Clinical Study Report Synopsis	
Drug Substance	AZD7648
Study Code	D9170C00001
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A Phase I/IIa, Open-Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of Ascending Doses of AZD7648 Monotherapy or in Combination with either Cytotoxic Chemotherapies or Novel Anti-Cancer Agents in Patients with Advanced Malignancies

Study dates:	First patient enrolled: 09 October 2019 Last patient last visit: 07 December 2022 Date of early study termination: 07 December 2022 The reason for early study termination was a strategic business decision based on the evolving benefit-risk profile of AZD7648. The dose-limiting systemic toxicity of AZD7648 with concurrent dosing of pegylated liposomal doxorubicin (PLD) was greater than expected and there was no emerging efficacy signal to balance the emerging benefit-risk profile. Termination of enrolment was communicated to the appropriate Healthy Authorities. The analyses presented in this report are based on a clinical Data Lock date of 13 March 2023
Phase of development:	Clinical pharmacology/Therapeutic exploratory (I/IIa)
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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

The study was conducted at 2 sites in the US and 3 sites in the UK.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The study objectives and criteria for evaluation are presented in Table S1.

Table S1 Objectives and Endpoints

Objectives	Endpoints/Variable
Primary	
• To investigate the safety and tolerability of AZD7648 when given orally to patients with advanced malignancies, as monotherapy and in combination with anti-cancer agents, and define the doses and schedules for further clinical evaluation.	• AEs/SAEs. • DLTs. • Physical examination. • ECOG-PS. • Vital signs. • ECG and ECHO (Combination Module 1 only). • Laboratory data.
Secondary	
• To characterise the PK of AZD7648, following a single dose and at steady state after multiple dosing, when given orally as monotherapy and in combination with anti-cancer agents[a]. • To characterise the effect of food on AZD7648 exposure (not conducted)[b].	• AUCinf and/or AUClast after a single dose and AUCτ after multiple doses. • Cmax after a single dose and multiple doses. • tmax. • Cmin. • t½λz. • Rac. • TCP. • AUClast and Cmax ratio for food effect (applicable for food effect cohort only in the Core Module expansion phase)[b]. Other PK parameters could also be estimated.
• To understand the CYP3A4 induction potential of AZD7648 (Core Module).	• Post-dose to pre-dose 4-β-hydroxy cholesterol ratio.
• To obtain a preliminary assessment of anti-tumour activity of AZD7648 as monotherapy and in combination with anti-cancer agents.	Radiological response evaluated using RECIST 1.1 • Best percentage change in TL. • Duration of response[b]. • ORR. • PFS. • OS (Part B only)[b].

AE: Adverse event; AUCinf: Area under plasma concentration-time curve from zero to infinity; AUClast: Area under the plasma concentration-curve from zero to the last quantifiable concentration; AUCτ: Area under plasma concentration-time curve in the dosing interval τ (τ = 24 for CCI dose and τ =12 for CCI dose); Cmax: Maximum observed plasma (peak) drug concentration after multiple doses; Cmin: Minimum observed plasma concentration after multiple doses; CSR: Clinical Study Report; DLT: Dose-limiting toxicity; ECG: Electrocardiogram; ECHO: Echocardiogram; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PK: Pharmacokinetic(s); Rac: Accumulation ratio; RECIST: Response Evaluation Criteria in Solid Tumours; SAE: Serious adverse event; TCP: Dose proportionality; TL: Target lesion; tmax: Time to reach maximum plasma concentration; t½λz: Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve, calculated as ln2/λz.

[a] Pharmacokinetic analysis was done but will not be discussed in the CSR. Results and reports are available in the appendices to the CSR.

[b] Analysis was not done as the study was terminated.

Study design

This was a modular Phase I/IIa, open-label, multi-centre, study of AZD7648 administered orally, either as a monotherapy, or in combination with either cytotoxic chemotherapies or novel anti-cancer agents in patients with advanced malignancies, with intensive safety monitoring to ensure the safety of the patients.

The study consisted of 2 modules:

Core Module, which was a dose escalation part of the study with AZD7648 monotherapy administered orally in evaluable patients with advanced solid tumours. AZD7648 was administered on Cycle 0 Day 1 at a starting dose of [redacted] mg, followed by a CCI [redacted] days. From Cycle 1, AZD7648 was administered in a CCI [redacted]. Dose escalation continued following Safety Review Committee (SRC) recommendation, and provided no Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 2 adverse events (AEs) were observed. The decision to escalate AZD7648 dose followed the principles of the Bayesian adaptive design, using the available data and considering the pharmacokinetic(s) (PK) from a minimum of 2 out of 3 patients enrolled in each dose cohort. The dose-limiting toxicity (DLT) period was from the first dose until the end of Cycle 1.

Combination Module 1, which consisted of a dose escalation part (Part A) and a safety and Proof of Concept part (Part B). Part A dose escalation and de-escalation followed the principles of the Bayesian adaptive design which combined prior expectations about the dose toxicity relationship and applied the data at the end of each cohort to recommend a dose for the next cohort. An SRC reviewed evaluable patients at each cohort and assessed if the study should progress to Part B. The study was terminated before Part B was started.

Target patient population and sample size

Male and female (of non-childbearing potential) patients aged 18 years or older at the time of signing the Informed Consent From (ICF) with histological or cytological confirmation of

advanced malignancy considered to be suitable for study treatment. For Combination Module 1, patients had to be suitable for treatment with pegylated liposomal doxorubicin (PLD) as per local prescribing information.

Approximately 192 evaluable patients were planned to be enrolled in the Core Module (95 evaluable patients: 46 patients in the dose escalation and up to 49 additional patients in optional expansion cohorts) and Combination Module 1 (97 evaluable patients: 30 patients in the dose escalation with the potential for an additional 30 patients once maximum tolerate dose [MTD] has been determined, and 37 patients in the expansion cohort).

Table S2 Enrolled patients

Planned number of patients	Number of patients enrolled	Number of patients included
Core Module		
46	18	14
Combination Module 1		
30	21	16

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

AZD7648 is a white film-coated tablet for oral administration, provided by AstraZeneca as [redacted] mg, [redacted] mg, [redacted] mg, and [redacted] mg tablets ([redacted]. The [redacted] mg and [redacted] mg tablets are caplet shaped. Five batches of AZD7648 were used in this study. Individual batch numbers and further information are included in the Clinical Study Report (CSR). For Combination Module 1, the starting dose was dependent on the emerging safety and tolerability data from the Core Module.

Pegylated liposomal doxorubicin was a commercially available 2 mg/mL suspension/dispersion for intravenous (IV) infusion at an initially recommended dose of 40 mg/m2 sourced by the site. Lot numbers not available. AZD7648 was administered 4 hours from the start of the IV infusion of PLD.

Duration of treatment

AZD7648:

Patients received a single dose on [redacted], followed by a [redacted]. Duration of treatment depended on how many cycles the patient participates. In Combination Module 1, AZD7648 was dosed continually for the [redacted] cycle with the possibility of intermittent dosing being explored thereafter.

Pegylated liposomal doxorubicin:

In Combination Module 1, PLD was administered once every 4 weeks for a maximum of 6 cycles.

Statistical methods

Descriptive statistics were used for all variables, as appropriate. Continuous variables were summarised by the number of observations, mean, standard deviation, median, upper, and lower quartiles, 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 summarised by frequency counts and percentages for each category. Descriptive statistics were only presented if $n \geq 3$. If no patients had data at a given time point, then only $n = 0$ was presented. If data was available for < 3 patients, no summary statistics other than minimum, maximum, and number of observations were presented. Unless otherwise stated, percentages were calculated out of the analysis set total and for modules (Core Module, Combination Module 1)/part (Part A: dose escalation)/doses. For continuous data, the mean and median were rounded to 1 additional decimal place compared to the original data. The standard deviation was rounded to 2 additional decimal places compared to the original data. Minimum and maximum were displayed with the same accuracy as the original data. For categorical data, percentages were rounded to 1 decimal place. SAS® version 9.4 was used for all analyses. All analyses were performed on data collected before intra-patient dose escalation. Data collected after intra-patient dose escalation was presented in listings only and was flagged. The actual dose at the time of the assessment was presented in the listings.

Study population

Core Module

Eighteen patients signed informed consent and were enrolled in the study, of which 14 patients were assigned to treatment and all received the assigned treatment. None of the patients completed the treatment by End of Study (EOS; EOS is defined as the last date of the last patient undergoing the protocol-defined assessment once the Sponsor decided to terminate the study). The most frequently reported reason for discontinuation was progressive disease, reported for 9 patients (64.3%). Four patients (28.6%) were discontinued due to meeting protocol-specified withdrawal criteria, and 1 patient (7.1%) in Cohort 6: AZD7648 CCI mg CCI [redacted] discontinued treatment due to an adverse event (AE) of Enterococcus sepsis.

Of the 14 patients assigned to treatment, 5 patients (35.7%) completed the study (ie, completed all treatment until disease progression and had all protocol-specified assessments), 4 patients (28.6%) were withdrawn due to disease progression, 3 patients (21.4%) died, and 2 patients (14.3%) due to the patient's decision.

Combination Module 1

Twenty-one patients signed informed consent, and were enrolled in Combination Module 1. Sixteen patients were assigned to treatment. For Cohort 1, the SRC approved the dose AZD7648 CCI mg CCI on a CCI + PLD 40 mg/m^2, which was not the dose originally intended by AstraZeneca. The intention was to dose Cohort 1 at CCI mg CCI CCI of each CCI + PLD 40 mg/m^2. Two patients received the unintended dose of AZD7648 CCI + PLD 40 mg/m^2 and experienced DLTs. One patient had a Grade 4 neutrophil count decreased and Grade 4 stomatitis and 1 patient had a Grade 3 neutrophil count decreased. Treatment was interrupted for both patients. At an ad-hoc SRC meeting it was decided that the 2 remaining patients in Cohort 1: AZD7648 CCI mg CCI days + PLD 40 mg/m^2 would receive a lower dose of AZD7648 CCI mg CCI for CCI days) + PLD 40 mg/m^2.

All 16 patients were reported to have discontinued treatment with AZD7648 and PLD by EOS. The most frequently reported reason for discontinuation of AZD7648 was progressive disease, reported for 7 patients (43.8%). Six patients (37.5%) discontinued due to protocol-specified withdrawal criteria being met, 2 patients (12.5%) due to a reason reported as other (1 patient due to PLD infusion reaction at Cycle 1 Day 1 and 1 patient due to the investigator decision [risk of additional toxicity outweighs chances of response to single agent]), and 1 patient (6.3%) discontinued treatment due to an AE of infusion related reaction.

The most frequent reason for discontinuation of PLD was progressive disease, reported for 8 patients (50.0%). Three patients (18.8%) discontinued due to protocol-specified withdrawal criteria being met, and 3 patients (18.8%) due to a reason reported as other (1 patient due to PLD infusion reaction at Cycle 1 Day 1, 1 patient due to the investigator decision [risk of additional toxicity outweighs chances of response to single agent], and 1 patient due to previous toxicity with the combination of the 2 drugs).

Of the 16 patients, 2 patients (12.5%) completed the study, ie completed all treatments until progression and undergone all protocol-specified assessments. The most frequently reported reason for withdrawal was progressive disease, reported for 6 patients (37.5%). Two patients (12.5%) were withdrawn due to death, not related to study treatment, 2 patients (12.5%) due to an AE (infusion reaction and acute myeloid leukaemia), and 2 patients (12.5%) were withdrawn due to decision by the investigator. One patient (6.3%) was withdrawn due to the patient's decision, and 1 patient (6.3%) due to a reason, reported as other (could only do remote visits post treatment discontinuation; radiographic assessments not possible remotely. None of the patients discontinued treatment or the study due to Coronavirus disease 2019 (COVID 19).

Summary of efficacy results

Core Module

Change in target lesion size over time: Modest efficacy was observed with AZD7648 monotherapy within the dose ranges investigated in the Core Module. Four patients had decrease in lesion size from baseline. One patient in Cohort 6: AZD7648 [redacted] mg [redacted] days had a percentage change from baseline of -29.2%, and was reported with stable disease at EOS.

Best objective response: None of the patients had a complete or partial response at EOS. Of the 12 patients evaluable for objective response, disease progression was reported for 5 patients (41.7%), 2 patients (16.7%) died, 4 patients (33.3%) had stable disease, and 1 patient (8.3%) had incomplete baseline assessments.

Eastern Cooperative Oncology Group performance status (ECOG-PS) over time: No significant shifts/changes in ECOG-PS from screening/baseline to last visit before or at study treatment discontinuation were noted.

Progression-free survival (PFS): Thirteen of the 14 patients (92.9%) had a PFS event (Response Evaluation Criteria in Solid Tumours [RECIST] progressions or death), with 1 patient (7.1%) censored without a PFS event. The median (80% confidence interval [CI]) PFS was 1.91 months [1.64 - 3.42]. The PFS rate at 3 months (80% CI) was 38.46% (21.66 - 55.05), and the PFS rate at 6 months (80% CI) was 23.08% (10.20 - 38.99).

Combination Module 1

Change in target lesion size over time: Limited efficacy was observed with AZD7648 in combination with PLD in the dose ranges investigated in Combination Module 1. One patient in Cohort 1: AZD7648 [redacted] mg [redacted] days + PLD 40 mg/m^2 had a confirmed partial response after 80 weeks with a change from baseline in lesion size of -76.8%.

Best objective response: Of the 15 patients included as evaluable for objective response, 1 patient (6.7%) in Cohort 1: AZD7648 [redacted] mg [redacted] days + PLD 40 mg/m^2 had a partial response confirmed, progressive disease was reported for 6 patients (40.0%), 1 patient (6.7%) died, and 4 patients (26.7%) had stable disease after 8 weeks. Three patients (20.0%) had incomplete post baseline assessments and were deemed non-evaluable.

ECOG-PS over time: Two patients (Cohort 1: AZD7648 [redacted] mg [redacted] + PLD 40 mg/m^2 and Cohort 3: AZD7648 [redacted] mg [redacted] days + PLD 40 mg/m^2) had restricted activity at screening and by study treatment discontinuation, normal activity.

Progression-free survival: Twelve of 16 patients (75.0%) had a PFS event (RECIST progressions or death), with 4 patients (25.0%) censored without a PFS event. The median

(80% CI) PFS was 1.97 months [1.81 - 6.11]. The PFS rate at 3 months (80% CI) was 41.67% (23.61 - 58.80), and the PFS rate at 6 months (80% CI) was 33.33% (17.05 - 50.54).

Summary of pharmacokinetic results

Pharmacokinetic analyses were performed but will not be discussed in the CSR. Pharmacokinetic data will be available in the appendices to the CSR.

Summary of safety results

Core Module

The most frequently reported AEs were in the system organ class (SOC) gastrointestinal disorders (9 patients [64.3%]), followed by respiratory, thoracic, and mediastinal disorders (7 patients [50.0%]). The most frequently reported AE by preferred term (PT) was diarrhoea, nausea, anaemia, and vomiting (reported by 4 patients [28.6%] each). The most commonly reported CTCAE Grade ≥ 3 events by SOC and PT were infections and infestations (3 patients [21.4%]), respiratory, thoracic, and mediastinal disorders (2 patients [14.3%]), and gastrointestinal disorders (2 patients [14.3%]). Six patients (42.9%) experienced AEs leading to AZD7648 interruptions, while 2 patients (14.3%) experienced AEs leading to AZD7648 dose reduction. Skin and subcutaneous tissue disorders, infections and infestations, and gastrointestinal disorders were the most common AEs leading to AZD7648 dose modifications. Dose-limiting toxicities of Grade 3 (alanine aminotransferase [ALT] increased and aspartate aminotransferase [AST] increased) were experienced by 1 patient (50.0%) in Cohort 7: AZD7648 CCI , with no DLTs observed in prior cohorts.

Five patients (35.7%) experienced a serious adverse event (SAE) during study. The most commonly reported SAE by SOC was infections and infestations (3 patients [21.4%]; COVID-19, Enterococcal sepsis, infection, and urosepsis reported by 1 patient [7.1%] each). One patient in Cohort 6: AZD7648 CCI had a Grade 3 SAE of dyspnoea, headache, and pruritus on Day 26 while on treatment. The SAEs were reported as resolved without treatment, and the investigator considered the SAEs as possibly related to AZD7648. The study treatment was permanently discontinued, and the patient was withdrawn from the study.

Three patients (21.4%) in Cohort 6: AZD7648 CCI reported SAEs leading to discontinuation of AZD7648: COVID-19, Enterococcal sepsis, infection, headache, dyspnoea, and pruritus. Only the SAEs of Grade 3 headache, dyspnoea, and pruritus reported by 1 patient were assessed as possibly related to AZD7648.

Four patients died during the study, 3 patients due to the disease under investigation, and 1 patient died, 15 days after last dose and 83 days after the first dose of AZD7648, due to the SAEs of Enterococcal sepsis and COVID-19.

There were no clinically important trends or changes over time from baseline in haematology, clinical chemistry, and urinalysis parameters. Across the haematology and clinical chemistry parameters, excursions of values outside the reference ranges over time were reported; these are in line with the patient population and their disease status.

There were no notable trends observed with respect to dose for electrocardiogram (ECG), vital signs, or physical findings during the study.

Combination Module 1

The most frequently reported AEs were in the SOC gastrointestinal disorders (13 patients [81.3%]), followed by blood and lymphatic disorders (12 patients [75.0%]), and general disorders and administration site conditions (11 patients [68.8%]). The most frequently reported AE by PT was fatigue (reported by 8 patients [50.0%]), anaemia (reported by 11 patients [68.8%]), stomatitis (reported by 8 patients [50%]), nausea (reported by 7 patients [43.8%]), and neutropenia and neutrophil count decreased (reported by 5 [31.3%] and 4 [25%] patients, respectively). The most commonly reported CTCAE Grade ≥ 3 events by SOC and PT were investigations, including neutrophil count decreased (4 patients [25.0%]), blood and lymphatic disorders, including neutropenia and anaemia (2 patients [12.5%] each), and gastrointestinal disorders, including stomatitis (2 patients [12.5%]), oral pain and pancreatitis (1 patients [6.3%] each). Nine patients (56.3%) experienced AEs leading to AZD7648 interruptions, while 2 patients (12.5%) experienced AEs leading to AZD7648 dose reductions. Neutropenia and infusion related reaction were AEs leading to AZD7648 dose interruptions, reported by 1 patient (6.3%) and 2 patients (12.5%), respectively. Dose-limiting toxicities were experienced by 2 patients (100%) in Cohort 1: AZD7648 CCI [redacted] + PLD 40 mg/m^2 (1 patient had Grade 3 neutropenia and 1 patient had Grade 4 neutropenia with Grade 4 stomatitis). A DLT of Grade 3 ALT increased was experienced by 1 patient (6.3%) in Cohort 3: AZD7648 CCI [redacted] days + PLD 40 mg/m^2.

Six patients (37.5%) experienced an SAE during the study. The most commonly reported SAE by system organ class and preferred term was infections and infestations (2 patients [12.5%]; arthritis bacterial and COVID-19 reported by 1 patient [6.3%] each) and injury, poisoning and procedure complications (2 patients [12.5%]; fall, femur fracture, hip fracture, and post procedural pulmonary embolism reported by 1 patient [6.3%] each). Three patients (18.8%) patients experienced an SAE considered as possibly related to AZD7648 during the study: stomatitis, biliary obstruction, and neutrophil count decreased.

Three patients (18.8%) reported AEs leading to discontinuation of AZD7648 and/or PLD: neutropenia, infusion related reaction, and ALT increased. Only the AE of ALT increased was assessed as possibly related to AZD7648 and the AE of infusion related reaction was assessed as possibly related to PLD.

Two patients died during the study, 1 patient due to the disease under investigation and 1 patient died 17 days after last dose and 57 days after the first dose of AZD7648 due to the AEs of post procedure pulmonary embolism, cardiac arrest, and hypotension.

There were no clinically important trends or changes over time from baseline in haematology, clinical chemistry, and urinalysis parameters. Across the haematology and clinical chemistry parameters, excursions of values outside the reference ranges over time were reported; these are in line with the patient population and their disease status.

There were no notable trends observed with respect to dose for ECG, vital signs, or physical findings during the study.

Conclusion(s)

- The most frequently reported AEs were related to haematology and gastrointestinal toxicities, with additional toxicity reported with AZD7648 + PLD combination therapy.
- Overall, AZD7648 was well tolerated in the monotherapy cohorts. It was agreed with the SRC to pause the dose escalation at AZD7648 CCI mg CCI CCI and that the MTD would not be declared, to allow future studies (if deemed safe) to potentially explore further monotherapy doses above this dose level.
- The safety and tolerability profile in the AZD7648 + PLD combination therapy cohorts did not show a favourable benefit-risk profile, which contributed to early termination of the study.
- AZD7648 did not demonstrate any significant efficacy signals as monotherapy in the Core Module and only limited efficacy in Combination Module 1 when given concurrently with PLD.
- The study was terminated early based on the evolving benefit-risk profile of AZD7648. The dose-limiting systemic toxicity of AZD7648 with concurrent dosing of PLD was greater than expected and there was no emerging efficacy signal to balance the emerging safety profile and consequently did not support a favourable benefit-risk profile.