105 (95.5%) patients had metastatic disease at baseline. Treatment groups were generally well balanced with respect to the site of disease localisation. In total, 90 patients provided both evaluable tissue and blood samples for the analysis of *PIK3CA* mutation status. Of these, 83% (75/90) concordance was observed between the 2 methods (28 patients with *PIK3CA* mutation detected and 47 patients with *PIK3CA* mutation not detected by both methods). Of the 15 discordant results, 80% (12/15) were *PIK3CA* mutation detected in tissue and *PIK3CA* mutation not detected in plasma. At the DCO, 28 January 2017, 7 (13.0%) patients were continuing on AZD5363 treatment and 6 (10.7%) patients were continuing on placebo treatment. Overall, 96 (87.3%) patients discontinued study treatment: 47 (87.0%) patients in the AZD5363 group and 49 (87.5%) patients in the placebo group. At the DCO, 10 (9.1%) patients were continuing on paclitaxel treatment.

Summary of pharmacokinetic results

Part A

The maximum geometric mean plasma concentration of AZD5363 was observed at 2 hours post-dose in all cohorts. The 24 hour post-dose paclitaxel plasma concentrations were similar on Day 2 (ie, before the initiation of AZD5363 dosing) to the 24 hour concentrations on Day 9 and Day 16, indicating that AZD5363 had no effect on paclitaxel plasma concentrations at 3.5 or 5.5 days (depending on the dosing schedule) after the most recent dose of AZD5363.

Part B

The maximum geometric mean AZD5363 plasma concentration was observed at 2 hours after the first AZD5363 dose. The pre-dose AZD5363 plasma concentrations were higher at Week 1, Day 5 than at Week 1, Day 3, but similar at Week 2, Day 2 and Week 3, Day 2, suggesting that steady state had been reached by Week 2. In Part B, the AZD5363 plasma concentrations were consistent with those observed in Part A in the 400 mg 4 days on, 3 days off dose cohort. The maximum geometric mean paclitaxel plasma concentration was observed at 2 hours after the start of infusion; paclitaxel plasma concentrations declined to low levels before the initiation of oral dosing of AZD5363 on Day 2. In Part B, the pre-AZD5363

paclitaxel plasma concentrations were similar in the AZD5363 and placebo groups and were consistent with those observed in Part A of the study.

Summary of pharmacodynamic results

Part A

Evaluation of changes in pGSK3β in platelet-rich plasma (PRP) was limited by the small number of samples available for analysis. In the lowest dosing group (Schedule 2, 360 mg bd), in which the number of samples was greater and adequate for comparison, the median value of pGSK3β (electrochemiluminescence unit [ECL]) decreased from baseline (Day 1 pre-paclitaxel) to 4 hours post-AZD5363 dose (from 219.9 ECL to 66.4 ECL). The maximum observed reduction was at 2 hours post-AZD5363 dose (to 66.0 ECL), indicating treatment-induced inhibition of pGSK3β. However, due to the limited data on pGSK3β, it is difficult to draw conclusions from these changes from baseline. Evaluation of changes in pPRAS40 in PRP after a single dose of AZD5363 on Day 2 was limited by the large number of baseline and post-treatment samples that were below the limit of detection (LoD). Overall, a marginal and transient effect on tPRAS40 and pAKT in PRP was observed.

Part B

Target inhibition was observed in the AZD5363 group at 2 to 8 hours post-AZD5363 dose Week 1; the median value of pGSK3β (ECL) decreased from baseline (Day 2 pre-AZD5363) to 8 hours post-dose AZD5363 (-35.67% change from baseline, from 1676.0 ECL to 977.0 ECL), with the maximum observed reduction at 4 hours post-AZD5363 dose (-50.39% change from baseline, to 950.0 ECL). The PRP samples collected at Week 3 pre-AZD5363 dose (after 3 days off-treatment), returned to baseline values (-0.86% change from baseline), with a reduction again at 4 hours post-AZD5363 dose (-56.72% change from baseline). As expected, there was no impact of placebo on pGSK3β. There was also no impact of paclitaxel on pGSK3β in PRP prior to treatment with AZD5363 or placebo. At Day 1, the day prior to start of AZD5363/placebo dosing, the change in the median value of pGSK3β was +1.39% at 2 hours and -1.43% at 4 hours post-paclitaxel dose on Day 1 in patients starting AZD5363 at Day 2, and -2.39% at 2 hours and +10.22% at 4 hours post-paclitaxel dose on Day 1 in patients starting placebo at Day 2. Evaluation of changes in pPRAS40 was limited by the small number of samples with detectable levels of pPRAS40; a total of 63 patients had baseline samples below the LoD, and many post-treatment samples were also below the LoD. Samples below the LoD were assigned the value of the LoD value of 6.25 U/mL, both at baseline and for post-treatment samples, impacting the population mean values as well as calculations to determine the magnitude of the change from baseline. Therefore, pPRAS40 data were not taken into account for the final conclusions. Changes in pAKT were marginal and transient, which is in line with Part A of the study.

Summary of efficacy results

Part A

In Part A, 2 (10.0%) patients had a confirmed RECIST 1.1 partial response (PR) in Schedule 1 and 2 (11.1%) patients had a confirmed RECIST 1.1 PR in Schedule 2. A total of 11 (55.0%) patients in Schedule 1 and 10 (55.6%) patients in Schedule 2 had stable disease (SD) ≥12 weeks. A similar proportion of patients had no PD at Week 12 in Schedule 1 (11 [55.0%] patients) and Schedule 2 (9 [50.0%] patients).

Part B

In Part B, overall PFS maturity was 76% at the time of PRIMA (84 progression events). There was a numeric improvement in the Kaplan-Meier (KM) median PFS in favour of the AZD5363 group compared with the placebo group (10.9 months [95% CI 8.3 months to 12.4 months] vs 8.4 months [95% CI 8.2 months to 10.8 months, respectively]); however, the difference was not statistically significant at the 20% alpha level (HR 0.80; 80% CI 0.6, 1.06; p=0.308). In the *PIK3CA* mutation detected subgroup, PFS maturity was 75% at the time of PRIMA (38 progression events). The KM median PFS was similar across the treatment groups (10.9 months [95% CI 8.7 months to 11.5 months] in the AZD5363 group and 10.8 months [95% CI 8.3 months to 14.3 months] in the placebo group), with differences not reaching statistical significance at the 20% alpha level. The PFS findings in patients with *PIK3CA* mutation status detected by plasma ctDNA vs tissue are consistent with the primary analyses. Sensitivity analyses of the PFS were also consistent with the primary analysis, thus showing no evidence of an evaluation time bias (ie, one treatment group being assessed more frequently than the other) nor attrition time bias (nature of censoring). No meaningful differences were observed between the treatment groups in any of the key secondary endpoints.

Summary of safety results

Part A

The AZD5363 MTD for Schedule 1 was determined to be 560 mg bd in combination with 90 mg/m^2 paclitaxel. Diarrhoea and neutropenia were recorded as dose-limiting toxicity (DLT) events in Schedule 1. With the exception of neutropenia, which is known to be associated with paclitaxel and could potentially be attributable solely to paclitaxel, the DLTs for AZD5363 in combination with paclitaxel were consistent with those observed in AZD5363 monotherapy studies (D3610C00001 and D3610C00004).

The AZD5363 MTD for Schedule 2 was determined to be 400 mg bd in combination with 90 mg/m^2 paclitaxel. Allergic reaction and skin rash were recorded as DLT events in Schedule 2 and are consistent with those observed in AZD5363 monotherapy studies.

At the declared MTDs, there did not appear to be substantial differences between the 2 dosing schedules with regards to patient tolerability of AZD5363 and paclitaxel in combination.

The safety and tolerability profile of paclitaxel did not appear to be affected/modified by the addition of AZD5363 at any dose or schedule (although patient numbers are small in the individual cohorts within Part A of this study).

The AE profile for AZD5363 in combination with paclitaxel was consistent with the emerging AZD5363 monotherapy data, the listed AEs for paclitaxel and those that are expected in this advanced cancer population.

Part B

The median total AZD5363/placebo treatment duration was longer in the AZD5363 group (325.5 days) compared with the placebo group (245.0 days); however, the median total paclitaxel treatment duration was shorter in the AZD5363 group (175.0 days) compared with the placebo group (210.0 days). The mean paclitaxel relative dose intensity was similar in the AZD5363 group (91.5%) and in the placebo group (92.5%) and the median number of paclitaxel treatment cycles received by patients was 6.0 cycles in both treatment groups.

Almost all patients in both treatment groups experienced at least 1 AE (51 [94.4%] patients in the AZD5363 group vs 50 [90.9%] patients in the placebo group).

The most frequently reported AEs in the AZD5363 group were: diarrhoea, alopecia, nausea, anaemia, fatigue, hyperglycaemia, vomiting, stomatitis, peripheral sensory neuropathy, pyrexia, rash maculo-papular, neuropathy peripheral, alanine aminotransferase (ALT) increased, cough, dysgeusia and aspartate aminotransferase (AST) increased. The most frequently reported AEs in the placebo group were: alopecia, neuropathy peripheral, diarrhoea, anaemia, nausea, myalgia and fatigue.

The proportion of patients with at least 1 AE that was assessed by the investigator as being causally related to AZD5363/placebo only was higher in the AZD5363 group (39 [72.2%] patients) compared with the placebo group (23 [41.8%] patients). The proportion of patients with at least 1 AE of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥3 was also higher in the AZD5363 group (32 [59.3%] patients) compared with the placebo group (17 [30.9%] patients). Few AEs of CTCAE grade ≥3 were reported at a frequency of >5% of patients in either treatment group.

Adverse events with an outcome of death only were uncommon (3 [5.6%] patients in the AZD5363 group [redacted]

Although there was a small numeric difference in serious AEs (SAEs) reported in the AZD5363 group (12 [22.2%] patients) compared with the placebo group (8 [14.5%] patients), no differences were observed in the preferred terms reported in each treatment group. Only

1 SAE (pneumonia) was reported with a frequency of ≥5% (4 [7.4%] patients in the AZD5363 group).

A total of 19 (35.2%) patients had dose reductions of AZD5363 in the AZD5363 group, with 1 dose reduction being most commonly reported (12 [22.2%] patients). All dose reductions in the AZD5363 group were due to AEs. Dose interruptions of AZD5363/placebo were more common in the AZD5363 group (66.7% of patients) compared with the placebo group (54.5% of patients). The most common reason for dose interruption of AZD5363/placebo was AEs (30 [55.6%] patients in the AZD5363 group vs 18 [32.7%] patients in the placebo group).

The proportion of patients who experienced at least 1 AE leading to discontinuation of AZD5363/placebo was low in both treatment groups (7 [13.0%] patients in the AZD5363 group vs 4 [7.3%] patients in the placebo group). A higher proportion of patients experienced at least 1 AE leading to discontinuation of paclitaxel in the AZD5363 group (17 [31.5%] patients) compared with the placebo group (11 [20.0%] patients). The AEs leading to discontinuation of paclitaxel which were reported in >1 patient in the placebo group were: neuropathy peripheral and peripheral sensory neuropathy. Overall, AEs leading to discontinuation of paclitaxel did not appear to be more severe in AZD5363 group compared with the placebo group.

With the exception of glucose homeostasis parameters, no consistent trends were seen in clinical laboratory parameters, vital signs or ECG observations.

Overall, AZD5363 in combination with paclitaxel appeared to be reasonably well tolerated in this study, with a low discontinuation rate. Toxicity appears to have been well managed with dose modifications and supportive care.

Conclusions

Part A

- AZD5363 400 mg bd in Schedule 2 (intermittent AZD5363 dosing of 4 days on-treatment followed by 3 days off-treatment) and AZD5363 560 mg bd in Schedule 1 (intermittent AZD5363 dosing of 2 days on-treatment followed by 5 days off-treatment), in combination with paclitaxel (3 weeks on-treatment and 1 week off-treatment), were well tolerated in patients with metastatic breast cancer.

- AZD5363 400 mg bd in Schedule 2 (intermittent AZD5363 dosing of 4 days on-treatment followed by 3 days off-treatment [3 weeks on-treatment and 1 week off-treatment]) was selected as the recommended dose for use in combination with paclitaxel in Part B of the study.

- At the declared MTDs, there did not appear to be substantial differences between the 2 dosing schedules with regard to patient tolerability of AZD5363 in combination with paclitaxel.

- The AE profile for AZD5363 in combination with paclitaxel was consistent with the emerging AZD5363 monotherapy data; the listed AEs for paclitaxel are those to be expected in this advanced cancer population.

- A total of 2 (10.0%) patients had a confirmed RECIST 1.1 PR in Schedule 1 and a total of 2 (11.1%) patients had a confirmed RECIST 1.1 PR in Schedule 2.

- A total of 11 (55.0%) patients in Schedule 1 and 10 (55.6%) patients in Schedule 2 had SD ≥12 weeks.

- A similar proportion of patients had no PD at Week 12 in Schedule 1 (11 [55.0%] patients) and Schedule 2 (9 [50.0%] patients).

- Evaluation of changes in pGSK3β and pPRAS40 in PRP during treatment were limited by the small number of samples available and evaluable for analysis.

- AZD5363, administered in Schedule 1 or Schedule 2 and initiated 24 hours after the weekly paclitaxel dosing, did not appear to influence the PK of paclitaxel.

Part B

- In Part B, the study did not meet its primary endpoint, with a PFS HR which was not statistically significant at the 20% alpha level. Thus, the addition of AZD5363 to paclitaxel did not improve the median PFS in the overall study population, nor in the *PIK3CA* mutation detected subgroup.

- No meaningful differences were observed between the treatment groups in any of the key secondary endpoints. Findings for the secondary endpoints were in line with those seen for the primary endpoint.

- AZD5363 was considered overall to be well tolerated and had no apparent marked impact on the tolerability and dose intensity of paclitaxel. A few patients discontinued AZD5363 due to AEs that were assessed by the investigator as being causally related to AZD5363 only in this part of the study. Toxicity appears to have been well managed with dose modifications and supportive care.

- Almost all patients in both treatment groups experienced at least 1 AE (51 [94.4%] patients in the AZD5363 group vs 50 [90.9%] patients in the placebo group).

- The proportion of patients with at least 1 AE of CTCAE grade ≥3 was higher in the AZD5363 group (32 [59.3%] patients) compared with the placebo group (17 [30.9%] patients). Few AEs of CTCAE grade ≥3 were reported at a frequency of >5% of patients in either treatment group.

- Adverse events with an outcome of death only were uncommon (3 [5.6%] patients in the AZD5363 group vs [redacted]

- [redacted]

- Although there was a small numeric difference in SAEs reported in the AZD5363 group (12 [22.2%] patients) compared with the placebo group (8 [14.5%] patients), no differences were observed in the preferred terms reported in each treatment group. Only 1 SAE (pneumonia) was reported with a frequency of ≥5% (4 [7.4%] patients in the AZD5363 group).

- A total of 19 (35.2%) patients had dose reductions of AZD5363 in the AZD5363 group; all dose reductions in the AZD5363 group were due to AEs.

- Dose interruptions of AZD5363/placebo were more common in the AZD5363 group (66.7% of patients) compared with the placebo group (54.5% of patients). The most common reason for dose interruption of AZD5363/placebo was AEs (30 [55.6%] patients in the AZD5363 group vs 18 [32.7%] patients in the placebo group).

- The proportion of patients who experienced at least 1 AE leading to discontinuation of AZD5363/placebo was low in both treatment groups (7 [13.0%] patients in the AZD5363 group vs 4 [7.3%] patients in the placebo group).

- A higher proportion of patients experienced at least 1 AE leading to discontinuation of paclitaxel in the AZD5363 group (17 [31.5%] patients) compared with the placebo group (11 [20.0%] patients). The AEs leading to discontinuation of paclitaxel which were reported in >1 patient in the placebo group were: neuropathy peripheral and peripheral sensory neuropathy.

- In general, similar safety results were observed in the *PIK3CA* mutation detected and not detected subgroups.

- With the exception of glucose homeostasis parameters, no consistent trends were seen in clinical laboratory parameters, vital signs or ECG observations.

- Evaluation of changes in pGSK3β in PRP showed target inhibition in the AZD5363 group at 2 to 8 hours post-AZD5363 dose Week 1, with the maximum observed reduction from baseline (Day 2 pre-AZD5363) at 4 hours post-AZD5363 dose. The PRP samples collected at Week 3 pre-AZD5363 dose (after 3 days off-treatment), returned to baseline values, with a reduction again at 4 hours post-AZD5363 dose.

As expected, there was no impact of placebo on pGSK3β. There was also no impact of paclitaxel on pGSK3β in PRP prior to treatment with AZD5363 or placebo. Evaluation of changes in pPRAS40 was limited by the small number of evaluable samples.

- The same recommended Phase II dose and schedule of AZD5363 in combination with paclitaxel are being tested in pAKT, the ongoing Phase II, double-blind, randomised, placebo-controlled study in patients with triple negative advanced or metastatic breast cancer (NCT02423603).