Clinical Study Report Synopsis	
Drug Substance	AZD4635
Study Code	D8730C00001
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A Phase I, Open-Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Anti-Tumor Activity of Ascending Doses of AZD4635 Both as Monotherapy and in Combination in Patients with Advanced Solid Malignancies

Study dates:
First patient enrolled: 17 June 2016
Last patient last visit: 31 December 2020
The analyses presented in this report are based on a clinical data lock date of 12 October 2021.

Phase of development:
Clinical pharmacology (I)

Co-ordinating Investigator:
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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study Centers

Patients were enrolled in 18 sites in the United States.

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
Investigate the safety and tolerability of AZD4635 monotherapy when given PO to patients with advanced solid malignancies	AEs, SAEs, vital signs, ECGs, laboratory parameters
Investigate the safety and tolerability of AZD4635 PO when given in combination with durvalumab to patients with advanced solid malignancies and AZD4635 in combination with abiraterone acetate, or enzalutamide to patients with mCRPC	
Define the MTD of AZD4635 in combination with durvalumab	
Define the RP2D of AZD4635 in combination with abiraterone acetate or enzalutamide	
Determine the safety, tolerability, and immune effects of AZD4635 when administered in combination with durvalumab to patients with NSCLC who have previously received immunotherapy (Phase 1b portion)	
Investigate the safety, tolerability, and PK of AZD4635 monotherapy capsule formulation when given to patients with advanced solid malignancies	AEs, SAEs, vital signs, ECGs, laboratory parameters, PK parameters
Investigate the safety and tolerability of AZD4635 capsule formulation in combination with durvalumab and oleclumab when given to patients with mCRPC or advanced solid tumor malignancy	AEs, SAEs, vital signs, ECGs, laboratory parameters
Define the RP2D of AZD4635 capsule formulation in combination with durvalumab and oleclumab when given to patients with mCRPC or advanced solid tumor malignancy	
Investigate the safety and tolerability of AZD4635 capsule formulation in combination with docetaxel when given to patients with mCRPC or advanced solid tumor malignancy	
Define the RP2D of AZD4635 capsule formulation in combination with docetaxel when given to patients with mCRPC or advanced solid tumor malignancy	
Secondary	
Determine the safety, tolerability, preliminary anti-tumor effects (RECIST, PFS, PSA, and CEA) of AZD4635 monotherapy as well as in combination with durvalumab, abiraterone acetate, oleclumab, enzalutamide, or docetaxel, in all cohorts of post-immunotherapy or immune checkpoint-naïve tumors	AEs, SAEs, vital signs, ECGs, laboratory parameters RECIST, PFS, PSA, and CEA
Characterize the single-dose and multiple-dose plasma PK of AZD4635 (and its metabolites SSP-005173X and SSP-005174X) following monotherapy as well as in combination with durvalumab, abiraterone acetate, oleclumab, enzalutamide, or docetaxel	Plasma PK parameters
Characterize the urine PK of AZD4635 and its metabolites	Urine PK parameters
Assess the PK of durvalumab, abiraterone, oleclumab and enzalutamide in combination with AZD4635	PK parameters

Table S1 Objectives and Endpoints

Objectives	Endpoints
To evaluate the immunogenicity of durvalumab and oleclumab in combination with AZD4635	Anti-drug antibodies
Characterize the effect of AZD4635 on QTc interval	ECG

AE, adverse event; CEA, carcino embryonic antigen; ECG, electrocardiogram; mCRPC, metastatic castrate-resistant prostate cancer; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; PFS, progression-free survival; PK, pharmacokinetic(s); PO, per os (oral administration); PSA, prostate-specific antigen; QTc, QT interval corrected for heart rate; RECIST, Response Evaluation Criteria for Solid Tumors; RP2D, recommended Phase II dose; SAE, serious adverse event

Exploratory objectives will be reported separately and will not form part of the clinical study report (CSR).

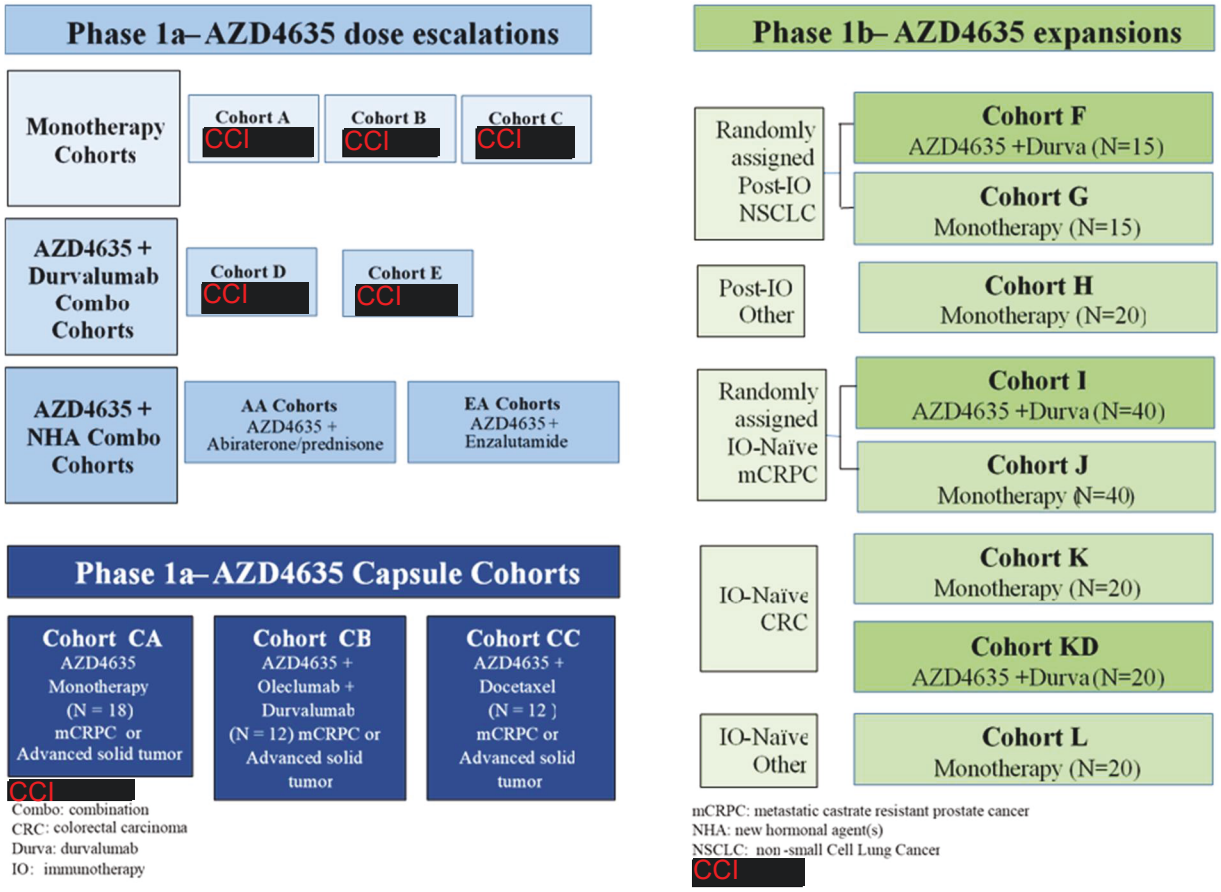
Study Design

This was a Phase I, open-label, multicenter study comprising a Phase Ia dose escalation and Phase Ib dose expansion of AZD4635 administered as monotherapy or in combination in patients with advanced solid malignancies (Figure 1). The study design allowed an escalation of dose with intensive safety monitoring to prioritize the safety of the patients.

The Phase Ia portion of the study was designed to assess the safety, tolerability, pharmacokinetics (PK), and preliminary anti-tumor activity of ascending oral doses of the AZD4635 nanosuspension as monotherapy (Cohorts A, B, and C), AZD4635 in combination with durvalumab Cohorts D and E), and AZD4635 in combination with abiraterone acetate or with enzalutamide (Cohorts AA and EA), or administered in capsule form as monotherapy in patients with advanced solid malignancies (Cohort CA) and in combination with durvalumab and oleclumab or docetaxel in patients with advanced solid malignancies (Cohorts CB and CC).

The Phase Ib portion of the study consisted of expansion cohorts in tumor types where there was a rationale for potential efficacy of the study treatments. Patients were randomly assigned between open-label cohorts with AZD4635 monotherapy and AZD4635 combined with durvalumab in non-small cell lung cancer (NSCLC) (Cohorts F/G) and metastatic castrate-resistant prostate cancer (mCRPC) (Cohorts I/J) in order to minimize bias. Patients with colorectal cancer (CRC), excluding microsatellite instability (MSI) high, were enrolled to AZD4635 monotherapy (Cohort K) and AZD4635 combined with durvalumab (Cohort KD) in patients with CRC. Patients with other tumor types were treated with AZD4635 monotherapy (Cohorts H and L).

Figure 1 Flow Chart of Study Design



Target Population and Sample Size

Patients were adults with advanced solid malignancies. The number of patients was based on the desire to obtain adequate tolerability, safety, PK, and biomarker data while exposing as few patients as possible to the investigational product (IP) and procedures. CCI [redacted]

Investigational Product and Comparator(s): Dosage, Mode of Administration and Batch Numbers

AZD4635 administered orally as a nanosuspension at doses CCI [redacted], dependent on cohort. Batch numbers: Available on request.

AZD4635 administered orally in a capsule formulation; doses CCI [redacted].
Batch numbers: CCI [redacted], CCI [redacted], CCI [redacted], CCI [redacted], CCI [redacted], CCI [redacted].

Durvalumab administered intravenously (IV) once every 4 weeks (Q4W) at a dose of 1500 mg (for patients > 30 kg in weight). If a patient's weight fell to ≤ 30 kg, weight-based dosing at 20 mg/kg was administered. Batch numbers: CCI, CCI, CCI, CCI, CCI, CCI, CCI.

Oleclumab administered IV 750 mg (in the event of a de-escalation), 1500 mg, and 3000 mg on Day 1 and Day 15 of each 28-day cycle Q2W × 4 followed by Q4W. Batch number: CCI.

Note: Batch numbers provided are those available electronically from March 2017 to end of study. Batches used prior to March 2017 are recorded in the paper trial master file and are available on request.

Duration of Treatment

Patients could continue to receive AZD4635, and/or the combination of AZD4635 and durvalumab, or AZD4635 combined with abiraterone acetate or enzalutamide as long as they continued to show clinical benefit, as judged by the Investigator, and in the absence of discontinuation criteria.

Statistical Methods

For all patients, the Response Evaluation Crivteria for Solid Tumors (RECIST) tumor response data were used to determine each patient's visit response (complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD], or not evaluable [NE]) according to RECIST version 1.1. It was also used to determine best objective response (BOR). Objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), duration of response (DoR), target lesion size, and prostate-specific antigen (PSA) and carcino embryonic antigen (CEA) responses were summarized.

Adverse events (AEs), serious adverse events (SAEs), deaths, and discontinuations due to AEs were summarized. Treatment-emergent AEs were summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term, with further splits by maximum Common Toxicity Criteria for Adverse Events (CTCAE) grade, causal relationship to any study medication, dose interruption or modification, and AEs classed as CTCAE Grade 3 or higher. Adverse events of special interest (AESIs) for durvalumab and oleclumab were summarized. Hematology, blood chemistry, lipid, cardiac enzyme, and coagulation parameters were summarized.

Study Population

CCI Across all cohorts, the main reasons for discontinuation from AZD4635 were objective and subjective disease progression. The

majority of patients in this study were aged over 50 years, White and had multiple prior lines of treatment. Overall the population was representative of patients with advanced solid malignancies.

Summary of Efficacy Results

Clinical activity was observed in the mCRPC immuno-oncology (IO)-naïve patients, but not in any of the other cohorts.

In mCRPC IO-naïve patients who received AZD4635 monotherapy:

- Median PFS was 8.3 (95% confidence interval [CI]: 6.0, 15.0) weeks
- 2 (5.0%) patients had a PR
- 9 (22.5%) and 7 (17.5%) patients had disease control at 14 and 22 weeks, respectively
- 3 (4.9%) patients had a PSA response.

In mCRPC IO-naïve patients who received AZD4635 + durvalumab:

- Median PFS was 14.7 (95% CI: 8.7, 29.3) weeks
- 4 (10.8%) patients had a PR, and 2 (5.4%) patients had a CR
- 13 (35.1%) and 11 (29.7%) patients had disease control at 14 and 22 weeks, respectively
- 10 (22.2%) patients had a PSA response.

Summary of Pharmacokinetic Results

Following a single dose of AZD4635 monotherapy (nanosuspension or capsule) or AZD4635 combination therapy (capsule), AZD4635 median time to maximum plasma concentration (tmax) and geometric mean terminal elimination half-life (t1/2λz) appeared generally similar across dose levels and between the nanosuspension and capsule formulations, with median tmax ranging from approximately 1 to 2 hours post dose and geometric mean t1/2λz ranging from approximately 9 to 17 hours, based on all capsule cohorts and the pooled nanosuspension monotherapy cohorts. Systemic exposure (all area under the plasma concentration versus time curves [AUCs] and maximum plasma concentrations [Cmax]) to AZD4635 generally increased with the increase in dose, and over the nanosuspension CCI [redacted] (dose levels with robust n due to pooling), the increase in systemic exposure to AZD4635 was approximately dose proportional.

Following multiple doses of AZD4635 monotherapy (nanosuspension) or combination therapy (nanosuspension or capsule), median tmax and geometric mean t1/2λz for AZD4635 appeared generally similar across cohorts/different combination therapies, between monotherapy and combination therapy, and between multiple and single doses of AZD4635. Following multiple doses of AZD4635 monotherapy (capsule), median tmax was approximately 2 to 4 hours,

which was slightly later than for the nanosuspension monotherapy and nanosuspension and capsule combination therapy treatments, but geometric mean t1/2λz was comparable between capsule and nanosuspension formulations. For both the capsule and nanosuspension monotherapy treatments, AZD4635 PK did not appear time-dependent. Some accumulation of AZD4635 in plasma was observed following multiple dosing of nanosuspension and capsule monotherapy, based on geometric mean accumulation ratio (Rac) area under the plasma concentration-time curve from time zero to 24 hours (AUC(0-24)) values ranging from approximately 1.4 to 2.1 for all capsule cohorts and the pooled CCI nanosuspension monotherapy. Summary PK parameters values for pooled CCI AZD4635 + durvalumab were similar to those for pooled CCI AZD4635 monotherapy, indicating durvalumab had no apparent impact on the PK of AZD4635.

Following single or multiple doses of AZD4635 monotherapy or combination therapy, the unbound systemic exposure to AZD4635 metabolites SSP-005173 and SSP-005174 was roughly 2% to 7% and 16% to 56%, respectively, of the corresponding unbound systemic exposure to parent drug AZD4635, with no discernible trend across cohorts and dose levels.

Urinary excretion of AZD4635 and its metabolites SSP-005173 and SSP-005174 was assessed over a 24-hour interval following single and multiple doses of AZD4635 monotherapy or in combination with durvalumab. There was negligible excretion of unchanged AZD4635 in urine, and urinary excretion of SSP-005173 and SSP-005174 was minimal, with approximately 0.50% to 2.0% and 0.13% to 0.43% of the administered AZD4635 dose excreted as SSP-005173 and SSP-005174, respectively. There were no apparent differences in urinary excretion of SSP-005173 and SSP-005174 between cohorts receiving AZD4635 in combination with durvalumab versus AZD4635 monotherapy.

Following multiple doses of CCI AZD4635 in combination with 1000 mg abiraterone acetate or 160 mg enzalutamide, the summary PK parameter values for abiraterone and enzalutamide and its metabolite N-desmethyl enzalutamide were roughly similar to those previously reported.

Summary of Safety Results

Across all cohorts, the median total treatment duration for AZD4635 ranged from 0.1 to 41.3 months.

The most frequently reported AEs across all treatments were nausea, fatigue, and vomiting. These AEs were also the most frequently reported AEs possibly related to AZD4635 in the AZD4635 monotherapy cohort: nausea (81 [52.9%] patients), vomiting (43 [28.1%] patients), and fatigue (31 [20.3%] patients). In the AZD4635 + durvalumab cohort, the most frequently reported AEs possibly related to AZD4635 were nausea (47 [48.5%] patients), vomiting

(17 [17.4%] patients), fatigue (15 [15.5%] patients), and decreased appetite (15 [15.5%] patients).

The proportion of patients with SAEs related to AZD4635 was low. The only SAE possibly related to treatment reported in more than 1 patient was type I diabetes mellitus (in the AZD4635 + durvalumab group).

Nausea and fatigue were the most common AEs leading to discontinuation of AZD4635 occurring in 6 (3.9%) patients and 4 (2.6%) patients, respectively, in the AZD4635 monotherapy group. All AEs leading to discontinuation of AZD4635 in the AZD4635 + durvalumab group occurred in 1 patient each.

For the AZD4635 monotherapy and AZD4635 + durvalumab patients, the most frequently reported AE of Grade 3 or higher was anemia (13 [8.5%] and 6 [6.2%], respectively). The high percentage of AEs with Grade 3 or above in the AZD4635 + docetaxel group (8 [61.5%] patients) was mainly driven by neutropenia.

CCI [redacted]

There were no significant safety concerns that preclude further development of AZD4635, either as monotherapy or in combination with durvalumab or other combination agents used in this study. Both capsule and nanosuspension formulations of AZD4635 were well tolerated.

Conclusions

- Clinical activity was observed in the mCRPC IO-naïve patients: in those who received AZD4635 monotherapy, median PFS was 8.3 (95% CI: 6.0, 15.0) weeks, and 2 (5.0%) patients had a PR. In those who received AZD4635 + durvalumab, median PFS was 14.7 (95% CI: 8.7, 29.3) weeks, 4 (10.8%) patients had a PR, and 2 (5.4%) patients had a CR. Clinical activity was not observed in other cohorts.
- Following single and multiple doses of AZD4635 monotherapy or combination therapy (nanosuspension or capsule), median tmax and geometric mean t1/2λz for AZD4635 were approximately 1 to 4 hours post dose and 9 to 17 hours, respectively, and appeared roughly similar across cohorts/different combination therapies, between monotherapy and combination therapy, and between multiple and single doses of AZD4635. For both the capsule and nanosuspension monotherapy treatments, AZD4635 PK did not appear time-dependent, and some accumulation (approximately 1.4- to 2.1-fold) of AZD4635 in plasma was observed following multiple dosing. There was negligible excretion of unchanged AZD4635 in urine over a 24-hour interval following single and multiple doses of AZD4635 monotherapy or in combination with durvalumab.

- Both capsule and nanosuspension formulations of AZD4635 were well tolerated. The most frequently reported AEs overall were nausea, fatigue, and vomiting. These AEs were also the most frequently reported AEs possibly related to AZD4635 in the AZD4635 monotherapy cohort. In the AZD4635 + durvalumab cohort, the most frequently reported AEs possibly related to AZD4635 were nausea, vomiting, fatigue, and decreased appetite. There were no significant safety concerns that preclude further development of AZD4635, either as monotherapy or in combination with durvalumab or other combination agents used in the study.