A Phase II Trial of AZD1775 Plus Carboplatin-Paclitaxel in Squamous Cell Lung Cancer

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A Phase II Trial of AZD1775 Plus Carboplatin-Paclitaxel in Squamous Cell Lung Cancer

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse Event
ALT	Alanine Aminotransferase
APP	**Advanced Practice Provider**
AST	Apartate Aminotransferase
ASCO	American Society of Clinical Oncology
AUC	Area Under the Curve
BID	Twice Daily
BOR	Best Confirmed Objective Response
BRCT	BRCA1 C Terminal
CDK	Cyclin-Dependent Kinases
CR	Complete Response
CRF	Case Report Form
CT	Cat Scan
CTCAE	Common Terminology Criteria for Adverse Events
DDR	DNA Damage Response
DLT	Dose Limiting Toxicity
ECOG	Eastern Cooperative Group
FDA	Food and Drug Administration
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PARP	Poly ADP Ribose Polymerase
PAXIP1	Paired Box Interacting protein 1

PD	Progressive Disease
PFS	Progression Free Survival
PPI	Protein-Protein Interactions
PR	Partial Response
RECIST	Response Criteria for Solid Tumors
RR	Response Rate
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SD	Stable Disease
SQCLC	Squamous Cell Lung Cancer
ULN	Upper Limit of Normal

1. INTRODUCTION

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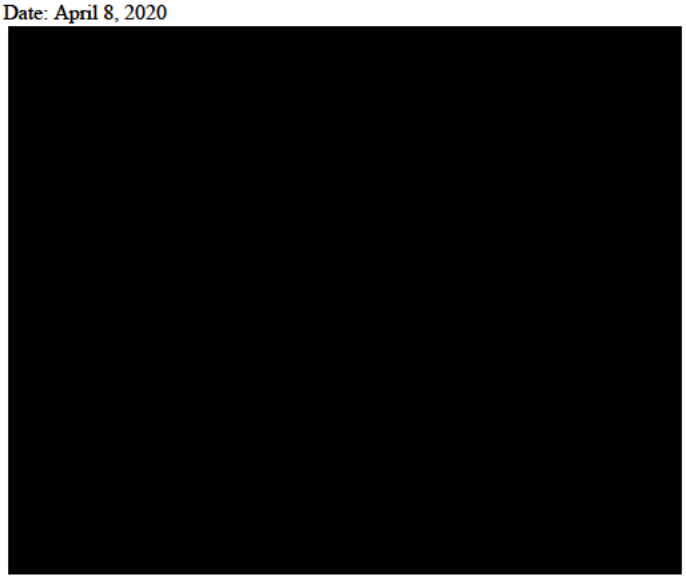

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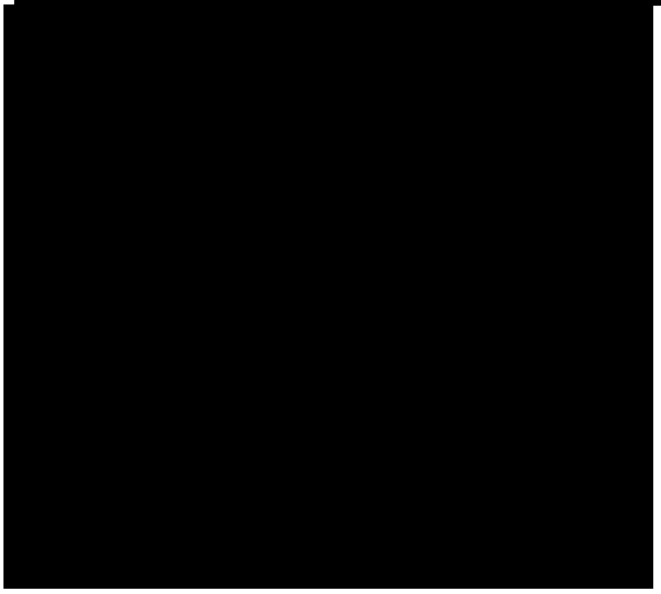

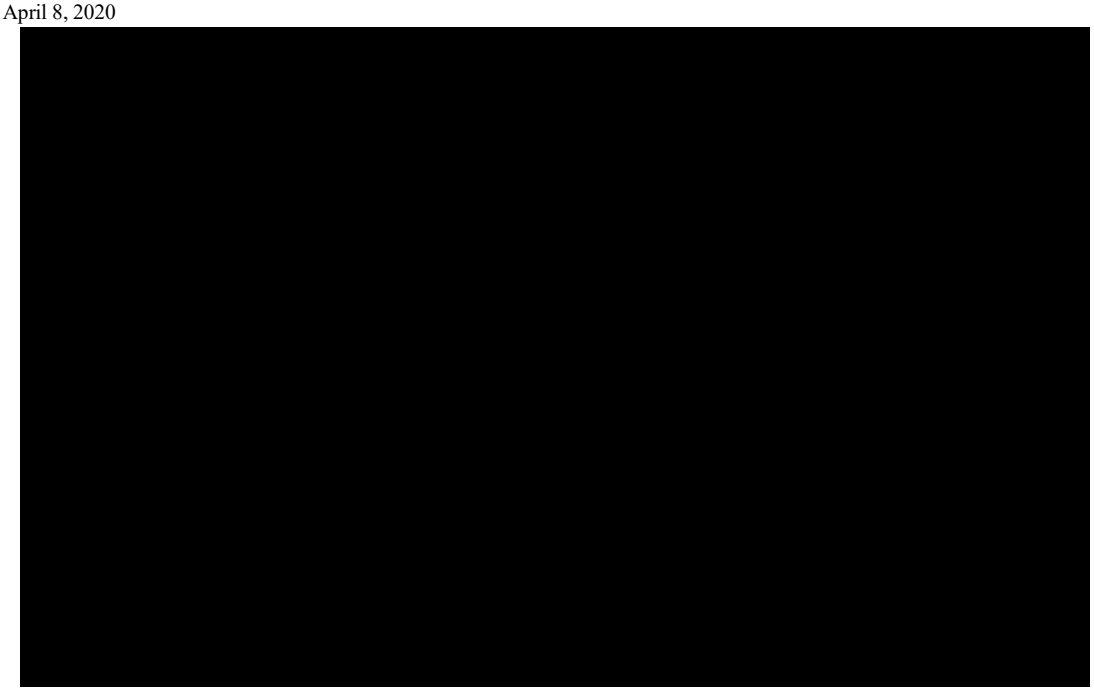

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Clinical Experience with AZD1775

AZD1775 has been administered to patients in 17 AstraZeneca-sponsored or Merck-sponsored clinical studies, 10 of which are ongoing.

For details, please see the current Investigator's Brochure.

The initial clinical study of AZD1775 (PN001) was designed to assess the safety and tolerability of AZD1775 monotherapy and in combination with cytotoxic agents. Patients in the initial part of this study were assigned to a single cycle of AZD1775 monotherapy in order to establish the clinical safety profile of the study drug (Schellens et al., ASCO 2009. Abstract: 3510). Following the initial monotherapy treatment cycle, patients continued to combination treatment, comprising AZD1775 with cisplatin, carboplatin, or gemcitabine (Leijen S et al., ASCO 2010. Abstract: 3067; Brana I., ASCO 2013. Abstract: 5518).

As of 11 November 2018, approximately 863 patients have been exposed to AZD1775 in AstraZeneca-sponsored or Merck-sponsored clinical studies. In addition, approximately 706 patients have also received AZD1775 as part of externally-sponsored scientific research. Based on the safety data from the completed adavosertib clinical studies and preliminary data from ongoing studies adverse drug reactions to adavosertib monotherapy include: anemia, neutropenia and febrile neutropenia, thrombocytopenia, QTc prolongation, gastrointestinal events such as dyspepsia, diarrhea, nausea and vomiting (with or without dehydration or serum electrolyte decreases), as well as decreased appetite. In addition, the following events are also considered expected during treatment with adavosertib in combination with cytotoxic chemotherapy: febrile neutropenia, leukopenia, stomatitis, asthenia, fatigue, mucosal inflammation and myalgia. Based on information emerging during the clinical development programme of adavosertib, potential risks where a causal relationship with adavosertib monotherapy has not been established include asthenia/fatigue, gastrointestinal hemorrhage, lymphopenia/lymphocyte count decreased, leukopenia/WBC count decreased, myalgia, stomatitis, sepsis and transaminases elevation. In addition, the following events are also considered potential risks for adavosertib in combination with cytotoxic chemotherapy: pancytopenia.
Refer to the IB for adavosertib for information on the potential benefits and assessment of potential and known risks.

The single-dose maximum tolerated dose (MTD) in both gemcitabine and cisplatin combination therapy is 200 mg of AZD1775. Dose-limiting toxicities (DLTs) tended to be hematologic in the gemcitabine group and constitutional in the cisplatin group. The single-dose MTD in combination with carboplatin was 325 mg of AZD1775; DLTs in this group were related to serum chemistry. Similar DLTs have been observed in the multiple-dose chemotherapy combinations. These types of toxicities are not unexpected for therapies that include full-dose chemotherapy. Patients should therefore be closely monitored for signs of gastrointestinal (including diarrhea), hematologic, and laboratory toxicities and managed clinically with supportive care measures. Based on these studies and the current ongoing trial in ovarian cancer (NCI# NCT01357161), the recommended phase II dose is as follows: AZD1775 225 mg twice daily (BID) day 1 to day 3 (5 doses) plus carboplatin AUC5 every 21 days/paclitaxel 175 mg/m^2 for 6 cycles followed by maintenance AZD1775.

In Study PN001, 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.

No complete or PRs were observed in either of Studies PN005 or PN008 at the time that they were terminated.

Significance

SQCLC is an incurable disease, with current therapy producing a survival benefit, although it is small. In addition, there is no FDA-approved triplet combination in this patient population. It was demonstrated that carboplatin in combination with paclitaxel has significant clinical activity in this disease with an overall response rate of 26%. This is remarkable; however, 74% of patients do not respond. Therefore, it is important to develop combination therapies to improve the efficacy and to discover resistance mechanisms. One potential class of agents that could be used in combination with platinum chemotherapy is WEE1 inhibitors. As it is likely that combination therapies will need to be developed to produce significant effects, we thus propose to perform a phase II study in which the combination is evaluated.

As a single agent, AZD1775 has not been extensively studied in clinical trials. Carboplatin has significant activity in lung cancer due to its ability to create DNA adducts that lead to DNA damage and cytotoxicity. p53 mutant SQCLC may be more dependent on the G2/M checkpoint for correction of DNA damage. In the setting of DNA damage occurring though platinum-induced adducts, a medication such as a WEE1 inhibitor, which further prevents functionality of this checkpoint, may lead to enhanced effects. There have been trials extensively testing the combination of a WEE1 inhibitor plus platinum chemotherapy in SQCLC patients.

Innovation

The sensitivity and resistance mechanisms to AZD1775 in combination with platins are currently unknown. Several possibilities exist, including the expression of key regulators of the cell cycle. We will perform pre- and post-treatment tumor biopsies of the patients, which will allow us to characterize the biomarkers in the clinical responders and the nature of the resistance mechanisms in the clinical non-responders.

1.2 Research hypothesis

Hypothesis: In patients with p53-mutant SQCLC with high expression of G2/M checkpoint proteins WEE1 and PAXIP1 (defined as WEE1 and/or PAXIP1 positive), we expect to find that treatment with carboplatin-paclitaxel and AZD1775 will improve progression-free survival (PFS).

1.3 Rationale for conducting this study

Rationale

The overall 5-year survival for non-small-cell lung cancer (NSCLC), which is used as a benchmark for putative cure from this disease, is presently only 15%[10]. The majority of patients will present with late-stage disease. SQCLC represents the second most common type of NSCLC. The trial's rationale is based on the fact that standard of care in first-line treatment for patients with advanced-stage SQCLC is platinum doublet chemotherapy[11-13]. While the phase II trial by Johnson et al demonstrated that compared to carboplatin-paclitaxel, carboplatin-paclitaxel plus bevacizumab offered statistically significantly improved time to progression in chemo-naive NSCLC patients (n = 67; 4.2 vs. 7.4 months; *P* = 0.023; respectively), the majority of the major bleeding events including hemoptysis occurred in those patients with squamous histology. Based on these findings, the phase III trial excluded patients with SQCLC. Furthermore, complete responses are rare and eventual progression is inevitable in patients with advanced SQCLC. Hence, there is a great need for the development of newer agents and innovatively designed clinical trials to test these newer agents.

In the lab, AZD1775 is a powerful anticancer drug; clinical trials are underway. The identification of a key molecular event that determines the biological response of cells to WEE1 inhibitor treatment may help to identify clinically relevant PD markers to assess tumor sensitivity or resistance at the early stages of therapy. In NSCLC cell lines, we have demonstrated that cisplatin has exhibited enhanced effects in combination with the AZD1775 (a WEE1 inhibitor).

2. STUDY OBJECTIVES

2.1 Primary objective

Determine the progression-free survival of carboplatin-paclitaxel plus AZD1775 in patients with advanced/metastatic SQCLC.

2.2 Secondary objectives

1. Estimate time-to-event variables, such as overall survival time, duration of overall response, and duration of stable disease.

2. Estimate the disease control rates (complete response, partial response, and stable disease).

2.3 Exploratory objectives

1. Assess pharmacodynamic endpoints in tumor tissue.

   a. Determine the frequency of tissue biomarkers (including WEE1, PAXIP1, phospho-Y15-CDK1).

   b. Examine potential resistance mechanisms in the tumors of clinical non-responders.

c. Compare tissue biomarkers with clinical covariates and outcomes.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

Study Design

This is a multicenter-center phase II trial of carboplatin, paclitaxel, and AZD1775 in patients with advanced/metastatic SQCLC. Patients will be treated with carboplatin AUC5 and paclitaxel 175 mg/m^2 plus AZD1775 225 mg once daily for one day and twice daily for two days for a total of 5 doses over days 1-3. Each cycle will be 21 days (Table 1). The doses of carboplatin, paclitaxel, and AZD1775 are based on prior phase I studies of AZD1775 in patients with advanced solid tumors (Schellens et al, ASCO 2011, #3068; Leijen et al., ASCO 2010. Abstract: 3067; Brana, ASCO 2013, Abstract: 5518) and ongoing phase II studies in ovarian cancer. Following 6 cycles of treatment, patients will then go on to continue maintenance treatment with AZD1775. Treatment will continue until disease progression, intolerable toxicity, or withdrawal from study. Radiographic evaluation will occur on days 0 (baseline), 42, and every two cycles there after by CT. The data will be summarized as clinical response measured continuously. Toxicities will be evaluated according to CTCAE v.4 guidelines. Archival tumor will be collected for correlative studies. In addition, serial pre- and post-treatment tumor biopsies will be performed in a minimum of 7-10 patients.

Inclusion of Women and Minorities: Both men and women of all races and ethnic groups are eligible for this trial.

Safety: CTCAE v.4 will be used to monitor patients for safety and tolerability. Careful toxicity assessment will be performed with standard laboratory studies (CBC, BUN, creatinine, electrolytes, and LFTs) before each treatment. In addition, a medical history and physical examination will be performed before each cycle.

Patients will receive intravenous (IV) treatments in a clinical research unit or infusion center, which is staffed by nurses experienced in the management of infusion reactions and cytokine release syndrome. All SAEs with a determination of SAE-relatedness to the investigational therapy will be reported as described in the data and safety monitoring plan detailed in the protocol.

Efficacy: Radiographic assessments will be performed every 2 cycles and will be assessed by RECIST v1.1. Patients who are found to have stable disease (SD), partial response (PR), or complete response (CR) at re-staging after the initial 4-6 cycles will receive additional AZD1775 every 21 days until evidence of disease progression. More specifically, as per standard of care practice, for patients who are noted to have additional tumor regression following 4 cycles of treatment and are tolerating the triplet combination, then 2 additional cycles will be administered per treating physician/PI discretion. Response rate, overall survival, and progression-free survival will be determined.

Table 1. Study Calendar. All screening and on study visits, labs, procedures, and scans windows are +/- 7 days unless otherwise specified in the footnotes.

Intervention	Screening	C1 D1	C1 D2-D3	C1 D15	C2-6 D1	C2-6 D2-D3	C7 D1 and beyond	End of treatment [N]	30+/-14 days Post study follow-up[N]	Survial Follow up[O]
Informed Consent	X									
History and Physical (H&P), including weight and height[A;]	X	X			X		X	X	X	
CBC	X[B]	X			X		X	X	X[B]	
CMP[C]	X[B]	X			X		X	X	X[B]	
PT/INR[D]	X			X						
Urinalysis	X[B]	X			X		X	X	X	
Pregnancy Test[E]	X[B]	X			X		X	X	X	
Muga or ECHO	X[F]									
ECG	X	X		X	X		X	X	X	
CT chest/abdomen (tumor assessments)	X[G]				X[H]		X[H]	X	X	
ECOG PS[I]	X[B]	X			X		X	X	X	
Toxicity Assessments[J]	X[B]	X	X	X	X	X	X	X	X	
Magnesium, Phosphorus	X	X			X		X	X	X	
Archival Tissue Collection	X	X								
AZD1775[K]		X	X		X	X	X			
Carboplatin/Paclitaxel [K]		X			X					
Optional Tumor Biopsy	X[L]			X[M]						
Survival follow-up										X

[A] Interval H&P can be performed by the treating physician or APP in the Moffitt Clinical Research Unit or the Thoracic Clinic. A physician or APP H&P must be performed within 14 days of cycle 1, day 1. Physical exam will include weight and vital signs. Height will need to be collected at screening.

[B] CBC, CMP, ECG, ECOG PS, urinalysis, PS, and serum pregnancy test (only for women of child bearing potential) will be performed every 21 days on day 1+/- 7 days of every subsequent cycle as long as patients remains on study drug. Toxicity Assessments will be continuous measure that is collected throughout the patients time on study.

[C] CMP includes sodium, potassium, chloride, bicarbonate, BUN, Cr, glucose, calcium, total protein, albumin, AST, ALT, total bilirubin, and alkaline phosphatase.

[D] The coagulation profile includes a prothrombin time or International Normalized Ratio (INR), and activated partial thromboplastin time (for only those who will undergo a biopsy).

[E] Pregnancy test is indicated only for female patients of child bearing age who are premenopausal. There must be negative serum pregnancy test within 72 hours prior to first study dose in all WOCBP.

[F] A baseline Echo or MUGA scans will be completed on or prior to C1D1. Results must be known prior to dosing the patient.

[G] Tumor measurements must occur no more than 30 days prior to starting the trial.

[H] To be completed on day 1 cycle 3 +/-7 days and then every other cycle +/- 7 days. After completing cycles of therapy, CT imaging will occur every 3 cycles. [EG:For those patients where shifts in the window do not occur, CT

scans will occur on: D1C3 (after 6 weeks), D1C5 (after 12 weeks), D1C7 (after 18 weeks), D1C10 (after 27 weeks), D1C13 (after 36 weeks), D1C16 (after 45 weeks) and so forth.]

[I] ECOG Performance status will be collected at time of physical exams.

[J] Toxicity will be measured against the Common Terminology Criteria for Adverse Events 4.0. SAE collection will initiate at time of consent while AE collection will initiate on C1D1 per section 6.4. Toxicity assessments will be a continuous measurement. On days 2-3 of each cycle, toxicity assessment details will be collected by patient documenting on pill diary. A specific visit is not required.

[K] The X in the study calendar implies agent dosing. Carboplatin AUC5 and paclitaxel 175 mg/m^2 plus AZD1775 225 mg once daily for 1 day and twice daily for two days for a total of 5 doses over days 1-3 every 21 days for 4-6 cycles followed by maintenance AZD1775 every 21 days.

[L] Pre-treatment tumor biopsy will be performed anytime within 30 days of beginning cycle 1 day 1 +/-7 days.

[M] Post-treatment tumor biopsy will be obtained on cycle 1 day 15+/-7 days.

[N] Patients are allowed to continue treatment until disease progression, until the patient is discontinued due to unacceptable toxicity, or until a decision to discontinue treatment by the patient or investigator. After withdrawal from or completion of protocol treatment, patients must be followed for any new AEs for 30 calendar days after the last dose of study drug or until initiation of new therapy, whichever occurs first. The 30- D a y Post Study Follow-Up visit will be performed 30 days (+/- 14 days) from last treatment dose.

[O] Patients will be followed every 3 months (±2 weeks) from the last disease assessment of response until death or until the study is terminated. Patients without disease progression at the time of study drug discontinuation should have CT Scan (if applicable) repeated at follow-up visits until disease progression has been observed OR until initiation of a subsequent line of systemic cancer therapy. Survival Follow-up visits will occur to collect survival status (e.g., date and cause of death), an information pertaining to the type and date of any post-study alternative cancer therapy administered. Patients may be contacted during outpatient visits or by telephone or the data can be collected from the electronic medical (if available.

4. SUBJECT SELECTION CRITERIA

All inclusion and exclusion criteria will be assessed within 28 days before initiation of therapy with the exception of radiographic studies. All eligibility criteria must be met prior to enrolling a subject. The study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH), WHO and any local directives and in compliance with the protocol. This clinical study will require IRB and IND approval. Informed consent will be obtained from each patient enrolled onto the study.

4.1 Inclusion criteria

For inclusion in the study, subjects should fulfill the following criteria:

1. Provision of informed consent prior to any study specific procedures.

2. Histologic or cytological diagnosis of SQCLC with advanced/metastatic stage, with no known curative treatment options. *Prior platinum-containing adjuvant, neoadjuvant, or definitive chemoradiation therapy given for locally advanced disease is considered first line therapy only if recurrent (local or metastatic) disease developed within 6 months of completing therapy. Subjects with recurrent disease > 6 months from completion on chemotherapy will be eligible.*

3. Female or male aged ≥18 years.

4. ECOG performance status of 0/1.

5. Prior chemotherapy in the adjuvant/neoadjuvant/consolidation setting is allowed.

6. Any prior palliative radiation must have been completed at least 7 days prior to the start of studies drugs and patients must have recovered from any acute adverse effects prior to the start of the study treatment.

7. Prior Immunotherapy with PD1i, PDL1i, anti-CTLA-4 or vaccines is allowed.

8. Patients must have normal organ and marrow function as defined below:

a) leukocytes	≥3,000/μL
b) absolute neutrophil count	≥1,000/μL
c) platelets	≥100,000/μL
d) total bilirubin	≤ 1.5 X normal institutional limits (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)
e) AST(SGOT)/ALT(SGPT)	≤ 2.5 X institutional upper limit of normal,
or	
	≤ 5 X institutional upper limit of normal for patients with liver metastases.
f) creatinine	≤ 2.0

9. Have archival tissue available or undergo a fresh biopsy where clinically feasible after discussion with the sponsor.

10. No reproductive toxicology nor teratogenic studies have been conducted with AZD1775 to date, and it is unknown whether the drug is excreted in human milk. Therefore, women of childbearing potential and men should agree to use adequate contraception prior to study entry and for the duration of study participation and women who are breast feeding are excluded from the study. Both women and men should be fully informed of the lack of reproductive toxicity testing, and women must have a negative pregnancy test prior to enrolment.

    Female patients are considered to be of childbearing potential unless:

    - they are post-menopausal (defined as older than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments),

    - there is documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy (but not tubal ligation), or

- they are 50 years or younger but have been amenorrhoeic for at least 12 months following the cessation of exogenous hormonal treatments and have serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels in the postmenopausal range for the institution.

Female patients who are of childbearing potential must agree to use adequate contraceptive measures (as defined below) for the duration of study participation, and for 90 days after the final dose of study drug; cessation of birth control after this point should be discussed with a responsible physician. They also may not be breast feeding and must have a negative serum or urine pregnancy test within 72 hours prior to start of study treatment.

Male patients who are sexually active with a female partner of childbearing potential must be either surgically sterilized or agree to use barrier contraception (i.e., condoms) for the duration of study participation, and for 90 days after the final dose of study drug; cessation of birth control after this point should be discussed with a responsible physician.

Female patients who are of child-bearing potential (as defined above) should use enhanced methods of contraception from the time of screening until 90 days after the final dose of study drug; cessation of birth control after this point should be discussed with a responsible physician. Acceptable methods of contraception include true abstinence in line with the preferred and usual lifestyle choice of the subject, tubal ligation, vasectomized partner, and methods listed in the table below. All methods of contraception (with the exception of total abstinence) should be used in combination with the use of a condom by their male sexual partner for intercourse. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

Effective Methods of Contraception

Barrier Methods	Intrauterine Device Methods	Hormonal Methods
• Cap plus spermicide • Sponge plus spermicide • Diaphragm plus spermicide	• Copper T • Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	Any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents) such as • Implants • Hormone shot or injection • Combined pill • Minipill • Patch

a This is also considered a hormonal method.

Male patients should be asked to avoid unprotected sex with all sexual partners but use condoms plus spermicide during the study, and for a washout period of 90 days after the last dose of study drug. Where a sexual partner of a male participant is a woman of child-bearing potential, patients should avoid procreation for 90 days after completion of study drug treatment. Patients should refrain from donating sperm from the start of dosing until 90 days after discontinuing study treatment. If male patients wish to father children they should be advised to arrange for freezing of sperm samples prior to the start of study treatment.

4.2 Exclusion criteria

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

1. Progressive, symptomatic untreated brain metastases.

2. Pregnancy or breast feeding.

3. A serious uncontrolled medical disorder or active infection that in the investigator's opinion would impair the patient's ability to receive study treatment.

4. Prior use of platinum or paclitaxel for stage IV NSCLC or concurrent use of other anticancer approved or investigational agents.

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

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

7. Grade >1 toxicity from prior therapy EXCEPT: Alopecia, anorexia, and/or endocrinopathies on replacement therapy.

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

9. Patients with known Hepatitis B or C or HIV infection.

10. Second primary malignancy, other than in situ malignancies or adequately treated basal cell carcinoma of the skin or other malignancy treated at least 2 years previously with no evidence of recurrence.

11. Any of the following cardiac diseases currently or within the last 6 months: unstable angina pectoris, acute myocardial infarction, congestive heart failure ≥ Class 2 (as defined by New York Heart Association (NYHA)), 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.)

12. Patient has had prescription or non-prescription drugs or other products (i.e., grapefruit juice) known to be sensitive to CYP3A4 substrates or CYP3A4 substrates with a narrow therapeutic index, or to be moderate to strong inhibitors or inducers of CYP3A4, which cannot be discontinued 2 weeks before Day 1 of dosing and withheld throughout the study until 2 weeks after the last dose of study drug (See Appendix A).

13. Co-administration of aprepitant and fosaprepitant during this study is prohibited (See Appendix A).

14. AZD1775 is an inhibitor of breast cancer resistance protein (BCRP). The use of statins including Atorvastatin which are substrates for BCRP are therefore prohibited and patients should be moved on to non-BCRP alternatives (See Appendix A).

15. Herbal preparations 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 (See Appendix A).

16. History of Torsades de pointes unless all risk factors that contributed to Torsades have been corrected.

17. Mean resting corrected QTc interval using the Fridericia formula (QTcF) >450 msec/male and >470 msec/female (as calculated per institutional standards) obtained from 1 electrocardiogram (ECGs).

5. STUDY CONDUCT

5.1 Subject enrollment and initiation of investigational product

After screening patient will be treated with AZD1775 PO in combination with IV carboplatin and paclitaxel every 3 weeks for 4-6 cycles at the discretion of the treating physician. Patients will be treated with carboplatin AUC5 and paclitaxel 175 mg/m^2 plus AZD1775 225 mg once daily for one day and twice daily for two days for a total of 5 doses over days 1-3. Following 4-6 cycles of treatment, AZD1775 will be continued for 5 doses over Days 1-3 for each subsequent cycle until disease progression, study withdrawal, or intolerance. The carboplatin and paclitaxel will be administered in the CRU or Infusion center and AZD1775 will be distributed to the patient by the investigational pharmacy.

5.2 Procedures for handling subjects incorrectly enrolled

Any patient identified to be incorrectly enrolled will be counted as a screen failure and be replaced. Any patients falling into this category may continue on treatment as long as there is no evidence of progressive disease by RECIST v 1.1 or evidence of intolerance. Patients will be allowed to re-screen.

5.3 Treatments

5.3.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Supplied by
AZD1775	225mg	AstraZeneca

Non-Investigational products	Dosage form and strength	Supplied by
Carboplatin*	AUC 5	Standard of Care
Paclitaxel*	175 mg/m2	Standard of Care

*Premedications are according to the institutional standards on Day 1 of each 21-day cycle. Chemotherapy will be infused per Institutional standards.

5.3.2 Doses and treatment regimens

Patient will receive AZD1775 225 mg once daily for one day and twice daily for two days for a total of 5 doses over days 1-3. AZD1775 will be administered

concomitantly with the Day 1 infusion of paclitaxel +carboplatin, followed by four additional doses of AZD1775 to be taken in approximate 12-hour intervals (BID for a total of 5 doses).

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 unless contraindicated or not well-tolerated. Dexamethasone or the 5-HT3 antagonist may be given by IV.
Please note: aprepitant [Emend] and fosaprepitant are not permitted due to known DDIs.

Due to frequent reports of diarrhea with AZD1775 administration, vigorous anti-diarrheal treatment loperamide (Imodium) is required at the first onset of diarrhea according to American Society of Clinical Oncology (ASCO) guidelines. Patients should be instructed to take oral loperamide (Imodium) 2 mg every 2 hours until diarrhea-free for at least 12 hours. Patients should be instructed to notify the Investigator or research staff for the occurrence of blood or black stools, symptoms of dehydration, fever, inability to take liquids by mouth, and inability to control diarrhea within 24 hours of using loperamide or other prescribed antidiarrheal medications.

If the patient misses a dose of AZD1775, the patient should take the dose as soon as possible, but not more than 6 hours after the missed scheduled dose, 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 the patient takes the AZD1775, the patient should be instructed not to retake the dose, but to wait until the next scheduled dose of AZD1775. If vomiting persists, the patient should contact the Investigator.

5.3.3 Labeling and storage

Investigational drugs are properly labeled as provided by AstraZeneca at all times and properly stored according to the supplier's recommendations. They are administered only upon written order of the authorized principal investigator, or his/her designee, who must be a member of the medical staff. All investigational drug supplies for patient use are kept in the pharmacy. Each drug is stored separately for each protocol. The pharmacy maintains a separate Drug Accountability Record Form, which reflects drug supply for each investigational agent and protocol. The form contains all of the necessary information regarding the disposition of the drug and the storage site. Other drug documentation (e.g., receipt of drug, internal transfers, returns, broken vials, etc.) is recorded on this form.

5.4 Concomitant and post-study treatment(s)

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.

5.4.1 The following treatments are prohibited while in this study (for a full list, see Appendix "A")

Prescription and non-prescription agents known to be moderate to strong inhibitors/inducers of CYP3A4 or sensitive CYP3A4 substrates or substrates of CYP3A4 with a narrow therapeutic window that cannot be discontinued 2 weeks before first dose of AZD1775 and withheld throughout the study until 2 weeks after the last dose of AZD1775 are prohibited. The use of grapefruit juice is prohibited 2 weeks prior to, during the study, and 2 weeks after the last dose of AZD1775.

– Strong Inhibitors of CYP3A4 include: azole antifungals (ketoconazole, fluconazole, voriconazole, and itraconazole), macrolide antibiotics (clarithromycin and erythromycin), calcium channel blockers, HIV protease inhibitors (indinavir, nelfinavir, and ritonavir), and cimetidine, aprepitant, and nefazodone.

– Inducers of CYP3A4: phenytoin, barbiturates, and rifampicin

– Substrates of CYP3A4: statins (lovastatin, simvastatin), midazolam, terfenadine, astemizole, and cisapride

Refer to Appendix "A" for a list of inhibitors, inducers and substrates of CYP3A4. Supportive care with a CYP3A4 inhibitor/inducer/substrate according to institutional guidelines in the context of standard of care chemotherapy will be exempt; however, concomitant treatment with aprepitant is not allowable per protocol. See AZD1775 IB for additional information.

• In vitro data suggest 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; please refer to Appendix A for a list of sensitive substrates of CYP2C19, or substrates of this enzyme with narrow therapeutic range.

• In vitro studies have shown that AZD1775 may be a substrate and inhibitor for human P-glycoprotein (P-gp). Caution should be exercised when inhibitors or substrates of P-gP are administered with AZD1775.

• Use of metformin is prohibited in this study as recent in vitro transporter data have shown that 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.

- Aprepitant or Fosaprepitant use is prohibited in this study. 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 ~40% 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. Therefore, concomitant treatment with aprepitant is not allowable per protocol until further evaluation. See AZD1775 Investigator's Brochure for more information.

• Atorvastatin use is prohibited in this study. 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. Modeling has predicted a substantial increase in the exposure of atorvastatin when coadministered with AZD1775, and the use of atorvastatin is therefore prohibited in the current study. Other drugs where the disposition is mediated via BCRP should be administered with caution, with dose modification considered or substituted by an alternative drug.

• 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 before first dose of AZD1775.

• AZD1775 has been shown to be a weak inducer of CYP1A2 in vitro. Taking into account the anticipated plasma concentrations (Cmax<1.5 μM) and the intermittent 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.

• Caution must be exercised with the concomitant use of aminoglycosides in keeping with the treatment guidelines for carboplatin.

• Paclitaxel is metabolized by CYP2C8 (mainly) and CYP3A4. Appendix D provides a list of CYP2C8 inhibitors that should be excluded as concomitant medications. This list is not all-inclusive, and for other concomitant medications, the Investigator and AstraZeneca will determine if they are known to significantly influence CYP2C8.

In addition, Investigators should look at a frequently updated drug reference such as Lexicomp to see if any medicine they want to prescribe is on a list of drugs to avoid.

5.4.2 Growth factors for neutrophils or RBCs used in accordance with established guidelines are allowed.

5.4.3 Palliative (limited-field) radiation therapy is permitted, if all of the following criteria are met:

1. Repeat imaging demonstrates no new sites of bone metastases.
2. The lesion being considered for palliative radiation is not a target lesion.

5.5 Dose Modifications

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 and chemotherapy will be allowed. Patients requiring >2 dose reductions of these drugs will be discontinued from the study drug and chemotherapy.

Brief treatment or visit delays (±7 days) for public holidays or weather conditions do not constitute a protocol violation but should be recorded in the electronic case report form (eCRF).

Any patient requiring a toxicity-related dose delay of more than 28 days from the intended day of the next scheduled dose must be discontinued from the study unless there is approval from the Study PI for the patient to continue.

The AZD1775 and chemotherapy dose level reductions are presented in **Table 2**.
The hematologic and non-hematologic Dose modifications and guidelines are as presented in **Tables 3-5**.

Table 2. AZD1775, Carboplatin and Paclitaxel Dose Level Reductions for Toxicity

Agent	**Starting Dose Level (DL)**	**DL-1**	**DL-2**
AZD1775	225 mg BID (5 doses over 2.5 days)	175mg BID (5 doses over 2.5 days)	125 mg BID (5 doses over 2.5 days)
Paclitaxel	175 mg/m2	150 mg/m2	125mg/m2
Carboplatin	AUC 5	AUC 4	AUC 3.5

Dose modification due to hematological toxicity
Complete blood counts (CBC) will be obtained for all patients at the beginning of each treatment cycle (Day 1). If hematologic toxicity occurs (see **Table 3**), treatment should be held and ANC and platelets should be monitored weekly until recovery. However, if the investigator determines that the hematologic toxicity was due to one study drug and not the other, treatment with the remaining study drug may continue as clinically appropriate or dose reductions can be done solely for the agent that is felt to be the cause of the AE. This should be clearly documented in the EMR.

Table 3. Day 1 Hematologic Dose Modifications and Management

Treatment Day Blood Counts and Toxicity			
ANC		**Platelets**	**Action**
≥1500/µL	And	≥75,000/µL	No dose modification or interruption
<1500/µL	Or	<75,000/µL	Delay by 1 week intervals until recovery[a]

a If hematologic parameters do not recover within 28 days, the patient should be removed from the study treatment.

Table 4. Neutropenia, Infection, Febrile Neutropenia Dose Modifications and Management

Grade 3 neutropenic fever (ANC <1000/µL +Temperature ≥101°F [38.5°C]) or neutropenic Infection **Documented infection with Grade 3 neutropenia** (ANC <1000/µL) **Grade 4 neutropenia** (ANC <500/µL >7 days **Grade 4 thrombocytopenia** (platelet count <25,000/µL >7 days)	Hold dose[b] until recovery. Then, upon resuming dosing, reduce paclitaxel or carboplatin, and AZD1775 to the next lower dose level[a].
Grade 4 febrile neutropenia or Grade 4 infection with neutropenia (both defined as septic shock) **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 patients. Patients requiring additional dose modifications due to toxicity will discontinue study treatment.
b Hold chemotherapy dose until hematologic parameters recover to adequate levels (i.e., ANC ≥1000/µL platelets ≥75,000/µL). If hematologic parameters have not recovered within 28 days, the patient will be removed from the study treatment.

Non-hematologic toxicity dose modifications

Dose modifications for non-hematologic toxicities should be based on toxicities occurring during the previous cycle. For toxicities that lead to a dose reduction, the dose will not be reescalated during subsequent cycles. Any patient who develops a Grade 3 or 4 nonhematologic toxicity, that does not resolve to ≤ Grade 1 within 28 days should be removed from the study treatment. However, if the investigator determines that the nonhematologic toxicity was due to one study drug and not the other, treatment with the remaining study drug may continue as clinically appropriate or dose reductions can be done solely for the agent that is felt to be the cause of the AE. This should be clearly documented in the EMR.

Based upon the maximum non-hematologic toxicities experienced during the previous cycle, dose adjustments for subsequent cycles are to be made according to the criteria defined in **Table 5** (unless specified per unique toxicities as noted below):

Table 5. Non-Hematologic Toxicity Dose Modification and Management

CTCAE v4.03	Paclitaxel	Carboplatin	AZD1775
Grade 0 - 2	No dose modification	No dose modification	No dose modification
Grade 3 [b,c,d]	Hold[a]	Hold[a]	Hold[a]
Grade 4[b]	Hold until toxicity resolves to Grade ≤1. Resume with 1 dose level reduction	Hold until toxicity resolves to Grade ≤1. Resume with 1 dose level reduction	Hold until toxicity resolves to Grade ≤1. Resume with 1 dose level reduction
Second repeat incidence of Grade 3 or 4 toxicity (except nausea, vomiting, fatigue, malaise, lethargy, anorexia, alopecia)	Discontinue treatment	Discontinue treatment	Discontinue treatment
Hepatic			
Grade 1-2	No dose modification	No dose modification	No dose modification
Grade 3 or 4 (manifested as elevations in ALT, AST, ALP or bilirubin)	Hold until resolves to Grade ≤1 or baseline, then resume paclitaxel with a 1 level dose reduction. If not resolved within 28 days discontinue paclitaxel.	Hold until resolves to Grade ≤1 or baseline, then resume carboplatin with a 1 level dose reduction. If not resolved within 28 days discontinue carboplatin.	Hold until resolves to Grade ≤1 or baseline, then resume study drug with a 1 level dose reduction. If not resolved within 28 days discontinue study drug.
Diarrhea or Mucositis			
Grade 3 or 4 (or requiring hospitalization)	Hold[a]	Hold[a]	Hold[a]
Renal			
Grade ≥ 2	Hold until resolves to Grade ≤1 or baseline, then resume	Hold until resolves to Grade ≤1 or baseline, then resume	Hold[a]

	paclitaxel with a 1 level dose reduction. If not resolved within 28 days discontinue paclitaxel or reduce 1 dose level. If AE reoccurs after 1 dose level reduction, reduce a second dose level once AE recovers to Grade ≤1.	carboplatin with a 1 level dose reduction. If not resolved within 28 days discontinue carboplatin.	
Neurotoxicity			
Grade 1	No dose modification	No dose modification	No dose modification
Grade 2	Hold until toxicity resolves to Grade ≤1. Resume with 1 dose level reduction.	Hold until toxicity resolves to Grade ≤1. Resume with 1 dose level reduction.	No dose modification
Grade 3 or 4	Discontinue treatment	Discontinue treatment	Discontinue treatment

a Hold until toxicity resolves to ≤ Grade 1, and then resumed at the same dose with no modification.
b Dose reduction for nausea and vomiting should be made only if Grade 3 or Grade 4 toxicity occurs in spite of maximum anti-emetics.
c For a Grade 3 pulmonary embolism, the dose should be held but the subsequent doses do not have to be reduced 1 dose level, at the Investigator's discretion.
d Grade 3 electrolyte value(s) (i.e., hypokalaemia), do not require a dose reduction once the electrolyte is ≤ Grade 1.

Non-hematologic toxicity management guidelines

5.5.1 Diarrhea

Patients should be instructed to notify the Investigator or research staff for the occurrence of blood or black stools, symptoms of dehydration, fever, inability to take liquids by mouth, and inability to control diarrhea within 24 hours of using loperamide or other prescribed antidiarrheal medications.

In the event of Grade 3 or 4 diarrhea, the following supportive measures are recommended: hydration and anti-diarrheals. If diarrhea is severe (i.e., requiring IV rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patient with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be hospitalized for IV hydration and correction of electrolyte imbalances.

5.5.2 Nausea and vomiting Anti-emetic therapy (excluding aprepitant [Emend] or fosaprepitant) may be used in accordance with standard practice and/or the discretion of the investigator.

5.5.3 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.

5.5.4 Motor neuropathy or muscle weakness

Any onset of > Grade 2 motor neuropathy or > Grade 2 muscle weakness should be evaluated by an electromyogram to rule out the possibility of chronic inflammatory demyelinating polyneuropathy (CIDP). With a diagnosis of CIDP the patient should be discontinued from study treatment.

5.5.5 Dose modifications for infusion reactions

Infusion reactions (e.g. rash, urticaria, erythema, pruritus, bronchospasm, and hypotension) can occur with the agents used in this study. There is increased risk of a reaction with carboplatin and paclitaxel. Carboplatin must be discontinued in patients experiencing a Grade 3 or 4 infusion reaction during treatment.

To identify the grade of a reaction, refer to the list below adapted for the General Disorders and Administration Site Conditions section of the NCI CTCAE v4.03:

- Grade 1: Mild transient reaction; infusion interruption not indicated; intervention not indicated.
- Grade 2: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids indicated for ≤24 hours).
- Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic mediation and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae. Note: any infusion that is interrupted and not resumed within the visit will be considered a Grade 3 reaction.
- Grade 4: Life-threatening consequences; urgent intervention indicated.

5.6 Treatment compliance

Patients participating in this study will be expected to be compliant with the medications and study schedule.

5.6.1 Accountability

Patient compliance will be monitored by pill diaries.

5.7 Discontinuation of investigational product

In the absence of treatment delays due to adverse event(s), treatment may continue for the time described above or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,

- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.8 Withdrawal from study

Patients can withdraw from the study or from further treatments at any time. Clarifications should be made with the patient whether they wish to withdraw from the study or from further treatment. The reason for study or treatment withdrawal and the date the patient was removed must be documented in the Case Report Form.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

Research data are kept in a secure database with limited access and through OnCore (a Web-based, password-protected database), with privacy protected to the full extent of the law. Authorized research investigators, the Department of Health and Human Services, and the Institutional Review Board may inspect the records. Final approvals have been obtained from the IRB. Additional protection is provided through the data safety and monitoring plan described below.

6.2 Data collection at enrollment and follow-up

6.2.1 Enrollment procedures

Informed consent must be obtained before any testing to determine a patient's eligibility. Once a patient is enrolled in the study, he/she will be assigned a simple 2 or 3 digit number, with the first patient assigned to 01 and so on. A separate spreadsheet with password protection will be maintained that contains the patient's study number along with personally identifiable information. Password protection will be maintained in order to keep patient information strictly confidential. Upon signing the informed consent form, the patient will be assigned a subject number by the investigator or his/her designee. Once assigned to a patient, a subject number will not be reused. If the patient fails to be started on treatment for any reason, the reason for not being started on treatment will be entered on the Screening Log CRF, and his/her demographic information will be captured in the OnCore system. All laboratory, radiologic, and pathologic data collected on trial participants will be assigned the unique treatment number and stored in a separate database (OnCore).

For external sites only

All subjects must be registered with the External Site Coordination (ESC) office to be able to participate in a trial. The participating site must fax or email the completed study specific eligibility checklist and registration forms, supporting documents and signed informed consent to the Coordinating Center. Unsigned or incomplete forms will be returned to the site. Once documents are received, the ESC Research Coordinator will review them to confirm eligibility and to complete the registration process. If eligibility cannot be confirmed, the research coordinator will query the site for clarification or additional documents as needed. Subjects failing to meet all study eligibility requirements will not be registered and will be unable to participate in the trial.

Upon completion of registration, the ESC Research Coordinator will provide the participating site with the study sequence number and randomization information, if indicated. Within 24-48 hours after registration, it is the site's responsibility to:

- Enter the demographic and on-study patient information into the Oncore database
- Order investigational agent(s) if indicated per protocol

It is the responsibility of the participating Investigator or designee to inform the subject of the research treatment plan and to conduct the study in compliance with the protocol as agreed upon with Moffitt Cancer Center and approved by the site's IRB.

To register a patient send the completed signed eligibility checklist along with the patient registration form and supporting documentation to the ESC via email at affiliate.research@moffitt.org or via fax at 813-745-5666, Monday through Friday between 8:00AM and 5:00PM (EST).

6.2.2 Follow-up procedures

Patients will be followed for 30 days after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

6.2.3 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 4.3 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6.3 Efficacy

In addition to a baseline scan, confirmatory scans should also be obtained 4-6 weeks following initial documentation of objective response. Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)[14]. Changes in the largest diameter

(unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used [15].

6.3.1 Disease Parameters

- *Measurable disease*. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). **Note:** Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it is appropriate to include them, only lesions that have clearly shown disease progression since prior irradiation will be considered or allowed.
- *Malignant lymph nodes*. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.
- *Non-measurable disease*. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable. **Note:** Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. “Cystic lesions” thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.
- *Target lesions.* All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as *target lesions* and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, 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. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.
- *Non-target lesions*. All other lesions (or disease sites) including any measurable lesions over the 5 target lesions, should be identified as *non-target lesions* and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

6.3.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- *Clinical lesions:* Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- *Chest x-ray:* Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- *Conventional CT and MRI:* This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans). Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI that greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, 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. It is beyond the scope of the RECIST guidelines 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.

6.3.3 Response Criteria

6.3.3.1 Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of the 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 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

6.3.3.2 Evaluation of Non-Target Lesions

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis). **Note:** If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.
- Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

6.3.3.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 2. For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*

CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 3. For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated

Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

6.3.4 Progression-Free Survival

Progression free survival (PFS) is defined as the time from start of treatment (Cycle 1, Day 1) until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anti-cancer therapy before progression. Clinical deterioration in the absence of radiographic evidence is not considered progression for purposes of determining PFS. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date they were first treated. Subjects who started any palliative local therapy or subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the palliative local therapy or subsequent anti-cancer therapy, whichever procedure occurred first.

The PFS time will always be derived based on scan/assessment dates not visit dates.

RECIST version 1.1 assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- Date of progression will be determined based on the earliest of the dates of the component that triggered the progression
- When censoring a patient for PFS the patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

6.3.5 Duration of Response

- Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented. If a patient does not progress following a response, then their duration of response will use the PFS censoring time.
- Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

6.3.6 Objective Response Rate

ORR is defined as the number of subjects whose best confirmed objective response (BOR) is a CR or PR, divided by the number of subjects who received at least one dose. BOR is defined as the best response designation, as determined by the RECIST v1.1, recorded between baseline and the date of objectively documented progression per RECIST 1.1 or the date of initiation of palliative local therapy or the date of initiation of subsequent anticancer therapy, whichever occurs first. For subjects without documented progression or palliative local therapy or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination. The final analysis of ORR will take place at the time of PFS analysis.

6.3.7 Overall Survival

OS is defined as the duration of time from the date for first treatment (Cycle 1 Day 1) to the date of death. A subject who has not died will be censored at last known date alive.

6.3.8 Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements can be made at an assessment, the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not have changed the assigned time-point response.

6.4 Safety

6.4.1 Definition of adverse events

An adverse event 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). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-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. SAE collection will initiate at time of consent while AE collection will initiate on C1D1.

Death as a result of disease progression is only to be assessed as efficacy measures and not as AEs or SAEs.

Adverse events will be assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0. CTCAE v4.0 can be accessed on the NIH/NCI website at http://ctep.cancer.gov/forms/CTCAEv4.pdfhttp://ctep.cancer.gov/forms/CTCAEv4.pdf.

CTCAE grade 5 (death) will not be used in this study; rather, this information will be collected in the End of Treatment or Survival Information CRF page. Adverse event monitoring should be continued for at least 4 weeks following the last dose of study treatment.

Adverse events (but not serious adverse events) occurring before starting study treatment but after signing the informed consent form are recorded on the Medical History/Current Medical Conditions Electronic Case Report Form (OnCore). Abnormal Lab values, vital signs or test results that do not induce clinical signs/symptoms or require therapy will not be considered clinically significant and will not be reported as Adverse Events. In addition, isolated abnormal laboratory values that are considered clinically significant (e.g., cause study discontinuation or constitutes in and of itself a Serious Adverse Event) should be recorded on the Adverse Events CRF. SAEs occurring after initiation of treatment are recorded on the Adverse Event CRF.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE grade 1-4)
2. Its relationship to AZD1775 (suspected/not suspected)
3. Its duration (start and end dates or if continuing at final exam)
4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

6.4.2 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- 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

- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

6.4.3 Recording of adverse events

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- 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

Description of AE
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 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Adverse Events based on signs and symptoms
When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events based on examinations and tests
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., anemia versus low hemoglobin 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.

Procedure for serious adverse event reporting

The conduct of the study will comply with all FDA, sponsor and IRB safety reporting requirements.

All serious adverse experience reports must include the patient number, age, sex, weight, severity of reaction (mild, moderate, severe), relationship to study drug (definitely related, probably related, possibly related, unlikely related, unrelated), date of administration of test medications and all concomitant medications, and medical treatment provided. A MedWatch Form 3500A will be used. The reports will include the appropriate HLMCC PMC, IRB, and FDA IND protocol reference numbers.

The Principal Investigator is responsible for evaluating all adverse events to determine whether criteria for “serious” and “unexpected” as defined above are present. All Serious Adverse Events regardless of cause will be entered into the H. Lee Moffitt Cancer Center & Research Institute research database (OnCore) and will be reported to the Moffitt Protocol Monitoring Committee (PMC).

All SAEs will be reported to HLMCC PMC, IRB, and FDA as per their requirements.

6.5 Instructions for Rapid Notification of Serious Adverse Events

Information about all adverse events, whether volunteered by the subject, discovered by the investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate. An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug (or therapy) even if the event is not considered to be related to study drug (or therapy). Study drug (or therapy) includes the drug (or therapy) under evaluation, and any reference or placebo drug (or therapy) given during any phase of the trial.

- If it is unclear what study treatment includes, list all drug(s), other therapies, changes to existing therapy, diagnostic procedure, etc. that are specified by the protocol

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events occurring starting after study treatment are recorded. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy and are recorded.

Information about all serious adverse events will be collected and recorded on the FDA MedWatch 3500a form. To ensure patient safety, each serious adverse event must also be reported to AstraZeneca within 24 hours of learning of its occurrence. A serious adverse event is an undesirable sign, symptom, or medical condition that:

1. is fatal or life-threatening
2. required or prolonged hospitalization
3. results in persistent or significant disability/incapacity
4. constitutes a congenital anomaly or a birth defect
5. is medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Events not considered to be serious adverse events are hospitalizations for the:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

Pregnancy, although not itself a serious adverse event, should also be reported on a serious adverse event form or pregnancy form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

Any serious adverse event occurring after the patient has provided informed consent, has started taking the study medication, and until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g., treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication). The period after discontinuing study drug may be extended if there is a strong suspicion that the drug has not yet been eliminated.

6.5.1 Instructions for rapid notification of serious adverse events

Reporting responsibility

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and AstraZeneca.

Reporting of serious adverse events

For External Sites

Information about all serious adverse events will be collected and recorded. To ensure patient safety, each serious adverse event must be reported to the PI and to the sponsor

expeditiously. Moffitt Cancer Center and all participating sites will report SAEs by completing an SAE report in OnCore, the electronic data capture system. The SAE must be reported by email (affiliate.research@moffitt.org) to the External Site Coordination (ESC) office within 2 working days. If applicable, the site should also follow protocol guidelines for additional reporting to government agencies. See Below.

All Sites Safety Reporting

Investigators and other site personnel must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AstraZeneca. A copy of the MedWatch/AdEERs report must be faxed or emailed to AstraZeneca via the AstraZeneca database at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

When reporting to AstraZeneca, a cover page should accompany the MedWatch/AdEERs form indicating the following:

- Investigator Sponsored Study (ISS)
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number

Investigative site must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator.

Send SAE report and accompanying cover page by way of Email to AEMailboxClinicalTrialTCS@astrazeneca.com ***or by fax to AstraZeneca's designated fax line: US: 302-886-4114, ex-US +46 31 776 37 34***

Serious adverse events that do not require expedited reporting to the FDA need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events.

All SAEs have to be reported to AstraZeneca, whether or not considered causally related to the investigational product. All SAEs will be documented. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

7. DATA SAFETY MONITORING PLAN

7.1 Data Monitoring Board

7.1.1 Risk to Subjects

7.1.1.1 Human Subject Involvement and Characteristics

Human subjects who have the diagnosis of advanced SQCLC are eligible to participate in the clinical trial described in this proposal. The risk to subjects will be outlined clearly and in detail in the informed consent. Women who are pregnant are not eligible.

7.1.2 Adequacy of Protection Against Risk

7.1.2.1 Recruitment and Informed Consent

Patients who present to the Thoracic Oncology Program at the Moffitt Cancer Center who have advanced SQCLC are offered participation in the clinical trial described in this proposal. The trial is explained in detail to the patients by one of the physician co-investigators on the trial, the patients are given the opportunity to read the informed consent document, they are given a chance to ask questions, and finally they sign the informed consent document in the presence of a witness. The physician who participates in the informed consent process also documents, in a clinic note, the nature of the consent process that occurred.

7.1.2.2 Protection Against Risk

To protect participants from excess risk, the above-mentioned study procedures and dose-escalation scheme were instituted. Additional protection is provided through the data safety and monitoring plan described below. The complete care of each patient, including the clinical management of all toxicities, are provided to the patient by physicians at the Moffitt Cancer Center. The clinical data are kept in the patient's individual Moffitt Cancer Center hospital record. Research data are kept in a locked room with limited access and through OnCore (a Web-based, password-protected database), with privacy protected to the full extent of the law. Authorized research investigators, the Department of Health and Human Services, and the Institutional Review Board may inspect the records. Final approvals have been obtained from the IRB.

Additional protection is provided through the data safety and monitoring plan described below.

7.1.3 Importance of the Knowledge to be Gained

The development of a well-tolerated and effective regimen in a disease could potentially at worst add to the armamentarium of available regimens and at best change standard of care. Specific strategies to improve the care of patients relapsing following chemotherapy for lung cancer are direly needed.

7.1.4 Data Safety and Monitoring Plan

The Data Safety & Monitoring Plan (DSMP) will ensure that this trial is well designed, responsibly managed, appropriately reported, and that it protects the rights and welfare of patients. The following internal and external review and monitoring processes provide oversight and active monitoring of this trial:

- The Principal Investigators (PI)
- The Clinical Trials Office (CTO)
- The Scientific Review Committee (SRC)
- The Protocol Monitoring Committee (PMC);
- The Research Compliance Division (RCD) of the Cancer Center's Compliance Office;
- Institutional Review Board (IRB).

The protocol includes a section that specifies the following with respect to Adverse Event reporting: what constitutes an adverse event (versus what is a serious adverse event), the entities to which adverse events should be reported, the timing of this reporting, and the person or persons responsible for reporting. This includes prompt (within one day of knowledge of the event) reporting to the IRB for unanticipated risks to subjects and reporting in writing within five working days to the IRB and sponsor.

7.2 Scientific Review Committee (SRC)

The Cancer Center maintains two full board Scientific Review Committees (SRC), meeting every other week (the first Wednesday and third Thursday of every month) as well as one Behavioral Ad-Hoc SRC.

Each SRC conducts a formal internal peer review of all clinical protocols and general scientific oversight of interventional clinical research. Protocols are reviewed for scientific merit, adequate study design, safety, availability of targeted study population, and feasibility of timely completion of all proposed research projects to be conducted by its assigned programs at the Cancer Center. Each SRC is responsible for evaluating the risk/benefit assessment and corresponding data and safety monitoring plan as part of the scientific review and approval process. The SRC will refer any potential conflicts of interest identified in the proposed research to the Conflict Committee.

7.3 PI Responsibility

The PI of each study is ultimately responsible for every aspect of the design, conduct, and actions of all members of the research team. This includes the final analysis of the protocol. The PI is responsible for ensuring that:

All protocols include a DSMP and procedures for its implementation commensurate with the risk and complexity of the study. The DSMP must include a structured adverse event determination, monitoring and reporting system, including standardized forms, and procedures for referring and/or treating subjects experiencing adverse events. The plan must include data and safety-monitoring procedures for subjects enrolled who may be receiving a part of their protocol-required treatment at community sites.

In all cases, the PI of the study will have primary responsibility for ensuring that the protocol is conducted as approved by the SRC and IRB. The PI will ensure that the monitoring plan is followed, that all data required for oversight of monitoring are accurately reported to a DSMB and/or to the PMC and IRB as required, that all adverse events are reported according to protocol guidelines, and that any adverse actions reflecting patient safety concerns are appropriately reported.

7.4 Protocol Monitoring Committee (PMC)

The PMC meets once a month. The PMC reviews and evaluates safety and/or efficacy data for all physician authored clinical intervention trials. The PMC ensures the safety of patients and the validity and integrity of data. PMC reviews SAEs, deviations, Interim analysis, interim and final reports from the external Data Monitoring Committee (DMC) as well as audits both internally and externally. The PMC can make the following determinations, Accepted, Acceptable with Corrective Action, and Tabled.

Investigators of studies, which are designated to be reviewed by the PMC for data and safety monitoring, shall provide an interim statistical analysis report of the study's progress and summary of adverse events and deviations based on the phase of the study and the associated risk of the study or more often if applicable. The external DSMB (if applicable) shall forward its report for high-risk studies designated for external review at least annually or more often if applicable.

7.5 Research Compliance Division (RCD)

RCD of the Corporate Compliance Office is the coordinating center for internal audits of clinical trials conducted at the Cancer Center and its affiliates. The audit procedure is a formal, comprehensive, source document review of all clinical trials. External audit reports that meet the criteria of the internal audit may be accepted in lieu of an internal audit.

The (RCD) shall provide a report to the PMC of internal audit findings for PMC action. A representative of the RCD will be present to discuss the audits with the PMC. For cause, audits will be discussed during an executive session of the PMC. Only members (voting and ex-officio) may attend this session.

7.6 The Institutional Review Board (IRB)

Data will be captured in OnCore, Moffitt's Clinical Trials Database. Regulatory documents and case report forms will be reviewed routinely by the MCC Clinical Research Monitoring Core for accuracy, completeness and source verification of data entry, validation of appropriate informed consent process, adherence to study procedures, and reporting of SAEs and protocol deviations according to MCC Monitoring Policies.

The trial will not be initiated without approval of the appropriate Institutional Review Board (IRB). All administrative requirements of the governing body of the institution will be fully complied with. This protocol, consent procedures, and any amendments must be approved by the IRB in compliance with current regulations of the Food and Drug Administration. A letter of approval will be sent to the institution(s) funding the study prior to initiation of the study and when any subsequent modifications are made. The IRB will be kept informed by the investigator as to the progress of the study as well as to any serious or unusual adverse events.

7.7 Suspension/Termination

The PMC and/or the IRB may vote to suspend or terminate approval of a research study not being conducted in accordance with the IRB, the Cancer Center and/or regulatory requirements or that has been associated with unexpected problems or serious harm to subjects. The PMC/IRB will notify the PI in writing of such suspension or terminations. It is the responsibility of the PMC/IRB Chairperson to ensure prompt written notification of any suspensions or terminations of PMC/IRB approval to the relevant Federal Agencies, including OHRP, FDA, the study sponsor/funding source and if applicable, the Affiliate Program.

7.8 Trial Discontinuation

For reasonable cause, the Investigator and/or sponsor may terminate this study prematurely. Conditions that may warrant termination include but are not limited to: the discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study or if the accrual goals are met. A written notification of termination will be issued.

7.9 Monitoring of the Study and Regulatory Compliance

The Principal Investigator and the Clinical Research Coordinator assigned to the case will be primarily responsible for maintaining all study-related documents including the clinical research forms. ONCORE will serve as the study database of record. All CRF entries will be verified with source documentation and will be maintained by the Data Management Specialist and Clinical Research Coordinator. The patient case books will be secured in a locked office within each institution's applicable department. The review of medical records will be done in a manner to assure that patient confidentiality is maintained.

For External Sites Only: Data Management and Monitoring/Auditing

Data will be captured in OnCore, Moffitt's Clinical Trials Database. Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly to verify data is accurate, complete, and verifiable from source documents; and the conduct of the trial is in compliance with the currently approved protocol/amendments, Good Clinical Practice (GCP), and applicable regulatory requirements.

To obtain access to OnCore, the External Site Coordination (ESC) office Coordinator will supply forms required to be completed by the site staff. Once the completed forms are received, the site coordinator will receive DUO access, logon/password, and information on how to access OnCore. The ESC office will provide OnCore training to the site once initial access is granted and on an ongoing basis, as needed.

7.10 Protocol Modifications

No modifications will be made to the protocol without the agreement of the investigators. Changes that significantly affect the safety of the patients, the scope of the investigation, or the scientific quality of the study will require Institutional Review Board approval prior to implementation, except where the modification is necessary to eliminate apparent immediate hazard to human subjects. Any departures from the protocol must be fully documented in the case report form and the source documentation.

7.11 Patient Privacy

In order to maintain patient confidentiality, all case report forms, study reports, and communications relating to the study will identify patients by initials and assigned patient numbers. The US Food and Drug Administration (FDA) may also request access to all study records, including source documentation for inspection.

7.12 Records Retention

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the study is discontinued and the U.S. FDA and the applicable national and local health authorities are notified.

8. BIOLOGICAL SAMPLING PROCEDURES

8.1 Pharmacodynamics

8.1.1 Collection of pharmacodynamic markers

In summary, archival tumor specimens and optional serial tumor biopsies will be collected. These samples will be used to evaluate potentially predictive biomarkers and complete other correlative studies. Archival tissue specimens will be collected on all participants. Approximately 125 µL of tumor sample is required for this purpose. Fresh tumor specimens will be collected by image-guided biopsy for those without available archival tissue. In addition optional pre- and post-treatment tumor biopsies will be obtained on at least 7-10 total patients during the study. The biopsies will be performed under image guidance (including but not limited to CT or ultrasound-guided core biopsies) as determined by the location of tumor and risks associated with each procedure. Tumor biopsies will be performed pretreatment and at cycle 1, day 15 ± 7 days.

The tumor collected through these methods will be analyzed to explore whether positive vs. negative biomarkers could predict response and resistance to the AZD1775-carboplatin-

paclitaxel combination. More specifically for the fresh tumor biopsies, on-site evaluations for tissue quality will be performed by the cytotechnologist to ensure viable tissue and for collection of adequate tumor sample. Four to 6 core biopsy samples will be collected. At a minimum, 2 will be placed in neutral-buffered formalin and embedded in paraffin wax and two core needle samples will be snap frozen and stored in liquid nitrogen.

Immunohistochemistry will be used to assess the levels of the proposed molecules (WEE1, PAXIP 1, p53 in order of priority) in histological tumor collected before and after therapy where appropriate. Additional biomarkers may be explored including but not limited to cleaved Parp. We will utilize advanced NGS DNA analyses to test and identify the p53 mutation type,. Further, exploratory correlative studies may be completed based on the additional data obtained from the utilization of an advanced DNA platform for p53 testing. The collection and interpretation of additional data has the potential to help address some of the critical barriers for effective personalized treatment.

8.1.2 Molecular Analyses

After obtaining the results from IHC, the associations between the biomarkers (PAXIP1 and WEE1) will be made using Spearman's correlation coefficient.

We will also test whether p53 mutation status (yes/no as determined by sequencing) is associated with patient response (CR+PR) using the unconditional test.[16]

In addition, univariable analyses (Cox regression analysis) will be performed to see whether the markers predict for PFS. The impact of the change in markers on PFS (and overall survival) and response will be examined using Cox proportional hazard model and logistic regression, respectively. The three biomarkers (WEE1, PAXIP1, and p53) will be tested separately and will be considered significant if $P < 0.05$. The change in both the PAXIP1 and WEE1 marker scores will be assessed using the normal scores test. All analyses will be carried out using SAS 9.3 statistical software (SAS, Inc, Cary, NC).

Pre- and post-treatment biopsies will be obtained on at least 7-10 total patients from the SQCLC study. The biopsies will be performed under image guidance (including but not limited to CT or ultrasound-guided core biopsies) as determined by the location of tumor and risks associated with each procedure. Tumor biopsies will be performed pretreatment and at cycle 1, day 15 ± 7 days. Here we will explore the extent to which changes between pre- and post-treatment levels correlate with response. This will be done on the percent change from the pre-treatment values for the 3 biomarkers using the Wilcoxon signed rank test at $\alpha = .05$.

8.2 Handling, storage and destruction of biological samples

8.2.1 Handling

The handling of the tissue samples will be per the laboratory manual.

8.2.2 Shipping

Tissue samples are to be Shipped to Dr Alvaro Monteiro's laboratory at:

Alvaro Monteiro's Laboratory
12902 Magnolia Drive, MRC-3 West
Tampa Florida 336122
813-745-6321/3322
ALVARO.MONTEIRO@MOFFITT.ORG

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

9.1 Description of analysis sets

Demographic and other baseline data (including disease characteristics) will be summarized descriptively for the ITT, safety and per protocol populations. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

9.1.1 Evaluable for response analysis set

Consists of all patients treated whom have a radiographic assessment for evaluation by RECIST v 1.1 following at least 3 days of treatment.

9.1.2 Safety analysis set

Consists of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment.

Please note: the statement that a patient had no adverse events (on the Adverse Event CRF) constitutes a safety assessment. Patients who have received at least one dose of study drug but who have no post-treatment safety data of any kind would be excluded from the safety population.

9.2 Methods of statistical analyses

Sample Size Justification. Historical data indicate a median PFS/time to progression of about 4 months for newly diagnosed, advanced-stage NSCLC patients treated with platinum doublet chemotherapy.[11-13,17,18] With a one-sided significance level of 0.10, a total of 51 patients will provide 91% power (obtained from PASS 13) to assess a median PFS of 4.0 months against a median PFS of 6.5 months (HR = 0.615). It is assumed that the accrual time will be 30 months. We expect to enroll 75 patients to have 51 evaluable subjects.

Statistical Considerations for the Primary Objective.

PFS. PFS is measured from date first study treatment to death, progression of disease, or the last follow-up data, whichever comes first. The final analysis will be undertaken when all patients have been followed for at least 6 months. With our assumptions, we anticipate that

roughly 24 patients would have had an event at 6 months, compared to an expectation of 33 events if AZD1775 wasn't part of the treatment regimen. The median survival will be estimated assuming an exponential distribution,[19] with patients not progressing at one year being censored at that time (3 times the null hypothesis median PFS).

We will test for the exponentiality of the survival distribution using the RPEXE fit[19] with α = 0.10. The exponential distribution assumption will be considered to hold until the first changepoint identified. If no changepoint is identified, exponentiality will be considered to hold to the median follow-up time of censored cases. If the exponential distribution is found not to hold to at least 8 months (two times the null hypothesis median survival), the lower 80% confidence bound of the Kaplan-Meier estimated median survival time (which corresponds to a one-sided test at α = 0.10) will be used to assess whether the median survival is greater than 4.0 months.

Statistical Considerations for the Secondary Objectives.

Overall survival analysis (OS). The median OS of treated stage IV SQCLC patients is ~ 10 months[20]. The median OS for patients treated with AZD1775 plus carboplatin/paclitaxel is unknown, but hypothesized to be greater than that of patients treated with chemotherapy alone. We will be able to estimate whether or not this is true by comparing the median OS of study patients with the historical control value of 10 months. The median survival will be estimated assuming an exponential distribution [19] with patients not progressing at 2.5 years being censored at that time (3 times the null hypothesis median OS).

Duration of response analysis. We will also estimate the duration of response using an exponential distribution survival model.[19] Disease control rates, DCR, ORR, SD, and PR will be summarized appropriately.

10. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

10.1 Overdose

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day**, i.e., immediately but no later than **the end of the next business day** 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.

10.2 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca through the same procedure as reporting SAE's described in section 6.5.1.

11. ADMINISTRATIVE PROCEDURES

11.1 Regulatory and Ethical Compliance

This clinical study was designed and shall be implemented and reported in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the Investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to AstraZeneca before study initiation.

11.3 Informed Consent

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.4 Optional Biopsy Consent

Studies with an optional biopsy component will have a separate acknowledgement covering those studies. This will be adapted for each Study based on a standard template used globally for all Studies. The optional biopsy informed consent will be submitted for ethical approval together with the Study Protocol and as part of the main informed consent form of the Study. If

a subject opts not to participate in the optional biopsy assessments, this in no way affects the subject's ability to participate in the main research Study.

11.5 Amendments to the Protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by AstraZeneca, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, AstraZeneca should be notified of this action and the IRB/IEC/REB at the study site should be informed within 10 working days.

11.6 Monitoring

Data will be captured in OnCore, Moffit's Clinical Trials Database. Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly to verify data is accurate, complete, and verifiable from source documents; and the conduct of the trial is in compliance with the currently approved protocol/amendments, Good Clinical Practice (GCP), and applicable regulatory requirements."

11.7 Study Drug Supply and Resupply, Storage, and Tracking/Drug Accountability

Study drugs must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, the *AZD1775* should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug and the medication number but no information about the patient.

The investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Patients will be asked to return all unused study drug and packaging at the end of the study or at the time of study drug discontinuation.

12. PROTOCOL ADHERENCE

12.1 Investigators ascertain they will apply due diligence to avoid protocol deviations

Publication of results: Any formal presentation or publication of data from this trial may be published after review and comment by AstraZeneca and prior to any outside submission. AstraZeneca must receive copies of any intended communication in advance of publication (at least fifteen working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge AstraZeneca' responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. Principal Investigation/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of AstraZeneca and, in accord with the trial contract and shall not permit disclosure of AstraZeneca confidential or proprietary information.

12.2 Disclosure and Confidentiality

The investigator agrees to keep all information provided by AstraZeneca in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by AstraZeneca (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided by AstraZeneca to the investigator may not be disclosed to others without direct written authorization from AstraZeneca, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

13. ETHICS AND GOOD CLINICAL PRACTICE

This study must be carried out in compliance with the protocol and the principles of Good Clinical Practice, as described in AstraZeneca standard operating procedures and:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

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Clinical Study Protocol

Drug Substance	AZD1775
Study Code	
Edition Number	1
Date	22 October 2014
Protocol Dated	22 October 2014

Appendix A
Disallowed Medications

15. APPENDIX A: 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 metabolized 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, aprepaitant, resulted in a 60% 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 (IC50 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 (IC50 14 μM) and a time-dependent inhibitor of CYP3A4 (Kinact 0.061/min, Ki 6.04 μM). The full impact of the time dependent inhibition is currently unknown, however, modeling 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 (IC50 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 (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. Modeling has predicted a substantial increase in the exposure of Atorvastatin when coadministered with Clinical Study Protocol Appendix D Drug Substance AZD1775 Study Code D6011C00003 Edition Number 1 Date 22 October 2014

AZD1775 and the use of Atoravastatin is therefore prohibited in the current study. 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 is prohibited 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.

CYP3A Inhibitors

Strong

- Clarithromycin
- Telithromycin
- Ketoconazole
- Itraconazole
- Fluvoxamine
- Nefazodone
- Ritonavir
- Indinavir
- Nelfinavir
- Saquinavir
- Atazanavir
- Amprenavir
- Conivaptan
- Fosamprenavir
- Grapefruit Juice
- Telaprevir
- Troleandomycin

Moderate

- Aprepitant
- Cimetindine
- Diltiazem
- Erythromycin
- Fluconazole
- Imatinib
- Nifedipine
- Posaconazole

- Seville oranges
- Star fruit
- Verapamil

CYP3A Inducers (strong and moderate)

- Barbutrates
- Bosentan
- Carbamazepine
- Efavirenz
- Etavirine
- Nafcillin
- Nevaripine
- Pheonobarbitone
- Phenytoin
- Rifampin
- St. John's Wort

CYP3A4 Sensitive Substrates or Substrates with a Narrow Therapeutic Range

- Alfentanil
- Alfuzosin
- Amiodarone
- Bexaroine
- Bortezomib
- Carbazitaxel
- Cyclophosphamide
- Cyclophosporine
- Dasatinib
- Dihydroergotamine
- Disopyramide

- Docetaxel
- Dofetilide
- Ebastine
- Eletriptan
- Eplerenone
- Ergotamine
- Erlotinib
- Etoposide
- Everolimus
- Fentanyl
- Gefitinib
- Halofantrine
- Ifosfamide
- Ironotecan
- Imatinib
- Ixabepilone
- Lapatinib
- Mosapride
- Nilotinib
- Paclitaxel
- Pazopanib
- Pimozide
- Propafenone
- Propofol
- Quinidine
- Ranolazine
- Romidepsin

- Sirolimus
- Sorafenib
- Sunitinib
- Tacrolimus
- Temsirolimus
- Theoophylline
- Thioridazine
- Thiotepa
- Tretinoin
- Vinblastine
- Vincristine
- Vinorelbine

CYP2C19 Sensitive Substrates or Substrates with a Narrow Therapeutic Range

- Bortezomib
- Cyclophosphamide
- Phenytoin
- S-mephenytoin

CYP1A2 Sensitive Substrates or Substrates with a Narrow Therapeutic Range

- Alosetron
- Duloxetine
- Erlotinib

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- Lidocaine
- Mexilietine
- Propafenone
- Tacrine
- Theophylline
- Tizanidine

P-gp Substrates

Digoxin.

  - 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).

P-gp Inhibitors (strong)

- Quinidine
- Valspodar

BCRP Substrates

- Atorvaststin
- Fluvastatin
- Rosuvastatin
- Simvastatin
- Topotecan