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

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Clinical Study Protocol

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Sponsor: AstraZeneca AB, 151 85, Södertälje, Sweden

EudraCT number: 2018-003688-73

VERSION HISTORY

Version 1.0, 27 November 2018

Initial creation of the 3 separate modular protocols: Core Module, Combination Module 1, and Combination Module 2.

Version 2.0, 18 March 2019

Changes to the modular protocols Core Module and Combination Module 2 are summarised below:

Changes to Core Module

On the basis of comments received from the Medicines & Healthcare Products Regulatory Agency (MHRA) in the United Kingdom, the following modifications have been made to this protocol.

Synopsis and Section 4.1.1 have been modified to specify a maximum of up to 5 additional combination modules will be added to this protocol beyond the initial 3 modules (Core Module and Modules 1 and 2). In addition, therapies to be used in combination with AZD7648 have been presented.

Inclusion Criterion 11 and Section 5.3.3 have all been updated to consistently specify (as already present in Inclusion Criterion 10) that study participants who are women of childbearing potential (WOCBP) or male must use acceptable contraceptive measures as defined in Section 5.3.3 from the time they sign the study consent through 12 weeks after the last dose of study agent.

The definition of "post-menopausal" following Inclusion Criterion 11 has been modified to state that a single FSH measurement may be used to confirm a post-menopausal state (in women not using hormonal contraception or hormonal replacement therapy) only after a subject has been amenorrhoeic for more than 12 months consistent with the Clinical Trial Facilitation Group Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials (15 Sep 2014).

Exclusion Criterion 3 has been modified to clarify that patients with active hepatitis B, hepatitis C or human immunodeficiency virus infections should be excluded from this clinical trial.

Section 5.3.3 has been modified to define vasectomized partner plus male condom as an acceptable contraceptive measure if the vasectomized partner is the sole sexual partner of the WOCBP trial participant and the vasectomised partner has received medical assessment

of the surgical success (as per the Clinical Trial Facilitation Group Recommendations Related to Contraception and Pregnancy Testing in Clinical Trial, 15 Sep 2014).

Changes to Module 2

Appendix G has been updated to consistently specify that study participants who are women of childbearing potential (WOCBP) or male must use acceptable contraceptive measures from the time they sign the study consent through 12 weeks after the last dose of study agent. In addition, Appendix G has been modified to define a vasectomized partner plus male condom as an acceptable contraceptive measure if the vasectomized partner is the sole sexual partner of the WOCBP trial participant and the vasectomised partner has received medical assessment of the surgical success (as per the Clinical Trial Facilitation Group Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials,15 Sep 2014.

Version 3.0, 09 August 2019
Changes to the protocol are summarised below:

Protocol unification. The 3 separate documents comprising the study: Core Module, Combination Module 1, and Combination Module 2, have been incorporated into one document. Sections 1 to 9, and 24 and 25 of the protocol contain information mainly related to the Core Module and the overall study. Sections 10 to 16 of the protocol contain additional information specific to the Combination Module 1. Sections 17 to 23 of the protocol contain additional information specific to the Combination Module 2.

Global formatting changes applied throughout the protocol:

- Modules 1 and 2 have been renamed to Combination Modules 1 and 2, and capitalisation has been used when referring to all modules, eg, Core Module, Combination Module 1, and Combination Module 2.
- Abbreviations are updated, as applicable.
- Minor grammatical and typographical changes applied.
- Patient Dispensing Card is changed to Patient Diary.

The schedule of assessments (SoA) tables (Table 1, Core Module; Table 14, Combination Module 1; and Table 18, Combination Module 2) have been updated as detailed below:

- Tumour gene mutations have been added as part of the medical history assessment and a footnote has been included.
- Formatting changes applied to provide clarity and consistency.

- The footnote regarding Visit Y is further clarified.
- Footnotes clarified for [redacted]
- The footnote on tumour assessments has been amended to clarify that objective disease progression needs to be confirmed.
- Pharmacokinetic (PK) scheduling times for blood have been clarified.
- 4-beta-hydroxy-cholesterol collection is not required at Visit Y (only applicable to the Core Module).

The synopsis has been updated to include treatment details for Combination Modules 1 and 2. It has also been clarified that intermittent dosing may be explored in the Core Module from Cohort 2 onwards (text is also included in **Section 6.1.2**).

The **Introduction** (section 2, and other sections within the protocol, as relevant) has been modified to clarify that safety and tolerability evaluations are the primary objectives of the study and preliminary efficacy is secondary.

Section 2.2 has been modified to include details for 2 additional studies for another DNA-PK selective inhibitor, M3814.

Exclusion Criterion 6b and 6c has been modified to include a recommended washout period for immuno-oncology agents and revised to provide further clarification to sites.

Section 6.1 has been modified to clarify target toxicity for dose escalation.

Section 6.1.2, Table 4 has been modified to include text consistent with the Cohort Management Plan.

Section 6.6 has been modified to update the platelet cut-off from ≥100 to ≥75 x 10^9/L for dose medication, to ensure consistency with dose modification guidelines. Further clarification is included on **Table 6** regarding action to be taken by sites in the event of grade 1 to 2 toxicity.

Sections 8.1.1 and 8.1.2 and Appendix H have been modified to clarify objective disease progression confirmation and that a modified response evaluation criteria in solid tumours (RECIST) 1.1 criteria will be used.

Table 8 has been modified to correct phosphatise to phosphatase.

Section 8.2.2 has been modified to further clarify physical examination timings and details (updates are also made to all the **SoA**).

Section 8.5 has been modified to remove details of plasma volumes used for analysis of PK blood samples. Text has also been added to clarify that intra-patient dose escalation is only allowed in the Core Module.

Section 8.5.1 has been modified to clarify that for the determination of PK pegylated liposomal doxorubicin (PLD) concentrations total doxorubicin will be reported (updates are also made to **Section 15.2** and **SoA Table 14**).

Section 8.5.2 has been modified to state that Covance will perform the analysis of 4β-hydroxy cholesterol.

Section 8.5.3 has been modified to include additional text on incurred sample reproducibly analysis.

Section 8.7.1 has been modified to remove text for a process which is not supported at sites/clinics.

Section 9.4.1 has been modified to clarify tumour lesion measurements (there was an error in bullet 2).

Section 9.4.1 has been modified to remove months 3, 6, and 9 from the progression-free survival rate (PFS) variable.

Section 9.4.1 has been modified to remove week 16 from the objective response rate (ORR) variable. Text has been included to clarify objective disease progression confirmation and that a modified RECIST 1.1 criteria will be used.

Section 9.5 has been modified to correct the number of interim analyses from 5 to 3.

Section 15.2 has been updated to include a table detailing PK sampling times for Combination Module 1. A similar table has also been included in **Section 22.2** for Combination Module 2.

Section 21.2 has been updated to include details of when olaparib should be taken in relation to AZD7648.

Version 4.0, 21 January 2021
Changes to the protocol are summarised below:

Grammatical, typographical, and formatting updates have been applied throughout the protocol.

Combination Module 2, AZD7648 + olaparib, has been removed from the study, as recent pre-clinical data no longer supports this combination. References to Module 2 have been removed throughout the protocol, including removal of the exploratory variable related to CCI [redacted]

A new proposed structure has been assigned to the main impurity observed in clinical batches and has led to reclassification of this impurity from class 5 (non-mutagenic) to class 3 (potential mutagenic). In line with ICH S9 and the concepts outlined in ICH Q3A(R2) the maximum clinical dose of AZD7648 will be limited to CCI mg/day (CCI mg CCI in order to limit exposure of this impurity to ≤ 1.0 mg/day while additional mutagenicity testing is conducted. Once mutagenicity testing has been completed, the dose restriction may be lifted via a further protocol amendment. Given the S9 patient population in this study, the early clinical research phase of development, and the intended treatment duration, this approach is considered appropriate and has been reviewed approved by relevant health authorities. This text is also included in **Tables 3** and **15**.

The schedule of assessments (SoA) tables (Table 1, Core Module and Table 14, Combination Module 1) have been updated:

- To include electrocardiograms for the Investigational Product Discontinuation (IP Disc) Visit.
- To include a footnote for the CCI [redacted]
- To clarify that in case of a positive pregnancy test during treatment, patients are discontinued from study treatment and not discontinued from the study. Patients will continue to be followed-up according to the study protocol.

Table 1 (SoA for Core Module) has been updated to correct the footnote for plasma CCI [redacted] at the Cycle 4 Onwards Visit.

Table 1 (SoA for Core Module) has been updated to remove ECHO=echocardiogram from the abbreviation list, as this test is not performed for this module.

Synopsis has been updated to change estimated date of last patient completed from Q3 2023 to Q2 2024.

Synopsis has been updated to revise the number of patients enrolled in the study. Patients have been removed for Combination Module 2 and for Combination Module 1 an additional 30 patients may be enrolled once maximum tolerate dose (MTD) has been determined. Sample size has been updated in **Sections 9.2** and **16.1**.

Figure 1 has been revised to remove the triple negative breast cancer (TNBC) arm and remove the subset of patients with HRR*m*-enriched ovarian cancer in treatment arm M1B1 and to remove Module 2.

Figure 2 has been updated to clarify the title.

Table 2 Study objectives the title for primary objective has been updated to match formatting of other objectives.

Sections 4.1.2, 9.2, 12.1, and 16.1 have been updated to include/clarify the number of evaluable patients and make text consistent across all modules.

Sections 4.1.2 bullet updated to harmonise with the text in Section 6.1.2 (the text in italics has been added): The planned next higher dose must be declared tolerated by the SRC *(based on assessment of 2 to 6 evaluable patients)*. Grammatical updates have also been made to the 2 other bullets in this list.

Section 4.1.4 a new section is included which gives guidance on how the study could continue in the event of a serious disruption (eg, coronavirus disease 2019 [COVID-19]) with details of mitigation that could be employed to ensure study continuity. The new text details the measures that may be implemented if a patient is not able to visit a study site to ensure that the clinical study can continue whilst minimising risk to the patient, maintaining compliance with Good Clinical Practice (GCP), and minimising risks to study integrity. These changes will only be initiated at a time of study disruption. **Appendix J** has also been included to provide further details.

Inclusion Criterion 11 has been updated to revise the definition of post-menopausal based on the Clinical Trial Facilitation Group Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials (version 1.1, 21 Sep 2020).

Exclusion Criterion 7 has been updated to clarify which steroid treatments are not permitted.

Exclusion Criterion 12e has been updated to clarify that for patients with documented/suspected Gilbert's disease bilirubin is ≥ 2 x upper limit normal (ULN) for exclusion.

Exclusion Criterion 12f has been updated to clarify that for aspartate aminotransferase or alanine aminotransferase the ULN for patients with liver metastases is ≥ 5 x ULN.

Exclusion Criterion 18 has been added: For food effect cohort only: insulin-dependent diabetes.

Exclusion Criterion 19 has been added for history and/or presence of COVID-19.

Section 5.4 has been updated to clarify that screen failures are patients who sign the informed consent but are not subsequently dosed with study treatment. The text has also been revised to clarify that the reason for screen failure is recorded in the case report form (CRF).

Tables 3 and 15 have been updated to include a CCI mg dosage formulation for AZD7648 and text is added to clarify that the tablets are oral and that intermediate strengths may be added at a later date.

Sections 6.1.2 Dose escalation scheme – Core Module:

- Text has been updated to clarify that sentinel dosing is applied 48 hours after Cycle 1, Day 1.
- Text has been updated to clarify that if enrolment is halted within a cohort the Safety Review Committee (SRC) will review all safety data, but review of the pharmacokinetic data was only required for Cohorts 1 to 4. This is also updated in **Table 4** and elsewhere in this section. Text in **Section 6.1.4** is also updated.
- The Illustrative Dose Escalation Schedules in **Tables 4 and 16** have been updated to reflect revised possible AZD7648 doses; to add Cohort n (escalate to MTD or maximum feasible dose [MFD]); to specify maximum CCI mg (CCI mg CCI dose levels and dosing days; and in Combination Module 1, to specify expected starting cohorts. Footnotes are also included for further information on maximum dose limit.
- Text has been updated to clarify that for SRC meetings prior to dose escalation where 3 patients have been enrolled, at least 2 patients will need to be evaluable for dose-limiting toxicity. This update is also applied to **Section 14.1.2**.
- Text has been updated to clarify the evaluable patient definition for dose escalation in Part A (the text in italics has been added):
  Has completed minimum safety evaluation requirements and has received at least 75% of the total amount of planned dose of AZD7648 (*and PLD for Combination Module 1*) during Cycle 1.
- The text describing the triggers for starting the additional modules has been updated (text struck-through and text in italics has been added):
  •Total drug exposure levels ≥ 50% of that predicted to be required for biological activity for a period defined for the specific combination. It is anticipated that the combination module will be triggered ~~after the CCI mg monotherapy cohort is declared~~

~~safe and tolerated~~ *once exposure (based on clinical PK exposure and emerging safety and tolerability data) is determined to be in a suitable therapeutic range.*

Section 6.1.2.1 the text related to administration of study drug and the fasted state in the food effect expansion cohort has been revised to be consistent with text in **Appendix I**. The time interval between Cycle 0, Day 1 and Cycle 1, Day 1 in both **Section 6.1.2.1** and **Appendix I** has been updated to 72 hours to allow for adequate washout. In this section the following sentence has also been deleted: Patients with insulin-dependent diabetes must be excluded from the food effect cohort, as this has been added as a new Exclusion Criterion.

Section 6.1.3 the grade for haematological toxicities for neutropenia and thrombocytopenia have been updated from grade 3 to grade ≥ 3 and therefore the lower limits have been removed. Units are also presented as mm^3 and 10^9/L. These changes are also applied to **Section 22.1**.

Section 8.4.2.1 clarification added that patients who become pregnant should be discontinued from study treatment but not from the study.

Table 10, Table 11, Table 12, and Table 17 have been updated to clarify post dose sampling timings for PK/CCI [redacted].

Section 8.6.3 the tumour biopsy collection times have been updated in line with the footnote on the SoA.

Section 9.2 has been updated to correct the cohort size from n =3 to 6 to n =1 to 6.

Section 9.4.1 has been modified to clarify that the starting point for the efficacy analyses for progression-free survival and overall survival should be the first dose at Cycle 1.

Table 13 has been revised to remove the TNBC arm and remove the subset of patients with HRR*m*-enriched ovarian cancer from the interim analysis for Combination Module 1.

Table 14 (SoA for Combination Module 1) has been updated as follows:

- **Parts A and B** have been updated to correct the cross-reference for echocardiograms (section 8.2 did not include details). **Section 15.2** has been added to describe echocardiograms.
- **Parts A and B** have been updated to include a tumour assessment from Cycle 3 and onwards Visits. The tumour assessment at the IP Disc Visit has been removed from Part A to be consistent with the other SoAs.
- **Part B** has been updated to add sample collections for CCI [redacted] and CCI [redacted] CCI [redacted] at the Cycle 1 Day 8 Visit, and to update the footnote for the CCI [redacted] sample at the Cycle 1 Day 15 Visit.

- **Parts A and B** have been updated to revise the AZD7648 dosing in line with updates made in Table 16. The footnotes are also updated to clarify dosing.

Figure 8 presenting breast cancer xenograft mean tumour volume has been replaced with an ovarian cancer figure.

Section 12.1 Part B of the study design (Combination Module 1) has been updated to remove the subset of patients with HRR*m*-enriched ovarian cancer. Text describing the use of pre-existing results and validation by accredited laboratories has been removed.

Section 12.3.1 the justification for the AZD7648 dose for Combination Module 1 has been revised.

Section 13.3 has been updated to add a reference to Appendix G for contraception restrictions.

Figure 9 has been revised to remove breast cancer from Part B.

Section 15.4 has been updated to remove reference to the HRR*m* patient biomarkers.

Section 16.1 text is updated as indicated in italics and strikethrough: a patient ~~systemic~~ *systematic* allocation algorithm will be followed. Text regarding prospective testing to confirm patients have advanced platinum-resistant ovarian cancer has been removed.

Appendix A 6 link updated from astrazenecaclinicaltrials.com to https://astrazenecagrouptrials.pharmacm.com.

Appendix G contraceptive requirements applicable to Combination Module 1 have been updated.

Version 5.0, 01 October 2021
Changes to the protocol are summarised below:

Grammatical, typographical, and formatting updates have been applied throughout the protocol.

Table 1 has been updated; the PK footnotes have been updated to refer to Table 10 for further details on sampling times for blood and urine collections.

Table 1 and Table 13 have been updated to further clarify that the pharmacogenetic sample is optional (a bracket was added to the (X) in column Cycle 1, Day 1) and a cross reference has been added to the Genetics Appendix D to provide further details.

Sections 4.1.2, 4.3.1, 6.1.2.1, and 6.1.3.2, and Tables 3, 4, 14, and 15 have been updated. Following a negative AMES test result which demonstrated that the main impurity did not have any mutagenic potential, the text related to mutagenicity testing and reduced dose range incorporated in Protocol Version 4 has been removed and the original text and AZD7648 dose ranges have been added.

Section 4.1.2 has been updated to correct the evaluable patient numbers in line with the rest of the CSP (**Section 9.2** has also been updated).

Section 4.4 has been updated to define a data cut-off point for each module or study part.

Section 6.1.2 has been updated to clarify that at the recommended Phase II dose (RP2D) up to 12 patients may be treated to explore chronic toxicity, as described in **Section 9.2**. The sample size and number of patients have also been updated in **Sections 9.2** and **1.2** to include 6 additional patients.

Section 6.1.3 confirmed laboratory abnormalities will need to be greater than 72 hours of duration to be considered a dose limiting toxicity (DLT); this has been reworded to exclude non-significant laboratory abnormalities.

Section 6.5.2 has been updated to provide advice on the administration of coronavirus disease 2019 (COVID-19) vaccinations during the study.

Section 8.1.2 text has been updated for tumour response data and objective response rate (ORR) efficacy analyses based on the SAP. The modified RECIST criteria will not be used for the ORR analysis for the Core Module or Combination Module 1 (**Section 9.4.1** has also updated).

Sections 8.4.2.1 and 8.4.2.2, and Appendix B2 have been revised to reword congenital abnormalities/abnormality to congenital anomalies/anomaly.

Section 8.6.1.1 and Table 12 the timings for the collection of peripheral blood samples for CCI has been changed from 2 to 8 hours post-dose to 2 to 4 hours post-dose for AZD7648. The footnotes (p and q) in **Table 1** have been updated to reflect these changes.

Section 8.6.1.4 and footnotes in Tables 1 and 13 (Part A and Part B) have been updated to include the collection of additional blood samples if immune-related events are suspected, to investigate safety signals.

Section 9.3 has been updated to reflect text used in the Statistical Analysis Plan (SAP). Two additional analysis sets “Evaluable for objective response” and “DLT evaluable set” have been added, and one has been removed (“Tumour biopsy set”).

Section 9.4.3.1 the statistical analysis for the assessment of pharmacokinetic food effect has been updated based on the SAP.

Section 9.5 has been moved to **Section 16** as the interim analysis applies to Combination Module 1 only. It has also been updated to remove text stating that the sample size for the interim analysis will be approved AstraZeneca governance.

Table 13 (Part A and Part B) has been updated to add footnotes to the Day Y and Day 8 columns to add further clarity for these visits.

Section 12.1 the wording regarding intermittent dosing schedules for the Combination Module 1 has been updated to clarify that intermittent schedules will be required.

Section 14.1.1, Table 14 has been updated to amend the starting dose instructions for AZD7648 in relation to PLD dosing for Combination Module 1.

Section 14.1.2 text for sentinel dosing has been added for Combination Module 1.

Section 15.3, Table 16 PK sampling times have been revised. For Part A Cycle 1, Day 1 the AZD7648 sample will be collected 2 hours (h) post-dose instead of 1 h to align with Tmax. The PLD samples will be taken 4 h after start of PLD infusion. The 10 to 12 h AZD7648 samples have been removed and 6 h samples will be taken instead (to reduce patient burden/time at site). The PK footnotes in **Table 13** (SoAs Part A and Part B) have been updated to refer to **Table 16** for further details on sampling times.

Section 15.4 has been added to include details for the collection of blood samples for CCI [redacted] in relation to PLD dosing in Combination Module 1 (including addition of **Table 17**). The footnotes in **Table 13** (Part A and Part B) have been updated to include relevant details.

Appendix D has been updated to correct the visit for collection of the sample for genetic research (it was changed from Visit 6 to the Cycle 1, Day 1 Visit).

Appendix H has been updated to state that CCI [redacted] will be used in an exploratory analysis.

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1 PROTOCOL SUMMARY

The structure of the protocol will follow a modular design. Sections 1 to 9, 16 and 17 of the protocol contain information mainly related to the Core Module and the overall study. Sections 10 to 16 of the protocol contain additional information specific to Combination Module 1. Further details on study design can be found in Section 4.1.1.

1.1 Schedule of Assessments – Core Module

The SoA for Combination Module 1 can be found in Section 10.1.

Table 1 Schedule of assessments – Core Module

	Screening	Single Dose				Multiple Dose									IP Disc	28-day FU After IP Disc	Details in Section
		Cycle 0				Cycle 1[a] Weekly Visit[b]					Cycle 2[a]		Cycle 3[a]	Cycle 4[a] On wards			
Day	**-28 to -1**	**1**	**2**	**3**	**4**	**1**	**Y[c]**	**8**	**15**	**22**	**1**	**15**	**1**	**1**			
Visit Window[d]	**-**	**-**	**-**	**-**	**-**	**-**	**-**		**-**	**-**	**±1**	**±1**	**±2**	**±2**	**-**	**±7**	
Informed consent	X																5.1
Demographics and medical history, including tumour gene mutations[e]	X																5.1
Physical examination	X	X	X[f]			X	X[f]	X[f]			X		X[f]	X[f]	X[f]	X[f]	8.2.2
Height	X																
Weight	X	X				X	X	X	X	X	X	X	X	X	X	X	8.2.3
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.2.4
ECG[g]	X	X	X	X	X	X	X	X			X		X	X	X		8.2.5
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.5
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[h]	X	8.3
Pregnancy test[i]	X	X[i]				X[i]					X		X	X	X		5.1
Haematology, coagulation, chemistry, urinalysis, tumour marker, TSH[j]	X	X				X	X	X	X	X	X	X	X	X	X	X	8.2.1
ECOG PS	X	X				X	X	X			X		X	X	X		8.2.6
Archival tumour[k]	X																8.8
Fresh tumour biopsy with biomarker analyses[l]	X						X	X							X		8.6.3
PK AZD7648 blood [m]		X	X	X	X	X	X	X			X		X		X		8.5

	Screening	Single Dose				Multiple Dose									IP Disc	28-day FU After IP Disc	Details in Section
		Cycle 0				Cycle 1[a] Weekly Visit[b]					Cycle 2[a]		Cycle 3[a]	Cycle 4[a] On wards			
Day	**-28 to -1**	**1**	**2**	**3**	**4**	**1**	**Y[c]**	**8**	**15**	**22**	**1**	**15**	**1**	**1**			
Visit Window[d]	**-**	**-**	**-**	**-**	**-**	**-**	**-**		**-**	**-**	**±1**	**±1**	**±2**	**±2**	**-**	**±7**	
PK AZD7648 urine[n]		X						X									8.5
4-beta-hydroxy-cholesterol		X						X			X						8.5.2
PD blood biomarker[o]	X					X^{p}	X^{q}	X^{q}			X^{p}				$X^{r,s}$		8.6.1.1 8.6.1.4
CCI	X					X^{p}	X^{q}	X^{q}	X^{q}		X^{p}	X^{q}	$X^{q,r}$	$X^{q,r}$	X^{r}		8.6.1.2
CCI	X					X^{p}	X^{q}	X^{q}	X^{q}		X^{p}	X^{q}	$X^{q,r}$	$X^{q,r}$	X^{r}		8.6.1.3
Tumour assessment	X												X^{t}	X^{t}			8.1.1 8.1.2
PGx (optional)						(X)											8.7
																Appendix D	
CCI		X				X	X	X	X	X	X	X	X	X			6.1
Patient diary dispensed	X																6.4

AE=Adverse Events; CCI; CCI DNA; ECG=Electrocardiogram; Disc=discontinuation; ECOG PS=Eastern Cooperative Oncology Group performance status; FU=Follow-up; IP=Investigational Product; PD=Pharmacodynamics; PGx=pharmacogenetic sample; PK=Pharmacokinetics; TSH=Thyroid stimulating hormone.

[a] 1 cycle = 28 days. Cycles repeat on a continuous basis with no interval between cycles.

[b] Weekly visit may be omitted if Visit Y is within 2 days of weekly visit.

[c] Visit Y is only utilised if the dosing schedule is intermittent. Visit Y represents the last AZD7648 dosing day in the first block of AZD7648 treatment in a cycle eg, CCI

[d] There are no visit windows in Cycle 0 and Cycle 1.

[e] With the patient's consent, as part of the medical history, any available information on known tumour gene mutations will be collected.

[f] Targeted physical examinations only required if clinically indicated (indication should be stated).

[g] Vital signs then ECG measurements will be collected prior to PK blood draws at all PK sample timepoints. Timepoints may be modified based on initial data obtained.

[h] Serious adverse events (SAEs) only to be collected between AZD7648 discontinuation and disease progression

[i] Women of child-bearing potential must have a negative urine or serum pregnancy test at screening, a confirmatory test before treatment on Day 1 (Cycle 0 or Cycle 1), at regular intervals during treatment and at AZD7648 discontinuation. If results are positive, the patient is ineligible/must be discontinued from study treatment and not discontinued from the study. The patient will continue to be followed up according to the study protocol.

[j] TSH to be measured at baseline and every 3 cycles. CRP to be collected at baseline, then on Day 1 from Cycle 1. Urinalysis at Cycle 0, Cycle 0+1 and Day 1 of each cycle. Tumour markers (if relevant) to be measured at baseline and on Day 1 of every cycle from Cycle 1 (only if elevated at baseline).

[k] Provision of archival tumour samples is mandatory for all patients. The samples may be submitted retrospectively.

[l] Fresh biopsy samples are encouraged in Part A (particularly in patients with accessible tumours) and are mandatory for patients enrolled into Part A PD expansion cohorts (or a PD subgroup of an efficacy expansion cohort). Serial biopsies will be collected during screening, on treatment (any time in Cycle 1 between Day 3 and Day 8 [or Y] 2 to 8 hours [h] post AZD7648 dosing), and on progression.

[m] Please refer to Table 10 for PK blood sample collection schedule. The date and time of blood draw should be noted for all samples. Cycle 0 PK bloods samples may discontinue once sufficient safety and PK data has been collected. For patients who undergo intra-patient dose escalation, please collect pre-dose and 1 h at the time of escalation (Cycle X, Day 1) and after one cycle (Cycle X+1, Day 1). The PK collection for the food effect cohort is listed separately in Section 8.5.

[n] Please refer to Table 10 for urine PK sample collection schedule. The urine PK sampling may discontinue once sufficient safety and PK data has been collected.

[o] CCI [redacted]

[p] Collect samples pre-dose and 2 to 4 h post-dose AZD7648 on Cycle 1, Day 1 and Cycle 2, Day 1 only (or nearest weekly visit if within 2 days), note time of blood draw.

[q] Only collect sample 2 to 4 h post–dose AZD7648 noting time of blood draw.

[r] From Cycle 3 Day 1, sample should be taken on each radiological assessment (±7 days), disease progression or treatment discontinuation.

[s] If any immune-related events are suspected, additional blood samples may be taken for further safety signal investigation.

[t] Tumour assessments should be conducted every 8 weeks (±1 week) from start of treatment (Cycle 1, Day 1) until confirmed objective disease progression; frequency may be adjusted after 2 years of treatment if the tumour is not changing in size (complete response [CR], partial response [PR], or stable disease [SD]).

[u] On clinic days, patients should not take the study treatment until instructed to do so by clinic staff.

1.2 Synopsis

Principal Investigator:

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Houston, Texas
77030
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Protocol Title:

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

Rationale:

In cancer cells, defective DNA damage response (DDR) promotes genomic instability, neoplastic transformation and proliferation. Such instability results in the formation of highly destructive double-strand breaks (DSBs) and cell death. DNA dependent protein kinase (DNA-PK) overexpression renders tumours resistant to DNA damage; therefore DNA-PK inhibition is an attractive therapeutic strategy. Preclinical data from both in vitro and in vivo systems supports this hypothesis and provides the rationale required to explore the clinical potential of the DNA-PK selective inhibitor AZD7648.

Study Design:

This is 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. The modular design allows for an escalation of the dose of AZD7648 alone or in combination with either cytotoxic chemotherapies or novel anti-cancer agents, with intensive safety monitoring to ensure the safety of the patients.

The study consists of 2 modules each evaluating the safety and tolerability of AZD7648 monotherapy or with a specific combination partner. The initial components are a Core Module of AZD7648 monotherapy and Combination Module 1 (AZD7648 in combination with pegylated liposomal doxorubicin [PLD]). Up to 5 additional combination modules may be added via a formal amendment (see Section 4.1.3) to allow further evaluation of AZD7648 in defined populations or novel combinations. These may include i) combination with a DDR agent eg, ataxia telangiectasia and Rad3-related protein (ATR) inhibitor; ii) combination with an immuno-oncology agent eg, a programmed death-ligand 1 (PD-L1) inhibitor; iii)

combination with a cytotoxic agent eg, paclitaxel; iv) combination with an antibody-drug conjugate; and v) combination with radiotherapy.

Combination Module 1 has 2 study parts: Part A consisting of dose escalation cohorts and Part B, a safety and proof of concept (PoC) Phase IIa expansion. Part A dose escalation and de-escalation will follow the principles of the Bayesian adaptive design which combines prior expectations about the dose toxicity relationship and applies the data at the end of each cohort to recommend a dose for the next cohort. A Safety Review Committee (SRC) will review evaluable patients at each cohort and assess if the study should progress to Part B. Optional expansion cohorts may also be triggered in Part A dose escalations, enrolling additional patients at appropriate dose(s) to explore further the safety, tolerability, pharmacodynamics (PD), pharmacokinetics (PK), biological activity and effect of food.

Main Objectives:

The primary objective is 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 to define the doses and schedules for further clinical evaluation.

Secondary objectives are i) to characterise the PK of AZD7648, following a single dose and at steady state after multiple doses, when given orally as monotherapy and in combination with anti-cancer agents, and to characterise the effect of food on AZD7648 exposure (if conducted); ii) to obtain a preliminary assessment of anti-tumour activity of AZD7648 as monotherapy and in combination with anti-cancer agents.

Tertiary/exploratory objectives are described in Section 3.

Study Period:

Estimated date of first patient enrolled: Q4 2019

Estimated date of last patient completed: Q2 2024

Number of Patients:

Approximately 192 evaluable patients may 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).

Treatments and Treatment Duration:

For the Core Module, a single dose of AZD7648 will be administered in the clinic (Cycle 0, Day 1) to enable collection of blood samples for PK analyses. This will be followed by a drug washout (no dose) of 3 to 7 days prior to Cycle 1, Day 1 AZD7648 administration.

In cohort 1, at Cycle 1, Day 1, the starting dose of AZD7648 will be [redacted] mg [redacted] on a continuous [redacted]. There is no interval between cycles. Using an accelerated titration design, dose escalation may occur with single patient cohorts up to and including [redacted] mg [redacted]. From [redacted] mg [redacted], a minimum of 3 patients will be enrolled into each dose cohort. Dose escalation will stop at the MTD, maximum feasible dose (MFD), or the recommended Phase II dose (RP2D). From Cohort 2 onwards, intermittent dosing schedules for AZD7648 may be explored.

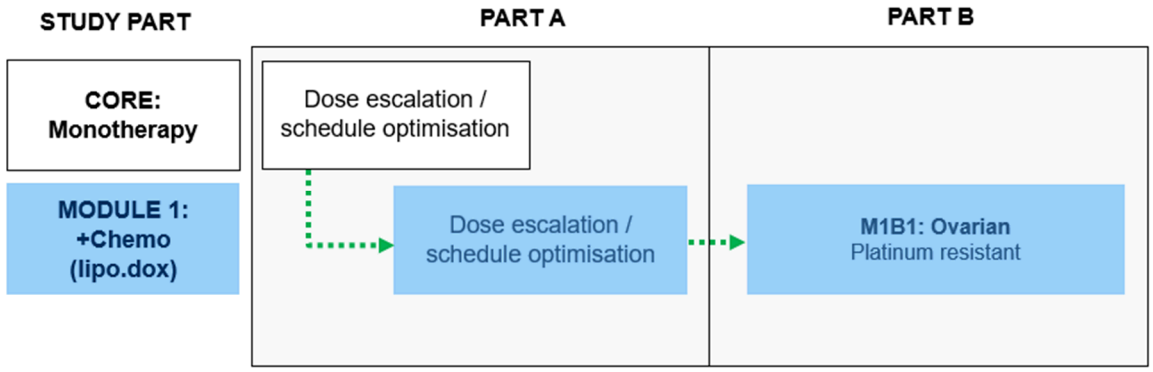
For Combination Module 1 the starting dose of AZD7648 is dependent on emerging safety and tolerability data from the Core Module. Intermittent dosing schedules for AZD7648 may be explored.

For Combination Module 1 the starting dose of PLD is 40 mg/m^2, administered by intravenous (IV) infusion once every 4 weeks, for a maximum of 6 cycles. AZD7648 will be administered 4 hours from the start of the IV infusion of PLD.

1.3 Schema

The general study design is shown in Figure 1.

Figure 1 Study design



Lipo.dox=pegylated liposomal doxorubicin.

2 INTRODUCTION

Study D9170C00001 is a Phase I/IIa, open-label, multi-centre, study of AZD7648 administered orally, either as monotherapy, or in combination with either cytotoxic chemotherapies or novel anti-cancer agents to patients with advanced malignancies. The modular design allows the evaluation of the safety, tolerability, and preliminary efficacy of multiple study treatments. The Core Module will investigate AZD7648 as a monotherapy, and Combination Module 1 will investigate AZD7648 administered in combination with pegylated liposomal doxorubicin (PLD).

Details related to study rationale, background and benefit/risk assessment for Combination Module 1 can be found in Section 11 (see Section 4.1.1 for further details on the modular structure).

2.1 Study rationale

The CCI . In cancer cells, CCI . Such instability results in an accumulation of CCI CCI . CCI Preclinical data from both in vitro and in vivo systems CCI

2.2 Background

DNA damage events occur frequently in any living cell and various mechanisms have evolved to deal with them. Different forms of DNA damage trigger responses by different repair mechanisms and signalling pathways (Figure 2).

Among DNA damage lesions, DSBs are the most cytotoxic. They induce cell cycle arrest and cell death if left unrepaired. NHEJ pathway of DSB repair occurs independently but is preferentially used during the early G1/S phases, where no template sister chromatid is available (Hartlerode and Scully 2009). This contrasts with the second major pathway of DSB repair, homologous recombination (HR), which occurs primarily in G2/M phases of the cell cycle when undamaged sister chromatids are available (San Filippo et al 2008).

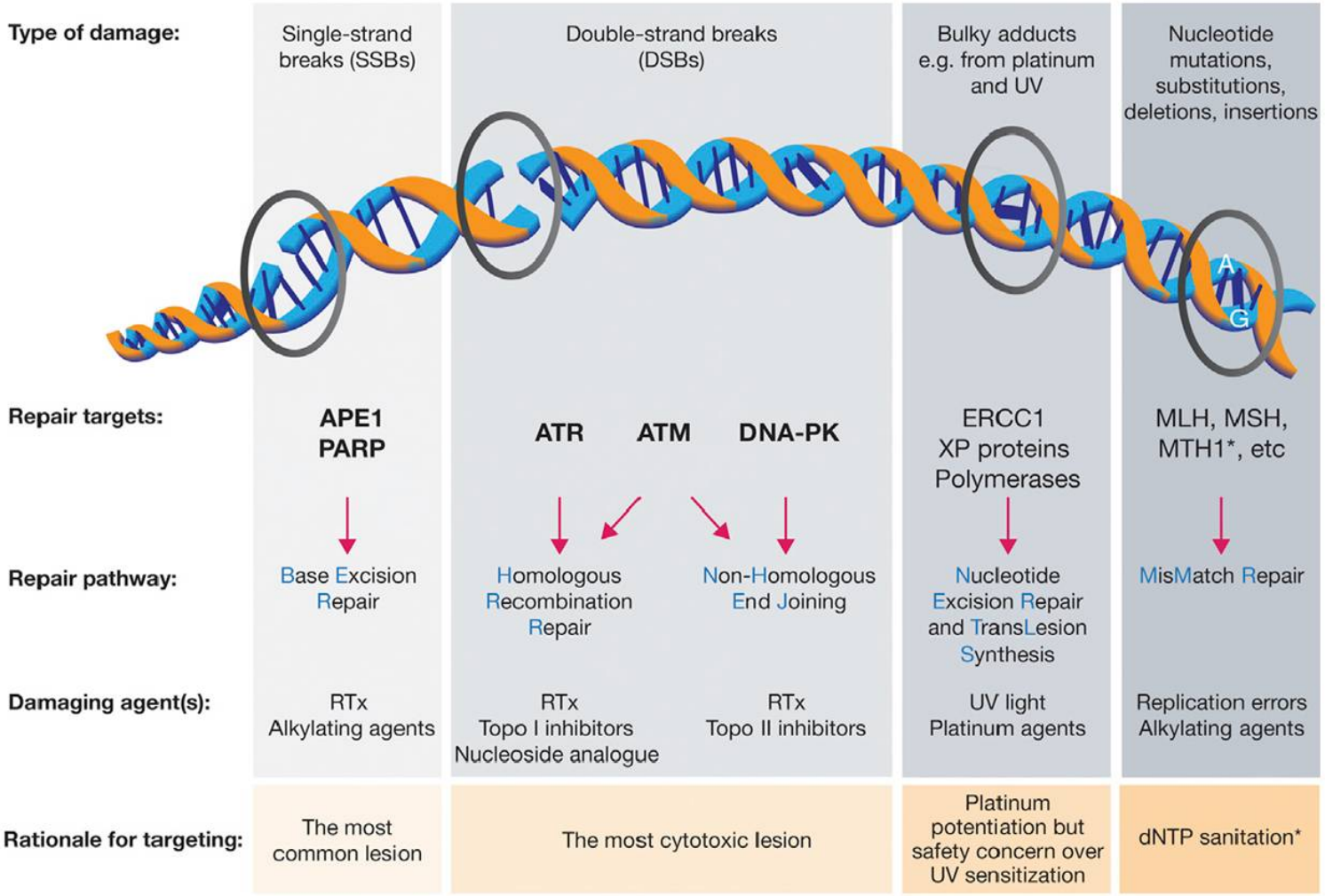
DNA-PK is a member of the phosphatidylinositol 3-kinase-related kinase (PIKK) family (that includes ataxia telangiectasia mutated [ATM] and ATR) and is a key modulator for the NHEJ

pathway of DNA repair elicited by DSBs (Jackson et al 1993) and for V(D)J recombination, a process that utilises NHEJ to promote immune system diversity (Blunt et al 1995).

DNA-PK is activated when it is recruited to DSBs by Ku70/80 heterodimer. Autophosphorylation of the DNA-dependent protein kinase catalytic subunit (DNA-PKcs), is critical for the regulation of DNA-end processing, enzyme inactivation, and complex dissociation (Chan et al 2002). Activated DNA-PKcs promotes DNA-end tethering (Graham et al 2016) which prevents DNA degradation by exonucleases (Yoo and Dynan 1999) and alters the activity of a wide range of substrates that mediate DNA-end processing and resolution (Figure 3) (Neal and Meek 2011).

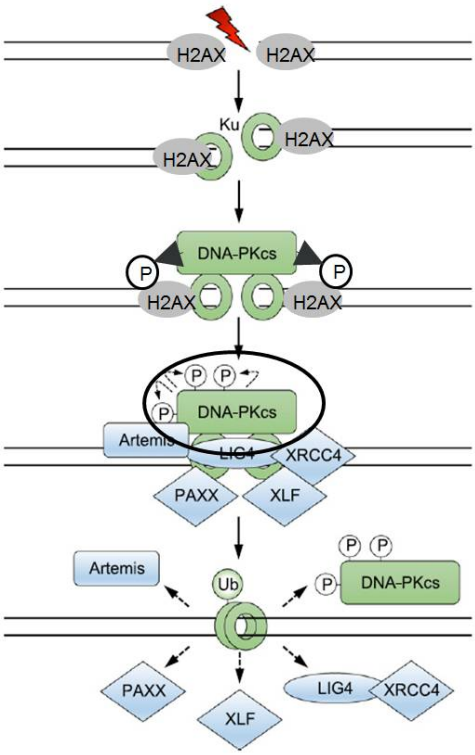
DNA-PK has also been implicated in a range of other biological processes, including modulation of chromatin structure, telomere maintenance, transcriptional regulation, and the response to replication stress (Figure 4) (Goodwin and Knudsen 2014).

Figure 2 DNA damage repair pathways including non-homologous end joining pathway



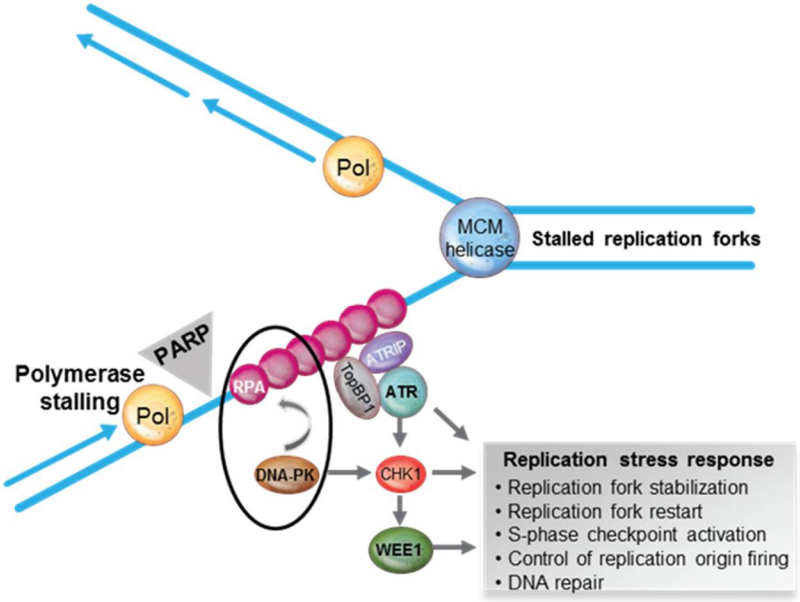
DNA-dependent protein kinase (DNA-PK) adds non-homologous end joining (NHEJ) repair targeting to the DNA damage response agent (DDR) portfolio.
APE1=apurinic/apyrimidinic endonuclease; ATM=ataxia telangiectasia mutated; ATR=ataxia telangiectasia and Rad3-related protein; PARP=poly ADP ribose polymerase; RTx=treatment; UV=ultraviolet; XP=xeroderma pigmentosum.

Figure 3 Role of DNA-PK in non-homologous end joining repair pathway



Phosphorylation of H2AX at DNA double-strand breaks (DSB) and auto-phosphorylation of DNA-dependent protein kinase catalytic subunit (DNA-PKcs) S2056 during non-homologous end joining (NHEJ) repair.

Figure 4 Role of DNA-PK in replication stress response



Phosphorylation of RPA32 by DNA-dependent protein kinase (DNA-PK) during replication stress response. Adapted from O'Connor 2015.

Upregulation of DNA-PK has been reported in various tumour types, correlates with poor clinical prognosis, and has been shown to correlate with decreased response to DNA damaging agents and therapeutic resistance in multiple cancers, such as colorectal cancer, oesophageal cancer, oral squamous cell carcinoma, and neuroblastoma (Goodwin and Knudsen 2014, Shintani et al 2003, Hosoi et al 2004, Shintani et al 2003, Tonotsuka et al 2006, Dolman et al 2015, Beskow et al 2009).

The concept of targeting DNA-PK as an anti-cancer strategy is based on exploiting tumour dependence on NHEJ repair. Synthetic lethal interactions have been identified between DNA-PK and multiple damage response factors including ATM and HR proteins suggesting that a DNA-PK inhibitor may show efficacy as monotherapy in specifically selected genetic backgrounds (Gurley et al 2001, Oken et al 1982, Riabinska et al 2013, Dietlein et al 201). Furthermore, combining a DNA-PK inhibitor with agents that increase levels of DNA DSBs in cells – such as radiation, topoisomerase 2 inhibitors (eg, doxorubicin) represents another rational strategy for clinical development of DNA-PK inhibitor.

There is currently one other DNA-PK selective inhibitor, M3814, known to be undergoing clinical trials. A Phase I study (NCT02316197) of M3814 showed that the drug was safe and tolerable at doses up to 400 mg BID with limited single-agent activity (Van Bussel et al 2017) and a Phase Ia/b study is now being conducted in combination with radiation and chemoradiation (NCT02516813). Preliminary results from 16 patients dosed across 3 cohorts (100 mg, 200 mg, and 400 mg once daily [QD]) in combination with radiation have shown that the combination was well tolerated, although some Grade 3 events of mucositis and odynophagia were observed. Two dose-limiting toxicities (DLTs) were observed at 400 mg QD therefore 300 mg QD is being explored. Initial efficacy data from 12 evaluable patients was reported to have 1 complete response (CR), 4 partial responses (PR) and 7 stable disease (SD) (Van Triest et al 2018). Two additional studies are also recruiting patients: a Phase I study (NCT03724890) to evaluate RP2D and/or MTD of M3814 in combination with avelumab with and without radiotherapy in solid tumours; and a Phase Ib/2 study (NCT03770689) to first define RP2D of M3814 in combination with capecitabine and radiotherapy followed by evaluation of the combination efficacy in patients with locally advanced rectal cancer. There are 2 other DNA-PK drugs, SF-1126 and CC-115, in Phase I clinical trials but, unlike AZD7648 and M3814, they are known to be multi-kinase inhibitor and dual-kinase inhibitor respectively.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD7648 is provided in the Investigator's Brochure (IB).

2.3 Benefit/risk assessment

The Core Module of the study is a first time in human (FTIH) Phase I/IIa dose escalation study with the DNA-PK inhibitor AZD7648. Detailed information about the known and

expected benefits and risks of AZD7648 may be found in the IB. The study design aims to minimise potential risks and although the potential benefits in patients are unknown at this time, non-clinical data demonstrates evidence of anti-tumour activity. Thus, the benefit/risk assessment for this Phase I/IIa study appears acceptable based on the lack of effective alternative treatments, the limited life expectancy due to malignant disease, and the strength of the scientific hypothesis under evaluation.

3 OBJECTIVES AND ENDPOINTS

Table 2 Study objectives

Primary objective:	**Endpoint/Variable:**
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	Adverse events (AEs)/serious adverse events (SAEs) DLTs Physical examination Eastern Cooperative Oncology Group performance status (ECOG PS) Vital signs Electrocardiogram (ECG) and Echocardiogram (ECHO; Combination Module 1 only) Laboratory data
Secondary objectives:	**Endpoint/Variable:**
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. To characterise the effect of food on AZD7648 exposure (if conducted)	Area under the curve (AUC) and/or AUC_{0-t} after a single dose and AUC_{tau} after multiple doses. Maximum plasma concentration (C_{max}) after a single dose and $C_{max,ss}$ after multiple doses Time to reach maximum plasma concentration (t_{max}) Minimum plasma concentration at steady state ($C_{min,ss}$) Half-life ($t_{1/2}$) Accumulation ratio Dose proportionality AUC_{0-t} and C_{max} ratio for food effect
To understand the cytochrome P450 3A4 (CYP3A4) induction potential of AZD7648	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 response evaluation criteria in solid tumours (RECIST) 1.1 • Percentage best change in target lesion (TL) • Duration of response • Objective response rate (ORR) • Progression-free survival (PFS) • Overall Survival (OS) (Part B only)

Tertiary/Exploratory objectives:	Endpoint/Variable:
CCI	CCI CCI
CCI	CCI CCI CCI CCI CCI CCI
CCI	CCI : CCI CCI CCI
CCI	CCI
CCI	CCI CCI CCI CCI
CCI	CCI

4 STUDY DESIGN

4.1 Overall design

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

For an overview of the study design see Figure 1, Section 1.3. For study flow charts and details of treatments given during the Core Module and Combination Module 1 see Sections 6.1, and 14.1, respectively.

For details on what is included in the safety, efficacy and exploratory endpoints, see Section 3 Objectives and Endpoints (applicable to the Core Module and Combination Module 1).

4.1.1 Modular protocol structure

The structure of the protocol will follow a modular design.

The initial module will be a Core Module relating to AZD7648 monotherapy. Additional combination modules may be added as described below, via a formal amendment, based on emerging supportive preclinical data and study rationale. The decision to initiate a combination module once regulatory approvals have been obtained will be made by the SRC. The starting dose/schedule of AZD7648 in further combination modules will not exceed the equivalent maximum exposure of AZD7648 found to be tolerated in the core module or from other studies in the clinical programme at that point.

List of Modules

The following starting modules for the study are included within this protocol.

1 **Core Module**: AZD7648 Monotherapy. Part A, dose escalation (which may include a food effect cohort)

2 **Combination Module 1**: AZD7648 + PLD. Part A, dose escalation and Part B, safety and PoC Phase IIa expansions

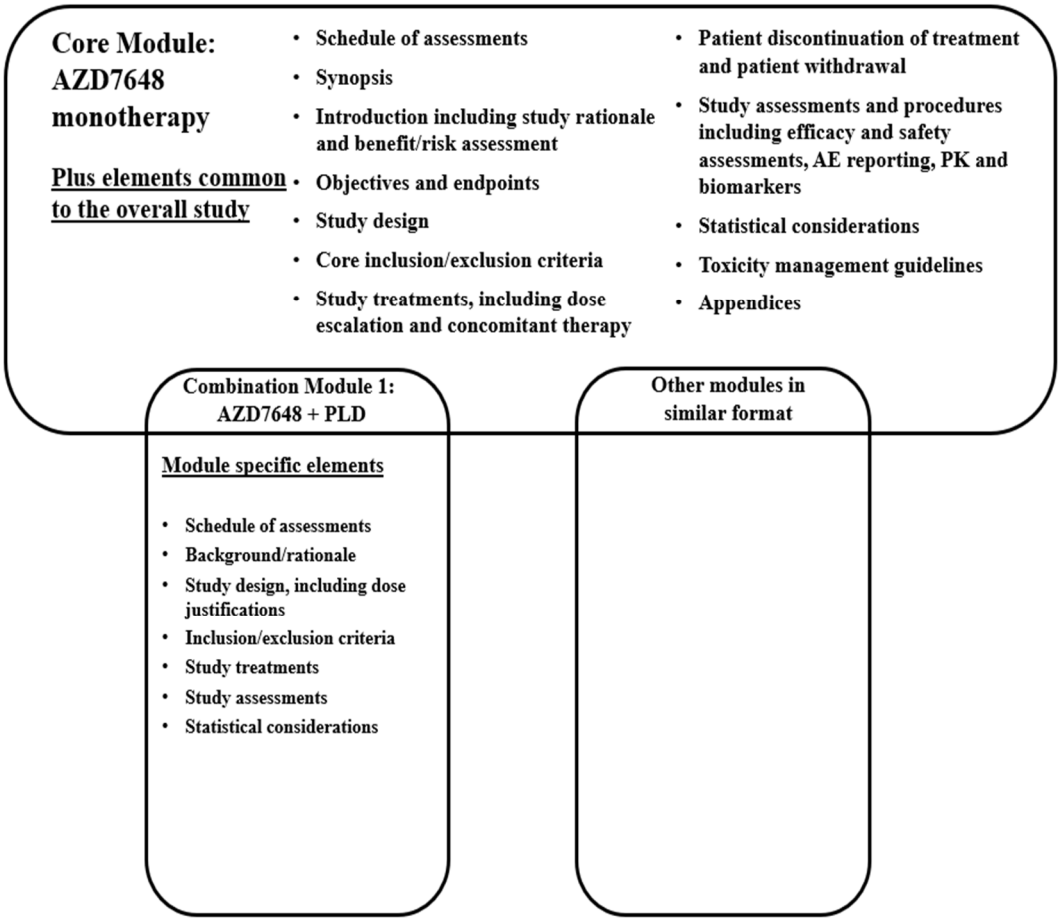
3 Up to 5 additional combination modules may be added as follows:

- Combination with a DDR agent eg, ATR inhibitor
- Combination with an immuno-oncology agent eg, PD-L1 inhibitor
- Combination with a cytotoxic agent eg, paclitaxel
- Combination with an antibody-drug conjugate

- Combination with radiotherapy/radiation therapy

The maximum number of modules in this protocol will be eight, inclusive of the Core Module. The modular protocol structure is shown in Figure 5.

Figure 5 Modular protocol structure



AE=adverse event; PK=pharmacokinetic; PLD=pegylated liposomal doxorubicin.

4.1.2 Core module study design: AZD7648 monotherapy

This part of the study is dose escalation (Part A) of AZD7648 monotherapy, administered orally, in approximately 46 evaluable patients with advanced solid tumours. Further details of the study design for Combination Module 1 can be found in Section 12.

The starting dose of AZD7648 is [redacted] mg [redacted]. A single dose of AZD7648 will be administered during [redacted]. From Cycle 1, Day 1, the initial schedule will be AZD7648 dosed on a continuous basis in a [redacted]. There will be no interval between cycles. Using an accelerated titration design (see Table 4), dose escalation may occur with single patient cohorts up to and including [redacted] mg [redacted] From [redacted] mg [redacted]

onwards, a minimum of 3 patients will be enrolled into each dose cohort. Dose escalation will stop at the maximum tolerated dose (MTD), maximum feasible dose (MFD), or the RP2D.

Dose escalations with single patient cohorts may proceed up to and including CCI mg CCI following SRC recommendation (informed by real-time PK analysis) and provided no CTCAE Grade ≥2 drug-related toxicity is observed. If either of these conditions is not met, the cohort will be expanded to recruit a minimum of 3 patients (maximum of 6 patients) in all subsequent cohorts. At this point, the decision to dose escalate AZD7648 will follow the principles of the Bayesian adaptive design, using all of the available data and considering the PK from a minimum of 2 out of the 3 patients enrolled into each dose cohort (data from all evaluable patients will be used to make the dose escalation decision). The DLT period is from the first dose until the end of Cycle 1 (inclusive of any non-dosing days). This DLT assessment period was selected as the major potential toxicities would be anticipated to present within this duration. Doses and/or schedules of AZD7648 will be defined by the SRC by taking the Bayesian adaptive design and PK into consideration.

Part A cohorts may be expanded at doses at or above the monotherapy Minimum Biologically Active Dose (MBAD) in parallel to continuing the dose escalation cohorts provided the dose has already been declared as tolerated. Further recruitment to such an expansion cohort will stop if the dose in that cohort is subsequently evaluated to be non-tolerated. The optional expansion cohort(s) are described in Section 6.1.2.1.

Escalation will stop at the MTD, MFD, or the RP2D.

To account for the dose range between starting dose and target dose level, intra-patient dose escalation is permitted as part of the monotherapy dose escalation to maximise patient benefit and minimise exposure to non-efficacious doses. However, the following criteria must be fulfilled before a patient is permitted to proceed with an intra-patient dose escalation:

- The planned next higher dose must be declared tolerated by the SRC (based on assessment of 2 to 6 evaluable patients).
- Agreement by the SRC that the patient is permitted to have an intra-patient dose escalation.
- Intra-patient dose escalation occurs on Day 1 following a scheduled scan assessment.

Whilst a patient is being considered for an intra-patient dose escalation, they should continue treatment at their allocated dose level. In the event of an intra-patient dose escalation, such patients will not be evaluable for DLT at the escalated dose.

No Part B expansion is planned in the Core Module but there are optional expansion options as described in Section 6.1.2.1.

4.1.3 Regulatory amendment for additional modules

To support amendment of the protocol for additional combination modules, AstraZeneca will provide a summary of all non-clinical and clinical data to support the proposed new combination and dosing schedule, this will include updating the following:

- Study objectives
- Background information providing rationale for the proposed patient population(s) and the proposed treatment plan(s)
- Specific study eligibility criteria
- A detailed description of the proposed study treatment plans
- A revised schedule of patient assessments
- A summary of safety data from the completed or ongoing cohort(s)/modules(s) and the proposed toxicity management plans for the proposed new combination
- A description of any dose modifications and the data (clinical safety information, clinical PK data, and non-clinical data) that support the safety of the proposed dose modifications for the combination regimen in question
- A clearly stated justification for the proposed sample size based on the objectives for that specific cohort/module; and
- A detailed description of the method and performance characteristics of any test that will be used to identify the patient population to be enrolled in the cohort/module, if the population will be selected based on a diagnostic assay.

4.1.3.1 Europe and Rest of World

AstraZeneca will provide a substantial amendment for review and approval.

4.1.3.2 United States of America

AstraZeneca will provide an amendment to the Food and Drug Administration (FDA) 30 days in advance of planned enrolment in the cohort for any future combination. AstraZeneca will begin enrolment of patients into that cohort in the United States (US) no sooner than 30 days from the date of submission and institutional review board (IRB) approval.

4.1.4 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this Clinical Study Protocol (CSP) and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study patients become infected with severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the patient's ability to conduct the study.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis (eg, coronavirus disease 2019 [COVID-19]), changes may be implemented to ensure the safety of study patients, maintain compliance with Good Clinical Practice (GCP), and minimise risks to study integrity.

The investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent (reconsent) for the mitigation procedures (note, in the case of verbal consent (reconsent), the Informed Consent Form (ICF) should be signed at the patient's next contact with the study site.
- Rescreening: Additional rescreening for **screen failure due to study disruption** and to confirm eligibility to participate in the clinical study can be performed in previously screened patients. The investigator should confirm this with the designated study physician.
- Home or Remote visit: Performed by a site qualified Health Care Professional (HCP) or HCP provided by a third-party vendor.
- Telemedicine visit: Remote contact with the patient using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- All necessary supplies and instructions for administration and documentation of study treatment administration will be provided if site is able to complete all safety assessments as per CSP.

Any deviations to the protocol necessary to safeguard patient safety or data validity as a result of COVID-19 related disruption will be recorded and any permanent changes requiring an amendment to the protocol will be communicated to Regulatory Authorities and IRBs / independent ethics committees (IEC) in line with relevant local guidance and procedures (see Appendix A 1).

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix J.

4.2 Scientific rationale for study design

The CCI [redacted] l. In cancer cells, CCI [redacted] n. Such instability results in CCI [redacted]

AZD7648 is a novel potent and highly selective oral inhibitor of DNA-PK. CCI

CCI

This FTIH study with AZD7648 will be conducted within the context of a modular protocol to evaluate the safety, tolerability, PK and anti-tumour activity of AZD7648 at increasing doses as a monotherapy (Core Module) and in combination with PLD (Combination Module 1), in patients with advanced malignancies. Whilst AZD7648 monotherapy may offer some clinical benefit to patients, preclinical evidence suggests that the greatest potential for benefit is likely to be achieved in combinations. Therefore, rather than completing an AZD7648 monotherapy escalation to RP2D before initiating combination dosing, the combination dosing phase of the study with PLD will commence as soon as sufficient safety and PK data have been obtained from the monotherapy escalation.

Key aspects of the study, such as the starting dose of AZD7648 in the Core Module, and the dose escalation, stopping criteria and cohort size of all study modules, are based upon accepted methodology for Phase I oncology studies. Furthermore, blood samples will be collected to enable characterisation of AZD7648 PK and, if appropriate, investigation of additional metabolites to enable AstraZeneca to fulfil regulatory requirements related to the testing of the safety of AZD7648 and its metabolites.

As part of the clinical drug development programme for AZD7648, AstraZeneca will CCI There are many potential benefits of this exploratory research, including: CCI Ultimately, this research will provide the information and understanding required to deliver safe and effective new medicines to patients.

4.3 Justification for dose

A dose of [redacted] mg/day is proposed as the starting dose in this FTIH Phase 1 study in patients with advanced cancer, including patients with solid tumours. This is based on international guidance for starting dose selection for agents in cancer patients (International Conference on Harmonisation [ICH] S9) which recommends that the starting dose should be set at a dose of 1/10 of the Severely Toxic Dose in 10% of the animals (STD 10) in rodent toxicity studies. If the non-rodent is considered the most appropriate species then 1/6th of the Highest Non-Severely Toxic Dose (HNSTD) observed in non-rodent studies is viewed as an

appropriate starting dose. For AZD7648, the non-rodent was considered to be the most sensitive species.

A rat STD 10 was not identified in the 1-month toxicology study. The highest dose tested (CCI mg/kg/day administered as CCI mg/kg CCI was tolerated in all animals and is considered to be the MTD as higher doses administered in the dose range finding study (CCI mg/kg/day administered as CCI mg/kg CCI led to body weight loss and clinical signs which were considered too severe for this dose to be suitable for longer term administration. At CCI mg/kg (CCI mg/m^2), body weight loss and decreased food intake was observed over the first few days of dose administration in both sexes. However, by days 4 to 5, animals started to gain weight and food consumption increased. Histopathological findings were restricted to decreased cellularity in lymphoid tissue, effects on the male reproductive tract and thyroid hypertrophy in females only. Full recovery from the histopathological changes was observed after 28 days off dose.

However, 1/10th of the MTD in rats gives a dog-equivalent dose of CCI mg/kg/day and a dose of CCI mg/kg/day was not tolerated in one male dog. The animal was removed from the study on Day 11 due to marked body weight loss together with decreased or absence of food intake and adverse clinical signs, including liquid faeces with red traces, decreased activity and vomiting. Histopathological examination showed mucosal degeneration, neutrophilic inflammation, ulceration, and haemorrhage in the gastrointestinal (GI) system and decreased cellularity in lymphoid tissue.

The human equivalent dose derived from 1/6th of the dog HNSTD (CCI mg/kg/day) was calculated to be CCI mg/kg, which equates to CCI mg for a CCI kg human. In an in vitro GI organoid model, human and dog results were similar. Therefore, the dog is considered an appropriate species and a starting dose of CCI mg/day is proposed for this study.

4.3.1 Justification for the dose escalation doses

The selection of the starting dose is based upon international guidance for an ICH S9 patient population, and is based on the HNSTD dose level. However, when considering proposed human starting dose margins to measured exposure in the dog study, there is a 23-fold margin to AUC and a 16-fold margin to C_{max} values recorded at the NOAEL of CCI mg/kg/day in the dog. At this dose level there were no significant toxicological findings. Therefore, assuming human PK values are as predicted from real-time PK analysis, and that there are no drug-related Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥2 events, a maximum of dose doubling is proposed.

4.4 End of study definition

The end of study is defined as the last visit of the last patient undergoing the protocol-defined assessments.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or recruitment is low. AstraZeneca may also terminate the entire study of individual cohorts prematurely if concerns for safety arise within this study or in any other study with any agent used in any of the study modules.

A patient is considered to have completed the study when he/she has completed his/her last scheduled visit or contact.

For each module or study part, there will be a data cut-off (DCO) defined as the earlier of 6 months after the last patient recruited starts study treatment (in module/study part) or after the final patient discontinues study treatment (in module/study part). Patients who are receiving treatment following the data cut-off (DCO) for the final analysis can either choose to discontinue from the study or, where the Investigator believes the patients are gaining clinical benefit, patients may continue to receive study treatment. All patients will receive follow-up care in accordance with standard local clinical practice. For patients who do continue treatment beyond the time of the final DCO, Investigators will continue to report all SAEs until 90 days after the last dose of study treatment. Additionally, any SAE or AE that is ongoing at the time of this DCO must be followed up to resolution unless the event is considered by the Investigator to be unlikely to resolve, or the patient is lost to follow-up.

Data analysis will be performed separately for each module or study part and a CSR will be written. Informal data cuts may be performed at regular intervals across all modules/parts to inform internal decision making.

See Appendix A 6 for guidelines for the dissemination of study results.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, are not permitted.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for the core and Combination Module 1 (if applicable). **Under no circumstances can there be exceptions to this rule.** If there are differences in cut-off values, the specific module takes precedence. For example, if the haematological parameters are stricter in the combination module rather than the Core Module, the Investigator should adhere to the combination module criteria. Patients who do not meet the entry requirements are screen failures, refer to Section 5.4.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3.

5.1 Inclusion criteria

The inclusion criteria that are applicable to all parts/cohorts of the study are described in this section. Please refer to Section 13.1 for additional specific criteria applicable to Combination Module 1.

Informed Consent

1 Capable and willing to give signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

2 Provision of signed and dated written genetic informed consent prior to collection of sample for exploratory genetic analysis (optional).

The ICF process is described in Appendix A 3.

Age

3 Patient must be at least 18 years of age, at the time of signing the ICF.

Type of Patient and Disease Characteristics

4 Patients must have histological or cytological confirmation of advanced malignancy considered to be suitable for study treatment.

5 ECOG PS of 0 to 1.

6 Life expectancy greater than 12 weeks.

7 Progressive cancer at the time of study entry.

8 **PD expansion cohorts (or PD expansion subgroup)**: Patients must have at least one tumour suitable for biopsy and consent to having biopsies collected.

Reproduction

9 Negative pregnancy test (urine or serum) prior to start of dosing for women of child-bearing potential (WOCBP). Women of child-bearing potential are defined as women between menarche and menopause who have not been permanently or surgically sterilised and are capable of procreation.

10 Female patients must be post-menopausal, surgically sterile, or using an acceptable method of contraception (acceptable methods of contraception are defined in Section 5.3.3) for the duration of the study (from the time they sign consent) and for 12 weeks after the last dose of study treatment to prevent pregnancy.

11 For the duration of the study (from the time they sign consent) and for 12 weeks after the last dose of study treatment, sexually active male patients must be willing to use contraception as is defined in Section 5.3.3.

Post-menopausal is defined as:

- No menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a

post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- Radiation-induced oophorectomy with last menses greater than 12 months ago.
- Chemotherapy-induced menopause with greater than 12 month interval since last menses.
- Surgical sterilisation (bilateral oophorectomy or hysterectomy).

5.2 Exclusion criteria

The exclusion criteria that are applicable to all parts/cohorts of the study are described in this section. Please also refer to Section 13.2 for additional specific criteria applicable to Combination Module 1.

Medical Conditions

1 Any unresolved toxicities from prior therapy CTCAE Grade ≥ 2 (with the exception of alopecia).

2 Spinal cord compression or brain metastases unless definitively treated (minimum of 3 weeks between completion of radiotherapy and first dose of study treatment and recovery from acute toxicity Grade ≥ 2), asymptomatic, stable (no clinical evidence of progression since completion of central nervous system-directed therapy) and not requiring steroids for at least 4 weeks. Disease outside the central nervous system must be present.

3 As judged by the Investigator, any evidence of severe or uncontrolled medical conditions including but not limited to:

   – Uncontrolled diabetes mellitus, uncontrolled seizures, active infection requiring systemic antibiotics, antifungal or antiviral drugs, severe chronic obstructive pulmonary disease, severe Parkinson's disease, active inflammatory bowel disease, psychiatric condition, active bleeding diatheses, renal transplant, or active infection including any patient with active hepatitis B, hepatitis C or human immunodeficiency virus.

4 Any other malignancy which has been active or treated within the past 3 years, with the exception of in situ cancer of the cervix, non-melanoma skin cancer, ductal carcinoma in situ, Stage 1 Grade 1 endometrial carcinoma, or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥ 5 years.

5 Refractory nausea and vomiting or unable to swallow and retain oral medication, chronic GI diseases or previous bowel resection with clinically significant sequelae that would preclude adequate absorption of AZD7648, GI symptoms CTCAE Grade > 1, history of

GI ulceration and gastrointestinal haemorrhage within 6 months of first study drug administration.

Prior/Concomitant Therapy

6 Receiving or having received anti-cancer treatment within the following periods prior to the first dose of investigational product:
   (a) Cytotoxic treatment: 3 weeks
   (b) Non-cytotoxic drugs, including small molecule investigational products: 3 weeks or 5 half-lives (whichever is longest)
   (c) Biological products including investigational immuno-oncology agents: 4 weeks
   (d) Radiation with a limited field for palliation: 1 week (3 months for radiation to the abdomen or pelvis)
   (e) Radiation to > 30% of the bone marrow or with a wide field: 4 weeks
   (f) Lung radiation: 60 days
   (g) Major surgery: 4 weeks; minor surgery or biopsy: 1 week

7 During the 4 weeks prior to the first dose, receiving corticosteroids at a dose of ≥ 10 mg prednisone/day or equivalent for any reason. Ongoing low dose steroids for longer than 3 months (excluding inhalational, nasal, creams, lotions, and gels) are not allowed.

8 Receiving or having received concomitant medications, herbal supplements and/or foods known to significantly modulate CYP3A4 activity (potent/strong inhibitors or inducers of CYP3A4). The required washout period prior to starting study treatment is 3 weeks (5 weeks for enzalutamide or phenobarbital) until 28 days after the last dose of study treatment. Patients can receive a stable dose of bisphosphonates or denosumab for bone metastases, before and during the study if these were started at least 2 weeks prior to study treatment.

Prior/Concurrent Clinical Study Experience

9 Prior exposure to a DNA-PK inhibitor or hypersensitivity to any excipient of the product.

Diagnostic Assessments

10 Cardiac dysfunction as defined by any of the following within 6 months of study entry:
   (a) Acute myocardial infarction
   (b) New York Heart Association Class II/III/IV heart failure
   (c) Unstable angina
   (d) Unstable cardiac arrhythmias eg, clinically important abnormalities in conduction or morphology of resting ECG such as complete left bundle branch block or third-degree- heart block

11 Any of the following cardiac criteria:

(a) Known reduced left ventricular ejection fraction below the institutional lower limit of normal (LLN)

(b) Mean resting corrected QT interval (QTc) > 470 milliseconds obtained from 3 ECGs in 24 hours using the Fridericia formula

(c) Any factors that increase the risk of QTc prolongation or arrhythmic events such as hypokalaemia, congenital long QT syndrome, immediate family history of long QT syndrome or unexplained sudden death under 40 years of age

12 Inadequate haematological or organ function as defined by:

(a) Haemoglobin < 90 g/L with no blood transfusions or erythropoietin within 14 days of obtaining these values or before starting treatment

(b) Absolute neutrophil count (ANC) < 1500 cells/mm3 (< 1.5 x 10^9/L) with no haematopoietic growth factors within 14 days of obtaining these values or before starting treatment

(c) Platelet count <100,000/mm^3 (< 100 x 10^9/L) with no platelet transfusions within 14 days of obtaining these values or before starting treatment

(d) International normalised ratio (INR) ≥ 1.5 or other evidence of impaired hepatic synthesis function

(e) Bilirubin ≥ 1.5 x upper limit normal (ULN) or ≥ 2 x ULN for patients with documented/suspected Gilbert's disease (or likely to be in 3 weeks)

(f) Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 2.5 x ULN if no demonstrable liver metastases or ≥ 5 x ULN in the presence of liver metastases (or likely to be in 3 weeks)

(g) Creatinine clearance (CrCl) < 50 mL/minute, as assessed using Cockcroft-Gault, ethylenediaminetetraacetic acid (EDTA) clearance or 24 hours urine collection

Other Exclusions

13 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

14 Judgement by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

15 Previous enrolment in the present study.

16 **For female patients only**: currently pregnant (confirmed with positive pregnancy test) or breast-feeding.

17 **For host genetics research study (optional):**

(a) Previous allogenic bone marrow transplant

(b) Non-leukocyte depleted whole blood transfusion within 120 days for the date of the genetic sample collection

18 **For food effect cohort only:** insulin-dependent diabetes.

19 History and/or presence of COVID-19:

(a) Previous severe course of COVID-19 (ie, hospitalisation, extracorporeal membrane oxygenation, mechanically ventilated)

(b) Clinical signs and symptoms consistent with COVID-19, eg, fever, dry cough, dyspnoea, sore throat, fatigue or confirmed current infection by appropriate laboratory test within the last 4 weeks prior to screening

5.3 Lifestyle restrictions

5.3.1 Fasting restrictions

AZD7648 tablets should be swallowed whole with water on an empty stomach (no food or drink other than water for 2 hours prior to dosing and 1 hour after dosing).

5.3.2 Dietary restrictions

During the studies, patients should avoid consuming grapefruits, Seville oranges, or other products that may contain these fruits as these may affect AZD7648 metabolism.

5.3.3 Contraception

Male patients

- Should use barrier contraceptives (ie, by use of condoms) during sex with all partners from the time they sign consent and for 12 weeks after the last dose of study treatment. If male patients wish to father children, they should be advised to arrange for freezing of sperm samples prior to the start of study treatment.
- A sexual partner of a male participant who is a WOCBP should also use a highly effective form of contraception.
- Men should not donate sperm for 12 weeks after the last dose of study drug.

Female patients

- Women with evidence of non-child-bearing potential at screening have no restrictions around contraception.
- From the time of signing consent, and for 12 weeks after the last dose of study treatment; WOCBP and their partners (who are sexually active) should agree to use 2 reliable methods of contraception in combination, or they must totally/truly abstain from any form of sexual intercourse. All hormonal methods of contraception should be used in combination with the use of a condom by their male sexual partner for intercourse. Total/true abstinence is when a patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the trial until at least 1 month after the last dose of study drug. Periodic abstinence (eg, calendar ovulation, symptothermal, post-ovulation methods, or declaration

of abstinence solely for the duration of the trial) and withdrawal are not acceptable methods of contraception.

- Contraceptives that are prone to drug-drug interactions may not be effective due to a potential CYP3A4 interaction with AZD7648. Contraception used must therefore include a condom and one of:
  - Medroxyprogesterone injections (eg, Depo-provera)
  - Intrauterine Device (IUD)
  - Levonorgestrol Intrauterine System (eg, Mirena)
  - Tubal occlusion
  - Vasectomised partner that is the sole sexual partner of the WOCBP trial participant provided the vasectomised partner has received medical assessment of the surgical success.

5.3.4 Concomitant medication

See Section 6.5, for details in restricted or prohibited medications.

5.3.5 Blood donation

Patients should not donate blood whilst participating in studies of AZD7648 and for at least 12 weeks after receiving the last dose of study treatment.

5.4 Screen failures

Screen failures are defined as patients who signed the ICF to participate in the clinical study but are not subsequently dosed with study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from Regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened patients should be assigned the same patient number as for the initial screening. However, rescreening should be documented so that its effect on study results, if any, can be assessed.

These patients should have the reason for screen failure recorded in the case report form (CRF).

6 STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study

participant according to the study protocol. Study treatment in the Core Module refers to AZD7648 (Table 3).

Further details on the combination treatment administered in Combination Module 1 can be found in Section 14.1.

6.1 Treatments administered

6.1.1 Investigational products

Table 3 Study treatments

Study treatment name:	**AZD7648**
Dosage formulation:	Provided as [redacted] mg, [redacted] mg, [redacted] mg, and [redacted] mg white film-coated oral tablets. The [redacted] mg and [redacted] mg tablets are round. The [redacted] mg and [redacted] mg tablets are caplet shaped. Note: In accordance with Quality IMPD, other intermediate strengths may be added at a later date.
Route of administration:	Oral tablets
Starting dose instructions:	During Part A (dose escalation), a single dose of AZD7648 will be administered in the clinic ([redacted]) to enable collection of blood samples for PK analyses. This is followed by a [redacted] In cohort 1, at [redacted] the starting dose and schedule of AZD7648 is [redacted] mg [redacted] on a [redacted]. AZD7648 will be administered orally on an empty stomach. On clinic days, patients should not take the study treatment until instructed to do so by clinic staff. Details of dose escalation and cohorts can be found in Section 6.1.2.
Packaging and labelling:	Study treatment will be provided in high-density polyethylene bottles. The bottles are induction sealed and closed with child-resistant polypropylene screw caps. Study treatment should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle specifies the appropriate storage. Each bottle will be labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirement. Label text will be translated into local language. The site must complete the Patient Diary with the details of the dosing instructions at the time of dispensing.
Provider:	AstraZeneca

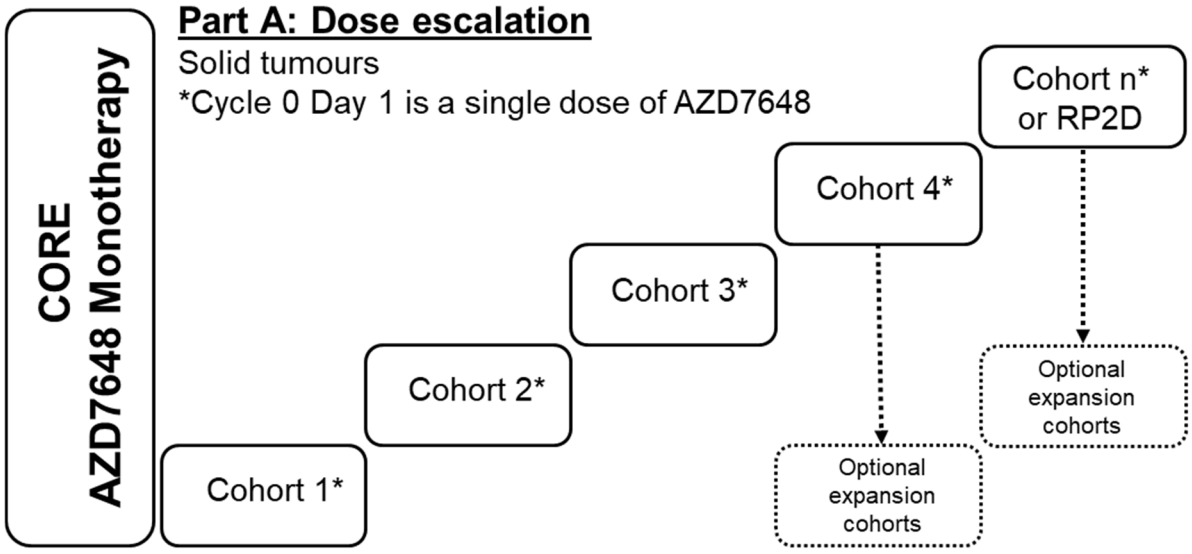
6.1.2 Dose escalation scheme – Core Module

The dose escalation study flow chart for the Core Module is presented in Figure 6; further details on the dose escalation for Combination Module 1 can be found in Section 14.1.2

AZD7648 will be administered as an oral dose, initially CCI (refer to Figure 7). The individual patient observation period will be for the duration of the sampling as detailed in the SoA (Table 1). When there is more than one patient enrolled to a dose cohort, sentinel dosing will be applied with a single patient exposed for a minimum of 48 hours after Cycle 1, Day 1 before further patients are enrolled at that dose level. In the absence of any significant toxicities in the first patient, the patients for the remainder of the cohort may be enrolled, concurrently or sequentially, based upon the decision of the SRC.

If significant toxicities are observed during the first 48 hours of observation in the first patient of the cohort, further enrolment into the cohort will be halted until the SRC has reviewed all the safety data (and the PK data for Cohorts 1 to 4) for that patient and cumulative data from all trial patients to determine the appropriate action.

Figure 6 AZD7648 monotherapy study flow chart



RP2D=recommended Phase II dose.

Where dosing is CCI the tablets should be taken approximately 12 hours apart. If a dose is missed, it is acceptable to take the scheduled dose up to 2 hours after the scheduled dose time. If greater than 2 hours, the missed dose should not be taken, and the patient should continue with the next dose at the allotted time. If vomiting occurs shortly after AZD7648 is swallowed, the dose should not be replaced. Resume dosing at the following scheduled dose.

Table 4 is an example dose escalation scheme. However, all potential dose escalation levels after the starting dose may be adjusted in light of emerging safety, tolerability, and/or PK data (see Section 4.3.1). Intermittent schedules may also be explored in the Core Module from Cohort 2 onwards.

Table 4 Example of AZD7648 monotherapy dose escalation scheme

Cohort	AZD7648 dose (mg), CCI unless otherwise stated
1	CCI
2	CCI
3	CCI
4	CCI
5	CCI
6	CCI
7	CCI
8	CCI
Cohort n (escalate to MTD or MFD)	No more than 50% increment
Maximum dose level	CCI

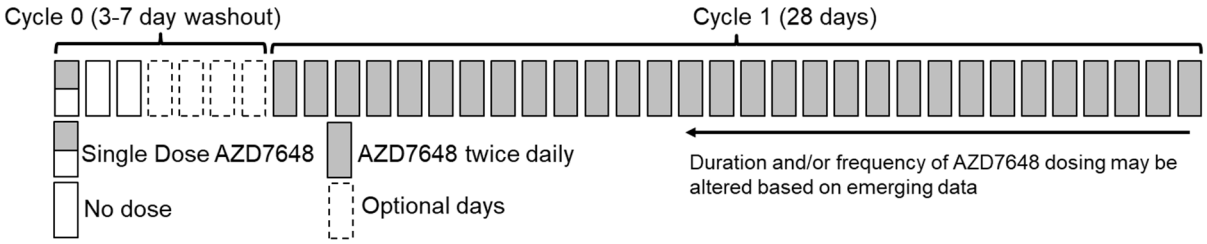
CCI=CCI; MFD=maximum feasible dose; MTD=maximum tolerated dose; CCI.

Actual doses and schedules may vary using Bayesian adaptive design modelling based on emerging safety and tolerability data, and/or pharmacokinetic (PK) data, and subject to Safety Review Committee (SRC) agreement. A maximum of dose doubling using single patient cohorts may be permitted up to and including the CCI mg CCI cohort, if the following conditions are met:

No common terminology criteria for adverse event (CTCAE) Grade ≥ 2 drug related toxicity.

SRC provides the recommendation following the review of all available data (and informed by real-time PK analysis for Cohorts 1 to 4).

Figure 7 Starting dose and schedule for AZD7648 monotherapy



Using an accelerated titration design, single patient cohorts may be enrolled up to and including CCI mg CCI provided that there is no CTCAE Grade ≥ 2 drug-related toxicity and with agreement by the SRC (informed by real-time PK analysis for Cohorts 1 to 4). From CCI mg CCI a minimum of 3 patients (and maximum of 6 patients) will be enrolled in each subsequent cohort. At the RP2D up to 12 patients may be treated to explore chronic toxicity. For SRC meetings prior to dose escalation where 3 patients have been enrolled, at least 2 patients will need to be evaluable for DLT. However, if patients are receiving treatment

within the DLT assessment period, the dose escalation review meeting should be deferred so that the SRC accounts for all patient data.

Dose escalation and de-escalation will follow the Bayesian adaptive design below.

- If no DLT at any dose has been observed, then dose escalation may occur without modelling. Dose doubling may be permitted in single patient cohorts up to and including CCI mg CCI if recommended by the SRC (informed by 'real-time' analysis of PK samples for Cohorts 1 to 4). However, if CTCAE Grade ≥ 2 drug-related toxicity is observed or at the recommendation of the SRC, cohorts may be expanded to recruit a minimum of 3 (and maximum of 6) patients in all subsequent cohorts.

  From CCI mg CCI (or once cohorts are recruiting a minimum of 3 patients), after the first DLT has been observed (at any dose), a Bayesian logistic regression model will be used to inform subsequent dose selections. After each cohort, cumulative data on the evaluable patients will be used to estimate the predicted probability of a DLT at each potential next dose.
- The recommendation for the next dose will be based on the following principles:
  - The recommendation for the next dose will be chosen to target a DLT of 25% for monotherapy and 30% for combination but ignoring any dose for which the model suggests the probability of a DLT exceeds 35%. This will allow efficient identification of the MTD whilst restricting the risk of overdosing.
- Dose escalation and de-escalation will be completed when any of the following occur:
  - The target toxicity of 25% (for monotherapy) and 30% (for combination) is reached and the required precision of the estimated MTD is achieved (ie, the ratio of the upper/lower 95% credible interval limits for the estimated MTD < 5.0).
  - The maximum number of evaluable patients for the dose escalation cohort has been reached.
  - There is no anticipated improvement in efficacy with increasing dose.
  - The MFD is achieved.
  - Decision made by the SRC to stop dose escalation.
- Prior established dose toxicity relationship at doses at which 10% and 50% (or similar) of patients experience DLTs will be used to inform the Bayesian model.
- Emerging data from the Core Module or any combination module of this study may also be used to inform the Bayesian model in another module of this study or other clinical studies.
- Dose increases will be permitted after review of data from a minimum of 2 out of the 3 patients enrolled into each dose cohort (data from all evaluable patients will be used to make the dose escalation decision).

There is no minimum time period required between completion of dosing in the last evaluable patient from one cohort and the start of dosing in the subsequent cohort.

To account for the dose range between the starting dose and target dose level, intra-patient dose escalations is permitted as part of the monotherapy dose escalation to maximise patient benefit and minimise exposure to non-efficacious doses. However, the following criteria must be fulfilled before a patient is permitted to proceed with an intra-patient dose escalation:

- The planned next higher dose must have been declared tolerated by the SRC (based on assessment of 2 to 6 evaluable patients).
- Agreement by the SRC that the patient is permitted to have an intra-patient dose escalation.
- Intra-patient dose escalation occurs on Day 1 following a scheduled scan assessment.

Whilst a patient is being considered for an intra-patient dose escalation, they should continue treatment at their allotted dose level. In the event of an intra-patient dose escalation, such patients will not be evaluable for DLT at the escalated dose.

After each patient has completed the DLT assessment period during the dose escalation phase of the study, the SRC will evaluate all available toxicity information (including AEs and laboratory abnormalities that are not DLTs), as well as available PK and PD information for the first cycle for all evaluable patients (data from Cycle 2 and beyond will also be evaluated if available). Additional CRF data may be included in the SRC review including vital signs, clinical chemistry/haematology, ECG results, PK and PD data, ad hoc safety reports, AEs from previous cohorts and optional expansions and any other emerging data. If appropriate, quantitative dose/exposure-response models will be used to describe the relationship for such data of interest to decide the next dose and/or schedule.

There is no limit to the number of intra-patient dose escalations that a patient can undergo.

Intermediate dose levels, dosing intervals and/or frequency, and/or schedules may be evaluated prior to declaring the RP2D, which will be guided by the evolving safety, preliminary efficacy, PK and PD data.

For decisions on dose escalation (Part A), an evaluable patient is defined as a patient that has received AZD7648 and either:

- Has completed minimum safety evaluation requirements and has received at least 75% of the total amount of planned dose of AZD7648 (and PLD for Combination Module 1) during Cycle 1

  or
- Has experienced a DLT during Cycle 0 or Cycle 1.

Triggers for Additional Modules

Combination modules, eg, Combination Module 1 (combination of AZD7648 + PLD) will start after PK data from monotherapy dose escalation has confirmed an understanding of the metabolic profile of AZD7648 and the dose selected as the starting dose for the combinations is safe and tolerated. Triggers that will initiate the start of additional combination modules may include (but are not limited to):

- PK dose proportional. PK exposure vs. dose is well understood.
- Total drug exposure levels ≥ 50% of that predicted to be required for biological activity for a period defined for the specific combination. It is anticipated that the combination modules will be triggered once exposure (based on clinical PK exposure and emerging safety and tolerability data) is determined to be in a suitable therapeutic range.
- No toxicity red flags eg, DLT rate greater than that anticipated for a tolerated cohort.

Multiple combination modules may be triggered simultaneously.

6.1.2.1 Optional Expansion Cohorts

In all modules of the study, Part A cohorts may be expanded at doses at or above the MBAD in parallel to continuing the dose escalation cohorts provided that the dose has been declared as tolerated. Using this design, tolerability and PK will be characterised in the Part A population whilst providing evidence of PD and clinical activity in the populations most likely to benefit from drug and potentially across several doses.

The optional Part A expansion cohorts may be initiated for 3 reasons:

- **PD expansion cohort** of up to 12 additional patients to obtain mandatory serial biopsies for signal searching of biological PD activity.
- **Efficacy expansion cohorts** of up to 25 additional patients (of which a subset of up to 12 in each cohort may have mandatory biopsies if PD data is also required) to explore clinical benefit.
- **Food effect expansion cohorts** of up to 12 patients at doses between the MBAD and RP2D.

The expansion cohorts will also explore further the tolerability, safety and PK activity at these doses.

Food Effect

At least one cohort may investigate the effect of food on AZD7648 PK. If a food effect cohort is included in the monotherapy expansion cohort, then up to 12 evaluable patients may be

included in the food effect cohort if the dose and schedule has already been declared tolerated by the SRC.

If the dose and schedule has not yet been declared tolerated, then initially up to 6 evaluable patients will be enrolled to the food effect cohort, and an additional 6 evaluable patients may be added once the dose and schedule has been declared tolerated by the SRC. A cross over design will be used for the food effect cohort. Each patient will be allocated to receive a single oral dose of AZD7648 on Cycle 0, Day 1 in either the fasted or fed state, followed by a single oral dose of AZD7648 in the other state for Cycle 1, Day 1 at least 72 hours later. Other criteria may be used for decision-making based on emerging AZD7648 PK data. After Cycle 1, Day 1 patients may continue to receive AZD7648 monotherapy (at or below the RP2D and schedule), and all dosing from that point onwards must be administered in the fasted state. For the fed dosing day, patients should ideally start the recommended meal 30 minutes prior to the planned administration of the study drug. The study drug should be administered 30 minutes after the start of the meal (or up to 45 minutes after the start of their meal if the patients couldn't complete at least 75% of their meal within 30 minutes). Patients will be considered evaluable if they completed at least 75% of their meal before the administration of the study drug and the study drug is administered between 30 to 45 minutes after the start of the meal. For the fasted state, patients must fast (water only) for ≥ 10 hours prior to taking a dose to ≥ 2 hour post-dose. For the fed state patients must fast overnight (minimum of 8 hours) prior to consuming a standardised meal in the clinic. The meal should consist of about 800 to 1000 total calories with around 54% of the calorific content made up from fat. The dose should be administered with 240 mL of water. Refer to Appendix I for full details.

6.1.3 Definition of dose-limiting toxicity

DLTs will be evaluated during Cycle 0 and Cycle 1 of treatment. Toxicity will be graded according to the National Cancer Institute CTCAE v5.0.

A DLT is defined as an AE that occurs from the first dose of study treatment up to and including Cycle 1, Day 28 (the DLT assessment period) that is assessed as unrelated to the disease, intercurrent illness, or concomitant medications and that, despite optimal therapeutic interventions, meets any of the following criteria:

Haematological Toxicities:

- Grade 4 neutropenia lasting > 4 days.
- Grade 4 thrombocytopenia.
- Grade ≥ 3 neutropenia (ANC < 1000 cells/mm^3 [< 1 x 10^9/L]) of any duration accompanied by fever ≥ 38.5ºC and/or systemic infection.
- Grade ≥3 thrombocytopenia (< 50,000/mm^3 [< 50 x 10^9/L]) with bleeding.

Non-haematological Toxicity CTCAE Grade ≥3 Including:

- Confirmed laboratory abnormalities greater than 72 hours of duration.
- Nausea or vomiting for more than 3 consecutive days despite administration of maximal anti-emetic therapy.
- Diarrhoea for more than 3 consecutive days despite administration of maximal anti-diarrhoeal therapy.
- QTc prolongation > 500 milliseconds or QTcF prolongation from baseline by 60 milliseconds confirmed on at least 2 separate ECGs.
- Any other toxicity that is greater than that at baseline AND is clinically significant and/or unacceptable, and does not respond to optimal therapeutic intervention within 72 hours AND is judged to be a DLT by the SRC.
- Any treatment-related event, including significant dose reductions, omissions or delays, judged to be a DLT by the SRC. Examples may include CTCAE Grade 2 toxicities that are clinically significant and/or unacceptable according to the Investigator, toxicities that result in an inability to administer at least 75% of study treatment during Cycle 1 or delay the administration of study treatment in the subsequent cycle by ≥ 7 consecutive days.

DLT Will not Include the Following:

- Transient isolated laboratory abnormalities which are not considered clinically significant and resolve to baseline within 72 hours without any intervention.
- Alopecia.
- Toxicity unrelated to treatment eg, related to the underlying disease or disease-related process under investigation.
- Grade 4 vomiting and diarrhoea lasting < 72 hours in the absence of maximal medical therapy.
- Grade 3 nausea, vomiting or diarrhoea that lasts < 48 hours and resolves to Grade ≤1 either spontaneously or with maximal medical therapy.
- Grade 3 fatigue < 5 days.
- Grade 3 hypertension in the absence of maximal medical therapy.
- Grade 3 electrolyte abnormalities that resolve to Grade ≤1 within 48 hours spontaneously or with conventional medical intervention and is not clinically complicated.
- Grade 3 rash that resolves to Grade ≤1 within 3 weeks.
- Grade 3 or Grade 4 elevation in serum amylase and/or lipase that are not associated with clinical or radiographic evidence of pancreatitis.

6.1.3.1 Definition of Maximum Tolerated Dose and Recommended Phase II Dose

The MTD is defined as the highest dose at which the predicted probability of a DLT is less than 25% (for monotherapy) or 30% (for combinations). At least 6 evaluable patients are required to determine the MTD (refer to Section 6.1.2 for a detailed description of the Bayesian adaptive design).

The RP2D will take into account the MTD (or alternative doses/schedules in the absence of MTD), MFD, PK, biological/clinical activity (PD data), as well as data beyond Cycle 1 during dose escalations.

6.1.3.2 Definition of Maximum Feasible Dose

A dose and schedule will be considered to be the MFD and dose escalation will stop if:

- There is evidence of saturation of absorption from emerging PK data that limits the exposure

  and/or
- An MFD has been reached, based on a maximum number of tablets per dose or day, or the maximum dose permitted based on CMC quality specifications (currently set against a maximum dose of CCI mg CCI = CCI mg/day), whichever is the lower dose.

6.1.4 Safety review committee

The SRC Remit document for this study will define the exact membership and who will be present for decisions to be made.

The SRC will guide all dose escalation and cohort expansion decisions in this study. The dose or schedule for subsequent cohorts or a decision to stop recruitment will be agreed by the SRC after review of the data from each cohort. When there are other patients that are ongoing at the time a review is planned, the SRC should defer their decision until these further patients become evaluable. The data which will be reviewed at a dose decision meeting includes (but is not limited to):

- All available safety information and laboratory abnormalities (including clinically significant AEs and laboratory safety variables).
- Data on exposure eg, any dose interruptions or reductions.
- All available PK (mandatory Cycle 0 and Cycle 1 PK data in single patient cohorts up to and including CCI mg CCI for Cohorts 1 to 4) and PD data.
- The dose recommended from the Bayesian model.

The SRC can decide at each meeting to:

- Determine DLTs
- Change the schedule of drug administration
- Stagger enrolment into a cohort based on toxicity in the sentinel patient
- Stop enrolment into a cohort
- Recommend a temporary halt on further dosing of patients to allow further evaluation of patients
- Stop further dosing of all patients in the study

- Escalate the dose
- Expand the cohort to a maximum of 6 evaluable patients
- De-escalate the dose
- Initiate the combination modules of AZD7648
- Stop the dose escalation
- Adjust the dosing frequency, schedule or sequence of AZD7648, with or without a concurrent change in dose
- Adjust the dosing frequency, schedule or sequence of the combination agent, with or without a concurrent change in dose
- Initiate optional expansion cohorts (PD and/or efficacy expansion and/or food effect cohorts)
- Declare the MTD, MFD, and/or RP2D for the Core Module or combination modules
- Initiate Part B cohort expansions
- Stop Part B of a study module
- Permit a patient to dose escalation (intra-patient dose escalation).

Investigators will be provided with written confirmation of the next dose level based upon the SRC decision. Regulators/ethics bodies will be formally notified, as required by local regulation, of an SRC recommendation to temporarily halt or prematurely stop the study.

6.2 Preparation/handling/storage/accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorised site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

6.3 Measures to minimise bias: randomisation and blinding

This is an open-label study; no blinding is required.

In case of parallel recruitment to Part A and Part B (in the combination modules), a suitable patient allocation system will be implemented to manage any potential bias.

If an unscheduled assessment is performed, and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

6.4 Treatment compliance

The first single dose of AZD7648 will be taken whilst the patient is in the clinic (Cycle 0, Day 1) and the administration of this dose will be recorded in the appropriate section of the CRF.

From Cycle 1 onwards, patients will self-administer AZD7648. All patients will be required to complete a Patient Diary, which must be returned to the clinic for review at each visit. The Patient Diary will contain detailed instructions on how to take the study treatment. The patient should be instructed to record the date and time that all dose(s) of AZD7648 were taken in the Patient Diary. If a dose is missed, the reason must be noted in the Patient Diary. The emergency address and telephone number should be written on a Patient Diary and the patient will be instructed to keep this in their possession at all times. A copy of the Patient Diary is provided in the study reference materials.

Study site staff will make tablet counts at regular intervals during treatment. Compliance will be assessed by the tablet count and the information will be recorded in the appropriate section of the CRF. After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the investigative site until reconciliation is completed by the study monitor. All patients must return their bottle(s) of AZD7648 at the appropriate scheduled visit, when a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded by the patient on their Patient Diary and by the site staff on the CRF.

Patients must return all containers and any remaining tablets at the end of the study.

Any change from the dosing schedule, does interruptions, dose reductions, dose discontinuations should be recorded in the CRF.

The Investigational Product Storage Manager is responsible for managing the study treatment from receipt by the study site until the destruction or return of all unused study treatment. The Investigator(s) is responsible for ensuring that the patient has returned all unused study treatment.

6.5 Concomitant therapy

Unless clinically indicated, patients should avoid taking additional non-study medications that may interfere with the study treatments. Any medication or vaccine, including over-the-counter or prescription medicines, that the patient is receiving at the time of enrolment or receives during the study must be recorded in the CRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Details of prohibited medications are detailed in Table 5 and Appendix F includes guidance regarding potential interactions with concomitant medications.

Table 5 Prohibited medications

Prohibited medication/class of drug:	
Unless stated otherwise, these medications are prohibited from the time that patients enter the main screening period until the last dose of study treatment. The pre-screen may be done whilst on prior therapy	
Any investigational anti-cancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, biologic or hormonal therapy, or any other novel agent for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment **Note**: concurrent use of hormones for non-cancer-related conditions, eg, insulin for diabetes and stable dose of hormone replacement therapy and luteinising hormone replacement therapy analogues (> 6 months) is acceptable. Palliative radiotherapy may be used for the treatment of pain, provided the Investigator does not consider these are indicative of clinical progression. Study treatment should be discontinued a minimum of 3 days before a patient undergoes palliative radiotherapy, and study treatment restarted within 4 weeks (provided any bone marrow toxicity has recovered)
Herbal medications and supplements	Should not be given concomitantly unless agreed by the Sponsor. This is due to their potential to modulate CYP3A4 activity (see below and further details in Appendix F)

Table 5 Prohibited medications

Prohibited medication/class of drug:	
Concomitant medications known to significantly modulate CYP3A4 activity	The principal enzyme for metabolising AZD7648 is CYP3A4. Patients should avoid concomitant medications and foods known to significantly modulate CYP3A4 activity (potent/strong inhibitors or inducers of CYP3A4). The required washout period prior to starting study treatment is 3 weeks (5 weeks for enzalutamide or phenobarbital) until 28 days after the last dose of study treatment See also Appendix F
Live virus and bacterial vaccines	Prohibited whilst the patient is receiving study treatment and during the 28-day follow-up period

6.5.1 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF.

If the Investigator, based on his medical judgement, feels that medications described above are essential to patient's wellbeing, such products may be administered with caution following discussion between the Investigator and the AZ Study Physician.

Patients who are taking warfarin may participate in this study; however, it is recommended that INR be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin, low molecular weight heparin, and new oral anticoagulants (NOACs) are permitted. The use of granulocyte-colony stimulating factor (G-CSF) is not permitted for primary prophylaxis or secondary prophylaxis during Cycle 0 or Cycle 1 (unless deemed by the investigator that this is essential to the patient's well-being). If required for secondary prophylaxis from Cycle 2 onwards, this should be administered following discussion between the Investigator and the AZ Study Physician.

6.5.2 Support medication

There is no antidote medication for AZD7648; restricted medications are described in Appendix F. Rescue medication for PLD in Combination Module 1 will follow the local label.

The use of rescue medications is allowable at any time during the study. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded in the CRF.

Concomitant medications or treatments (eg, paracetamol or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as described in Table 5), are to be administered as prescribed by the Investigator.

Best supportive care, including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management (including palliative radiotherapy) should be used for all patients, when necessary.

Inactivated viruses, such as those in the influenza vaccine are permitted during the study.

AstraZeneca recommends avoiding administering COVID-19 vaccination for 72 hours prior to administration of the first dose of study drug, or during the dose-limiting toxicity period, to avoid biases in the interpretation of safety data due to the potential overlap of vaccine-related AEs with study drug-related AEs.

6.6 Dose modification

Details of dose escalation can be found in Section 6.1.2.

Study treatment will be repeated in 28-day cycles. The dosing criteria for Day 1 of a new cycle of study treatment (blood tests should be reviewed prior to dosing) and continuation of treatment are:

- ANC $\geq$ 1500 cells/mm^3 ($\geq$ 1.5 x 10^9/L)
- platelets $\geq$ 75,000/mm^3 ($\geq$ 75 x 10^9/L)

If a patient experiences a clinically significant and/or unacceptable toxicity (including a DLT) study treatment will be interrupted (and appropriate treatment administered) for a maximum of 28 days until resolution of the toxicities to the patient's baseline or until improvement (CTCAE Grade $\leq$ 2) (Table 6). Clinically significant abnormal laboratory values must be repeated at regular intervals until resolved to the patient's baseline or until improvement (CTCAE Grade $\leq$ 2). If the patient is showing clinical benefit and the toxicity resolves to the patient's baseline or until improvement (CTCAE Grade $\leq$ 2), treatment can be restarted; guidelines are provided below for dose modifications (Table 7).

If the toxicity does not resolve to the patient's baseline or to CTCAE Grade $\leq$ 2 within 28 days of onset, treatment with AZD7648 must be discontinued.

Table 6 Management of AZD7648 treatment related toxicity

Event (CTCAE V5.0)	Action
Grade 1 to 2 toxicity (all events)	Investigator judgement to continue treatment or interrupt dose (maximum 28 days), except for Day 1 of a new cycle of study treatment, as described above. Initiate optimal supportive care and causality investigation. Consider resuming at the same dose level when toxicity has resolved or is resolving with prophylactic treatment (if appropriate). If toxicity recurs on rechallenge and does not resolve in < 7 days despite optimal supportive care, consider a dose reduction.
Grade 3 to 4 toxicity (1st event)	Interrupt study treatment, initiate optimal supportive care and causality investigation. Maximum treatment interruption is 28 days. When toxicity has resolved or is resolving with prophylactic treatment (Grade ≤ 2 or returns to baseline), consider re-starting AZD7648 with 1 dose level reduction and prophylactic treatment (if appropriate).
Grade 3 toxicity (recurrence of same AE)	Interrupt study treatment, initiate optimal supportive care and causality investigation. Maximum treatment interruption is 28 days. When toxicity has resolved or is resolving (Grade ≤ 2 or returns to baseline), consider re-starting AZD7648 with 1 dose reduction and prophylactic treatment (if appropriate). After 2 dose reductions, consider permanent discontinuations of AZD7648 for Grade 3 events.
Grade 4 toxicity (recurrence of same AE)	Patients should permanently discontinue AZD7648.

Table 7 Dose modification of study treatment AZD7648

First dose reduction	Previously determined “acceptable safety” dose level.
Second dose reduction	Previously determined “acceptable safety” dose level.
Third dose reduction	Consider permanent discontinuation of AZD7648 unless the patient is deriving clinical benefit.

Patients enrolled into the first 3 dose cohorts are permitted to dose reduce to the previous dose cohort, but must discontinue if a dose reduction is required in the first dose level.

6.7 Treatment after the end of the study

Patients are permitted to either receive standard of care therapy, or to continue to receive study treatment following the end of the study if, in the opinion of the Investigator, they are continuing to receive benefit from treatment. After discontinuation of study treatment, the Investigator will be at liberty to define further the most appropriate anti-cancer treatment. Subsequent anti-cancer treatment is expected to be initiated following the cancer recurrence or development of a new cancer. Information on subsequent anti-cancer therapies should be recorded on the clinical database.

7 PATIENT DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

7.1 Discontinuation of study treatment

Patients may be discontinued from study treatment in the following situations. Note that discontinuation from study treatment is NOT the same as a complete withdrawal from the study:

- Disease progression (confirmed progression or symptomatic deterioration or confirmed progression by RECIST criteria).
- Adverse event, eg, study treatment-related toxicity that fail to recover to CTCAE Grade ≤2 or the patient's baseline within 28 days. Patients that withdraw due to treatment-related toxicity must be observed until resolution of toxicity to CTCAE Grade ≤1 or the patient's baseline.
- Patient or Investigator decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
- Pregnancy.
- Non-compliance with the CSP (Investigator or patient).
- Patients incorrectly initiated on study treatment.
- Unexpected, significant or unacceptable risk to the patients enrolled in the study.
- Lack of evaluable and/or complete data.
- Decision to modify the development plan of the drug.
- Sponsor termination of study due to unfavourable risk-benefit.

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Temporary discontinuation

See Section 6.6 for further details on study treatment interruptions.

7.1.2 Rechallenge

See Section 6.6 for further details on study treatment interruptions.

7.1.3 Procedures for discontinuation of study treatment

The Investigator should instruct the patient to contact the site before or at the time if study treatment is stopped. A patient that decides to discontinue study treatment will always be asked about the reason(s) and the presence of any AEs. The date of last intake of study treatment should be documented in the CRF. All study treatment should be returned by the patient at their next on-site study visit or unscheduled visit. Patients permanently

discontinuing study treatment should be given locally available standard of care therapy, at the discretion of the Investigator.

Discontinuation of study treatment, for any reason, does not impact on the patient's participation in the study. The patient should continue attending subsequent study visits and data collection should continue according to the study protocol. If the patient does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the patient, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

7.2 Lost to follow-up

A patient will be considered potentially lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient or next of kin by eg, repeat telephone calls, certified letter to the patient's last known mailing address or local equivalent methods. These contact attempts should be documented in the patient's medical record.
- Efforts to reach the patient should continue until the end of the study. Should the patient be unreachable at the end of the study the patient should be considered lost to follow-up with unknown vital status at end of study and censored at latest follow-up contact.

7.3 Withdrawal from the study

A patient may withdraw from the study (eg, withdraw consent), at any time (study treatment **and** assessments) at his/her own request, without prejudice to further treatment.

A patient who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, he/she may request destruction of any samples taken, and the Investigator must document this in the site study records.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AE. The Investigator will follow up patients as medically indicated.

AstraZeneca or its delegate will request Investigators to collect information on patients' vital status (dead or alive; date of death when applicable) at the end of the study from publicly available sources, in accordance with local regulations. Knowledge of the vital status at study end in all patients is crucial for the integrity of the study.

See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. All study treatment should be returned by the patient.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA.

The Investigator will ensure that data are recorded on the CRF. The Web Based Data Capture system will be used for data collection and query handling.

The Investigator ensures the accuracy, completeness and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed CRF. A copy of the completed CRF will be archived at the study site.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The number of samples taken, as well as the volume required for each analysis, may be changed during the study as emerging data become available. However, the estimated total volume of blood that will be drawn from each patient in this study during screening and the first cycle of treatment will not exceed approximately 350 mL (over a 1 month period). Any additional requirements are specified within the relevant section of Combination Module 1. Safety laboratory assessments will be performed locally at each centre's laboratory by means of their established methods. Therefore, the number of samples/blood volumes is patient to site-specific change.

8.1 Efficacy assessments

8.1.1 Tumour assessments by CT or MRI

RECIST 1.1 guidelines for measurable and non-measurable TLs and non-target lesions (NTLs) and the objective tumour response criteria are presented in Appendix H of this protocol.

At baseline, the imaging modalities used for assessment should be contrast enhanced computed tomography (CT) (magnetic resonance imaging [MRI] where CT is contraindicated) scans of the brain, chest, abdomen and pelvis (including liver and adrenal glands) and should encompass all areas of known predilection for metastases in the disease under evaluation, and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Follow-up CT or MRI assessments will cover chest, abdomen and pelvis with any other regions imaged at baseline where disease was present. Any other sites at which new disease is suspected should also be appropriately imaged. A CT/MRI scan of the brain should be performed in all patients at the main screen.

Radiological examinations performed in the conduct of this study should be retained at site as source data. All treatment decisions will be based on site assessment of scans. Baseline radiological assessments should be performed no more than 28 days before the start of study treatment, and ideally should be performed as close as possible to the start of study treatment. Scans obtained as part of standard clinical practice, prior to informed consent, but within the 28-day period are acceptable. The radiological confirmatory scans should be performed no less than 4 weeks after the prior assessment of tumour and preferably at the next scheduled visit (in the absence of clinically significant deterioration).

The methods of assessment used at baseline should be used at each subsequent follow-up assessment through to objective confirmed radiological disease progression, as defined by

RECIST 1.1 and as determined by the Investigator. Tumour assessments should be performed every 8 weeks (2 cycles) (± 1 week) or earlier, if disease progression is suspected. If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression then the patient should continue to be followed (unless they withdraw consent) until confirmed objective disease progression, as defined by RECIST 1.1. Scans confirming progression should not be conducted within 1 week after a progression biopsy to allow for reduction in inflammation.

If scans are performed outside of scheduled visit window interval and the patient has not progressed, every attempt should be made to perform the subsequent scans at their scheduled visits whilst the patient remains on study treatment. If the patient interrupts treatment or incurs a treatment delay, scans should continue to occur at the protocol-defined frequency.

It is important to follow the assessment schedule as closely as possible. Please refer to the SoA.

8.1.2 Tumour evaluation

Categorisation of objective tumour response assessment will be based on the RECIST 1.1 criteria of response: CR, PR, and SD (see Appendix H). The CR and PR will need to be confirmed. In addition, the objective tumour response assessment will also be assessed for exploratory analysis on a modified RECIST 1.1 (mRECIST) criteria considering progression only when confirmed. The mRECIST will not be used for the Core Module or Combination Module 1, but will be used if any immune oncology (IO) combination modules are added to the study in the future. TL progression will be calculated in comparison to when the tumour burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of progression, tumour response will be calculated in comparison to the pre-dose tumour measurements obtained before starting treatment.

If the Investigator is in doubt as to whether progression has occurred, particularly with response to NTLs or the appearance of a new lesion, it is advisable to continue treatment until the Investigator reassesses the patient's status at the next scheduled assessment (confirmation) or sooner if clinically indicated.

To achieve 'unequivocal progression' based on non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of 1 or more NTLs is usually not sufficient to qualify for unequivocal disease progression status.

If repeated scans confirm progression, then the date of the initial scan should be declared as the date of progression. All RECIST assessment images will be reviewed at site. Duplicates

may be collected and stored by an AstraZeneca appointed representative, and sent for independent central RECIST review, if deemed appropriate.

8.1.3 Survival assessment

In Part B of Combination Module 1, survival status will be obtained for all patients who receive study treatment. Vital status (dead or alive; date of death) will be collected every 3 months (±1 week) post-permanent discontinuation of study treatment. To aid the interpretation of the survival analysis, the use of subsequent anti-cancer therapies, after discontinuation of study treatment, will also be recorded on the CRF.

Survival status will continue to be collected until the earlier of 12 months after the last patient has discontinued treatment in a given module or 75% of patients have died in the module. The patient does not have to attend the clinic for the assessment to be carried out; it can either be done via a telephone call, or through a review of the patient's notes, or using public records. If the site becomes aware that a patient has died prior to the final analysis, the relevant CRF on the database should be completed at that time.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Clinical safety laboratory assessments

See Table 8 for the list of clinical safety laboratory tests to be performed and to the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the Laboratory Manual and the SoA.

The Investigator should assess the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.7. Further details on CTCAE Grade 3 or 4 laboratory values defined as DLTs can be found in Section 6.1.3. Clinically significant abnormal laboratory values must be repeated at regular intervals until resolved to the patient's baseline or to CTCAE Grade ≤2.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate CRF.

The haematology, coagulation, clinical chemistry, and urinalysis will be performed at the local laboratory (a copy of laboratory reports will be available as source data).

Table 8 Laboratory safety variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count) [a]	S/P-Alkaline phosphatase
B-Platelet count	S/P-Aspartate transaminase
B-Reticulocyte count	S/P-Alanine transaminase
Coagulation	S/P-Albumin
INR	S/P-Potassium
Activated Partial Thromboplastin Time (APTT)	S/P-Calcium, total
Urinalysis (dipstick)	S/P-Sodium
U-Hb/Erythrocytes/Blood	S/P-Urea nitrogen
U-Protein/Albumin	S/P-Phosphate
U-Glucose	S/P-Magnesium
	S/P-Gamma-glutamyl transferase
	S/P-Total protein
	Thyroid stimulating hormone (TSH) [b]
	C-reactive protein (CRP) [b]
	Tumour markers

[a] If absolute differentials are not available, % differentials (differential includes neutrophils, lymphocytes, monocytes, basophils, eosinophils) will be provided.

[b] TSH to be measured at baseline and every 3 cycles. CRP to be collected at baseline, then on Day 1 from Cycle 1. Urinalysis at Cycle 0, Cycle 0+1 and Day 1 of each cycle. Tumour markers (if relevant) to be measured at baseline and on Day 1 of every cycle from Cycle 1 (only if elevated at baseline).

NB. In case a patient shows an AST **or** ALT ≥ 3 x ULN together with total bilirubin (TBL) ≥ 2 x ULN please refer to Appendix E 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law (HL), for further instructions.

8.2.2 Physical examinations

Physical examinations will be conducted at visits described in the SoA; height will be measured at screening only.

A complete physical examination will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, pelvis, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.

Investigators should pay special attention to clinical signs related to previous serious illnesses, new or worsening abnormalities may qualify as AEs, see Section 8.3.7 for details.

Targeted physical examinations will be performed throughout the treatment period, at the discretion of the Investigator eg, for new or worsening symptoms and/or signs.

8.2.3 Body weight

Body weight will be recorded at each visit as indicated in the SoA.

8.2.4 Vital signs

- Oral temperature (in degrees Celsius), pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in supine or sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (eg, television, mobile phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of one pulse rate measurement, one blood pressure measurement, and one temperature measurement.
- Vital signs will be measured prior to ECG and PK blood draws at all PK sample timepoints. Timepoints may be modified based on initial data obtained.

8.2.5 Electrocardiograms

- In Part A: triplicate 12-lead ECG will be obtained for all timepoints using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. For triplicate ECG measurements, 3 individual ECG tracings should be obtained in succession, no more than 2 minutes apart. The full set of triplicates should be completed within 5 minutes.
- In Part B, triplicate 12-lead ECG will be obtained for screening only, at all other timepoints a single 12-lead ECG will be obtained.
- ECGs will be obtained after the patient has been resting. All ECGs should be recorded with the patient in the same physical position.
- ECGs will be measured after vital signs and prior to PK blood draws at all PK sample timepoints. Timepoints may be modified based on initial data obtained.

8.2.6 Performance status

The patient's performance status will be assessed at screening using the ECOG PS scale. Patients must have an ECOG PS of 0 to 1 to be eligible for enrolment.

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis (Oken et al 1982, see Table 9).

Table 9 Eastern Cooperative Oncology Group Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Vital status (dead or alive; date of death) will be collected during survival follow-up for patients entered in the study, and for patients that are screen failures

8.3 Collection of adverse events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

AE will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorised representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow-up AEs see Section 8.3.3.

8.3.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.2 Time period and frequency for collecting AE and SAE information

AEs will be collected from time of signature of ICF throughout the treatment period and including the 28-day follow-up visit after treatment discontinuation.

All SAEs will be recorded from the time of signing of ICF until the 28-day follow-up visit after treatment discontinuation. Only SAEs related to the study treatment and/or procedure will be recorded thereafter (during the progression follow-up).

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix B. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study patients. However, if the Investigator learns of any SAE, including a death, at any time after a patient's last visit and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator may notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix B.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All events will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up.

Any AEs that are unresolved at the patient's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 AE data collection

The following variables will be collected for each AE:

- Adverse event (verbatim)
- The date and time when the AE started and stopped
- The CTCAE grade (v5.0) and changes in CTCAE grade with the date they changed
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product(s) (yes or no)
- Action taken with regard to study treatment
- Adverse event caused patient's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- Adverse event is serious due to
- Date of hospitalisation
- Date of discharge

- Probable cause of death (as applicable)
- Date of death (as applicable)
- Autopsy performed (as applicable)
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.5 Causality collection

The Investigator will assess causal relationship between study treatment and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the study treatment?'

For SAEs, causal relationship will also be assessed for other medications and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

8.3.6 AEs based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study site staff *'Have you had any health problems since the previous visit/you were last asked?'* or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.7 AEs based on examinations and tests

The results from the CSP mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and clinical safety laboratory tests should therefore only be reported as AEs if they fulfil any of the criteria for a SAE, a DLT or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease progression (see Section 8.3.9).

8.3.8 Hy's law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 x ULN together with TBL ≥ 2 x ULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of HL.

8.3.9 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the study treatment is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events which are unequivocally due to disease progression should not be reported as an AE during the study.

8.3.10 New cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

8.3.11 Deaths

All deaths that occur during the study treatment period, or within the protocol-defined follow-up period after the administration of the last dose of study treatment, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the study Investigator at the next monitoring visit and should be documented in the CRF in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study Investigator as an SAE within 24 hours. It should also be documented in the Statement of Death page in the CRF. The report should contain a comment regarding the co-involvement of disease progression, if appropriate, and should assign main and contributory causes of death.

- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in the CRF. A post-mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual timeframe.

Deaths occurring after the protocol-defined safety follow-up period or after the administration of the last dose of study treatment should be documented in the Statement of Death page. If the death occurred as a result of an AE that started post the defined safety follow-up period and the AE is considered to be due to a late onset toxicity to study treatment, then it should also be reported as an SAE with an outcome of death.

8.4 Safety reporting and medical management

8.4.1 Reporting of SAEs

All SAEs have to be reported, whether or not considered causally related to the study treatment, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the CRF, an automated email alert is sent from the electronic data capture system to the designated AstraZeneca representative.

If the electronic data capture system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

For further guidance on the definition of a SAE, see Appendix B of the CSP.

8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study patient has received any study treatment

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.2.1 Maternal Exposure

If a patient becomes pregnant during the course of the study, study treatment should be discontinued immediately but the patient will remain in the study.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study treatment may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs during the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.4.1) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

8.4.2.2 Paternal Exposure

Information on the pregnancy of a patient's partner must be obtained directly from the patient's partner. Therefore, prior to obtaining information on the pregnancy, the Investigator must obtain the consent of the patient's partner.

Male patients must refrain from fathering a child or donating sperm during the study and for 90 days following the last dose of study treatment.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth,

or congenital anomaly) should, if possible, be followed up and documented. To capture information about a pregnancy from the partner of a male patient, consent must be obtained from the male patient's partner in order to collect information related to the pregnancy and outcome; the male patient should not be asked to provide this information. A consent form specific to this situation must be used.

The outcome of any conception occurring from the date of the first dose until 90 days after the last dose of study treatment should be followed up and documented.

8.4.3 Overdose

For this study, any dose of AZD7648 in excess of those specified in the protocol will be considered an overdose. Further details on the combination treatments can be found in the relevant combination module protocol.

There is currently no specific treatment in the event of overdose of AZD7648 and possible symptoms of overdose are not established.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study treatment occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 8.3.2. For other overdoses, reporting must occur within 30 days.

8.4.4 Medication error

If a medication error occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error (see Section 8.3.2) and within 30 days for all other medication errors.

The definition of a medication error can be found in Appendix B.

8.4.5 Management of IP-related toxicities

Details of DLTs can be found in Section 6.6.

8.5 Pharmacokinetics

Venous blood samples (2 mL) for determination of concentrations of AZD7648 and the potential metabolites (if any) in plasma will be taken at times presented in Table 10. Samples will be split to provide plasma for the primary analysis and secondary/backup analyses. The backup sample may be used for the metabolite identification work. Blood and urine samples for PK analysis will be collected as specified below (Table 10) and in the SoA (Table 1).

Full details of sample handling procedures, storage and shipping will be provided in the lab manual. The date and time of collection of each sample will be recorded.

Urine samples (~10 mL) for the determination of AZD7648 concentration will be taken from the total urine sample provided during each of the collection intervals. The date and time of collection and the volume of each total urine collection will be recorded. Approximately 50 mL of the urine sample may also be used to identify metabolites, if any.

Results will only be reported for samples shipped within a timeframe for which the stability of AZD7648 in the samples has been validated and shown to be acceptable.

All patients start with a single dose of AZD7648 to fully profile the PK of AZD7648, followed by an approximately 3 to 7 day washout. If the half-life of AZD7648 is shorter than expected the washout period can be shortened or may not be required at all.

Pharmacokinetic samples will be taken at the times indicated in Table 10.

Table 10 AZD7648 PK sample collection schedule in monotherapy cohorts

	Blood	Urine
Cycle 0, Day 1	Pre-dose, and 15 minutes (min), 30 min, 60 min, 2 hours (h), 4 h, 8 h, 10 h to12 h post-dose	Pre-dose, and 0 to 8 h, 8 to 24 h post-dose
Cycle 0, Day 2	24 h post-dose	
Cycle 0, Day 3	48 h post-dose	
Cycle 0, Day 4	72 h post-dose	
Cycle 1, Day 1	Pre-dose	
Cycle 1, Day 8 (or Visit Y for intermittent schedules)	Pre-dose, and 15 min, 30 min, 60 min, 2 h, 4 h, 8 h, 10 to12 h post-dose	0 to 8 h, 8 to 24 h post-dose note: urine not requited at Visit Y

	Blood	Urine
Cycle 2, Day 1	Pre-dose	
Cycle 3, Day 1	Pre-dose	
Cycle X, Day 1 (if a patient has a dose escalation to another dose, then, at the time of escalation); this provides the starting exposure at the time of escalation	Pre-dose and 1 h post-dose	
Cycle X+1, Day 1 (if a patient has a dose escalation at Cycle X then, at the next cycle Day 1)	Pre-dose and 1 h post-dose	
Discontinuation	Any 1 sample between 0 to 72 h post-last dose	

Please refer to Section 15.3 for PK collection details for Combination Module 1.

For patients who undergo intra-patient dose escalation (applicable to Core Module only), PK samples at pre-dose and 1 hour on the day of escalation (Cycle X, Day 1) and after one cycle (Cycle X+1, Day 1) of escalation will be obtained. Other PK time points maybe added as appropriate based on the emerging PK data.

PK Window

The following time windows will be allowed:

- 5 minutes (min) for samples taken up to 1 hour (h) post-dose
- 10 min for samples taken between 2 and 9 h
- 1 h for samples taken between 10 and 24 h post-dose
- 2 h for samples taken between 25 and 72 h

The timing of the PK samples may be adjusted during the study, dependent on emerging data, in order to ensure appropriate characterisation of the plasma concentration-time profiles. After 2 or more cohorts have been completed the timing of later PK samples will be re-assessed based on emerging PK data and the desire to characterise 80% of the AUC in all patients. The total number of samples taken from each patient will not exceed that presented in Table 10.

If a patient misses any doses of AZD7648 within 3 days of PK sampling, the Investigator should contact the AstraZeneca PK representative as to any effect on the changes required on the timing of the PK assessments. All other assessments, including laboratory safety assessments, vital signs and RECIST should continue to be performed as per study plan, relative to baseline assessments.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Any residual sample remaining after PK analysis has been performed may be used for exploratory biomarker research and characterisation of metabolites, if consent for this exploratory research has been obtained

Pharmacokinetic Sampling for Food Effect (if conducted)

Pharmacokinetic samples for food effect will be taken at the times indicated in Table 11.

Table 11 AZD7648 PK sample collection schedule in food effect cohort

	Blood
Cycle 0, Day 1	Pre-dose, and 15 minutes (min), 30 min, 60 min, 2 hours (h), 4 h, 8 h, 10 to 12 h post-dose
Cycle 0, Day 2	24 h post-dose
Cycle 0, Day 3	48 h post-dose
Cycle 0, Day 4	72 h post-dose
Cycle 1, Day 1	Pre-dose, and 15 min, 30 min, 60 min, 2 h, 4 h, 8 h, 10 to 12 h post-dose
Cycle 1, Day 2	24 h post-dose
Cycle 1, Day 3	48 h post-dose
Cycle 1, Day 4	72 h post-dose; continuous dosing starts here
Cycle 2, Day 1	Pre-dose
Cycle 3, Day 1	Pre-dose
Discontinuation	Any 1 sample between 0 to 72 h post-last dose

8.5.1 Determination of drug concentration

Samples for determination of AZD7648 and PLD (as total doxorubicin) concentrations in plasma, and AZD7648 concentrations in urine will be analysed by Covance on behalf of AstraZeneca, using appropriate bioanalytical methods. Full details of the analytical methods used will be described in a separate Bioanalytical Report.

All samples still within the known stability of the analytes of interest (ie, AZD7648 and PLD,) at the time of receipt by the bioanalytical laboratory will be analysed.

In addition, the PK samples may be subjected to further analyses in order to further investigate the presence and/or identity of drug metabolites. Any results from such analyses will be reported separately from the CSR.

8.5.2 Determination of 4β-hydroxy cholesterol concentrations for assessment of CYP3A4 induction potential

Blood samples will be collected from all patients at pre-dose of Cycle 0, Day 1; Cycle 1, Day 8, and Cycle 2, Day 1 in the AZD7648 monotherapy for the determination of 4β-hydroxy cholesterol concentrations in plasma. Analysis of 4β-hydroxy cholesterol will be performed by Covance on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical methods used will be described in a separate Bioanalytical Report.

8.5.3 Storage and destruction of pharmacokinetic samples

PK samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report.

8.6 Pharmacodynamics

The assessment of CCI [redacted]

CCI [redacted]

Investigation of PK/PD Relationship

Where possible, population modelling and simulation methods will be used as part of the evaluation to assess relationships between emerging safety, tolerability, PK and PD and covariates data. AstraZeneca will be responsible for these analyses and, if conducted, will be reported separately from the CSR.

8.6.1 Collection of blood for pharmacodynamics biomarker analysis

8.6.1.1 Collection of peripheral blood for pharmacodynamics biomarker analysis

The collection of blood-based CCI [redacted] is mandatory in all parts of the study to obtain a preliminary assessment of CCI [redacted]. Peripheral blood

samples will be collected pre-dose and 2 to 4 hours post-dose for AZD7648 as detailed in Table 12 and the SoA. In addition, there will be PK samples collected at the same time as PD samples to allow exploration of the exposure/PD relationships (see Table 10). The exact time of PD samples collection will be noted.

CCI [redacted]

CCI [redacted]

CCI [redacted].

Peripheral whole blood subpopulations may also be enumerated to determine any PD effects of potential immunological relevance, such as changes in the number of B lymphocytes or regulatory T lymphocytes.

The number of samples taken, as well as the volume required for each analysis, may be changed during the study as new data on AZD7648 becomes available. The estimated total volume of blood that will be drawn from each patient in this study for mandatory samples by

the end of Cycle 1 is as follows; for Part A dose escalation approximately 180 mL, and for patients in the Part B efficacy expansion approximately 180 mL.

Details of sample collection, processing, shipping and storage will be described in the Laboratory Manual.

8.6.1.2

CCI

CCI

.

8.6.1.3

CCI

CCI

8.6.1.4 Collection of additional blood samples

If any immune-related events are suspected, additional blood samples may be taken for further safety signal investigation. Blood samples will be collected as detailed in the SoAs.

8.6.2 Storage, re-use and destruction of pharmacodynamic samples

Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. The results of any investigation will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

A full chain of custody is maintained for all samples throughout their life cycle.

The Principal Investigator at each centre keeps full traceability of collected biological samples from the patients whilst in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples whilst in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

Details of sample collection, processing, shipping and storage will be described in the Laboratory Manual.

8.6.3 Collection of tumour samples for pharmacodynamics assessments

Fresh tumour biopsies are optional for all patients, unless they are enrolled into a Part A PD expansion cohort in which case, they are mandatory.

- Serial biopsies will be collected during screening, on treatment (any time in Cycle 1 between Day 3 and Day 8 [or Y] 2 to 8 hours post AZD7648 dosing), and on progression.
- A PK sample should also be taken at the time of any biopsy sample.

These samples will be analysed for the effects on CCI [redacted]

On-treatment biopsy timing may be refined with emerging PK and/or PD data during the course of the study.

Accessible lesions are defined as tumour lesions which are amenable to repeat biopsy, unless clinically contraindicated or the patient has withdrawn consent. Failure to obtain sufficient tumour sample after making best efforts to biopsy the tumour will not be considered a protocol deviation.

8.7 Genetics

8.7.1 CCI [redacted]

Approximately 10 mL blood sample for DNA isolation will be collected from patients who have consented to participate in the genetic analysis component of the study. Participation is optional. Patients who do not wish to participate in the genetic research may still participate in the study.

A pharmacogenetic sample will be collected at baseline and analysed for CCI [redacted]. This sample may also be analysed for other patient-selection markers and as a reference sample CCI [redacted] Only CCI [redacted]

See Appendix D for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in Appendix D.

8.7.2 Storage and destruction of genetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples may be stored for a maximum of

15 years or as per local regulations from the date of the Last Patient's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

No personal details identifying the individual will be available to AstraZeneca or designated organisations working with the DNA.

8.8 Biomarkers

Provision of archival tumour samples is mandatory for all patients. The samples may be submitted retrospectively. Details of sample collection, processing, shipping and storage will be described in the Laboratory Manual.

Archival Tumour Samples

Formalin fixed tumour tissue embedded in paraffin blocks are to be requested for all patients. If baseline biopsy samples can also be collected, retrieval of the archival diagnostic tumour material is still highly encouraged, to provide data on how the tumour has evolved since diagnosis. Archival samples from either primary or metastatic tumour will be accepted but tissue from the primary tumour is preferred. Where multiple archival samples are available, the most recently obtained is preferred.

Tumour tissue blocks are strongly preferred, however, freshly prepared unstained slides (minimum 10, preferably 20) of 4 micron sections from the archival tumour block are accepted if tumour blocks cannot be submitted. Associated pathology report should be provided along with the samples.

The analysis of archival tumour tissue may include, but is not limited to:

- CCI [redacted]
- Immunohistochemical staining for CCI [redacted]
- Gene expression analysis
  - To analyse exploratory biomarkers to assess correlations CCI [redacted].
  - To explore the feasibility of reliably identifying CCI [redacted] and to enable future diagnostic development, if required.

Other Optional Samples for Biomarker Research

Optional pre-dose plasma and serum sample and/or surplus blood, urine or tissue including patient specific archival or fresh tumour tissue, if available.

Samples will be used for potential future exploratory research and assay development for factors that may influence the development of AZD7648 to treat human disease and/or response to AZD7648 (where response is defined broadly to include efficacy, tolerability or safety). CCI [redacted] . CCI [redacted]

8.8.1 Storage, re-use and destruction of biomarker samples

Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study treatment to generate hypotheses to be tested in future research.

8.9 Health Economics

Health Economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

No statistical hypotheses are planned in this study.

9.2 Sample size determination

Approximately 192 evaluable patients may be enrolled in the Core Module (95 evaluable patients: 46 patients in the dose escalation (Part A) 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).

Core Module: Monotherapy AZD7648

Part A: will require approximately 46 evaluable patients across approximately 10 cohorts (n = 1 to 6 per cohort) to provide a model-based estimate of MTD with a target toxicity of 25% in patients with advanced solid tumours. The RP2D will be declared on data available

from a minimum of 6 evaluable patients, but up to 12 patients may be treated at the RP2D to explore chronic toxicity.

Expansion cohorts: as described in Section 6.1.2.1, 3 cohorts may be initiated; the anticipated sample sizes are:

- PD expansion cohort: up to 12 additional patients
- Efficacy expansion cohort: up to 25 additional patients (a subset of up to 12 patients which may have mandatory biopsies if PD data is also required)
- Food effect expansion cohort: up to 12 additional patients

Sample size details for Combination Module 1 can be found in Section 16.2.

9.3 Populations for analyses

For purposes of analysis, the following analysis sets are defined:

Analysis set	Definition
Enrolled	All patients who sign the ICF
Safety set	All patients who received at least 1 dose of any study treatment
DLT evaluable set	All patients who received at least 1 dose of any study treatment and either experienced DLT during the cycle 0 or 1, or who completed minimum safety evaluation requirements and has received at least 75% of the total amount of planned dose of AZD 7648 (and PLD for Combination Module 1). In the event of an intra-patient dose escalation, such patients will not be evaluable for DLT at the escalated dose
PK set	All patients who received at least 1 dose of any study treatment and have at least 1 reportable PK concentration without any protocol deviations that might affect PK
PD set	All patients who received at least 1 dose of any study treatment with at least 1 reportable PD measurement
Evaluable for efficacy set	All patients who received at least 1 dose of any study treatment and have a baseline tumour assessment
Evaluable for objective response	All patients who had a measurable baseline disease [a] by RECIST 1.1 assessment and received at least 1 dose of any study treatment

a Measurable disease is defined as having at least one measurable target lesion, not previously irradiated, which is ≥ 10 mm in the longest diameter (LD) (except lymph nodes which must have short axis ≥ 15 mm)

9.4 Statistical analyses

The statistical analyses will be performed by Parexel or other designated third-party providers, under the direction of the Biostatistics Group, AstraZeneca. Further detail will be provided in the Statistical Analysis Plan (SAP).

Data from each part/module will be presented separately. All patients who undergo intra-patient dose escalation will be analysed & reported as per their starting dose.

Methods common to all modules are detailed below.

Demographic Data

Characteristics of the patients, including medical history and disease characteristics at baseline will be listed for each patient and summarised by cohort.

Reasons for discontinuation of study treatment will be listed including the study day of treatment discontinuation and will be summarised by cohort.

Exposure

Exposure to each study treatment, ie, total amount of study treatment received will be listed for all patients.

Total treatment duration (=date of last dose minus date of first dose + 1) and actual treatment duration (=total treatment duration excluding dose interruptions not in accordance with the protocol) will be summarised for each study treatment and cohort by the following: mean, standard deviation, minimum, maximum, median, and number of observations. In addition, the number and percentage of patients with at least 1 non-protocolled dose interruption and at least 1 dose reduction will be presented separately for the initial period of evaluability defined as 28 days and for any time following this initial period of the study.

9.4.1 Efficacy analyses

These are secondary variables.

The efficacy assessment of Part A (dose escalation) will be done using ORR. All efficacy endpoints will be used in Part B (expansions) efficacy assessment.

Tumour Response Data

Data will be summarised for dosed patients with measurable disease at baseline and separately for dosed patients with a baseline tumour assessment, unless otherwise specified.

Data will be listed and summarised by cohort using the following response categories: CR, PR, SD, disease progression and not evaluable (NE).

Waterfall plots (bar charts) indicating the percentage best change from baseline in sum of the diameters of TLs may be produced by cohort.

Tumour response includes the following variables:

- Percentage best change in TL
- Duration of response
- PFS
- ORR

Derivation of tumour response variables

Every 8 weeks (2 cycles), or earlier if disease progression is suspected, patients will be programmatically assigned a RECIST visit response of CR, PR, SD, and disease progression depending on the status of their disease compared to baseline and previous assessments.

Progression of TLs will be calculated in comparison to when the tumour burden was at a minimum (ie, smallest sum of diameters previously recorded during the study). In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

If a patient has had a tumour assessment, which cannot be evaluated, then the patient will be assigned a response of NE unless there is evidence of progression in which case the response will be assigned as disease progression.

For TL measurements, if ⅓ of the TL sizes are missing then a scaling up rule will be applied as follows:

- If ≤ ⅓ of lesions recorded at baseline are missing then the results will be scaled up (based on the baseline sizes) to give an estimated sum of diameters and this will be used in calculations (this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the baseline sum of diameters excluding the lesions that are missing and determining at what rate the lesions are changing).
- If > ⅓ of lesions recorded at baseline are missing, then the TL response will be NE. However, if the sum of non-missing TL diameters would result in disease progression (ie, if using a value of 0 for missing lesions the sum of diameters has still increased by > 20% or more compared to the smallest sum of diameters on study), disease progression takes precedence over NE.
- A response of CR will not be allowed if any of the TL data are missing.

Percentage Best Change in TL

Percentage change in tumour size will be determined for patients with measurable disease at baseline and is derived at each visit by the percentage change in the sum of the diameters of TLs.

Duration of Response

Duration of response is defined as the time from the date of first documented response (which is subsequently confirmed) until date of documented progression or death in the absence of disease progression (ie, date of PFS event or censoring – date of first response + 1). The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint.

The time of the initial response will be defined as the latest of the dates contributing towards the first visit that was PR or CR that was subsequently confirmed. If a patient does not progress following a response, then their duration of response will use the PFS censoring time.

PFS

PFS is defined as the time from first dose of any study treatment at Cycle 1 until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from study therapy or receives another anti-cancer therapy prior to progression (ie, date of PFS event or censoring – date of first dose + 1). Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits.

ORR

ORR will be assessed per RECIST criteria. ORR is defined as the percentage of patients who have a confirmed visit response of CR or PR prior to any evidence of progression (as defined by RECIST 1.1). Note that responses that occur after the start of subsequent anti-cancer therapy must be excluded from the derivation of ORR.

A visit response of CR is defined when all TLs and NTLs present at baseline have disappeared (with the exception of lymph nodes which must be <10mm to be considered non pathological) and no new lesions have developed since baseline. A visit response of PR is defined when the sum of diameters of the TLs has decreased by 30% or more compared to baseline (with no evidence of progression) and the NTLs are at least stable with no evidence of new lesions.

In the case of SD, measurements should have met the SD criteria at least once after the study start.

When the Investigator reassesses the progression of the patient at a later date, the date of the initial scan should be declared as the date of progression if the repeat scans confirm progression.

Overall Survival

Overall survival is defined as the time from first dose of any study treatment at Cycle 1 until death due to any cause regardless of whether the patient withdraws from study treatment or receives another anti-cancer therapy (ie, date of death or censoring – date of first dose + 1). Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

Survival calls will be made in the week following the date of DCO for the analysis, and if patients are confirmed to be alive or if the death date is after the DCO date these patients will be censored at the date of DCO.

9.4.2 Safety analyses

These are primary variables.

All safety analyses will be performed on the safety analysis set. All patients who receive at least 1 dose of study treatment will be included in the assessment of the safety profile. At the end of the study, appropriate summaries of all safety data will be produced, as defined below.

Data from all cycles of initial treatment will be combined in the presentation of safety data. AEs will be listed individually by patient and cohort. For patients who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial dose group. The number of patients experiencing each AE will be summarised by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term and CTCAE grade. The number and percentage of patients with AEs in different categories (eg, causally related, CTCAE Grade ≥ 3 etc) will be summarised by dose regimen, and events in each category will be further summarised by MedDRA system organ class and preferred term, by dose group. SAEs will be summarised separately.

Any AE occurring before the first dose of study treatment (ie, before study Day 1) will be included in the data listings but will not be included in the summary tables of AEs. Treatment-emergent AEs occurring prior to first dose of investigational product (ie, before study Day 1) which subsequently worsen in severity following dosing will be included in the summary tables.

Any AE occurring within the defined 28-day follow-up period after discontinuation of study treatment will be included in the AE summaries. Any AEs in this period that occur after a patient has received further therapy for cancer (following discontinuation of study treatment) will be flagged in the data listings. AEs occurring after the 28-day follow-up period after discontinuation of study treatment will be listed separately, but not included in the summaries.

Haematology, clinical chemistry, vital signs, ECG data, ECOG PS, physical examination, demographic data, medical histories and concomitant medications will be listed individually by patient and suitably summarised. For all laboratory variables, which are included in the current version of CTCAE, the CTCAE grade will be calculated. Summary statistics of mean, median, standard deviation, minimum, maximum and number of observations will be used for continuous variables. Categorical variables will be summarised by frequency counts and percentages for each category [n (%)].

Details of any deaths will be listed for all patients.

Graphical presentations of safety data may be presented as is deemed appropriate. This may include, but is not restricted to, presentation of parameters against time, concentration or shift plots. Appropriate scatter plots may also be considered to investigate trends in parameters compared to baseline.

ECG Changes

QTc will be calculated using Fridericia's formula.

$QTcF = QT/(RR^{1/3})$

Clinical decisions at the site will be made based on QTcF.

9.4.3 Other analyses

PK, PD, and biomarker research and pharmacogenetics exploratory analyses will be described in a separate document. The population PK analysis and PD analyses will be presented separately from the main CSR.

9.4.3.1 PK Analyses

PK of AZD7648 is a secondary variable.

The PK Analysis Set includes patients who have reportable plasma concentrations and PK parameters and who have no important protocol deviations or AEs that may impact on PK.

Following single dose the following parameters maybe determined: C_{max}, time to reach maximum plasma concentration (t_{max}), terminal rate constant (λ_z), terminal half-life ($t_{1/2}\lambda_z$), area under the plasma concentration-time curve from zero to 24 hours (AUC_{0-24}), from zero to the time of the last measurable concentration (AUC_{0-t}) and from zero to infinity (AUC), apparent plasma clearance (CL/F), apparent volume of distribution ($V_{ss/f}$; $V_{z/f}$), mean residence time (MRT), renal clearance (CLR) and amount of drug excreted unchanged (Ae; % dose).

Following multiple dose (assuming SS conditions): Maximum plasma concentration at steady state ($C_{max,ss}$), time to C_{ss} max ($t_{max,ss}$), $C_{min,ss}$, area under the plasma concentration-time curve from zero to the end of the dosing interval (AUC_{ss}), apparent plasma clearance at steady state ($CL_{ss/f}$), extent of accumulation on multiple dosing (RAC), time dependency of the PK. Where possible other appropriate PK parameters may also be determined.

PK analysis of plasma concentration data for AZD7648 will be performed by AstraZeneca, or a CRO on behalf of AstraZeneca, using actual elapsed sampling times and standard Non Compartmental methods.

Statistical Analysis Methods for Assessment of Pharmacokinetic Food Effect

To evaluate the effect of food on the PK obtained after dosing with AZD7648 tablet, the primary PK parameters will be analysed using a linear mixed Effects model with treatment (fed/fasted) as a fixed effect and patient as a random effect to compare AUC0-t and Cmax in the fed state with AUC0-t and Cmax in the fasted state respectively. Log-transformation of exposure measurements (AUC0-t and Cmax) will be performed prior to analysis. The point estimate and 90% confidence interval (CI) for the ratio of geometric means for fed and fasted states will be provided. The food effect on a log scale (fed – fasted) and its upper and lower confidence limits will be exponentially back transformed to (and presented in) the linear scale. Further details will be provided in the SAP.

COMBINATION MODULE 1 – AZD7648 AND PEGYLATED LIPOSOMAL DOXORUBICIN

This section contains additional information specific to Combination Module 1; please refer to Sections 1 to 9 for information which applies to the overall study.

10 PROTOCOL SUMMARY

10.1 Schedule of Assessments – Combination Module 1

The SoA for the lead-in and on-treatment period for Combination Module 1 is shown in Table 13 below.

Table 13 Schedule of assessments – Combination Module 1

Part A:

	Screening	Single Dose				Multiple Dose										IP Disc	28-day FU After IP Disc	Details in Section
		Cycle 0				Cycle 1[a] Weekly Visit[b]					Cycle 2[a]		Cycle 3[a]	Cycle 4-6[a]	Cycle 7+[a]			
Day	**-28 to -1**	**1**	**2**	**3**	**4**	**1**	**Y[b,c]**	**8[b,c]**	**15**	**22**	**1**	**15**	**1**	**1**	**1**			
Visit Window[d]	-	-	-	-	-	-	-	-	-	-	±1	±1	±2	±2	±2	-	±7	
Informed consent	X																	5.1
Demographics and medical history, including tumour gene mutations[e]	X																	5.1
Physical examination	X	X	X[f]			X	X[f]				X		X[f]	X[f]	X[f]	X[f]	X[f]	8.2
Height	X																	8.2
Weight	X	X				X	X	X	X	X	X	X	X	X	X	X		8.2
Vital signs[g]	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	8.2
ECG[g]	X	X				X	X				X		X	X	X	X		8.2
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.5 14.3
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[h]	X	8.3
Pregnancy test[i]	X	X[i]				X[i]					X		X	X	X	X		5.1
Haematology, coagulation, chemistry, urinalysis, tumour marker, TSH[j]	X	X				X	X	X	X	X	X	X	X	X	X	X	X	8.2
ECOG PS	X	X				X	X				X		X	X	X	X		8.2
ECHO[k]	X													X	X			15.2

	Screening	Single Dose				Multiple Dose										IP Disc	28-day FU After IP Disc	Details in Section
		Cycle 0				Cycle 1[a] Weekly Visit[b]					Cycle 2[a]		Cycle 3[a]	Cycle 4-6[a]	Cycle 7+[a]			
Day	**-28 to -1**	**1**	**2**	**3**	**4**	**1**	**Y[b,c]**	**8[b,c]**	**15**	**22**	**1**	**15**	**1**	**1**	**1**			
Visit Window[d]	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**±1**	**±1**	**±2**	**±2**	**±2**	**-**	**±7**	
Archival tumour[l]	X																	8.8
Fresh tumour biopsy with biomarker analyses[m]	X						X									X		8.8 15.5
PK AZD7648 blood [n]		X	X	X	X	X	X	X			X		X			X		8.5
PK PLD blood[n]						X					X							8.5 15.3
CCI	X					X[p]	X[q]	X[q]			X[p]					X[r,s]		8.6.1.1 8.6.1.4
CCI	X					X[p]	X[q]	X[q]	X[q]		X[p]	X[q]	X[q,r]	X[p,r]	X[q,r]	X[r]		8.6.1.2
CCI	X					X[p]	X[q]	X[q]	X[q]		X[p]	X[q]	X[q,r]	X[q,r]	X[q,r]	X[r]		8.6.1.3
Tumour assessment	X												X[t]	X[t]	X[t]			8.1
PGx (optional)						(X)												8.7
																		Appendix D
CCI		X				X	X	(X)	(X)	(X)	X	(X)	X	X	X			14.1
PLD dosing						X					X		X	X				14.1

CCI; Disc=discontinuation; DNA=deoxyribonucleic acid; ECG=Electrocardiogram; ECHO=Echocardiography; ECOG PS=Eastern Cooperative Oncology Group performance status; FU=Follow-up; IP=Investigational Product; PD=Pharmacodynamics; PGx=pharmacogenetic sample; PK=Pharmacokinetics; PLD=Pegylated liposomal doxorubicin; TSH=Thyroid-stimulating hormone.

[a] 1 cycle = 28 days. Cycles repeat on a continuous basis with no interval between cycles.

[b] Weekly visit may be omitted if Visit Y is within 2 days of weekly visit.

[c] Visit Y is only utilised if the dosing schedule is intermittent. Visit Y represents the last AZD7648 dosing day in the first block of AZD7648 treatment in a cycle eg, CCI

[d] There are no visit windows in Cycle 0 and Cycle 1.

[e] With the patient's consent, as part of the medical history, any available information on known tumour gene mutations will be collected.

[f] Targeted physical examinations only required if clinically indicated (indication should be stated).

[g] Vital signs then ECG measurements will be collected prior to PK blood draws at all PK sample timepoints. Timepoints may be modified based on the initial data obtained.

[h] Serious adverse events (SAEs) only to be collected between AZD7648 discontinuation and disease progression.

[i] Women of child-bearing potential must have a negative urine or serum pregnancy test at screening, a confirmatory test before treatment on Day 1 (Cycle 0 or Cycle 1), at regular intervals during treatment and at AZD7648 discontinuation. If results are positive, the patient is ineligible/must be discontinued from the study treatment and not discontinued from the study. The patient will continue to be followed up according to the study protocol.

[j] TSH to be measured at baseline and every 3 cycles. CRP to be collected at baseline, then on Day 1 from Cycle 1. Urinalysis at Cycle 0, Cycle 0 + 1 and Day 1 of each cycle. Tumour markers (if relevant) to be measured at baseline and on Day 1 of every cycle from Cycle 1 (only if elevated at baseline).

[k] LVEF assessment (ECHO or MUltiGated Angiography [MUGA]) and review must occur at screening and prior to dosing at Cycle 4 Day 1 and Cycle 7 Day 1 (-7 day window).

[l] Provision of archival tumour samples are mandatory for all patients. The samples may be submitted retrospectively.

[m] Fresh biopsy samples are encouraged in Part A (particularly in patients with accessible tumours) and are mandatory for patients enrolled into Part A optional PD expansion cohorts (or a PD subgroup of an optional efficacy expansion cohort). Serial biopsies will be collected during screening, on treatment (any time in Cycle 1 between Days 3 and Visit Y 2 to 8 hours [h] post AZD7648 dosing), and on progression.

[n] CCI

[o] I CCI

[p] On Cycle 1, Day 1 and Cycle 2, Day 1 (or nearest weekly visit if within 2 days) collect the samples on arrival at clinic, then 4 h after the start of the PLD infusion (before AZD7648 tablet ingestion), and finally 2 to 4 h after AZD7648 treatment. Note time of each blood draw.

[q] Only collect sample 2 to 4 h post –dose AZD7648 noting time of blood draw.

[r] From Cycle 3, Day 1, sample should be taken on each radiological assessment (±7 days), disease progression or treatment discontinuation.

[s] If any immune-related events are suspected, additional blood samples may be taken for further safety signal.

[t] Tumour assessments should be conducted every 8 weeks (±1 week) from start of combination treatment (Cycle 1, Day 1) until confirmed objective disease progression; frequency may be adjusted after 2 years of treatment if the tumour is not changing in size (complete response [CR], partial response [PR], or stable disease [SD]).

[u] On clinic days, patients should not take the study treatment until instructed to do so by clinic staff. (X) indicates that an AZD7648 intermittent dosing schedule may be explored.

Part B:

	Screening	Multiple Dose										IP Disc	28-day FU After IP Disc	Survival	Details in Section
		Cycle 1[a] Weekly Visit[b]					Cycle 2[a]		Cycle 3[a]	Cycle 4-6[a]	Cycle 7+[a]				
Day	**-28 to -1**	**1**	**Y[b,c]**	**8[b,c]**	**15**	**22**	**1**	**15**	**1**	**1**	**1**				
Visit Window[d]	**-**	**-**	**-**	**-**	**-**	**-**	**±1**	**±1**	**±1**	**±2**	**±2**	**-**	**±7**		
Informed consent	X														5.1
Demographics and medical history, including tumour gene mutations[e]	X														5.1
Physical examination	X	X	X[f]				X[f]		X[f]	X[f]	X[f]	X[f]	X[f]		8.2
Height	X														8.2
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X		8.2
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X		8.2
ECG[g]	X	X	X				X		X	X	X	X			8.2
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X		6.5 14.3
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X[h]	X		8.3
Pregnancy test[i]	X	X[i]					X		X	X	X	X			5.1
Haematology, coagulation, chemistry, urinalysis, tumour marker, TSH[j]	X	X	X	X	X	X	X	X	X	X	X	X	X		8.2
ECOG PS	X	X	X				X		X	X	X	X			8.2
ECHO[k]	X									X	X				15.2
Archival tumour[l]	X														8.8

	Screening	Multiple Dose										IP Disc	28-day FU After IP Disc	Survival	Details in Section
		Cycle 1[a] Weekly Visit[b]					Cycle 2[a]		Cycle 3[a]	Cycle 4-6[a]	Cycle 7+[a]				
Day	**-28 to -1**	**1**	**Y[b,c]**	**8[b,c]**	**15**	**22**	**1**	**15**	**1**	**1**	**1**				
Visit Window[d]	-	-	-	-	-	-	±1	±1	±1	±2	±2	-	±7		
Fresh tumour biopsy with biomarker analyses[m]	X		X									X			8.8 15.5
PK AZD7648 blood[n]		X	X				X		X			X			8.5
PK PLD blood[n]		X					X								8.5 15.3
CCI	X	X[o]	X[p]	X[p]			X[o]					X[q,r]			8.6.1.1 8.6.1.4
CCI	X	X[o]	X[p]	X[p]	X[p]		X[o]	X[p]	X[p,q]	X[p,q]	X[p,q]	X[q]			8.6.1.2
CCI	X	X[o]	X[p]	X[p]	X[p]		X[o]	X[p]	X[p,q]	X[p,q]	X[p,q]	X[q]			8.6.1.3
Tumour assessment	X								X[s]	X[s]	X[s]				8.1
Survival assessment														X[t]	8.1
PGx (optional)		(X)													8.7 Appendix D
AZD7648 dosing[u]		X	X	(X)	(X)	(X)	X	(X)	X	X	X				14.1
PLD dosing		X					X		X	X					14.1

CCI; CCI; Disc=discontinuation; DNA=deoxyribonucleic acid; ECG=Electrocardiogram; ECHO=Echocardiography; ECOG PS=Eastern Cooperative Oncology Group performance status; FU=Follow-up; IP=Investigational Product; PD=Pharmacodynamics; PGx=pharmacogenetic sample; PK=Pharmacokinetics; PLD=Pegylated liposomal doxorubicin; TSH=Thyroid-stimulating hormone.

[a] 1 cycle = 28 days. Cycles repeat on a continuous basis with no interval between cycles.

[b] Weekly visit may be omitted if Visit Y is within 2 days of weekly visit.

[c] Visit Y is only utilised if the dosing schedule is intermittent. Visit Y represents the last AZD7648 dosing day in the first block of AZD7648 treatment in a cycle eg, CCI

[d] There are no visit windows in Cycle 1.

[e] With the patient's consent, as part of the medical history, any available information on known tumour gene mutations will be collected.

[f] Targeted physical examinations only required if clinically indicated (indication should be stated).

[g] Vital signs then ECG measurements will be collected prior to PK blood draws at all PK sample timepoints. Timepoints may be modified based on the initial data obtained.

[h] Serious adverse events (SAEs) only to be collected between AZD7648 discontinuation and disease progression.

[i] Women of child-bearing potential must have a negative urine or serum pregnancy test at screening, a confirmatory test before treatment on Day 1 (Cycle 1), at regular intervals during treatment and at AZD7648 discontinuation. If results are positive, the patient is ineligible/must be discontinued from study treatment and not discontinued from the study. The patient will continue to be followed up according to the study protocol.

[j] TSH to be measured at baseline and every 3 cycles. CRP to be collected at baseline, then on Day 1 from Cycle 1. Urinalysis at on Day 1 of each cycle. Tumour markers (if relevant) to be measured at baseline and on Day 1 of every cycle from Cycle 1 (only if elevated at baseline).

[k] LVEF assessment (ECHO or MUltiGated Angiography [MUGA]) and review must occur at screening and prior to dosing at Cycle 4 Day 1 and Cycle 7 Day 1 (-7 day window).

[l] Provision of archival tumour samples are mandatory for all patients. The samples may be submitted retrospectively.

[m] CCI [redacted]

[n] CCI

[o] CCI [redacted]

[p] Only collect sample 2 to 4 h post–dose AZD7648 noting time of blood draw.

[q] From Cycle 3, Day 1, sample should be taken on each radiological assessment (±7 days), disease progression or treatment discontinuation.

[r] If any immune-related events are suspected, additional blood samples may be taken for further safety signal investigation.

[s] Tumour assessments should be conducted every 8 weeks (±1 week) from start of combination treatment (Cycle 1, Day 1) until confirmed objective disease progression; frequency may be adjusted after 2 years of treatment if the tumour is not changing in size (complete response [CR], partial response [PR], or stable disease [SD]).

[t] Survival follow-up every 12 weeks (±1 week) following confirmed objective disease progression. Vital status (dead or alive; date of death) will be collected every 3 months (±1 week) post-permanent discontinuation of study treatment.

[u] On clinic days, patients should not take the study treatment until instructed to do so by clinic staff. (X) indicates an intermittent dosing schedule forAZD7648, as determined in Part A.

11 INTRODUCTION

Combination Module 1 will investigate the safety, tolerability, and preliminary efficacy of AZD7648 administered in combination with PLD.

11.1 Study rationale

Doxorubicin is an inhibitor of topoisomerase-II that generates topoisomerase-DNA adducts and DSBs and used as a cancer therapy. PLD is FDA approved for treatment of ovarian cancer and multiple myeloma offering the same efficacy with less cardiotoxicity and haematotoxicity than the uncapsulated form. CCI

. CCI

11.2 Background

As described in Section 2.2 the DNA-PK inhibitor AZD7648 is being developed as an anti-cancer therapy for patients with advanced malignancies. Combination Module 1 will investigate the safety, tolerability, PK, PD, and preliminary efficacy (anti-tumour activity) of AZD7648 in combination with PLD in patients with advanced malignancies. Combination Module 1 consists of the following parts: AZD7648 combined with PLD in dose escalation (Part A) and PoC expansion in patients with platinum-resistant ovarian cancer (Part B).

Epithelial ovarian cancer, which accounts for 90% of all ovarian cancers, is further subdivided into various cell types, grades, and anatomic locations. The most common form is high-grade serous ovarian cancer, which accounts for approximately 70% of all epithelial ovarian cancer. Historically, the treatment of ovarian cancer has been surgical cytoreduction followed by adjuvant chemotherapy. Ovarian cancer remains a deadly malignancy because most patients develop recurrent disease that is resistant to chemotherapy, including platinum. For platinum-resistant patients (patients who relapse ≤ 6 months after any line of platinum-based chemotherapy or having disease progression whilst receiving platinum-based chemotherapy in the ≥ second-line setting), other chemotherapies including PLD are used. For partially platinum-sensitive patients (patients who relapse > 6 to 12 months from the last platinum-based chemotherapy) and platinum-sensitive patients (patients who relapse > 12 months from the last chemotherapy), patients may derive benefit from further platinum-based chemotherapies. Time from last platinum treatment to relapse remains an integral measure for defining patient populations and predicting outcomes for treatments, although response rates fall on a continuum (Wilson et al 2017).

A brief background on PLD, including its mechanisms of action, is provided below. For detailed descriptions of the chemistry, pharmacology, efficacy, and safety of AZD7648 and PLD, refer to the IB (AZD7648) or Summary of Product Characteristics (PLD).

11.2.1 Pegylated liposomal doxorubicin

11.2.1.1 Overview of pegylated liposomal doxorubicin

Doxorubicin is an inhibitor of topoisomerase 2 that generates topoisomerase-DNA adducts and DSBs and used as a cancer therapy. PLD has been approved by FDA and the European Medicines Agency for treatment of ovarian cancer and multiple myeloma offering the same efficacy with less cardiotoxicity and haematotoxicity than the uncapsulated form. Doxorubicin directly generates DSBs and therefore could potentiate the activity of DNA-PK inhibitor, which is the critical component of NHEJ DNA DSB repair.

11.2.1.2 Pegylated liposomal doxorubicin data

DOXIL® (FDA-approved):

DOXIL is indicated for the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy.

DOXIL was studied in 3 open-label, single-arm, clinical studies of 176 patients with metastatic ovarian cancer (Trials 1, 2 and 3). One hundred forty-five of these patients were refractory to both paclitaxel- and platinum-based chemotherapy regimens, defined as disease progression while on treatment or relapse within 6 months of completing treatment. Patients received DOXIL at 50 mg/m^2 every 3 or 4 weeks for 3-6+ cycles in the absence of DLT or disease progression. In a pooled analysis of Trials 1-3, the response rate for all patients refractory to paclitaxel and platinum agents was 13.8% (95% CI 8.1, 19.3). The median time to progression (TTP) was 15.9 weeks, the median time to response was 17.6 weeks and the duration of response was 39.4 weeks.

In an open-label Trial 4, a total of 474 patients with epithelial ovarian cancer after platinum-based chemotherapy were randomised to receive either DOXIL 50 mg/m^2 every 4 weeks or topotecan 1.5 mg/m^2 daily for 5 consecutive days every 3 weeks. Patients were stratified according to platinum sensitivity (response to initial platinum-based therapy and a progression-free interval of > 6 months off treatment) and the presence of bulky disease (tumour mass > 5 cm in size). The median TTP showed no statistically significant difference between the 2 arms (4.1 months in the DOXIL arm and 4.2 months in the topotecan arm). The median OS was 14.4 months in the DOXIL arm and 13.7 months in the topotecan arm. The median duration of response was 6.9 months in the DOXIL arm and 5.9 months in the topotecan arm.

Caelyx (EMA-approved):

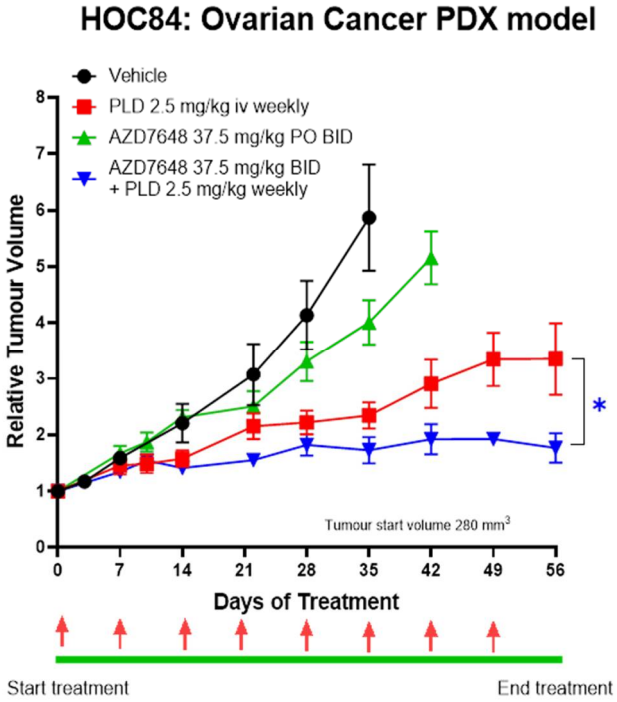
A Phase III comparative study of Caelyx versus topotecan in patients with epithelial ovarian cancer following the failure of first-line, platinum-based chemotherapy was completed in 474 patients. There was a benefit in OS for Caelyx-treated patients over topotecan-treated patients as indicated by a hazard ratio of 1.216 (95% CI: 1.000, 1.478), p = 0.050. The

survival rates at 1, 2 and 3 years were 56.3%, 34.7% and 20.2% respectively on Caelyx, compared to 54.0%, 23.6% and 13.2% on topotecan.

Preclinical data:

Preclinical studies support the hypotheses that a combination of AZD7648 with a DNA-damaging agent such as PLD would demonstrate synergistic anti-tumour activity (Figure 8).

Figure 8 Ovarian cancer xenograft – mean tumour volume



PDX = patient-derived xenograft; PLD = pegylated liposomal doxorubicin.

11.3 Benefit/risk assessment

As described in Section 2.3 patients enrolled to this study have advanced cancer with a limited number of treatment options available, including chemotherapy such as PLD. The survival outcome and toxicity profile of chemotherapy in this setting mean that other active therapies are highly desirable and present a potential advantage for patients.

The study design aims to evaluate and determine a dose and schedule of AZD7648 in combination with PLD and identify patient populations who may respond favourably to the combination. Based upon the available non-clinical and clinical safety data, the limited survival benefit provided by the current treatment options, the limited life expectancy due to advanced malignant disease, and the hypothesis of a synergistic effect of the 2 agents, the investigation of the potential therapeutic efficacy of the combination of AZD7648 with PLD

in patients with advanced or platinum-resistant ovarian cancer is acceptable, and the overall benefit/risk assessment supports the proposed study design.

12 STUDY DESIGN

12.1 Overall design

Combination Module 1 will evaluate the safety, tolerability, PK, PD, and preliminary efficacy (anti-tumour activity) of AZD7648 (given orally) in combination with PLD (given IV) as below:

Part A: Dose escalation of AZD7648 in combination with PLD in approximately 30 evaluable patients with advanced solid tumours in whom PLD is an appropriate therapy. Prior information for PLD toxicity will be based on the locally approved label, whilst prior information for AZD7648 toxicity will be based on emerging data from the monotherapy arm (Core Module).

The starting dose of PLD will be 40 mg/m^2 administered IV once every 4 weeks for up to 6 cycles. Patients who respond or have stable disease following 6 cycles of PLD, are permitted to continue AZD7648 at the monotherapy RP2D (or lower dose) from the Core Module during the 'continuation phase'. Although AZD7648 is administered continuously as monotherapy, it is anticipated that an intermittent schedule will be required in combination. Two intermittent schedules that may be explored, including but not limited to, are: i) an intermittent within cycle schedule starting from [redacted] dosing eg, [redacted] days on/[redacted] days off, and/or ii) an [redacted] starting from [redacted] dosing eg, [redacted] days on/[redacted] days [redacted]. The duration and/or frequency of dosing for both schedules may be altered based on emerging data and multiple schedules may be run concurrently if agreed by the SRC.

The PLD dose is consistent with local clinical practice (common usage of 40 mg/m^2).

Part B: A safety and PoC Phase 2a expansion is planned to assess the combination in approximately 37 evaluable patients with advanced ovarian cancer who have relapsed within 12 months of completing a platinum-containing therapy. This includes patients who have platinum-resistant disease who have not received more than one cytotoxic regimen for platinum-resistant disease and patients with partial platinum sensitivity.

Sites must send formalin-fixed paraffin embedded (FFPE) tissue for retrospective central laboratory confirmation of advanced ovarian cancer.

12.2 Scientific rationale for study design

[redacted]

CCI [redacted]

12.3 Justification for dose

12.3.1 Justification for AZD7648 dose

The actual starting dose of AZD7648 for this module will be dependent on clinical PK exposure and emerging safety and tolerability data seen during the monotherapy escalation (refer to the Core Module). However, the actual AZD7648 starting dose will be triggered when the equivalent AZD7648 monotherapy dose cohort is declared tolerated in the Core Module. The starting schedule of AZD7648 from CCI [redacted] dosing, CCI [redacted] t (an intermittent within cycle schedule). Therefore, the total per cycle dose in the combination is ≤ 25% of the per cycle dose administered as continuous monotherapy.

12.3.2 Justification for pegylated liposomal doxorubicin dose

Although PLD is approved at a dose of 50 mg/m^2 every 4 weeks, it is common for patients to require a dose reduction to 40 mg/m^2 due to AEs such as palmar-plantar erythrodysesthesia, stomatitis or haematological toxicity. Several large studies including combinations (eg, AURELIA trial) have deployed a starting dose of PLD of 40 mg/m^2. For these reasons, 40 mg/m^2 has been selected as the starting dose in Combination Module 1.

13 STUDY POPULATION

13.1 Inclusion criteria

Patients are eligible to be included in the study only if all the inclusion criteria apply. **Please also refer to Section 5.1 for the inclusion criteria applicable to all modules in the study.** If the criteria in the modules is different from that in the Core Module criteria, the module-specific criteria should be followed. Inclusion criteria applicable to Combination Module 1 only are described in this section.

Part A and B

1 Patients must meet the eligibility criteria described in the Core Module.

2 Suitable for treatment with PLD as per local prescribing information.

3 Left ventricular ejection fraction above the institutional lower limit of normal, assessed by echocardiography or MUltiGated Angiography (MUGA).

Part B only

1 Provision of FFPE specimen from the primary tumour is mandatory. An archival tissue specimen is preferred but a new tissue sample may be used (if, for example, it is routine at a site to undertake biopsy of metastatic lesions). If an archival FFPE specimen is not available, a fresh tumour biopsy (FFPE) is mandatory.

2 Histologically confirmed advanced epithelial* ovarian, fallopian tube or primary peritoneal cancer which has relapsed within 12 months of completing a minimum of 4 cycles of platinum-containing chemotherapy regimen and for whom PLD is an appropriate therapy. Time to relapse after last platinum is based on Investigator assessment. Prior maintenance treatment is allowed and does not count as a line of therapy, including bevacizumab or PARPi, but treatment must be discontinued prior to study entry.

   * Patients with carcinosarcoma histology may be included; patients with stromal, sex cord or germ cell tumours are excluded.

3 For platinum-resistant patients, ≤ 1 prior line of cytotoxic chemotherapy for the treatment of platinum-resistant disease. Patients must have had a radiological or CA-125 response to initial chemotherapy in the platinum-resistant setting, with no evidence of disease progression within 28 days of completing chemotherapy.

   OR

   For partially-platinum sensitive patients, there is no restriction on the number of prior lines of cytotoxic chemotherapy.

   (platinum-resistant is defined as a platinum-free interval of ≤ 6 months after any line of platinum-based chemotherapy or disease progression whilst receiving platinum-based chemotherapy in the ≥ second-line setting. Partially-platinum sensitivity is defined as a platinum-free interval of > 6 to 12 months after the last line of platinum-based chemotherapy.)

4 ECOG performance status performance status 0-1.

5 At least one lesion, not previously irradiated (or with evidence of disease progression following radiation), that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with CT or MRI and which is suitable for accurate repeated assessment AND/OR patients with an assessable Ca 125 by GCIG CA-125 response criteria (pre-treatment sample must be at least twice the upper limit of normal within 2 weeks prior to starting treatment).

13.2 Exclusion criteria

Patients must not enter Combination Module 1 of the study if any of the exclusion criteria apply. **Please also refer to Section 5.2 for the exclusion criteria applicable to all modules in the study.** If the criteria in the modules is different from that in the Core Module criteria,

the module-specific criteria should be followed. Exclusion criteria applicable to Combination Module 1 only are described in this section.

Part A and B

1 Any contraindication to the PLD or any excipients as per local prescribing information eg, hypersensitivity.

2 Patients who have had drainage of their ascites during the preceding 4 weeks prior to enrolment of the study (patients with indwelling peritoneal catheters are permitted).

3 Patients who have had a previous CTCAE Grade ≥ 4 haematological toxicity with PLD.

Part B only

1 Patients with platinum refractory disease (defined as disease progression whilst receiving first-line platinum-containing therapy or within 1 month of completion).

2 Prior anthracycline therapy, including prior treatment with PLD in any setting.

3 History of clinical symptoms requiring hospital admission for acute bowel obstruction within 3 months of study enrolment.

4 History of abdominal fistula, GI perforation, intra-abdominal abscess, rectosigmoid or bowel involvement eg, bowel invasion on CT.

5 Prior (or anticipated need for) radiotherapy to pelvis or abdomen, major surgery anticipated during study treatment or within 4 weeks before starting study treatment.

13.3 Lifestyle restrictions

Restrictions for PLD should follow the institutional guidelines.

Please refer to Appendix G for contraception restrictions.

14 STUDY TREATMENTS

Study treatment in Combination Module 1 refers to AZD7648 and PLD (Table 14).

14.1 Treatments administered

14.1.1 Investigational products

Table 14 Study treatments

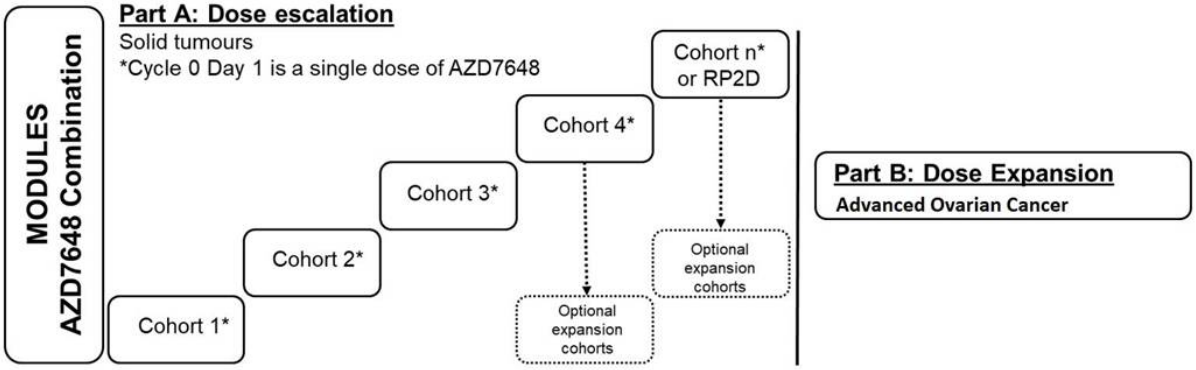
Study treatment name:	AZD7648	Pegylated liposomal doxorubicin
Dosage formulation:	Provided as [redacted] mg, [redacted] mg, [redacted] mg, and [redacted] mg white film-coated oral tablets. The [redacted] mg and [redacted] mg tablets are round. The [redacted] mg and [redacted] mg tablets are caplet shaped. Note: In accordance with Quality IMPD, other intermediate strengths may be added at a later date.	2 mg/mL suspension/dispersion for IV use (eg, Caelyx, Doxil or equivalent).
Route of administration:	Oral tablets	IV infusion
Starting dose instructions:	The starting dose of AZD7648 is dependent on emerging data from the Core Module. **AZD7648 will be administered [redacted] of PLD.**	The starting dose of PLD is 40 mg/m^2, administered by IV infusion once every 4 weeks, for a maximum of 6 cycles.
Packaging and labelling:	Study treatment will be provided in high-density polyethylene bottles with child-resistant polypropylene screw caps. Each bottle will be labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirement. Label text will be translated into local language. The site must complete the Patient Diary with the details of the dosing instructions at the time of dispensing.	The site must complete the Patient Diary with the details of the dosing instructions at the time of dispensing.
Provider:	AstraZeneca	Sourced by site

14.1.2 Dose escalation scheme

For Combination Module 1, the dose escalation schedule is presented in Figure 9. When there is more than one patient enrolled to a dose cohort, sentinel dosing will be applied with a single patient exposed for a minimum of 48 hours after Cycle 1, Day 1 before further patients are enrolled at that dose level. In the absence of any significant toxicities in the first patient, the patients for the remainder of the cohort may be enrolled, concurrently or sequentially, based upon the decision of the SRC.

For each cohort in dose escalation a SRC will review the safety of the first and each subsequent cohort.

Figure 9 AZD7648 combinations study flow chart



RP2D=recommended Phase II dose

The starting dose of PLD is 40 mg/m^2, administered by IV infusion once every 4 weeks, for a maximum of 6 cycles (Table 15). Patients who are deriving clinical benefit may continue AZD7648 beyond 6 cycles as monotherapy in the continuation phase; using a dose and schedule declared tolerated in the Core Module.

During Part A (dose escalation), a single dose of AZD7648 will be administered to enable collection of blood samples for PK analyses, followed by a drug washout of [redacted] (Figure 10). The dose of PLD may also be escalated to 50 mg/m^2 (or de-escalated to 30 mg/m^2) every 4 weeks with agreement of the SRC. Intermittent schedules for AZD7648 will also be explored.

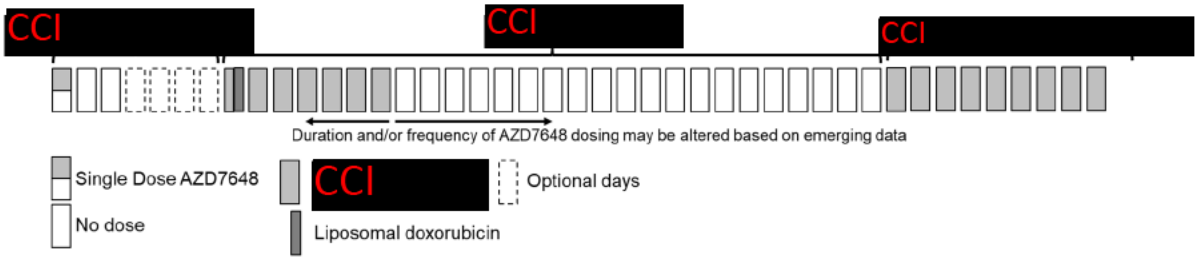
Table 15 Illustrative AZD7648 dose escalation schedule

Cohort	PLD dose (mg/m^2)	AZD7648 dose CCI (mg)	No. days of AZD7648 in each cycle
-1	30	CCI	CCI
Starting Cohort 1	40	CCI	CCI
2	40	CCI	CCI
3	40	CCI	CCI
4	40	CCI	CCI
Cohort n	40	Escalate to monotherapy MTD or MFD in no more than 50% increments	CCI
Maximum dose level	50	CCI	CCI

CCI=CCI ; MFD=maximum feasible dose; MTD=maximum tolerated dose; PLD=pegylated liposomal doxorubicin.

Actual doses and schedules may vary using Bayesian adaptive design modelling based on emerging safety and tolerability data, and subject to Safety Review Committee (SRC) agreement. The dose of PLD may also be escalated to 50 mg/m^2 (or de-escalated to 30 mg/m^2) administered once every 4 weeks.

Figure 10 Illustration of starting dose and schedule for AZD7648 in combination with PLD



For Combination Module 1, informative prior estimates of dose-toxicity relationship from relevant internal and external studies will be combined with prior estimates of AZD7648 dose-toxicity relationship emerging from the Core Module (monotherapy) of the study. The model incorporates terms for each monotherapy and for the combination (interaction term). A non-informative prior will be used for the interaction term.

A minimum of 3 and a maximum of 6 patients per cohort will be enrolled in Part A cohorts. For SRC meetings prior to dose escalation where 3 patients have been enrolled, at least 2 patients will need to be evaluable for DLT. However, if patients are receiving treatment within the DLT assessment period, the dose escalation review meeting should be deferred so that the SRC accounts for all patient data. Additional CRF data may be included in the SRC review including vital signs, clinical chemistry / haematology, ECG results, PK and PD data,

ad hoc safety reports, AEs from previous cohorts and optional expansions and any other emerging data.

Dose escalation and de-escalation will follow the Bayesian adaptive design described in Section 6.1.2.

14.2 Treatment compliance

PLD will be administered on site and will be recorded in the appropriate section of the CRF.

14.3 Concomitant therapy

14.3.1 Effect of pegylated liposomal doxorubicin on other drugs

No formal medicinal product interaction studies have been performed with PLD, although Phase II combination trials with conventional chemotherapy agents have been conducted in patients with gynaecological malignancies. Exercise caution in the concomitant use of medicinal products known to interact with standard doxorubicin hydrochloride. PLD, like other doxorubicin hydrochloride preparations, may potentiate the toxicity of other anti-cancer therapies. During clinical trials in patients with solid tumours (including breast and ovarian cancer) who have received concomitant cyclophosphamide or taxanes, no new additive toxicities were noted. Caution must be exercised when giving any other cytotoxic agents, especially myelotoxic agents, at the same time.

14.4 Dose modification

Refer to Section 6.6 for management of treatment related toxicity applicable to all study modules.

If the toxicity does not resolve to the patient's baseline or to CTCAE Grade ≤ 2 within 28 days of onset, treatment with AZD7648 and PLD must be discontinued. However, if toxicity is clearly attributed to PLD alone, the patient is permitted to continue receiving AZD7648 as monotherapy following discussion between the Investigator and the AZ Study Physician. If PLD is discontinued due to reasons other than toxicity, AZD7648 monotherapy may continue following discussion between the Investigator and the AZ Study Physician.

15 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Table 13).

15.1 Management of study treatment-related toxicities

At this time, there are limited safety data regarding the combination of AZD7648 and PLD. Given the differing mechanisms of action of AZD7648 and PLD, the potential for potentiation of toxicities is thought to be limited. Some toxicities, for example pneumonitis and asthenia/fatigue may, on theoretical grounds, be potentiated in the combination arm and particular attention should be paid to these.

In the event of toxicity in this combination module of the study which cannot be managed by supportive measures alone, stopping one or both study treatments should be an Investigator decision based on the available information and, if necessary, following discussion with the Sponsor.

The following general guidance should be followed for management of toxicities:

- Treat each of the toxicities with maximum supportive care (including withholding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned study treatment along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted for AZD7648. In addition, guidelines on AZD7648 dose modifications are provided in Section 6.6 and 14.4. In the event of toxicity that cannot be managed by following the toxicity management guidelines for AZD7648 and PLD, consider stopping treatment.

All dose modifications should be documented with clear reasoning and documentation of the approach taken.

Management of PLD related toxicities will be performed in accordance with local practice.

15.2 Echocardiogram

An echocardiogram or MUGA scan will be conducted on all patients at screening for Parts A and B, and at the timepoints in the SoA (Table 13). The screening echocardiogram or MUGA scan will not be required if a previous echocardiogram or MUGA scan was performed 6 months prior to screening, unless there has been a change in the patient's cardiac status.

15.3 Pharmacokinetics

Venous blood samples (2 mL) for determination of concentrations of PLD (as total doxorubicin), will be taken at the times presented in the SoA (Table 13) in addition to the venous blood samples (2 mL) for determination of concentrations of AZD7648 in plasma. The date and time of collection of each sample will be recorded. Further details can be found in Section 8.5.

Pharmacokinetic samples will be taken at the times indicated in Table 16.

Table 16 AZD7648 and PLD PK sample collection schedule

	Part A		Part B	
	Blood for AZD7648	**Blood for PLD**	**Blood for AZD7648**	**Blood for PLD**
Cycle 0, Day 1	Pre-dose and 15 minutes (min), 30 min, 60 min, 2 hours (h), 4 h, 6 h, and 8 h post-dose		Cycle 0 not applicable (NA)	
Cycle 0, Day 2	24 h post-dose		NA	
Cycle 0, Day 3	48 h post-dose		NA	
Cycle 0, Day 4	72 h post-dose		NA	

15.4 Pharmacodynamics

Refer to Section 8.6.1 for further details which also apply to this Module.

Peripheral blood samples will be collected 4 hours after the start of the PLD infusion and 2 to 4 hours post-dose for AZD7648 as detailed in Table 17 and the SoAs. In addition, there will be PK samples collected at the same time as PD samples to allow exploration of the exposure/ PD relationships (see Table 16). The exact time of PD samples collection will be noted.

CCI

CCI

a CCI

15.5 Biomarkers

Please refer to Section 8.8 for biomarkers for exploratory testing.

A tumour tissue block for archival samples is preferred for central testing. If a tissue block is unavailable, unstained sections from the FFPE block may be submitted. Please refer to the Laboratory Manual for specific instructions and guidelines.

Where sites submit a fresh tumour biopsy, this must be FFPE.

Biological samples will be collected as detailed in the Laboratory Manual for the reasons listed below:

- To carry out retrospective central confirmation and prospective screening, when required (Part B only).
- Alternative biomarkers may be evaluated as determined by additional data associated with disease progression or response to study drugs evaluated as part of this protocol.

16 STATISTICAL CONSIDERATIONS

16.1 Interim analysis

One interim analysis is planned during Part B of the study, as described in .

Table 18 Interim analysis

Drug combination (module)	Population	TV%	LRV%	Sample size (N)	Interim (n)
AZD7648 + PLD (Combination Module 1)	Acquired platinum-resistant ovarian cancer	30	15	37	21

LRV=lower reference value; PLD=pegylated liposomal doxorubicin; TV=target value.

The sample size for the interim analysis has been determined by Lalonde criteria set for ORR (LRV% and TV% defined in Table 18). The sample size ensures success (Go) if there is a ≥ 80% chance of exceeding the LRV and stop if there is < 10% chance of exceeding the TV. Recruitment will not be stopped for the interim analysis.

The SAP will describe the planned interim analysis in greater detail.

16.2 Sample size determination

Part A will require approximately 30 evaluable patients across approximately 5 cohorts (n = 3 to 6 per cohort) to provide a model-based estimate of MTD within target toxicity (30%). Once MTD has been determined, an additional 30 evaluable patients may be recruited to investigate intermittent dosing schedules. If two schedules recruit patients at the same time, a patient systematic allocation algorithm will be followed.

Part B will require approximately 37 evaluable patients with advanced platinum-resistant ovarian cancer.

17 REFERENCES

Beskow et al 2009
Beskow C, Skikuniene J, Holgersson A, Nilsson B, Lewensohn R, Kanter L, et al. Radioresistant cervical cancer shows upregulation of the NHEJ proteins DNA-PKcs, Ku70 and Ku86. Br J Cancer. 2009; 101(5): 816-21.

Blunt et al 1995
Blunt T, Finnie NJ, Taccioli GE, Smith GC, Demengeot J, Gottlieb TM, et al. Defective DNA-dependent protein kinase activity is linked to V(D)J recombination and DNA repair defects associated with the murine scid mutation. Cell. 1995; 80(5): 813-23.

Chan et al 2002
Chan DW, Chen BP, Prithivirajsingh S, Kurimasa A, Story MD, Qin J, et al. Autophosphorylation of the DNA-dependent protein kinase catalytic subunit is required for rejoining of DNA double-strand breaks. Genes Dev. 2002; 16(18): 2333-8.

Dietlein et al 2014
Dietlein F, Thelen L, Jokic M, Jachimowicz RD, Ivan L, Knittel G, et al. A Functional Cancer Genomics Screen Identifies a Druggable Synthetic Lethal Interaction between MSH3 and PRKDC. Cancer Discov. 2014; 4: 592–605.

Dolman et al 2015
Dolman ME, van der Ploeg I, Koster J, Bate-Eya LT, Versteeg R, Caron HN, et al. DNA-Dependent Protein Kinase as Molecular Target for Radiosensitization of Neuroblastoma Cells. PLoS ONE. 2015; 10(12): e0145744.

Goodwin and Knudsen 2014
Goodwin JF and Knudsen KE. Beyond DNA repair: DNA-PK function in cancer. Cancer Discov. 2014; (10):1126-39.

Graham et al 2016
Graham TG, Walter JC, Loparo JJ. Two-Stage Synapsis of DNA Ends during Non-homologous End Joining. Mol Cell. 2016; 61(6): 850-8.

Gurley et al 2001
Gurley KE, Kemp CJ. Synthetic lethality between mutation in Atm and DNA-PK(cs) during murine embryogenesis. Curr Biol. 2001; 11: 191–4.

Hartlerode and Scully 2009
Hartlerode and Scully. Mechanisms of double-strand break repair in somatic mammalian cells. Biochem J. 2009; 423(2): 157-68.

Hosoi et al 2004
Hosoi Y, Watanabe T, Nakagawa K, Matsumoto Y, Enomoto A, Morita A, et al. Upregulation of DNA-dependent protein kinase activity and Sp1 in colorectal cancer. Int J Oncol. 2004; 25(2): 461-8.

Jackson et al 1993
Jackson S1, Gottlieb T, Hartley K. Phosphorylation of transcription factor Sp1 by the DNA-dependent protein kinase. Adv Second Messenger Phosphoprotein Res. 1993; 28: 279-86.

Neal and Meek 2011
Neal and Meek. Choosing the right path: does DNA-PK help make the decision? Mutat Res. 2011; 711(1-2): 73-86.

NCCN 2011
NCCN Guidelines for Patients (Metastatic Breast Cancer). https://www.nccn.org/patients/guidelines/stage_iv_breast/.

O'Connor 2015
O'Connor MJ. Targeting the DNA Damage response in cancer. Mol Cell. 2015; 60(4): 547-60.

Oken et al 1982
Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 1982:5; 649-655.

Riabinska et al 2013
Riabinska A, Daheim M, Herter-Sprie GS, Winkler J, Fritz C, Hallek M, et al. Therapeutic targeting of DNAa robust non-oncogene addiction to PRKDC in ATM-defective tumors. Sci Transl Med. 2013; 5:189ra78.

San Filippo et al 2008
San Filippo J, Sung P, Klein H. Mechanism of eukaryotic homologous recombination. Annu Rev Biochem. 2008; 77: 229-57.

Shintani et al 2003
Shintani S, Mihara M, Li C, Nakahara Y, Hino S, Nakashiro K, et al. Up-regulation of DNA-dependent protein kinase correlates with radiation resistance in oral squamous cell carcinoma. Cancer Sci. 2003; 94: 894–900.

Tonotsuka et al 2006
Tonotsuka N, Hosoi Y, Miyazaki S, Miyata G, Sugawara K, Mori T, et al. Heterogeneous expression of DNA-dependent protein kinase in esophageal cancer and normal epithelium. Int J Mol Med. 2006; 18: 441–447.

Van Bussel et al 2017
Van Bussel M, Mau-Soerensen M, Damstrup L, Nielsen D, Verheul HMW, Aftimos PG. A multicentre phase I trial of the DNA-dependent protein kinase (DNA-PK) inhibitor M3814 in patients with solid tumors. J Clin Oncol 35, 2017 (suppl: abstr 2556).

Van Triest et al 2018
Van Triest B, Damstrup L, Falkenius J, Budach V, Troost E, Samuels M, et al. A phase 1a/1b trial of the DNA-PK inhibitor M3814 in combination with radiotherapy in patients with advanced solid tumors: Dose-escalation results. J Clin Oncol 36, 2018 (suppl: abstr2518).

Wilson et al 2017
Wilson MK, Pujade-Lauraine E, Aoki D, Mirza MR, Lorusso D, Oza AM et al. Fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup: recurrent disease. Ann Oncol. 2017;28(4):727-32.

Yoo and Dynan 1999
Yoo and Dynan. Geometry of a complex formed by double strand break repair proteins at a single DNA end: recruitment of DNA-PKcs induces inward translocation of Ku protein. Nucleic Acids Res. 1999; 27(24): 4679-86.

18 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical and Study Oversight Considerations

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, informed consent form (ICF), Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an institutional review board (IRB)/independent ethics committee (IEC) by the Investigator, Sponsor or designee and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of serious adverse events (SAEs) or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

A 2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Regulatory authorities. Investigators

are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed consent process

The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorised representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or the patient's legally authorised representative.

If a patient declines to participate in any voluntary exploratory genetic research component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study.

If a patient's partner becomes pregnant during or within 6 months after the study, the partner will be asked to sign the "Adult Study Informed Consent Form for Pregnant Partners of Study Patients" and provide information about the pregnancy accordingly.

A patient who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorised designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The patient will give a separate agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will indicate this in the ICF. If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action

documented. If samples already have been analysed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

A 4 Data protection

Each patient will be assigned a unique identifier by the Sponsor. Any patient records or data sets transferred to the Sponsor will contain only the identifier; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from Regulatory authorities.

A 5 Committees structure

No Data Monitoring Committee will be used in this study; however a safety review committee (SRC) will closely monitor patient safety on an ongoing basis. The SRC Members will include the following:

- Principal Investigator, or delegate, who will chair the committee
- Study Chair (if not Principal Investigator)
- Principal Investigator or delegate from investigational site
- AstraZeneca Medical Science Director or delegate
- AstraZeneca Global Safety Physician, or delegate

The Sponsor or Clinical Research Organisation Medical Monitor, or delegate, should always be present at the SRC.

The AstraZeneca Clinical Pharmacology Scientist, study Statistician, Patient Safety Scientist, study Leader and other AstraZeneca and non-AstraZeneca technical experts may also be invited as appropriate. The SRC Remit document for this study will define the exact membership and who will be present for decisions to be made.

A 6 Dissemination of clinical study data

A description of this clinical trial will be available on https://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical trial and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data quality assurance

All patient data relating to the study will be recorded on printed or electronic case report form (CRF) unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and Regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A 8 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Source data may include but is not limited to: medical history and physical examination notes, hospital discharge summary, autopsy report when available, results of relevant diagnostic tests completed.

A 9 Study and site closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

A 10 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multi-centre studies only in their entirety and not as individual site data. In this case, a co-ordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Event Definitions and Additional Safety Information

B 1 Definition of adverse events

An adverse event (AE) is the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

B 2 Definitions of serious adverse event

A serious adverse event (SAE) is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardise the patient or may require medical treatment to prevent one of the outcomes listed above

B 3 Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

B 4 Hospitalisation

Outpatient treatment in an emergency room is not in itself a SAE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

B 5 Important medical event or medical treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the patient or may require medical treatment to prevent 1 or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment.
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine.
- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation.
- Development of drug dependency or drug abuse.

B 6 Intensity rating scale:

The grading scales found in the revised National Cancer Institute common terminology criteria for adverse event (CTCAE) version 5.0 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

It is important to distinguish between SAEs and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 7 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a ‘reasonable possibility’ that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgement. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 8 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study treatment that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure whilst the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- Occurred.
- was identified and intercepted before the patient received the drug.
- did not occur, but circumstances were recognised that could have led to an error.

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion.
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the patient.
- Drug not administered as indicated, for example, wrong route or wrong site of administration.
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet.
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature.
- Wrong patient received the medication.
- Wrong drug administered to patient.

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Patient accidentally missed drug dose(s) eg, forgot to take medication.
- Accidental overdose (will be captured as an overdose).
- Patient failed to return unused medication or empty packaging.
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AZ product.

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Appendix C Handling of Human Biological Samples

C 1 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their life cycle.

The Investigator at each centre keeps full traceability of collected biological samples from the patients whilst in storage at the centre until shipment or disposal (where appropriate).

The sample receiver keeps full traceability of the samples whilst in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AZ-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

C 2 Withdrawal of Informed Consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

The Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca.
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented.
- Ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site.
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories
(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm**)**. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient
- temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used

Appendix D Genetics

D 1 Use/analysis of DNA

Genetic variation may impact a patient's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting patients.

AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.

In addition, collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Genetic research may consist of the analysis of the structure of the patient's DNA, ie, the entire genome.

The results of genetic analyses may be reported in the CSR or in a separate study summary.

The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained whilst research on the study treatment in this protocol continues but no longer than 15 years or other period as per local requirements.

D 2 Genetic research plan and procedures

Selection of Genetic Research Population

Study Selection Record

All patients will be asked to participate in this genetic research. Participation is voluntary and if a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described in the main body of the CSP and provide informed consent for the genetic sampling and analyses.

Exclusion Criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant.
- Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection.

Withdrawal of Consent for Genetic Research:

Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7 of the main CSP.

Collection of Samples for Genetic Research

The blood sample for genetic research will be obtained from the patients at the Cycle 1, Day 1 Visit. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an AE, such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at the Cycle 1, Day 1 Visit, it may be taken at any visit until the last study visit. Only 1 sample should be collected per-patient for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Coding and Storage of DNA Samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years, from the date of last patient last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated

organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).

The link between the patient enrolment code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed Consent

The genetic component of this study is optional and the patient may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the patient must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely withdrawal from the genetic aspect of the study at any time.

Patient Data Protection

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient's identity and also have access to his or her genetic data. In addition, Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

Data Management

Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organisations to analyse the samples.

AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual patient data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical Methods and Determination of Sample Size

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan may be prepared where appropriate.

Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

E 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory and/or elevated TBL from a local laboratory.

The Investigator will also review Adverse Event (AE) data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug induced liver injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Serious Adverse Events (SAEs) and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3× ULN **together with** total bilirubin (TBL) ≥ 2×ULN at any point during the study following the start of study treatment, irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 ×ULN, where no other reason, other than the study treatment, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified time frame within which the elevations in transaminases and TBL must occur.

E 3 Identification of potential Hy's Law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Determine whether the subject meets PHL criteria (see Section E2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF.

E 4 Follow-up

E 4.1 Potential Hy's Law criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

E 4.2 Potential Hy's Law criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Appendix E, Section 6. Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment).
- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.

- For subjects that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change# in the subject's condition
- The Study Physician contacts the Investigator to provide guidance, discuss and agree an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to this contact the Investigator will:
  - Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician.
  - Complete the three Liver CRF Modules as information becomes available.

E 5 Review and assessment of potential Hy's Law cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from the date the PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other patient matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF.
- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AZ standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes:

- The 'Medically Important' serious criterion should be used if no other serious criteria apply.
- As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If there is an unavoidable delay of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Actions required when potential Hy's Law criteria are met before and after starting study treatment

This section is applicable to patients with liver metastases who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on-study treatment occurrence of PHL criteria being met, the Investigator will determine if there has been a **significant change** in the patients' condition[#] compared with the last visit where PHL criteria were met.[#]

- If there is no significant change, no action is required.
- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Appendix E, Section 4.2.

A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the study Physician if there is any uncertainty.

E 7 Actions required for repeat episodes of potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study, eg, chronic or progressing malignant disease, severe infection or liver disease, or did the patient meet PHL criteria prior to starting study treatment and at first on study treatment visit, as described in Section 6 of this Appendix

If **No**: Follow the process described in Appendix E, Section 4.2 for reporting PHL as an SAE .

If **Yes**: Determine if there has been a significant[#] change in the patient's condition compared with when PHL criteria were previously met.

- If there is no significant change, no action is required.
- If there is a significant change, follow the process described in Appendix E, Section 4.2 for reporting PHL as an SAE.

A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the study Physician if there is any uncertainty.

Appendix F Guidance Regarding Potential Interactions with Concomitant Medications

F 1 Restrictions regarding drugs affecting CYP3A4

There are currently no data confirming that there is a pharmacokinetic interaction between these agents and AZD7648; any potential interaction is considered on the basis of preclinical and in vitro human data only. The principal enzymes for metabolising AZD7648 are CYP3A, therefore potent cytochrome P450 3A4 (CYP3A4) inhibitors or inducers may increase or decrease exposure to AZD7648, respectively. Potent inhibitors or inducers of CYP3A4 should not be combined with AZD7648. Moderate CYP3A inhibitors and inducers should be used with caution.

These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to modulate CYP3A4 activity. Appropriate medical judgement is required. Please contact AstraZeneca with any queries you have on this issue. Please refer to full prescribing information for all drugs prior to co-administration with AZD7648.

Table 1 Drugs Known to be Inhibitors of CYP3A

Potent CYP3A4 inhibitors may increase exposure to AZD7648
boceprevir
clarithromycin
conivaptan
elvitegravir/ritonivir
fluconazole
grapefruit juice[ab]
indinavir
itraconazole
ketoconazole
lopinavir/ RIT
mibefradil
nefazodone
nelfinavir
posaconazole
ritonavir
saquinavir
telaprevir
telithromycin
tipranavir/ ritonivir
troleandomycin
voriconazole

List created using the University of Washington Drug-Drug Interaction Database January 2013.

[a] Double-strength grapefruit juice.

[b] Patients should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits eg, grapefruit juice or marmalade) during the study **(**eg, no more than a small glass of grapefruit juice (120 mL) or half a grapefruit or 1-2 teaspoons (15 g) of Seville orange marmalade daily)

Table 2 Drugs Known to be Potent Inducers of CYP3A4

Potent Inducers (AZD7648 AUC may decrease or CL increase)
avasimibe
carbamazepine
enzalutamide
mitotane
phenobarbital
phenytoin
rifabutin
rifampin
St John's Wort

AUC=area under curve; CL= apparent total body clearance.
[Not available on the US market].

[a] Ritonavir has dual effects of simultaneous CYP3A inhibition and induction, and the net pharmacokinetic outcome during chronic ritonavir therapy is inhibition of CYP3A activity.

Appendix G Acceptable Birth Control Methods

Pegylated liposomal doxorubicin is regarded as a compound with medium/high foetal risk.

Women of childbearing potential and their partners, who are sexually active, must agree to the use of one highly effective form of contraception [as listed below] and their partners must use a male condom. This should be started from the signing of the informed consent and continue throughout the period of taking study treatment and for 12 weeks after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (see below).

Male patients must use a condom from the signing of the informed consent, during treatment and for 12 weeks after the last dose of study drug(s) when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients should also use a highly effective form of contraception if they are of childbearing potential (as listed below). Male patients should not donate sperm throughout the period of taking study drug(s) and for 12 weeks following the last dose of study drug(s).

Acceptable non-hormonal birth control methods include:

- Total/True abstinence: When the patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the trial and for 12 weeks after the last dose of study drug. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial) and withdrawal are not acceptable methods of contraception.
- Vasectomised sexual partner PLUS male condom. Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
- Tubal occlusion PLUS male condom.
- IUD PLUS male condom. Provided coils are copper-banded.

Acceptable hormonal methods:

- Normal and low dose combined oral pills PLUS male condom.
- Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone based pill.
- Hormonal shot or injection (eg, Depo-Provera) PLUS male condom.
- Etonogestrel implants (eg, Implanon, Norplant) PLUS male condom.
- Norelgestromin / EE transdermal system PLUS male condom.
- Intrauterine system [IUS] device (eg, levonorgestrel releasing IUS -Mirena®) PLUS male condom.

- Intravaginal device (eg, EE and etonogestrel) PLUS male condom.

Appendix H Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

Introduction

This Appendix details the implementation of response evaluation criteria in solid tumours (RECIST) 1.1 guidelines (Eisenhauer et al, 2009) for the study with regards to Investigator assessment of tumour burden including protocol-specific requirements for this study.

Definition of Measurable, Non-measurable, Target and Non-target Lesions

Patients with at least 1 lesion (measurable and/or non-measurable) that can be accurately assessed at baseline by computed tomography (CT), MRI or plain X-ray should be included in this study. Patients with previously irradiated TLs can be included in this study provided that there has been progression in the irradiated site following the treatment.

Measurable Lesions

A lesion, not previously irradiated, that can be measured accurately at baseline as ≥ 10 mm in the longest diameter (except lymph nodes) which must have a short axis ≥ 15 mm with CT or MRI and which is suitable for accurate repeated measurements.

Non-measurable Lesions

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm short axis at baseline). Nodes with < 10 mm short axis are considered non-pathological and should not be recorded as non-target lesions (NTLs).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that are not measurable by CT or MRI.
- Previously irradiated lesions as localised post-radiation changes, which affect lesion sizes, may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and should be selected as NTLs at baseline and followed up as part of the NTL assessment.
- Skin lesions assessed by clinical examination.
- Brain metastasis.

Special Cases

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.

- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these non-cystic lesions should be selected as the TLs.

Target Lesions

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TLs at baseline.

Non-target Lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline.

Methods of Measurement

The Same Method of Assessment and the Same Technique Should Be Used to Characterise Each Identified and Reported Lesion at Baseline and During Follow-up.

The methods to be used for RECIST assessment are summarised in Table 1 and those excluded for tumour assessments in this study are discussed below, with the rationale provided.

Table 1 Summary of Methods of Assessment

Target Lesions	Non-target lesions	New Lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Plain X-ray (includes chest X-ray)	Plain X-ray (includes chest X-ray)
	Clinical examination	Clinical examination
		Ultrasound
		Bone scan
		FDG-PET

CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TLs selected for response assessment and to assess NTLs and identification of new lesions.

In this study it is recommended that CT examinations will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contraindicated. For assessment of brain lesions MRI is the preferred method.

Clinical Examination

Clinical examination will not be used for assessment of TLs. Clinically detected lesions can be selected as TLs if they are then assessed by CT or MRI scans. Clinical examination can be used to assess NTLs in patients that also have other lesions assessable by CT, MRI or plain X-ray and to identify the presence of new lesions.

X-rays

Plain X-ray

Plain X-rays may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

Chest X-ray

Chest X-rays will not be used for assessment of TLs as they will be assessed by CT or MRI examination. Chest X-rays can, however, be used to assess NTLs and to identify the presence of new lesions.

Ultrasound

Ultrasound examination will not be used for assessment of TLs and NTLs as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

Endoscopy and Laparoscopy

Endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour measurements.

Tumour Markers

Tumour markers will not be used for tumour response assessments per RECIST 1.1.

In this study the following marker, CCI , is being collected for separate analysis. However the results will not contribute to tumour response based on RECIST 1.1 assessment.

Cytology and Histology

Histology will not be used as part of the tumour response assessment per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or stable disease (SD). In such circumstances, the cytology is necessary to differentiate between response/SD (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or the appearance of a clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTLs or disease progression due to new lesions.

Isotopic Bone Scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI or X-ray at baseline should be recorded as NTLs and followed by the same method as per baseline assessment.

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and X-ray is recommended where bone scan findings are equivocal.

FDG-PET Scan

FDG-PET (fluorodeoxyglucose positron emission tomography) scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake (defined as when an uptake greater than twice that of the surrounding tissue is observed) not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

Tumour Response Evaluation

Schedule of Evaluation

Baseline tumour assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 28 days before the start of study treatment. In Combination module 1, follow-up assessments

should be performed every 8 weeks (± 1 week) after the start of treatment until discontinuation of study treatment or withdrawal of consent.

If AZD7648 is combined with any immuno-oncology drugs (in future combination modules) modified RECIST will be used in an exploratory analysis. If progression is not confirmed, then the overall visit response as per modified RECIST should be assessed as SD/partial response (PR) or CR and the patient should continue scheduled RECIST 1.1. CT/MRI scans. If progression is confirmed the overall visit response should be assessed as progressive disease as per modified RECIST.

Target Lesions

Documentation of Target Lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved, should be identified as TLs at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions) but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimetres. At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

Special Cases:

- For TLs measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is > 5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into 2 or more parts, then record the sum of the diameters of those parts.
- If 2 or more TLs merge then the sum of the diameters of the combined lesion should be recorded for 1 of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.

- When a TL has had any intervention eg, radiotherapy, embolisation, surgery etc, during the study, the size of the TL should still be provided where possible.

Evaluation of target lesions

Table 2 provides the definitions of the criteria used to determine objective tumour visit response for TLs.

Table 2 Overall Visit Response for Target Lesions

Complete Response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progressive Disease	At least a 20 % increase in the sum of diameters of TLs, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20 %, the sum must also demonstrate an absolute increase of at least 5 mm.
Not Evaluable (NE)	Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides NE as a TL response.

Non-Target lesions

Evaluation of Non-target Lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline. Measurements are not required for these lesions but their status should be followed at subsequent visits. At each visit, an overall assessment of the NTL response should be recorded by the Investigator. Table 3 provides the definitions of the criteria used to determine and record overall response for NTLs at the investigational site at each visit.

Table 3 Overall Visit Response for Non-Target Lesions

Complete Response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-progressive disease	Persistence of 1 or more NTLs.

Table 3 Overall Visit Response for Non-Target Lesions

Progressive Disease	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in 1 lesion only or in several lesions. In all cases the progression MUST clinically significant for the physician to consider changing or stopping therapy.
Not Evaluable (NE)	Only relevant when 1 or some of the NTLs were not assessed and in the Investigator's opinion they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in TLs, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of 1 or more NTLs is usually not sufficient to qualify for unequivocal progression status.

New Lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of 1 or more new lesions is assessed as progression.

A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

Symptomatic Deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with 'symptomatic deterioration' requiring discontinuation of study treatment without objective evidence of disease progression at that time will undergo no further tumour

assessments in this study. Tumour response data for such patients will be censored at the date of their last RECIST assessment.

Evaluation of Overall Visit Response and Best Overall Response

The overall visit response will be derived using the algorithm shown in Table 4.

Table 4 Overall Visit Response

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non-CR/Non-progressive disease	No	PR
CR	NE	No	PR
PR	Non- progressive disease or NE	No	PR
SD	Non- progressive disease or NE	No	SD
NA	Non-CR/Non- progressive disease	No	SD (Non-CR/non-progressive disease)
NE	Non- progressive disease or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	progressive disease
Any	progressive disease	Yes or No	progressive disease
Any	Any	Yes	progressive disease

CR = complete response, PR = partial response, SD = stable disease, IR = incomplete response, NE = not evaluable, NA = not applicable (relevant when no TLs/NTLs at baseline)

Specifications for Radiological Imaging

These notes are recommendations for use in clinical studies. The use of standardised protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

CT Scan

CT scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomical regions of interest.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST 1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

Anatomic Coverage

Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

Intravenous Contrast Administration

Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of intravenous contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow- up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of TLs on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study then the recommended methods are: CT thoracic examination without contrast and abdominal and pelvic MRI with contrast. If MRI cannot be performed then CT without intravenous contrast is an option for the thorax, abdomen and pelvic examinations.

Slice Thickness and Reconstruction Material

It is recommended that CT scans be performed at 5 mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for the measurable lesion

definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TLs should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not "selected" images of the apparent lesion.

MRI Scan

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium-enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the specific body part being imaged as well as the scanner utilised. It is beyond the scope of this Appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the imaging modality of choice.

FDG-PET Scans

FDG-PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. If FDG-PET scans are included in a protocol, an FDG uptake period of 60 min prior to imaging has been decided as the most appropriate for imaging of patients with malignancy. Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 min post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical trial.

PET/CT Scans

At present, low dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for tumour measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. However, this is not recommended because the PET portion of the CT introduces additional data that may bias an Investigator if it is not routinely or serially performed.

REFERENCES

Eisenhauer et al, 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 2009;45:228-247.

Wolchok et al, 2009
Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15:7412-20.

Appendix I Food Effect Cohort Plan

Summary

- The food effect cohort of the study comprises a cross over design.
- Each patient in the food effect cohort will initially receive a single oral dose of AZD7648 (dose to be decided by the SRC) on Cycle 0, Day 1 in either the fasted or fed state. The Parexel project manager (in appropriate consultation with AZ study team) will advise each site on whether a particular patient participating in the food effect cohort has been allocated to the fed or fasted group for their Cycle 0, Day 1 dose.
- The patient will then cross over to receive their single Cycle 1, Day 1 dose in the opposite state to their Cycle 0, Day 0 dose. So, if the patient had the Cycle 0, Day 1 dose in the fasted state, the Cycle 1, Day 1 dose will be taken in the fed state, after a high fat breakfast meal. If the patient had the Cycle 0, Day 1 dose in the fed state, the Cycle 1, Day 1 dose will be taken in the fasted state (water only for ≥2 hours prior to taking a dose to ≥1 hour post-dose). The Cycle 1, Day 1 dose should be given in the morning at least 72 hours after the Cycle 0, Day 1 dose.

Meal and Timing Requirements

- Please note that for the fasted state, patients must fast (water only) for ≥ 10 hours prior to taking a dose to ≥ 2 hour post-dose. For the fed state patients must fast overnight (minimum of 10 hours) prior to consuming a standardised meal in the clinic.
- For the fed dosing day, the meal should consist of about 800 to 1000 total calories, with around 54% of the calorific content made up from fat. The dose should be administered with 240 mL of water.
- Patients should ideally start the recommended meal 30 min prior to planned administration of the study drug and aim to consume at least 75% of the meal within 30 min.
- If the patient takes less than 30 min to complete the meal, it is still expected that the drug is dosed not earlier than 30 min after the start of the meal.
- If the patient is unable to consume at least 75% of the meal within 30 min an additional 15 min will be allowed.
- The study drug should be administered after a minimum of 75% of the meal is completed between 30 min and up to 45 min after starting the meal.
- Please note that patients will only be considered evaluable for the food effect cohort if they eat at least 75% of their meal within a maximum of 45 min. Patients will remain in the Part A continuous scheduling cohort and should continue to receive their dose and undergo planned sampling/procedures even if they have been unable to consume the required amount of food within the 45 min window, but will not be considered evaluable for the food effect cohort.
- After Cycle 1, Day 1 patients may continue to receive AZD7648 monotherapy (continuous dosing) and all dosing from that point onwards must be administered in the fasted state.

- Pharmacokinetic samples will be taken at the times indicated in the study protocol.
- Please note that patients with insulin-dependent diabetes must be excluded from the food effect cohort(s). Eligibility of patients with Diabetes Type I or uncontrolled Type II (HbA1c > 7 mmol/L assessed locally) will be judged by the Investigator.

Summary of 5 High-fat Breakfast Meals

In accordance with FDA guidance (FDA Guidance for Industry 2002), the high fat meal should have a total of approximately 800 to 1000 kcal, with approximately 50-60% of the calorific content made up from fat. The meal should therefore derive approximately 150, 250 and 500 to 600 kcal from protein, carbohydrate and fat respectively, as shown in Table 1.

Some high fat breakfast meal examples are given in Table 2 to Table 6. The exact composition of the meal may vary as long as the totals are similar to those detailed in Table 1.

Table 1 Calorie Composition

	Protein (kcal)	Carbohydrate (kcal)	Fat (kcal)	Total (kcal)	Fat (%)
Target	150	250	500-600	800-1000	50
Regular	215	266	543	1000	54.3
Gluten Free	197.2	232	497	890	53.5
Lactose Free	198	252	504	956	53
Vegetarian	161.4	208	449	800	56

Table 2 Regular High Fat

	Kcals	Fat	CHO	Protein
1 cup whole milk	150	8	12	8
1/2 cup cheerios (1 container)	70	1	14	1
1/2 slice French toast	110	3.5	15.5	4.5
2 turkey sausage patties	160	12	-	14
3.5 oz scrambled eggs	160	11.89	4	13.36
2 slices provolone cheese	160	12	2	10
1 slice toast	80	1	15	3
3 packets butter	100	11	-	-
1 sugar free syrup	10	-	4	-

	Kcals	Fat	CHO	Protein
Totals		60.39g	66.5g	53.86g
	1000 kcal	543 kcal	266 kcal	215 kcal
		54.3% kcals	26.6% kcals	21.5% kcals

Table 3 Gluten Free High Fat

	Kcals	Fat	CHO	Protein
1 cup whole milk	150	8	12	8
3/4 cup cereal (rice chex 1 container)	70	-	16	1
1 slice gluten-free bread	120	2.5	23	2
1 pouch cream cheese	70	7	1	1
2 turkey sausage patties	160	12	-	14
3.5 oz scrambled eggs	160	11.89	4	13.36
2 slices provolone cheese	160	12	2	10
Totals		53 g	58g	49.3g
	890 kcals	477 kcal	232 kcals	197.2 kcals
		53.5%	26%	22%

Table 4 Lactose Free High Fat

1 cup Lactaid whole milk	**160**	**8**	**13**	**8**
2 hard-boiled eggs	156	10	2	12
3 turkey sausage	240	18	-	21
1 slice whole grain toast	120	3	19	5
3 packets butter	100	11	-	-
½ Belgium waffle	170	6	25	3.5
1 sugar free syrup	10		4	
Totals	956 kcals	56g	63g	49.5g
		504 kcal	252 kcal	198 kcal
		53%	26.3%	20.7%

Table 5 Vegetarian High Fat

1 cup whole milk	**150**	**8**	**12**	**8**
1 slice French toast	220	7	31	9
1 sugar free syrup	10	-	3	-
3 packets butter	100	11	-	-
3.5 oz scrambled eggs	160	11.89	4	13.36
2 slices provolone cheese	160	12	2	10
Totals		49.89 g	52g	40.36g
	800 kcals	449 kcal	208 kcal	161.4 kcal
		56%	26%	20%

Table 6 Continental Breakfast

	Kcals	**Fat**	**CHO**	**Protein**
Tea/ coffee	0	0	0	0
Yogurt	176	13	7	6
Cheese	152	11	0	11
Bread	110	0	24	3
1 croissant	189	9	23	4
butter	147	16	0	0
sugar	40	0	10	0
Ham (2 slices)	143	7	0	20
Totals		57	64	45
	959 kcals	519 kcals	258 kcals	181 kcals
		54%	27%	19%

FDA Guidance for Industry 2002
Food-Effect Bioavailability and Fed Bioequivalence Studies. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). December 2002. Available at: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070241.pdf. Accessed 16 October 2018.

Appendix J Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study patients become infected with SARS-CoV-2 or similar pandemic infection) during which patients may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following notification from the Sponsor and instructions on how to perform these procedures will be provided at the time of implementation.

J 1 Reconsent of Study Patients During Study Interruptions

During study interruptions, it may not be possible for the patients to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections J 2 to J 5. Local and regional regulations and/or guidelines regarding reconsent of study patients should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the informed consent form [ICF] should be signed at the patient's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

J 2 Rescreening of Patients To Reconfirm Study Eligibility

Additional rescreening for **screen failure due to study disruption** can be performed in previously screened participants. The investigator should confirm this with the designated study physician.

In addition, during study disruption there may be a delay between confirming eligibility of a patient and either enrolment into the study or commencing of dosing with investigational product. If this delay is outside the screening window specified in in the appropriate Schedule of Assessment Table, the patient will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a patient in addition to that detailed in Section 5.4.

J 3 Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified Health Care Professional (HCP) from the study site or third-party vendor service will visit the patients home / or other remote location as per local standard operating

procedures (SOPs), as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the clinical study protocol (CSP).

J 4 Telemedicine Visit to Replace On-site Visit (where applicable)

In this appendix, the term telemedicine visit refers to remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the patients will allow adverse events, concomitant medication, Eastern Cooperative Oncology Group performance status (ECOG PS) to be reported and documented.

J 5 At-home or Remote Location IP Administration Instructions

If a site visit is not possible, at-home or remote location administration of investigational product may be performed by a qualified HCP, provided this is acceptable within local regulation/guidance, or by the patient or his/her caregiver. The option of at-home or remote location investigational product administration ensures patients safety in cases of a pandemic where patients may be at increased risk by traveling to the site/clinic. This will also minimize interruption of investigational product administration during other study disruptions, eg, site closures due to natural disaster. All necessary supplies and instructions for administration and documentation of investigational product administration will be provided if site is able to complete all safety assessments as per CSP.

J 6 Data Capture During Telemedicine or Home / Remote Visits

Data collected during telemedicine or home / remote visits will be captured by the qualified HCP from the study site or third-party vendor service, or by the patient themselves eg, details of self-administration of study medication in diary card.

Appendix K Abbreviations

Abbreviation or special term	Explanation
AE	adverse event
ALP	alkaline phosphatise
ALT	alanine aminotransferase
AML	acute myeloid leukaemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATM	ataxia telangiectasia mutated
ATR	ataxia telangiectasia and Rad3-related protein
AUC	area under the curve
CCI	CCI
BRCA*m*	breast cancer gene 1 and 2 mutations
CAP	College of American Pathologists
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum plasma concentration
$C_{min,ss}$	minimum plasma concentration at steady state
COVID-19	coronavirus disease 2019
CR	complete response
CrCl	creatinine clearance
CRF	case report form (electronic/paper)
CSP	clinical study protocol
CSR	clinical study report
CT	computed tomography
CCI	CCI
CTCAE	common terminology criteria for adverse event
CCI	CCI
CYP3A4	cytochrome P450 3A4
DCO	data cut-off
DDR	DNA damage response agent
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DNA-PK	DNA-dependent protein kinase
DNA-PKcs	DNA-dependent protein kinase catalytic subunit

Abbreviation or special term	Explanation
DSB	double-strand break
ECG	electrocardiogram
ECHO	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
EDTA	ethylenediaminetetraacetic acid
FDA	food and drug administration
FFPE	formalin-fixed paraffin embedded
FTIH	first time in human
gBRCA*m*	germline breast cancer gene 1 and 2 mutations
GCP	good clinical practice
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
HCP	Health Care Professional
HNSTD	highest non-severely toxic dose
h	hour
HR	homologous recombination
CCI	CCI
HL	Hy's Law
IB	Investigator's brochure
ICF	informed consent form
ICH	international conference on harmonisation
IEC	independent ethics committee
INR	international normalised ratio
IRB	institutional review board
IV	intravenously
MBAD	minimum biologically active dose
MDS	myelodysplastic syndrome
MedDRA	medical dictionary for regulatory activities
MFD	maximum feasible dose
Min	minute
mPFS	median progression-free survival
mRECIST	modified response evaluation criteria in solid tumours (RECIST) 1.1
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	MUltiGated Angiography

Abbreviation or special term	Explanation
NA	not applicable
NE	not evaluable
NHEJ	non-homologous end joining
NOACs	new oral anticoagulants
NTL	non-target lesions
ORR	objective response rate
OS	overall survival
PARPi	poly ADP ribose polymerase inhibitor
CCI	CCI
PD	pharmacodynamics
PD-L1	programmed death-ligand 1
PDX	patient-derived xenograft
PFS	progression-free survival
PGx	pharmacogenetic sample
PHL	potential Hy's Law
PIKK	phosphatidylinositol 3-kinase-related kinase
PK	pharmacokinetics
PLD	pegylated liposomal doxorubicin
PoC	proof of concept
PR	partial response
CCI	CCI
QTc	corrected QT interval
RECIST	response evaluation criteria in solid tumours
RNA	ribonucleic acid
RP2D	recommended Phase II dose
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
STD 10	severely toxic dose in 10% of the animals
SoA	schedule of assessments
SRC	safety review committee
SSB	single-strand break
$t_{1/2}$	half-life
TL	target lesion

Abbreviation or special term	Explanation
t_{max}	time to reach maximum plasma concentration
TBL	total bilirubin
TSH	thyroid-stimulating hormone
ULN	upper limit normal
US	United States
WOCBP	women of child-bearing potential

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