AstraZeneca

**Clinical Study Protocol**

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|---|---|
| Drug Substance | AZD1775 |
| Study Code | D6015C00001 |
| Version | 5 |
| Date | |

# A Phase Ib, Open-Label, Multi-Centre Study to Assess the Safety, Tolerability, Pharmacokinetics, and Anti-tumour Activity of AZD1775 Monotherapy in Patients with Advanced Solid Tumours

**Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden**

# VERSION HISTORY

| **Version 5.0, (Amendment 4)** |
|---|
| Changes to the protocol are summarised below:<br>• Updated the following text to align with the revised Project Specific Safety Requirements (PSSR), dated 20 February 2017:<br>  • Section 1.3.2 Potential risks<br>  • Section 6.6 Overdose<br>  • Section 6.8.2 and Table 9 Non-haematologic toxicity dose modification<br>  • Section 6.8.3.1 Diarrhoea<br>• Deleted text relating to the definition of an on-study patient (see Section 4.2).<br>• Specified that patients still receiving AZD1775 after the primary data cut-off will have a Final Protocol Visit (FPV) aligning with their next scheduled visit focused on capturing safety information. Following the FPV, patients will be treated in accordance with local practice as deemed appropriate by the Investigator (see Table 2 and footnote 'bb' and Section 4.3.2.3).<br>• Clarified that blood samples for exploratory biomarker research will be collected at treatment discontinuation and disease progression for subjects that continue on the study treatment after FPV (see Section 5.5.1).<br>• Clarified that an optional biopsy will be performed on consenting patients that continue after the FPV (see Section 5.5.7).<br>• Clarified that after the FPV, drug accountability information must continue to be collected until the patient discontinues treatment. In addition, patients must continue to be monitored for all SAEs, pregnancies and overdoses for 30 days after the last dose of AZD1775 (see Sections 4.3.2.3 and 9.4 ).<br>• Clarified that all safety data collected after the primary analysis and up to (and including) the last of the FPV will be listed and/or summarized as appropriate (see Sections 8.3 and 9.4).<br>Other changes:<br>• Replaced SCRI Innovations with Innovations.<br>• Clarifications for improved readability, minor errors corrected, and minor corrections were made for purpose of consistency. |

**Version 4.0, 23 August 2016 (Amendment 3)**

Changes to the protocol are summarised below:

- The contents from the previous protocol have been placed into a new template.
- Clarified Inclusion Criteria for renal function (see Section 3.1)

  Revised text:
  Serum creatinine ≤1.5 x the ULN **or** a calculated creatinine clearance (CrCl) ≥45 mL/min measured by the Cockcroft-Gault method or 24-hour urine CrCl.

- Clarified Exclusion Criteria for CNS disease (see Section 3.2)

  Revised text:
  Known malignant central nervous system (CNS) disease other than neurologically stable, treated brain metastases – defined as metastasis having no evidence of progression or haemorrhage for at least 2 weeks after treatment. Must be off any systemic corticosteroids for the treatment of brain metastases for at least 14 days prior to enrolment.

- Because prostate cancer patients, who are on stable treatment with LHRH analogues, could stop LHRH and restart it at a later date which could lead to tumour flares, Exclusion Criteria was updated to include patients on stable anti-hormonal treatment (see Section 3.2).

  Added text:
  No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal anticancer therapy radiotherapy (except for palliative local radiotherapy), biological therapy or other novel agent is to be permitted while the patient is receiving study medication. Patients on LHRH analogue treatment for more than 6 months are allowed entry into the study and may continue at the discretion of the investigator.

- Revised text regarding collection of blood pharmacokinetic samples during Part B expansion (see Section 5.3.2 and Table 5).

  Revised text:
  PK blood samples will be required from all patients enrolled at approximately 3-5 investigational sites to ensure we have evaluable data from at least 50 patients. These required samples may become optional once there are samples from at least 50 patients. PK blood sampling is highly recommended for all patients at the remaining sites. PK blood sample collections will be taken from consenting patients pre-dose and 2-4 hours post-dose on Day 3 or Day 10 of Cycle 1, Cycle 2, and Cycle 4, and beyond Cycle 4 every 2 cycles (see Table 5). The date and actual time of all PK samples must be recorded.

- Added a section on Repeat biopsies and Pharmacokinetic analysis set (Section 5.4.2 and 8.2.5, respectively).
- The reporting of disease progression was clarified (Section 6.4.8).

- Added pharmacogenetics (PGx) sample collection information (Section 5.5 and Study Plan Tables 1 and 2).
- Added an exploratory objective to clarify how the PGx samples will be used (see Synopsis and Section 2).
- Explanation of a pharmacodynamics response is added in Section 8.9.
- A revised definition of TNBC and SCLC patients was added to boost recruitment into the biomarker-positive cohorts in the Synopsis, Inclusion criteria (Section 3.1), Subject enrolment and randomisation (Section 3.3), and Archived or recent tumour tissue (Section 5.4.3) sections.
- Added Metformin and BCRP substrates with a narrow therapeutic index to the restrictive concomitant medication list and revised text (Section 7.8.2 and Appendix G).

  Revised text:
  Metformin **should be used with caution**. AZD1775 has been shown to be an inhibitor of MATE1 and MATE2K transporters. A drug interaction with substrates of either transporter cannot be ruled out, the most important substrate known to date being metformin.

- Revised text in Footnote 'u' to clarify that AZD1775 should be taken 2 hours before eating and again 2 hours after eating. Noted that ECGs will be taken on Cycles 1 and Cycle 2 on Day 3 or Day 10 within table (see Study Plan Table 2).
- To support more robust decision-making on the benefit-risk assessment for the ovarian cancer (BRCA1/2 mutation with progression on PARPi) cohort, the number of patients has increased from 20 to 40 patients (Figure 1 and Section 8.1). This increases the approximate total number of patients treated from 152 to 172 patients.
- Deleted the Medical Emergencies contact list.
- The study schema was revised to accurately reflect each cohort (Figure 2).

Other changes:

Clarifications for improved readability, minor errors corrected, and minor corrections were made for purpose of consistency.

**Version 3.0, 12 November 2015 (Amendment 2)**

Changes to the protocol are summarised below:

- This clinical study protocol (CSP) has been changed from a three-part study to a two-part study. Numerous sections throughout the CSP have been updated to reflect the changes

including the Study Plan tables 4 and 5, enrolment process (5.2), inclusions criteria (Section 4.1), biomarker collections, and dosing (Section 5.5).

- Part A (Section 5.5.1) discusses that during the safety lead-in, the AZD1775 starting dose was reduced to 175 mg BID because 200 mg BID was not well-tolerated.
- Adverse events (AEs) associated with AZD1775, and DLTs observed during the safety lead-in includes diarrhoea, vomiting and anaemia (Sections 5.10.3.1).
- Mandatory anti-emetic prophylaxis has been instituted (Section 5.10.3.2).
- Part B (Section 5.5.2) has been updated and the expansion cohorts have been better organised by tumour type and molecular profile to evaluate anti-tumour activity. The tumour types to be evaluated are: 1) ovarian cancer (BRCA1/2 mutation [PARP-failures]), 2) ovarian cancer (BRCA wild-type) with more than 3 prior lines of treatment, 3) TNBC, and 4) SCLC. The expansion cohort for squamous non-small cell lung cancer populations were replaced with advanced small cell lung cancer.

Other changes:

Clarifications for improved readability, references updated, minor errors corrected, and minor corrections were made for purpose of consistency.

**Version 2.0, 12 May 2015 (Amendment 1)**

Changes to the protocol are summarised below:

- The criterion for SqNSCLC patients was revised to indicate the number of prior treatments required before study enrolment (Section 4.1).

  Revised text:

  SqNSCLC cancer defined as a histologically confirmed diagnosis of squamous NSCLC (excludes large cell, adenocarcinoma, neuroendocrine, and mixed NSCLC/small-cell histologies) and must have received at least 1 chemotherapy-containing regimen for advanced disease (recurrent or metastatic). NSCLC tumours are eligible if the predominant histology is squamous cell. If small-cell elements are present or the tumour is assessed as 'not otherwise specified' (NOS) histologically, the patient is not eligible.

- To correct a typographical error made in the exclusion criteria #10 for QTc interval (Section 4.2).

  Revised text:

  Corrected QT interval (QTc) < ≥470 msec (as calculated per institutional standards) at study entry or congenital long QT syndrome (see Section 6.4.8). In addition, Part A safety lead-in patients must have baseline triplicate ECGs and the Part B and Part C patients will

have ECGs collected at baseline if clinically indicated.

- Whole blood collections for immune profiling flow cytometry – Part A safety lead-in patients header was corrected to match content (Section 6.7.2)

  Revised text:

  **Whole blood collections for immune profiling flow cytometry ~~– Part A safety lead-in patients~~**

| **Version 1.0, 25 March 2015** |
| --- |
| Initial creation |

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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# PROTOCOL SYNOPSIS

## A Phase Ib, Open-Label, Multi-Centre Study to Assess the Safety, Tolerability, Pharmacokinetics, and Anti-tumour Activity of AZD1775 Monotherapy in Patients with Advanced Solid Tumours

**Principal Investigator**

**Study site(s) and number of patients planned**

Approximately 172 total patients will be treated at approximately 20 investigational sites in the United States and Canada.

| Study period | | Phase of development |
|---|---|---|
| Estimated date of first patient enrolled | Q2 2015 | 1 |
| Estimated date of last patient completed | Q1 2018 | 1 |

**Study design**

This open-label, multi-centre, Phase Ib study is designed to evaluate the safety, tolerability, pharmacokinetics, and anti-tumour activity of oral AZD1775 monotherapy. The study is divided into two parts: Part A safety lead-in cohort of patients with advanced solid tumours, and Part B expansion cohorts in which patients will be organised by tumour type and molecular profile to evaluate anti-tumour activity. Initially, a retrospective molecular analysis of tumour samples may be performed on approximately the first 15 patients under each tumour type. These patients will be allocated to the biomarker-negative or positive cohort retrospectively, once their genetic profile analysis result is available from the central lab. To ensure balance between the biomarker-positive and biomarker-negative cohorts, a switch to prospective molecular analysis at study entry will be required as patient enrolment advances after this point. A quality check of the submitted pathology material will be performed for both groups pre-treatment.

Treatment with AZD1775 monotherapy may continue until disease progression, unacceptable toxicity, or other discontinuation criteria has occurred as described in Section 3.9. Alternative dosing regimens and schedules may be studied depending on toxicities and emerging data.

**Part A – safety lead-in cohort (closed to enrollment 2015)**

AZD1775 (200 mg BID PO) will be taken in 12 hour intervals over 3 days (Days 1-3) for a total of 6 doses on week 1 and week 2 of each 21-day cycle (see Figure 2).

During the safety lead-in, the AZD1775 starting dose was reduced to 175 mg BID because 200 mg BID was not well-tolerated. Adverse events (AEs) associated with AZD1775, and DLTs observed during the safety lead-in included diarrhoea, vomiting and anaemia. In addition to reducing the starting dose of AZD1775, mandatory anti-emetic prophylaxis has been instituted (see Section 6.8.3.2). The Part A safety lead-in patient enrolment has been completed.

**Part B – expansion cohorts**

Part B expansion cohorts will investigate AZD1775 monotherapy in advanced tumour types with molecular biomarkers of interest. The tumour types to be evaluated are: ovarian cancer TNBC, and SCLC.

All tumour samples will be analysed for a range of cancer-related genes such that clinical response can be correlated to the gene aberrations. .

*BRCA* wild-type is defined as no evidence of deleterious or suspected deleterious mutation in *BRCA1* or *BRCA2* genes. *BRCA1* and/or *BRCA2* variants that are classified as "Variants of uncertain clinical significance" or "Variant of unknown significance (VUS)", as well as "Variant, favour polymorphism" or "benign polymorphism" are considered to be *BRCA* wild-type.

Biomarker 'positive' for the TNBC and SCLC cohorts to be analysed include amplifications in *CCNE1, MYC*, *MYCN* or *MYCL1*.

Biomarker 'negative' is defined as the absence of the qualifying amplification for TNBC or SCLC as specified above. Investigation of biomarker 'negative' results based on emerging signals may be explored through additional expansion cohort(s).

**Determination of MTD**

The AZD1775 dose (175 mg BID PO) and schedule (Days 1-3, Week 1 and 2, Q 21-days) for the Part B expansion is the dosing schedule that was defined in the Part A safety lead-in.

**Study Objectives**

**Primary Objectives:**

**Part A**

| Primary Objective: | Outcome Measure: |
|---|---|
| To evaluate the safety and tolerability of AZD1775 monotherapy administered in 21-day cycles for patients with advanced solid tumours (BID PO x 3 days [weeks 1 and 2]). | Safety parameters: treatment-emergent adverse events (TEAEs) graded according to NCI CTCAE v4.03, laboratory parameters, physical examinations, vital signs, etc. The number and incidence of TEAEs and abnormal findings will be examined. |

**Part B**

| Primary Objective: | Outcome Measure: |
|---|---|
| To evaluate the anti-tumor activity of AZD1775 monotherapy in previously treated patients with ovarian cancer, triple-negative breast cancer (TNBC) and small cell lung cancer (SCLC) | ORR, DCR, DoR, and PFS based on RECIST v1.1. |

**Secondary Objectives:**

**Part A**

| Secondary Objective: | Outcome Measure: |
|---|---|
| To evaluate the anti-tumor activity of AZD1775 monotherapy in previously treated patients with ovarian cancer, triple-negative breast cancer (TNBC) and small cell lung cancer (SCLC) | Objective response rate (ORR) defined as CR or PR based on tumour assessments as determined by Response Evaluation Criteria in Solid Tumours (RECIST) v1.1.<br>Disease Control Rate (DCR) defined as CR, PR, or stable disease (SD), based on tumour assessments as determined by RECIST v1.1.<br>Duration of response (DoR), defined as the time from first documented tumour response until the date of documented progression or death from any cause.<br>Progression-free survival (PFS) and overall survival (OS). |
| To characterize the pharmacokinetic (PK) profile of AZD1775. | Plasma PK parameters of AZD1775 pre-dose and post-dose |
| To characterize the effect of AZD1775 on QTc. | QTc interval |
| To identify genetic alterations from archived or recent tumour tissue and correlated with clinical outcomes. | Measurement of the presence of genetic alterations in TNBC and SCLC patients responding to AZD1775. |

**Part B**

| Secondary Objective: | Outcome Measure: |
|---|---|
| To characterize the pharmacokinetic (PK) profile of AZD1775. | Plasma PK parameters of AZD1775 pre-dose and post-dose |
| To characterize the effect of AZD1775 on QTc. | QTc interval |
| To identify genetic alterations from archived or recent tumour tissue and correlated with clinical outcomes. | Measurement of the presence of genetic alterations in TNBC and SCLC patients responding to AZD1775. |
| To investigate the effect of AZD1775 treatment on previously observed changes of peripheral immunological biomarkers associated with an anti-tumour immune response. | Levels of immunologically relevant cytokines and chemokines involved in the Th1-driven immune responses. |

**Exploratory Objective**

| Exploratory Objective: | Outcome Measure: |
|---|---|
| To collect and store deoxyribonucleic acid (DNA) for future research into genes/genetic variations that may influence PK or response to AZD1775 (i.e. absorption, distribution, metabolism, excretion, safety and efficacy) and/or susceptibility to/development of cancers. | Correlation of polymorphisms with variation in Pharmacokinetics (PK), Pharmacodynamics (PD), Pharmacogenetics (PGx), safety or response observed in subjects treated with AZD1775.<br>Data generated may be reported separately and may also form part of a pooled analysis with other AZD1775 studies. |

**Target patient population**

Patients must have received previous treatment with chemotherapy for metastatic or recurrent disease. Prior immunotherapy is allowed, but will not be counted as a prior treatment regimen. Prior radiation must have been completed at least 7 days prior to the start of treatment with recovery from any acute adverse effects, and an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score of 0 or 1. Measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST v1.1) is not required in the safety lead-in cohort (Part A), but is mandatory for Part B expansion cohorts.

**Investigational product, dosage, and mode of administration**

AZD1775 is available as dry-filled capsules containing 25 or 100 mg of drug substance. Additional information about the investigational product (IP) may be found in the Investigational Brochure (IB).

**Duration of treatment**

Patients in all parts of the study will be allowed to continue on therapy as long as they have no limiting toxicity or disease progression, have not withdrawn from the study, and are considered by the investigator to still be receiving clinical benefit. Any patient meeting these criteria will be followed for a minimum of 12 months before database lock (DBL).

**Statistical methods**

No formal hypothesis testing will be conducted in this open-label Phase Ib study. Descriptive statistical and graphical displays will be used to summarise the safety data, PK data, and preliminary anti-tumour activity data by dose level cohort (see Section 8). A full description of the statistical methods and analyses will be provided in a statistical analysis plan (SAP).

Details regarding sample size are provided in Section 8.1.

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

| Abbreviation or special term | Explanation |
|---|---|
| AE | Adverse event (see definition in Section 6.1) |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| ASCO | American Society of Clinical Oncology |
| AST | Aspartate aminotransferase |
| AUC | Area under the curve |
| BID | Twice a day |
| BRCA | Breast cancer gene 1/2 |
| CBC | Complete blood count |
| CDK | Cyclin-dependent kinases |
| CI | Confidence interval |
| CL/F | Oral clearance from plasma |
| c-myc | Cellular analog of myclocytomatosis viral oncogene |
| CR | Complete response |
| CrCl | Creatinine clearance |
| CSA | Clinical study agreement |
| CSP | Clinical study protocol |
| CSR | Clinical study report |
| CT | Computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Event |
| ctDNA | Circulating free DNA |
| CV | Coefficient of variation |
| DBL | Database lock |
| DCR | Disease control rate |
| DLT | Dose-limiting toxicity |
| DNA | Deoxyribonucleic acid |

| Abbreviation or special term | Explanation |
|---|---|
| DoR | Duration of response |
| EC | Ethics Committee, synonymous with Institutional Review Board (IRB) |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group (Performance Status) |
| eCRF | Electronic case report form |
| EOT | End of study treatment |
| FDA | Food and Drug Administration |
| FFPE | Fixed-formalin paraffin-embedded |
| 5-FU | 5-fluorouracil |
| FNA | Fine needle aspiration |
| FPV | Final Protocol Visit |
| GCP | Good Clinical Practice |
| GFR | Glomerular filtration rate |
| $G_{mean}$ | Geometric mean |
| GMP | Good manufacturing practice |
| IATA | International Air Transport Association |
| IB | Investigator's Brochure |
| IC | Informed consent |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| Innovations | Sarah Cannon Development Innovations |
| IP | Investigational Product |
| LMWH | Low molecular weight heparin |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | magnetic resonance imaging |
| MTD | maximum tolerated dose |
| NCI | National Cancer Institute |
| NE | Not evaluable |
| NSCLC | Non-small-cell-lung cancer |
| NTL | Non-target lesion |
| NYHA | New York Heart Association |

| Abbreviation or special term | Explanation |
|---|---|
| OAE | Other Significant Adverse Event (see definition in Section 8.7.3) |
| ORR | Objective response rate |
| PBMC | Peripheral blood mononuclear cell |
| PD | Progressive disease |
| PDx | Pharmacodynamics |
| PFS | Progression-free survival |
| PgP | p-glycoprotein |
| PGx | Pharmacogenetics |
| PI | Principal Investigator |
| PK | Pharmacokinetic |
| PO | By mouth/orally |
| PR | Partial response |
| PS | Performance status |
| QD | Once daily |
| RANKL | Receptor activator of nuclear factor Kappa-B ligand |
| RECIST | Response Evaluation Criteria in Solid Tumours |
| RR | Response rate |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SCLC | Small cell lung cancer |
| SD | Stable disease |
| SDV | Source data verification |
| Sq | Squamous |
| SRT | Safety review team |
| TEAE | Treatment-emergent adverse event |
| TL | Target lesion |
| TNBC | Triple negative breast cancer |
| ULN | Upper limit of normal |
| WoCBP | Women of childbearing potential |

# 1. INTRODUCTION

## 1.1 Background

Unrepaired DNA damage may result in mutation or cell death. Complex signalling networks regulate the integrity of the genome and initiate cell cycle arrest, repair and apoptotic responses if errors are detected. This allows the deoxyribonucleic acid (DNA) to be repaired before the cell undergoes replication and/or division. Cancer cells undergo an array of genetic changes including mutations in the DNA repair pathways (Ashwell and Zabludoff 2008).

AZD1775 is an inhibitor of WEE1, a checkpoint protein tyrosine kinase. WEE1 phosphorylates and inhibits cyclin-dependent kinases 1 (CDK1) and 2 (CDK2), and is involved in regulation of the intra-S and G2 cell cycle checkpoint arrest for premitotic DNA repair (Parker and Piwnica-Worms 1992). Normal cells ensure genomic integrity by repairing DNA that is damaged before cell cycle progression through these checkpoints. Phosphorylation is vital for regulation of the cell cycle and progress through the cell cycle depends on cyclin-dependent kinases (De Witt Hamer et al 2011). CDK1 (also called cell division cycle 2, or CDC2) activity promotes the G2 phase of the cell cycle into mitosis. In response to DNA damage, WEE1 inhibits CDK1 to prevent the cell from dividing until the damaged DNA is repaired (G2 checkpoint arrest). Inhibition of WEE1 is expected to release a tumour cell from chemotherapeutically-induced arrest of cell replication. *In vitro* experiments demonstrate that AZD1775 has synergistic cytotoxic effects when administered in combination with various DNA damaging agents that have divergent mechanisms of action. Therefore, the primary objective of the clinical development of AZD1775 has been to study its use as a chemosensitising drug in combination with a cytotoxic agent (or combination of agents) for treatment of advanced solid tumours.

CDK2 activity drives a cell into and through the S-phase of the cell cycle where the genome is duplicated in preparation for cell division. Inhibition of WEE1 is expected to cause aberrantly high CDK2 activity in S-phase cells that, in turn, leads to unstable DNA replication structures and ultimately DNA damage. If a tumour has high baseline DNA damage or DNA replication stress, inhibition of WEE1 alone may produce anti-tumour activity. Tumours with mutations in DNA damage repair genes or oncogenes inducing a high level of replication stress may therefore be responsive to single agent therapy with AZD1775. Therefore, it is anticipated that AZD1775 may have independent anti-tumour activity in the absence of added chemotherapy.

The tumour suppressor protein p53 regulates the G1 checkpoint. As the majority of human cancers harbour abnormalities in this pathway they become more dependent on S- and G2-phase checkpoints (Sherr 1996). Thus, S- and G2-checkpoint abrogation caused by inhibition of WEE1 may selectively sensitize p53-deficient cells to anti-cancer agents (Wang et al 2001).

*In vitro* and *in vivo* preclinical models, AZD1775 selectively enhanced chemotherapy-induced death of cells deficient in p53 signalling. Tumour context-specific sensitisation to the DNA

damaging agents, gemcitabine and platinums, was observed in TOV21G (ovarian carcinoma) cell lines matched for wild-type and knock-down of p53.

### 1.1.1 AZD1775

AZD1775 is a potent inhibitor of WEE1 that has significant selectivity over other tested protein kinases. In *in vitro* studies, AZD1775 inhibits WEE1 activity and induces DNA damage as well as G2 checkpoint escape in cell-based assays. AZD1775 increases cytotoxicity when used in combination with DNA damaging agents, such as gemcitabine, cisplatin, carboplatin, and topotecan, in p53-deficient cell lines. In *in vivo* studies, AZD1775 was well tolerated and showed enhancement of anti-tumour efficacy by gemcitabine, carboplatin, cisplatin, 5-fluorouracil (5-FU), and capecitabine in nude rat xenograft tumour models. Similarly, in nude mouse xenograft models, AZD1775 treatment resulted in significant tumour growth inhibition at tolerated doses, and also enhanced the anti-tumour growth effect of gemcitabine, carboplatin, and radiation therapy (AZD1775 IB).

AZD1775 has been studied extensively in preclinical xenograft models as a radiation or chemotherapy sensitizer. The data have demonstrated enhancement of chemotherapeutic effect in combination with carboplatin, cisplatin and gemcitabine in p53-deficient colon and lung carcinoma cells, and when given with 5-FU in p53-deficient colon and pancreatic cells, but not wild-type (WT)-p53 colon cancer cells (Hirari et al 2009, Hirari et al 2010).

Lung, breast, and prostate cancer human tumour cells were tested for radiosensitization by AZD1775 using clonogenic survival assays using both p53-deficient and WT-p53 cell lines. The p53-deficient cells were radiosensitized by AZD1775 *in vitro* and *in vivo* (Bridges et al 2011).

It is suggested that WEE1 inhibition has selective toxicity to cancer cells compared to normal cells. WEE1 was identified as a target in the CAL51 breast cancer cells in a functional genomic screen and a relationship between high levels of WEE1 expression and sensitivity to WEE1 inhibition was shown. The cancer cells also appear to be more dependent on the function of WEE1. The loss or inhibition of WEE1 in the cancer cells causes an accumulation of DNA double-strand breaks as measured by the accumulation of γH2AX (Murrow et al 2010). A WEE1 inhibitor, such as AZD1775 has been identified as a potential useful molecular target in triple negative breast cancer (TNBC).

A recent study of 305 cell lines treated with AZD1775 provided a rationale for WEE1 inhibition as a potent anticancer therapy without chemotherapy or radiation. PKMYT1 was the focus as a possible predictive marker for AZD1775 response. PKMYT1 phosphorylates and inhibits CDK1 and CDK2 like WEE1 and for that reason was considered for investigation as to whether as a kinase, it produces a cell-based response to AZD1775. The knockdown of PKMYT1 increased markers of DNA damage induced by AZD1775. Of the 305 cell lines treated with AZD1775, expression of PKMYT1 was below average in 73% of the 33 most sensitive cell lines (Guertin et al 2013).

Single-agent potential with AZD1775 has been validated both in *in vitro* and *in vivo* studies (Guertin et al 2013). Independent evaluation of NCI-60 cell lines and hollow fibre studies support single-agent activity of AZD1775 in some colon cancer, melanoma, ovarian cancer, and lung cancer cell lines. AZD1775 as a single-agent caused significant apoptotic cell death in patient-derived sarcoma samples, suggesting that WEE1 inhibition should be considered in sarcomas (Kreahling et al 2012).

Small-cell lung cancer (SCLC) remains one of the most difficult cancers to treat. Most patients will present with advanced or extensive-stage disease and not survive the first-year from diagnosis. Topotecan is the only FDA-approved agent in the relapsed setting and only for patients with recurrent disease at least 60 days from first-line platinum-doublet chemotherapy (sensitive-relapse SCLC). No agent is approved for patients with disease that progresses during or within 60 days of first-line platinum-doublet chemotherapy (refractory-relapsed SCLC). Newer approaches to therapy are needed.

SCLCs harbour multiple genomic alterations involved in cell cycle regulation (90+%), oncogenic signalling (15-25%), and double-strand break repair (DSB, 9%). The most common genetic alterations in SCLC occur in: *TP53* (90%), retinoblastoma 1 (RBI, 85%) (Byers et al 2014), *MYC* gene family (*MYC*, *MYCN*, and *MYCL1* - ~5% each), *RAS* (2%), and *BRCA1/2* (3%). These alterations, and in particular, combinations of these alterations, force cancer cells to depend on the G2-M checkpoint for restoring cell cycle function and division – where the WEE1 kinase is targeted by AZD1775. For example, it is estimated that 18% of SCLCs harbour mutations in cell cycle regulation (*TP53*) and in oncogenic signalling (*MYC* or *RAS*). Likewise, 3% of SCLCs harbour mutations in cell cycle regulation (TP53) and DSB repair (*BRCA1/2*). Thus, the high unmet medical need and prevalence of somatic alterations make SCLC an important cancer setting to investigate AZD1775.

### 1.1.2 Clinical experience

As of 11 November 2015, a total of 443 patients have been exposed to AZD1775 in AstraZeneca-sponsored or Merck-sponsored clinical studies, and 200 patients received AZD1775 as part of externally-sponsored scientific research. These patients have received single doses per cycle as high as 1300 mg of AZD1775 as monotherapy, 325 mg of AZD1775 in a single-dose in combination with chemotherapy, and 325 mg twice a day (BID) in a multiple-dose regimen in combination with chemotherapy. Refer to the current version of the AZD1775 Investigator's Brochure.

The completed or terminated early studies include:

- **NCT00648648** (except for Part 3): a first-time-in-patients (FTIP), Phase I, dose-escalation study evaluating AZD1775 both as monotherapy and combination therapy with gemcitabine, cisplatin, or carboplatin in adult patients with advanced solid tumours.

- **NCT010477007**: a Phase I, dose-escalation study evaluating AZD1775 as monotherapy (Part 1), combination therapy with 5-FU (Part 2), and combination therapy with 5-FU plus

cisplatin (Part 3) in adult Japanese patients with advanced solid tumours was terminated early due to portfolio prioritization in oncology at Merck after 3 patients had been enrolled in Part 1 and 8 patients had been enrolled in Part 2. Part 3 was not initiated.

- **NCT01076400**: a Phase I/IIa, dose-escalation study evaluating AZD1775 in combination with topotecan plus cisplatin in adult patients with cervical cancer was terminated early due to portfolio prioritization in oncology at Merck after 7 patients had been enrolled in the dose-escalation part of the study. Phase IIa was not initiated.

In Study **NCT00648648**, of 176 evaluable patients who received AZD1775 (either single or multiple doses) as monotherapy or in combination with gemcitabine, cisplatin, or carboplatin, a partial response (PR) (confirmed and unconfirmed) was observed in 17 (9.7%) patients, and stable disease (SD) was observed in 94 (53.4%) patients.

Nine patients received AZD1775 monotherapy. Single ascending doses of AZD1775 up to 1300 mg were well tolerated; the MTD was not evaluated.

In Study **NCT010477007**, patients in Part 1 received single-cycle 65 mg PO BID dosing of AZD1775 for 5 days as monotherapy. In Part 2a, patients received 20 mg AZD1775 BID in combination with 5-FU. A cohort of 3 patients was enrolled at the starting dose level of AZD1775 65 mg BID and no serious adverse events (SAEs) were experienced.

An ongoing study **NCT01748825** sponsored by the National Cancer Institute (NCI) Cancer Therapy Evaluation Program, in collaboration with AstraZeneca, is investigating AZD1775 monotherapy. The MTD for monotherapy treatment in patients with advanced refractory solid tumours was found to be 225 mg BID x 5 on Weeks 1 and 2 of a 3-week schedule. Paired biopsies were obtained from 5 patients on this dose and schedule. The biopsies showed that a decrease in pCDC2 was observed in the post-treatment biopsy in 3 of the biopsy pairs with an average of 80% reduction. The same biopsies were analysed for increases in γH2AX, an indicator of DNA damage. Three of the 5 biopsy pairs showed a post-treatment increase in γH2AX, with an average of 404% induction observed in these 4 biopsy pairs (Do et al 2015). This study is also evaluating a once daily (QD) schedule for monotherapy starting at a 200 mg dose. Twenty-five patients have been recruited for the BID schedule and 3 for the QD schedule.

Refer to the AZD1775 IB for additional information.

### 1.1.3 Pharmacokinetics

The PK data of AZD1775 following a single oral administration showed a moderate rate of absorption with a time of maximum concentration ($T_{max}$) occurring at 3 to 4 hours. Post-peak plasma concentrations declined essentially in a mono-exponential manner with a terminal half-life ($t_{1/2}$) in the region of 10 hours. Exposure as measured by maximum plasma drug concentration ($C_{max}$) observed after a dose and area under the curve $(AUC)_{0-\infty}$ increased in a dose-proportional manner over the dose range of 325 to 1300 mg. Following single (100 to

325 mg) and multiple dose administrations of AZD1775 (25 to 325 mg BID and 100 to 200 mg QD) with carboplatin, cisplatin, and gemcitabine, plasma exposure of AZD1775 was consistent with predictions based on the single-dose regimen. Preliminary investigation of drug-drug interactions in Study NCT00648648 suggest a 60% increase in the exposure of AZD1775 in the presence of aprepitant (moderate CYP3A4 inhibitor), but no effect with the concomitant administration of steroids (moderate CYP3A4 inducers). Preliminary studies also suggested that the Pre-marketed Oral Formulation (PMF) of AZD1775 was similar to that of the Fit-For-Purpose (FFP) formulation. Based on the preliminary comparison of the results of AZD1775 PK parameters at the 225 mg PK dose, PK estimates in Asian patients were 30-45% higher than in Western patients.

### 1.1.4 Safety

Based on the safety data from the 3 completed clinical studies and preliminary data from ongoing studies, the most frequent adverse events (AEs) observed were blood and lymphatic disorders (leukopenia, lymphopenia, neutropenia, thrombocytopenia, anaemia, febrile neutropenia, pancytopenia), gastrointestinal disorders (diarrhoea, vomiting, nausea, abdominal pain, constipation), general disorders and administration site conditions (fatigue, fever, chills), and investigation findings (haematology and serum chemistry). Cardiac disorders (tachycardia, palpitations, QTc prolongation) and gastrointestinal haemorrhage were not observed frequently, but are considered to be important potential risks.

### 1.1.5 Research hypothesis

The research hypothesis is that AZD1775 monotherapy will demonstrate anti-tumour activity in select tumour types as measured by ORR, DCR, DoR, and PFS, and will have an acceptable safety profile.

## 1.2 Rationale for conducting this study

The overall purpose for conducting this study is to find a safe and tolerable schedule and dose of single-agent AZD1775 for patients with advanced or metastatic tumours. A monotherapy regimen may improve the overall safety profile, optimize dosing, and thus maximize WEE1 inhibition and anti-tumour efficacy. The monotherapy experience to date has been limited to either single dosing before combination treatment, or the NCI experience using 225 mg PO BID for 5 doses over 2.5 days in a small cohort of patients with refractory tumours. The schedule chosen for this study extends the dosing of AZD1775 dosing to six doses over three days. By dosing at 175 mg BID, the total dose over the three days equates to the two and a half days schedule and is considered more practical.

This study will provide an opportunity to further explore the safety and efficacy of a monotherapy regimen in select tumour settings. Additionally, a more practical 3 day BID (weeks 1 and 2) schedule will be studied.

## 1.3 Benefit/risk and ethical assessment

### 1.3.1 Potential benefits

Investigations of AZD1775 when combined with chemotherapy have been tolerated and have shown efficacy (refer to AZD1775 IB). Overall risks and benefits support the administration of oral AZD1775 monotherapy to patients with ovarian cancer, SCLC and TNBC according to this clinical protocol.

Refer to the IB for AZD1775 for more information on the potential benefits.

### 1.3.2 Potential risks

Based on the safety data from the completed AZD1775 clinical studies and preliminary data from ongoing studies, adverse drug reactions to AZD1775 monotherapy include: anaemia, neutropenia, thrombocytopenia, QTc prolongation, and gastrointestinal events such as dyspepsia, diarrhoea, nausea and vomiting (with or without dehydration or serum electrolyte decreases), as well as decreased appetite.

Based on information emerging during the clinical development programme of AZD1775, potential risks with AZD1775 monotherapy include asthenia/fatigue, febrile neutropenia, gastrointestinal haemorrhage, lymphopenia/lymphocyte count decreased, leukopenia/WBC count decreased, myalgia, stomatitis, sepsis and transaminase elevation.

All patients will be closely monitored as described in the treatment schedule specific Study Plan and Assessments tables. Guidelines for managing adverse events including dose adjustments, treatment delays, AZD1775 holds, mandatory prophylactic antiemetic medications, and supportive care guidelines are provided.

The safety of patients will be assessed during Part A dose escalation of the study by the Safety Review Team (SRT) (see Section 10.7). In addition, emerging pharmacokinetic data for plasma exposure and safety will be evaluated to inform the dose escalation or dosing regimen decisions.

The investigation of AZD1775 in this patient population appears acceptable, based upon the safety profile and the lack of effective alternative treatments available to patients. Thus, the benefit/risk ratio for this Phase Ib study supports the administration of AZD1775 to patients with refractory solid tumours.

Refer to the IB for AZD1775 for more information on the potential benefits and assessment of potential and known risks.

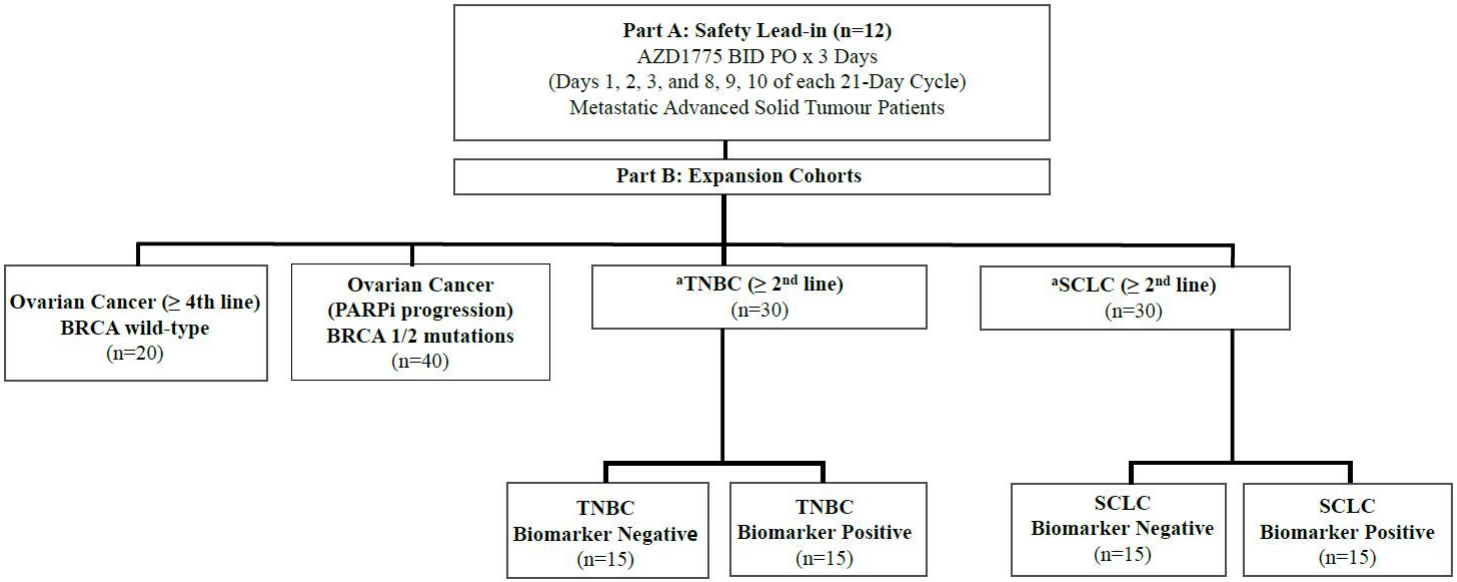
## 1.4 STUDY DESIGN

This open-label, multi-centre, Phase Ib study is designed to evaluate the safety, tolerability, pharmacokinetics, and anti-tumour activity of oral AZD1775 monotherapy. The study is divided into two parts: Part A safety lead-in cohort of patients with advanced solid tumours,

and Part B expansion cohorts in which patients will be organised based on tumour type and molecular profile to evaluate anti-tumour activity. Initially, a retrospective molecular analysis of tumour samples may be performed on approximately the first 15 patients under each tumour type. These patients will be allocated to the biomarker-negative or positive cohort retrospectively, once their genetic profile analysis result is available from the central lab. To ensure balance between the biomarker-positive and biomarker-negative cohorts, a switch to prospective molecular analysis at study entry will be required as patient enrolment advances after this point. A quality check of the submitted pathology material will be performed for both groups pre-treatment.

Treatment with AZD1775 monotherapy may continue until disease progression, unacceptable toxicity, or other discontinuation criteria has occurred as described in Section 3.9. Alternative dosing regimens and schedules may be studied depending on toxicities and emerging data.

**Figure 1 AZD1775 schema**




All tumour samples will be analysed for a range of cancer-related genes such that clinical response can be correlated to the gene aberrations.

- *BRCA* wild-type is defined as no evidence of deleterious or suspected deleterious mutation in *BRCA1* or *BRCA2* genes. *BRCA1* and/or *BRCA2* variants that are classified as "Variants of uncertain clinical significance" or "Variant of unknown significance (VUS)", as well as "Variant, favour polymorphism" or "benign polymorphism" are considered to be BRCA wild-type.
- Biomarker 'positive' TNBC and SCLC cohorts are defined as amplifications in *CCNE*, *MYC*, *MYCL1* or *MYCN*.
- Biomarker 'negative' TNBC and SCLC cohorts are defined as the absence of the qualifying amplifications as specified in Sections 3.3, 5.5.5 and 7.2.2.

[a] Potential to recruit and treat up to an additional 20 patients (total N = 50), to explore additional genetic profiles of interest or gain additional information on existing genetic profile, based on emerging signals.

# 2. STUDY OBJECTIVES

## 2.1 Primary objective

### Part A

| Primary Objective: | Outcome Measure: |
|---|---|
| To evaluate the safety and tolerability of AZD1775 monotherapy administered in 21-day cycles for patients with advanced solid tumours (BID PO x 3 days [weeks 1 and 2]). | Safety parameters: treatment-emergent adverse events (TEAEs) graded according to NCI CTCAE v4.03, laboratory parameters, physical examinations, vital signs, etc. The number and incidence of TEAEs and abnormal findings will be examined. |

### Part B

| Primary Objective: | Outcome Measure: |
|---|---|
| To evaluate the anti-tumor activity of AZD1775 monotherapy in previously treated patients with ovarian cancer, triple-negative breast cancer (TNBC) and small cell lung cancer (SCLC) | ORR, DCR, DoR, and PFS based on (RECIST) v1.1. |

## 2.2 Secondary objectives

### Part A

| Secondary Objective: | Outcome Measure: |
|---|---|
| To characterize the pharmacokinetic (PK) profile of AZD1775. | Plasma PK parameters of AZD1775 pre-dose and post-dose |
| To characterize the effect of AZD1775 on QTc. | QTc interval |
| To identify genetic alterations from archived or recent tumour tissue and correlated with clinical outcomes. | Measurement of the presence of genetic alterations in ovarian cancer, TNBC, and SCLC patients responding to AZD1775. |

### Part B

| Secondary Objective: | Outcome Measure: |
|---|---|
| To characterize the pharmacokinetic (PK) profile of AZD1775. | Plasma PK parameters of AZD1775 pre-dose and post-dose |

| | |
|---|---|
| To characterize the effect of AZD1775 on QTc. | QTc interval |
| To identify genetic alterations from archived or recent tumour tissue and correlated with clinical outcomes. | Measurement of the presence of genetic alterations in TNBC and SCLC patients responding to AZD1775. |
| To investigate the effect of AZD1775 treatment on previously observed changes of peripheral immunological biomarkers associated with an anti-tumour immune response. | Levels of immunologically relevant cytokines and chemokines involved in the Th1-driven immune responses. |

## 2.3 Exploratory objective

| **Exploratory Objective:** | **Outcome Measure:** |
|---|---|
| To assess genetic variations that may influence PK or response to AZD1775 (i.e., absorption, distribution, metabolism, excretion, safety and efficacy) and/or susceptibility to/development of cancers. | Correlation of polymorphisms with variation in Pharmacokinetics (PK), Pharmacodynamics (PD), safety or response observed in subjects treated with AZD1775. |

# 3. SUBJECT SELECTION, ENROLMENT, RANDOMISATION, DISCONTINUATION, AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

## 3.1 Inclusion criteria

Patients must meet the following criteria in order to be included in the study:

1. Has read and understands the informed consent form (ICF) and has given written IC prior to any study procedures.

2. Male or female patient ≥18 years of age.

3. Patient must have received previous chemotherapy for recurrent or metastatic disease. Patients may have received previous treatment with immunotherapy but this would not be considered an additional line of treatment as long as it was given without a cytotoxic agent.

4. Measurable disease is required for Part B expansion cohorts according to RECIST v1.1 criteria.

5. Radiation therapy must be completed at least 7 days prior to start of study treatment and patients must have recovered from any acute adverse effects prior to start of study treatment.

6. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score of 0-1.

7. Baseline (within 14 days of study drug administration) laboratory values as follows:

   - Absolute neutrophil count (ANC) ≥1500/μL
   - Haemoglobin (Hgb) ≥9 g/dL
   - Platelets ≥100,000/μL
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 x upper limit of normal (ULN) or ≤5 x ULN if known hepatic metastases.
   - Serum bilirubin within normal limits (WNL) or ≤1.5 x the ULN in patients with liver metastases; or total bilirubin ≤3.0 x ULN with direct bilirubin WNL in patients with well documented Gilbert's Syndrome.
   - Serum creatinine ≤1.5 x the ULN or a calculated creatinine clearance (CrCl) ≥45 mL/min measured by the Cockcroft-Gault method or 24-hour urine CrCl:

$$\text{Estimated CrCl (glomerular filtration rate [GFR])} = \frac{(140 - \text{age[years]}) \times (\text{weight [kg]}) \times F^{a}}{(72 \times \text{serum creatinine mg/dL})}$$

[a] where F = 0.85 for females and F = 1 for males

8. Female patients who are not of childbearing potential and fertile females of childbearing potential must agree to use adequate contraceptive measures (see Appendix F for definition) from 2 weeks prior to the study and until 1 month after study treatment discontinuation, who are not breastfeeding, and who have a negative serum or urine pregnancy test within 3 days prior to start of study treatment.

9. Male patients should be willing to abstain or use barrier contraception (i.e., condoms) for the duration of the study drug exposure and for 3 months after treatment discontinuation.

10. Predicted life expectancy ≥12 weeks.

11. Willingness and ability to comply with study and follow-up procedures.

**Inclusion criteria specific to Part A expansion cohort (closed to enrolment October 2015 and therefore not applicable):**

12. Must have a histologically or cytologically documented, locally advanced or metastatic solid tumour, excluding lymphoma, for which standard therapy does not exist or has proven ineffective or intolerable.

13. Has agreed to the collection of archival tumour tissue or recent tumour biopsy tissue, if taken for routine clinical purposes at baseline if archival tissue is not available, for molecular biomarker analyses.

**Inclusion criteria specific to Part B expansion cohort:**

14. For inclusion to Part B, the patient must fit into one of the following tumour specific cohorts:

- Ovarian cancer defined as a histologically confirmed diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal cancer refractory to standard therapies or for which no standard therapy exists.
    - Patients with confirmed BRCA wild-type from a prior test conducted by a clinical laboratory that has received international or country specific certification.
    - Patients who have already received 3 or more prior lines of therapy for advanced disease (recurrent or metastatic).
    - Patients with confirmed BRCA1 and/or BRCA2 mutation from a prior test conducted by a clinical laboratory that has received international or country specific certification, who have progressed while receiving and/or following treatment with a PARP-inhibitor for advanced disease (recurrent or metastatic).
- TNBC defined as histologically confirmed diagnosis of breast cancer that must be triple-negative, defined as minimal or no expression of oestrogen and progesterone receptors (<10% of cells positive by immunohistochemistry [IHC]), and minimal or no expression of HER2 (IHC staining of 0 or 1+ or FISH-).
    - Patients must have already received at least 1 chemotherapy-containing regimen for advanced disease (recurrent or metastatic).
- SCLC defined as a histologically confirmed diagnosis of SCLC
    - Patients must have received no more than 1 chemotherapy-containing regimen for advanced disease (recurrent or metastatic) and must relapse at least 90 days following that treatment.

15. Provision of an adequate tissue sample is mandatory for study eligibility. Tumour samples for biomarker identification will be sent for a pathology quality control (QC) check to ensure that the molecular analysis will be possible with the material provided. If the tumour tissue sample does not pass the pathology QC check, the investigative site will be informed and additional tissue will be requested (see Section 3.3).

## 3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

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

2. Participation in another clinical study with an investigational product during the last 21 days.

3. Any chemotherapy within 3 weeks of the first dose of AZD1775.

4. Use of anti-cancer treatment drug ≤21 days or 5 half-lives (whichever is shorter) prior to the first dose of AZD1775. For study drugs for which 5 half-lives is ≤21 days, a minimum of 10 days between termination of the study drug and administration of AZD1775 treatment is required.

5. Major surgical procedures ≤28 days of beginning study treatment, or minor surgical procedures ≤7 days. No waiting required following port-a-cath placement or central nervous access placement.

6. Grade >1 toxicity from prior therapy (except alopecia or anorexia).

7. No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal anti-cancer therapy, radiotherapy [except for palliative local radiotherapy]), biological therapy or other novel agent is to be permitted while the patient is receiving study medication. Patients on LHRH analogue treatment for more than 6 months are allowed entry into the study and may continue at the discretion of the Investigator.

8. Patient has an inability to swallow oral medications. Note: Patient may not have a percutaneous endoscopic gastrostomy (PEG) tube or be receiving total parenteral nutrition (TPN).

9. Known malignant central nervous system (CNS) disease other than neurologically stable, treated brain metastases – defined as metastasis having no evidence of progression or haemorrhage for at least 2 weeks after treatment . Must be off any systemic corticosteroids for the treatment of brain metastases at least 14 days prior to enrolment.

10. Patient has had prescription or non-prescription drugs or other products known to be sensitive CYP3A4 substrates or CYP3A4 substrates with a narrow therapeutic index, or to be moderate to strong inhibitors/inducers of CYP3A4 which cannot be discontinued two weeks prior to Day 1 of dosing and withheld throughout the study until 2 weeks after the last dose of study drug. The use of sensitive substrates of CYP3A4, such as atorvastatin, simvastatin and lovastatin is also prohibited in this study. Co-administration of aprepitant or fosaprepitant during this study is prohibited (see Section 7.8.3 and Appendix G).

11. Caution should be exercised when inhibitor or substrates of P-glycoprotein (P-gp), substrates of CYP1A2 with a narrow therapeutic range, sensitive substrates of CYP2C19 or CYP2C19 substrates with a narrow therapeutic range are administered with AZD1775.

- Transporter studies (in vitro) have shown that AZD1775 is an inhibitor of breast cancer resistance protein (BCRP). Please refer to Appendix G for use with BCRP substrates.
- Herbal preparation are not allowed throughout the study. These herbal medications include but are not limited to St. John's wort, kava, ephedra (mahung), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto and ginseng. Patients should stop using these herbal medications 7 days prior to the first dose of study treatment.

12. Any known hypersensitivity or contraindication to the components of the study drug AZD1775.

13. Any of the following cardiac diseases currently or within the last 6 months as defined by New York Heart Association (NYHA) ≥ Class 2 (see Appendix E)

- Unstable angina pectoris
- Congestive heart failure
- Acute myocardial infarction
- Conduction abnormality not controlled with pacemaker or medication
- Significant ventricular or supraventricular arrhythmias (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible).

14. Patients with mean resting corrected QT interval (specifically QTC calculated using the Fridericia formula [QTcF]) ≥450 msec for males and ≥470 msec for females from 3 electrocardiograms (ECGs) performed within 2-5 minutes apart at study entry or congenital long QT syndrome (see Section 5.2.4). In addition, Part A safety lead-in patients must have baseline triplicate ECGs and the Part B patients will have an ECG collected at baseline and triplicate ECGs if clinically indicated.

Triplicate ECGs will be obtained with PK collections as presented in the Study Plan tables.

15. Pregnant or lactating women.

16. Serious active infection at the time of enrolment, or another serious underlying medical condition that would impair the ability of the patient to receive study treatment.

17. Presence of other known active invasive cancers.

18. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.

19. Previous enrolment in the present study.

## 3.3 Subject enrolment

Investigator(s) should keep a record, the subject screening log, of subjects who entered pre-study screening.

The Principal Investigator (PI) at each site will:

Obtain a signed ICF from the potential patient before any study specific procedures are performed. Obtain study identifier according to the instructions provided in the Study Reference Manual.

For inclusion in i) the optional exploratory genetic research and ii) the optional tumour biopsy, patients must fulfil the following criteria:

- Provision of informed consent for genetic research
- Provision of informed consent for optional tumour biopsies

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study, or for any of the following:

- Previous allogenic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

If a patient declines to participate in the optional exploratory genetic research or the optional tumour biopsies, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study.

- Assign potential subject a unique enrolment number

- A sufficient quantity of archival or recent tumour tissue samples must be available to enrol into an expansion cohort (Part B). Molecular profile assessments may be performed on archived or fresh tumour tissue taken for routine clinical purposes if archived tissues are unavailable.

  All tumour samples will be analysed for a range of cancer-related genes such that clinical response can be correlated to the gene aberrations.

  *BRCA* wild-type is defined as no evidence of deleterious or suspected deleterious mutation in *BRCA1* or *BRCA2* genes. *BRCA1* and\or *BRCA2* variants that are classified as 'Variants of uncertain clinical significance' or 'Variant of unknown significance (VUS)' are eligible, as well as 'Variant, favour polymorphism' or 'benign polymorphism'.

  TNBC and SCLC biomarker 'positive' cohorts to be analysed include amplifications in *CCNE1, MYC*, *MYCL1* or *MYCN.*

  Biomarker 'positive' TNBC and SCLC cohorts are defined as amplifications in *CCNE1*, *MYC*, *MYCL1*, or *MYCN*. Biomarker 'negative' TNBC and SCLC cohorts are defined as the absence of the qualifying amplification (as specified in Sections 3.2, 5.4.3, and 7.2.2). .

  Patients may not have to wait for confirmation of the pathology QC check if molecular analysis results are already available to confirm the specific biomarker of interest (i.e., *BRCA1* or *BRCA2* genes in ovarian cancer, amplification of at least one of the following genes: *CCNE1*, *MYC*, *MYCL* or *MYCN* in TNBC or SCLC). The results must be from a certified laboratory and approved by the Sponsor or designee on a case-by-case basis. However, submission of archived or fresh tumour tissue to the Central Laboratory is required for analysis (see Laboratory Manual). Patients with previous genetic profile testing results from a Sponsor approved certified laboratory tumour samples are considered insufficient by the pathology QC check will be allowed to remain on-study.

Determine patient eligibility. See Sections 3.1 and 3.2

If a subject withdraws from participation in the study, then his/her enrolment code cannot be reused.

Human protection committee/Institutional Review Board (IRB) approval of this protocol and associated consent form(s) is required before any patient may be enrolled into the study.

## 3.4 Procedures for handling incorrectly enrolled patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, receive study medication. There can be no exceptions to this rule. Patients who are enrolled but

subsequently found not to meet all the eligibility criteria must not be initiated on treatment and must be withdrawn from the study.

When a patient does not meet all the eligibility criteria but is incorrectly started on treatment, the Investigator should inform the Medical Monitor immediately and a discussion should occur between the Medical Monitor and the Investigator regarding whether to continue or discontinue the patient from treatment. The Medical Monitor must ensure all decisions are appropriately documented.

## 3.5 Methods for assigning treatment groups

This is an open-label study and no randomisation details are required.

## 3.6 Methods for ensure blinding

This is open-label; therefore, unblinding procedures are not applicable.

## 3.7 Methods for unblinding

This is open-label; therefore, unblinding procedures are not applicable.

## 3.8 Restrictions

The following restrictions apply while the patient is receiving study medication and for the specific times before and after.

**Female Patients**

- Women of childbearing potential (WoCBP) may be included only if acceptable contraception is in place for 2 weeks before study entry, for the duration of the study and for 1 month after the last dose of AZD1775 (see Appendix F for definitions of non-childbearing potential and acceptable contraceptive methods).

- WoCBP is defined as: women between menarche and menopause who have not been permanently or surgically sterilized and are capable of procreation.

- All WoCBP must have a negative pregnancy test within 3 days prior to study entry and prior to starting each treatment cycle.

**Male Patients**

- Male patients who are involved in the study must agree to avoid procreative sex and unprotected sex (i.e. using acceptable forms of contraception as described in Appendix F) and must not donate sperm during the study and for 3 months after the last dose of AZD1775. When the female partner is pregnant or not using effective birth control, men should be advised to abstain while in the study and for 3 months after the last dose of AZD1775.

- Female partners, who are of child-bearing potential, of men participating in clinical studies of AZD1775 will also be required to use effective contraceptive measures (detailed in Appendix F) while their partner is on study drug and for 3 months thereafter.

- Male patients will be advised to arrange for freezing of sperm samples prior to the start of the study should they wish to father children while on AZD1775 or during the 3 months after stopping AZD1775.

## 3.9 Discontinuation of investigational product

Patients may be discontinued from AZD1775 in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment

- Adverse event

- Confirmed disease progression

- Pregnancy

- Severe non-compliance to study protocol

- Development of any study specific criteria for discontinuation

- Investigator decision

### 3.9.1 Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue the investigational product or withdraw from the study without prejudice to further treatment. A subject that decides to discontinue investigational will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an Investigator(s). Sites will also immediately inform AstraZeneca of the withdrawal. If possible, they will be seen and assessed by and Investigator(s). Adverse events will be followed up (See Section 6 ) and all unused study drug should be returned by the subject.

If a subject withdrawn from the study, see Section 3.10.2.

## 3.10 Criteria for withdrawal

Reasons for withdrawal from the study:

- Withdrawal of consent

- Incorrectly enrolled/treated patient

- AE
- Death
- Patient is lost to follow-up

If a patient wishes to withdraw his/her consent to both treatment and study assessments, they should be asked if they are willing to continue with survival follow-up (which can be conducted by telephone). If a patient wishes to withdraw his/her consent to further participation in the study entirely, including survival follow-up, this should be clearly documented in the patient medical record and in the clinical study database (eCRF).

The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of analysis should be obtained by the site personnel by checking the patient's medical record, hospital records, contacting the patient's general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can still be obtained by site personnel from publicly available resources, only where it is possible to do so under applicable local laws.

### 3.10.1 Screen failures

Screen failures are patients who have signed an ICF and do not fulfil the eligibility criteria for the study and therefore must not be treated with investigational product. These patients should have their reason for study withdrawal recorded as 'Incorrect Enrolment to Treatment' (i.e. patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not treated patients).

### 3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment.

A patient who withdraws his/her consent to continue participation in the study will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up AEs outside of the clinical study. If a subject withdraws from participation in the study, then his/her enrolment code cannot be reused. Withdrawn subjects will not be replaced.

## 3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug,
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

## 3.12 Lost to follow-up

Patients will be considered lost to follow-up only if no contact has been established in 2 or more follow-up attempts (24 weeks ±1 week) by the time the study is completed and there is insufficient information to determine the patient's status at that time.

**Note:** Patients who refuse to continue participation in the study, including phone contact, should be documented as 'withdrawal of consent' rather than 'lost to follow-up'. Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing person is re-established, the patient should not be considered lost to follow-up and any evaluations should resume according to the protocol.

# 4. STUDY PLAN AND TIMING OF PROCEDURES

The study plan and timing for procedures and assessments are described in Table 2.

**Table 1 Study Plan: Part A Safety Lead-In AZD1775 (21-day cycle) - closed to enrolment October 2015**

| | Screening[a] | AZD1775 (Cycle = 21-days) | | | | | | | | | Restage Every 6 weeks[k] (±7 days) | Off Treatment | | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | Cycle 2 | | Cycle 3 | Cycle 4 & Beyond | | EOT Visit[l] (±2 days) | 30-Day Safety F/U[m] | PFS F/U[n,z] |
| **Assessments** | **Baseline** | **D1** | **D3** | **D8** | **D10** | **D15** | **D1** (±3 days) | **D8** | **D1** (±3 days) | **D1** (±3 days) | | | | |
| Informed consent | X | | | | | | | | | | | | | |
| Archived/recent tumour sample | X[b] | | | | | | | | | | | | | |
| Prior genomic testing report(s) | X[w] | | | | | | | | | | | | | |
| Medical/surgical history | X | | | | | | | | | | | | | |
| Physical Examination | X | X | | | | | X | | X | X | | X | | |
| ECOG performance status | X | X | | | | | X | | X | X | | X | | |
| Vital signs[c] | X | X | | | | | X | | X | X | | X | | |
| Haematology | X | X | | X | | X | X | X | X | X | | X | | |
| Clinical Chemistry[d] | X | X | | | | | X | | X | X | | X | | |
| Coagulation (PT or INR with PTT)[e] | X | | | | | | | | | | | | | |
| Pregnancy test (urine or serum)[g] | X | X[g] | | | | | X[g] | | X[g] | X[g] | | X[g] | | |
| 12-Lead ECG | X[f] | X[f] | X[f] | | X[f] | | | | | | | | | |
| CT Scan/MRI of the Chest[i] | X | | | | | | | | | | X[h,j,k] | X | | X |
| CT Scan/MRI of the Abdomen and Pelvis[i] | X | | | | | | | | | | X[h,j,k] | X | | X |
| Tumour marker[w] | X | X[w] | | | | | X[w] | | X[w] | X[w] | | X[w] | | |

**Table 1 Study Plan: Part A Safety Lead-In AZD1775 (21-day cycle) - closed to enrolment October 2015**

| | Screening[a] | AZD1775 (Cycle = 21-days) | | | | | | | | | Restage Every 6 weeks[k] (±7 days) | Off Treatment | | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | Cycle 2 | | Cycle 3 | Cycle 4 & Beyond | | EOT Visit[l] (±2 days) | 30-Day Safety F/U[m] | PFS F/U[n,z] |
| **Assessments** | **Baseline** | **D1** | **D3** | **D8** | **D10** | **D15** | **D1** (±3 days) | **D8** | **D1** (±3 days) | **D1** (±3 days) | | | | |
| PK sample collection | | X[s] | X[s] | | X[s] | | | | | | | | | |
| ctDNA/cytokine[p] (Plasma sample) | | X[p] | | | | X[p] | X[p] | | | X[p] | X | X[(at PD)] | | X[(at PD only)] |
| Whole blood sample for flow cytometry | X[q] | X[q] | | | | X[q] | X[q] | | | X[q] | | | | |
| Optional Whole blood for PGx[r] | | X | | | | | | | | | | | | |
| Optional tumour biopsy[s] | X | | | | | | | | | | | X [(at PD)] | | X [(at PD only)] |
| Concomitant medication | X | X | | | | | X | | X | X | | X | X | X |
| Adverse events | | X | | X | | X | X | X | X | X | | X | X | |
| Dispense AZD1775[u,v,y] | | X | | X | | X | X | | X[t,v] | X[t,v] | | | | |
| Review/Collect Dosing Diary[v] | | | | X | X | X | X | | X | X | | X | | |

a The physical examination, medical history (capture previous treatment medications and response to each prior treatment regimen), concomitant medications recorded ≤14 days prior to trial entry, ECOG PS, haematology (complete blood count (CBC) with 5-part differential [neutrophils, lymphocytes, monocytes, basophils, and eosinophils] and platelets, clinical chemistry, and 12-lead ECG should be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 3 days prior to the initiation of treatment they do not have to be repeated on Cycle 1 Day 1. Scans to document evaluable disease (i.e., tumour measurement) should be performed ≤28 days prior to initiation of treatment and should be performed as close to the start of treatment as possible.

b An archival (or recent tissue preferred) tumour sample is required for this study at screening (see Section 5.4.3).

c Vital signs (resting heart rate, blood pressure, temperature and weight) at the Screening visit will include height. After Screening, height will not be measured. Vital signs and weight will be obtained prior to study drug administration according to institutional practice, at the end of treatment (EOT) visit, and PFS follow-up assessment.

d Clinical chemistry will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, total calcium, $CO_2$, alkaline phosphatase (ALP), AST, ALT, total bilirubin, total protein, and albumin.

e Coagulation performed at baseline only (PT or INR with PTT). Repeat at the beginning of every cycle if patient on Coumadin.

f An ECG will be collected at baseline to confirm eligibility (see Section 3.2). Cycle 1 Day 1 pre-dosing triplicate 12-lead ECGs will be collected within approximately 2-5 minutes intervals to determine the mean resting corrected QTc using the Fridericia formula (QTcF) <470 msec for females and <450 for males. Part A patients will also have 12-lead ECGs obtained after the patient has been resting semi-supine position for 10 minutes. For each time point three ECG recordings should be taken at approximately 2-5 minute intervals. ECGs will be obtained with PK collection as follows: Cycle 1 Day 1 and on Cycle 1 Day 3 or Day 10. ECG collected from time (h) post AZD1775 dose: pre-dose, 1h, 2, 4, 6, 8 and 12h post dose. Repeated ECGs should be performed on the same equipment if possible.

g Pregnancy tests will only be performed in women of childbearing potential 3 days prior to first dose of study treatment. This will be repeated at the beginning of each treatment cycle and at the EOT visit (see Section 5.2.6).

h Patients will be restaged after every 2 cycles (every 6 weeks [±7 days]). Patients with progressive disease or unacceptable toxicity should be discontinued from the study treatment; patients with SD or response to therapy will continue treatment.

i CT scans/MRIs of the chest and abdomen and pelvis are required at baseline, every 2 cycles (6 weeks), and EOT.

j The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during subsequent imaging procedures. Patients continuing study treatment for a minimum of 1 year may have the tumour imaging assessments expanded to every 4 cycles (12 weeks [±7 days]).

k Patients without evidence of undue toxicity may continue treatment with study drugs until disease progression occurs as long as they are achieving clinical benefit and desire to continue therapy.

l Patients discontinuing AZD1775 should be scheduled for an End of Study Treatment (EOT) Visit as soon as possible after their last dose. If treatment is discontinued during a study visit, the EOT visit does not need to be repeated. The reason for stopping treatment and date must be recorded in the electronic case report form (eCRF).

m After discontinuation from AZD1775, patients must be followed for AEs for 30 days, after their last dose or until new therapy. This can be done via telephone contact at the Investigator's discretion. All concomitant medications received 30 days after the last dose of study medication should be recorded in the medical record and eCRF. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the Investigator, these values are not likely to improve, because of the underlying disease. In this case, the Investigator must record his or her reasoning for this decision in the patients' medical records and as a comment in the eCRF. All patients who have Grade 3 or 4 laboratory abnormalities per NCI CTCAE v4.03 at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the Investigator, not likely that these values are to improve. In this case, the Investigator must record his or her reasoning for making this decision in the patients' medical records and as a comment on the eCRF.

n A patient discontinuing from AZD1775 in the absence of progressive disease (PD) should continue to have the PFS follow-up assessments until PD has been assessed by the Investigator or the patient begins a new course of cancer therapy or withdraws from the study. Post follow-up for patients without disease progression will be every 12 weeks (±1 week) from the last date study drug was administered (refer to Sections 4.3 and 4.3.2.1).

o intentionally blank

p ctDNA and cytokine plasma samples will be collected pre-dose Cycle 1 Day 1, Cycle 1 Day 15, pre-dose on Cycle 2 Day 1, Cycle 4 Day 1, Cycle 6 Day 1, thereafter Day 1 every 2 cycles (e.g. about 6 weeks) and at the time of disease progression (see Section 5.6.1). Patients continuing study treatment for a minimum of 1 year may have the ctDNA and cytokine collection expanded to every 4 cycles (12 weeks [±7 days]). Patients in PFS follow-up will have a sample collected at the time of PD. Details for processing, handling, and shipping are in the Laboratory Manual.

q A whole blood sample will be collected for immune profiling flow cytometry at baseline (within 2 weeks of initiation of dosing), pre-dose Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1 pre-dose, and Cycle 4 Day 1 pre-dose (see Section 5.6.2).

r Optional whole blood PGx samples (10 mL) will be taken pre-dose on Cycle 1 Day 1 (see Section 5.6.2). If for any reason the sample is not drawn at Cycle 1 Day 1, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study. This sample is **optional** and must be taken from patients who have provided informed consent for genetic sampling and analysis.

s Optional tumour biopsies (from the primary tumour or metastatic site) will be collected from consenting patients with easily accessible tumours (see Section 5.5.5). Tumour samples may be collected at screening or baseline before dosing and at the time of disease progression. This sample is **optional** and must be taken from patients who have provided informed consent for tumour biopsies. All tumour biopsies will be collected, stored and shipped as detailed in the Investigator Laboratory Manual.

t PK collections during safety lead-in patients Cycle 1 Day 1 and steady state collections on Cycle 1 Day 3 or Day 10 (see Section 5.3.1). Sample collected from time (h) ± 15 minutes post-AZD1775 dose: pre-dose, 1h, 2, 4, 6, 8 and 12h post dose. Details for processing, handling, and shipping are in the Laboratory Manual.

u AZD1775 (200 mg PO) BID Days 1-3 and 8-10 of each treatment cycle. AZD1775 should be taken with 8 ounces of water approximately 2 hours before or 2 hours after food. Note: the AZD1775 BID starting dose is reduced to 175 mg (Days 1-3, week 1 and week 2 of each 21-day cycle) because 200 mg BID was not well-tolerated.

v Dispense AZD1775 at the beginning of each new treatment cycle, and review and document AZD1775 dosing compliance with the patient at each visit.

w When applicable, tumour markers that are elevated and are used by the Investigator to monitor for tumour response will be collected at baseline, Day 1 of each cycle and at the end of treatment. The tumour marker analysis will be performed by a local laboratory.

x Previous individual patient genomic profile reports should be provided for this study at baseline or screening.

y All patients must receive a 5-HT3 antagonist, ondansetron (Zofran) 8 mg PO BID or granisetron (Kytril) 1 mg PO BID prior to each dose of AZD1775. Additional doses of 5-HT3 antagonist may be used if needed. In addition, dexamethasone 4 mg PO will be given with each AZD1775 dose as a minimum on the first day of dosing AZD1775 of every 3-5 days dosing period, unless contraindicated or not well-tolerated. Dexamethoasone may be continued on further days of dosing, potentially at a lower dose. Dexamethasone or the 5-HT3 antagonist may be given by IV. Promethazine (Phenergan), prochlorperazine (Compazine), and benzodiazepine may still be used as additional adjunctive treatments during AZD1775 therapy. Please note: aprepitant [Emend] and fosaprepitant are not permitted due to known drug-drug interactions. Patients should be strongly encouraged to maintain liberal oral fluid intake.

z Patients discontinuing from AZD1775 in the presence of PD will be followed every 3 months after the last dose of study drug for survival.

**Table 2 Study Plan: Part B Expansion Cohorts**

| | Pre-Screening[a] Day -42 to -1 | Screening[b] Day -28 to -1 | AZD1775 (Cycle = 21-days) | | | | | | | | | | Restage Every 6 wks[h,j,k] (±7d) | Off Treatment | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cycle 1 | | | | | Cycle 2 | | | Cycle 3 | Cycle 4 and Beyond | | EOT Visit[l] (±2d) | 30-Day Safety F/U[m] | PFS F/U[n, aa] | FPV [bb] |
| **Assessments** | | **Baseline** | **D1** | **D 2 - 4** | **D8** | **D 3 or 10** | **D 15** | **D1** (±3d) | **D8** | **D 3 or 10** | **D1** (±3d) | **D1** (±3d) | | | | | |
| Informed consent | X[a] | X | | | | | | | | | | | | | | | |
| Archived/Recent tumour sample | X | | | | | | | | | | | | | | | | |
| Prior genomic testing report(s) | X[w] | | | | | | | | | | | | | | | | |
| Medical/surgical history | | X | | | | | | | | | | | | | | | |
| Physical Examination | | X | X | | | | | X | | | X | X | | X | | | X |
| ECOG performance status | | X | X | | | | | X | | | X | X | | X | | | X |
| Vital signs[c] | | X | X | | | | | X | | | X | X | | X | | | X |
| Haematology[b] | | X | X | | X | | X | X | X | | X | X | | X | | | X |
| Clinical Chemistry[d] | | X | X | | | | | X | | | X | X | | X | | | X |
| Coagulation (PT or INR with PTT)[e] | | X | | | | | | | | | | | | | | | |
| Pregnancy test (urine or serum)[g] | | X | X[g] | | | | | X[g] | | | X[g] | X[g] | | X | | | X |
| 12-Lead ECG[f] | | X | X[f] | | | X | | | | X | | | | | | | X |
| ctDNA/cytokine[q] (Plasma sample) | | | X[q] | | | | X[q] | X[q] | X[q] | | | X[q] | X[q] | X (at PD | | X (at PD only) | X (at PD only) |
| Whole blood sample for flow cytometry (Ovarian cancer patients only) | | X[r] | X[r] | | | | X[r] | X[r] | X[r] | | | X[r] | | | | | |
| Optional Whole blood for PGx[s] | | | X | | | | | | | | | | | | | | |
| PBMC Ovarian cancer patients only | | | X[x] | | X[x] | | | | X[x] | | | X[x] | | | | | |

**Table 2 Study Plan: Part B Expansion Cohorts**

| | Pre-Screening[a] Day -42 to -1 | Screening[b] Day -28 to -1 | AZD1775 (Cycle = 21-days) | | | | | | | | | | Restage Every 6 wks[h,j,k] (±7d) | Off Treatment | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cycle 1 | | | | | Cycle 2 | | | Cycle 3 | Cycle 4 and Beyond | | EOT Visit[l] (±2d) | 30-Day Safety F/U[m] | PFS F/U[n, aa] | FPV[bb] |
| **Assessments** | | **Baseline** | **D1** | **D 2 - 4** | **D8** | **D 3 or 10** | **D 15** | **D1** (±3d) | **D8** | **D 3 or 10** | **D1** (±3d) | **D1** (±3d) | | | | | |
| PK sample collection | | | | | | X[o] | | | | X[o] | | D 3 or 10[o] | | | | | |
| Optional tumour biopsy[u] | | X | | | | | | | | | | | | X (at PD | | X (at PD) | X |
| On-treatment biopsy | | | | X[z] | | | | | | | | | | | | | |
| CT Scan/MRI of the Chest[i] | | X | | | | | | | | | | | X[h,j,k] | X | | X | |
| CT Scan/MRI of the Abdomen and Pelvis[i] | | X | | | | | | | | | | | X[h,j,k] | X | | X | |
| Tumour marker[v] | | X | X[v] | | | | | X[v] | | | X[v] | X[v] | | X | | | |
| Concomitant medication | | X | X | | | | | X | | | X | X | | X | X | X | X |
| Adverse events | | X | X | | X | | X | X | X | | X | X | | X | X | X | X |
| Dispense AZD1775[t,y] | | | X | | | | | X | | | X[t] | X | | | | | X |
| Review/Collect Dosing Diary[r] | | | X | | | | | X | | | X | X | | X | | | X |

a A pre-screening ICF must be collected to allow for the collection of tumour tissue samples and for pathology QC check. Tumour tissue samples will be QC'd to ensure the analysis will be possible with the material provided. If the tumour tissue sample is determined inadequate the site will be informed, and additional tumour tissue may be submitted if available (see Section 3.3). When the tumour tissue sample is deemed acceptable the patient may enter the screening period and a second ICF for the main treatment protocol will be required. Refer to the Laboratory Manual for instructions.

b The physical examination, medical history (capture previous treatment medications and response to each prior treatment regimen), concomitant medications recorded ≤14 days prior to trial entry, ECOG PS, haematology (complete blood count (CBC) with 5-part differential [neutrophils, lymphocytes, monocytes, basophils and eosinophils] and platelets), clinical chemistry, and 12-lead ECG should be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 3 days prior to the initiation of treatment they do not have to be repeated on Cycle 1 Day 1. Scans to document evaluable disease (i.e. tumour measurement) should be performed ≤28 days prior to initiation of treatment and should be performed as close to the start of treatment as possible.

c Vital signs (resting heart rate, blood pressure, temperature and weight) at the Screening visit will include height. After Screening, height will not be measured. Vital signs and weight will be obtained prior to study drug administration according to institutional practice, end of treatment (EOT) visit, PFS follow-up assessment, and the final protocol visit (FPV).

d Clinical chemistry will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, total calcium, $CO_2$, alkaline phosphatase (ALP), AST, ALT, total bilirubin, total protein, and albumin.

e Coagulation performed at baseline only (PT or INR with PTT). Repeat at the beginning of every cycle if patient on Coumadin.

f An ECG will be collected at baseline to confirm eligibility (see Section 3.2). Cycle 1 Day 1 pre-dosing triplicate 12-lead ECGs will be collected within approximately 2-5 minutes intervals to determine the mean resting corrected QTc using the Fridericia formula (QTcF) <470 msec for females and <450 for males if clinically indicated. Thereafter, patients will have an ECG only as clinically indicated. Repeated ECGs should be performed on the same equipment if possible.

g Pregnancy tests will only be performed in women of childbearing potential 3 days prior to first dose of study treatment. This will be repeated at the beginning of each treatment cycle. the EOT visit. and at the FPV (see Section 5.2.6).

h Patients will be restaged after every 2 cycles (every 6 weeks [±7 days]). Patients with progressive disease or unacceptable toxicity should be discontinued from the study treatment; patients with SD or response to therapy will continue treatment. Tumour status will be compared to baseline and confirmation of response will be evaluated by physical examination, anatomic imaging measurement, and performance status

i CT scans/MRIs of the chest and abdomen and pelvis are required at baseline and every 2 cycles (6 weeks).

j The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during subsequent imaging procedures. Patients continuing study treatment for a minimum of 1 year may have the tumour imaging assessments expanded to every 4 cycles (12 weeks [±7 days]).

k Patients without evidence of undue toxicity may continue treatment with study drugs until disease progression occurs as long as they are achieving clinical benefit and desire to continue therapy.

l Patients discontinuing AZD1775 should be scheduled for an EOT visit as soon as possible after their last dose. If treatment is discontinued during a study visit, the EOT visit does not need to be repeated. The reason for stopping treatment and date must be recorded in the electronic case report form (eCRF). The EOT visit is is **not** required for subjects continuing treatment after the FPV.

m After discontinuation from AZD1775, patients must be followed for AEs for 30 days, after their last dose or until new therapy. This can be done via telephone contact at the Investigator's discretion. All concomitant medications received 30 days after the last dose of study medication should be recorded in the medical record and eCRF. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the Investigator, these values are not likely to improve because of the underlying disease. In this case, the Investigator must record his or her reasoning for this decision in the patients' medical records and as a comment in the eCRF. All patients who have Grade 3 or 4 laboratory abnormalities per NCI CTCAE v4.03 at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the Investigator, not likely that these values are to improve. In this case, the Investigator must record his or her reasoning for making this decision in the patients' medical records and as a comment on the eCRF.

n A patient discontinuing from AZD1775 in the absence of progressive disease (PD) should continue to have the PFS follow-up assessments until PD has been assessed by the Investigator or the patient begins a new course of cancer therapy or withdraws from the study. Post follow-up for patients with disease progression will be every 12 weeks (±1 week) from the last date study drug was administered (refer to Sections 4.3 and 4.3.2.1).

o Blood PK samples will be collected from consenting patients pre-dose and 2-4 hours post dose on Cycle 1 Day 3 or Day 10, Cycle 2 Day 3 or Day 10 and Cycle 4 and beyond every 2 cycles Day 3 or Day 10. These samples may become optional once there are samples from 40-50 patients (at least 10 patients from each expansion cohort). Patients will also have 12-lead ECGs obtained after the patient has been resting semi-supine position for 10 minutes before the PK sample collection. For each time point three ECG recordings should be taken at approximately 2-5 minute intervals. Details for processing, handling, and shipping are in the Laboratory Manual.

p Intentionally Blank

q ctDNA and cytokine plasma samples will be collected pre-dose Cycle 1 Day 1, Cycle 1 Day 15, and pre-dose on Cycle 2 Day 1, Cycle 2 Day 8, 2-4 hours after dosing, pre-dose on Cycle 4 Day 1 and Cycle 6 Day 1, thereafter Day 1 every 2 cycles (about 6 weeks) and at the time of disease progression (see Section 5.6.1). Patients continuing study treatment for a minimum of 1 year may have the ctDNA and cytokine collection expanded to every 4 cycles (12 weeks [±7 days]). Patients continuing treatment after FPV will have a ctDNA sample collected at the time the time of progression. Details for processing, handling, and shipping are in the Laboratory Manual.

r A whole blood sample will be collected from ovarian patients only for immune profiling flow cytometry at baseline (within 2 weeks of initiation of dosing), pre-dose Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1 pre-dose, Cycle 2 Day 8, 2-4 hours after first dose of the day, and Cycle 4 Day 1 pre-dose (see Section 5.6.2). Details for processing, handling, and shipping are in the Laboratory Manual.

s Optional whole blood PGx samples (10 mL) will be taken pre-dose on Cycle 1 Day 1 (see Section 5.6.5). If for any reason the sample is not drawn at Cycle 1 Day 1, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study. This sample is **optional** and must be taken from patients who have provided informed consent for genetic sampling and analysis.

t Dispense AZD1775 at the beginning each new treatment cycle, and review and document AZD1775 dosing compliance with the patient at each visit. AZD1775 BID Days 1-3 and 8-10 of each treatment cycle. AZD1775 should be taken with 8 ounces of water approximately 2 hours before and again 2 hours after food. Note: the AZD1775 BID starting dose is reduced to 175 mg (Days 1-3, week 1 and week 2 of each 21-day cycle) because 200 mg BID was not well-tolerated.

u Optional tumour biopsies (from the primary tumour or metastatic site) will be collected from consenting patients including those that continue after FPV, with easily accessible tumours (see Section 5.5.5). Tumour samples may be collected pre-dose at screening or baseline and at the time of disease progression. This sample is **optional** and must be taken from patients who have provided informed consent for tumour biopsies. All tumour biopsies will be collected, stored, and shipped as detailed in the Investigator Laboratory Manual.

v When applicable, tumour markers that are elevated and are used by the Investigator to monitor for tumour response will be collected at baseline, Day 1 of each cycle and at the end of treatment. The tumour marker analysis will be performed by a local laboratory.

w Previous individual patient genomic profile reports should be provided for this study at enrolment.

x Whole blood samples for PBMC analysis (see Section 5.4.1) are to be collected from all ovarian cancer patients in Part B. Samples are to be collected on Cycle 1 Day 1 and Day 8 pre-dose, Cycle 2 Day 8, 2-4 hours after dosing, and Cycle 4 Day 1 pre-dose.

y All patients must receive a 5-HT3 antagonist, ondansetron (Zofran) 8 mg PO BID or granisetron (Kytril) 1 mg PO BID prior to each dose of AZD1775. In addition, dexamethasone 4 mg PO will be given with each AZD1775 dose as a minimum on the first day of dosing AZD1775 of every 3-5 days dosing period, unless contraindicated or not well-tolerated. Dexamethasone or the 5-HT3 antagonist may be given by IV. Promethazine (Phenergan), prochlorperazine (Compazine), and benzodiazepine may still be used as additional adjunctive treatments during AZD1775 therapy. Please note: aprepitant [Emend] and fosaprepitant are not permitted due to known drug-drug interactions. Patients should be strongly encouraged to maintain liberal oral fluid intake.

z An on-treatment tumour biopsy is required for all patients with surface-accessible lesions, at any time 12 hours after the third administered dose of AZD1775 on Day 2 or later on Day 3 or the first 12 hours on Day 4 during Cycle 1 of AZD1775 unless medically contraindicated in the opinion of the Investigator. Details for processing, handling, and shipping are in the Laboratory Manual.

aa Patients discontinuing from AZD1775 in the presence of PD will be followed every 3 months after the last dose of study drug for survival. Patients may be contacted during outpatient visits or by telephone (see Section 4.3.2.2).

bb The Final Protocol Visit (FPV) assessments are to only be performed on patients that continue AZD1775 after implementation of Revised Protocol Version 5 and should be aligned with the patient's next scheduled visit. After the FPV, patients will continue to receive AZD1775 until disease progression, or until they no longer derive clinical benefit, or until they fulfil any discontinuation criteria, in the opinion of the Investigator. Drug

accountability information must continue to be collected in patient source documents until the patient discontinues the treatment. After the FPV, only SAEs, pregnancy test results, and overdoses will be collected until 30 (±7) days following the patient's last dose of AZD1775. The EOT visit is not required for patients continuing treatment after the FPV.

## 4.1 Enrolment/screening period

### 4.1.1 Enrolment procedures

Enrolment procedures are described in Section 3.3. The screening period begins once the patient has signed the informed consent. Screening evaluations are described in Table 1 and Table 2.

## 4.2 Treatment period

AZD1775 will be administered orally as instructed by the Investigator or research staff. Patients will be eligible to continue to receive study treatment as long as they are continuing to show clinical benefit, as judged by the investigator, have no evidence of disease progression, and do not meet any criteria for discontinuation or withdrawal (see Section 3.9 and Section 3.9.1).

## 4.3 Follow-up period

Patients discontinuing AZD1775 should be scheduled for an End of Treatment (EOT) visit as soon as possible after their last dose. At that visit all assessments listed in the EOT visit column in Table 1 and Table 2 will be performed. If treatment is discontinued during a study visit, the EOT visit does not need to be repeated. The reason for stopping treatment and the date must be recorded in the electronic case report form (eCRF).

### 4.3.1 30-day safety evaluation

After discontinuation from AZD1775, patients must be followed for AEs for 30 days, after their last dose (see Section 6) or until new cancer therapy is started. This can be done via telephone contact at the Investigator's discretion. All concomitant medications received up to 30 days after the last dose of study medication should be recorded in the medical record and eCRF.

All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the Investigator, these values are not likely to improve because of the underlying disease. In this case, the investigator must record his or her reasoning for this decision in the patients' medical records and as a comment in the eCRF.

All patients who have Grade 3 or 4 laboratory abnormalities (per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.03 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE), at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the investigator, not likely that these values are to improve. In this case, the investigator must record his or her reasoning for making this decision in the patients' medical records and as a comment on the eCRF.

### 4.3.2 Follow-up period

#### 4.3.2.1 Follow-up for patients who discontinue treatment prior to disease progression

Patients discontinuing from AZD1775 in the absence of PD should continue to have the progression-free survival (PFS) assessments performed according to Table 1 or Table 2 until PD has been assessed by the Investigator or the patient begins a new course of cancer therapy or withdraws from the study. If PD has been assessed patients, will then be followed for survival.

#### 4.3.2.2 Survival follow-up

Patients with documented disease progression will be followed every 3 months for survival status (e.g., date and cause of death) for up to 2 years, death, or until time of final data collection for the progression-free survival analysis, whichever comes first. Patients may be contacted during outpatient visits or by telephone. Information pertaining to the type and dates of administered post-treatment therapy will be collected when available (see Table 2).

#### 4.3.2.3 Final Protocol Visit and Beyond

The Final Protocol Visit (FPV) requirement applies only to patients who continue AZD1775 after the implementation of the Revised Clinical Study Protocol (CSP) Version 5.

Beyond the FPV, patients may continue to receive AZD1775 if they are deriving clinical benefit, in the opinion of the Investigator, and not fulfilling any of the discontinuation criteria. Such patients are to be treated in accordance with local practice and as deemed appropriate by the Investigator to ensure continued safety monitoring of the patient while receiving the investigational product. It is recommended to continue observing ongoing patients at the frequency indicated within the study plan as described in Table 2. Restrictions regarding concomitant medications (refer to Section 7.8) will be followed while the patient is receiving AZD1775. A change in AZD1775 dose/schedule should only occur for safety reasons, based on the Investigator's judgement, and should generally follow the approach for dose reduction and discontinuation as described in this protocol. Combining AZD1775 with other systemic anti-cancer therapy is not allowed.

If a patient is no longer receiving benefit from AZD1775 beyond the FPV in the opinion of the treating physician, then the study drug should be stopped. The Investigator will inform AstraZeneca when a patient discontinues the study drug. Patients must return unused medication during routine clinic visits, and drug accountability information must continue to be collected in patient source documents until the patient discontinues treatment. In addition, provided that patient gives proper informed consent, a DNA blood sample for future biomedical research should be obtained at the time of AZD1775 discontinuation, if due to disease progression. Patients will continue to be monitored for all SAEs, pregnancies, and overdoses for 30 days after the last dose of the investigational product.

# 5. STUDY ASSESSMENTS

The Sarah Cannon Development Innovations, LLC (Innovations) Trial Master electronic data capture (EDC) system will be used for data collection and query handling. The investigator will ensure that data are promptly and accurately recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

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 (CSA). The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

## 5.1 Efficacy assessments

### 5.1.1 Tumour assessments

RECIST v1.1 criteria will be used to assess patient response to treatment by ORR and DCR. The RECIST v1.1 guidelines for measurable, non-measurable, target and non-target lesions (NTL) and the objective tumour response criteria (CR, PR, SD or progression of disease) are presented in Appendix D.

The same method of assessment of tumour burden used at baseline (computed tomography [CT] scans or magnetic resonance imaging [MRI] of the chest and abdomen/pelvis) must be used at each subsequent follow-up assessment (see Table 1 or Table 2). CT scan or MRI of chest and abdomen/pelvis are mandatory and must be repeated every 2-4 cycles.

Following the baseline assessment, efficacy for all patients will be assessed by objective tumour assessments every 6 weeks ±1 week after start of treatment until objective disease progression as defined by RECIST v1.1 or withdrawal from study.

Categorisation of objective tumour response assessment will be based on the RECIST v1.1 criteria of response: CR (complete response), PR (partial response), SD (stable disease) and PD (progression of disease). Target lesion progression will be calculated in comparison to when the tumour burden was at a minimum (i.e. smallest sum of longest diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, or SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

If the Investigator is in doubt as to whether progression has occurred, particularly with regard to NTLs or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated, and reassess the patient's status. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.

To achieve 'unequivocal progression' on the basis of 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 one or more (NTL) is usually not sufficient to quality for unequivocal progression status.

It is important to follow the assessment schedule as closely as possible. Please refer to the study plan in Table 1 or Table 2. Patients will be assessed by standard criteria. For the purposes of this study, patients should be evaluated for radiographic tumour response every six weeks (±1 week [cycle length dependent]). The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and throughout the study. Overall tumour response and progression will be calculated according to RECIST 1.1 (see Appendix D) at the designated time points.

Tumour status will be compared to baseline and confirmation of response will be evaluated by physical examination, anatomic imaging measurement, and performance status.

## 5.2 Safety assessments

### 5.2.1 Laboratory safety assessment

Blood samples for determination of clinical chemistry, haematology, coagulation, and PK will be taken at the times indicated in the Study Plan (see Table 1 or Table 2).

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

The clinical chemistry and haematology will be performed at a local laboratory. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the study centre.

The following laboratory variables will be measured as a minimum (some of these variables may be measured at baseline only):

**Table 3 Safety Laboratory Variables**

| Haematology (2.7 mL whole blood sample) | Clinical chemistry (2.7 mL serum or plasma sample) |
|---|---|
| B-Haemoglobin | S/P-Albumin |
| B-Leukocyte | S/P-Alanine transaminase (ALT) |
| B-Haematocrit | S/P-Aspartate transaminase (AST) |
| B-Red blood cell count | S/P-Alkaline phosphatise (ALP) |
| B-Absolute leukocyte differential count | S/P-Bilirubin, total |
| Neutrophils | S/P-Calcium, total |

| | |
|---|---|
| Lymphocytes | S/P-Creatinine |
| Monocytes | S/P-Chloride |
| Basophils | S/P-Potassium |
| Eosinophils | S/P-Sodium |
| B-Platelet count | S/P-Urea nitrogen or blood urea nitrogen |
| **Coagulation (1.8 mL sample)** | |
| B-PT or INR with PTT | |
| **Pregnancy test** (Blood or urine) | |

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. 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 6.4 and Section 6.5.

NB. In case a patient shows an AST or ALT ≥3xULN and total bilirubin ≥ 2x ULN, please refer to Appendix C 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law' for further instructions.

### 5.2.2 Physical examination

A complete physical examination will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems at the times indicated in the Study Plan (refer to Table 1 and Table 2).

If new or aggravated physical findings imply deterioration compared with baseline, the finding should be reported as an AE (Section 6.4.6). Performance status will be assessed using the ECOG performance status criteria (see Study Plan [Table 1 and Table 2].

### 5.2.3 Tumour assessments

Baseline tumour imaging studies (e.g., CT scans or MRI of the chest and abdomen/pelvis) will be performed within 28 days prior to the first dose of study drug and will be repeated at the completion of Cycle 2. The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during subsequent imaging procedures. Tumour imaging studies will be repeated every 6 weeks to assess response. Patients continuing study treatment for a minimum of 1 year may have the tumour imaging assessments expanded to every 4 cycles (12 weeks [±7 days]).

### 5.2.4 Electrocardiograms

All patients must have a screening 12- lead safety electrocardiogram (ECG) (paper ECG printout of 10 seconds for Investigator review) in order to meet eligibility criteria (see Section 3.2).

The patients in the Part A Safety Lead-in will have triplicate ECGs collected at each PK collection time point (see Table 1). Triplicate ECGs will be collected in Part B patients at baseline if clinically indicated (see Table 2).

Triplicate ECG recordings should be taken within an approximate 5-minute period. Additional ECGs may be taken at any other time the Investigator deems necessary for safety during the administration period. Twelve-lead ECGs will be obtained after the patient has been resting semi-supine for at least 10 minutes before the start of each recording and they must be in the same supine body position (maximum 30 degrees flexion in the hip and feet not in contact with the footboard) at the recording time point; except for the baseline ECG following the administration of AZD1775. For each time point during the PK collections for Part A, 3 ECG recordings should be taken at approximately 2-5 minutes interval. The mean QTcF interval for all 3 ECGs must be ≤450 msec for male patients and ≤470 msec for female patients prior to the initiation of treatment. A standardised ECG machine should be used and the patient should be examined using the same machine throughout the study if possible.

Part A - ECGs will be obtained before the PK blood collection as follows: Screening, Cycle 1 Day 1 and on Cycle 1 Day 3 or Day 10. ECG collected from time (h) post AZD1775 dose: pre-dose, 1h, 2, 4, 6, 8 and 12h post dose. Repeated ECGs should be performed on the same equipment if possible.

Part B - Patients will have ECGs performed at screening and baseline as indicated in the Study Plan detailed in Table 2. Patients consenting to the PK blood collections will have ECGs performed before the PK collection pre-dose and at 2-4 hours post dose as outlined in Table 2 and repeated only if clinically indicated.

After paper ECGs have been recorded, the Investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided as to whether or not the abnormality is clinically significant or not clinically significant. A paper copy of each ECG recording should be filed in the patient's medical records. Only overall evaluation (normal/abnormal) will be recorded in the eCRF. If there is a clinically significant abnormal unscheduled ECG finding during the treatment period, this should be recorded on the AE eCRF, according to standard AE collection and reporting processes (see Section 6). If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the Investigator, it should be reported as a concurrent condition. For all ECGs details of rhythm, PR, R-R, QRS and QTc intervals and an overall evaluation will be recorded.

### 5.2.5 Vital signs

Vital signs to be assessed include: resting heart rate, blood pressure, temperature and weight at the screening visit and at times shown in the study plan. Height will be measured at the screening visit only. Vital signs and weight will be obtained prior to study drug administration according to institutional practice (see Table 1 and Table 2).

### 5.2.6 Pregnancy test

Pre-menopausal women of childbearing potential must have a negative urine or serum pregnancy test within 3 days prior to starting study treatment. A confirmatory test will be performed before treatment at the start of each cycle, the EOT visit, and the FPV. In the event of suspected pregnancy during the study, the test should be repeated and, if positive, the patient discontinued from study treatment immediately.

### 5.2.7 Tumour markers

An elevated tumour marker (e.g. CA-125, CEA, PSA) that is used by the investigator to monitor for tumour response will be collected at baseline, Day 1 of each cycle, and at the end of treatment. The results will be recorded in the eCRF. The tumour marker analysis will be performed by a local laboratory.

## 5.3 Pharmacokinetics

### 5.3.1 Collection of blood pharmacokinetic samples during safety lead-in (Part A only – closed to enrolment October 2015)

Pharmacokinetic (PK) samples will be collected during the safety lead-in portion of the study during Cycle 1 Day 1 and Cycle 1 Day 3 or Day 10. Steady state PK collections may occur on Day 3 or Day 10 of Cycle 1. The Investigator may select the PK collection day that fits best for the clinic and the patient for the second set of PKs. The date and actual time of the PK sample will be recorded.

**Table 4 Cycle 1 Day 1 and Cycle 1 Day 3 or Day 10 safety lead-in PK collections**

| Time (h) post first AZD1775 dose | 0 | 1 | 2 | 4 | 6 | 8 | 12 |
|---|---|---|---|---|---|---|---|
| **Swallow AZD1775** | X | | | | | | |
| **PK Sample** | X[a] | X[b] | X[c] | X[c] | X[c] | X[c] | X[c] |

[a] PK sample may be collected the day before dosing.
[b] ±5 minutes.
[c] ±15 minutes

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.

If a patient misses any doses of AZD1775 a day prior to PK sampling, the Medical Monitor should be contacted regarding the changes required for 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.

Details on sample processing, handling, and shipment are provided in the Laboratory Manual.

### 5.3.2 Collection of blood pharmacokinetic samples during Part B expansion

PK blood samples will be required from all patients enrolled at approximately 3-5 investigational sites to ensure we have evaluable data from at least 50 patients. These required samples may become optional once there are samples from at least 50 patients. PK blood sampling is highly recommended for all patients at the remaining sites. PK blood sample collections will be taken from consenting patients pre-dose and 2-4 hours post-dose on Day 3 or Day 10 of Cycle 1, Cycle 2, and Cycle 4, and beyond Cycle 4 every 2 cycles. The date and actual time of all PK samples must be recorded.

**Table 5 Part B PK collections**

| **Cycle 1, 2, and 4 (and beyond cycle 4 every 2 cycles) Day 3 or Day 10** | | |
|---|---|---|
| **Time (h) post first AZD1775 dose** | **0** | **2-4 hours** |
| **Swallow AZD1775** | X | |
| **PK Sample**[a] | X | X |

[a] ±15 minutes

Details on sample processing, handling, and shipment are provided in the Laboratory Manual.

### 5.3.3 Determination of drug concentration in pharmacokinetic samples

Samples for determination of AZD1775 concentrations in plasma will be analysed by Covance on behalf of Clinical Bioanalysis Alliance, AstraZeneca R&D, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

### 5.3.4 Storage, re-use and destruction of pharmacokinetic samples

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

Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic 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 Clinical Study Report but separately in a Bioanalytical Report.

Any residual back-up PK samples will be kept in at Covance and will be disposed of after the CSR is finalized.

## 5.4 Pharmacodynamics

### 5.4.1 Peripheral blood mononuclear cell (PBMC) samples for pharmacodynamics studies

Peripheral blood mononuclear cell (PBMC) blood samples will be collected in Part B only. A whole blood (8 ml) sample will be drawn for pharmacodynamic analysis at Cycle 1 Day 1 pre-dose, Cycle 1 Day 8 pre-dose, Cycle 2 Day 8 2-4 hours after dosing, and Cycle 4 Day 1 pre-dose.

Details on sample processing, handling, and shipment are provided in the Laboratory Manual.

The results of this PBMC research will be reported separately and will not form part of the CSR.

### 5.4.2 Repeat biopsies

Part B of the study is designed in part to provide evidence of proof of mechanism (POM). For the Wee1 inhibitor AZD1775, this means to demonstrate that following treatment of patients there is a measurable decrease from baseline in readouts of activity of the Wee1 kinase.

The baseline Wee1 pharmacodynamic (PD) marker pCDK1 (pCDC2) will be retrospectively assessed from the baseline biopsy. A post-treatment biopsy will then be taken after first dose on day 2 or day 3 of the first cycle of treatment.

These paired biopsies will be considered evaluable for POM if assessable by Immunohistochemistry (IHC) for the biomarker above and if the concurrent pharmacokinetic (PK) blood sample is consistent with the patient having had adequate pharmacological exposure to AZD1775.

We estimate that we would need at least 7 patients with evaluable paired biopsies in order to have confidence in an assessment of POM (see statistical calculations below).

A patient showing the target decrease of 50% or more (evaluated as number of cells showing positive staining in post vs pre dose) in pCDK1 will be considered a pharmacodynamic responder. This value is based on preclinical data correlating with anti-tumour efficacy, using the same assay to be used on clinical samples. We have set a POM target value of 50% of

patients having a pharmacodynamic response in their tumour biopsy. With n=7 biopsies, we would accept having established POM if 4 out the 7 biopsies show the desired biomarker change.

### 5.4.3 Storage re-use, and destruction of pharmacodynamic samples

The primary pharmacodynamic (PD) samples will be kept in the AZ Biobank for 15 years for future needs.

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

## 5.5 Biomarker analysis

The patient's consent to the use of donated biological samples is mandatory.

Biological samples (e.g., archived tumour samples) will be collected and may be analysed for exploratory biomarkers to assess correlations with disease activity, effects of study drug, clinical outcomes and toxicity.

Details on sample processing, handling, and shipment are provided in the Laboratory Manual.

The results of exploratory biomarker research will be reported separately and will not form part of the CSR.

### 5.5.1 Exploratory biomarker research – Part A and Part B

Blood samples for plasma ctDNA and cytokine collections will be taken at the times presented in Table 1 and Table 2. Specifically at the following times:

- Before the first dose of AZD1775
- Cycle 1 Day 15
- Cycle 2 Day 1 pre-dose
- Cycle 2 Day 8, 2-4 hours post first dose of day
- Cycle 4 Day 1 pre-dose
- Cycle 6 Day 1 pre-dose
- Day 1 every 2 cycles after completing Cycle 6. Patients continuing study treatment for a minimum of 1 year may have the ctDNA and cytokine collection expanded to every 4 cycles (12 weeks [±7 days]).

– At disease progression (AZD1775 discontinuation)

For patients continuing on AZD1775 after the implementation of the Revised Clinical Study Protocol Version 5, DNA blood samples (2 x 10 mL) for future biomedical research should be obtained at the time of AZD1775 discontinuation if due to disease progression (unless informed otherwise by AstraZeneca). The samples will be processed on site, as per the laboratory manual, to yield plasma for analysis of oncology biomarkers which may correlate with drug response or resistance, including analysis of circulating tumour DNA.

Details on sample processing, handling, and shipment are provided in the Laboratory Manual.

The results of exploratory biomarker research will be reported separately and will not form part of the CSR.

### 5.5.2 Whole blood collections for immune profiling flow cytometry

Whole blood samples will be collected from for immune profiling flow cytometry in all Part A patients and Part B ovarian cancer patients as follows:

– Baseline (within 2 weeks of initiation of dosing)

– Cycle 1 Day 1 pre-dose

– Cycle 1 Day 15

– Cycle 2 Day 1 pre-dose

– Cycle 2 Day 8, 2-4 hours post first dose of the day (Part B patients only)

– Cycle 4 Day 1 pre-dose

The flow cytometry sample assessment may include but is not limited to activated and memory T cells, proliferating T cells, surface Treg, TBNK and MDSCs. These sample collections have unique shipping requirements which are detailed in the Laboratory Manual along with the sample processing and handling requirements.

The results of this research will be reported separately and will not form part of the CSR.

### 5.5.3 Storage, re-use and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the Clinical Study Report 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 drug to generate hypotheses to be tested in future research.

### 5.5.4 Tumour-derived and plasma circulating tumour DNA samples

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

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood or other appropriate sample type. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the subject enrolment and the DNA number will be maintained and stored in a secure environment, with restricted access within the Laboratory Information Management System (LIMS) at AstraZeneca. 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 to trace samples for destruction in the case of withdrawal of consent when the subject has requested disposal/destruction of collected samples not yet analysed.

### 5.5.5 Archived or recent tumour tissue

A sufficient quantity of archival or fresh tumour tissue must be available to enrol a patient to Part B to identify molecular biomarkers of interest. Molecular biomarker assessments will be performed centrally from archival tumour tissue or from fresh tumour tissue if the latter is being taken for routine clinical purposes and archival tumour tissue is unavailable.

After signing a 'pre-screening' ICF, tumour samples will be submitted for a pathology QC check to ensure that the molecular analysis will be possible with the material provided. If the tumour tissue sample does not pass the QC check, the investigative site will be informed and additional tissue will be requested.

The patients' molecular profiles will be established using a Sponsor-approved method and clinical laboratory (see Laboratory Manual).

All tumour samples will be analysed for a range of cancer-related genes such that clinical response can be correlated to the gene aberrations. TNBC and SCLC biomarker 'positive' cohorts to be analysed include amplifications in CCNE1, MYC, MYCN, or MYCL1.

Biomarker 'negative' is defined as the absence of the qualifying amplification for TNBC or SCLC as specified above. Investigation of biomarker 'negative' results based on emerging signals may be explored through additional expansion cohort(s).

Patients may not have to wait for confirmation of the pathology QC check if genetic profile results are available to confirm the specific biomarker of interest (i.e., *BRCA1* or *BRCA2* genes in ovarian cancer, amplification *CCNE1*, *MYC*, *MYCN*, or *MYCL1* in TNBC or SCLC). The results must be from a certified laboratory and approved by the Sponsor or designee on a case-by-case basis. Submission of archived or fresh tumour tissue to the Central Laboratory will be required. If the tumour sample is considered insufficient by the pathology QC check at the time of analysis the patient will remain on-study.

The preferred tumour tissue samples are block(s) rather than slides, with minimum tumour attributes of $\geq$10mm$^2$ surface area; $\geq$30% tumour cell content, if biopsy, ideally a block contains multiple cores. If a block is unavailable, unstained 5µm sections should be provided as follows:

- Large resection >10 slides
- Small biopsy (core needle, bronchial, FNA, effusions) >15-20 slides

Please refer to the Laboratory Manual for additional guidance.

Gene expression profiling (GEP) technology, next generation sequencing (NGS) and immunohistochemical (IHC) analysis will be used to identify the mutations of interest.

A full report of the molecular biomarker panel will subsequently be made available to investigators upon request. Refer to the Investigator Laboratory Manual for instructions.

Details of sample collection, processing, storage, and shipment are provided in the Laboratory Manual.

### 5.5.6 On-treatment tumour biopsy (surface-accessible lesion)

An on-treatment tumour biopsy is required for all patients with surface-accessible lesions, at any time, 12 hours after the third administered dose of AZD1775 on Day 2, or later on Day 3, or during the first 12 hours on Day 4 of Cycle 1 unless medically contraindicated in the opinion of the Investigator.

This biopsy is needed to demonstrate that there is a measurable decrease from baseline in readouts of activity of the Wee1 kinase via analysis of the levels of phosphorylated CDC2 (pCDC2) in tumour samples, following treatment with AZD1775. The collection of baseline and on-treatment biopsies is essential to guarantee the comparison of pCDC2 levels before and during treatment and to provide evidence that patients receive a biologically active dose.

A 'surface accessible lesion' is a lesion that does not require the patient to undergo general anaesthesia for the biopsy procedure, does not require CT-guided interventional radiology involvement and could, for example, be a clearly palpable tumour-involved node or similar.

### 5.5.7 Optional biopsies

Optional during this study and will be requested from consenting patients with easily accessible tumours:

- At baseline/screening before dosing
- At the time of disease progression including from consenting patients that continue treatment after the FPV.

Patients will sign a separate informed consent for the tumour tissue biopsies. The tumour biopsy procedure will be performed by core needle, under radiological guidance, or surgically if the site of disease is superficial and palpable or visible. It is mandated that the core biopsy be removed directly from the tumour *in situ* and not cored from a surgically removed tumour. This is to ensure the best possible quality of the biopsy, as the blood/nutrient supply to the tumour is not disrupted prior to biopsy collection.

All tumour biopsies will be collected, stored, and shipped as detailed in the Laboratory Manual.

Any residual samples remaining after analysis will be retained for any potential subsequent retrospective analysis of other response related and/or cancer related biomarkers. It is not intended that data derived from residual sample analysis will be reported in the CSR.

Informed consent must be obtained from any patient who agrees to provide tissue for tumour tissue sample testing.

### 5.5.8 Labelling and shipment of biological samples

The PI ensures that samples are labelled and shipped in accordance with the Laboratory Manual, and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix B 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

### 5.5.9 Chain of custody of biological samples

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

The PI at each centre retains full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate).

The sample receiver keeps full traceability of the samples while 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.

### 5.5.10 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of optional donated biological samples, then the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca or its representatives are not obliged to destroy the results of this research.

As collection of these biological samples is a voluntary part of the study then the patient may continue in the study.

The PI:

- Ensures AstraZeneca or its representatives are notified immediately of the patient's withdrawal of informed consent to the use of donated biological samples
- Ensures that biological samples from that patients, if stored at the study site, are immediately identified, disposed/destroyed/repatriated, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed/repatriated and the action documented and returned to the study site
- Ensures that the patients and AstraZeneca or its representatives are informed about the sample disposal

AstraZeneca or its representatives ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed and the action documented returned to the study site.

In the event that analysis/research has already been performed, AstraZeneca or its representatives will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

AstraZeneca or its representatives ensures that biological samples are returned to the source at the end of a specified period as described in the informed consent.

## 5.6 Pharmacogenetics

### 5.6.1 Background and rationale

AstraZeneca intends to perform genetic research in the AZD1775 clinical development programme to explore how genetic variations may affect the clinical parameters associated with AZD1775. Collection of deoxyribonucleic acid (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. Future research may suggest other genes or gene categories as candidates for influencing not only response to AZD1775, but also to ovarian cancer, TNBC or SCLC for which AZD1775 may be evaluated. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to disease or disease evolution and drug action.

### 5.6.2 Pharmacogenetics research objectives

The objective of this research is to collect and store DNA for future exploratory research into genes/genetic variations that may influence response (i.e., distribution, safety, tolerability and efficacy) to AZD1775, as well as susceptibility to or evolution of ovarian cancer, TNBC or SCLC.

The benefits of being able to explore associations between genes and clinical outcomes within the AZD1775 programme are potentially many and include:

- Analysis of genes that may affect efficacy, safety, and tolerability (for example, but not limited to, drug metabolising enzymes and drug transporters).

- Genetic research into genes that may contribute to the development of, or susceptibility to ovarian cancer, TNBC and SCLC.

### 5.6.3 Genetic research plan and procedures

**Selection of genetic research population**

Subjects will be asked to participate in this genetic research. Participation is voluntary and if a subject declines to participate there will be no penalty or loss of benefit. The subject will not be excluded from any aspect of the main study.

### 5.6.4 Discontinuation of subjects from this genetic research

Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment.

### 5.6.5 Collection of pharmacogenetics samples

The subject's consent to participate in the pharmacogenetics research components of the study is optional.

The blood sample (10 mL) for genetic research will be obtained from the subjects at Cycle 1 Day 1. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an adverse event (AE), such subjects would be important to include in any genetic analysis. If for any reason the sample is not drawn prior to the first dose of AZD1775, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study.

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

### 5.6.6 Storage, re-use and destruction of pharmacogenetics samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years from the date of the Last Subject'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 Clinical Study Report itself or as an addendum, or separately in a scientific report or publication.

For all samples the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA).

The samples and data for genetic analysis in this study will be single coded. The link between the subject enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access within the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. 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 to trace samples for destruction in the case of withdrawal of consent when the subject has requested disposal/destruction of collected samples not yet analysed.

### 5.6.7 Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 10.

### 5.6.8 Informed consent

The genetic component of this study is optional and the subject 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 subject 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 subject and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely discontinue from the genetic aspect of the study at any time.

### 5.6.9 Subject data protection

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, 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 subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

### 5.6.10 Data management

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse the samples.

The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate.

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.

### 5.6.11 Statistical methods and determination of sample size

The number of subjects 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 will be prepared when appropriate.

# 6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

## 6.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram [ECG]). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including lead-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

## 6.2 Definitions of serious adverse event

A SAE is an AE occurring during any study phase (i.e. lead-in, treatment, 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/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect in the offspring of the treated patient
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix A to the Clinical Study Protocol (CSP).

## 6.3 Data collection of safety-related study variables

### 6.3.1 Specification on AE data collection principles to ensure consistent approach throughout the project

The Clinical Study Protocols (CSPs) used in AZD1775 clinical studies will contain standard text relating to Patient Safety including definitions of adverse events and serious adverse events (SAEs). These standard texts should generally not be omitted or amended.

#### 6.3.1.1 Adverse events of special interest related to AZD1775

There are no AESI for AZD1775 which require additional data collection.

## 6.4 Recording of adverse events

### 6.4.1 Time period for collection of adverse events

Adverse events will be collected from time of signature of informed consent throughout the treatment period and including the follow-up period. SAEs occurring in the follow-up period should be collected for 30 days after the last dose of study drug, regardless of the investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the investigator feels the events were related to either study drug, drug delivery system, or a protocol procedure.

Following discontinuation of study treatment, SAEs considered related to study procedures should continue to be collected while subjects are followed-up for disease progression.

For each patient who discontinues study treatment for a reason other than disease progression:

- Follow-up information on all ongoing AEs should continue to be collected until the survival follow-up.

- SAEs considered related to study procedures must continue to be collected and reported using standard SAE timelines and process until the end of progression follow-up (i.e., disease progression).

- All deaths must continue to be collected after progression and during the survival follow-up.

### 6.4.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment or other assessment/visit as appropriate in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca or their representatives 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.

If an Investigator learns of any SAEs, including death, at any time after a patient has completed the study and he/she considers there is a reasonable possibility that the event is related to AZD1775, the Investigator should notify Innovations.

### 6.4.3 Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- CTCAE grade/maximum CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the investigational product (IP) (yes or no)
- Action taken with regard to IP
- AE 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 serious AE
- Date Investigator became aware of SAE
- Reason AE is serious
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication(s)

- Causality assessment in relation to module-specific combination treatments
- Description of SAE

The grading scales found in the revised NCI CTCAE v4.03 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria should be utilized that converts mild, moderate and severe events. A copy of the current CTCAE version can be downloaded from the Cancer Therapy Evaluation Program website http://ctep.cancer.gov.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.1. 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. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE in Section 6.2.

### 6.4.4 Causality collection

The Investigator will assess causal relationship between IP 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 investigational product?'*

For SAEs, causal relationship will also be assessed for other medication 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 A to the CSP.

### 6.4.5 Adverse Events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel '*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 eCRF. When collecting AEs, the recording of a diagnosis is preferred (when possible) to the recording of 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.

### 6.4.6 Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of the study treatment unless clearly due to the progression of disease under study (see Section 6.4.8).

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 (e.g. 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.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

Cases where a patient shows elevation in liver biochemistry may require further evaluation and occurrences of AST **or** ALT ≥3x ULN together with total bilirubin ≥ 2xULN may need to be reported as SAEs. Please refer to Appendix C 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law' for further instructions on cases of increases in liver biochemistry and evaluation of potential Hy's Law cases.

### 6.4.7 Hy's Law

Cases in which a patient shows an AST or ALT ≥ 3xULN and total bilirubin ≥ 2xULN may need to be reported as SAEs. Prompt reporting of cases meeting Hy's law criteria (via SAE expedited reporting system) is required for compliance with regulatory guidelines. The investigator is responsible for, without delay, determining whether a patient meets potential Hy's law (PHL) criteria.

Please refer to Appendix C for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

### 6.4.8 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP 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 of 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 AEs during the study.

Events including diagnosis or signs and symptoms or the abnormal results of an investigation including those leading to hospitalization, which constitute or result from:

a) 'unequivocal progression' (i.e., representative of overall disease status change, not a single lesion increase) of non-measurable/non-target disease, or

b) progression of malignancy under study (target disease), as determined per RECIST 1.1 criteria, should not be reported as AEs or SAEs.

### 6.4.9 New cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New 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.

### 6.4.10 Handling of deaths

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

- Death, which is unequivocally due to disease progression, should be communicated to the study monitor at the next monitoring visit and should be documented in the eCRF module, but should not be reported as a SAE during the study.

- Where death is not clearly due to disease progression of the disease under study the AE causing the death should be reported by entering into the WBDC system as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes.

- Death with an unknown cause should always be reported as a SAE but every effort should be made to establish a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results (with translation of important parts into English) should be reported in an expedited fashion to an AstraZeneca representative within the usual timeframes.

## 6.5 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to AZD1775, or to a study procedure(s). All SAEs will be recorded in the eCRF/CRF.

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

The designated Innovations representative works with the Investigator to ensure that all the necessary information is provided 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 adverse events 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 one calendar day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

SAE information will be sent via secure e-mail connection or via fax. The Innovations Safety Department standard paper SAE Report with supporting relevant source documents (e.g. history and physical [H&P], hospital discharge summary, autopsy report when available, results of relevant diagnostic tests completed to evaluate the event) will be attached and sent via:

- Secure email (Innovations SAE mailbox: CANN.SAE@SCRI-Innovations.com) or by
- Fax (Innovations safety fax number): + 1-866-807-4325

Transmission of the SAE report Form should be confirmed by the site personnel submitting the report.

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

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

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

Investigators or other site personnel send relevant CRF modules by fax to the designated AstraZeneca representative

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to Innovations Safety Department as soon as it is available; these reports should be submitted using the Innovations SAE Report Form. The detailed SAE reporting process will be provided to the sites in the SAE reporting guidelines contained in the trial reference manual.

The appointed study Medical Monitor works with the Investigator to ensure that all the necessary information is provided to the Innovations Safety Department **within 1 calendar day** of initial receipt of the information for fatal and life threatening events and **within 5 calendar days** of initial receipt of the information for all other SAEs.

For fatal or life-threatening adverse events 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 one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Investigators must report SAEs and follow-up information to their responsible Institutional Review Board (IRB) according to the policies of the responsible IRB. For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately.

AstraZeneca or their representative will provide Regulatory Authorities, Ethics Committees (EC) and PIs with clinical safety updates/reports according to local requirements.

## 6.6 Overdose

A dose of AZD1775 in excess of that specified according to the protocol will constitute an overdose. There is currently no known antidote to AZD1775, and the treatment of overdose should be supportive for the underlying symptoms. Such overdoses should be recorded as follows:

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

If an overdose of AZD1775 occurs in the course of the study, then the Investigators or other site personnel will inform the Innovations Safety Department immediately or **no later than 24 hours** of when he or she becomes aware of it.

The Innovations Safety Department representative works with the Investigator to ensure that all relevant information is provided.

For overdoses associated with SAE, standard reporting timelines apply (see Section 6.5). For other overdoses, reporting should be done within24 hours.

## 6.7 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the Innovations Safety Department during the course of the study and within 1 month of the last dose of study treatment.

### 6.7.1 Maternal exposure

If a patient becomes pregnant during the course of the study, AZD1775 should be discontinued immediately and the patient should be removed from the study. Pregnancies

must be avoided in females of child-bearing potential during treatment with AZD1775, and up to a period of ONE (1) menstrual cycle after stopping treatment with AZD1775.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/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 abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then Investigator or other site personnel informs the Innovations Safety Department 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 within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

### 6.7.2 Paternal exposure

Men must avoid fathering a child, unprotected sex, and must not donate sperm during treatment with AZD1775 and 3 months following the last dose.

Pregnancy of a patient's partner is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

To capture information about a pregnancy from the partner of a male patient, the male patient's partner consent must be obtained to collect information related to the pregnancy and outcome; the male patient should not be asked to provide this information. The outcome of any conception occurring should be followed up and documented.

## 6.8 Dose modifications

Toxicity will be assessed utilizing the NCI CTCAE v4.03 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE), unless otherwise specified.

The DLT criteria in Section 7.2.1 will be used to assess the safety lead-in cohort during Part A Cycle 1. Toxicity occurring in patients beyond Cycle 1 of the Part A safety lead-in will be graded and the appropriate dose modification or supportive care will be administered to decrease the signs and symptoms thereof according to this section.

The DLT criteria evaluations do not apply to Part B. Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity. Dose reductions or holds and initiation of supportive care are allowed as clinically indicated by the treating physician. A maximum of 2 dose reductions for the AZD1775 will be allowed. Patients requiring >2 dose reductions will be discontinued from the study drug. Dose reductions are presented for AZD1775.

**Table 6 AZD1775 Dose Level Reductions for Toxicity**

| Dose Level | AZD1775[a] | Schedule 21-day cycle |
|---|---|---|
| Starting Dose[b] | 175 mg PO BID | Days 1-3 and 8-10 |
| Dose Level -1 | 150 mg PO BID | Days 1-3 and 8-10 |
| Dose Level -2 | 125 mg PO BID | Days 1-3 and 8-10 |

[a] AZD1775 taken in 12 hour intervals
[b] **Note:** the AZD1775 starting dose is reduced to 175 mg BID because 200 mg BID was not well-tolerated.

Any patient requiring a toxicity-related dose delay of more than 21 days from the intended day of the next scheduled dose must be discontinued from the study unless there is approval from the Medical Monitor for the patient to continue.

### 6.8.1 Dose modifications due to hematologic toxicity

Complete blood counts (CBC) will be obtained for all patients at the beginning of each treatment cycle (Day 1). If hematologic toxicity occurs, treatment should be held and ANC and platelets should be monitored weekly (or more often as clinically indicated) until recovery.

**Table 7 Day 1 Haematologic Dose Modifications and Management**

| Treatment Day Blood Counts and Toxicity | | | |
|---|---|---|---|
| **ANC** | | **Platelets** | **Action** |
| ≥1000/μL | And | ≥75,000/μL | No dose modification or interruption |
| <1000/μL | Or | <75,000/μL | Delay by 1 week intervals until recovery |

If haematologic parameters do not recover within 21 days, the patient should be removed from the study treatment.

**Table 8 Neutropenia, Infection, Febrile Neutropenia Dose Modifications and Management**

| **Any Day** | |
|---|---|
| **Grade 3 neutropenic fever** (ANC <1000/μL + Temperature ≥101°F [38.5°C]) or neutropenic infection<br>**Documented infection with Grade 3 neutropenia** (ANC <1000/μL)<br>**Grade 4 neutropenia**<br>(ANC <500/μL >7 days<br>**Grade 4 thrombocytopenia** (platelet count <25,000/μL >7 days) | **Hold dose until recovery.**<br>**Then, upon resuming dosing, reduce AZD1775 to the next lower dose level[a].** |
| **Grade 4 febrile neutropenia or Grade 4 infection with neutropenia** (both defined as septic shock)<br>**Thrombocytopenic haemorrhage** (gross occult bleeding) associated with a platelet count <50,000/μL | **Discontinue treatment and follow for disease progression.** |

a No more than two dose reductions will be allowed for any patient. Patients requiring additional dose modifications due to toxicity will discontinue study treatment.

### 6.8.2 Non-haematologic toxicity dose modifications

Substantial acute toxicities should be managed as medically indicated and with temporary suspension of investigational product, as appropriate. Dose reductions or holds and initiation of supportive care are allowed as clinically indicated by the treating physician.

Dose reductions of AZD1775 should be considered if the toxicity is considered to be related to AZD1775 (i.e., in monotherapy studies or in combination studies) if the relationship cannot be wholly attributed to the combination agent (each combination agent should be considered on an individual basis). Dose re-escalation is not permitted.

In general, if a patient experiences a Grade 1/Grade 2 non-haematological toxicity, no dose modification is required (except QTc prolongation; see table below). If a patient experiences a Grade 3 or Grade 4 toxicity which is not attributable to the disease or disease-related processes under investigation, dosing will be interrupted and/or the dose reduced, and supportive therapy administered as required. Any patient who develops a Grade 3 or 4 non-haematologic toxicity that does not resolve to ≤ Grade 1 within 21 days should be removed from the study treatment unless approved by the Medical Monitor.

**Table 9 AZD1775 dose modifications for QTc interval prolongation**

| **Electrocardiogram QT corrected interval prolonged** | |
|---|---|
| **QTc Value** | AZD1775 |
| QTc 450-480 ms (males) or 470-480 (females) | Hold. Once QTc interval has returned to pretreatment status and correction of possible electrolyte imbalance has been made, resume at next lower dose level. |
| QTc 481-500 ms | Hold. Seek cardiologist advice. |
| QTc ≥501 ms | Discontinue treatment |
| Shift from baseline of ≥60ms | Discontinue treatment |

### 6.8.3 Non-haematologic toxicity management guidelines

#### 6.8.3.1 Diarrhoea

Due to frequent reports of diarrhoea with AZD1775 administration, vigorous anti-diarrhoeal treatment loperamide (Imodium) is required at the **first** onset of diarrhoea according to American Society of Clinical Oncology (ASCO) guidelines. Oral loperamide (Imodium) 4 mg should be administered at the first onset of diarrhea and then 2 mg every 2 hours until diarrhoea-free for at least 12 hours. The first dose of loperamide could be lowered to 2 mg if the diarrhoea is recurrent and if, in the opinion of the treating physician, the diarrhoea is not severe.

Patients should be instructed to notify the Investigator or research staff of the occurrence of bloody or black stools, symptoms of dehydration, fever, inability to take liquids by mouth, and inability to control diarrhoea within 24 hours of using loperamide or other prescribed anti-diarrhoeal medications.

If diarrhoea is severe (i.e., requiring intravenous [IV] rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhoea or any diarrhoea associated with severe nausea or vomiting should be hospitalised for IV hydration and correction of electrolyte imbalances.

#### 6.8.3.2 Nausea and vomiting (mandatory anti-emetic prophylaxis)

All patients must receive a 5-HT3 antagonist, ondansetron (Zofran) 8 mg BID PO or granisetron (Kytril) 1 mg BID PO prior to each dose of AZD1775. Additional doses of 5-HT3 antagonist may be used if needed. In addition, dexamethasone 4 mg PO will be given with each AZD1775 dose as a minimum on the first day of dosing AZD1775 of every 3-5 days dosing period, unless contraindicated or not well-tolerated. Dexamethasone may be continued on further days of dosing, potentially at a lower dose. Dexamethasone or the 5-HT3 antagonist may be given by IV.

Promethazine (Phenergan), prochlorperazine (Compazine), and benzodiazepine may still be used as additional adjunctive treatments during AZD1775 therapy.

**Please note:** aprepitant [Emend] and fosaprepitant are not permitted due to known DDIs.

Patients should be strongly encouraged to maintain liberal oral fluid intake.

Suitable alternative medications may be used, with adequate justification, in those studies where the use of any of the above medications might interfere with other study procedures or deemed insufficient.

#### 6.8.3.3 Febrile neutropenia

Patients experiencing febrile neutropenia with significant symptoms should be managed in a hospital setting according to standard procedures, with the urgent initiation of IV antibiotic therapy. Patients with febrile neutropenia without symptoms should be managed according to standard guidelines.

# 7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

## 7.1 Identity of investigational product(s)

AZD1775 is available as dry-filled capsules containing 25 or 100 mg of drug substance. Additional information about the investigational product (IP) may be found in the IB.

All study drugs must be kept in a secure place under appropriate storage conditions. The IP label on the bottle and the IB specifies the appropriate storage.

| Investigational product | Dosage form and strength | Manufacturer |
|---|---|---|
| AZD1775 | 25 or 100 mg capsules | AstraZeneca |

## 7.2 Dose and treatment regimens

AZD1775 will be taken by mouth in approximate 12 hour intervals over 3 days at the start of week 1 and 2 of each 21-day cycle (Days 1-3 and 8-10), for a total of 12 doses with each cycle (see Figure 2). Mandatory prophylactic anti-emetic therapy will be administered as described in Section 6.8.3.2.

AZD1775 should be taken with 8 ounces of water approximately 2 hours before and again 2 hours after food. If BID dosing and a patient misses one of the two daily doses according to schedule, the dose should be taken as soon as possible, but not more than 6 hours after the missed dose was scheduled. If greater than 6 hours, the missed dose should be skipped and the patient should take the next dose when scheduled.

If vomiting occurs after a patient takes the AZD1775 dose, the patient should be instructed not to retake the dose, but to wait until the next scheduled dose of AZD1775. If no dose is scheduled for the following day, the dose will not be 'made up'. If vomiting persists, the patient should contact the Investigator.

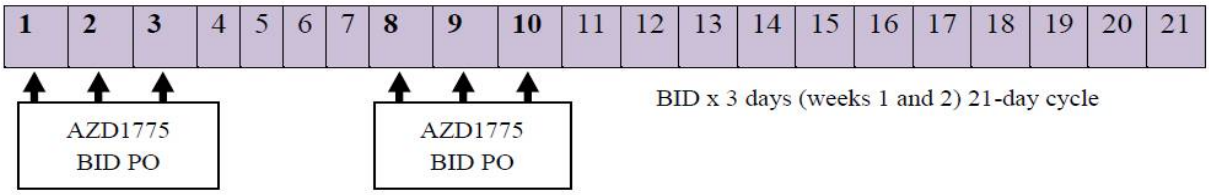
AZD1775 dosing compliance should be reviewed with the patient at the beginning of each new treatment cycle when study drug is dispensed. All patients will be required to complete a dosing diary, which must be returned to the clinic for review at each visit. The patient should be instructed to record each date and time the dose(s) were taken on the dosing diary. If a dose is missed, the reason must be noted in the diary. A copy of the dosing diary is provided in the study reference materials.

Patients should be advised to return any unused AZD1775 in the original bottles, in addition to returning any empty bottles.

**Figure 2 21-day cycle**

**AZD1775 dosing schedule, 21-day cycle**

**Day of Cycle**



### 7.2.1 Part A: Safety lead-in cohort (closed to enrolment – October 2015)

The safety and tolerability of AZD1775 monotherapy in patients with advanced solid tumours will be assessed in a safety lead-in cohort. Patients in the safety lead-in will receive the planned dose and schedule for the study, 200 mg PO BID for 3 days at the start of weeks 1 and 2 of each 21-day cycle. Pharmacokinetic and pharmacodynamics samples will be collected from all Part A patients (see Section 5.3.1). During the safety lead-in, the AZD1775 starting dose was reduced to 175 mg BID because 200 mg BID was not well-tolerated. Adverse events (AEs) associated with AZD1775, and DLTs observed during the safety lead-in included diarrhoea, vomiting and anaemia. In addition to reducing the starting dose of AZD1775, mandatory anti-emetic prophylaxis has been instituted (see Section 6.8.3.2). The Part A safety lead-in patient enrolment has been completed.

After approximately 12 evaluable patients have completed Cycle 1, a Safety Review Team (SRT [see Section 10.7]) will review the accumulated safety and tolerability data of the AZD1775 monotherapy dose and schedule. Patients must complete Cycle 1 safety evaluations which will conclude on Cycle 2 Day 1, and must receive at least 75% of the planned Cycle 1 dose to be considered evaluable. Patients receiving less than 75% of Cycle 1 dose will be replaced unless they experienced a confirmed DLT by the SRT.

At the end of Part A, if no safety signals are reported and the PK profile appears acceptable, the Part B tumour specific expansion cohorts will begin enrolment.

Dose-limiting toxicities thought to be related to the study drug during the safety lead-in phase will be defined as any of the following toxicities not attributable to the disease or disease-related processes under investigation, that occur from the first dose of study treatment up to the last day of Cycle 1 (first 21 days) and that meets at least 1of the haematological or non-haematological criteria below:

1. Haematological toxicity ≥ Grade 4 present for more than 7 days including:
   - Infection with febrile neutropenia
2. Grade 3 thrombocytopenia associated with Grade ≥2 bleeding
3. Non-haematological toxicity ≥ Grade 3
4. Grade ≥3 total bilirubin, hepatic transaminase (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) or alkaline phosphatase (ALP) lasting >48 hours.
5. Changes in liver function tests (LFTs) consistent with the definition of Hy's Law (see Appendix C).
6. Any other toxicity that is clinically significant and/or unacceptable that does not respond to supportive care, results in a disruption of dosing schedule of more than

7 days, or is judged to be a DLT by the Investigator in collaboration with the Medical Monitor.

A DLT excludes:

- Alopecia of any grade
- Isolated laboratory changes of any grade without clinical sequelae or clinical significance

If appropriate the DLT observation period can be expanded by up to 2 weeks in case of treatment delay due to study drug-related adverse events. Treatment will be considered non-tolerated if 2 or more of the first 6 evaluable patients experience a DLT in the safety lead-in cohort. If the initial dose or schedule of the treatment is not tolerated, patient enrolment to the treatment will be stopped and either the schedule will be taken no further or the dose level or schedule of AZD1775 may be adjusted to evaluate safety in a second 6 patient cohort at the next lower dose level or revised schedule. The DLT criteria apply only to the safety lead-in patients during Cycle 1. Safety lead-in patients continuing treatment beyond Cycle 1 will have dose modifications applied according to Section 6.8.

If fewer than 2 out of the first 6 evaluable patients experience a DLT, enrolment will continue to approximately 12 evaluable patients to further evaluate safety. If 4 or more of 12 evaluable patients experience a DLT then the treatment will be considered not tolerated.

Investigators will be notified in a timely manner of any safety outcomes so that they may notify their Institutional Review Boards (IRBs).

#### 7.2.1.1 Reporting a DLT

Any DLT occurring in a patient in the safety lead-in cohort during Cycle 1 must be reported to the Medical Monitor by the Investigator or designee within 24 hours of first knowledge, and to the Innovations Safety Department as an SAE when appropriate (see Section 6.5).

### 7.2.2 Part B: Expansion cohort

The AZD1775 dose (175 mg BID PO) and schedule (Days 1-3, Weeks 1 and 2, Q 21-days) for the Part B expansion is the dosing schedule that was defined in the Part A safety lead-in.

Part B expansion cohorts will investigate AZD1775 monotherapy in patients with advanced tumour types with molecular biomarkers of interest. The tumour types to be evaluated are:

- **Ovarian cancer** defined as a histologically confirmed diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal cancer refractory to standard therapies or for which no standard therapy exists.
    - Patients with confirmed BRCA wild-type from a prior test conducted by a clinical laboratory that has received international or country specific

certification, who have already received 3 or more prior lines of therapy for advanced disease (recurrent or metastatic).

- Patients with confirmed *BRCA1* and/or *BRCA2* mutation from a prior test conducted by a clinical laboratory that has received international or country specific certification, who have progressed while receiving and/or following treatment with a PARP-inhibitor for advanced disease (recurrent or metastatic).

- **TNBC** defined as histologically confirmed diagnosis of breast cancer that must be triple-negative, defined as minimal or no expression of oestrogen and progesterone receptors (<10% of cells positive by immunohistochemistry [IHC]), and minimal or no expression of HER2 (IHC staining of 0 or 1+ or FISH-).

    - Patients must have already received at least 1 chemotherapy-containing regimen for advanced disease (recurrent or metastatic).

- **SCLC** defined as a histologically confirmed diagnosis of SCLC

    - Patients must have received no more than 1 chemotherapy-containing regimen for advanced disease (recurrent or metastatic) and must have relapsed at least 90 days following that treatment.

All tumour samples will be analysed for a range of cancer-related genes such that clinical response can be correlated to the gene aberrations.

BRCA wild-type is defined as having no evidence of deleterious or suspected deleterious mutation in *BRCA1* or *BRCA2* genes. *BRCA1* and/or *BRCA2* variants that are classified as 'variants of uncertain clinical significance' or 'variants of unknown significance (VUS)', as well as 'variants, favour polymorphism' or 'benign polymorphism', are considered to be BRCA wild-type.

Biomarker 'positive' cohorts to be analysed include:

- Amplification of at least one of the following genes: CCNE1, MYC, MYCL, or MYCN in TNBC or SCLC

TNBC and SCLC biomarker 'positive' cohorts to be analysed include amplifications of *CCNE1*, *MYC*, *MYCN* or *MYCL1*.

Biomarker 'negative' is defined as the absence of the qualifying amplification for TNBC or SCLC as specified above. There is the potential to recruit and treat up to an additional 20 patients (total N = 50) in the TNBC and SCLC cohorts, to explore additional genetic profiles of interest or gain additional information on the existing genetic profile, based on emerging signals.

Identification of biomarkers of interest based on emerging science is anticipated as the study proceeds. Initially, a retrospective molecular analysis of tumour samples may be performed on approximately the first 15 patients under each tumour type. These patients will be allocated to the biomarker 'negative' or 'positive' cohort retrospectively, once their genetic profile analysis result is available from the central lab. To ensure balance between the biomarker-positive and biomarker-negative cohorts, a switch to prospective molecular analysis at study entry will be required after this point. A QC check of the submitted pathology material will be performed for both groups pre-treatment.

## 7.3 Restaging during treatment

Tumour assessments will be performed on all patients at Screening (within 28 days of first dose) as outlined in the Study Plan Table 1 and Table 2 until objective disease progression as defined by RECIST v1.1 or other withdrawal criteria is met (see Sections 5.1.1 and 3.10). Tumour assessments and restaging will be performed every 6 weeks. Patients continuing study treatment for a minimum of 1 year may have the tumour imaging assessments expanded to every 4 cycles (12 weeks [±7 days]).

## 7.4 Labelling

Details are specified in the document explaining the reconstitution procedures and other handling procedures for the investigational product.

## 7.5 Storage

AZD1775 should be kept in a secure place under appropriate storage conditions. A description of the appropriate storage conditions is specified in the document explaining the reconstitution procedures and other handling procedures for the investigational products.

## 7.6 Compliance

The administration of all study drugs (including investigation products) should be recorded in the appropriate sections of the eCRF.

## 7.7 Accountability

Study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The Investigational Product Storage Manager is responsible for managing the study drug from receipt by the study site until the return of all unused study drug to AstraZeneca. AstraZeneca will provide the study documents 'Procedures for drug accountability' and 'Procedures for drug storage' which describes the specific requirements. The Investigator(s) is responsible for ensuring that the subject has returned all unused study drug.

## 7.8 Concomitant and other treatment(s)

All concomitant medications received within 14 days before the first dose of study medication and 30 days after the last dose of study medication should be recorded. Concomitant medications must be recorded in the appropriate sections of the eCRF.

### 7.8.1 Permitted concomitant medications

| Supportive Medication/Class of drug: | Usage: |
|---|---|
| Anti-emetics (excluding aprepitant [Emend] and fosaprepitant) | Premedication with anti-emetics is mandatory (excluding aprepitant [Emend] and fosaprepitant) as presented in Section 6.8.3.2. |
| Loperamide (Imodium) | Loperamide (Imodium) is required for the first onset of diarrhoea according to ASCO guidelines (see Section 6.8.3.1). |
| Medications including but not limited to the following:<br>• Bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors (e.g. denosumab).<br>• Patients requiring therapeutic warfarin or Coumadin-derivative anticoagulants will be monitored with INR and Prothrombin Time (PT) as clinically indicated.<br>• Low molecular weight heparin, rivaroxaban, or equivalent anticoagulant therapy is permitted where clinically indicated. | Medications may be administered for maintenance of existing conditions prior to study enrolment or for a new condition that develops while on study. |

### 7.8.2 Restricted concomitant medications

The following treatments and the medications listed in Appendix G should be used with caution while in this study. Any further questions regarding concomitant treatments should be referred to the Medical Monitor.

| Restricted Medication/Class of drug: | Usage: |
|---|---|
| *In vitro* data suggests that AZD1775 may also be a weak reversible inhibitor of CYP2C19. | Caution should be exercised with concomitant administration of AZD1775 and agents that are sensitive substrates of CYP2C19, or substrates of this enzyme with narrow therapeutic range. Refer to Appendix G for a list of sensitive substrates of CYP2C19, or substrates of this enzyme with narrow therapeutic range. |

| | |
|---|---|
| AZD1775 has been shown to be a weak inducer of CYP1A2 *in vitro* with a maximum measured response between donors of 39.9% to 93.1% (at 10 µM) and 18.6% to 32.5% (at 5 µM) of the positive control omeprazole (50 µM), respectively. Given the nature of the AZD1775 dosing schedule, however, the risk of induction in the clinic is considered low. | Be initially vigilant when using substrates of CYP1A2 with a narrow therapeutic range. |
| Inhibitors or substrates of P-gp. *In vitro* studies have shown that AZD1775 may be a substrate and inhibitor for human P-glycoprotein (P-gp). | Caution should be exercised when agents that are inhibitors or substrates of P-gp are administered concomitantly with AZD1775 (see Appendix G). |
| Metformin | Metformin should be used with caution. AZD1775 has been shown to be an inhibitor of MATE1 and MATE2K transporters. A drug interaction with substrates of either transporter cannot be ruled out, the most important substrate known to date being metformin. |
| BCRP substrates with narrow therapeutic index | Recent *in vitro* transporter studies have shown AZD1775 to be an inhibitor of BCRP (IC50 5.1 µM). This finding is particularly relevant for drugs administered orally where exposure is normally limited by BCRP-mediated efflux, in particular some statins, such as rosuvastatin. Other drugs where the disposition is mediated via BCRP should be administered with caution, dose modification considered or substituted by an alternative drug. |

### 7.8.3 Prohibited concomitant medications

The following treatments and the medications listed in Appendix G are prohibited while in this study. Any further questions regarding concomitant treatments should be referred to the Medical Monitor.

| Prohibited Medication/Class of drug: | Additional Information |
|---|---|
| Anticancer agents other than the study medications. | If such agents are required for a patient, then the patient must first be withdrawn from the study. |
| Concomitant treatment with aprepitant and fosaprepitant is not allowable per protocol until further evaluation.<br>Potent or moderate inhibitors or inducers of CYP3A4, sensitive CYP3A4 substrates, and CYP3A4 substrates with a narrow therapeutic window should be avoided until additional data on drug-drug interaction becomes available. | No formal clinical drug interaction studies have been performed with AZD1775. An exploratory assessment of the effect of aprepitant on AZD1775 exposure in oncology patients suggests that there is a drug interaction between AZD1775 and aprepitant, as exposure to AZD1775 increased by ~60% when aprepitant was co-administered with AZD1775. The observed increase in AZD1775 exposure is likely the result of CYP3A4 inhibition by aprepitant. This increase in exposure is statistically significant. At the selected MTDs, this increase may also be of clinical importance.<br>The use of sensitive substrates of CYP3A4, such as atorvastatin, simvastatin and lovastatin are prohibited in this study (see Appendix G). |
| Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. | Patients should stop using these herbal medications 7 days prior to first dose of AZD1775. |

### 7.8.4 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form.

Patients may receive palliative radiotherapy during the trial only for local pain control, and only if in the opinion of the treating Investigator the patient does not have PD. The radiation field cannot encompass a target lesion. Radiation to a target lesion is considered PD and the patient should be removed from study treatment.

# 8. STATISTICAL ANALYSIS BY ASTRAZENECA

## 8.1 Sample size estimate

Approximately up to 172 patients may be enrolled and treated in this study (see Figure 1): 12 in the Part A safety lead-in cohort, and a maximum of up to 160 in Part B with tumour specific cohorts (ovarian [n=60], TNBC [n=50]), and SCLC [n=50]).

Approximately 12 evaluable patients will be enrolled and treated in Part A (dose escalation). Patients must complete Cycle 1 safety evaluations and must receive at least 75% of the planned Cycle 1 dose in order to be considered evaluable. Patients receiving less than 75% of the Cycle 1 dose will be replaced unless they experience a confirmed DLT. At the end of Part A, if no safety signals are reported and the PK profile appears acceptable, the Part B tumour-specific expansion cohorts will begin enrolment.

In Part B, in the TNBC and SCLC cohorts, approximately 15 biomarker positive and 15 biomarker negative patients will be enrolled and treated. An additional 20 patients in each tumour cohort may be enrolled and treated to further explore genetic profiles of interest. In addition, 60 ovarian cancer patients will be treated. Therefore, approximately up to 172 patients may be treated in the study (Part A and Part B combined).

## 8.2 Description of analysis sets

### 8.2.1 All subjects set

The All Subjects Set will include all patients who have signed the informed consent form (i.e. screening failures plus patients treated). The All Subjects Set will be used to describe the patient disposition and patient deaths on study.

### 8.2.2 Full analysis set

The Full Analysis Set (FAS) will include all patients who were treated with at least one non-zero dose of AZD1775. This population will be used for the primary analyses of the efficacy endpoints.

### 8.2.3 Safety analysis set

The Safety Analyses Set will include all patients who received at least one (non-zero) dose of AZD1775 and had at least one subsequent safety assessment.

### 8.2.4 Dose-limiting analysis set

The DLT analysis set will include all patients in the Part A safety lead-in cohort who received at least 75% of the AZD1775 dose and completed the minimum safety evaluation requirements during the first 21 days of treatment or who experienced a DLT during the first 21 days of treatment regardless of the amount of drug received.

The patients in the DLT analysis set will be used for the determination of safety of the dose and schedule of AZD1775 in Part A.

### 8.2.5 Pharmacokinetic analysis set

The PK analysis set will include all patients who receive the AZD1775 dose and provide at least one PK sample.

If a patient has a major protocol deviation that affects the evaluability of the PK profile, then the patient will not form part of the PK analysis set.

Major protocol deviations include changes to the procedures that may impact the quality of the data or any circumstances that can alter the evaluation of the PK. Examples include, but may not be limited to: vomiting following oral dosing occurring within the time frame of 2 times the median $t_{max}$, sample processing errors that lead to inaccurate bioanalytical results, incomplete dose administered, incomplete PK profile collected, and/or use of disallowed concomitant medication. In the case of a major protocol deviation, affected PK data collected will be excluded from the summaries and statistical analyses, but will still be reported in the study result listings. Major deviations will be listed and summarised in the CSR.

### 8.2.6 Pharmacokinetic analysis set

The PK analysis set will include all patients who receive the AZD1775 dose and have full PK sampling up to 10 hours post-dose.

If a patient has a major protocol deviation that affects the evaluability of the PK profile, then the patient will not form part of the PK analysis set.

Major protocol deviations include changes to the procedures that may impact the quality of the data, or any circumstances that can alter the evaluation of the PK. Examples include, but may not be limited to: vomiting following oral dosing occurring within the time frame of 2 times the median $t_{max}$, sample processing errors that lead to inaccurate bioanalytical results, incomplete dose administered, incomplete PK profile collected, and/or use of disallowed concomitant medication. In the case of a major protocol deviation, affected PK data collected will be excluded from the summaries and statistical analyses, but will still be reported in the study result listings. Major deviations will be listed and summarised in the CSR.

## 8.3 Methods of statistical analyses

In this open-label, Phase Ib study, no formal hypothesis testing will be conducted. Descriptive statistical and graphical displays will be employed to assess the safety and efficacy of AZD1775 monotherapy in the patient populations of interest.

A comprehensive description of the statistical analyses and data summaries for this study will be documented in a Statistical Analysis Plan (SAP) which will be finalized prior to DBL. Note that data will be presented separately for each part of the study.

The study will have a primary data cut-off for the primary analysis (see Section 9.4). Following the primary analysis data cut-off, no further statistical analysis of the data will be conducted. All safety data collected after the primary analysis and up to (and including) the last of the FPVs will be listed and/or summarised as appropriate. A CSR addendum will be prepared to include such data.

### 8.3.1 Demographic and baseline data

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

### 8.3.2 Exposure

Exposure to AZD1775 (i.e. total amount of study drug received) will be listed and summarised for all patients in Part A and by expansion cohorts in Part B. Total exposure, time on study drug, and dose intensity will be summarised, along with the number and percentage of patients with at least one dose interruption and at least one dose reduction. Reason for discontinuation of study treatment will be summarised.

### 8.3.3 Safety analysis

In Part A DLTs will be summarised. For all parts of the study the following minimum data summaries will be presented by cohort using the Safety Analysis Set:

- TEAEs of any CTCAE grade – summarized by MedDRA preferred term and system organ class and CTCAE maximum grade
- Related TEAEs of any CTCAE grade – summarized by MedDRA preferred term and system organ class and CTCAE maximum grade
- SAEs
- Deaths summarized by primary cause
- Laboratory parameters (haematology and chemistry), vital signs, ECG data and concomitant medications including evaluations for potential DILI and QTc prolongation signals.

## 8.4 Efficacy

### 8.4.1 Objective response rate

In the expansion cohorts of Part B, the ORR (according to RECIST v1.1) will be computed and presented along with an exact 95% confidence interval (CI) using the method of Clopper and Pearson (Clopper and Pearson 1934).

### 8.4.2 Disease control rate

In the expansion cohorts of Part B, the DCR will be computed and presented along with an exact 95% CI using the method of Clopper and Pearson.

### 8.4.3 Changes in target lesion

Waterfall plots (bar charts) indicating the best percentage change from baseline in tumour size will be produced for the expansion cohorts in Part B.

### 8.4.4 Progression-free survival

Informational summaries and Kaplan Meier plots, without formal statistical comparisons, will be produced for expansion cohorts in Part B.

### 8.4.5 Duration of response

Informational summaries and Kaplan Meier plots, without formal statistical comparisons, will be produced for expansion cohorts in Part B.

### 8.4.6 Biomarker analysis

In Part B the number and proportion of patients having a genetic alteration in relevant tumour markers at baseline will be presented.

The relationship between clinical outcomes (ORR, DCR, DoR, and PFS) and the presence of genetic alterations in each marker will be summarised using methods appropriate for each specific clinical outcome as specified in the SAP. This analysis may be used to inform selection of TNBC and SCLC expansion cohorts in Part B.

### 8.4.7 Sub-group analyses

The details of any analyses and selection of the prognostic factors and/or baseline characteristics will be pre-specified in the SAP or reported as ad hoc evaluations in the CSR.

## 8.5 Timing of analyses

### 8.5.1 Part A: safety lead-in cohort

A formal analysis of safety data will take place after 12 evaluable patients have completed the Cycle 1 DLT evaluation.

### 8.5.2 Part B: tumour specific expansion cohorts

A formal analysis of safety and efficacy data will take place in each expansion cohort when the target number of patients have completed at least two cycles of treatment. This will include an analysis of the biomarker data in the TNBC and SCLC cohorts to inform selection of further expansion cohorts.

### 8.5.3 Final analysis

The final analysis will take place when all expansion cohorts in Part B have completed patient enrolment and follow-up as per the CSP (see Section 4.2) or at an earlier time if the study is stopped for reasons of safety. At this time all analyses will be performed according to the SAP for the purpose of generating the CSR.

## 8.6 Evaluation and calculation of variables by AstraZeneca or delegate

### 8.6.1 Calculation or derivation of efficacy variable(s)

#### 8.6.1.1 Tumour response rate

Patients will undergo regular tumour assessments until documented objective disease progression as defined by RECIST v1.1 (Eisenhauer et al 2009). At each restaging visit the RECIST data for a patient will be assigned a response of CR, PR, SD, or PD depending on the status of the disease compared with baseline and previous assessments (see Appendix D).

The objective response rate is defined as the number of the patients with a confirmed best overall response of CR or PR divided by the number of patients in the Full Analysis Set (FAS [see Section 8.2.2]). Similarly, the disease control rate is defined as the percentage of FAS patients with a best overall response of CR or PR or SD.

Progression of Target Lesions (TL) will be calculated in comparison with what the tumour burden was at a minimum (i.e., smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, or SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

If a patient has had a tumour assessment that cannot be evaluated, then the patient will be assigned a visit response of non-evaluable (NE) (unless there is evidence of progression in which case the response will be assigned as PD).

For TL measurements, if ≤1/3 of the TL sizes are missing (either not evaluable or not read, or the scan was not done) then a scaling up rule will be applied as follows:

- If ≤1/3 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 >1/3 of lesions recorded at baseline are missing, then the target lesion response will be NE. However, if the sum of non-missing target lesion diameters would result in PD (i.e., if using a value of 0 for missing lesions the sum of diameters has still increased by >20% or more compared with the smallest sum of diameters on study and has an absolute increase ≥5 mm) PD takes precedence over NE.

- A visit response of CR will not be allowed if any of the TL data are missing.

#### 8.6.1.2 Progression-free survival

Progression-free survival is defined as the time from date of first dose of AZD1775 until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anti-cancer

therapy prior to progression. 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.

If the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable RECIST assessment. If the patient has no evaluable visits or does not have baseline data they will be censored at 0 days unless they die within two visits of baseline.

Progression-free survival will be derived based on scan/assessment dates not visit dates. If RECIST assessments/scans contributing towards a particular visit are performed on different dates then the date of progression will be determined based on the earliest of the dates of the component that triggered the progression. With regard to censoring, a patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

#### 8.6.1.3 Changes in tumour size

Percent changes in tumour size from baseline will also be determined for patients with measurable disease at baseline and is derived at each visit as the % change in the sum of the diameters of Target Lesion (TLs) TLs. % change = [(post baseline TL sum – baseline TL sum) / baseline TL sum] *100.

#### 8.6.1.4 Duration of response

Duration of response is defined as the time from the date of first documented response until the date of documented progression or any cause death. In the case where a patient does not progress following response, the duration of response censoring time will be the same as the PFS censoring time.

## 8.7 Calculation or derivation of safety variable(s)

### 8.7.1 Exposure to investigational product

The total time on study treatment, as well as total exposure to study treatment and the amount delivered relative to the intended amount will be summarised. The number of patients with pauses and reductions and the dose intensity of AZD1775 will also be summarised.

### 8.7.2 Adverse events, laboratory changes, vital signs

Safety profiles will be assessed in terms of AEs and laboratory data, vital signs, and ECG data that will be collected for all patients. Treatment-emergent AEs are defined as any AE which initiates on or after the first day of study drug up through 30 days after study drug discontinuation.

### 8.7.3 Other significant adverse events (OAE)

During the evaluation of the AE data, the Medical Monitor will review the list of AEs that were not reported as SAEs and other adverse events (OAEs). Based on the expert's

judgement, significant adverse events of particular clinical importance may, after consultation with the Medical Science Director, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

## 8.8 Calculation or derivation of pharmacokinetic variables

Pharmacokinetic analysis of plasma for AZD1775 concentration data will be performed by Covance on behalf of AstraZeneca. The actual sampling times will be used in the parameter calculations and PK parameters will be derived using standard non-compartmental methods

Where possible the following PK parameters will be determined for AZD1775

- $C_{max}$
- C8hr
- Time to $C_{max}$ ($t_{max}$)
- Time of last detectable concentration ($t_{last}$)
- Terminal half-life ($t_{½\lambda z}$)
- Area under the plasma concentration-time curve from zero to 8 hours ($AUC_{(0-8)}$), from zero to the time of the last measurable concentration ($AUC_{(0-t)}$), and from zero to 12 h ($AUC_{(0-12)}$).

Following the multiple dose part of the study (Day 3 or Day 10) the following additional parameters will be calculated

- Accumulation on day 3 or 10 compared to day 1 for $C_{max}$ and $AUC_{(0-12)}$
- $C_{trough}$

The $C_{max}$ and $t_{max}$ parameters will be determined by inspection of the concentration time profiles. Where possible the terminal elimination rate constant ($\lambda z$) will be calculated by log-linear regression of the terminal portion of the concentration-time profiles where there are sufficient data and the terminal (elimination) half-life ($t_{½\lambda z}$) will be calculated as ln 2/$\lambda z$. The area under the concentration-time curve up to the last quantifiable sample ($AUC_{[0-t]}$) and the $AUC_{(0-8)}$ will be calculated using the linear up, log down trapezoidal rule. Where appropriate, the $AUC_{(0-t)}$ will be extrapolated to infinity using $\lambda z$ to obtain AUC. The area under the concentration-time curve across the dosing interval, $AUC_{ss}$ will be calculated using the linear

up, log down trapezoidal rule. The apparent clearance (CL/F following the single dose and $CL_{ss}/F$ following multiple dosing) will be determined from the ratio of dose/AUC or dose/$AUC_{ss}$. The volume of distribution ($V_{ss}$, $V_{ss}/F$ or Vz/F) will be determined from the MRT x CL/F and/or the accumulation ratio (RAC) will be calculated as the ratio of the $AUC_{(0-8)}$ on Cycle 3 Day 1. The time dependency of the pharmacokinetics on multiple dosing will be assessed by the calculation of the ratio of $AUC_{(ss)}$/AUC(single dose).

## 8.9 Pharmacokinetics/Pharmacodynamic Analysis

The plasma concentration data for AZD1775 may be analysed using a population PK approach, which may include exploring the influence of covariates on PK, if the data allows. A population pharmacodynamics approach will be used to investigate the relationship between PK and selected primary, secondary and/or exploratory endpoints, where deemed appropriate. Results may be reported separately from the CSR for the main study. The PK, pharmacodynamics, demographic, safety and tumour response data collected in this study may also be combined with similar data from other studies and explored using population pharmacokinetic and/or pharmacokinetic-pharmacodynamics methods. The results of any such analyses will be reported separately from the CSR.

**Pharmacodynamic response**

At least 7 patients (any tumour type acceptable) should consent to and complete the optional paired biopsy testing for this response to be evaluated. The target response rate is defined as 50% with a value of 25% being considered too low to be of interest. Assuming the probability of a false positive and a false negative to be 20% and 10% respectively, if 4/7 patients respond then we can conclude that the response rate is greater than 25% and consistent with 50% (lower boundary one sided 80% CI = 35%). However, if 1/7 patients respond then we do not have sufficient evidence that the response rate is 50% (upper boundary one sided 90% CI = 45%). For information with 4/7 (57%) responders the exact 2-sided 80% confidence interval would be (27%, 83%).

# 9. STUDY MANAGEMENT

## 9.1 Pre-study activities

Before the first patient is entered into the study, it may be necessary for a designee of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca

or its representatives. This will be documented in a Clinical Study Agreement between the AstraZeneca designee and the investigator.

## 9.2 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca designee will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study specific procedures and EDC system(s) utilised.

The PI will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing and other staff).

## 9.3 Monitoring of the study

During the study, AstraZeneca or its designee will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (e.g., clinic charts).
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca designee will be available between visits if the investigator(s) or other staff at the centre requires information and advice about the study conduct.

### 9.3.1 Source data

Refer to the CSA for location of source data.

### 9.3.2 Study agreements

The PI at each centre should comply with all the terms, conditions, and obligations of the Study Agreement with the Principal Investigator, or equivalent, for this study. In the event of any inconsistency between this CSP and the Study Agreement with Principal Investigator, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Study Agreement with Principal Investigator shall prevail. Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or any subjects are enrolled.

### 9.3.3 Archiving of study documents

The Study Agreement with the Principal Investigator, or equivalent, for this study. In the event of any inconsistency between this CSP and the Study Agreement with Principal Investigator, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Study Agreement with Principal Investigator shall prevail. Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or any subjects are enrolled.

### 9.3.4 Deviation from the clinical study protocol

The Investigator(s) must not deviate from or make any changes to the protocol without documented agreement between the Principal Investigator and AstraZeneca or the IRB approval based on its deliberations. However, this shall not apply to cases where the deviation or change is necessary to avoid an immediate hazard to the subjects or for other compelling medical reasons, or where the changes involve only logistical or administrative aspects of the clinical study (e.g., changes to the organisation/structure of the AstraZeneca, the name/department name of the study site, the address or phone number of the study site or AstraZeneca, the job title of the Investigator, and monitors).

The Investigator(s) should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to the subjects or for other medically compelling reason, the Investigator should prepare and submit the records explaining the reasons thereof to AstraZeneca and the head of study site, and retain a copy of the records.

The Investigator(s) may deviate from or make a change to the protocol without documented agreement between the Principal Investigator and AstraZeneca or the IRB approval, only in the event of a medical emergency, e.g., it is only way to avoid an immediate hazard to the subjects. In such case, the Principal Investigator must notify details of the deviation or change, the reason, and a proposed revision in the protocol if required, to AstraZeneca and the head of the study site and IRB via the head of the study site as soon as possible, in order to obtain their approval. A certificate of approval by the head of the study site as well as AstraZeneca should be obtained via the head of the study site.

## 9.4 Study timetable and end of study

The end of study is defined as "the last visit of the last subject undergoing the study'. The end of study definition applies to the entire study and not for a specific region.

There will be a primary data cut-off for preparation of a CSR, as well as a final data cut-off after the primary analysis and following Revised Clinical Protocol Edition 5 implementation. Any patients still receiving AZD1775 at the time of the primary data cut-off will complete a FPV, which should align with the next scheduled visit following implementation of the Revised Clinical Protocol Edition 5. Refer to Section 4.3.2.3 for further information regarding the FPV.

Following the primary analysis data cut-off, no further statistical analysis of the data will be conducted. All safety data collected after the primary analysis and up to (and including) the last FPV will be listed and/or summarised as appropriate. A CSR addendum will be prepared to include such data.

Investigators must report SAEs, overdoses, and pregnancies to the AstraZeneca representative in accordance with Section 6.5, and continue to maintain study drug accountability as long as patients are receiving treatment with the study drug.

Planned duration of the study period: Begin in Q2 2015 and end by the last visit of the last patient undergoing the study or at the time of optional tumour biopsy collection due to progression.

Investigators will be notified by AstraZeneca when recruitment is complete. The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD1775.

**Discontinuation or suspension of the whole study programme**

If AstraZeneca decides to prematurely terminate or suspend the study, the Principal Investigator/Investigator, the head of the study site, and regulatory authorities should receive written notification of the reasons for the premature termination or suspension.

The Principal Investigator/Investigator will immediately notify the decision to the subjects, give appropriate medical treatment; take necessary measures, and record treatment or measures provided on the source documents.

**Completion of the study**

Upon terminating the study, the Principal Investigator/Investigator will report in writing the completion of the study as well as the summary of the results to the head of the study site in accordance with the study site's rules. The head of the study site, who is informed of the

termination by the Investigator, will provide a written notification of the results to the IRB and AstraZeneca.

## 9.5 Data management by AstraZeneca or delegate

Data management will be performed by Innovations according to the Data Management Plan. Data will be entered in the EDC system at the study site. Trained study personnel will be responsible for entering data on the observations, tests, and assessments specified in the protocol into the EDC system and according to the eCRF Instructions. The eCRF Instructions will also guide the study site in performing data entry. Data entered in the EDC system will be immediately saved to a central database and changes tracked to provide an audit trail. The data will then be Source Data Verified (SDV), reviewed/queried and updated as needed. The PI is responsible for signing the eCRF and this can be delegated to a trained investigator. The eCRF is signed electronically as per the eCRF instructions.

Data Management determines the format of the data to be received from external vendors and coordinates the flow of data to an external environment or clinical database (if applicable). Data Management will ensure that the data collection tool (e.g., IWRS, etc.) will be tested / validated as needed. The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the WHO Drug Dictionary. All coding will be performed by AstraZeneca or delegate.

Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail. The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The study Data Management Plan will describe in greater detail the methods used to collect, check, and process clinical data. It will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

All decisions on the evaluability of the data from each individual patient must have been made and documented. Following DBL, required amendments to the database due to critical errors will only be allowed with the appropriate supporting documentation. Non-critical errors will not result in amendments to the database but will be captured via the appropriate documentation. The data will be frozen and then locked to prevent further editing. When all data have been coded, validated, signed and locked, clean file will be declared and the final database will be locked. Copy of the eCRF will be archived at the study site when the study has been closed.

Data associated with biological samples will be transferred from laboratories internal or external to AstraZeneca. Any genotype data generated in this study will be stored in the

AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse samples. The results from this genetic research will be reported separately from the CSR for the main study. 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.

# 10. ETHICAL AND REGULATORY REQUIREMENTS

## 10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

The applicable regulatory requirements in Japan are 'Good Clinical Practice for Trials on Drugs (MHLW Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications

## 10.2 Subject data protection

The Master Informed Consent Form will explain that:

- Study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation
- Patient data will be maintaining confidentiality in accordance with national data legislation
- For data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, an IRB may require direct access to parts of the hospital or practice source records relevant to the study, including subjects' medical history
- All data computer processed by AstraZeneca will be identified by study code and enrolment code (E-code)

AstraZeneca will not provide individual genotype results to a patient, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

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. Also Regulatory authorities may

require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

## 10.3 Ethics and regulatory review

An IRB should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The head of the study site will ensure the distribution of these documents to the applicable IRB, and the Principal Investigator to the Investigator and study site staff.

The opinion of the IRB should be given in writing. The head of the study site should submit a notification of direction/determination as well as a copy of the IRB written approval to AstraZeneca and the Principal Investigator before enrolment of any subject should into the study.

The IRB should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

A valid contract between the study site and AstraZeneca should be signed before the Investigator can enrol any subject into the study. The protocol should be re-approved by the IRB annually.

The head of the study site should seek the opinion of the IRB with respect to the appropriateness of continuing the study at the study site at least once a year when the duration of the study exceeds one year. The Principal Investigator should submit progress reports to the IRB via the head of the study site at the time of the protocol re-approval.

Before enrolment of any subject into the study, the final study protocol, including the final version of the ICF, should be approved by the national regulatory authority with notification provided, according to local regulations. AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, IRB, the head of the study site and the Principal Investigator with safety updates/reports according to local requirements.

The head of the study site should submit a written report to the IRB providing the details of all safety relative information reported by AstraZeneca.

Each PI is responsible for providing the EC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca or designee will provide this information to the PI so that he/she can meet these reporting requirements.

## 10.4 Informed consent

The PIs at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.
- Ensure each patient is notified that they are free to discontinue from the study at any time.
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File.
- Ensure a copy of the signed ICF is given to the patient.
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an EC/IRB.

## 10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca. If it is necessary for the study protocol to be amended, the amendment should be submitted to the Head of the Study Site and be approved by its IRB. If applicable, AstraZeneca should submit a notification to the regulatory authority before it is implemented. If a protocol amendment requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the centre's IRB should be notified. Approval of the revised Informed Consent Form by AstraZeneca and by the IRB is required before the revised form is used. If an administrative change is required, such a change should be notified to or approved by each IRB according to local requirements.

## 10.6 Audits and inspections

Authorised designees of AstraZeneca, a regulatory authority, or an EC/IRB may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact the AstraZeneca designee immediately if contacted by a regulatory agency about an inspection at the centre.

All study data may undergo a reliability review and onsite-GCP inspection by the regulatory authorities.

## 10.7 Overall safety monitoring

A Safety Review Team (SRT) will be established by Innovations for this study. Reviewers may include the study PI, Medical Monitor, Lead Biostatistician, Safety Director, Safety Lead, Clinical Data Analyst, Clinical Project Manager, and Sponsor representatives. The roles and responsibilities of the SRT and the Medical Monitor are described in the Safety Data Handling Plan.

The timing and frequency of safety evaluations may be revised, in consultation with the SRT, in response to emerging data.

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# Appendix A Additional Safety Information

## Further guidance on the definition of a serious adverse event (SAE)

### Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the adverse event (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).

### Hospitalisation

Out-patient treatment in an emergency room is not in itself a serious AE, 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.

### Important medical event or medical intervention

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 intervention to prevent one 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 should 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.

### A guide to interpreting the causality question

The following factors should be considered 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?

- Dechallenge 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 judgment. 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.

# Appendix B 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. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) 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 (HIV) 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
- 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 C Actions Required in Cases of Combined Increases of Aminotransferase and Total Bilirubin – Hy-s Law

## Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on the managing liver abnormalities can be found in Section 6.4.6 of the protocol.

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 potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (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 Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

## Definitions

### Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

### Hy's Law (HL)

AST or ALT ≥ 3x ULN **together with** TBL ≥ 2xULN, where no other reason, other than the IMP, 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 (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

## 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 ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

**Follow-up**

**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 Clinical Study Protocol (CSP).

**Potential Hy's Law Criteria met**

If the patient does meet PHL criteria the Investigator will:

- Notify the AZ representative who will then inform the central Study Team

The Study Physician (SP) contacts the Investigator, to provide guidance, discuss and agree an approach for the study subject's follow-up and the continuous review of data. Subsequent to this contact, the investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

**Review and Assessment Review of Potential Hy's Law Cases**

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks 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. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If 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, record the AE /SAE in the CRF accordingly and follow 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:

- Report an 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 3 weeks, 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:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

- 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 met. Update the SAE report according to the outcome of the review.

**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 e.g. chronic or progressing malignant disease, severe infection or liver disease?

If No: follow the process described in Potential Hy's Law Criteria met of this Appendix.

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 Potential Hy's Law Criteria not met of this Appendix

[#] 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 total bilirubin) 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.

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# Appendix D 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 RECIST 1.1 Guidelines (Eisenhauer et al 2009) for the D6015C00001 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

Only patients with measurable disease at baseline should be included in the study. Measurable disease is defined by the presence of at least one measurable lesion which has not been previously irradiated.

**Measurable:**

A lesion, not previously irradiated, 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 computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

**Non-measurable:**

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15mm short axis at baseline*).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Previously irradiated lesions**
- Skin lesions assessed by clinical examination***
- Brain metastasis***

*Nodes with <10mm short axis are considered non-pathological and should not be recorded or followed as NTL.

**Localised post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and must be selected as Non-Target Lesions (NTL) at baseline and followed up as part of the NTL assessment.

**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 should be selected as target lesions.

**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 target lesions (TL) at baseline.

**Non-Target lesions:**

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

## METHODS OF ASSESSMENT

**The same method of assessment and the same technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits.**

A summary of the methods to be used for RECIST assessment is provided below and those excluded from tumour assessments for this study are highlighted, with the rationale provided.

**Summary of methods of assessments**

| Target Lesions | Non-Target Lesions | New Lesions |
|---|---|---|
| CT (preferred) | CT (preferred) | CT (preferred) |
| MRI | MRI | MRI |
| | Clinical examination | Clinical examination |
| | X-ray, Chest x-ray | X-ray, Chest x-ray |
| | | 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 TL selected for response assessment and to assess NTL and identification of any new lesions.

In the D6130C00001 study it is recommended that CT examinations of the chest, abdomen, and pelvis will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous (i.v.) contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For brain lesion assessment, MRI is the preferred method.

### Clinical examination

In the D6130C00001 study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as target lesions if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

### X-ray

### Chest X-ray

In the D6130C00001 study, chest x-ray assessment will not be used for assessment of TL as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

### Plain X-ray

In the D6130C00001 study plain x-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

### Ultrasound

In the D6130C00001 study, ultrasound examination will not be used for assessment of TL and NTL 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

In the D6130C00001 study, endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

### Tumour markers

In the D6130C00001 study tumour markers will not be used for tumour response assessments as per RECIST 1.1.

### Cytology and histology

In the D6130C00001 study histology will not be used as part of the tumour response assessment as 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. In such circumstances, the cytology is necessary to differentiate between response / stable disease (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 appearance of clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTL, 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 NTL and followed by the same method as per baseline assessment.

In the D6130C00001 study 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

In the D6130C00001 study FDG-PET 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* 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.

*A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

# TUMOUR RESPONSE EVALUATION

## Schedule of evaluation

Baseline assessments should encompass chest, abdomen and pelvis 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. Follow-up assessments will be performed every 6 weeks +/- 1 week window interval after start of treatment until objective disease progression as defined by RECIST 1.1. or withdrawal from study Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

If an unscheduled assessment was 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 in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

## Target lesions (TL)

### 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 TL 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 millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

### Special cases:

- For TL 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 > 5mm, 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 two or more parts, then record the sum of the diameters of those parts.
- If two or more TL merge then the sum of the diameters of the combined lesion should be recorded for one 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 5mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5mm.
- 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 e.g. radiotherapy, embolisation, surgery etc., during the study, the size of the TL should still be provided where possible.

**Evaluation of target lesions**

This section provides the definitions of the criteria used to determine objective tumour visit response for TL.

**Evaluation of target lesions**

| | |
|---|---|
| Complete Response (CR) | Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to < 10 mm. |
| Partial Response (PR) | At least a 30% decrease in the sum of the diameters of TL, 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 (PD) | At least a 20% increase in the sum of diameters of target lesions, 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 5mm. |
| Not Evaluable (NE) | Only relevant if any of the target lesions 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 not evaluable as a target lesion response |

**Non-Target lesions (NTL)**

**Evaluation of non-target lesions**

All other lesions (or sites of disease) not recorded as TL should be identified as NTL 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. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

**Evaluation of non-target lesions**

| | |
|---|---|
| Complete Response (CR) | Disappearance of all non-target lesions since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis). |
| Non CR/Non PD | Persistence of one or more NTL |
| Progression (PD) | Unequivocal progression of existing non-target lesions. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy. |
| Not Evaluable (NE) | Only relevant when one or some of the non-target lesions were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall non-target lesion assessment at this visit.<br>Note: For patients without target lesions at baseline, this is relevant if any of the non-target lesions were not assessed at this visit and the progression criteria have not been met. |

To achieve 'unequivocal progression' on the basis of non-target lesions, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target lesions, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions 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 one 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: i.e. 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 treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

### Evaluation of Overall Visit Response

The overall visit response will be derived using the algorithm shown below.

**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 PD | No | PR |
| CR | NE | No | PR |
| PR | Non PD or NE | No | PR |
| SD | Non PD or NE | No | SD |
| NE | Non PD or NE | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not applicable (only relevant if there were no NTL*s* at baseline).

## CONFIRMATION OF RESPONSE

In the D6130C00001 study, imaging for confirmation of response (CR or PR) should be performed at next scheduled visit (certainly no less than 4 weeks) following the date the criteria for response were first met.

# SPECIFICATIONS FOR RADIOLOGICAL IMAGING

These notes are recommendations for use in clinical studies. The use of standardized 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 anatomic region 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.

**IV contrast administration**: Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of IV 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 target lesions 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 pelvis MRI with contrast. If MRI cannot be performed then CT

without i.v. contrast is an option for the thorax, abdomen and pelvis examination. For brain lesions assessment, MRI is the preferred method.

**Slice thickness and reconstruction interval:** It is recommended that CT scans be performed at 5mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for 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 TL 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 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. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45 (2009) 228-247.

# Appendix E Stages of Heart Failure – New York Heart Association Classification

**The Stages of Heart Failure – New York Heart Association Classification**

**Class I (Mild)**

No Limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea (shortness of breath).

**Class II (Mild)**

Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.

**Class III (Moderate)**

Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation, or dyspnoea.

**Class IV (Severe)**

Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, physical discomfort is increased.

**Reference**

The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston (MA): Little, Brown & Co; 1994:253-256.

# Appendix F Definition of Women of Childbearing Potential

**Women of Child Bearing Potential (WoCBP) -** Women between menarche and menopause who have not been permanently or surgically sterilized and are capable of procreation.

**Women NOT of Childbearing Potential -** Women who are permanently or surgically sterilized or postmenopausal (definitions below):

**Permanent sterilisation** includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal occlusion. Tubal occlusion is considered a highly effective method of birth control but does not absolutely exclude possibility of pregnancy. (The term occlusion refers to both occluding and ligating techniques that do not physically remove the oviducts).

- Women who have undergone tubal occlusion should be managed on trials as if they are of WoCBP (e.g. undergo pregnancy testing etc. as required by the study protocol).

- Women will be considered postmenopausal if they are amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women under 50 years old will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range.

- Women over 50 years of age will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatments.

**ACCEPTABLE CONTRACEPTION METHODS**

Highly effective method of birth control is defined in Note 3 in ICH Guidance M3 (Nonclinical Safety Studies for the conduct of Human Clinical trials for Pharmaceuticals) as one that results in a low failure rate (e.g. less than 1 percent per year) when used consistently and correctly.

The following methods of highly effective contraception are considered acceptable by

Note that women should have been stable on their chosen method of birth control for a minimum of 2 weeks before entering the trial. Generic names and examples of trade names are given. As trade names may vary, investigators should check the generic name of any contraception to ensure suitability.

Acceptable contraception methods are:

- Total sexual abstinence (abstinence must be for the total duration of the trial and the follow-up period)
- Vasectomised sexual partner plus male condom (with participant assurance that partner received post-vasectomy confirmation of azoospermia)
- Tubal occlusion plus male condom
- Intra-uterine Device (IUD) - provided coils are copper-banded, plus male condom
- Intra-uterine system (IUS) Levonorgestrel Intra Uterine System (e.g, Mirena), plus male condom
- Medroxyprogesterone injections (Depo-Provera) plus male condom
- Etonogestrel implants (eg, Implanon, Norplan) plus male condom
- Normal and low dose combined oral contraceptive pills, plus male condom
- Norelgestromin / ethinylestradiol transdermal system plus male condom
- Intravaginal device (eg ethinylestradiol and etonogestrel ) plus male condom
- Cerazette (desogestrel) plus male condom. Cerazette is currently the only highly efficacious progesterone based pill

**UNACCEPTABLE CONTRACEPTION METHODS**

The following methods are considered not to be highly effective and are therefore not acceptable contraceptive methods in AstraZeneca clinical trials:

- Triphasic combined oral contraceptives (COCs)
- All progesterone only pills, except Cerazette
- All barrier methods, if intended to be used alone
- Non-copper containing Intra-Uterine Devices (IUDs)
- Fertility awareness methods
- Coitus interruptus

# Appendix G Disallowed Medications and Medications to be Administered with Caution

## DISALLOWED MEDICATIONS AND MEDICATIONS TO BE ADMINISTERED WITH CAUTION

Formal drug-drug interaction studies have not yet been performed with AZD1775, therefore, the potential for drug-drug interaction described in this protocol are based on findings from *in vitro studies* and clinical experience.

*In vitro* data has shown that AZD1775 is metabolised predominantly by CYP3A4, with an FMO3 and/or FMO5 component. As a result, there is potential for the exposure of AZD1775 to be effected by drugs which inhibit or induce the metabolism of CYP3A4. In the clinic, coadministration of AZD1775 with the moderate CYP3A4 inhibitor, aprepitant, resulted in a 40% increase in the plasma levels of AZD1775. Drugs known to be moderate to strong inhibitors/inducers of CYP3A4 are therefore prohibited for use in the current study, including aprepitant.

*In vitro* data suggests that AZD1775 may be a weak reversible inhibitor of CYP2C19 ($IC_{50}$ 12 uM). Caution should therefore be exercised when AZD1775 is coadministered with agents that are sensitive substrates of CYP2C19, or substrates of this enzyme with a narrow therapeutic range.

Based on *in vitro* studies, AZD1775 has been shown to be a weak reversible inhibitor ($IC_{50}$ 14 μM) and a time-dependent inhibitor of CYP3A4 ($K_{inact}$ 0.061/min, $K_i$ 6.04 μM). The full impact of the time dependent inhibition is currently unknown, however, modelling data has predicted an 8-10 fold increase in the exposure of sensitive CYP3A4 substrates when administered with AZD1775 (250 mg BID for 5 doses). To date, no significant DDI effects have been reported in the clinic that may be related to the TDI finding. However, sensitive CYP3A4 substrates or substrates of CYP3A4 with a narrow therapeutic window are prohibited.

AZD1775 has been shown to be a weak inducer of CYP1A2 *in vitro* (39% increase in activity of positive control). Given the nature of the AZD1775 dosing schedule, however, the risk of induction in the clinic is considered low. No specific precautions are recommended at this time, except to be initially vigilant when using substrates of CYP1A2 with a narrow therapeutic range.

Transporter studies (*in vitro*) have shown that AZD1775 is both a substrate and inhibitor ($IC_{50}$ 20 μM) of P-gp. Maximum impact of these finding is likely to occur for drugs administered orally at the same time as AZD1775. Caution should therefore be exercised when agents that are inhibitors or substrates of P-gp are administered concomitantly with AZD1775.

Recent *in vitro* transporter studies have shown AZD1775 to be an inhibitor of BCRP ($IC_{50}$ 5.1 μM). This finding is particularly relevant for drugs administered orally where exposure is normally limited by BCRP-mediated efflux, in particular some statins, such as rosuvastatin. Other drugs where the disposition is mediated via BCRP should be administered with caution, dose modification considered or substituted by an alternative drug.

Use of metformin should be used with caution in this study as recent *in vitro* transporter data have shown AZD1775 is an inhibitor of Multidrug and Toxin Extruder 1 (MATE1) and MATE2K.

Caution should be used when administering drugs that are substrates of these transporters (e.g. cimetidine, acyclovir, fexofenadine) as the clinical relevance of AZD1775 inhibition of the MATE pathway is not known in these compounds.

Herbal preparations/medications can be substrates, inhibitors and inducers, similar to any registered medication. Herbal preparations are therefore not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.

In addition, any other drugs should be avoided at the Investigator's discretion if, in their opinion, the co-administration with AZD1775 may increase the risk of a clinically significant drug interaction.

A list of the main CYP3A4 substrates, inhibitors (strong and moderate) and inducers, CYP2C19 substrates, P-gp substrates and inhibitors and BCRP substrates are shown below. This is not an exhaustive list and further details can be found at Expert Opin. Drug Metab. Toxicol. (2013) 9(6):737-751.

# CYP3A4 Inhibitors

## Strong

Boceprevir
Clarithromycin
Cobicistat (GS-9350)
Conivaptan
Danoprevir
Elvitegravir
Fosamprenavir
Grapefruit juice
Idelalisib
Indinavir
Itraconazole
Ketoconazole
LCL161
Lopinavir
Mibefradil
Nefazodone
Nelfinavir
Posaconazole
Ritonavir
Saquinavir
Telaprevir
Telithromycin
Tipranavir
Troleandomycin
Voriconazole

## Moderate

ACT-178882
Amprenavir
Aprepitant
Atazanavir
Casopitant
Ciprofloxacin
Crizotinib
Darunavir
Dronedarone
Diltiazem
Erythromycin
FK1706
Fluconazole
Fosamprenavir
Imatinib
Ledipasvir
Lomitapide
Netupitant
Schisandra sphenanthera
Tofisopam
Verapamil

**Weak**

Almorexant
Alprazolam
AMD070
Amiodarone
Amlodipine
Atorvastatin
Azithromycin
Berberine
Bicalutamide
Blueberry juice
Chlorzoxazone
Cilostazol
Cimetidine
Clotrimazole
Cranberry juice
Cyclosporine
Daclatasvir
Delavirdine
Everolimus
Faldaprevir
Fluvoxamine
Fosaprepitant (IV)
Ginkgo
Goldenseal
GSK1292263
GSK2248761
Isoniazid
Ivacaftor
Lacidipine
I Linagliptin
Lomitapide
M100240
Nilotinib
Oral contraceptives
Pazopanib
Peppermint oil
Propiverine
Ranitidine
Ranolazine
Resveratrol
Roxithromycin
Seville orange juice
Simeprevir
Sitaxentan
Suvorexant
Tabimorelin
Tacrolimus
Teriflunomide
Ticagrelor
Tipranavir/ritonavir
Tolvaptan
Zileuton

**CYP3A4 Inducers (Strong and Moderate)**

Avasimibe
Bosentan
Carbamazepine
Efavirenz
Enzalutamide
Etravirine
Genistein
Lersivirine
Lopinavir
Mitotane
Nafcillin
Phenobarbital
Phenytoin
Rifabutin
Rifampin
Ritonavir
Semagacestat
St John's Wort
Thioridazine
Tipranavir

Modafinil

**CYP3A4 Inducers (Weak)**

Amprenavir
Aprepitant
Armodafinil
AZD 7325
Bexarotene
Boceprevir
Brivaracetam
Clobazam
Danshen
Dexamethasone
Echinacea
Eslicarbazepine
Garlic
Gingko
Ginseng
Glycyrrhizin
LCL161
Methylprednisolone
Nevirapine
Oritavancin
Oxcarbazepine
PA-824
Pleconaril
Prednisone
Quercetin
Raltegravir
Ritonavir
Rufinamide
Sorafenib
Stribild
Telaprevir
Terbinafine
Ticagrelor
Ticlopidine
Topiramate
Troglitazone
Vemurafenib
Vicriviroc and ritonavir
Vinblastine

**CYP3A and CYP3A4 Sensitive Substrates or Substrates with a Narrow Therapeutic Range**

ABT-384
Alfentanil
Aprepitant
Alfuzosin
Almorexant
Alpha-Dihydroergocryptine
Amiodarone
Aplaviroc
Aprepitant
Astemizole
Atazanavir
Atorvastatin
Avanafil
Bexarotine
BIRL 355
Bortezomib
Bosutinib
Brecanavir
Brotizolam
Budesonide
Buspirone
Capravirine
Carbamazepine
Casopitant
Cisapride,
Conivaptan
Cyclophosphamide
Cyclosporine
Danoprevir
Darifenacin
Darunavir
Dasatinib
Dihydroergotamine
Disopyramide
Dronedarone
Docetaxol
Dofetilide
Doxorubicin
Ebastine
Eletriptan
Elvitegravir
Eplerenone
Ergotamine
Erlotinib
Etoposide
Everolimus
Felodipine
Fentanyl
Fluticasone
Gefitinib
Halofantrine
Ibrutinib
Ifosfamide
Imatinib
Indinavir
Ironotecan
Ivacaftor
Ixabepilone
L-771,688
Lapatinib
Levomethadyl (LAAm)
Lomitapide
Lopinavir
Lovastatin
Lurasidone
Maraviroc,
Midazolam
Midostaurin
Mosapride
Neratinib
Nilotinib
Nisoldipine
Paclitaxel
Pazopanib
Perospirone
Pimozide
Propafenone
Propofol
Quetiapine
Quinidine
Ranolazine
Ridaforolimus
Romidepsin
Saquinavir
Sildenafil
Simeprevir
Simvastatin
Sirolimus
Tacrolimus
Temsirolimus
Terfenadine
Ticagrelor
Theoophylline
Thioridazine
Thiotepa
Tilidine
Tipranavir
Tolvaptan
Triazolam
Tretinoin
Ulipristal
Vardenafil
Vicriviroc
Voclosporin

**CYP2C19 Sensitive Substrates or Substrates with a Narrow Therapeutic Range**

Diazepam
Gliclazide
Lansoprazole
(R)-Lansoprazole
(S)-Lansoprazole
(S)-Mephenytoin
(R)-Mephobarbital
Omeprazole
(R)-Omeprazole
Pantoprazole
(+)-Pantoprazole
Rabeprazole
Tilidine

**CYP1A2 Sensitive Substrates or Substrates with a Narrow Therapeutic Range**

Alosetron
Caffeine
Duloxetine
Melatonin
Ramelteon
Tacrine
Theophylline
Tizanidine

**P-gp Inhibitors (Strong)**

Cyclosporine
Elacridar
Erythromycin
Itraconazole
Ketoconazole
LY335979Quinidine
Ritonavir
Valspodar
Verapamil

**P-gp Substrates**

Colchicine
Digoxin
Fexofenadine
Indinavir
Paclitaxel

Toptecan
Vincristine

If a patient requires initiation of digoxin during the study, or is already receiving treatment with digoxin, monitoring of digoxin levels is recommended according to local practice (as the levels of digoxin may increase). Monitoring of digoxin levels is also recommended when the patient has completed dosing with study treatment (as the levels of digoxin may then decrease).

**BCRP Substrates**

Daunorubicin
Doxorubicin
Rosuvastatin
Sulfasalazine
Topotecan

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