AstraZeneca

Amended Clinical Study Protocol	
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AN OPEN LABEL, PHASE I STUDY TO ASSESS THE MAXIMUM TOLERATED DOSE OF ZD6474 (ZACTIMA™) GIVEN CONCOMITANTLY WITH RADIATION THERAPY OR CONCOMITANTLY WITH WEEKLY CISPLATIN CHEMOTHERAPY AND RADIATION THERAPY IN PATIENTS WITH PREVIOUSLY UNTREATED, UNRESECTED, STAGE III-IV HEAD AND NECK SQUAMOUS CELL CARCINOMA

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The following Amendment(s) and Administrative Changes are included in this amended protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
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PROTOCOL SYNOPSIS

AN OPEN LABEL, MULTI-CENTER, PHASE I STUDY TO ASSESS THE MAXIMUM TOLERATED DOSE OF ZD6474 (ZACTIMA™) GIVEN CONCOMITANTLY WITH RADIATION THERAPY OR CONCOMITANTLY WITH WEEKLY CISPLATIN CHEMOTHERAPY AND RADIATION THERAPY IN PATIENTS WITH PREVIOUSLY UNTREATED, UNRESECTED, STAGE III-IV HEAD AND NECK SQUAMOUS CELL CARCINOMA

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Study center(s) and number of patients planned

This multi-center study will be conducted in the United States in approximately 48 evaluable patients with previously untreated, unresected stage III-IV Head and Neck squamous cell carcinoma (HNSCC). Recruitment of patients will be done by investigational sites that have expertise in treating patients with head and neck cancer.

Study period		**Phase of development**
Estimated date of first patient enrolled (FSI)	July 2006	I
Estimated date of last patient completed (LSO)	July 2009	

Objectives

The primary objective of this study is to determine the safety profile, tolerability and maximum tolerated dose (MTD) of ZD6474 in combination with radiation therapy (RT) and ZD6474 in combination with RT and cisplatin chemotherapy, for approximately 8-9 weeks of study therapy, in patients with previously untreated, unresected, stage III-IV head and neck squamous cell carcinoma (HNSCC).

The secondary objectives of the study are:

To define the objective tumor response rates (ORR) (defined as complete response [CR] + partial response [PR]), disease control rate (DCR) (defined as CR+PR+stable disease [SD]≥12 weeks), and locoregional control rates (LRCR) (defined as CR+PR+SD≥12 weeks excluding distant disease) per Response Evaluation Criteria in Solid Tomors (RECIST) criteria

To assess rate of locoregional recurrence (LRR) and distant disease recurrence at two years.

To assess progression-free survival (PFS) and duration of locoregional control.

To investigate whether there is any change in the steady state exposure to ZD6474 due to RT or RT + cisplatin or the method of administration

To investigate whether there is any change in the exposure to cisplatin due to ZD6474 as assessed by total platinum

The exploratory objectives of the study are:

1. To investigate the correlation between epidermal growth factor receptor (EGFR) gene amplification, EGFR protein expression, vimentin protein expression, E-cadherin protein expression, and ZD6474 efficacy and toxicity in pre-treatment tumor samples from those patients where such tumor material is available.

2. To investigate the correlation between inhibition of EGFR and vascular endothelial growth factor receptor (VEGFR) signalling pathways, tumor cell and endothelial cell apoptosis, tumor microvessel density, and ZD6474 dose, efficacy and toxicity in pre-treatment and on-treatment tumor samples from those patients where such tumor material is available.

3. To investigate the correlation between markers of tumor hypoxia (hypoxia inducible factor[HIF], VEGF) and ZD6474 dose, efficacy and toxicity in pre-treatment and on-treatment tumor samples from those patients where such tumor material is available.

4. To investigate the correlation between changes in gene and protein expression, and ZD6474 dose, efficacy and toxicity in pre-treatment and on-treatment tumor samples from those patients where such tumor material is available.

5. To investigate the correlation between levels of circulating protein biomarkers and circulating endothelial cells with ZD6474 dose, efficacy and toxicity in pre-treatment and on-treatment plasma samples.

6. To investigate the relationship between ZD6474 Pharmacokinetics and safety, efficacy, and pharmacodynamics endpoints.

Study design

This is a Phase I, open-label, multi-center study. It is designed to determine the safety profile, tolerability and MTD of ZD6474 in combination with RT and ZD6474 in combination with RT and cisplatin chemotherapy, for approximately 8 to 9 weeks, in patients with previously untreated, unresected, stage III-IV HNSCC.

Target patient population

Male and female patients aged 18 years or older with histologically or cytologically confirmed previously untreated, unresected stage III-IV head and neck squamous cell carcinoma.

Study therapy

ZD6474 (100 mg, 200 mg, or 300 mg) in tablet form will be dosed orally or via dispersal, once daily, preferably at the same time each morning.

Cisplatin (30 mg/m^2) administered IV over 2 hours weekly during weeks 1-7 of RT

Radiation therapy (2 Gy/day, 5 days per week) to a total dose of 66 Gy over 6 weeks to involved areas (Treatment Regimen 1), or to a total dose of 70 Gy to involved areas over 7 weeks (Treatment Regimen 2) (See Section 3.4.3).

Duration of treatment

Patients will receive 2 weeks of ZD6474 monotherapy followed by either ZD6474 + RT for 6 weeks or ZD6474 + RT/cisplatin for 7 weeks, or until they meet criteria for discontinuation as defined in Section 3.3.6.2.

Once therapy has been completed, patients will be followed for safety, response, survival, and relapse for 2 years.

Outcome variables

- **Primary outcome variable:**
  - Safety: Adverse events (AE), physical examination (PE), vital signs including blood pressure (BP), heart rate (HR), electrocardiogram (ECG) and laboratory findings including clinical chemistry, hematology and urinalysis.
- **Secondary outcome variables**
  - Efficacy: ORR, DCR, LRCR per RECIST criteria.
  - LRR +/- distant disease at 2 years
  - PFS and duration of locoregional control
  - Pharmacokinetic:
    - ZD6474: C_{max}, t_{max}, $AUC_{(0-24)}$
    - Cisplatin: total C_{max}, $AUC_{(0-t)}$
- **Patient reported outcomes (PROs) – Not applicable**
- **Health economics– Not applicable**
- **Pharmacodynamic outcome variables**
  - EGFR gene amplification, EGFR protein expression, E-Cadherin protein protein expression, vimentin protein expression
  - EGFR/pEGFR, VEGFR/pVEGFR, Akt/pAkt, MAPK/pMAPK, microvessel density, apoptosis/TUNEL/caspase
  - HIF, CD31, and VEGF protein expression in tumor tissue
  - Gene and protein expression profiles in tumor tissue
  - VEGF, sVEGFR2, PIGF, VEGF-B, VEGF-C, CEC, bFGF in blood
  - PK: Individual predicted values of plasma concentrations, AUC_{ss}, $C_{ss,\ max}$, CL/F; Safety: AEs, including changes in QTc; Efficacy: ORR, DCR; PD: Those pharmacodynamic endpoints from the exploratory objectives identified as requiring further evaluation.
- **Genetics – Not applicable**

Statistical methods

The primary objective of the study is to determine the MTD and overall safety profile of orally administered escalating doses of ZD6474 in combination with RT and in combination with RT and cisplatin chemotherapy in patients with previously untreated, unresected stage III-IV HNSCC.

The estimate of MTD is defined as the dose level below the unacceptable dose level where at least 2 of 6 (33%) of the patients experience DLT. An estimate of MTD will be defined for each of the two regimens.

The safety population will comprise all subjects who received at least 1 dose of study treatment. Safety will be assessed through summaries of the frequency and severity of adverse events, changes in laboratory test results, changes in vital signs, and ECGs. Appropriate summaries of these data will be presented.

The sample size is dependent on the number of dose escalations within each of the two treatment regimens. Within each treatment regimen, a traditional dose escalation design with 3 dose levels and cohorts of 6 evaluable patients will be used. An additional cohort of 6 patients will be enrolled at the MTD for additional safety information. A maximum of 48 evaluable patients will be required to complete this study.

Efficacy data for this study will be summarized and analyzed on an intention-to-treat (ITT) basis. The efficacy analysis population will consist of all subjects who received at least 1 dose of ZACTIMA. Analyses of the secondary variables are purely descriptive in nature. No formal statistical comparisons between the treatment regimens will be made.

Objective tumor response rates for each treatment regimen and associated 95% confidence intervals will be presented. Similarly, disease control rates and locoregional control rates for each treatment regimen and associated 95% confidence intervals for each treatment regimen will be presented. The 2-year locoregional recurrence rates and 2-year recurrence rates for each treatment regimen and associated 95% confidence intervals will be presented. Point estimates of PFS and duration of locoregional control and associated 95% confidence intervals and Kaplan-Meier plots will be presented for each treatment regimen. Appropriate statistical summaries of exploratory endpoints will be provided.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Explanation
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event (see definition in Section 4.7.1.1)
AJCC	American Joint Committee on Cancer
AKT	Protein Kinase B
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
Assessment	An observation made on a variable involving a patientive judgement
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve from zero to infinity
$AUC_{(0-24)}$	Area under the plasma concentration-time curve from zero to 24 hours post doe
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from zero to time t
AUC_{ss}	Area under plasma concentration-time curve during any dosing interval at steady state
bFGF	Basic fibroblast growth factor
BSA	Body surface area
BUN	Blood urea nitrogen
°C	Degree Centigrade
C_{max}	Maximum concentration
$C_{ss, max}$	Maximum steady state plasma concentration
CEC	Circulating endothelial cell
CEP	Endothelial progenitor cell
CI	Confidence Interval
CL/F	Total body clearance of drug from plasma after an oral dose
COSTART	Coding Symbols for a Thesaurus of Adverse Reaction Terms

Abbreviation or special term	Explanation
CR	Complete response
CRF	Case Report Form
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events (National Institutes of Health, National Cancer Institute)
CTV	Clinical target volume
DCR	Disease control rate
DLT	Dose limiting toxicity
DVH	Dose-volume histogram
E-CADHERIN	Cell adhesion molecule
ECG	Electrocardiogram
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organization for Research and Treatment of Cancer
FSI	First patient in
GCP	Good Clinical Practice
GTV	Gross tumor volume
HDPE	High-density polythene
HIF	Hypoxia Inducible Factor
HNSCC	Head and neck squamous cell carcinoma
IB	Investigator's Brochure
ICRU	International Commission on Radiation Units
IC_{50}	Inhibitory concentration
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMRT	Intensity-modulated radiation therapy
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
KDR	Kinase insert domain receptor
LBBB	Left bundle branch block

Abbreviation or special term	Explanation
LD	Longest diameter
LDH	Lactate dehydrogenase
LRCR	Locoregional control rate
LRR	Locoregional recurrence
LSO	Last patient out
Mab	Monoclonal antibody
MAPK	Mitogen-Activated Protein Kinase
Measurement	An observation made on a variable using a measurement device.
MedDRA	Medical Dictionary for Regulatory Activities
MLC	Multileaf collimator
MmHg	Millimeter of mercury
MRI	Magnetic resonance imaging
Msec	Millisecond
MTD	Maximum tolerated dose
NE	Not Evaluable
NCI	National Cancer Institute
NCR	No Carbon Required
NG	Nasogastric tube
NTD	Non-tolerated dose
OAE	Other Significant Adverse Event (adverse event of clinical importance, other than SAE and those AEs leading to discontinuation of the patient from study treatment; see Section 4.7.1.1).
ORR	Objective response rate
Outcome variable	A variable (usually a derived variable) specifically defined to be used in the analysis of a study objective.
Parameter	A quantity (usually unknown) that characterizes the distribution of a variable in a population of patients.
PBMC	Peripheral blood mononuclear cell
PEG	Percutaneous endoscopic gastrostomy
PFG	Percutaneous fluoroscopic gastronomy
PFS	Progression-free survival

Abbreviation or special term	Explanation
PK	Pharmacokinetic
Principal investigator	A person responsible for the conduct of a clinical study at an investigational study site. Every investigational study site has a principal investigator.
PR	Partial response
PTV	Planning target volume
PVC	Premature ventricular contraction
QT	The interval between Q and T on ECG
QTc	QT interval corrected for heart rate by the Bazett's method
RECIST	Response Evaluation Criteria in Solid Tumors
RT	Radiation therapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious adverse event (see definition in Section 4.7.1.1).
SAP	Statistical Analysis Plan
SAS	Statistical analysis software
SD	Stable Disease
SDV	Source Data Verification
SMQ	Special MedRA query
SOC	System organ class
SVC	Superior vena cava
TKI	Tyrosine kinase inhibitor
ULN	Upper limit of normal
ULRR	Upper limit of reference range
V_{ss}	Apparent volume of distribution
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VEGFR2	Vascular endothelial growth factor receptor-2
WBC	White blood count
WHO	World Health Organization

1. INTRODUCTION

1.1 Background

1.1.1 Head and Neck Squamous Cell Carcinoma

Primary head and neck squamous cell carcinoma (HNSCC) constitutes 3% of all newly diagnosed cancers in the USA and approximately half a million cases worldwide. Survival rates of patients with head and neck cancer have improved modestly over the last few decades. Locoregional recurrence remains the main form of treatment failure. For patients treated with primary radiotherapy alone, attempts to enhance locoregional disease control have included the exploration of altered fractionation schemes and addition of concurrent chemotherapy.

Concurrent chemoradiation is now a standard of care for patients with locoregionally advanced squamous cancer of the head and neck who are not good candidates for resection or who refuse resection and desire organ preservation. There is lack of consensus, however, regarding the best chemoradiation regimen. Intermittent high-dose cisplatin (100 mg/m^2 IV q 3 weeks x 2-3 cycles) with concurrent radiation has been studied in large randomized trials in various settings and has been associated with improved locoregional control and survival benefit (Adelstein, et al 2003, Forastiere, et al 2003).

There are advantages in using a weekly schedule. First, a putative radiosensitizing effect of cisplatin can be better exploited by repeated applications. Others have used cisplatin predominantly for radiosensitizing effects and applied a low dose every day before the radiotherapy session. (Shibamoto, et al 2000, Bertelink, et al 2002). The weekly regimen has been previously tested. (Bachaud, et al 1996).

Second, this application is practicable and well tolerated with respect to chemotherapy-related side effects such as hematotoxicity, nephrotoxicity, neurotoxicity, and nausea. Finally, the classic Radiation Therapy Oncology Group simultaneous radiochemotherapy regimen with 100 mg/m^2 of cisplatin every 3 weeks only reaches a dose intensity for cisplatin of only 60% of the scheduled dose (Forastiere 1993).

Accelerated fractionation, either throughout the radiation, or with concomitant boost technique has shown improved locoregional control relative to conventional fractionation in an Radiation Therapy Oncology Group (RTOG) four-arm trial (Fu, et al, 2000).

These strategies result in improved local disease control at the price of increased toxicity. Further therapy options are clearly needed to both improve outcomes and toxicity profiles.

1.1.2 Tumor Angiogenesis in HNSCC

EGFR overexpression has been identified as an independent negative prognostic indicator in head and neck cancer, associated with both decreased disease-free and cause-specific overall survival (Grandis, et al 1998). In addition, overexpression is correlated with radioresistance with data suggesting that cell survival and repopulation after exposure to radiation depend in part upon activation of EGFR and transforming growth factor-alpha in an autocrine loop

(Akimoto, et al 1999). Inhibition of EGFR activity with the blocking antibody, cetuximab (Bonner, et al 2000), and the tyrosine kinase inhibitor (TKI) gefitinib has enhanced radiosensitivity in vitro and in vivo through pro-apoptotic and anti-angiogenic effects (Huang, et al 2002; Shintani, et al., 2003).

Likewise, the combination of chemotherapy with anti-EGFR therapy is frequently associated with enhanced cytotoxicity. Both gefitinib and erlotinib have been studied in patients with recurrent squamous cancer of the head and neck, most of whom had progressed on or after chemotherapy. These phase II single agent trials have yielded response rates of 11 and 6%, respectively in this refractory population (Souliere, et al., 2004; Cohen, et al, 2003).

A phase III randomized trial of radiation and cetuximab vs. radiation alone has shown that treatment of locoregionally advanced head and neck cancer with concomitant high-dose radiotherapy plus cetuximab improves locoregional control and reduces mortality without increasing the toxicity to normal tisuues (Bonner, et al., 2006).

Another aspect of tumorigenesis that has been under investigation for several decades has now become the focus of intensive study. Observations made more than eighty years ago demonstrated the hypervascular nature of most tumors. Subsequent studies suggested that tumor cells could actually stimulate new blood vessel formation, a process known as angiogenesis. This work led to the hypothesis that tumors are "angiogenesis-dependent." This field has evolved considerably over the last 20 years to the point where tumors are no longer considered separately from their stromal environment. The growth of tumors is dependent on their ability to parasitize their host, recruiting blood vessels to allow them to utilize host nutrients and oxygen. Solid tumor progression is critically dependent upon the ability of tumor-derived growth factors to stimulate signaling responses in host endothelial cells, thereby enabling new tumor blood vessel formation from the existing vasculature (angiogenesis). Angiogenesis is thought to be a relatively quiescent process in healthy adults, the only tissue in which it occurs routinely being proliferating endometrium. Therefore, it is hypothesized that therapeutic approaches that target the process of angiogenesis will be relatively specific for pathological angiogenesis in tumors (Folkman, 1970). Thus, tumor cells, endothelial cells, and the stromal matrix define at least three compartments that represent potential targets for cancer therapy. It is now generally accepted that solid tumors require the development of new blood vessels (neoangiogenesis) in order to grow and metastasize. Therefore, research has been aimed at developing inhibitors of this process.

Anti-angiogenic agents represent a new class of therapeutic agents that act through a novel mechanism. By working to impede the growth of endothelial cells that nourish a tumor, these agents can theoretically inhibit tumor growth with increased specificity and decreased toxicity.

Anti-angiogenic therapy is attractive because of its specificity: neovascularization is restricted to wound healing in normal adults and reproductive processes in females. Endothelial cells, which form the inner lining of capillaries, are an especially attractive target because their normal DNA content and relatively long half-life make them less likely to develop drug resistance. As a result of this specificity, anti-angiogenic therapy has proven to be much less

toxic than traditional chemotherapy. Furthermore, as expected, most currently available anti-angiogenic agents have shown cytostatic rather than cytotoxic activity in preclinical studies. Used alone, these agents would be expected to produce stable disease. However, several of the newer anti-angiogenic agents, including ZD6474, appear to have more potent anti-tumor activity.

Vascular endothelial growth factor (VEGF) is a key angiogenic factor implicated in tumor blood vessel formation. Tumor VEGF expression has been clinically associated with disease progression in a range of solid malignancies. VEGF expression is elevated by diverse stimuli, which include proto-oncogene activation (Rak, et al 1995) and hypoxia (Dibbens, et al 1999), the latter frequently arising in solid tumors because of inadequate perfusion. In addition to its angiogenic role, VEGF also has a profound permeabilizing effect on the vasculature, which may also contribute to tumor progression by enhancing nutrient and catabolite exchange and presenting a reduced barrier to tumor cell intravasation during metastasis.

Two high-affinity receptors for VEGF with associated tyrosine kinase activity have been identified on human vascular endothelium: fms-like-tyrosine kinase (Flt-1) and kinase insert domain-containing receptor (KDR). Although the relative contributions of KDF and Flt-1 signaling in mediating tumor progression have not been resolved, a number of studies suggest KDR performs a predominant role. Selective activation of KDR alone has been found sufficient for induction of endothelial cell proliferation, migration, and tubule formation in vitro, and can produce a vascular permeabilising response comparable to that of native VEGF (Ortega, et al 1997, Ogawa, et al 1998). Normal tissue distribution of KDR is endothelial specific, and the receptor has been shown to be preferentially expressed at sites of active angiogenesis (Plate, et al 1994). Receptor tyrosine kinases (RTKs) have been shown to be important mediators of signal transduction in cells. These proteins characteristically consist of an extracellular ligand-binding domain connected through a transmembrane motif to an intracellular tyrosine kinase domain. Binding of ligand to the receptor results in receptor dimerisation and activation of the RTK domain. This enzyme activity catalyses transfer of the gamma phosphate group from ATP to tyrosine residues on the receptor itself as well as various intracellular substrate proteins. These changes in tyrosine phosphorylation status are responsible for propagation of a signaling cascade. Specific inhibition of the tyrosine kinase associated with KDR would be expected to block VEGF-mediated signaling in endothelial cells.

1.1.3 ZD6474 (ZACTIMA™)

ZD6474 is an inhibitor of the tyrosine kinase domain of the VEGF receptor-2 (KDR or VEGFR-2). It is expected that this molecule may be beneficial in a broad range of human malignancies, and perhaps other diseases, that are dependent upon VEGF-mediated angiogenesis. ZD6474 has shown excellent reversible inhibition of tumor cell growth in a broad range of pre-clinical models, including lung cancer xenografts. Regression of some established tumors in animals were observed following oral administration. Pre-clinical toxicology shows the agent to be well tolerated after 6 months of daily administration. ZD6474 also inhibits the epidermal growth factor receptor (EGFR) tyrosine kinase, though at an inhibitory concentration (IC_{50}) of 500 nanomolar (nM), which was higher than that for

VEGFR-2 (40 nM) (Ciardiello, et al 2003, Wedge, et al 2002). Two phase I studies were conducted in the West and in Japan, which demonstrated a maximum tolerated dose of 300 mg, with common adverse events (AEs) being diarrhea, rash, an asymptomatic QTc prolongation. Subsequently, a randomized double-blind study was conducted to compare ZD6474 at 100 mg or 300 mg in combination with docetaxel to docetaxel plus placebo. The results of this study demonstrated that ZD6474 combined with docetaxel prolonged progression-free survival in patients with non-small cell lung cancer (NSCLC).

1.1.3.1 Summary of adverse events (AEs) in other studies

The most common AEs associated with ZD6474 in the phase I and other monotherapy studies included rash, diarrhea and asymptomatic QTc prolongation. In Study 6474IL/0006, patients with advanced or metastatic NSCLC were enrolled after failure of prior platinum-based chemotherapy. Patients were randomized to treatment with a standard dose of docetaxel and either placebo or 100 mg of ZD6474 or 300 mg of ZD6474. The median duration of therapy for each arm (docetaxel/placebo, docetaxel /ZD6474 100 mg, and docetaxel /ZD6474 300 mg) was 65 days, 91days, and 61.5 days, respectively. More patients who received 300 mg ZD6474 (22.7%) discontinued therapy as a result of AEs compared to those who received 100 mg (4.8%) or placebo (12.6%).

The AE profile was similar for all three treatment regimens, although somewhat higher frequencies were observed for the 100 mg ZD6474 arm compared with placebo, and for the 300 mg ZD6474 arm compared with 100 mg ZD6474.

The most frequent AEs observed in this study were similar to those observed in prior trials for ZD6474 or reported for docetaxel in the literature. The most common AEs and their frequencies as reported in the 300 mg ZD6474, 100 mg ZD6474 and placebo arms, respectively, were diarrhea (50.0%, 38.1%, 24.4%), fatigue (45.5%, 40.5%, 26.8%), neutropenia (31.8%, 26.2%, 19.5%) and nausea (29.5%, 26.2%, 19.5%). Rash was observed in 15.9%, 16.7% and 9.8% of patients in the three arms.

Gastrointestinal events (77.3%, 59.5%, 41.5%), and skin events (72.7%, 64.3%, 41.5%) were more common in the ZD6474-containing arms. For all arms the majority of these events were common toxicity criteria (CTC) grade 1 and 2; however CTC grade 3/4 event were more prominent in the ZD6474 300 mg arm. Cardiac disorders occurred more frequently in ZD6474-containing arms (15.9%, 14.3%, 2.4%). The majority were CTC grade 1/2 and included a variety of terms, none ventricular. The frequency of respiratory events (50.0%, 57.1%, 46.3%) was similar in all arms. Neutropenia (31.8%, 26.2%, 19.5%) and related terms were more common in ZD6474-containing arms, but this did not result in an increase infection. There was little difference in frequency of other hematologic events.

Approximately 10% of patients receiving ZD6474 developed an AE of hypertension. The majority of events were CTC grade 1 or 2, and no events were CTC grade 4. There were no serious adverse events (SAEs) of hypertension. The maximum median rise in both systolic and diastolic blood pressure was approximately 8 mm Hg in patients who received ZD6474 300 mg, and approximately 4 mm Hg in patients who received ZD6474 100 mg

For the analysis of AEs that might have been caused by QT prolongation, AstraZeneca utilized the broad Special MedDRA Query (SMQ) for QT prolongation. The terms queried included electrocardiogram (ECG) QT corrected interval prolonged, ECG QT interval abnormal, ECG QT prolonged, long QT syndrome, long QT syndrome congenital, Torsades de Pointes, ventricular tachycardia, cardiac death, sudden cardiac death, sudden death, cardiac arrest, cardiac fibrillation, cardiorespiratory arrest, ECG repolarization abnormality, ECG J wave abnormality, ECG U-wave abnormality, loss of consciousness, syncope, syncope vasovagal, ventricular arrhythmia, ventricular fibrillation, and ventricular flutter.

The only event that was actually reported in the randomized phase was ECG QT (corrected) interval prolonged, which occurred in 7, 5, and 2 patients treated with ZD6474 300 mg, ZD6474 100 mg, and placebo, respectively.

In addition, AstraZeneca reviewed the data for patients who experienced a confirmed prolongation of the ECG QTc interval, as specified in the protocol. Seven patients had confirmed QTc prolongation in this study. Five (16%) occurred on the ZD6474 300 mg/docetaxel arm, 4 of which occurred in the first 28 days and 1 at day 70. Two (12%) occurred on the ZD6474 100 mg /docetaxel arm, at days 22 and 43. No patients with confirmed QTc prolongation in study 6474IL/0006 experienced a potentially relevant AE. One patient in the run-in phase of trial 6 had received ZD6474 300 mg plus docetaxel, was hospitalized with a post-obstructive pneumonia as well as hypokalemia resulting from prednisone and fluorinef given to treat adrenal insufficiency resulting from adrenal metastases. He was noted to have a QTc interval of 626 msec. During this hospitalization he developed a 12 beat run of ventricular tachycardia, which was asymptomatic and resolved without treatment. For additional information, please refer to the current version of the Investigator's Brochure.

1.2 Rationale for this study

It seems reasonable to theorize that small molecule inhibitors of the tyrosine kinase function of EGFR would have similar effects as cetuximab when combined with RT, with the advantages of an oral or percutaneous fluoroscopic gastrostomy (PFG) route of administration and absence of acute hypersensitivity reactions. In terms of combining ZD6474 with RT, experiments have been conducted based on the hypothesis that inhibition of both the EGF and VEGF receptor will lead to improved oxygenation based on restructuring of the chaotic network of vasculature associated with tumor expansion and thereby enhancing the effect of radiation. These experiments have shown that although ZD6474 caused regression of EGFR positive tumors, it only slowed the growth of EGFR negative ones, but combinations of ZD6474 and RT concomitantly resulted in superior therapeutic efficacy compared to RT followed by ZD6474 or vice versa (Frederick, et al., 2006). Thus, we propose to study the combination of ZD6474 and RT as well as the combination of ZD6474 with cisplatin and RT for loco-regionally advanced HNSCC in a phase I study to determine the MTD for each combination.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to determine the safety profile, tolerability and MTD of ZD6474 in combination with RT and ZD6474 in combination with RT and cisplatin chemotherapy, for approximately 8 to 9 weeks of study therapy, in patients with previously untreated, unresected, stage III-IV HNSCC.

2.2 Secondary objectives

The secondary objectives of the study are:

1. To define the objective tumor response rates (ORR) (defined as complete response [CR] + partial response [PR]), disease control rate (DCR) (defined as CR+PR+stable disease [SD]≥12 weeks), and locoregional control rates (LRCR) (defined as CR+PR+SD≥12 weeks excluding distant disease) per Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

2. To assess rate of locoregional recurrence (LRR) and distant disease recurrence at two years.

3. To assess progression-free survival (PFS) and duration of locoregional control.

4. To investigate whether there is any change in the steady state exposure to ZD6474 due to RT or RT + cisplatin or the method of administration.

5. To investigate whether there is any change in the exposure to cisplatin due to ZD6474 as assessed by total platinum

2.3 Exploratory objectives

1. To investigate the correlation between epidermal growth factor receptor (EGFR) gene amplification, EGFR protein expression, vimentin protein expression, E-cadherin proein expression, and ZD6474 efficacy and toxicity in pre-treatment tumor samples from those patients where such tumor material is available.

2. To investigate the correlation between inhibition of EGFR and vascular endothelial growth factor receptor (VEGFR) signalling pathways, tumor cell and endothelial cell apoptosis, tumor microvessel density, and ZD6474 dose, efficacy and toxicity in pre-treatment and on-treatment tumor samples from those patients where such tumor material is available.

3. To investigate the correlation between markers of tumor hypoxia (hypoxia inducible factor [HIF], VEGF) and ZD6474 dose, efficacy and toxicity in pre-treatment and on-treatment tumor samples from those patients where such tumor material is available.

4. To investigate the correlation between changes in gene and protein expression, and ZD6474 dose, efficacy and toxicity in pre-treatment and on-treatment tumor samples from those patients where such tumor material is available.

5. To investigate the correlation between levels of circulating protein biomarkers and circulating endothelial cells with ZD6474 dose, efficacy and toxicity in pre-treatment and on-treatment plasma samples.

6. To investigate the relationship between ZD6474 pharmacokinetics and safety, efficacy, and pharmacodynamics endpoints.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

This Clinical Study Protocol has been subjected to peer review according to AstraZeneca standard procedures.

This is a phase I, multi-center, open-label, non-comparative, dose-escalation study of 3 doses of ZD6474 in combination with RT and 3 doses of ZD6474 in combination with RT + cisplatin in patients with previously untreated, unresected HNSCC to determine a MTD for each treatment regimen. Approximately 48 evaluable patients will be enrolled during an approximately 24-month period.

There will be two treatment regimens. Patients will be assigned to a treatment regimen based on their disease stage (see Table 7). Patients with a disease stage of T1N2a or T2N2a are eligible for either regimen and assignment to a treatment regimen will be at investigator discretion. Within each treatment regimen, there will be a cohort of patients receiving a specified dose. The starting ZD6474 dose in each treatment regimen will be 100 mg. The planned doses to be explored in the study are 100 mg, 200 mg, and 300 mg.

A minimum of 6 patients will be enrolled in each cohort for each regimen (6 potential cohorts total). One cohort expansion (to a total of 12 patients) will occur in each regimen at MTD once the MTD is identified.

All patients will receive ZD6474 for 14 days prior to the initiation of RT or RT/chemotherapy and concurrently with 6 weeks of RT or 7 weeks of RT/chemotherapy. The study plans (see Table 1 and Table 2) indicates the number and timing of the planned clinic visits for each regimen. Additionally, patients will have ECGs performed to monitor the QTc interval (using Bazett's correction).

Patients will be followed by the RECIST criteria. Patients will be treated for approximately 8 to 9 weeks or until they have a dose limiting toxicity (DLT)(see Section 3.1.1.1) or until they meet criteria for discontinuation (Section 3.3.6.2), whichever comes first.

All patients will be asked to consent to providing 3 tumor samples. This will comprise of one mandatory archival tissue sample and optional fresh pre- and post-dose ZD6474 tissue samples. The tissue samples will be retrieved and forwarded as indicated in Appendix F.

Patients who have consented to the optional tissue sample collection will have a baseline biopsy performed prior to ZD6474 treatment initiation. A follow-up biopsy will be performed after 14 days of ZD6474 monotherapy and prior to the initiation of concomitant therapy. It is strongly recommended that patients undergo both the pre- and post-dose biopsies to characterize the effects of ZD6474 dosing on EGFR and VEGFR signalling pathways.

3.1.1 Dose escalation of cohort

Dose escalation in each treatment regimen will occur based on the toxicity information, during treatment and through 30 days followup, from the six patients in each cohort. Prior to each dose escalation decision, the Safety Review Committee (see Section 6.8) will meet to review the available safety and tolerability data from patients within that cohort. Following review of this data, the safety review committee will decide if the criteria for proceeding with dose escalation has been met. The dose escalation decision will be formally minuted, and minutes will be distributed to each site.

3.1.1.1 Definition of dose limiting toxicity, non-tolerated dose, and maximum tolerated dose

Dose Limiting Toxicity (DLT)

DLT must be attributable to the protocol treatment (ZD6474 and RT and/or ZD6474 and cisplatin/RT) in the opinion of the investigator. A DLT will consist of any of the following:

- Non-hematologic CTCAE ≥ grade 3 toxicity despite optimal symptomatic care, such as nausea, vomiting, diarrhea, rash
- QTc prolongation as defined in section 3.9.3.
- Hematologic CTCAE grade 4 toxicity (excluding neutropenia if duration < 8 days)
- CTCAE grade 3 thrombocytopenia associated with bleeding (but not applicable to patients on therapeutic anticoagulation)
- Toxicity inside the RT field, CTCAE grade 4:
  - Dysphagia
  - Mucositis/stomatitis
  - Skin toxicity
  - Xerostomia

  - Hypogeusia

- Any delay in RT > 5 days due to toxicity

Lymphopenia is an expected adverse event with RT, and will not be considered a DLT.

ZD6474 is associated with rash, diarrhea, and QTc prolongation. Management protocol has been defined for each adverse event (see Section 3.9 for guidance on the management of toxicity). Treatment of patients based on management protocol will be considered part of optimal symptomatic care.

In the event of a DLT, treatment will be stopped and supportive therapy administered as required. If the toxicity resolves or reverts to CTCAE Grade 0 or 1 or baseline level within 21 days of onset of the DLT and the patient is showing clinical benefit, study treatment may be may be resumed at a reduced dose only upon agreement between the investigator and AstraZeneca.

Non-tolerated Dose (NTD)

The NTD cohort is defined as the dose level at which 2 or more patients (33%) experience a DLT and the DLT assessment is attributable to study treatment and not disease.

Maximum Tolerated Dose (MTD)

The MTD is defined as the dose level immediately below the NTD.

3.1.1.2 Criteria for dose escalation

The following criteria will govern dose escalation to the next dose:

  - If <2 of 6 evaluable patients experience a DLT, the dose will be defined as tolerable and the dose will be escalated to the next dose level

  - If ≥2 of 6 evaluable patients experiences a DLT, this dose will be considered a NTD. Enrollment into this dose will be immediately stopped and no dose escalation to the next dose level will occur. The preceding dose would be considered the MTD.

Once the MTD for ZD6474 has been determined (separately for each treatment regimen), an additional 6 patients will be enrolled in the MTD cohort for each treatment regimen and will receive a complete course of study therapy.

3.1.2 Definition of evaluable patient

To be considered evaluable, a patient must have met eligibility criteria and must have completed study treatment as defined or experienced a DLT. A patient will be non-evaluable:

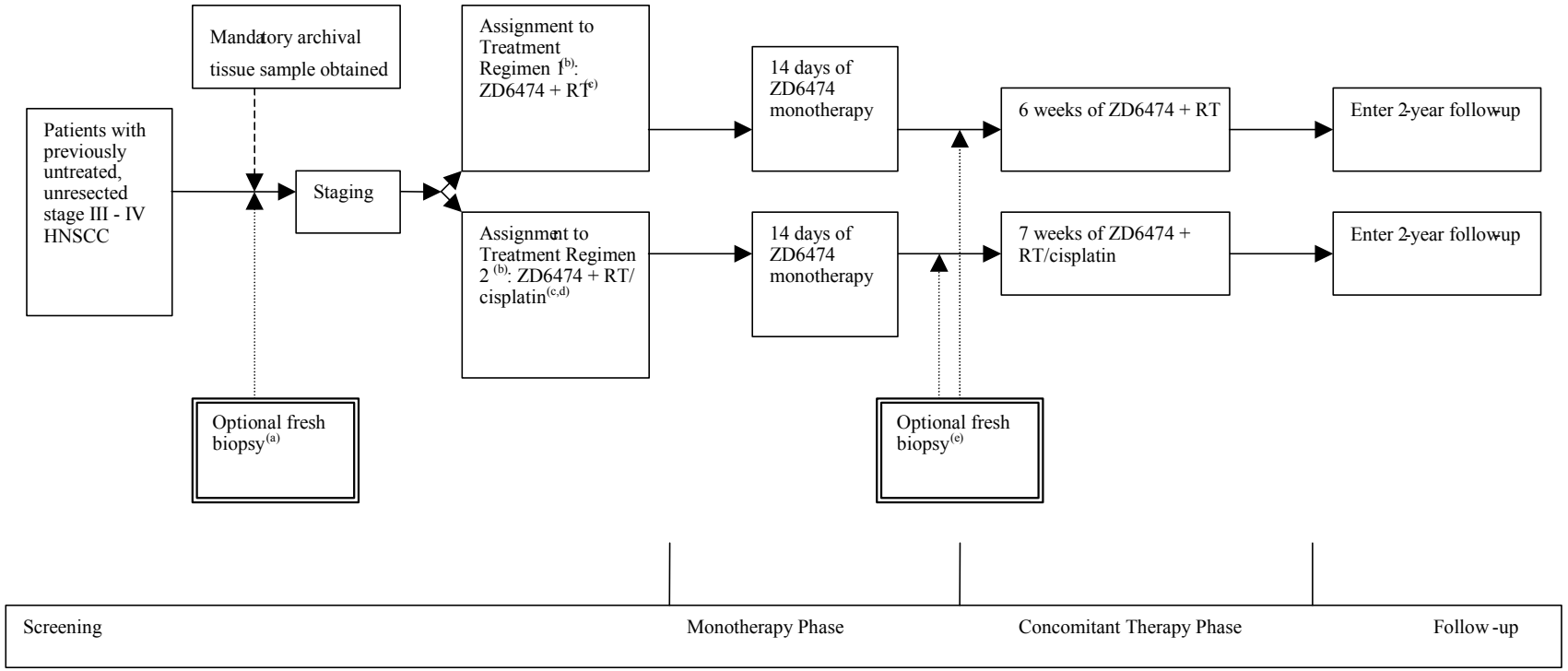
  - if they experience a ZD6474 delay > 3 weeks as a result of rash, diarrhea, or QTc prolongation attributable only to ZD6474 and not considered a DLT

- if they experience a cisplatin delay > 3 weeks that is not considered a DLT

- if they experience a RT delay > 10 days that is not related to toxicity

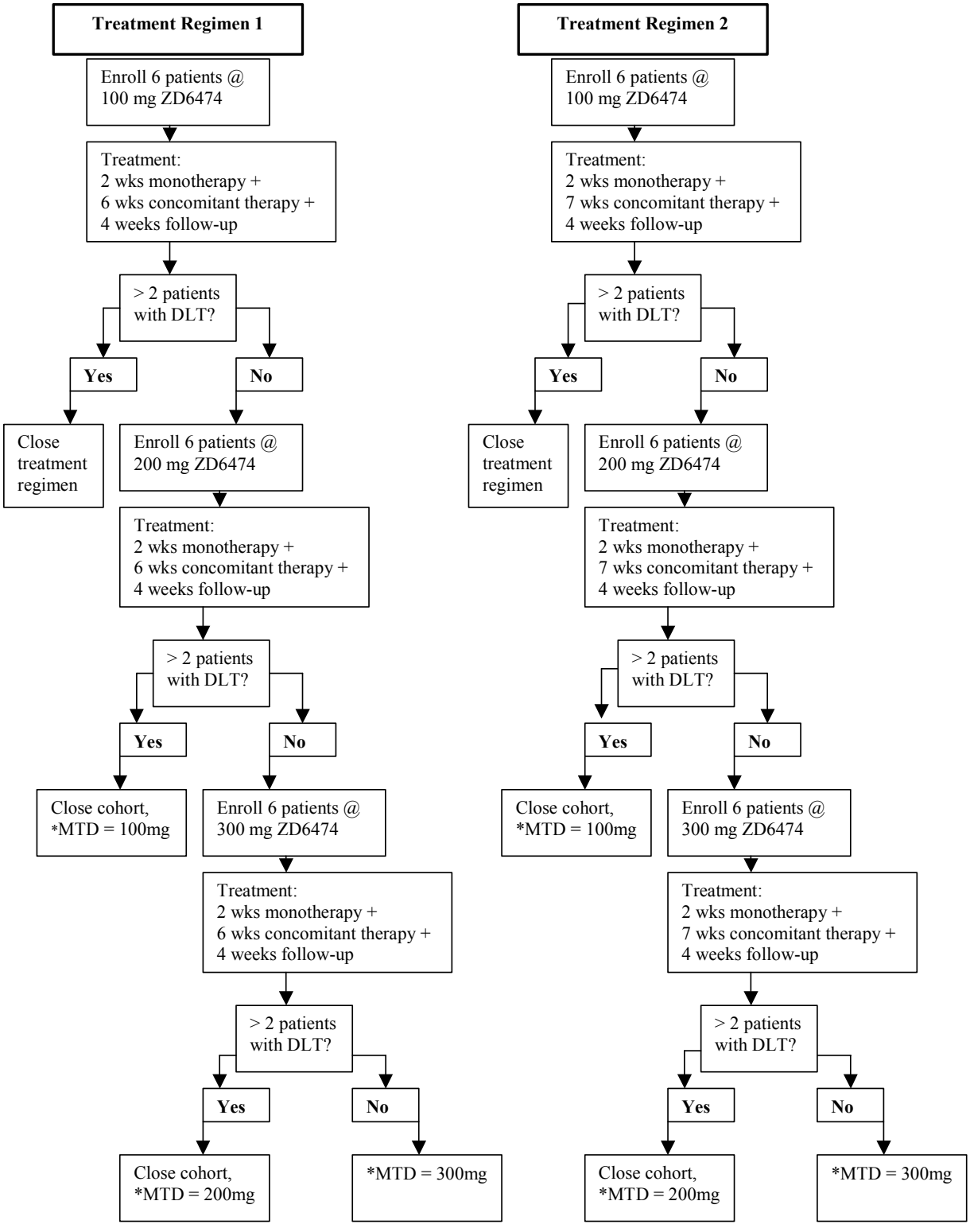
Patients who are non-evaluable will be replaced so that the safety of the dose and treatment regimen can be evaluated. If 2 or more patients in a cohort have experienced a DLT, the cohort will be closed and any further non-evaluable patients will not be replaced.

Figure 1 Study flow chart



(a) ≤2 days prior to first dose of ZD6474
(b) Patients who have successfully completed the screening process will be assigned to a treatment regimen based on their disease stage. Patients with a disease stage of T1N2a or T2N2a are eligible for either treatment regimen. Assignment to a treatment regimen for patients with stage T1Na or T2Na only will be at investigator discretion. Eligible tumor types in Treatment Regimen 1: T1N1, T1N2a, T2N1, T2N2a; eligible tumor types in Treatment Regimen 2: T1N2a, T2N2a, T2N2b, T2N2c, T2N3, T3 or T4 any N
(c) Radiotherapy treatment planning (dental exam, treatment planning, simulation, etc) prior to commencement of monotherapy.
(d) Hearing exam
(e) Within (+/-) 24 hours from last dose of ZD6474 monotherapy, but must be before first dose of cisplatin or radiotherapy

Figure 2 Dose escalation schema



* Once MTD is determined (separately for each treatment regimen), an additional 6 patients will be enrolled in each MTD cohort.

Table 1 Study plan – Treatment Regimen 1

	Screen	Monotherapy Phase		Concomitant Therapy Phase							
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**FU[b]**
Week		**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**Disc**	
Day	**-21 dys**	**D1**	**D8**	**D15[a]**	**D22**	**D29**	**D36**	**D43**	**D50**	**D58**	**Q3mos[b]**
Informed consent	X										
Medical history	X										
Inclusion/ exclusion criteria	X										
Physical examination	X	X	X	X	X	X	X	X	X	X	X[b]
Vital signs/weight	X	X	X	X	X	X	X	X	X	X	X[b]
ECG[c,d]	X[c]	X[d]	X	X		X				X	
Clinical chemistry / Hematology (see Table 13)	X		X	X	X	X	X	X	X	X	
Urinalysis	X		X	X	X	X	X	X	X	X	
RECIST	X										X[b]
WHO performance status	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	
Pregnancy tests (females)	X										
Dispense study medication		X				X					
Adverse events	X	X	X	X	X	X	X	X	X	X	X[b]
Plasma biomarkers[e]	X[e]	X	X	X					X		
PBMC/CECs[e]	X[e]	X	X	X					X		
PK sampling[f]				X[f]				X[f]	X[f]		

Table 1 Study plan – Treatment Regimen 1

	Screen	Monotherapy Phase		Concomitant Therapy Phase							
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**FU[b]**
Week		**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**Disc**	
Day	**-21 dys**	**D1**	**D8**	**D15[a]**	**D22**	**D29**	**D36**	**D43**	**D50**	**D58**	**Q3mos[b]**
Archival tumor sample	X										
Tumor Biopsy (optional)[g,e,h]	X[e,g]			X[g,h]							
Dental exam	X										
Radiotherapy[i,j]	X[j]			X[i]	X[i]	X[i]	X[i]	X[i]	X[i]		

NOTE: All visits have a +/- 3 day window.

[a] Radiation after at least 14 days of monotherapy

[b] During follow-up, patients will be seen 30 days and 60 days post last dose for evaluation of safety (PE, vitals, AEs); at 90 days post last dose and every 3 months thereafter until the end of 2 years post-active treatment follow-up, patients will be evaluated for response, progression-free survival and relapse (PE, vitals, RECIST)

[c] QTc with Bazett's correction unmeasurable or ≥480 msec on screening ECG (Note: If a patient has QTc interval ≥480 msec on the screening ECG, two additional ECGs should be done [at least 24 hours apart]. The average QTc from the three screening ECGs must be ≤ 480 msec in order for the patient to be eligible for the study)

[d] Baseline QTc (using the Bazett's correction) will be determined by the average of 3 consecutive ECGs (within 5-10 minutes of one another) on Day 1. If the screening QTc is obtained with 3 consecutive ECGs within 3 days before Day 1, then the screening QTc will be considered to be the baseline, and repeat ECGs will not be necessary on Day 1.

[e] Tumor biopsy and plasma biomarker at screening should be done after all other screening procedures are done and after patient determined to be eligible

[f] PK – multiple timepoints on days 15, 43, and 50; see schedule below

[g] Biopsy – pre-dose and between monotherapy and concomitant therapy

[h] Within (+/-) 24 hours from last dose of ZD6474 monotherapy, but must be before first dose of cisplatin or radiotherapy

[i] Radiotherapy – once daily, 5 fractions per week

[j] Radiation treatment planning and simulation prior to initiation of monotherapy

Table 2 Study plan – Treatment Regimen 2

Screen		**Monotherapy Phase**		**Concomitant Therapy Phase**								
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**FU[b]**
Week		**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**W9**	**Disc**	
Day	**-21 dys**	**D1**	**D8**	**D15[a]**	**D22**	**D29**	**D36**	**D43**	**D50**	**D58**	**D65**	**Q3mos[b]**
Informed consent	X											
Medical history	X											
Inclusion/ exclusion criteria	X											
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X[b]
Vital signs/weight	X	X	X	X	X	X	X	X	X	X	X	X[b]
ECG[c,d]	X[c]	X[d]	X	X		X				X		
Clinical chemistry / Hematology (See Table 13)	X		X	X	X	X	X	X	X	X	X	
Urinalysis	X		X	X	X	X	X	X	X	X	X	
RECIST	X											X[b]
WHO performance status	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy tests (females)	X											
Dispense study medication		X				X				X		
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X[b]
Plasma biomarkers[e]	X[e]	X	X	X					X			
PBMC/CECs[e]	X[e]	X	X	X					X			

Table 2 Study plan – Treatment Regimen 2

Screen		**Monotherapy Phase**		**Concomitant Therapy Phase**								
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**FU[b]**
Week		**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**W9**	**Disc**	
Day	**-21 dys**	**D1**	**D8**	**D15[a]**	**D22**	**D29**	**D36**	**D43**	**D50**	**D58**	**D65**	**Q3mos[b]**
PK sampling[f]				X[f]				X[f]	X[f]			
Archival tumor sample	X											
Tumor Biopsy (optional)[g,e,h]	X[e,g]			X[g,h]								
Dental exam	X											
Hearing assessment[i]	X[i]											
Radiotherapy[j,k]	X[j]			X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]		
Chemotherapy[l]				X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]		

Note: All visits have a +/- 3 day window

[a] Radiation after at least 14 days of monotherapy

[b] During follow-up, patients will be seen 30 days and 60 days post last dose for evaluation of safety (PE, vitals, AEs); at 90 days post last dose and every 3 months thereafter until the end of 2 years post-active treatment follow-up, patients will be evaluated for response, progression-free survival and relapse (PE, vitals, RECIST)

[c] QTc with Bazett's correction unmeasurable or $\geq$480 msec on screening ECG (Note: If a patient has QTc interval $\geq$480 msec on the screening ECG, two additional ECGs should be done [at least 24 hours apart]. The average QTc from the three screening ECGs must be $\leq$ 480 msec in order for the patient to be eligible for the study)

[d] Baseline QTc (using the Bazett's correction) will be determined by the average of 3 consecutive ECGs (within 5-10 minutes of one another) on Day 1. If the screening QTc is obtained with 3 consecutive ECGs within 3 days before Day 1, then the screening QTc will be considered to be the baseline, and repeat ECGs will not be necessary on Day 1.

[e] Tumor biopsy and plasma biomarker at screening should be done after all other screening procedures are done and after patient determined to be eligible

[f] PK – multiple timepoints on days 15, 43, and 50; see schedule below

[g] Biopsy – pre-dose and between monotherapy and concomitant therapy

[h] Within (+/-) 24 hours from last dose of ZD6474 monotherapy, but must be before first dose of cisplatin or radiotherapy

[i] Hearing assessment only required for patients in chemotherapy treatment regimen

[j] Radiotherapy – once daily, 5 fractions per week

[k] Radiation treatment planning and simulation prior to initiation of monotherapy

[l] Chemotherapy – only for treatment regimen 2; infusion once a week, starting at week 3

Table 3 PK sample schedule - ZD6474

	Day 15	Day 43	Day 50
Pre-dose	X	X	X
2 hours post dose	X		X
4 hours post dose	X		X
6 hours post dose	X		X
24 hours post dose	X		X

Table 4 PK sample schedule – cisplatin

	Day 15	Day 43	Day 50
Pre-dose	X		X
Prior to end of infusion	X		X
2.5 hours post dose	X		X
3 hours post dose	X		X
4 hours post dose	X		X
6 hours post dose	X		X
8 hours post dose	X		X
24 hours post dose	X		X

3.2 Rationale and risk/benefit assessment

3.2.1 Rationale for study design, doses and control groups

This is a phase I study to determine the safety profile, tolerability and MTD of ZD6474 in combination with RT (Treatment Regimen 1) or in combination with RT + cisplatin (Treatment Regimen 2).

Patients will receive ZD6474 monotherapy for 14 days prior to the initiation of concomitant study therapy. Patients who are assigned to Treatment Regimen 1 will receive ZD6474 administered orally or via dispersal on a daily basis in combination with RT delivered once daily, 5 fractions per week. Patients who are assigned to Treatment Regimen 2 will receive ZD6474 administered orally or via dispersal on a daily basis in combination with RT, delivered once daily, 5 fractions per week and cisplatin (30 mg/m^2) infused weekly. The length of concomitant treatment for Treatment Regimen 1 is an estimated 6 weeks. The length of concomitant treatment for Treatment Regimen 2 is an estimated 7 weeks. The number of patients is based on the desire to gain adequate information while exposing as few patients as possible to the study medication and procedures.

For early stage disease, radiation, similar to surgery, can produce similar rates of cure. For locoregionally advanced disease, concurrent chemoradiation is now a standard of care for patients who are unresectable or desire organ preservation. Because of severe toxicities associated with high dose cisplatin in combination with radiation, low-dose combination has been explored with improved tolerance and comparable efficacy (Glicksman, et al, 1997; Lau, et al, 2006). Thus, selection of treatment modality in head and neck cancer is based on a variety of considerations that must be discussed with the patient.

3.2.2 Risk/benefit and ethical assessment

New therapies are necessary for treatment of HNSCC because approximately 40 percent of patients with locally advanced disease relapse after chemoradiation after 2 years (Lau, et al., 2006). Scientific rationale suggests that ZD6474 may add to current standard of care treatment. This is a safety-tolerability study to evaluate the feasibility of combining ZD6474 with RT and ZD6474 with cisplatin and RT in the group of patients where the prescribed therapy is standard of care. Thus far, approximately 500 patients have received ZD6474 alone or in combination with chemotherapy. The management protocol to treat ZD6474 associated toxicity is well defined based on phase II studies in NSCLC and other tumors.

3.3 Selection of study population

3.3.1 Study selection record

Investigator(s) must keep a record of patients who were considered for enrollment but were never enrolled eg, patient screening log. This information is necessary to establish that the patient population was selected without bias.

3.3.2 Inclusion criteria

For inclusion in the study patients must fulfill all of the following criteria:

1. Provision of informed consent

2. Female or male aged 18 years and over

3. Histologically or cytologically confirmed (from the primary lesion and/or lymph nodes) squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx that has not been previously treated or resected

4. Stage III to IV disease (See Appendix H), with no proven hematogenous metastatic disease

5. WHO performance status of 0-1 (Appendix C)

6. One or more measurable lesions at least 10 mm in the longest diameter by spiral CT scan or 20 mm with conventional techniques (according to RECIST guidelines, Appendix D)

7. Patients with a history of non-melanoma skin cancer, or other previous malignancies treated at least 3 years prior to the current tumor from which the patient has remained continually disease-free and patients with in situ carcinoma of the cervix and adequately treated basal cell or squamous cell carcinoma of the skin are eligible

8. Life expectancy of $\geq$ 12 weeks

9. Negative pregnancy test for women of childbearing potential

3.3.3 Exclusion criteria (applicable to both treatment regimens)

Any of the following is regarded as a criterion for exclusion from the study:

1. Presence of simultaneous primary tumors

2. Women who are currently breast-feeding

3. Men or women unwilling to use an acceptable method of contraception while on study

4. Major surgery within 4 weeks, or incompletely healed surgical incision

5. Any concomitant medications that may affect QTc or induce CYP3A4 function and cannot be discontinued (see Appendix E for the list of medications that may affect QTc and Section 3.7.2 of the protocol for the list of all concomitant medications)

6. Any previous anti-cancer therapy given for treatment of current diagnosis

7. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.5 x ULRR or alkaline phosphatase >2.5 x ULRR

8. Serum bilirubin > ULRR

9. Serum creatinine >1.5 x ULRR or creatinine clearance ≤50 mL/minute (calculated by Cockcroft-Gault formula)

10. Significant cardiac event (eg. myocardial infarction, super vena cava (SVC) syndrome), within 3 months before entry, or presence of cardiac disease that in the opinion of the Investigator increases the risk of ventricular arrhythmia

11. History of arrhythmia (multifocal premature ventricular contractions [PVCs], bigeminy, trigeminy, ventricular tachycardia or uncontrolled atrial fibrillation), which is symptomatic or requires treatment (CTCAE grade 3) or asymptomatic sustained ventricular tachycardia. Atrial fibrillation controlled on medication permitted

12. Congenital long QT syndrome or a 1st degree relative with an unexplained sudden death under 40 years of age (except for Sudden Infant Death Syndrome)

13. QT prolongation with other medications that required discontinuation of that medication

14. Presence of left bundle branch block (LBBB)

15. QTc with Bazett's correction unmeasurable or ≥480 msec on screening ECG (Note: If a patient has QTc interval ≥480 msec on the screening ECG, two additional ECGs should be done [at least 24 hours apart]. The average QTc from the three screening ECGs must be ≤ 480 msec in order for the patient to be eligible for the study)

16. Potassium <4.0 meq/l despite supplementation; serum calcium (ionized or adjusted for albumin), or magnesium out of normal range despite supplementation

17. Hypertension not controlled by medical therapy (systolic blood pressure greater than 160 millimeter of mercury mmHg or diastolic blood pressure greater than 100 mmHg)

18. Evidence of severe or uncontrolled systemic disease or any concurrent condition which in the investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardize compliance with the protocol

19. Participation in an investigational study, or receipt of an investigational drug, within the past 30 days and during study.

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

21. Previous enrollment in the present study

3.3.4 Exclusion criteria (applicable to Treatment Regimen 2 only)

Any of the following is regarded as a criterion for exclusion from the study for patients who are assigned to receive cisplatin chemotherapy:

1. Pre-existing neuropathy CTCAE grade 2 or worse.

2. Known severe hypersensitivity to cisplatin or any of the excipients of the product

3. Evidence of pre-existing moderate to severe decline of hearing capacity

4. Neutrophils <1.5 x 10^9/L or platelets <100 x 10^9/L

5. Creatinine clearance ≤ 60 mL/minute (calculated by Cockcroft-Gault formula)

3.3.5 Restrictions

1. Patients who are blood donors should not donate blood during the trial and for 3 months following their last dose of study treatment.

2. Due to the experimental nature of ZD6474, female patients must be one year post-menopausal, surgically sterile, or using an acceptable method of contraception (oral contraceptives, barrier methods, approved contraceptive implant, long-term injectable contraception, intrauterine device or tubal ligation). Male patients must be surgically sterile or using an acceptable method of contraception during their participation in this study.

3.3.6 Withdrawal from study and discontinuation of treatment

3.3.6.1 Withdrawal from study

Patients will be considered to have withdrawn from the study if informed consent is withdrawn or if they are non-evaluable (see Section 3.1.2) and have completed 60 days of follow-up.

3.3.6.2 Discontinuation of treatment

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient from this study are:

- Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment

- Safety reasons as judged by the investigator and/or AstraZeneca. These patients will continue to be assessed for safety unless they withdraw their consent from study participation.

- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca

- Incorrect enrollment of the patient (ie, the patient does not meet the required inclusion/exclusion criteria or the patient is not allocated study drug as described in the protocol) unless continuing on the study treatment, in the opinion of the investigator and/or study team physician, would not involve any risk or discomfort to the patient.

Ineligible patients who are not discontinued from study treatment will not be considered evaluable and will be replaced in the cohort.

- Patient lost to follow-up
- Progressive Disease
- Death
- Other (i.e. investigator discretion)

3.3.6.3 Procedures for discontinuation

Patients who discontinue should always be asked about the reason(s) for their discontinuation and the presence of any adverse events (AEs). If possible, they should be seen and assessed by an investigator(s). Adverse events should be followed up; the patient should return investigational products. The discontinuation visit should occur after the last dose of ZD6474, chemotherapy, or radiation therapy, whichever comes last.

Patients who have a new or worsening CTCAE grade 3 or 4 laboratory value at the time of discontinuation must have further tests performed and the results recorded on the appropriate Case Report From (CRF) until the laboratory values have returned to CTCAE grade 1 or baseline; unless these values are not likely to improve because of the underlying disease. In such cases, the investigator must record their opinion in the patient's medical records. Laboratory abnormalities should not be reported as AEs unless any criterion for a serious adverse event (SAE) is fulfilled, the laboratory abnormality causes the patient to discontinue from the study, or the investigator insists the abnormality should be reported as an AE.

At discontinuation all on-going study-related toxicities and SAEs must be followed until resolution, unless in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

3.3.7 Follow-up

After completion of study therapy, patients will enter the follow-up phase of the study. During follow-up, patients will be seen 30 days and 60 days post last dose for evaluation of safety (Physical exam [PE], vitals, AEs); at 90 days post last dose and every 3 months thereafter until the end of 2 years post-active treatment follow-up, patients will be evaluated for response, PFS, and relapse (PE, vitals, RECIST). Late radiation morbidities will also be assessed and scored (see appendix I) during follow-up. Non-evaluable patients (see 3.1.2) will be followed for safety for 60 days only.

After discontinuation from treatment, patients must be followed up for all existing and new AEs for 60 calendar days after the last dose of study drug. All new AEs occurring during that period must be recorded (if SAEs, they must be reported to AstraZeneca within 24 hours) and followed up for resolution as above.

The date of first cancer therapy after discontinuation of treatment will be collected.

3.4 Treatments

Additional descriptive information for ZD6474 can be found in the Investigator Brochure.

Refer to current prescribing information for more descriptive information on cisplatin.

3.4.1 ZD6474

ZD6474 will be supplied as white film-coated tablets. The formulation numbers and descriptions are provided below:

Table 5 Formulation numbers of ZD6474

Tablet strength (mg)	Formulation number
ZD6474 100 mg tablet	F013025
ZD6474 300 mg tablet	F013383

AstraZeneca Pharmaceuticals Investigational Products will pack ZD6474 study material into white high-density polythene (HDPE) bottles with child resistant, tamper evident closures. Study medication must be kept out of the reach of children. Patients will be supplied with sufficient medication for the study.

3.4.1.1 ZD6474 Doses and treatment regimens

Patients in the study will be dispensed bottles of open-label ZD6474 tablets; each bottle will contain ZD6474 100 mg or 300 mg tablets. As determined by the dosing cohort, the patient will take 1 x 100 mg tablet (100 mg dose), 2 x 100 mg tablet (200 mg dose) or 1 x 300 mg tablet (300 mg dose).

There are no food restrictions for the administration of ZD6474. Patients will take the required dose daily, according to their cohort, at the same time of day each morning until they complete the 2-week monotherapy phase plus the 6-week or 7-week concomitant treatment period or until they meet a criteria for discontinuation (See Section 3.3.6.2) whichever comes first.

ZD6474 tablets must be taken whole. Patients who are unable to swallow tablets may dissolve the tablet and administer via the dispersal method as described in section 3.4.1.2.

For those patients assigned to Treatment Regimen 2, ZD6474 must be taken prior to the administration of cisplatin due to the timings of the required ECG and PK samples.

If the patient does not take the dose in the morning, he or she may take that day's dose at any time up to 10 p.m. that same day. However, if a patient misses taking their scheduled dose and is unable to take the missed dose on the same day, he or she must take the next scheduled dose

and the missed dose will not be made up. The missed dose must be documented on the appropriate CRF. The dose of study treatment may be repeated if vomiting occurs within 30 minutes of taking the study treatment.

3.4.1.2 ZD6474 tablet dispersion

Instructions for dispersing ZD6474 tablets

Do not crush tablets. Drop the number of ZD6474 tablets required for a single dose into an appropriate container (ideally glass to help confirm removal of all the dispersed material) containing approximately 2 ounces (or 50 mL) of water (either drinking water, sterile water for injection, or purified water) at room temperature. Stir the liquid occasionally to ensure complete break-up of the tablets. When the tablets have broken up into a fine dispersion (approximately 10 to 15 minutes) it can be administered to the patient. Administration to the patient should occur immediately after dispersion is complete whenever possible.

To ensure delivery of the whole dose, rinse the container with a similar amount of water to ensure removal of any material adhering to the walls of the container and administer the additional water to the patient.

Stability summary

Experimentation has shown that ZD6474 tablets will break up into a fine dispersion within 10 to 15 minutes when they are dropped whole into water (either drinking water, sterile water for injection, or purified water) at room temperature. The dispersion should be administered to the patient immediately if possible. In the event of a delay in administration, the dispersion is chemically stable up to 4 hours after preparation.

The data confirms that aqueous dispersal of ZD6474 (as described above) has no detrimental effects on the release of the active pharmaceutical ingredient (API) when compared to administration of the intact tablet and that a delay of up to 4 hours between preparation of the dispersion and administration will not have any detrimental effect on the assay and degradation products or the release of API in the dispersed tablet.

Effect of variation in pH and temperature of water for dispersion

The temperature and pH of the water used to prepare the dispersed tablet may vary in the clinic. The effect of pH of the water used for dispersion was evaluated over the range pH 5–8. Over this range, the pH of the water used for dispersing the tablets has no significant effect on the dispersion times.

The temperature range defined in the USP for controlled room temperature excursions that are experienced in hospitals is 15 °C to 30 °C. Over this range, the temperature of the water does have an effect on tablet dispersion times with the tablets taking longer to disperse at lower temperatures. All tablets tested dispersed within 10 minutes.

Compatibility with delivery devices

The dispersed tablet may be administered by nasogastric tube or gastrostomy tube. To ensure that the dose is not affected by the method of delivery, the ZD6474 content and degradation products were determined after the dispersion had been passed through the delivery tube. See Table 6 for details of the feeding tubes tested.

Table 6 Feeding tube equipment tested

Tube No	Feeding tube type	Product details	Product Code	Lot No
1	Nasogastric	Flocare nasointestinal feeding tube from Nutricia (CH10). (PD Ref. P/4163/07)	35231	200509353
2	Gastrostomy	Flocare PEG set from Nutricia (CH14). (PD Ref. P/4163/08)	35428	200506132
3	Nasogastric	CORFLO Controller PILL-NG entereal feeding tube from Viasys (10FR). (PD Ref. P/4163/011)	20-2551	18864

No significant difference was observed between the delivered dose obtained for the feeding tubes and the content of ZD6474 in the control sample, indicating that the patient should receive the full dose when the dispersed tablet is administered using a feeding tube.

For the assay and degradation products results, no significant difference was observed between the results obtained for the feeding tubes and those obtained for intact tablets indicating that there are no compatibility issues with any of the tubes.

The administration method and any change in that method must be recorded on the appropriate CRF.

3.4.1.3 Labeling of ZD6474

For the 100 mg and 300 mg cohorts, 1 bottle of ZD6474 will be dispensed at visits 2 and 6, and additionally as required. For the 200 mg cohort, 2 bottles of ZD6474 (100 mg tablets) will be dispensed at visits 2 and 6, and additionally as required.

Information on the bottle will indicate the study number, unique batch number, contents, caution, and storage conditions and will have blank spaces for the patient Ecode (to be written in by the site personnel at the center at the time of dispensing). Dosing instructions will be included on the label.

3.4.1.4 Storage

All investigational products must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage and shipment conditions are specified on the investigational product bottle label.

3.4.1.5 Accountability

The study treatment(s) must be used only as directed in the protocol. Records of overall dispensing and returns will be maintained by each center, separately from the CRFs recording the treatment dispensed to individual patients.

Patients must return all unused medication and empty containers to the Investigator, who will retain these along with any study treatment not dispensed, until they are collected by AstraZeneca Pharmaceuticals authorized personnel.

The Investigator must maintain accurate records accounting for the receipt of the investigational products and for the disposition of the material. This record keeping consists of a dispensing record including the identification of the person to whom the drug was dispensed, the quantity and date of dispensing, and any unused drug returned to the Investigator. This record is in addition to any drug accountability information recorded on the paper CRFs. At the termination of the study or at the request of the sponsor, the Investigator must send any unused supplies for destruction in liaison with AstraZeneca.

3.4.2 Cisplatin chemotherapy

3.4.2.1 General aspects

Patients must be in the hospital or cancer center for the administration of cisplatin to be given concurrently with RT. Patients must be adequately pre-hydrated.

Cisplatin is available commercially and supplied by the investigator's pharmacy. Each vial contains 10 mg of DDP, 19 mg of sodium chloride, 100 mg of mannitol and hydrochloric acid for pH adjustment. One vial is reconstituted with 10 ml of sterile water, pH range 3.5-4.5.

Unopened vials will be stored in accordance with the manufacturer's recommendation on the label.

3.4.2.2 Calculation of the body surface area

Doses of cisplatin will be calculated based on body surface area (BSA) determined using the patient's actual and concurrent weight. BSA should be recalculated using current weight prior to initiating each infusion. The method used to calculate BSA can be the site's standard.

3.4.2.3 Courses of cisplatin

Cisplatin will be administered weekly to patients in Treatment Regimen 2 for a 7-week treatment period. The dose of cisplatin is 30 mg/m^2 IV. The doses of cisplatin should be diluted in 2 liters of dextrose 5% in 1/2 or 1/3 normal saline containing mannitol 37.5 grams. This solution should be infused over 2 hours and will be administered simultaneously (in accordance with institutional practice) with the afternoon session of RT. The first course of cisplatin should begin on the first Monday of RT.

Before initiating treatment with cisplatin, the following criteria must be met:

- Neutrophils >1.0 x10^9/L
- Platelets >75 x10^9/L
- Creatinine clearance >60 ml/min
- Suggested premedication: granisetron, 0.7 to 1.0 mg IV or ondansetron 32 mg IV should be given 30 minutes before cisplatin chemotherapy. A more aggressive prophylactic antiemetic regimen and any "as-needed" antiemetics may be given at the discretion of the Investigator. Any pre-existing dehydration must be corrected before cisplatin administration.
- Suggested intravenous pre-hydration with 1-2 liters of sodium chloride 0.9% over 8 to12 hours.
- Urinary output: >100 ml/hour over 2 hours before starting each administration of cisplatin. If this level is not reached give furosemide (Lasix®) 20 mg IV.
- Replace potassium (K) and magnesium (Mg) as needed.
- Check for presence of ototoxicity

3.4.3 Radiotherapy

The assignment of a radiation treatment depends on the treatment regimen.

Patients will be treated with intensity-modulated radiation therapy (IMRT). It is expected, however, that a few patients on Treatment Regimen 2 may require treatment with non-IMRT. Non-IMRT may be required for patients in whom very little normal tissues can be spared with IMRT, very advanced tumors where the boundaries of the target volumes are unclear, or patients who may not be able to tolerate the treatment position for a sufficient duration for IMRT.

3.4.3.1 Radiation Doses for Treatment Regimen 1

IMRT doses:

Primary Target : 66 Gy called CTV1_66 (2.2 Gy/fraction in 30 fractions)

- Secondary Targets : 54 Gy called CTV2_54 (1.8 Gy/fraction in 30 fractions)

Intermediate Targets: 60 Gy called CTV3_60 (2 Gy/fraction in 30 fractions)

3.4.3.2 Radiation Doses for Treatment Regimen 2

IMRT doses:

Primary Target : 70 Gy called CTV1_70 (2 Gy/fraction in 35 Fractions)

Secondary Targets : 56-59.5 Gy called CTV2_56 -59.5 (1.6-1.7Gy/fraction in 35 fractions)

Intermediate Targets: 59.5-63 Gy called CTV3_59.5-63(1.7-1.8Gy/fraction in 35 fractions)

Non-IMRT doses:

Primary Target : 70 Gy called CTV1_70 (2 Gy/fraction in 35 fractions)

Secondary Targets : 50-56 Gy called CTV2_50-56 (2 Gy/fraction)

Intermediate Targets: 56-60 called CTV3_56-60 (2 Gy/fraction)

3.4.3.3 Treatment Planning

Treatment planning CT scans will be required to define tumor, clinical, and planning target volumes. MRI scans are optional. The treatment planning CT scan should be acquired with the patient in the same position and immobilization device as for treatment.

All tissues to be irradiated must be included in the CT scan. It is recommended but not required that the CT scan thickness be 0.3 cm through the region that contains the primary target volumes. MRI scans may be included to assist in definition of target volumes, especially when targets extend near the base of skull. If possible, the treatment immobilization device should also be used for the MRI scan. If this is not possible, it may be necessary to employ image correlation methods to correlate the MRI and CT scans. IV contrast may be utilized to better visualize normal anatomic structures and delineate normal vasculature.

The immobilization device should include neck and shoulder immobilization. A thermoplastic face mask alone may not provide sufficient neck immobilization. A description of the immobilization system used by each institution should be provided.

The Gross Tumor Volume (GTV), Clinical Target Volume (CTV) and Planning Target Volume (PTV) and normal tissues must be outlined on all CT slices in which the structures exist.

The treatment plan used for each patient will be based on an analysis of the volumetric dose, including dose-volume histogram (DVH) analyses of the PTV and CTV and critical normal structures. A “forward” iterative planning or “inverse” planning using computerized optimization are allowed. The treatment aim will be the delivery of radiation to the PTVs and the exclusion of noninvolved tissue as feasible.

3.4.3.4 Volume and ICRU Reference Point Definitions

The definition of volumes will be in accordance with the 1993 ICRU Report #50: Prescribing, Recording and Reporting Photon Beam Therapy.

- ***The Gross Tumor Volume (GTV)*** is defined as all known gross disease determined from CT, clinical information, endoscopic findings and MRI in the case of tumors treated after biopsy alone.

- ***The Clinical Target Volumes (CTV)*** is defined as the GTV plus areas considered to contain potential microscopic disease, delineated by the treating physician. The margin between the each GTV and its CTV will typically be 1-2 cm, with a minimum of 5 mm except in those areas where the GTV is immediately adjacent to critical normal structures known to be uninvolved.

- ***The Planning Target Volume (PTV)*** is defined as the CTV plus a margin to compensate for various uncertainties, such as systematic treatment setup variables, organ motion, and organ displacement (e.g., laryngeal motion). The PTV should exclude air when expanding outside the patient's external contours. A 5 mm margin around the CTV is recommended in all directions, except where the CTV is immediately adjacent to critical normal tissues such as the spinal cord or brainstem, optic chiasm, optic nerves, (in which case, the margin from CTV to PTV will be at treating physician's discretion). The recommended margin from CTV to PTV where the spinal cord or brainstem or optic apparatus is not a concern is 5 mm (0.5 cm).

3.4.3.5 Target and Critical Normal Tissue Definitions

Treatment Regimen 1

The primary targets are PTV66 containing the primary tumor and lymph nodes containing clinical or radiographic evidence of metastases.

The secondary target is the PTV54 which contains lymph node groups or surgical neck levels at risk of subclinical metastases.

An optional target volume PTV60 may be defined at the discretion of the treating physician. It will contain subclinical disease deemed to be at higher risk than the PTV54 (first echelon nodes or dissected neck area containing lymph node metastases and requiring a higher dose than PTV54).

Treatment Regimen 2

The primary targets are PTV70 containing the primary tumor and lymph nodes containing clinical or radiographic evidence of metastases.

The secondary target is the PTV56-59.5 which contains lymph node groups or surgical neck levels at risk of subclinical metastases.

An optional target volume PTV59.5-63 may be defined at the discretion of the treating physician. It will contain subclinical disease deemed to be at higher risk than the PTV56-59.5 (first echelon nodes or dissected neck area containing lymph node metastases and requiring a higher dose than PTV56-59.5).

Lymph node groups at risk include the following:

1. Submental nodes (surgical level IA): In cases where the floor of mouth or level IB are involved

2. Submandibular nodes (surgical level IB): All cases except primary palate tumors which do not extend to the tonsil or base of tongue. Only the ipsilateral level IB is a target, unless tumor crosses the midline. Level IB is a target in the neck side with upper jugular metastases in all cases

3. Upper deep jugular (junctional, parapharyngeal) nodes: all cases (at the neck side ipsilateral to the primary tumor)

4. Subdigastric (jugulodigastric) nodes, midjugular, lower neck, and supraclavicular nodes (levels II through IV): all cases, bilaterally

5. Posterior cervical nodes (level V): all cases, at the neck side where there is an evidence of jugular nodal metastases

6. Retropharyngeal nodes: in cases involving the oropharynx or hypopharynx

The lymph node groups at risk will be determined and their volumes (CTVs) will be outlined on the treatment planning CT according to image-based nodal classification. Alternatively, the surgical neck levels at risk will be determined and will be outlined as CTVs on the planning CT according to Nowak et al..

3.4.3.6 Equipment

Megavoltage equipment capable of delivering static intensity modulation with a multileaf collimator (MLC) or dynamic intensity modulation (using a MLC or tomotherapy) is required.

A conventional anterior low-neck field is allowed or the lower neck field may be encompassed as part of the entire planning target volume rather than a separate matching lower neck field.

Megavoltage equipment capable of delivering high energy photons and electrons are required. Therefore, participating centres should have access to either:

- A 4 to 8 MV photon linear accelerator equipped with a MLC

- Electron beams with energies from 8 to 14 MeV

In case of a CTV close to the skin surface the use of a spoiler or the interposition of bolus material might be required to ensure adequate subcutaneous coverage.

3.4.3.7 Dose Specification

The prescription dose is the isodose which encompasses at least 95% of the PTV.

No more than 20% of any PTV will receive >110% of its prescribed dose.

No more than 1% of any PTV will receive <93% of its prescribed dose.

No more than 1% or 1 cc of the tissue outside the PTVs will receive >110% of the dose prescribed to the primary PTV.

Treatment Regimen 1: Prescription dose to the PTV

Prescription dose to the PTVs shall be according to the following:

Primary Target PTV66: The gross tumor and lymph node metastasis including non-palpable lymph nodes suspicious for metastasis according to radiologic criteria will receive 30 fractions of 2.2 Gy/fraction, total 66 Gy.

An additional boost of 4 Gy using a supplemental electron field may be added at the discretion of the radiation oncologist. For Example T1N2a disease where the node is bulky or slow responding.

Secondary Targets PTV54: The secondary target encompasses the elective lymph node groups or surgical neck levels at risk of subclinical metastases and low risk regions adjacent to the primary tumor such as the contralateral base of tongue (in base of tongue primaries) or the pterygoid plates and muscles (in tonsil primaries). This will receive 54 Gy in 30 fractions.

Intermediate Targets PTV60: The subclinical regions felt to be at intermediate risk such as the nodal region immediately adjacent to involved nodes. This will receive 60 Gy in 30 fractions of 2 Gy.

This regimen should not be used with concurrent cisplatin.

Treatment Regimen 2: Prescription dose to the PTV

Prescription dose to the PTVs shall be according to the following:

Primary Target PTV70: The gross tumor and lymph node metastasis including non-palpable lymph nodes suspicious for metastasis according to radiologic criteria will receive 35 fractions of 2 Gy/fraction, total 70 Gy.

Secondary Targets PTV56-59.5: The secondary target encompasses the elective lymph node groups or surgical neck levels at risk of subclinical metastases and low risk regions adjacent to the primary tumor such as the contralateral base of tongue (in base of tongue primaries) or the pterygoid plates and muscles (in tonsil primaries). This will receive 56-59.5 Gy in 35 fractions at 1.6-1.7 Gy/fraction.

Intermediate Targets PTV59.5-63: The subclinical regions felt to be at intermediate risk such as the nodal region immediately adjacent to involved nodes .This will receive PTV59.5-63 Gy in 35 fractions of 1.7-1.8 Gy/fraction.

3.4.3.8 Radiation treatment and dose – Treatment Regimen 1

Patients who are receiving Treatment Regimen 1 will all be treated with IMRT.

For IMRT planning, the plan normalization should ensure that 95% of the PTV is covered by the prescribed dose.

For all treatment techniques, the maximum dose should not exceed **115%** of the prescribed dose. However, if a boost to involved areas is used, the maximum dose can be increased to a value that is 10% higher than the value of the boost dose. This maximum dose is allowed to spill outside of the involved region into the 66 Gy region.

For IMRT planning, 98% of the PTV66 should be covered by a dose that is 92% of this prescribed dose (i.e., by 64 Gy). This limits the amount of underdose of this target.

Primary Tumor Grossly Involved Lymph Nodes

Final dose (using shrinking field technique or IMRT): 66 Gy to all sites of gross disease based on both clinical exam and radiologic imaging.

Grossly involved Neck Lymph Nodal Regions

Final dose (using shrinking field technique or IMRT): grossly involved high risk lymph node disease based on both clinical exam and radiologic imaging: 66 Gy. An additional boost of 4 Gy using a supplemental electron field may be added at the discretion of the radiation oncologist. For Example T1N2a disease where the node is bulky or slow responding.

Intermediate Risk Region

The dose to intermediate targets is 60Gy. This includes subclinical regions felt to be at intermediate risk such as the nodal region immediately adjacent to involved nodes or adjacent to primary tumor. This will receive 30 fractions of 2Gy/fraction, total 60Gy

Univolved Low Risk lymph nodes

Secondary Targets PTV54: The secondary target encompasses the elective lymph node groups or surgical neck levels at risk of subclinical metastases and low risk regions adjacent to the primary tumor such as the contralateral base of tongue (in base of tongue primaries) or the pterygoid plates and muscles (in tonsil primaries). This will receive 54 Gy in 30 fractions at 1.8 Gy/fraction using IMRT or 50 Gy at 2 Gy/fraction if the low neck is treated with a non-IMRT technique (split field).

This includes ipsilateral low risk lymph nodes, contralateral low lymph nodes, and other non-dissected lymph node regions (Levels 2-5 [plus level 1 for oral cavity cancers], and for pharyngeal cancers, the retropharyngeal lymph node region).

Treatment will be delivered once daily, 5 fractions per week, over 6 weeks. All targets will be treated simultaneously. Breaks in treatment should be minimized. Break in treatment time of more than 5 days will be considered a major variation and requires documentation underlying the specific reasons for the treatment break (ex. related to study drug and/or chemotherapy and/or RT.

The reported doses for each PTV shall include the prescription dose as well as the maximum point dose, % target volume receiving > 110% and >115% of its prescribed dose and the % target volume receiving < 93% of the prescribed dose, and the mean dose to the PTV.

The method used for tissue heterogeneity calculations shall be reported. Corrected dose distributions shall be calculated and submitted for quality control/quality assurance. The dose prescription is to be based on a dose distribution corrected for heterogeneities.

3.4.3.9 Radiation treatment and dose – Treatment Regimen 2

Patients who are receiving Treatment Regimen 2 may be treated with IMRT or non-IMRT. For simple field arrangements and multi-section CT-based 2D planning, the fields should provide prescribed dose coverage to 95 to 100% of the PTV. For 3D conformal planning, prescribed dose should also cover at least 95% of this volume.

For IMRT planning, it is recommended that plan normalization should ensure that 95% of the PTV is covered by the prescribed dose.

For all treatment techniques, the maximum dose should not exceed **115%** of the prescribed dose. However, if a boost to involved areas is used, the maximum dose can be increased to a value that is 10% higher than the value of the boost dose. This maximum dose is allowed to spill outside of the involved region into the 70 Gy region.

For IMRT planning, 98% of the PTV70 should be covered by a dose that is 92% of this prescribed dose (i.e., by 64 Gy). This limits the amount of underdose of this target.

Primary Tumor

Final dose (using shrinking field technique or IMRT): 70 Gy to all sites of gross disease based on both clinical exam and radiologic imaging.

Grossly involved Neck Lymph Nodes

Final dose (using shrinking field technique or IMRT): grossly involved high risk lymph node disease based on both clinical exam and radiologic imaging: 70 Gy in 35 Fractions at 2 Gy per fraction.

Intermediate Risk regions

The dose to intermediate targets is 59.5-63 Gy. This includes subclinical regions felt to be at intermediate risk such as the nodal region immediately adjacent to involved nodes or adjacent

to primary tumor. This will receive 35 fractions of 1.7-1.8 Gy/fraction, total 59.5-63 Gy.

Univolved Low Risk lymph nodes

Secondary Targets PTV56-59.5: The secondary target encompasses the elective lymph node groups or surgical neck levels at risk of subclinical metastases and low risk regions adjacent to the primary tumor such as the contralateral base of tongue (in base of tongue primaries) or the pterygoid plates and muscles (in tonsil primaries). This will receive 56-59.5 Gy in 35 fractions at 1.6-1.7 Gy per fraction using IMRT or 50 Gy at 2 Gy per fraction if the low neck is treated with a non-IMRT technique (split field).

This includes ipsilateral low risk lymph nodes, contralateral low lymph nodes, and other non-dissected lymph node regions (Levels 2-5 [plus level 1 for oral cavity cancers], and for pharyngeal cancers, the retropharyngeal lymph node region).

Treatment will be delivered once daily, 5 fractions per week, over 7 weeks. All targets will be treated simultaneously. Breaks in treatment should be minimized. Break in treatment time of more than 5 days will be considered a major variation and requires documentation underlying the specific reasons for the treatment break (ex. related to study drug and/or chemotherapy and/or radiation.

The reported doses for each PTV shall include the prescription dose as well as the maximum point dose, % target volume receiving > 110% and >115% of its prescribed dose and the % target volume receiving < 93% of the prescribed dose, and the mean dose to the PTV.

The method used for tissue heterogeneity calculations shall be reported. Corrected dose distributions shall be calculated and submitted for quality control/quality assurance. The dose prescription is to be based on a dose distribution corrected for heterogeneities.

3.4.3.10 Planning goals

(a) Parotid glands:

- Mean dose to either parotid < 26 Gy or
- At least 50% of the either parotid gland will receive < 30 Gy or
- At least 20 cc of the combined volume of both parotid glands will receive <20Gy.

(b) Submandibular/sublingual glands and oral cavity:

- Reduce the dose as much as possible. (Record the mean doses to the ipsilateral and contralateral submandibular glands)

3.4.3.11 Planning priorities

Critical normal structure constraints followed by the prescription goals are the most important planning priorities. The priorities in addressing the protocol aims and constraints will be in the following order:

- Critical Normal Structure Constraints
- Prescription Goals
- Planning Goals: salivary glands

3.4.3.12 Delineation of organs at risk

It is recommended that the dose to any point within the spinal cord should not exceed 48 Gy to any volume larger than 0.03 cc (approximately equivalent to a 3x3x3 mm cube). Spinal cord dose must be clearly documented. For non-IMRT plans, spinal cord blocks should be inserted into all fields at a dose of 40-44 Gy to achieve this goal.

It is recommended that DVHs be generated for all critical normal structures and the unspecified tissues. Dose constraints to normal tissues should be as follows.

- Glottic Larynx 2/3 below 45 Gy
- Brainstem 54 Gy , Maximum dose to anterior surface 60Gy
- Spinal cord 45 Gy
- Mandible 70 Gy
- Unspecified tissue outside the targets: < 110% of the prescribed dose to PTV70
- Oral cavity avoidance: 35 Gy
- Cochlear < 45 Gy

For tumors which approach the base of skull:

- Optic Nerve 54 Gy
- Optic chiasm 54 Gy
- Globes 50 Gy
- Brain 60 Gy

Participants are strongly encouraged to remain within these limits.

3.4.3.13 Supportive care

Placement of a gastrostomy tube *(PEG or PFG)* before treatment begins is strongly recommended to optimise nutrition and hydration during combined therapy.

Aggressive oral and skin care, and analgesics are recommended.

The use of pilocarpine is not encouraged; however, if used, record all details on the CRF.

3.4.3.14 Dental exams

All patients receiving RT should have an oral and dental examination including clinical and radiological examination. Usual management consists of:

- Avulsions when preservation is not possible.
- Other dental restoration procedure for superficial caries not involving pulpal tissue.
- Endodontic treatment for caries involving pulpal tissue.
- Maintenance of optimal hygiene and systematic lifetime fluoride topical application methods.

When avulsions are required, they should be performed according to well-established procedures and should be as non-traumatic as possible. Alveolectomy and primary closure should be attempted at the time of extraction. If the site of extraction is within the irradiated volume, surface coverage of exposed bone should be obtained before starting RT, which usually requires 10 days.

Elective post-treatment extractions should be avoided. However, if extraction needs to be performed, prophylactic antibiotic should be given postoperatively for 10-15 days.

3.4.3.15 Treatment verification

Verification and orthogonal films or images are required. For all forms of IMRT dose delivery, orthogonal films or images that localize the isocenter placement shall be obtained.

3.4.3.16 Portal films

Portal films (either hard copy or EPI) will be obtained for all fields on the first day of treatment and at the time of each field reductions if any. It is also recommended to obtain port films of selected fields once a week during treatment. Portal films will be compared to localization films and all discrepancies must be corrected.

3.4.3.17 Neck dissection

If a neck dissection is planned for > 3 cm lymph nodes after radio-chemotherapy, the dose to the involved lymph nodes may be limited to 50.4-63 Gy. This information must be clearly

documented in the treatment record. When there is *(are)* positive node*(s)* in the lower neck, an additional field may be necessary to deliver a supplemental dose to the positive node*(s)*.

3.4.3.18 Quality Assurance

All sites will undergo Quality Assurance on equipment conformity and treatment delivery. A further Quality Control check will be performed on the first patient enrolled at each site to check conformity to the radiotherapy schedule.

3.5 Treatment Regimens

Patients who have successfully completed the screening process will be assigned to a treatment regimen based on their disease stage (see Table 7). Patients with a disease stage of T1N2a or T2N2a are eligible for either treatment regimen. Assignment to a treatment regimen for patients with stage T1N2a or T2N2a only will be at investigator discretion.

Prior to starting the combination therapy, all patients will receive ZD6474 monotherapy, according to their cohort assignment, for 14 days.

The treatment regimens consist of: Treatment Regimen 1- ZD6474 + RT or Treatment Regimen 2 – ZD6474 + RT/cisplatin.

Table 7 Assignment of patients to a treatment regimen

Treatment regimen	Description	Disease stage	N
Treatment Regimen 1	ZD6474 + RT	T1N1, T1N2a, T2N1, T2N2a	24
Treatment Regimen 2	ZD6474 + RT/ cisplatin	T1N2a, T2N2a, T2N2b, T2N2c and T2N3, T3 and T4 any N	24

N Maximum number of evaluable patients

Enrollment will occur in both treatment regimens concurrently. Each treatment regimen consists of 3 potential cohorts: ZD6474 100 mg, 200 mg or 300 mg. Once patients have been assigned a treatment regimen, they will be assigned to the current cohort for that treatment regimen.

Table 8 Treatment Regimen 1 dosing cohorts

Dosing Cohort	1A	1B	1C
ZD6474	100 mg	200 mg	300 mg
RT	66 Gy	66 Gy	66 Gy
N [a,b]	6[b]	6[b]	6[b]

a Once MTD has been determined for this treatment regimen, an additional 6 patients will be enrolled into the MTD cohort.

b Each cohort must contain 6 evaluable patients (see section 3.1.2 for definition of evaluable). Non-evaluable patients will be replaced.
N Maximum number of evaluable patients

Table 9 Treatment Regimen 2 dosing cohorts

Dosing Cohort	2A	2B	2C
Cisplatin	30 mg/m^2	30 mg/m^2	30 mg/m^2
ZD6474	100 mg	200 mg	300 mg
RT	70 Gy	70 Gy	70 Gy
N [a,b]	6[b]	6[b]	6[b]

a Once MTD has been determined for this treatment regimen, an additional 6 patients will be enrolled into the MTD cohort.
b Each cohort must contain 6 evaluable patients (see section 3.1.2 for definition of evaluable). Non-evaluable patients will be replaced.
N Maximum number of evaluable patients

See section 3.1.1 for information regarding dose escalation.

Six evaluable patients will be enrolled in each dose cohort, for each treatment regimen. To be considered evaluable, a patient must have completed study treatment as defined or experienced a dose limiting toxicity (see section 3.1.1.1). Non-evaluable patients will be replaced.

For each treatment regimen, once the MTD for ZD6474 is determined, or the dose levels have been explored up to 300 mg, (which can occur independently for Treatment Regimens 1 & 2), 6 additional patients will be enrolled into each treatment regimen at the MTD.

Treatment Regimen 1

Cohort 1A:

- ZD6474 100 mg (dose orally or via dispersal) monotherapy daily for 14 days
- ZD6474 100 mg daily concomitantly with RT for approximately 6 weeks

If Cohort 1A is tolerable, dose escalation to Cohort 1B will occur (see section 3.1.1.2). If Cohort 1A is not tolerable, this treatment regimen will be closed.

Cohort 1B:

- ZD6474 200 mg (dose orally or via dispersal) monotherapy daily for 14 days
- ZD6474 200 mg daily concomitantly with RT for approximately 6 weeks

If Cohort 1B is tolerable, dose escalation to Cohort 1C will occur (see section 3.1.1.2). If Cohort 1B is not tolerable, the MTD will be Cohort 1A.

Cohort 1C:

- ZD6474 300 mg (dose orally or via dispersal) monotherapy daily for 14 days
- ZD6474 300 mg daily concomitantly with RT for approximately 6 weeks

If Cohort 1C is tolerable, then MTD will be Cohort 1C (See section 3.1.1.2). If Cohort 1C is not tolerable, the MTD will be Cohort 1B.

Once the MTD for ZD6474 has been determined for this regimen, an additional 6 patients will be enrolled into the MTD cohort and will receive a complete course of RT (approximately 6 weeks). Once patients have completed the course of concomitant therapy, they will be followed for safety, response, PFS, and relapse for 2 years.

Treatment Regimen 2

Cohort 2A:

- ZD6474 100 mg (dose orally or via dispersal) monotherapy daily for 14 days
- ZD6474 100 mg daily concomitantly with cisplatin (30 mg/m^2 IV weekly) and RT for approximately 7 weeks

If Cohort 2A is tolerable, dose escalation to Cohort 2B will occur (see section 3.1.1.2). If Cohort 2A is not tolerable, this treatment regimen will be closed.

Cohort 2B:

- ZD6474 200 mg (dose orally or via dispersal) monotherapy daily for 14 days
- ZD6474 200 mg daily concomitantly with cisplatin (30 mg/m^2 IV weekly) and RT for approximately 7 weeks

If Cohort 2B is tolerable, dose escalation to Cohort 2C will occur (see section 3.1.1.2). If Cohort 2B is not tolerable, the MTD will be Cohort 2A.

Cohort 2C:

- ZD6474 300 mg (dose orally or via dispersal) monotherapy daily for 14 days
- ZD6474 300 mg daily concomitantly with cisplatin (30 mg/m^2 IV weekly) and RT for approximately 7 weeks

If Cohort 2C is tolerable, then MTD will be Cohort 2C (See section 3.1.1.2). If Cohort 2C is not tolerable, the MTD will be Cohort 2B.

Once the MTD for ZD6474 has been determined for this regimen, an additional 6 patients will be enrolled into the MTD cohort and will receive a complete course of RT/chemotherapy. Once patients have completed the course of concomitant therapy, they will be followed for safety, response, PFS, and relapse for 2 years.

3.5.1 Method of assigning patients to treatment regimens

As patients are screened for the study, they must be allocated an E-code. The E-code is a 7-digit number made up of the center number and the patient number within that particular center (eg, the first patient screened at center number 0001 would be assigned the E-code E0001001, the second patient screened would be E0001002 and so on). This number is the patient's unique identifier and is used to identify the patient on the CRFs.

Patient eligibility will be established before treatment regimens are assigned. Patients who have successfully completed the screening process will be assigned to a treatment regimen based on their disease stage (see Table 7). Patients with a disease stage of T1N2a or T2N2a are eligible for either treatment regimen. Assignment to a treatment regimen for patients with stage T1N2a or T2N2a only will be at investigator discretion.

If a patient discontinues from the study, the patient E-code number will not be reused, and the patient will not be allowed to re-enter the study.

3.6 Blinding and procedures for unblinding the study – Not applicable

3.7 Pre-study, concomitant and post-study treatment(s)

Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator(s). The administration of all medication (including investigational products) must be recorded in the appropriate sections of the CRF.

3.7.1 Suggested pre-medication for cisplatin

Granisetron 0.7-1 mg IV or ondansetron 32 mg IV will be given 30 minutes before cisplatin chemotherapy. Anti-emetics can be given at the discretion of the Investigator. If anti-emetics are given more than once or regularly, ECGs should be done weekly during the concomitant treatment phase.

Any pre-existing dehydration must be corrected prior to cisplatin administration. It is suggested that IV pre-hydration with 1 liter of sodium chloride 0.9% with 12.5 grams of mannitol, 10 mEq of potassium chloride and 16 mEq of magnesium sulfate be administered at 500 ml/hr over 2 hours.

3.7.2 Other concomitant treatment

Supportive care measures and symptomatic treatment for any treatment-associated toxicity may be instituted once the first signs of toxicity occur.

Concomitant use of the known potent inducers of CYP3A4: rifampicin, phenytoin, carbamazepine, barbiturates and St John's Wort are not allowed within 2 weeks of study or during the study.

Concomitant use of medications generally accepted as having a risk of causing Torsades de Pointes (see Appendix E Table 1) are not allowed within 2 weeks of study or during study. These drugs should also be avoided for up to 4 weeks following discontinuation of study treatment.

Drugs with a possible risk of Torsades de Pointes (see Appendix E Table 2) are not allowed within 2 weeks of study entry but may be allowed during study (see next paragraph).

The following medications can be taken by patients, but require additional monitoring:

- Co-administration of drugs that in some reports might be associated with Torsades de Pointes but at this time lack substantial evidence of Torsades de Pointes (see Appendix E, Table 2) should be avoided if possible. However, these drugs will be allowed, at the discretion of the Investigator, if considered absolutely necessary. In such cases, the patient must be closely monitored including regular checks of QTc and electrolytes. The ECG must be checked within 24 hours of commencing the concomitant medication and then at least once per week while the patient remains on the medication. The frequency of ECG monitoring could revert to the standard schedule if no ECG prolongation has been noted during 4 weeks of co-administration of a drug from Appendix E, Table 2. The electrolytes should be maintained within the normal range using supplements if necessary.

- Warfarin is allowed in therapeutic and low-doses and these patients should be monitored regularly for changes in their International Normalized Ratio (INR), at the discretion of the Investigator.

Other medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator(s). The administration of all medication (including investigational products) must be recorded in the appropriate sections of the CRF.

3.8 Treatment compliance

It is the Investigator or institution's responsibility to establish a system for handling study treatments, including investigational medicinal products, to ensure the following:

- Deliveries of such products from AstraZeneca Pharmaceuticals are correctly received by a responsible person (eg, a pharmacist)

- Such deliveries are recorded

- Study treatments are handled and stored safely and properly

- Study treatments are only dispensed to study patients in accordance with the protocol
- Any unused products are returned for destruction in liaison with the AstraZeneca project team

At the end of the study, it must be possible to reconcile delivery records with records of usage and returned stocks. Any discrepancies must be accounted for. Certificates of delivery and return must be signed, preferably by the Investigator or a pharmacist.

Patients should be given clear instructions on how and when to take their study treatment. Their tablet returns should be counted to check for compliance. Discrepancies between the number of tablets returned and the expected number of tablets returned should be discussed with the patient and the reasons for non-compliance documented.

If the patient is not compliant after counseling on the importance of taking study medication as instructed, the investigator may withdraw the patient from study treatment.

3.9 Management of Toxicity

3.9.1 Cisplatin toxicity

In the event of the following toxicities, cisplatin should be withheld. When the toxicity has resolved (to CTCAE grade 1 or baseline), cisplatin may be administered at 75% of the original dose (ie 22.5 mg/m^2), unless the patient withdraws consent:

- Neutropenia (ANC $<0.5 \times 10^9$/L [CTCAE grade 4]) $\geq$ 7 days
- Febrile neutropenia ($\geq$ CTCAE grade 3)
- Thrombocytopenia ($\geq$ CTCAE grade 3) that results in bleeding
- Renal toxicity: creatinine clearance <40ml/min
- Peripheral neuropathy ($\geq$ CTCAE grade 3), cisplatin should be stopped and not restarted
- Allergic reaction/hypersensitivity ($\geq$ CTCAE grade 3) that is clearly related to cisplatin, cisplatin should be stopped. A rechallenge is permitted at the investigator's discretion.
- Ototoxicity ($\geq$ CTCAE grade 3). Patients with clinically significant hearing loss must not receive additional cisplatin. If patients develop clinical evidence of ototoxicity, further audiometric evaluation is required.
- Other CTCAE grade 3 or 4 non-hematologic toxicity (including cutaneous reactions, edema)

For other toxicity, if cisplatin must be withheld for more than 3 weeks for resolution of toxicity, or if CTCAE grade 3 or 4 toxicity reoccurs following the dose reduction, treatment with cisplatin should not be restarted.

Patients should not be retreated with subsequent cycles of cisplatin until platelets recover to a level > 75 x 10^9/L and ANC > 1.0 x 10^9/L.

Table 10 Cisplatin dose reduction and delay

Toxicity	**CTCAE GRADE**			
	1	**2**	**3**	**4**
Neutropenia[a]				
≤7 days duration	No change	No change	No change	No change
>7 days duration	No change	No change	No change	Delay, dose reduce
Febrile neutropenia	No change	No change	Delay, dose reduce	Delay, dose reduce
Thrombocytopenia (that results in bleeding)	No change	No change	Delay, dose reduce	Delay, dose reduce
Peripheral neuropathy	No change	No change	Discontinue cisplatin	
Allergic reaction/ hypersensitivity	No change	No change	Discontinue cisplatin	
Ototoxicity	No change	No change	Discontinue cisplatin	
Other non-haematological toxicities[c]	No change	No change	Delay, dose reduce[d]	

[a] Daily measurements needed until resolution to grade 2
[b] Cisplatin should be discontinued in case of grade 2 renal toxicity, or persistent grade 1 renal toxicity that cannot be resolved by hydration
[c] Except nausea and vomiting , including cutaneous reactions and edema
[d] At the investigator's discretion

The reduced dose for cisplatin is 75% of the original dose.

In the event that cisplatin treatment is stopped, patients may be switched to weekly carboplatin at investigator's discretion. Patients who received cisplatin for at least 4 of the 7 weeks will be considered evaluable. Patients who receive fewer than 4 weeks of cisplatin either meet a criteria for DLT or meet the definition of non-evaluable (see Section 3.1.2 for more information).

In the event of changes to cisplatin therapy ZD6474 should be continued if tolerated.

3.9.2 Radiotherapy toxicity

Interruptions in RT may be necessitated by skin reaction, mucositis, ulceration, edema, or other acute complication. The reason for and the length of any such interruption must be documented. RT will be continued without interruption if at all possible. In order to relieve morbidity, RT may be interrupted for:

- Confluent mucositis
- Moist desquamation unresponsive to topical dressing
- Stomatitis resulting in weight loss greater than 15%

The use of tube feedings is encouraged to minimize treatment interruptions. Every effort should be made to avoid an interruption to the RT schedule by taking aggressive preventative measures.

Treatment breaks must be clearly indicated in the treatment record along with the reason*(s)* for the treatment break. Treatment breaks, if necessary, should ideally not exceed five treatment days at a time and ten treatment days total. Treatment breaks should be allowed only for healing of severe acute toxicity reactions and/or intercurrent illness, and not for social or logistical reasons.

Expected acute toxicity:

- Epilation
- Xerostomia
- Hypogeusia
- Dysphagia
- Expected late morbidity:
- Permanent xerostomia
- Persistent Dysphagia

Mandibular osteoradionecrosis will occur in < 5% of the patients, but may be reduced by thorough dental evaluation and treatment before irradiation, which is required.

Radiation-induced myelopathy is not anticipated provided that the cervical spinal cord dose remains < 48 Gy. However, special attention should be directed in follow-up exams to any numbness, paresthesia, or L'hermitte's signs, particularly in the first 6-12 months of follow-up.

In the event that RT is interrupted for more than 2 days every attempt should be made to keep the overall radiotherapy regime within the 6 or 7 weeks of treatment. This may be achieved by providing treatment for 6 days per week +/- extra fractions on individual days. In order to avoid therapy ending early in the week (e.g. Monday) extra fractions may be administered either twice daily occasionally or using additional days (e.g. Saturday).

The following table (see Table 11) provides guidance on RT treatment delay. Symptom management and RT interruption are at investigator discretion.

Table 11 RT treatment delay

Toxicity	**CTCAE GRADE**			
	1	**2**	**3**	**4**
Mucositis/Stomatitis (w/ weight loss >15%)	No change	No change	Delay	Delay
Moist Desquamation (unresponsive to topical dressing)	No change	No change	Delay	Delay
Xerostomia	No change	No change	Delay	Delay
Hypogeusia	No change	No change	Delay	Delay
Dysphagia	No change	No change	Delay	Delay
Periodontal disease	No change	No change	Delay	Delay

Interrupting and restarting radiotherapy with chemotherapy and ZD6474

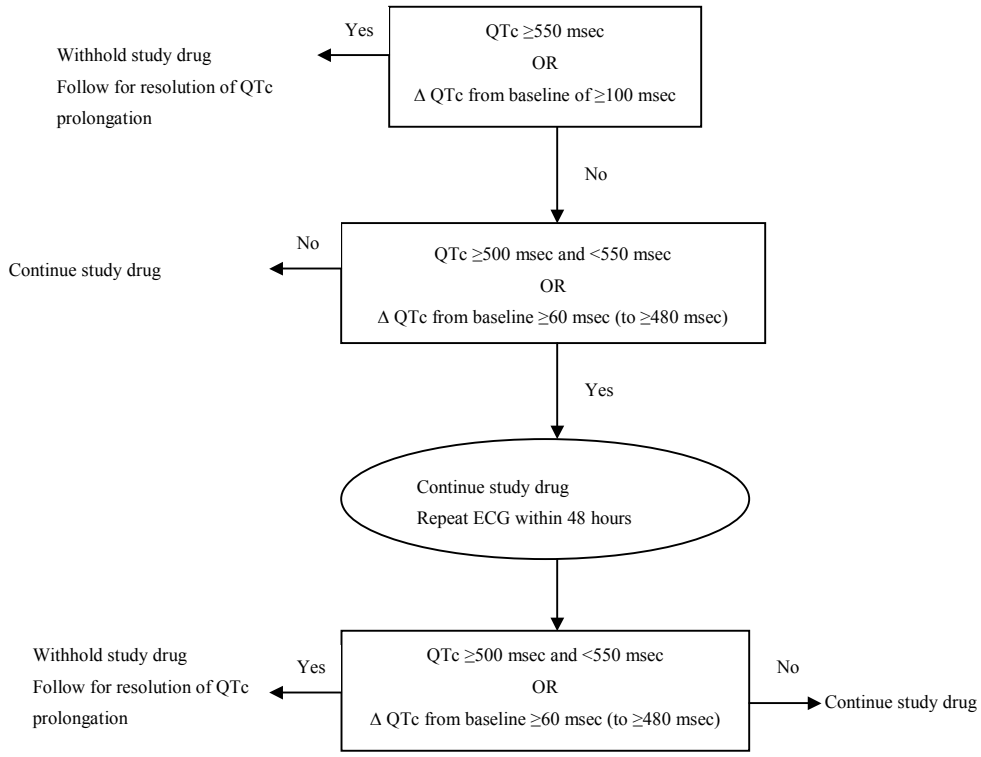
Interruptions of cisplatin or ZD6474 should be followed as outlined in the section 3.9. If RT has been interrupted, cisplatin and ZD6474 should be delayed until the RT is restarted. Restarting of cisplatin should not occur unless the criteria outlined in section 3.4.2.3 are met.

3.9.3 QTc prolongation

Patients will have ECGs performed to monitor the QTc interval (using Bazett's correction) as outlined in the study plan and the following chart. The investigator should monitor electrolytes.

The screening QTc must be <480 msec. If a patient has QTc interval ≥480 msec on the screening ECG, two additional ECGs should be done [at least 24 hours apart]. The average QTc from the three screening ECGs must be ≤ 480 msec in order for the patient to be eligible for the study. Baseline QTc will be determined by the average of 3 consecutive ECGs (within 5-10 minutes of one another) on day 1. If the screening QTc is obtained with 3 consecutive ECGs within 3 days before day 1, then the screening QTc will be considered to be the baseline, and repeat ECGs will not be necessary on day 1.

Figure 3 Flow chart detailing management of QTc prolongation



For this study QTc prolongation is defined as:

- A single QTc value of ≥550 millisecond (msec) or an increase of ≥100 msec from baseline;

OR

- Two consecutive QTc measurements, within 48 hours of one another, where either of the following criteria are met for both QTc values:
    - A QTc interval ≥500 msec, but <550 msec, or
    - an increase of ≥60 msec, but <100 msec, from baseline QTc to a QTc value ≥480 msec

Management of patients with QTc prolongation

For a single QTc value of ≥550 msec or an increase of ≥100 msec from baseline, ZD6474 must be withheld. ECGs and electrolytes will be followed 3 times a week until QTc falls below 480 msec**.** ZD6474 treatment may be resumed at a lower dose after QTc recovers to <480 msec.

For a QTc interval ≥500 msec, but <550 msec, or an increase of ≥60 msec but <100 msec from baseline QTc to a QTc value ≥480 msec, ZD6474 may be continued but a repeat ECG must be obtained within 48 hours. If QTc prolongation is confirmed ZD6474 should be withheld. ECG and electrolytes should be checked 3 times a week until QTc falls below 480 msec. ZD6474 treatment may be resumed at a lower dose after the QTc recovers to <480 msec. If the patient does not meet the criteria for QTc prolongation at the repeat ECG, then the patient should continue treatment with study medication and resume the ECG schedule as outlined in the Study Plan (see Table 1 or Table 2).

The reduced dose for 300 mg is ZD6474 200 mg daily. The reduced dose for 200 mg is ZD6474 100 mg daily. The reduced dose for 100 mg arm is ZD6474 100 mg every other day. If QTc prolongation recurs after all dose reductions as detailed, the patient will permanently discontinue treatment with ZD6474.

If ZD6474 is restarted at a reduced dose after the QTc prolongation has resolved, ECGs should be performed weekly thereafter. If ZD6474 must be withheld for greater than 3 weeks to allow for QTc prolongation to recover to less then 480 msec, then the patient will not be restarted on study medication

3.9.4 Gastrointestinal toxicity

Nausea, vomiting, or both may be controlled with anti-emetic therapy.

3.9.5 Diarrhea

Diarrhea should be treated with standard medications to avoid dose modification or interruption, if possible. Electrolyte supplementation with regular laboratory monitoring should be used, when appropriate, to maintain electrolytes within normal limits. No dose modifications will be made because of grade 1 or 2 diarrhea. If grade 3 diarrhea develops, ZD6474 or ZD6474 + cisplatin should be withheld until diarrhea resolves to grade 1 or below. RT can continue during dose interruption for diarrhea. Patients who are clinically unstable because of diarrhea or other inter-current medical illness must be admitted and evaluated using telemetry, until clinically stable. Upon recovery, treatment may resume at a permanently reduced dose. The reduced dose for 300 mg is ZD6474 200 mg daily. The reduced dose for 200 mg is ZD6474 100 mg daily. The reduced dose for 100 mg arm is ZD6474 100 mg every other day. If diarrhea recurs after all dose reductions as detailed, the patient will permanently discontinue treatment with ZD6474.

Decrease cisplatin is to 75% of the original dose (ie, 22.5 mg/m^2). If ZD6474 + RT or ZD6474 + RT/cisplatin must be withheld for more than 3 weeks for resolution of diarrhea, the

patient will not restart treatment with study medication. If grade 3 or 4 diarrhea recurs after this dose reduction, the patient must permanently discontinue study treatment.

3.9.6 Cutaneous toxicity

To reduce the risk of development or minimize severity of skin rash, and to minimize the requirement for study therapy dose reduction, it is strongly recommended that all patients follow a program of sun protective measures while receiving study therapy. Such measures should include application of sunblock (with a minimum sun protection factor (SPF) of 45), and adoption of clothing protection in full sun. In addition, it is suggested that all patients should be instructed to report any rash or associated symptoms to the Study Investigator.

If a patient develops a skin rash, the following actions are recommended to the investigator for the management of this reaction:

- The rash should be graded as soon as possible according to the CTCAE cutaneous toxicity criteria (CTCAE, Version 3).

- If a rash of CTCAE grade 2 or higher is detected, immediate symptomatic treatment should be provided.

- If a rash of CTCAE grade 3 or higher is detected, ZD6474 should be withheld until recovery to grade 1 or baseline. Upon recovery to grade 1 or baseline, ZD6474 may resume at a permanent reduced dose. The reduced dose for 300 mg is ZD6474 200 mg daily. The reduced dose for 200 mg is ZD6474 100 mg daily. The reduced dose for 100 mg arm is ZD6474 100 mg every other day.

If severe cutaneous toxicity recurs after dose reduction as detailed, the patient will permanently discontinue treatment with ZD6474.

If ZD6474 must be withheld for >3 weeks due to cutaneous toxicity, the patient will be discontinued. Recurrence of grade 3 or above skin toxicity for more than 2 times may result in patient discontinuation.

3.9.7 Other toxicity

If any other grade 3 or 4 toxicity that is not outlined above develops and is attributable to either ZD6474 + RT or ZD6474 + RT/cisplatin, ZD6474 + RT or ZD6474+ RT/cisplatin should be withheld until the toxicity resolves to grade 1 or baseline. Upon recovery, treatment may resume at a permanent reduced dose. The reduced dose for 300 mg is ZD6474 200 mg daily. The reduced dose for 200 mg is ZD6474 100 mg daily. The reduced dose for 100 mg arm is ZD6474 100 mg every other day. If toxicity recurs after all dose reductions as detailed, the patient will permanently discontinue treatment with ZD6474.

If ZD6474 + RT or ZD6474 + RT/cisplatin must be withheld for more than 3 weeks for resolution of toxicity, the patient will not restart treatment with study medication. If grade 3 or 4 toxicity recurs after dose reduction, the patient must permanently discontinue study

treatment. Patients who develop CTCAE grade 3 hypertension may continue on therapy if blood pressure is controlled on increased anti-hypertensive medication. If blood pressure cannot be stabilized with increased anti-hypertensive medication, study treatment must be discontinued and cannot be resumed until blood pressure is controlled to baseline level. Patients with CTCAE grade 4 hypertension should discontinue study treatment and cannot resume therapy until blood pressure is controlled to baseline level. If study treatment must be interrupted for more than 3 weeks to allow for toxicity to resolve, the patient's participation the study will be discontinued.

The following table (see Table 12) summarizes the guidance on ZD6474 treatment delay.

Table 12 ZD6474 dose reduction and delay

Toxicity	**CTCAE grade**			
	1	**2**	**3**	**4**
QTc Prolongation (see section 3.9.3)				
Nausea/vomiting	No change	No change	Delay, dose reduce	Delay, dose reduce
Diarrhea	No change	No change	Delay, dose reduce	Delay, dose reduce
Cutaneous	No change	No change	Delay, dose reduce	Delay, dose reduce

4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

4.1 Primary variable

Safety and tolerability are the primary endpoints. Safety and tolerability will be assessed from data on the adverse events, physical examinations, vital signs including blood pressure, heart rate, ECGs and laboratory findings.

4.2 Screening and demographic measurements

Before a patient enters the study, they will be assessed to ensure that they meet eligibility criteria (see Sections 3.3.2, 3.3.3, and 3.3.4). Patients who do not meet these criteria will not be allowed to enroll.

The following must be assessed within 3 weeks before the first dose of study medication is administered:

- Radiological and clinical tumor assessment (per RECIST)
- Medical history, including all previous but now resolved significant medical conditions

The following must be assessed within 7 days before the first dose of study medication is administered:

- 12-lead ECG
- Physical examination, including vital signs and weight
- Concomitant medications
- WHO Performance Status (see Appendix C)
- Full hematology, biochemistry and urinalysis testing (see Table 13)
- Hearing assessment (for patients who would receive cisplatin)
- Collection of blood for pharmacodynamic biomarker testing

The following must be assessed within 3 days before the first dose of study medication is administered:

- Serum pregnancy test in women of childbearing potential

The collection of blood and tumor for pharmacodynamic biomarker testing are study procedures that are done at screening. The patient's eligibility for the study must be confirmed via screening procedures before completing these study procedures.

4.3 Patient-Reported Outcomes (PROs) – Not applicable

4.4 Health Economic measurements and variables – Not applicable

4.5 Pharmacokinetic measurements and variables

The methods for collection of biological samples and derivation of pharmacokinetic variables are presented below in Sections 4.5.1 and 4.5.2

4.5.1 Collection of biological samples

Venous blood will be taken at the sampling times shown in the study plan, into tubes containing lithium heparin anticoagulant and thoroughly mixed. The blood samples will then be centrifuged within 15 minutes of collection by spinning at 1000 G for 10 minutes. The plasma should be taken off immediately and stored in a plain tube at -20 ºC before transportation to the central holding laboratory. The date and the time of collection will be recorded on the appropriate CRF. Further details on collection, labeling, and shipping are in appendix F and the central laboratory manual.

4.5.2 Drug concentration measurements, and derivation or calculation of pharmacokinetic parameters

The PK analysis will be performed by the Clinical Pharmcokineticist, AstraZeneca, Alderly Park, UK.

A PK analysis plan will be prepared prior to the commencement of this analysis.

4.5.2.1 ZD6474

(a) Analysis for secondary endpoint

ZD6474 plasma concentration-time data will be analysed using non-compartmental methods by WinNonlin Version 4.1 Enterprise. The methodology will determine C_{max} and t_{max} for each patient directly from their plasma concentration-time profiles, and $AUC_{(0-24)}$ will be calculated by the linear trapezoidal rule.

(b) Analysis for exploratory endpoint

Plasma concentrations of ZD6474 will be analyzed using non-linear mixed effects models. PK structural models and inter- and intra-individual variance models will be developed. These will be based on previous knowledge and examination of diagnostic scatter plots. If data from the study is identified as insufficient to define the PK, additional data will be included from previous clinical trials. Following this modelling of the relationship between PK and measures of safety, efficacy and the pharmacodynamic endpoints will be done. In a similar manner to the pharmacokinetics model, accuracy will be undertaken through diagnostic plots. A PK analysis plan will be prepared prior to the commencement of this analysis.

4.5.2.2 Cisplatin as total platinum

Total platinum plasma concentration-time data will be analysed using non-compartmental methods by WinNonlin Version 4.1 Enterprise. The methodology will determine C_{max}, generally at the end of infusion, for each patient directly from their plasma concentration-time profiles, and $AUC_{(0-t)}$ will be calculated by the linear trapezoidal rule to a common time t for each subject.

4.6 Pharmacodynamic measurement and variables

4.6.1 Blood biomarkers

4.6.1.1 Rationale for collection of blood biomarkers

Circulating endothelial cells have emerged as a potentially useful surrogate biomarker for VEGF pathway inhibitors for several reasons (Beaudry et al., 2005a; Monestiroli et al., 2001; Rafii et al., 2002; Shaked et al., 2005). Increased levels of CECs have been observed in cancer patients and have been associated with disease progression (Beerepoot et al., 2004; Mancuso et al., 2001). In addition, CECs are known to be mobilized in response to VEGF in both murine models (Asahara et al., 1999; Takahashi et al., 1999) and in humans (Kalka et al.,

2000), and they are known to express VEGFR-2 (Peichev et al., 2000; Reyes et al., 2002). At least two distinct populations of CECs have been identified, bone marrow-derived circulating endothelial progenitor cells (CEPs), which appear to make at least a minor contribution to tumor neovascularization (Peters et al., 2005), and mature CECs, which are thought to be shed from established vessels (Lin et al., 2000; Solovey et al., 1999). VEGF pathway inhibitors and other antiangiogenic therapeutic agents have been shown to inhibit VEGF-mediated CEP mobilization in murine models (Beaudry et al., 2005a; Bertolini et al., 2003; Hattori et al., 2001; Schuch et al., 2003; Shaked et al., 2005). It has been demonstrated in preclinical studies that ZD6474 can have differential effects on mature CECs and on CEPs in murine models and that a rise in the mature CEC level is associated with a decrease in tumor angiogenesis (Beaudry et al., 2005b).

Preliminary results from several clinical studies of antiangiogenic or vascular targeting agents have been consistent with preclinical studies (Heymach et al., 2003; Mancuso et al., 2005; Norden-Zfoni et al., 2005; Radema et al., 2002). Recently, we have monitored changes in CEC during treatment with a multitargeted tyrosine kinase that inhibits VEGFR-1, -2, and -3 and other receptors, for patients with metastatic GIST (Sawano et al., 2001) and demonstrated that patients experiencing clinical benefit had a significantly greater rise in mature CECs during the first 14 days of treatment than patients with progressive disease (Norden-Zfoni et al., 2005). These findings suggested that early changes in CECs may be useful biomarkers for biologic activity and clinical benefit for VEGF pathway inhibitors such as ZD6474.

Plasma and serum protein expression has also been investigated as a biomarker of patient prognosis and drug biologic activity. In one study, treatment with a VEGFR-2–specific antibody resulted in a dose-dependent rise in plasma VEGF concentration in both normal and tumor-bearing mice (Bocci et al., 2004). A soluble form of VEGFR-2 has also been identified in both mouse and human plasma (Ebos et al., 2004; Gora-Tybor et al., 2005; Robak et al., 2003; Wierzbowska et al., 2003).We also assessed soluble biomarkers during therapy, including plasma VEGF and soluble VEGFR-2 during treatment with the multitargeted VEGFR inhibitor (Norden-Zfoni et al., 2005). VEGF levels increased 2.9-fold during the first cycle of treatment while soluble VEGFR-2 levels decreased 1.7-fold. The changes in the soluble VEGFR-2 level correlated with trough plasma levels of the drug. These data suggested that plasma VEGF and soluble VEGFR-2 may serve as pharmacodynamic biomarkers of inhibitor activity. Other ligands in the VEGF pathway (PlGF, VEGF-B, VEGF-C) will also be assessed.

4.6.1.2 Collection and handling of blood biomarker samples

Venous blood (7mL) will be collected from all patients at screening, day 1, day 8, day 15, and day 50 for analysis of CECs in PBMCs.

Venous blood (10 mL) will be collected at screening, day 1, day 8, day 15, and day 50 for analysis of plasma biomarkers.

See laboratory manual for further details regarding sample collection, preparation, and shipment.

4.6.1.3 Blood biomarker analysis

Analysis of CECs will be performed by four-color flow cytometry as previously described (Mancuso et al., 2001; Norden-Zfoni et al., 2005) using established method. Based on earlier data the analysis will focus on time points in the first two weeks of therapy. Peripheral blood mononuclear cells (PBMCs) will be collected at the time point indicated in the study table.

Plasma biomarkers will be measured from frozen plasma using established ELISA techniques.

4.6.2 Tumor biopsy for biomarkers

4.6.2.1 Rationale for collection of tumor biopsy for biomarkers

One approach to assessing the biologic activity of a drug is to obtain tumor biopsy specimens before and during therapy and measure the drug's effects, such as reduced microvessel density, induced apoptosis, or an inhibited targeted pathway. Laser scanning microscopy (LSC) has previously been used to assess paired tumor biopsy samples obtained in three clinical trials of the small-molecule VEGFR inhibitors, as well tumor xenografts (Davis et al., 2005b; Heymach et al., 2004). In murine tumors, a 50% post-treatment reduction in VEGFR phosphorylation was associated with increased endothelial apoptosis, decreased microvessel density, and decreased tumor growth. In tumors from patients, VEGF receptor inhibition was insufficient to induce endothelial apoptosis in almost all cases, and this observation may provide a possible explanation for the lack of antiangiogenic activity and clinical responses observed for these two agents. In a subsequent trial, LSC was used to assess pre- and post-treatment biopsy samples from 20 patients with metastatic gastrointestinal stromal tumor (GIST) treated with a small molecule VEGFR inhibitor (Davis et al., 2005a). Patients with clinical benefit had a 9.6-fold increase in endothelial apoptosis, whereas patients with progressive disease had a 1.8-fold increase ($P < 0.01$). There was also a greater decrease in PDGFR phosphorylation in patients with clinical benefit than in those with progressive disease. These changes were observed after only 1–2 weeks of treatment with SU11248. These data demonstrate that receptor activation and downstream effects such as apoptosis can be assessed quantitively in tumor biopsy samples and that such changes may be predictive of clinical outcome after treatment with a receptor tyrosine kinase inhibitor.

4.6.2.2 Collection and handling of tumor biopsy

All patients will be asked to consent to providing 3 tumor samples. These will consist of one mandatory archival tissue sample and optional fresh pre- and post-dose ZD6474 tumor biopsies. At each tumor biopsy time point, the goal will be to obtain 2 to 3 cores.

The archival tissue sample will be formalin fixed, paraffin embedded.

The first core from the optional fresh tumor biopsies will be frozen in OCT and liquid nitrogen. The second core will be formalin fixed, paraffin embedded. If a third core is available, it should be split in half with one half embedded in paraffin and the other half snap frozen without OCT.

See Appendix F and central laboratory manual for further details regarding sample collection, preparation, and shipment.

4.6.2.3 Tumor biomarker analysis

For this trial, we propose to quantitatively assess phosphorlyation of VEGFR and downstream signaling (i.e. phophoAKT), as well as tumor cell and tumor endothelial apopstosis and tumor angiogenesis by CD31 staining, using LSC in paired tumor biopsy specimens from patients prior to treatment with ZD6474 and after two weeks of exposure to the drug.

The formalin fixed, paraffin embedded tumor samples will be analyzed for EGFR/Her2 gene amplification by FISH, EGFR/Her2, E-Cadherin and vimentin protein expression by IHC, and Akt/pAkt, MAPK/pMAPK, and pEGFR by IHC. If formalin fixed paraffin embedded samples are available from a 3rd core biopsy, these will be analysed for markers of tumor hypoxia and vasculature (HIF, VEGF, CD31).

Tumor samples frozen in OCT will be assessed for phosphorylation of VEGFR and downstream signalling as well as tumor cell and tumor endothelial apoptosis using ASC. These samples will be analyzed for VEGFR/pVEGFR as well as CD31/TUNEL/caspase, and staining for angiogenesis and apoptosis.

If snap frozen tumor samples (frozen is the absence of OCT) are available from a 3rd core biopsy, these may be used to assess changes in gene and protein expression profiles using expression array and proteomic, and to analyse drug concentration in tumor tissue.

Additional tests on these tissue samples may be done in the future. All testing will be for research purposes only. Mandatory archival tissue samples will be returned to the site at the end of the study. Tissue samples from optional pre- and post-dose ZD6474 biopsies will not be returned to the site unless a patient withdraws consent. Any tissue samples remaining after all testing is complete will be destroyed.

4.7 Safety measurements and variables

The methods for collecting safety data are described below.

4.7.1 Adverse events

4.7.1.1 Definitions

The definitions of AEs, SAEs and other significant adverse events (OAEs) are given below. It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The principal investigator is responsible for ensuring this.

Adverse event

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 (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the

abnormal results of an investigation (eg, 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 development of a new cancer should be regarded as an AE. New cancers are those that are not the primary reason for administration of study treatment and have been identified after inclusion of the patient into the study.

Serious adverse event

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

- results in death
- is immediately life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital abnormality or birth defect
- is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

The causality of SAEs (ie, their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant case report form must answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by any of the following – study medication – other medication?". For further guidance on the definition of a SAE and a guide to the interpretation of the causality question, see Appendix B to the Clinical Study Protocol.

Note that SAEs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as "yes".

Other Significant Adverse Events (OAE)

OAEs will be identified by the Drug Safety Physician and if applicable also by the Clinical Study Team Physician during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment, will be classified as OAEs. Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment. For each OAE, a narrative may be written and included in the Clinical Study Report.

Deaths

All deaths that occur during the study and follow-up period (both cancer-related and other) must be reported. All deaths except those due to unequivocal progression of disease that occur within the study period or within 60 days after the administration of last dose of study treatment must be reported to the study monitor for the purposes of SAE reporting. Deaths as a result of disease progression are not considered SAEs, but must be collected on the appropriate CRF. The site should continue to follow all patients for survival beyond the 60-day period after the administration of last dose of study treatment and collect information around the death on the appropriate CRF.

An AE form should be completed for all deaths except those due to unequivocal progression of disease. The AE causing death must be reported to the study monitor as a SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

Death as a result of progression of disease alone should be reported to the study monitor at the next monitoring visit and should be documented on the relevant CRF, but should not be reported as an AE or SAE.

4.7.1.2 Recording of adverse events

AEs and SAEs will be collected throughout the study and will be recorded from the time of informed consent and followed up to resolution or for 60 days after the last administration of study treatment.

The following variables will be recorded for each AE: onset, resolution, action taken, outcome, causality (yes or no), and whether it constitutes an SAE or not. The CTCAE, Version 3.0 grade should be recorded where applicable.

All AEs will be recorded on the CRF provided. A description of the event, including its date of onset and resolution, whether it constitutes a SAE or not, any action taken (e.g., changes to study treatment, other treatment given, and follow-up tests) and outcome, should be provided along with the Investigator's assessment of causality (the relationship to the study treatment). AEs will also be graded according to the CTCAE, Version 3.0, and changes tracked on the relevant CRF.

For an AE to be a suspected drug-related event, there should be at least a reasonable possibility of a causal relationship between the study drug and the AE (see Appendix B for guidelines on interpretation of causality).

a) Disease progression

Any events that are unequivocally due to progression of disease must not be reported as an AE.

b) Lack of efficacy

When there is deterioration in the condition for which the study treatment is being used (i.e., HNSCC), there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless AstraZeneca or the reporting physician considers that the study treatment contributed to the deterioration, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

c) Abnormal lab values/vital signs

- The reporting of laboratory / vital signs abnormalities as both laboratory findings and AEs should be avoided. They should not be reported as AEs unless any one of the following are met:
- Any criterion for an SAE is fulfilled
- The laboratory / vital signs abnormality causes the patient to discontinue from the study treatment
- The laboratory / vital signs abnormality causes the patient to interrupt the study treatment
- The laboratory / vital signs abnormality causes the patient to modify the dose of study treatment
- The laboratory / vital signs abnormality requires intervention
- The investigator believes that the abnormality should be reported as an AE

If an abnormal laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom should be reported as an AE and the associated laboratory result or vital sign should be considered additional information that must be collected on the relevant CRF. AEs will be coded using the MedDRA.

Any clinically significant abnormal findings and QTc prolongations during the treatment period will be recorded as AEs.

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

d) Overdose

Should an overdose (accidental or deliberate) occur, it must be reported in accordance with the procedures described in Section 9.3, regardless of whether the overdose was associated with any symptom or not. All symptoms associated with the overdose should be reported as AEs.

Pregnancy

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 9.4. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

c) Handling unresolved AE/SAEs at completion/withdrawal

All study-related toxicities and SAEs must be followed until resolution or for 60 days after the last administration of study treatment, unless, in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

AEs will be coded using the MedDRA.

4.7.1.3 Reporting of serious adverse events

Investigators and other site personnel must inform appropriate AstraZeneca representatives of any SAE that occurs in the course of the study within 1 day (ie, immediately but no later than the end of the next business day) of when he or she becomes aware of it.

Follow-up information on SAEs must also be reported by the investigator within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca within 1 day as described above. For a non-serious AE that become serious but which is not fatal or life-threatening a report should be received within 5 days.

The AstraZeneca representative will work with the investigator to compile all the necessary information and ensure that the appropriate AstraZeneca Drug Safety Department receives a report by day 1 for all fatal and life-threatening cases and by day 5 for all other SAEs.

All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s). All SAEs will be recorded in the CRF. The investigator is responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

Follow-up information on SAEs must also be reported by the investigator within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca within 1 day as described above. For a non-serious AE that become serious but which is not fatal or life-threatening a report should be received within 5 days.

The AstraZeneca representative will work with the investigator to compile all the necessary information and ensure that the appropriate AstraZeneca Drug Safety Department receives a report by day 1 for all fatal and life-threatening cases and by day 5 for all other SAEs.

4.7.2 Laboratory safety measurements and variables

The local laboratory for the site will be utilized for routine hematology and biochemistry assessments and urinalysis. A vendor to be selected by AstraZeneca will be utilized for other required laboratory procedures

4.7.2.1 Methods of assessment

Routine hematology and biochemistry assessments will be performed at the local laboratory for the study center.

All patients who have any CTCAE grade 3 or 4 laboratory values (CTCAE, Version 3.0) at the time of withdrawal must be followed up until they have returned to CTCAE grade 1 or 2, unless the values are not likely to improve because of the underlying disease. Additional samples may be taken, as clinically indicated.

The following laboratory parameters will be evaluated. See Table 14 and Table 15 for total volume of blood samples to be collected.

Table 13 Laboratory safety variables

Type of assessment	Variables
Hematology	hemoglobin, platelet count, WBC[a], APTT[b], INR[b,] ANC
Clinical chemistry	
Hepatic function	ALP, ALT, AST, total bilirubin
Renal function	BUN, creatinine
Other	Albumin, inorganic phosphate, magnesium, potassium, sodium, calcium/ionized calcium, chloride, bicarbonate, total protein, glucose, LDH
Urinalysis	Proteins, blood, glucose

Abbreviations: ALP = alkaline phosphatase; ALT = Alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransaminase; BUN = blood urea nitrogen; INR = International Normalized Ratio; LDH = lactate dehydrogenase; WBC = white blood cell count

a total, with manual or automated differentiation, according to study plan

b at screening only, unless patient is on anticoagulation therapy and requires additional evaluation

4.7.2.2 Derivation or calculation of outcome variables

Section 4.7.1.2 provides details on how AEs based on laboratory tests will be recorded and reported.

4.7.3 ECG

4.7.3.1 Methods of assessment

12-lead ECG must be performed at screening (within 7 days of first dose). The screening QTc must be <480 msec. If a patient has QTc interval ≥480 msec on the screening ECG, two additional ECGs should be done (at least 24 hours apart). The average QTc from the three screening ECGs must be ≤ 480 msec in order for the patient to be eligible for the study.

Baseline QTc (using the Bazett's correction) will be determined by the average of 3 consecutive ECGs (within 5-10 minutes of one another) on Day 1. If the screening QTc is obtained with 3 consecutive ECGs within 3 days before Day 1, then the screening QTc will be considered to be the baseline, and repeat ECGs will not be necessary on Day 1.

When possible ECGs should be performed at the same time throughout the study. ECGs must be performed 4-8 hours after the patient takes their oral medication on day 1, day 8, day 15, day 29 and at day 58. In the event of QTc prolongation, the QTc will be re-evaluated within 48 hours). The criteria for QTc prolongation are :

- A single QTc value of ≥550 msec, or an increase of ≥100 msec from baseline;

OR

- Two consecutive QTc measurements, within 48 hours of one another, where either of the following criteria are met for both QTc values:

  A QTc interval of ≥500 msec, but <550 msec;

  OR

  An increase of ≥60 msec, but <100 msec from baseline QTc, to a value ≥480 msec

In the event of a QTc prolongation see Section 3.9.3.

4.7.3.2 Derivation or calculation of outcome variables

Any clinically significant abnormal findings observed and recorded during the treatment period will be recorded as AEs. The following parameters will be recorded for each ECG: date and time of ECG, heart rate (beats/min), QRS duration (ms), PR interval (ms), QT interval (ms), QTcB interval (ms), QTcF interval (ms), sinus rhythm (yes/no) and overall evaluation (normal/abnormal).

4.7.4 Vital signs and physical examination

4.7.4.1 Methods of assessment

Full physical examinations will be performed including height (screening only), weight, blood pressure, pulse, and temperature at the screening visit and as outlined in the study plan (see Table 1 and Table 2). Blood pressure should be measured after the patient has been sitting for 5 minutes.

Performance status will be assessed using the WHO criteria (Appendix C) at baseline and as outlined in the study plan (see Table 1 and Table 2). The same observer should assess performance status each time.

A hearing assessment should be completed at screening for any patient who would receive cisplatin.

4.7.4.2 Derivation or calculation of outcome variables

Any new conditions reported during the study will be recorded on the AE forms. Only those findings that are in addition to the condition being treated will be recorded as AEs, see Section 4.7.1.2 for reporting of AEs. Conditions that are considered by the Investigator to be unequivocally disease-related will not be recorded as AEs

4.8 Efficacy measurements and variables

4.8.1 Objective response rate (ORR), disease control rate (DCR), and locoregional control rate (LRCR)

4.8.1.1 Methods of assessment

The RECIST criteria will be used to perform the objective tumor assessments and determine a patient's best overall objective tumor response; details are given in Appendix D.

Baseline radiological tumor assessments should be performed no more than 3 weeks before the start of study treatment, at completion of treatment, and every 3 months during follow-up.

Up to 10 target lesions (no more than 5 lesions per organ) can be selected at screening; these target lesions, which must be measurable (as defined in Appendix D) will be monitored by the investigator throughout the study, and tumor measurements will be collected.

All other (nontarget) lesions will also be monitored throughout the study, and an overall assessment of nontarget lesions will be made and recorded as "present", "present with progression" or "absent".

Lesions must be assessed using the same method and technique on each occasion. Lesions will be recorded on the CRF in the same order as they were recorded at screening. Details of any new lesions will also be collected.

Disease progression is a criteria for discontinuation from the study. A patient is determined to have progressed if they have progression of target lesions, clear progression of existing non-

target lesions or the appearance of one or more new lesions (see Appendix D). Progression of target lesions is defined as at least a 20% increase in the sum of the longest diameter (LD) of target lesions taking as references the smallest sum of LD recorded.

Categorization of the objective tumor response assessments will be based on the RECIST criteria for target and nontarget lesions. Response will be classified as CR, PR, SD, or progressive disease (PD).

For patients with an objective response of CR or PR, confirmations of response by repeat imaging must be performed, at not less than 4 weeks following the date of response.

4.8.1.2 Derivation or calculation of outcome variables

A patient's best objective response is calculated using data from assessments performed at baseline, during treatment, and during the follow-up period.

The RECIST criteria will be used to define objective response. Responders are those patients with a best objective response of CR or PR. Response must be confirmed by repeat imaging at not less than 4 weeks following date of response.

The overall objective response rate (ORR) will be calculated as the percentage of patients with a best response of CR or PR.

DCR rate will be calculated as the percentage of patients with a best response of CR or PR or SD $\geq$ 12 weeks.

LRCR will be calculated as the percentage of patients with a best response of CR or PR or SD $\geq$ 12 weeks, excluding distant disease.

The revised (May 2000) WHO definitions (RECIST) for measurable, nonmeasurable, target, and nontarget lesions, and the objective tumor response criteria are presented in Appendix D. The RECIST criteria will be used to determine objective tumor response. Objective tumor response will be determined using a computer program, and the responses will be used in the summaries of PFS, ORR, DCR, and locoregional control. A patient's best objective tumor response will be used for the summaries of objective tumor response.

4.8.2 Locoregional recurrence (LRR) and recurrence

4.8.2.1 Methods of assessment

The RECIST criteria will be used to perform the objective tumor assessments and determine a patient's best overall objective tumor response (see appendix D)

4.8.2.2 Derivation or calculation of outcome variable

Locoregional recurrence event is determined as the first new occurrence of a lesion in the head and neck area (associated with the primary tumor) or neck lymphatic nodes without distant metastases.

Recurrence is determined as the event of locoregional recurrence or the appearance of distant metastasis.

After two years of follow-up, the locoregional recurrence rate at two years will be determined as the percentage of patients who had a best overall response of CR and had locoregional recurrence with distant metastasis. Similarly, the recurrence rate at two years will be determined as the percentage of patients who had a best overall response of CR and subsequently progressed (distant or locoregional).

4.8.3 Progression-free survival (PFS) and duration of locoregional control

4.8.3.1 Methods of assessment

PFS and duration of locoregional control are determined using data from RECIST assessments performed at baseline, during treatment, and during the follow-up period.

The date of first documented locoregional progression or recurrence and a first documented distant disease metastasis will be determined.

4.8.3.2 Derivation or calculation of outcome variable

PFS will be defined from the date of first dose to the date of objective progression (locoregional or distant) or death (by any cause in the absence of progression). Patients who have not progressed or died at the time of statistical analysis will be censored at the time of their latest objective tumor assessment. This includes patients who are lost to follow-up or have withdrawn consent. For patients lost to follow-up without having progressed, death will be considered an event; otherwise the patient will be censored for PFS at the time of their last tumor assessment date.

Locoregional control will be defined as the absence of progression of locoregional disease at the scheduled follow-up visits. The duration of locoregional control is defined as the time of first dose until the first documented progression or recurrence of locoregional disease (excluding distant metastasis) or until death from any cause.

4.9 Volume of blood sampling and handling of biological samples

The total volume of blood that will be drawn from each patient in this study is as follows:

Table 14 Volume of blood to be drawn – Treatment Regimen 1

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Plasma biomarkers		10	5	50
PBMCs/CECs		7	5	35
Pharmacokinetic - ZD6474		4	11	44
Safety	Clinical chemistry	6	9	54

Table 14 Volume of blood to be drawn – Treatment Regimen 1

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
	Haematology	4.5	9	40.5
Total			39	223.5

Table 15 Volume of blood to be drawn – Treatment Regimen 2

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Plasma biomarkers		10	5	50
PBMCs/CECs		7	5	35
Pharmacokinetic - ZD6474		4	11	44
Pharmacokinetic – cisplatin		4	16	64
Safety	Clinical chemistry	6	9	54
	Haematology	4.5	9	40.5
Total			55	287.5

4.9.1 Analysis of biological samples

4.9.1.1 Pharmacokinetic sample stability

Stability of ZD6474 has been documented for 12 months in work done by AstraZeneca. Samples stored for longer than 12 months will not be analyzed.

4.10 Genetic measurements and co-variables – Not applicable

5. DATA MANAGEMENT

AstraZeneca will perform the data management portion of this study. CRFs will be provided for the recording of all data. The forms will be in three-part carbonless paper. The Principal Investigator/sub-investigator or designee will record data on observations, tests, and assessments specified in the protocol on the CRFs provided by AstraZeneca. Data will be recorded directly and legibly onto the CRFs, in black or blue ball-point pen. To ensure the recorded the quality of the CRFs, they are required to follow the “Instructions for the Investigator” provided by AstraZeneca for filling out, changing and/or correcting CRFs. Corrections should be made legibly and initialed and dated by approved personnel; the reasons for significant changes must be provided. Correction fluid or covering labels must not be used.

The top 2 sheets of the CRFs will be collected by the monitor and sent to AstraZeneca data management, the investigator will retain the 3rd copy.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Statistical evaluation – general aspects

A comprehensive Statistical Analysis Plan (SAP) will be prepared and archived before database lock. The statistical analyses will be descriptive in nature. The process for closing the database and analyzing the data will occur after the last patient recruited has completed 8 weeks of treatment and the pharmokinetic follow-up information is obtained.

6.2 Description of outcome variables in relation to objectives and hypotheses

The objective and outcome variables are listed in the table below.

Table 16 Objectives and outcome variables

Objective	Variable(s)
Primary	
To determine the safety profile, tolerability and MTD of ZD6474 in combination with RT and ZD6474 in combination with RT/cisplatin chemotherapy, in patients with previously untreated, unresected, stage III-IV HNSCC	AEs, PEs, vitals, laboratory data, ECGs
Secondary	
To define the ORR, DCR, and LRCR per RECIST criteria	ORR, DCR, LRCR by RECIST
To assess rate of LRR and distant disease recurrence at two years.	LRR +/- distant disease at 2 years
To assess PFS and duration of locoregional control.	PFS and duration of locoregional control
To investigate whether there is any change in the steady state exposure to ZD6474 due to RT or RT + cisplatin or method of administration	ZD6474: C_{max}, t_{max}, $AUC_{(0-24)}$
To investigate whether there is any change in the exposure to cisplatin due to ZD6474 as assessed by total platinum	Cisplatin: total C_{max}, $AUC_{(0-t)}$

Table 16 Objectives and outcome variables

Objective	Variable(s)
Exploratory	
To investigate the correlation between epidermal growth factor receptor (EGFR) gene amplification, EGFR protein expression, vimentin protein expression, E-cadherin proein expression, and ZD6474 efficacy and toxicity in pre-treatment tumor samples	EGFR gene amplification, EGFR protein expression, E-Cadherin protein expression, vimentin protein expression
To investigate the correlation between inhibition of EGFR and vascular endothelial growth factor receptor (VEGFR) signalling pathways, tumor cell and endothelial cell apoptosis, tumor microvessel density, and ZD6474 dose, efficacy and toxicity in pre-treatment and on-treatment tumor samples	EGFR/pEGFR, VEGFR/pVEGFR, Akt/pAkt, MAPK/pMAPK, microvessel density, apoptosis/TUNEL/caspase 3
To investigate the correlation between markers of tumor hypoxia (HIF, VEGF) and ZD6474 dose, efficacy and toxicity in pre-treatment and on-treatment tumor samples	HIF, VEGF and CD31
To investigate the correlation between changes in gene and protein expression, and ZD6474 dose, efficacy and toxicity in pre-treatment and on-treatment tumor samples	Gene and protein expression profiles in tumor tissue
To investigate the correlation between levels of circulating protein biomarkers and circulating endothelial cells with ZD6474 dose, efficacy and toxicity in pre-treatment and on-treatment plasma samples	VEGF, sVEGFR2, PIGF, VEGF-B, VEGF-C, CEC, bFGF in blood
To investigate the relationship between ZD6474 PK and safety, efficacy, and pharmacodynamics endpoints	PK: Individual predicted values of plasma concentrations, AUC_{ss}, $C_{ss, max}$, CL/F Safety: AEs, including changes in QTc Efficacy: ORR, DCR PD: Those PD endpoints from the exploratory objectives identified as requiring further evaluation.

Abbreviations: AE = adverse event; CR = complete response; DCR = disease control rate; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; LRCR = locoregional control rate; LRR = locoregional recurrence; ORR = objective response rate; PE = physical exam; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; VEGF = vascular endothelial growth factor; VEGFR2 = vascular endothelial growth factor receptor-2; WHO PS = World Health Organization Performance Status

6.2.1 Primary outcome variables

The primary outcome variables are MTD and safety.

6.2.2 Secondary outcome variables

The secondary objectives of the study are:

1. Objective tumor response rates (CR and PR) and DCR and LRCR per RECIST
2. Rate of LRR and distant disease recurrence at 2 years
3. PFS and duration of locoregional control
4. Steady state exposure to ZD6474: C_{max}, t_{max}, $AUC_{(0-24)}$
5. Total cisplatin: total C_{max}, $AUC_{(0-t)}$

6.2.3 Exploratory outcome variables

The exploratory pharmacodynamic variables of the study are:

1. EGFR gene amplification, EGFR protein expression, E-Cadherin protein protein expression, vimentin protein expression
2. EGFR/pEGFR, VEGFR/pVEGFR, Akt/pAkt, MAPK/pMAPK, microvessel density, apoptosis/TUNEL/caspase
3. HIF, CD31, and VEGF protein expression in tumor tissue
4. Gene and protein expression profiles in tumor tissue
5. VEGF, sVEGFR2, PIGF, VEGF-B, VEGF-C, CEC, bFGF in blood
6. PK: Individual predicted values of plasma concentrations, AUC_{ss}, $C_{ss, max}$, CL/F; Safety: AEs, including changes in QTc; Efficacy: ORR, DCR; PD: Those pharmacodynamic endpoints from the exploratory objectives identified as requiring further evaluation

6.3 Description of analysis sets

All patients will be included in the analysis according to the treatment received. Data from patients who withdraw from the study, or who have missing values for other reasons, will be included in the analysis in such a way as to minimize any possible bias. A strategy for dealing with data that is affected by protocol deviations will be agreed upon by the study team physician, study team pharmacokineticist, and statistician before any formal statistical analysis is performed.

All patients who received at least one dose of ZD6474 will be included in the safety analysis. For patients who have a dose modification, all adverse event data (due to drug toxicity or otherwise) will be assigned to the actual dose of study drug that the patient had been given at the time of the event.

6.4 Method of statistical analysis

The statistical analysis to be performed will be descriptive in nature. Summary statistics of the main primary and secondary endpoints will be presented by dose and treatment regimen. Listings of the data by treatment regimen, dose level and by patient will be produced. The baseline and demographic characteristics of the patients will be produced. Additional exploratory analyses may be performed, if appropriate.

6.4.1 Primary variable

The primary objective of the study is to determine the MTD and overall safety profile of orally administered escalating doses of ZD6474 in combination with RT and in combination with RT and cisplatin chemotherapy in patients with previously untreated, unresected stage III-IV HNSCC.

The MTD dose will be determined for each treatment regimen as defined in section 3.1.1.1. The estimate of MTD is defined as the dose level below the unacceptable dose level where at least 2 of 6 (33%) of the patients experience DLT.

DLTs will be listed individually by patient, dose level of ZD6474, and treatment regimen. The number of patients experiencing each adverse event will be summarized by treatment regimen, dose level, CTCAE grade, and total administered dose of study drug.

Descriptive statistics will be used to summarize the safety data. Safety will be assessed through summaries of the frequency and severity of adverse events, changes in laboratory test results, changes in vital signs, and ECGs. Adverse events (both by MEDRA preferred term, MEDRA system organ class (SOC) and according to the CTCAE grade) will be listed individually by patient, dose level and cycle. The number of patients experiencing each adverse event will be summarized by treatment regimen, dose level, cycle, CTCAE grade, and total administered dose of study drug.

Hematology and biochemistry data will be listed by treatment regimen, dose, and by worst CTCAE grade. The worst CTCAE grade over the course of the study will be summarized by dose. The distribution of the worst CTCAE grades over the course of the study will be summarized by cycles to assess cumulative toxicity. Shift table summaries will be presented to show the largest change from baseline in CTCAE grade by dose.

Medical conditions collected from the physical exams will be listed for each patient. Medical conditions, past and present, will be summarized by treatment regimen, dose and COSTART body system.

Descriptive statistics of vital signs and ECG data will be summarized by treatment regimen and dose.

6.4.2 Secondary variables

Analyses of the secondary variables are purely descriptive in nature. No formal statistical comparisons between the treatment regimens will be made.

6.4.2.1 ORR, DCR, and LRCR

Objective tumor response rates for each treatment regimen and associated 95% confidence intervals will be presented. Similarly, disease control rates and locoregional control rates for each treatment regimen and associated 95% confidence intervals for each treatment regimen will be presented.

6.4.2.2 2-year locoregional recurrence rate and 2-year recurrence rate

The 2-year locoregional recurrence rates and 2-year recurrence rates for each treatment regimen and associated 95% confidence intervals will be presented.

6.4.2.3 PFS and duration of locoregional control

Point estimates of PFS and duration of locoregional control and associated 95% confidence intervals and Kaplan-Meier plots will be presented for each treatment regimen.

6.4.2.4 Pharmacokinetics

The effect of RT or RT plus cisplatin or method of administration on exposure to ZD6474 will be compared within and across each group and dose level both with time and dose. Study data will also be compared to ZD6474 data alone that has been generated from other studies conducted by AstraZeneca in other cancer types.

The effect of radiation or radiation plus cisplatin on exposure to cisplatin as assessed by total platinum will be compared within and across each dose level of ZD6474 with time. Study data will also be compared to cisplatin data alone that has been generated from other studies, both by AstraZeneca and others.

6.4.3 Exploratory variables

6.4.3.1 Pharmacodynamic biomarkers

Analysis of pharmacodynamic biomarker data will be exploratory in nature. Appropriate summaries of these levels will be produced to investigate the level of correlation with ZD6474 dosing.

6.4.3.2 Pharmacokinetic-pharmacodynamic

The relationship between measures of safety and efficacy and pharmacodynamic endpoints will be explored by means of a population PK-PD analysis approach.

6.5 Determination of sample size

No formal patient number calculations have been performed since the number of patients is dependent on the number of dose escalations within each of the two treatment regimens. Within each treatment regimen, a traditional dose escalation design with 3 dose levels and cohorts of 6 to 12 evaluable patients will be used. If appropriate, patients who are non-evaluable as defined in (see section 3.1.2) will be replaced so that the safety of the dose and treatment regimen can be evaluated. An additional cohort of 6 patients will be enrolled at the MTD for additional safety information. A maximum of 48 evaluable patients will be required to complete this study.

6.6 Interim analyses (Not applicable)

There will be no planned interim analysis.

6.7 Data and safety monitoring board (Not applicable)

6.8 Safety review committee

Prior to each dose-escalation, the Safety Review Committee will review and assess the available safety data. The Safety Review Committee comprising the Principal Investigators, the Study Team Physician and the Drug Safety Physician (or nominated deputy in each case) will assess the available safety and PK data. The committee must comprise a minimum of 3 physicians but may also include other team members, if appropriate (e.g. statistician, pharmacokineticist, etc). Progression to the next dose will only occur if the committee considers that the non-tolerated dose has not been defined.

No formal statistical analyses will be performed for safety review.

7. STUDY MANAGEMENT

7.1 Monitoring

Before first patient into the study, a representative of AstraZeneca will visit the investigational study site to:

determine the adequacy of the facilities

discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator

During the study, a monitor from AstraZeneca or company representing AstraZeneca will have regular contacts with the study site, including visits to:

provide information and support to the investigator(s)

confirm that facilities remain acceptable

confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the CRFs, and that investigational product accountability checks are being performed

- perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study). This will require direct access to all original records for each patient (eg, clinic charts).

The monitor or another AstraZeneca representative will be available between visits if the investigator(s) or other staff at the center need information and advice.

7.2 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the center to perform audits or inspections, including source data verification. The purpose of an AstraZeneca audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator should contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at his or her center.

7.3 Training of staff

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

7.4 Changes to the protocol

Study procedures will not be changed without the mutual agreement of the Co-ordinating Investigator and AstraZeneca.

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (Amended Protocol) must be notified to or approved by each IRB or IEC, and if applicable, also the local regulatory authority, before implementation. Local requirements must be followed.

If a protocol amendment requires a change to a particular center's Informed Consent Form, then AstraZeneca and the center's IRB or IEC must be notified. Approval of the revised Informed Consent Form by AstraZeneca and by the IRB or IEC is required before the revised form is used.

AstraZeneca will distribute amendments and new versions of the protocol to each principal investigator(s).

The principal investigator at each center must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the Clinical Study Protocol shall prevail.

7.5 Study agreements

The principal investigator at each centre must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the Clinical Study Protocol shall prevail.

7.6 Study timetable and end of study

Before a patient's enrollment in the study and any study-related procedures are undertaken the following should be fulfilled:

signed Clinical Study Protocol and other agreements between AstraZeneca and the Principal Investigator/Study Site.

approval of the study by the IRB/IEC

approval of the study, if applicable, by the regulatory authority.

The end of study will be declared after the last patient has completed 2 years of follow-up or withdrawn.

8. ETHICS

8.1 Ethics review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favourable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to AstraZeneca before he or she can enrol any patient into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the

investigational product. AstraZeneca will provide this information to the Principal Investigator.

Progress reports and notifications of serious and unexpected adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

8.2 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

For studies including genetic analysis special precautions are taken as described in Section 4.10.

8.3 Informed consent

The principal investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any procedure specifically for the study.

The principal investigator(s) must store the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient.

The tumor biomarker component of this study is optional and the patient may participate in the study without participating in the tumor biomarker component. To participate in the tumor biomarker component of the study, the patient must sign and date both the consent form for the non-tumor biomarker component of the study and the tumor biomarker component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study center. The principal investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely discontinue the tumor biomarker component of the study at any time.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

8.4 Patient data protection

The Master Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, patients will authorise the collection, use and

disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study.

The Master Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data that is computer processed by AstraZeneca will be identified by *cohort dose assignment code / study code*.

The Master Informed Consent Form will also explain that for data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, an IRB or IEC may require direct access to parts of the hospital or practice records relevant to the study, including patients' medical history.

9. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

9.1 AstraZeneca emergency contact procedure

In the case of a medical emergency you may contact the Clinical Study Team Physician. If an emergency occurs outside of office hours and the Clinical Study Team Physician is not available, contact the Pittsburgh Poison control center (PPCC) at telephone number listed below from 7:00 pm to 8:00 am (east coast time). The AstraZeneca Information Center is available at telephone number: 1-800-236-9933 from 8 am to 7 pm (east coast time).

Role in the study	**Name**	**Address & telephone number**
CST Leader	Rebecca Dennis	AstraZeneca Pharmaceuticals, LP 1800 Concord Pike Wilmington, DE 19803 302-885-1424
Project Physician	Mitch Goldman, MD	AstraZeneca Pharmaceuticals, LP 1800 Concord Pike Wilmington, DE 19803 302-885-1502
24-hour emergency cover at central R&D site	Information Center at AstraZeneca (business hours) Pittsburgh Poison Control Center (after hours)	8:00 AM – 7:00 PM EST 1800 Concord Pike, PO Box 15437, Wilmington, DE 19850 Tel: 001 800 236 9933 7:00 PM – 8:00 AM EST 3705 Fifth Avenue Pittsburgh, PA 15213 Tel: 001 412 681 6669

9.2 Procedures in case of medical emergency

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and should be reported as such, see Section 4.7.1.1.**

9.3 Procedures in case of overdose

There is currently no known antidote to ZD6474. In the event of an overdose (> 1 dose within 24 hours), symptomatic and supportive care should be given, and all details should be recorded.

Use of study medication in doses in excess of that specified in the protocol should not be recorded in the CRF as an AE of 'Overdose' unless there are associated symptoms or signs.

- An overdose with associated SAEs should be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the CRFs.

- An overdose with associated non-serious AEs should be recorded as the AE diagnosis/symptoms on the relevant AE forms in the CRFs. In addition, the overdose should be reported on the separate AZ "Clinical Study Overdose Report Form."

- An overdose without associated symptoms should not be recorded as an AE in the CRFs. The overdose should be reported on the separate AZ "Clinical Study Overdose Report Form".

9.4 Procedures in case of pregnancy

In the event of pregnancy occurring while a patient is receiving ZD6474, the study drug should be discontinued and AstraZeneca should be contacted for advice.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to AstraZeneca on the pregnancy outcomes report form.

10. REFERENCES

Adelstein DJ, Li Y, Adams GL, Wagner Jr. H, Kirsh JA, Ensley JF, Schuller DE, Forastiere AA. An intergroup Phase III comparison of standard radiation therapy and two Schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell hed and neck cancer. J Clin Oncol 21:92-98, 2003

Akimoto T, Hunter NR, Buchmiller L, Mason K, Ang KK, Milas L. Inverse relationship between epidermal growth factor receptor expression and radiocurability of murine carcinomas. Clin Cancer Res 5:2884-2890, 1999.

Asahara T., Takahashi T., Masuda H., Kalka C., Chen D., Iwaguro H., Inai Y., Silver M. and Isner J. M. (1999) VEGF contributes to postnatal neovascularization by mobilizing bone marrow-derived endothelial progenitor cells. Embo J 18, 3964-72.

Bachaud JM, Cohen-Jonathan E, Alzieu C. Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: Final report of a randomized trial. Int J Radiat Oncol Biol Phys 1996;36:999-1004.

Bartelink H, Van den Bogaert W, Horiot JC, Jager J, van Glabbeke M. Concomitant cisplatin and radiotherapy in a conventional and modified fractionation schedule in locally advanced head and neck cancer: a randomized phase II EORTC trial. Eur J Cancer 2002; 38: 667-673.

Beaudry P., Force J., Naumov G., Wang A., Baker C. H., Ryan A., Soker S., Johnson B. E., Folkman J. and Heymach J. V. (2005a) Differential effects of VEGFR-2 inhibitor ZD6474 on circulating endothelial progenitors and mature circulating endothelial cells: implications for use as a surrogate marker of antiangiogenic activity. Clin Cancer Res in press.

Beaudry P., Force J., Naumov G. N., Wang A., Baker C. H., Ryan A., Soker S., Johnson B. E., Folkman J. and Heymach J. V. (2005b) Differential effects of vascular endothelial growth factor receptor-2 inhibitor ZD6474 on circulating endothelial progenitors and mature circulating endothelial cells: implications for use as a surrogate marker of antiangiogenic activity. Clin Cancer Res 11, 3514-22.

Beerepoot L. V., Mehra N., Vermaat J. S., Zonnenberg B. A., Gebbink M. F. and Voest E. E. (2004) Increased levels of viable circulating endothelial cells are an indicator of progressive disease in cancer patients. Ann Oncol 15, 139-45.

Bertolini F., Paul S., Mancuso P., Monestiroli S., Gobbi A., Shaked Y. and Kerbel R. S. (2003) Maximum tolerable dose and low-dose metronomic chemotherapy have opposite effects on the mobilization and viability of circulating endothelial progenitor cells. Cancer Res 63, 4342-6.

Bocci G., Man S., Green S. K., Francia G., Ebos J. M., du Manoir J. M., Weinerman A., Emmenegger U., Ma L., Thorpe P., Davidoff A., Huber J., Hicklin D. J. and Kerbel R. S. (2004) Increased plasma vascular endothelial growth factor (VEGF) as a surrogate marker for

optimal therapeutic dosing of VEGF receptor-2 monoclonal antibodies. Cancer Res 64, 6616-25.

Bonner JA, Raisch KP, Trummell HQ, Robert F, Meredith RF, Spencer SA, Buchsbaum DJ, Saleh MN, Stackhouse MA, LoBuglio AF, Peters GE, Carroll WR, Waksal HW. Enhanced Apoptosis with Combination C225/Radiation Treatment Serves as the Impetus for Clinical Investigation in Head and Neck Cancers. J Clin Oncol 18(21):47s-53s, 2000.

Bonner, JA, et al. N Engl J Med 2006;354:567-78, 2006

Ciardiello F, Caputo R, Damiano V, Caputo R, Troiani T, Vitagliano D, Carlomagno F, Veneziani BM, Fontanini G, Bianco AR, Tortora G. Antitumor effects of ZD6474, a small molecule vascular endothelial growth factor receptor tyrosine kinase inhibitor, with additional activity against EGFR tyrosine kinase. Clin Cancer Res. 2003 Apr; 9 (4):1546-56.

Cohen EW, Rosen F, Stadler WM, Recant W, Stenson K, Huo D, Vokes EE. Phase II Trial of ZD1839 in Recurrent or Metastatic Squamous cell Carcinoma of the Head and Neck. J Clin Oncol 21(10):1980-1987, 2003.

Davis D., McConkey D., Heymach J., Desai J., Bello C., George S., Jackson J., Baum C., Shalinsky D. and Demetri G. (2005a) Pharmacodynamic Analysis of Target Receptor Tyrosine Kinase Activity and Apoptosis in GIST Tumors Responding to Therapy with SU11248. J Clin Oncol (2005 ASCO Annual Meeting Proceedings) 23, 3006.

Davis D. W., Takamori R., Raut C. P., Xiong H. Q., Herbst R. S., Stadler W. M., Heymach J. V., Demetri G. D., Rashid A., Shen Y., Wen S., Abbruzzese J. L. and McConkey D. J. (2005b) Pharmacodynamic analysis of target inhibition and endothelial cell death in tumors treated with the vascular endothelial growth factor receptor antagonists SU5416 or SU6668. Clin Cancer Res 11, 678-89.

Dibbens JA, Miller DL, Damert A, Risau W, Vadas MA, Goodall GJ. Hypoxic regulation of vascular endothelial growth factor mRNA stability requires the cooperation of multiple RNA elements. Mol Biol Cell 10(4):907-19, 1999.

Ebos J. M., Bocci G., Man S., Thorpe P. E., Hicklin D. J., Zhou D., Jia X. and Kerbel R. S. (2004) A naturally occurring soluble form of vascular endothelial growth factor receptor 2 detected in mouse and human plasma. Mol Cancer Res 2, 315-26.

Erlotinib Investigator's Brochure 6th Edition, OSI Pharmaceuticals (Section 4.1.2).

Folkman J. Tumor Angiogenesis: Therapeutic Implications. N Engl J Med 1970; 285; 1182-1186.

Forastiere A. Cisplatin and radiotherapy in the management of locally advanced head and neck cancer. Int J Radiat Oncol Biol Phys 1993; **27**: 465-470.

Forastiere A, Goepfert H, Pajak TF, Weber R, Morrison W, Glisson B, Trotti A, Ridge JA, Chao C, Peters G, Lee D-J, Leaf A, Ensley J, and Cooper J. Concurrent chemotherapy and rdiotherapy for organ perservation in advanced laryngeal cancer. NEJM 349:2091-8, 2003.

Frederick B, Gustafson D., Bianco C., Ciardiello F., Dimery I., Raben D. ZD6474, an inhibitor of VEGFR and EGFR tyrosine kinase activity in combination with radiotherapy. *International Journal of Radiation Oncology, Biology, Physics. 64(1):33-7, 2006 Jan 1.* UI**:** 16377413

Fu KK, Pajak TF, Trotti A, Jones CU, Spencer SA, Phillips TL, Garden AS, Ridge JA, Cooper JS, Ang KK. A radiation therapy oncology group (RTOG) Phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. Int J Radiat Oncol Biol Phys, 48:7-16, 2000.

Glicksman AS, Wanebo HJ, Slotman G, Liu L, Landmann C, Clark J, Zhu TC, Lohri A, Probst R.Concurrent platinum-based chemotherapy and hyperfractionated radiotherapy with late intensification in advanced head and neck cancer. Int J Radiat Oncol Biol Phys. 1997 Oct 1;39(3):721-9.

Gora-Tybor J., Blonski J. Z. and Robak T. (2005) Circulating vascular endothelial growth factor (VEGF) and its soluble receptors in patients with chronic lymphocytic leukemia. Eur Cytokine Netw 16, 41-6.

Grandis JR, Melhem MF, Gooding WE, Day R, Holst VA, Wagener MA, Drenning SD, Tweardy DJ. Levels of TGFalpha and EGFR protein in head and neck squamous cell carcinoma and patient survival. J Clin Oncol 90(11)824-832, 1998.

Hattori K., Dias S., Heissig B., Hackett N. R., Lyden D., Tateno M., Hicklin D. J., Zhu Z., Witte L., Crystal R. G., Moore M. A. and Rafii S. (2001) Vascular endothelial growth factor and angiopoietin-1 stimulate postnatal hematopoiesis by recruitment of vasculogenic and hematopoietic stem cells. J Exp Med 193, 1005-14.

Heymach J., Kulke M., Fuchs C., Force J., Connors S., Sidor C., George D., Eder J., Folkman J. and Soker S. (2003) Circulating endothelial cells as a surrogate marker of antiangiogenic activity in patients treated with endostatin. Proc Am Soc Clin Oncol 22, 979.

Heymach J. V., Desai J., Manola J., Davis D. W., McConkey D. J., Harmon D., Ryan D. P., Goss G., Quigley T., Van Den Abbeele A. D., Silverman S. G., Connors S., Folkman J., Fletcher C. D. and Demetri G. D. (2004) Phase II Study of the Antiangiogenic Agent SU5416 in Patients with Advanced Soft Tissue Sarcomas. Clin Cancer Res 10, 5732-40.

Huang S-M, Li J, Armstrong EA, Harari PM. Modulation of radiation response and tumor-induced angiogenesis after epidermal growth factor receptor inhibition by ZD1839 (Iressa)1. Cancer Res 62:4300-4306, 2002.

Jeremic B, Shibamoto Y, Milicic B, et al. Hyperfractionated radiation therapy with or without concurrent low-dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: a prospective randomized trial. J Clin Oncol 2000; **18**: 1458-1464.

Kalka C., Masuda H., Takahashi T., Gordon R., Tepper O., Gravereaux E., Pieczek A., Iwaguro H., Hayashi S. I., Isner J. M. and Asahara T. (2000) Vascular endothelial growth factor(165) gene transfer augments circulating endothelial progenitor cells in human subjects. Circ Res 86, 1198-202.

Lau H, Brar S, Hao D, MacKinnon J, Yee D, Gluck S. Concomitant low-dose cisplatin and three-dimensional conformal radiotherapy for locally advanced squamous cell carcinoma of the head and neck: Analysis of survival and toxicity. Head Neck. 2006 Mar;28(3):189-96.

Lin Y., Weisdorf D. J., Solovey A. and Hebbel R. P. (2000) Origins of circulating endothelial cells and endothelial outgrowth from blood. J Clin Invest 105, 71-7.

Mancuso P., Burlini A., Pruneri G., Goldhirsch A., Martinelli G. and Bertolini F. (2001) Resting and activated endothelial cells are increased in the peripheral blood of cancer patients. Blood 97, 3658-61.

Mancuso P., Colleoni M., Calleri A., Orlando L., Maisonneuve P., De Braud F., Rocca A., Rabascio C., Raia V., Goldhirsch A. and Bertolini F. (2005) Circulating endothelial cell kinetic predicts survival in breast cancer patients receiving metronomic chemotherapy. Proc Amer Assoc Cancer Res 2005 46, abstract # 1165.

Monestiroli S., Mancuso P., Burlini A., Pruneri G., Dell'Agnola C., Gobbi A., Martinelli G. and Bertolini F. (2001) Kinetics and viability of circulating endothelial cells as surrogate angiogenesis marker in an animal model of human lymphoma. Cancer Res 61, 4341-4.

Norden-Zfoni A., Manola J., Desai J., Morgan J., Bello C., Deprimo S. E., Shalinsky D. R., Baum C., Demetri G. D. and Heymach J. V. (2005) Levels of circulating endothelial cells (CECs) and monocytes as pharmacodynamic markers for SU11248 activity in patients (pts) with metastatic imatinib-resistant GIST. Proc Am Soc Clin Oncol 24, 9036.

Ogawa S, Oku A, Sawano A, Yamaguchi S, Yazaki Y, Shibuya M. A novel type of vascular endothelial growth factor, VEGF-E (NZ-7 VEGF), preferentially utilizes KDR/Flk-1 receptor and carries a potent mitotic activity without heparin-binding domain. J Biol Chem 273(47):31273-82, 1998.

Ortega N, Jonca F, Vincent S, Favard C, Ruchoux MM, Plouet J. Systemic activation of the vascular endothelial growth factor receptor KDR/flk-1 selectively triggers endothelial cells with an angiogenic phenotype. Am J Pathol 151(5):1215-24, 1997.

Peichev M., Naiyer A. J., Pereira D., Zhu Z., Lane W. J., Williams M., Oz M. C., Hicklin D. J., Witte L., Moore M. A. and Rafii S. (2000) Expression of VEGFR-2 and AC133 by

circulating human CD34(+) cells identifies a population of functional endothelial precursors. Blood 95, 952-8.

Peters B. A., Diaz L. A., Polyak K., Meszler L., Romans K., Guinan E. C., Antin J. H., Myerson D., Hamilton S. R., Vogelstein B., Kinzler K. W. and Lengauer C. (2005) Contribution of bone marrow-derived endothelial cells to human tumor vasculature. Nat Med 11, 261-2.

Plate KH, Breier G, Weich HA, Mennel HD, Risau W. Vascular endothelial growth factor and glioma angiogenesis: coordinate induction of VEGF receptors, distribution of VEGF protein and possible in vivo regulatory mechanisms. Int J Cancer 59(4):520-9, 1994.

Radema S. A., Beerepoot L. V., Witteveen P. O., Gebbink M. F., Wheeler C. and Voest E. E. (2002) Clinical evaluation of the novel vascular-targeting agent, ZD6126: assessment of toxicity and surrogate markers of vascular damage. Proc Am Soc Clin Oncol, 439.

Rafii S., Lyden D., Benezra R., Hattori K. and Heissig B. (2002) Vascular and haematopoietic stem cells: novel targets for anti-angiogenesis therapy? Nat Rev Cancer 2, 826-35.

Rak J, Mitsuhashi Y, Bayko L, Filmus J, Shirasawa S, Sasazuki T, Kerbel RS. Mutant ras oncogenes upregulate VEGF/VPF expression: implications for induction and inhibition of tumor angiogenesis. Cancer Res 55(20):4575-80, 1995.

Reyes M., Dudek A., Jahagirdar B., Koodie L., Marker P. H. and Verfaillie C. M. (2002) Origin of endothelial progenitors in human postnatal bone marrow. J Clin Invest 109, 337-46.

Robak E., Sysa-Jedrzejewska A. and Robak T. (2003) Vascular endothelial growth factor and its soluble receptors VEGFR-1 and VEGFR-2 in the serum of patients with systemic lupus erythematosus. Mediators Inflamm 12, 293-8.

Sawano A., Iwai S., Sakurai Y., Ito M., Shitara K., Nakahata T. and Shibuya M. (2001) Flt-1, vascular endothelial growth factor receptor 1, is a novel cell surface marker for the lineage of monocyte-macrophages in humans. Blood 97, 785-91.

Schuch G., Heymach J. V., Nomi M., Machluf M., Force J., Atala A., Eder J. P., Jr., Folkman J. and Soker S. (2003) Endostatin inhibits the vascular endothelial growth factor-induced mobilization of endothelial progenitor cells. Cancer Res 63, 8345-50.

Shaked Y., Bertolini F., Man S., Rogers M. S., Cervi D., Foutz T., Rawn K., Voskas D., Dumont D. J., Ben-David Y., Lawler J., Henkin J., Huber J., Hicklin D. J., D'Amato R. J. and Kerbel R. S. (2005) Genetic heterogeneity of the vasculogenic phenotype parallels angiogenesis; Implications for cellular surrogate marker analysis of antiangiogenesis. Cancer Cell 7, 101-11.

Shintani S., Li C., Mihara M., Terakado N., Yano J., Nakashiro K., Hamakawa H. Enhancement of tumor radioresponse by combined treatment with gefitinib (Iressa, ZD1839),

an epidermal growth factor receptor tyrosine kinase inhibitor, is accompanied by inhibition of DNA damage repair and cell growth in oral cancer. [Journal Article] *International Journal of Cancer. 107(6):1030-7, 2003 Dec 20.* UI: 14601066

Solovey A., Gui L., Ramakrishnan S., Steinberg M. H. and Hebbel R. P. (1999) Sickle cell anemia as a possible state of enhanced anti-apoptotic tone: survival effect of vascular endothelial growth factor on circulating and unanchored endothelial cells. Blood 93, 3824-30.

Soulieres D., Senzer NN., Vokes EE., Hidalgo M., Agarwala SS., Siu LL. Multicenter phase II study of erlotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with recurrent or metastatic squamous cell cancer of the head and neck**.** *Journal of Clinical Oncology. 22(1):77-85, 2004 Jan 1.* UI: 14701768

Takahashi T., Kalka C., Masuda H., Chen D., Silver M., Kearney M., Magner M., Isner J. M. and Asahara T. (1999) Ischemia- and cytokine-induced mobilization of bone marrow-derived endothelial progenitor cells for neovascularization. Nat Med 5, 434-8.

Wedge SR, Ogilvie DJ, Dukes M, Kendrew J, Chester R, Jackson JA, Boffey SJ, Valentine PJ, Curwen JO, Musgrove HL, Graham GA, Hughes GD, Thomas AP, Stokes ES, Curry B, Richmond GH, Wadsworth PF, Bigley AL, Hennequin LF. ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. Cancer Res. 2002 Aug 15;62(16):4645-55.

Wierzbowska A., Robak T., Wrzesien-Kus A., Krawczynska A., Lech-Maranda E. and Urbanska-Rys H. (2003) Circulating VEGF and its soluble receptors sVEGFR-1 and sVEGFR-2 in patients with acute leukemia. Eur Cytokine Netw 14, 149-53.

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Clinical Study Protocol: Appendix B	
Drug Substance	ZD6474
Study Code	D4200C00062
Appendix Edition Number	1.0
Appendix Date	26 April 2006

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

Examples of such events are:

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

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

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Clinical Protocol: Appendix C

Drug Substance	ZD6474
Study Code	D4200C00062
Appendix Edition Number	1.0
Appendix Date	26 April 2006

Appendix C
WHO Performance Status

1. WHO PERFORMANCE STATUS

	Score
Fully active, able to carry out all usual activities without restrictions and without the aid of analgesia.	0
Restricted in strenuous activity, but ambulatory and able to carry out light work or pursue a sedentary occupation. This group also contains subjects who are fully active, as in grade 0, but only with the aid of analgesics.	1
Ambulatory and capable of all self-care, but unable to work. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled, unable to carry out any self-care and confined totally to bed or chair.	4

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Clinical Study Protocol Appendix D	
Drug Substance	ZD6474
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Appendix D
Definitions of Measurable, Non-measurable, Target and Non-target Lesions and Objective Response Criteria based on revised RECIST for Investigator Site Review (Therasse, et al)

1. INTRODUCTION

This appendix details the implementation of RECIST for the D4200C00062 head and neck squamous cell carcinoma study in regards to the investigator site review.

2. DEFINITION OF MEASURABLE AND NON-MEASURABLE LESIONS

Measurable	Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques using effective slice thicknesses >5 mm; or as ≥ 10 mm with spiral computerized tomography (CT) scan using effective slice thicknesses ≤ 5mm.
Non-measurable	All other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral computerized tomography [CT] scan) and truly non-measurable lesions.

Lesions that are considered as truly non-measurable include the following:

- Bone lesions;
- Leptomeningeal disease;
- Ascites;
- Pleural / pericardial effusion;
- Inflammatory breast disease;
- Lymphangitis cutis/pulmonis;
- Abdominal masses that are not confirmed and followed by imaging techniques;
- Cystic lesions

3. METHODS OF MEASUREMENT

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 when both methods have been used to assess the anti-tumor effect of a treatment.

3.1 Clinical lesions

Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

3.2 Chest x-ray

According to RECIST, lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

3.3 CT and MRI

CT and MRI might be the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen and pelvis. Head & neck and extremities usually require specific protocols.

3.4 Ultrasound

Ultrasound (US) should not be used to measure tumor lesions for objective response evaluation. It is however a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

3.5 Endoscopy and laparoscopy

The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained.

3.6 Tumor markers

According to RECIST, tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

3.7 Cytology and histology

These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is

mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

4. TUMOR RESPONSE EVALUATION

4.1 Assessment of overall tumor burden and measurable disease

To assess objective response, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only subjects with measurable disease at baseline should be included where measurable disease is defined by the presence of at least one measurable lesion.

If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

4.1.1 Documentation of "target" and "non-target" lesions

All measurable lesions up to a maximum of 10 lesions representative of all involved organs (maximum of 5 lesions per organ) should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

The longest diameter will be measured and recorded for all target lesions identified at baseline at follow-up assessments and the sum LD calculated. If a lesion splits into two or more parts, then the sum of the LDs of those parts is recorded. If two or more lesions merge, then the LD of the combined lesion should be recorded for one of the lesions and zero recorded for the other lesion. If a lesion becomes too small to measure, then the size below which measurement cannot be accurately obtained should be substituted for the LD and used in the sum LD. If a lesion cannot be measured accurately due to progression, then the maximum measurable LD should be used in the sum LD and response assessment.

If a lesion has become non measurable or evaluable for some other reason and it is not possible to assign an estimate of the longest diameter then this lesion should be excluded from response assessment.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or "present with progression."

5. RESPONSE CRITERIA

5.1 Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	At least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD.
Progressive Disease (PD)	At least a 20% increase in the sum of LD of target lesions taking as references the smallest sum LD recorded since the treatment started.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD since the treatment started.

Note: Appearance of new lesions only counts towards the overall visit response, not towards the response of target or non-target lesions.

5.2 Evaluation of non-target lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level.
Non-Complete Response (non-CR/Non-Progression [non-PD])	Persistence of one or more non-target lesion or/and maintenance of tumor marker level above the normal limits.
Progression (PD)	Unequivocal progression of existing non-target lesions.

Note: Appearance of new lesions only counts towards the overall visit response, not towards the response of target or non-target lesions.

5.3 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). Best overall response will be derived as part of the study analysis by AstraZeneca. In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease. See text for more details.

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 ensure "symptomatic deterioration" patients continue to have objective tumor assessments at discontinuation from the study, and until progression is confirmed by imaging.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

6. CONFIRMATORY MEASUREMENT

6.1 Confirmation

6.1.1 Confirmation of objective response

The main goal of confirmation of objective response is to minimize the risk of overestimation of the response rate. This aspect of response evaluation is particularly important in non-randomized trials where response is the primary endpoint. In this setting, to be assigned a status of PR or CR, changes in tumor measurements must be confirmed, preferably by an

additional study at 4 weeks (not less than four weeks) after date of first response. This is an additional scan which does not replace any of the scheduled visit assessments.

6.2 Specifications for Radiological Imaging

These notes are recommendations for use in clinical studies and as such these protocols for computed tomography (CT) and magnetic resonance imaging (MRI) scanning may differ from those employed in clinical practice at various institutions. The use of standardized protocols allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

6.2.1 Computed Tomography (CT)

CT scans of the thorax, abdomen and pelvis should be contiguous throughout the anatomical region of interest. As a rule of thumb, the minimum size of the lesion should be no less than double the slice thickness. Lesions smaller than this are subject to significant "partial volume" effects and such a lesion may appear to have "responded" or "progressed" on subsequent examinations, when in fact they remain the same size. This minimum lesion size for a given slice thickness at baseline ensures that any lesion appearing smaller on subsequent examinations will truly be decreasing in size.

The type of CT scanner is important regarding the slice thickness and minimum sized lesion. For spiral (helical) CT scanners, the minimum size of any given lesion at baseline may be 10 mm, provided the images are reconstructed contiguously at 5mm intervals. For conventional CT scanners, the minimum sized lesion should be 20 mm using a contiguous slice thickness of 10 mm.

The fundamental difference between spiral and conventional CT is that conventional CT acquires the information only for that particular slice thickness scanned, which is then expressed as a two dimensional representation of that thickness or volume as a gray scale image. The next slice thickness needs to be scanned before it can be imaged and so on. Spiral CT acquires the data for the whole volume imaged, typically the whole of the thorax or upper abdomen in a single breath hold of about 20-30 seconds. To view the images, a suitable reconstruction algorithm is selected, by the machine, so the data are appropriately imaged. As suggested above, for spiral CT, 5 mm re-constructions can be made thereby allowing a minimum sized lesion of 10 mm.

Spiral CT is now the "standard" in most hospitals involved in cancer management in US, Europe and Japan, so the comments related to spiral CT are pertinent. However, some institutions involved in clinical trials will have conventional CT, but the number of these scanners will decline as they are replaced by spiral CT.

Other body parts, where CT scans are of different slice thickness, (such as the neck, which are typically of 5 mm thickness) or in the young pediatric population, where the slice thickness may be different, the minimum sized lesion allowable will be different. However, it should be double the slice thickness. The slice thickness and the minimum sized lesion should be specified in the study protocol.

In subjects in whom the abdomen and pelvis have been imaged, oral contrast agents should be given to accentuate the bowel from other soft tissue masses. This is almost universally undertaken routinely.

Intra-venous (IV) contrast agents should also be given, unless contra-indicated for medical reasons, such as allergy. This is to accentuate vascular structures from adjacent lymph node masses and to help enhance liver and other visceral metastases. Although in clinical practice its use may add little, in the context of a clinical study where objective response rate based on measurable disease is the endpoint, unless an IV contrast agent is given, a significant number of otherwise measurable lesions will not be measurable. In subjects in whom the disease is apparently restricted to the periphery of the lungs, for example, the use of IV contrast agents appears unnecessary, but the aim of a clinical study is to ensure lesions are truly resolving, and there is no evidence of new disease at other sites scanned, eg, small metastases in the liver.

The method of administration of IV contrast agents is variable. Rather than try to institute rigid rules regarding methodology of administration of contrast agents and the volume injected, it is appropriate to suggest that an adequate volume of a suitable contrast agent should be given such that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given subject.

All images from each examination should be included and not "selected" images of the apparent lesion. This is to ensure that if a review is undertaken, the reviewer can satisfy him/herself that no other abnormalities co-exist. All window settings should be included, particularly in the thorax where lung and soft tissue windows should be considered.

When measuring lesions, lesions should be measured on the same window setting on each examination. It is not acceptable to measure a lesion on lung windows on one examination, then on soft tissue settings on the next. In the lung, it does not really matter whether lung or soft tissue windows are used for intra-parenchymal lesions, provided a thorough assessment of nodal and parenchymal disease has been undertaken and the target lesions are measured as appropriate using the same window settings for repeated examinations throughout the study.

6.2.2 Magnetice Resonance Imaging (MRI)

MRI is a complex issue. MRI is entirely acceptable and capable of providing images in different anatomical planes. It is important therefore that when it is used lesions must be measured in the same anatomical plane using the same imaging sequences on subsequent examinations. MRI scanners vary in the images produced. Some of the factors involved include the magnet strength (high field magnets require shorter scan times, typically 2-5 minutes), the coil design and subject co-operation. Wherever possible, the same scanner should be used. For instance, the images provided by a 1.5T scanner will differ from those using a 0.5T scanner. Although, a comparison can be made, it is not ideal.

Moreover many subjects with advanced malignancy are in pain, so their ability to remain still for the duration of a scan sequence, in the order of 2-5 minutes is limited. Any movement

during the scan time leads to motion artifacts, degradation of image quality such that the examination will probably be useless.

For these reasons, CT is at this point in time the imaging modality of choice.

The same imaging modality must be used throughout the study to measure disease. Different imaging techniques have differing sensitivities, so any given lesion may have different dimensions at any given time if measured with different modalities. It is therefore, not acceptable to interchange different modalities throughout a trial and use these measurements. It must be the same technique throughout.

References

Therasse P Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. Journal of the National Cancer Institute. 2000 Feb 2;92(3):205-216

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Clinical Study Protocol Appendix E	
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Appendix E
Medications Known to Prolong QT

1. MEDICATIONS KNOWN TO PROLONG THE QT INTERVAL AND/OR INDUCE TORSADES DE POINTES (TDP)

It has been recognized for a number of years that certain prescription medications can prolong the QT/QTc interval and cause a form of acquired Long QT syndrome, known as drug induced LQTS. The drugs that prolong the QT interval and/or have a risk of inducing Torsade de Pointes (TdP) are listed below. We have divided these into two groups based on their known or perceived risk of causing TdP:

Group 1. Drugs that are generally accepted by authorities to have a risk of causing Torsades de Pointes

Concomitant use of these drugs is not allowed during the study or within 2 weeks of study start (at least four weeks for levomethadyl). These drugs should also be avoided for up to 4 weeks following discontinuation of study treatment:

Table 1 Group 1 Drugs

Drug (Generic Names)	Drug Class (Clinical Usage)	Comments
Albuterol (by parenteral administration)	Bronchodilator (asthma)	Inhaled Albuterol at normal doses acceptable
Amiodarone	Anti-arrhythmic (heart rhythm)	F>M, TdP Cases in Literature
Arsenic trioxide	Anti-cancer (leukaemia)	TdP Cases in Literature
Bepridil	Anti-anginal (heart pain)	F>M
Chlorpromazine	Anti-psychotic/antiemetic (schizophrenia/nausea)	TdP Cases in Literature
Chloroquine	Anti-malaria (malaria infection)	
Cisapride	GI stimulant (stimulates GI motility)	Open Prescription Restricted F>M
Disopyramide	Anti-arrhythmic (heart rhythm)	F>M
Dofetilide	Anti-arrhythmic (heart rhythm)	
Domperidone	Anti-nausea (nausea)	
Droperidol	Sedative/hypnotic (anaesthesia adjunct)	TdP Cases in Literature
Erythromycin	Antibiotic/GI stimulant (infection/GI motility)	F>M
Halofantrine	Anti-malarial (malaria infection)	F>M
Haloperidol	Anti-psychotic (schizophrenia, agitation)	
Ibutilide	Anti-arrhythmic (heart rhythm)	F>M

Table 1 Group 1 Drugs

Drug (Generic Names)	Drug Class (Clinical Usage)	Comments
Levomethadyl	Opiate agonist (narcotic dependence)	
Mesoridazine	Anti-psychotic (schizophrenia)	
Methadone	Opiate agonist (pain control/ narcotic dependence)	F>M
Pentamidine	Anti-infective (pneumocystis pneumonia)	F>M
Pimozide	Anti-psychotic (Tourette's tics)	F>M, TdP Cases in Literature
Procainamide	Anti-arrhythmic (heart rhythm)	
Quinidine	Anti-arrhythmic (abnormal heart rhythm)	F>M
Salbutamol (by parenteral administration)	Bronchodilator (asthma)	Inhaled salbutamol at normal doses acceptable
Sotalol	Anti-arrhythmic (heart rhythm)	F>M
Sparfloxacin	Antibiotic (bacterial infection)	
Thioridazine	Anti-psychotic (schizophrenia)	

Group 2. Drugs that in some reports may be associated with Torsades de Pointes but at this time lack substantial evidence of causing Torsades de Pointes.

Concomitant use of these drugs is not allowed at study entry or within 2 weeks of study start. These drugs will be allowed during the study, at the discretion of the Investigator, if considered absolutely necessary. In such cases, the patient must be closely monitored, including regular checks of QTc and electrolytes (see section 3.7.2).

Table 2 Group 2 Drugs

Drug (Brand Names)	Drug Class (Clinical Usage)	Comments
Alfuzocin	Alpha 1-blocker (Benign prostatic hyperplasia)	
Amantadine	Dopaminergic/Anti-viral/Anti-infective (Parkinson's disease)	
Amitriptyline	Tricyclic anti-depressant (depression)	
Amoxapine	Tricyclic anti-depressant (depression)	
Azithromycin	Antibiotic (bacterial infection)	

Table 2 Group 2 Drugs

Drug (Brand Names)	Drug Class (Clinical Usage)	Comments
Citalopram	Anti-depressant (depression)	
Clarithromycin	Antibiotic (bacterial infection)	TdP Cases in Literature
Clomipramine	Tricyclic antidepressant (depression)	
Chloral hydrate	Sedative (sedation/insomnia)	
Clozapine	Anti-psychotic (schizophrenia)	
Desipramine	Tricyclic anti-depressant (depression)	TdP Cases in Literature
Dolastron	Anti-nausea (nausea and vomiting)	
Doxepin	Anti-depressant (depression)	TdP Cases in Literature
Felbamate	Anti-convulsant (seizures)	
Flecainide	Anti-arrhythmic (heart rhythm)	Association not clear
Fluconazole	Anti-fungal (fungal infection)	
Fluoxetine	Anti-depressant (depression)	Association not clear
Foscarnet	Antiviral (HIV infection)	
Fosphenytoin	Anticonvulsant (seizures)	
Gatifloxacin	Antibiotic (bacterial infection)	
Gemifloxacin	Antibiotic (bacterial infection)	
Granisetron	Anti-nausea (nausea and vomiting)	
Imipramine	Anti-depressant (depression, pain, other)	TdP Cases in Literature
Indapamide	Diuretic (stimulates urine & salt loss)	TdP Cases in Literature, QT in animals
Isradipine	Anti-hypertensive (high blood pressure)	
Levofloxacin	Antibiotic (bacterial infection)	Association not clear
Lithium	Anti-mania (bipolar disorder)	
Mexilitine	Anti-arrhythmic (abnormal heart rhythm)	
Moexipril/HCTZ	Anti-hypertensive (high blood pressure)	
Moxifloxacin	Antibiotic (bacterial infection)	

Table 2 Group 2 Drugs

Drug (Brand Names)	Drug Class (Clinical Usage)	Comments
Nicardipine	Anti-hypertensive (high blood pressure)	
Nortriptyline	Tricyclic antidepressant (depression)	
Octreotide	Endocrine (acromegaly/carcinoid diarrhoea)	
Ofloxacin		
Ondansetron	Anti-emetic (nausea and vomiting)	
Paroxetine	Anti-depressant (depression)	
Protriptyline	Tricyclic antidepressant (depression)	
Quetiapine	Anti-psychotic (schizophrenia)	
Risperidone	Anti-psychotic (schizophrenia)	
Roxithromycin	Antibiotic (bacterial infection)	
Salmeterol	Sympathomimetic (asthma, COPD)	
Sertraline	Antidepressant (depression)	Association not clear
Solifenacin	Muscarinic receptor antagonist (treatment of overactive bladder)	
Tacrolimus	Immune suppressant	TdP Cases in Literature
Tamoxifen	Anti-cancer (breast cancer)	
Telithromycin	Antibiotic (bacterial infection)	
Tizanidine	Muscle relaxant	
Trimipramine	Tricyclic antidepressant (depression)	
Vardenafil	Phosphodiesterase inhibitor (vasodilator)	
Venlafaxine	Antidepressant (depression)	
Voriconazole	Anti-fungal (fungal infection)	
Ziprasidone	Anti-psychotic (schizophrenia)	

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Clinical Pharmacology Study Protocol: Appendix F	
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Appendix F
Handling and shipment of tumour biopsy

1. INSTRUCTIONS FOR HANDLING TUMOUR BIOPSY SAMPLES

1.1 Introduction

All patients must provide a mandatory archival tumor tissue sample prior to enrollment in the study. All patients will be asked to undergo two tumour biopsy procedures to obtain tissue for molecular analysis.

Appropriate informed consent will be obtained, and associated risks will be clearly explained to the patient.

1.2 Collection of tumor biopsy samples

Lesions amenable to biopsy are those that are accessible by CT guidance or directly accessible lymph nodes and superficial involvement of the head and neck or skin, which are accessible percutaneously.

From a single core biopsy a 2-cm by 18-20-gauge core can be obtained (20-30mg). Multiple core biopsies can be performed over the guide wire with little additional risk. Whenever possible, 3 core biopsies should be obtained to ensure adequate tissue for analysis.

The first core will be frozen in OCT and liquid nitrogen, and the second core paraffin-embedded. If further cores are obtained the third core will be divided into 2 sections, one section will be snap frozen without OCT and the other section paraffin embedded.

If a tumour sample was not obtained on biopsy, the patients will still be allowed to continue in the study.

1.3 Methods for preparing tumor biopsy samples

1.3.1 Formalin-fixed paraffin embedded tissue blocks

- Place biopsy samples immediately into a 4% neutral buffered formalin solution (usually referred to as 10% formalin) and leave for 8 to 16 hours (maximum 24 hours) at room temperature.

- Process the fixed specimen through routine specimen dehydration using graded ethanols to xylene, then embed the specimen longitudinally in paraffin wax under vacuum at 60ºC in a 4 cm x 2.5 cm plastic embedding mould.

- Paraffin blocks should be stored in a dark site at room temperature until transported.

1.3.2 OCT Frozen tumour biopsies

- Place tissue core in aluminium mold (available from wheatonsci.com, 20mm aluminium seal, 1000 pieces per case, no hole, unlined).

- Place a drop of OCT in the mold before adding the tissue in order to reduce potential flotation.
- Add tissue.
- Slowly fill the mold with OCT.
- Place mold in container of liquid nitrogen so that the OCT freezes slowly and preserves tissue architecture.

1.3.3 Snap frozen tumour biopsies

Tumour biopsy tissue from the third core should be divided at time of collection. One half should be prepared as previously described in section 1.3.1. The other half should be placed in a plain cryotube without preservative and immersed in liquid nitrogen for rapid freezing. The snap frozen sample should be stored frozen at –80 °C until shipment to the central holding laboratory.

1.3.4 Archival tissue sample

All patients must provide a mandatory archival tumor tissue sample prior to enrolment in the study. Archival tissue samples should be submitted as formalin-fixed, paraffin-embedded blocks. Alternatively, archival tissue samples may be submitted as 10 unstained slides

1.4 Shipment of tumour biopsy samples

The frozen and paraffin embedded tumour biopsy samples as well as the archival samples will be shipped to Quest for storage until ready for shipment to the analyzing labs. Frozen biopsy samples should be shipped as whole cores and packed securely on dry ice to avoid breakage during transit. Ideally frozen samples should only be shipped on Mondays to avoid risk of samples arriving at weekends and thawing. Paraffin embedded samples can be shipped at ambient temperatures. See lab manual for additional shipping information.

2. ANALYSIS OF TUMOR TISSUE

The formalin fixed, paraffin embedded tumor samples will be analyzed for EGFR/Her2 gene amplification by FISH, EGFR/Her2, E-Cadherin and vimentin protein expression by IHC, and Akt/pAkt, MAPK/pMAPK, and pEGFR by IHC. If formalin fixed paraffin embedded samples are available from a 3rd core biopsy, these will be analysed for markers of tumor hypoxia and vasculature (HIF, VEGF, CD31).

Tumor samples frozen in OCT will be assessed for phosphorylation of VEGFR and downstream signalling as well as tumor cell and tumor endothelial apoptosis using ASC. These samples will be analyzed for VEGFR/pVEGFR as well as CD31/TUNEL/caspase, and staining for angiogenesis and apoptosis.

If snap frozen tumor samples (frozen is the absence of OCT) are available from a 3rd core biopsy, these may be used to assess changes in gene and protein expression profiles using expression array and proteomic, and to analyse drug concentration in tumor tissue.

Additional tests on these tissue samples may be done in the future. All testing will be for research purposes only. Mandatory archival tissue samples will be returned to the site at the end of the study. Tissue samples from optional pre- and post-dose ZD6474 biopsies will not be returned to the site unless a patient withdraws consent. Any tissue samples remaining after all testing is complete will be destroyed.

References

A Bardelli et al (2003) Mutational analysis of the tyrosine kinome in colorectal cancers Science 300, 949.

D Eberhard et al (2004) Correlation of mutations in EGFR and k-ras with clinical outcomes in NSCLC patients treated with erlotinib and carboplatin. Poster presentation EORTC meeting, Geneva.

TG Graeber et al (1996) Hypoxia mediated selection of cells with diminished apoptotic potential in solid tumours Nature 379, 88-90.

TJ Lynch et al (2004) Activating mutations in the Epidermal Growth Factor Receptor underlying responsiveness of Non Small Cell Lung Cancer to gefitinib. New England J Medicine 350, 2129-2139.

JG Paez et al (2004) EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 304, 1497-1500

JL Yu et al (2002) Effect of p53 status on tumour response to antiangiogenic therapy. Science 295, 1526-1528.

Clinical Study Protocol Appendix G	
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Appendix G
Collection and handling of blood samples

Further details on the collection, processing, storing, labelling, and shipping of study-required biological samples are available in the central laboratory manual.

1. PHARMACOKINETICS (PK) SAMPLES

Venous blood (4 mL) will be collected at the sampling times shown in the study plan, into tubes containing lithium heparin anticoagulant. Gently invert the tubes several times to ensure sample is thoroughly mixed. Within 15 minutes of collection, the blood samples will be centrifuged by spinning at 1000 G for 10 minutes.

After centrifugation, the plasma should be taken off immediately and stored in a plain tube at -20 ºC before transportation to the central holding laboratory.

The date and the time of collection will be recorded on the appropriate CRF.

2. PLASMA BIOMARKERS

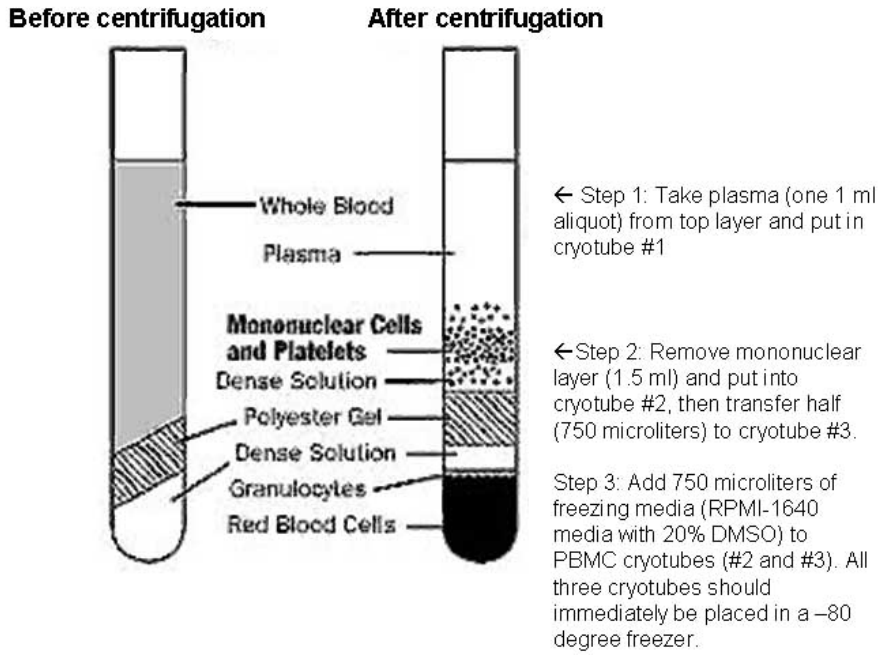
Venous blood (10 mL) will be collected at the sampling times shown in the study plan, into precooled (ice bath) EDTA collection tubes. Gently invert 5-6 times to ensure adequate mixing and prevent coagulation. Cool the tubes immediately in an ice bath. Within **30 minutes,** centrifuge at 1200g, for 15 minutes. The obtained plasma supernatant is then transferred to a second centrifugation tube and centrifuged at 10,000g for 10 minutes.

After centrifugation, the platelet-poor EDTA plasma supernatant should be taken off immediately and transferred by pipette into two cryovials and stored at -20 ºC before transportation to the central holding laboratory.

3. PBMC/CEC SAMPLES

Venous blood (7mL) will be collected at the sampling times shown in the study plan, into a BD Vacutainer CPT™ tube with Sodium Citrate (Becton Dickinson product #362761). The tube should be gently inverted several times to ensure mixing with the anticoagulant. Within two hours, the CPT tube should be centrifuged at room temperature for 25 minutes at 1600g. A centrifuge with horizontal rotor is recommended.

After centrifugation, the mononuclear cells will be visible in a whitish layer just under the plasma (See diagram below).



A 1 mL aliquot from the plasma layer should be transferred to a labeled cryotube (Nunc, product #377267). Then remove the mononuclear layer (1.5 ml) and put into cryotube #2. Transfer half of mononuclear cells (750 microliters) to cryotube #3, so that both tubes #2 and #3 each have 750 microliters. Add 750 microliters of freezing media (RPMI-1640 media with 20% dimethyl sulfoxide) to both PBMC cryotubes (#2 and #3).

All three cryotubes should immediately be placed in a –80 °C freezer until shipment to the central holding laboratory.

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Clinical Study Protocol: Appendix H	
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Appendix H
AJCC STAGING FOR HEAD & NECK, 6th Edition

AJCC STAGING HEAD & NECK, 6th Edition

STAGING-PRIMARY TUMOUR (T)

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

Tis Carcinoma in situ

PHARYNX

Oropharynx

T1 Tumour 2 cm or less in greatest dimension

T2 Tumour more than 2 cm but not more than 4 cm in greatest dimension

T3 Tumour more than 4 cm in greatest dimension

T4a Tumour invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible.

T4b Tumour invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery.

Hypopharynx

T1 Tumour limited to one subsite of hypopharynx and 2 cm or less in greatest dimension.

T2 Tumour invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest diameter without fixation of hemilarynx.

T3 Tumour measures more than 4 cm in greatest dimension or with fixation of hemilarynx.

T4a Tumour invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, oesophagus or central compartment soft tissue.

T4b Tumour invades prevertebral fascia, encases carotid artery, or involves mediastinal structures.

LARYNX

Supraglottis

T1 Tumour limited to one subsite of supraglottis with normal vocal cord mobility

T2 Tumour invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx.

T3 Tumour limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex).

T4a Tumour invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of the neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or oesophagus).

T4b Tumour invades prevertebral space, encases carotid artery, or invades mediastinal structures.

Glottis

T1 Tumour limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility

T1a Tumour limited to one vocal cord

T1b Tumour involves both vocal cords

T2 Tumour extends to supraglottis and/or subglottis, or with impaired vocal cord mobility

T3 Tumour limited to the larynx with vocal cord fixation, and/or invades paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex).

T4a Tumour invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or oesophagus).

T4b Tumour invades prevertebral space, encases carotid artery, or invades mediastinal structures.

Subglottis

T1 Tumour limited to the subglottis

T2 Tumour extends to vocal cord(s) with normal or impaired mobility

T3 Tumour limited to larynx with vocal cord fixation

T4a Tumour invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or oesophagus).

T4b Tumour invades prevertebral space, encases carotid artery, or invades mediastinal structures.

REGIONAL LYMPH NODES (N) Excluding Nasopharynx

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in a single ipsilateral node, 3 cm or less in greatest dimension.

N2 Metastasis in a single ipsilateral node, more than 3 cm, but not more than 6 cm in greatest

dimension, or in multiple ipsilateral lymph nodes, none greater than 6 cm in greatest dimension, or bilateral or contralateral nodes, none more than 6 cm in greatest dimension.

N2a Metastasis in a single ipsilateral node more than 3 cm, but not more than 6 cm in greatest dimension.

N2b Metastasis in multiple ipsilateral nodes, none more than 6 cm in greatest dimension.

N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension.

N3 Metastases in a lymph node, more than 6 cm in greatest dimension.

DISTANT METASTASIS (M)

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

STAGE GROUPING Excluding Nasopharynx

Stage 0	T*is*, N0, M0	
Stage I	T1, N0, M0	
Stage II	T2, N0, M0	
Stage III	T3, N0, M0	T1-3, N1, M0
Stage IVA	T4a, N0-2, M0	Any T, N2, M0
Stage IVB	T4b, Any N, M0	Any T, N3, M0
Stage IVC	Any T, Any N, M1	

AstraZeneca

Clinical Study Protocol: Appendix I	
Drug substance:	ZD6474
Study Code:	D4200C00062
Appendix Edition No:	1.0
Appendix Date:	26 April 2006

Appendix I
RTOG/EORTC Late radiation morbidity scoring schema

ORGAN TISSUE	0	Grade 1	Grade 2	Grade 3	Grade 4	5
SKIN	None	Slight atrophy Pigmentation change Some hair loss	Patch atrophy; Moderate telangiectasia; Total hair loss	Marked atrophy; Gross telangiectasia	Ulceration	
SUBCUTANEOUS TISSUE	None	Slight induration (fibrosia) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic Slight field contracture <10% linear reduction	Severe induration and loss of subcutaneous tissue Field contracture >10% linear measurement	Necrosis	
MUCOUS MEMBRANE	None	Slight atrophy and dryness	Moderate atrophy and telangiectasia Little mucous	Marked atrophy with complete dryness Severe telangiectasia	Ulceration	DEATH DIRECTLY RELATED TO RADIATION LATE EFFECTS
SALIVARY GLANDS	None	Slight dryness of mouth Good response on stimulation	Moderate dryness of mouth Poor response on stimulation	Complete dryness of mouth No response on stimulation	Fibrosis	
SPINAL CORD	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono, para/ quadraplegia	
BRAIN	None	Mild headache Slight lethargy	Moderate headache Great lethargy	Severe headaches Severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis Coma	
EYE	None	Asymptomatic cataract Minor corneal ulceration or keratitis	Symptomatic cataract Moderate corneal ulceration Minor retinopathy or glaucoma	Severe keratitis Severe retinopathy or detachment Severe glaucoma	Panophthalmitis/ Blindness	

ORGAN TISSUE	0	Grade 1	Grade 2	Grade 3	Grade 4	5
LARYNX	None	Hoarseness Slight arytenoid oedema	Moderate arytenoid oedema Chondritis	Severe oedema Severe chondritis	Necrosis	
LUNG	None	Asymptomatic or mild symptoms (dry cough) Slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough) Low grade fever Patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis Dense radiographic changes	Severe respiratory insufficiency/ Continuous O_2/ Assisted ventilation	
HEART	None	Asymptomatic or mild symptoms Transient T wave inversion & ST changes Sinus tachycardia >110 (at rest)	Moderate angina on effort Mild pericarditis Normal heart size Persistent abnormal T wave and ST changes Low ORS	Severe angina Pericardial effusion Constrictive pericarditis Moderate heart failure Cardiac enlargement EKG abnormalities	Tamponade/ Severe heart failure/ Severe constrictive pericarditis	
ESOPHAGUS	None	Mild fibrosis Slight difficulty in swallowing solids No pain on swallowing	Unable to take solid food normally Swallowing semi-solid food Dilatation may be indicated	Severe fibrosis Able to swallow only liquids May have pain on swallowing Dilation required	Necrosis/ Perforation Fistula	
SMALL/LARGE INTESTINE	None	Mild diarrhoea Mild cramping Bowel movement 5 times daily Slight rectal discharge or bleeding	Moderate diarrhoea and colic Bowel movement >5 times daily Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis/ Perforation Fistula	

ORGAN TISSUE	0	Grade 1	Grade 2	Grade 3	Grade 4	5
LIVER	None	Mild lassitude Nausea, dyspepsia Slightly abnormal liver function	Moderate symptoms Some abnormal liver function tests Serum albumin normal	Disabling hepatitic insufficiency Liver function tests grossly abnormal Low albumin Oedema or ascites	Necrosis/ Hepatic coma or encephalopathy	
KIDNEY	None	Transient albuminuria No hypertension Mild impairment of renal function Urea 25-35 mg% Creatinine 1.5-2.0 mg% Creatinine clearance >75%	Persistent moderate albuminuria (2+) Mild hypertension No related anaemia Moderate impairment of renal function Urea>36-60 mg% Creatinine clearance (50-74%)	Severe albuminuria Severe hypertension Persistent anaemia (<10g%) Severe renal failure Urea >60 mg% Creatinine >4.0 mg% Creatinine clearance <50%	Malignant hypertension Uraemic coma/Urea >100%	
BLADDER	None	Slight epithelial atrophy Minor telangiectasia (microscopic haematuria)	Moderate frequency Generalized telangiectasia Intermittent macroscopic haematuria	Severe frequency and dysuria Severe generalised telangiectasia (often with petechiae) Frequent haematuria Reduction in bladder capacity (<150 cc)	Necrosis/ Contracted bladder (capacity <100 cc) Severe hemorrhagic cystitis	
BONE	None	Asymptomatic No growth retardation Reduced bone density	Moderate pain or tenderness Growth retardation Irregular bone sclerosis	Severe pain or tenderness Complete arrest of bone growth Dense bone sclerosis	Necrosis/ Spontaneous fracture	

ORGAN TISSUE	0	Grade 1	Grade 2	Grade 3	Grade 4	5
JOINT	None	Mild joint stiffness Slight limitation of movement	Moderate stiffness Intermittent or moderate joint pain Moderate limitation of movement	Severe joint stiffness Pain with severe limitation of movement	Necrosis/ Complete fixation	