A Phase II Trial of Induction Chemotherapy with Carboplatin and Paclitaxel, Followed by Concurrent Chemoradiation with ZD1839 (IRESSA®), 5-Fluorouracil, Hydroxyurea, and Twice-daily Radiation, Followed by Adjuvant ZD1839 Monotherapy in Patients with Locally Advanced Head and Neck Cancer

Chicago Oral Cancer Center and Affiliated Institutions

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A Phase II trial of Induction Chemotherapy with Carboplatin and Paclitaxel, Followed by Concurrent Chemoradiation with ZD1839 (IRESSA®), 5-Fluorouracil, Hydroxyurea, and Twice-daily Radiation, Followed by Adjuvant ZD1839 Monotherapy in Patients with Locally Advanced Head and Neck Cancer

Investigator

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Trial center(s) and number of patients planned

4 centers, 85 patients planned

Trial period		**Phase of development**
Estimated date first patient enrolled	December 2002	II
Estimated date last patient enrolled	May 2006	

Objectives

Primary

- To explore the activity of ZD1839 added to concurrent chemoradiotherapy and as adjuvant monotherapy in patients with locally advanced head and neck cancer. Activity is described in terms of response rate (complete responses only).

Secondary

- To explore the tolerability and feasibility of ZD1839 added to concurrent chemoradiotherapy.
- To assess quality of life (QoL)
- To define any toxcities of ZD1839 used in concurrent chemoradiotherapy and as adjuvant therapy

Exploratory

- To assess pharmacodynamics of ZD1839 in vivo and correlate clinical outcome with inhibition of tyrosine kinase activity
- To assess in vivo effects of week on/week off hyperfractionated radiotherapy

Trial design

Single arm, two-stage, phase II trial of induction therapy with carboplatin and paclitaxel, followed by ZD1839, 5-FU, hydroxyurea, and hyperfractionated radiotherapy, followed by adjuvant ZD1839 alone.

Background and rationale

Concurrent chemoradiotherapy has proven efficacy in locally advanced head and neck cancer with overall survival and local control improved compared to radiotherapy alone. Induction chemotherapy can reduce distant failure rate. Despite this, there is still a 40% failure rate in patients with locally advanced head and neck cancer.

Head and neck cancer has a rate of epidermal growth factor receptor (EGFR) expression of 90%. ZD1839 inhibits EGFR activation through interference with its tyrosine kinase intracellular domain. ZD1839 has demonstrable single agent activity in head and neck cancer. By adding ZD1839 to our current institutional standard of induction chemotherapy followed by concurrent chemoradiotherapy, we hope to improve local and distant control and overall survival. Furthermore, adding adjuvant ZD1839 could prevent recurrence or second primary malignancies.

Patient population

- Patients with stage III or IV carcinoma of the head and neck
- Patients with squamous cell carcinoma of unknown primary originating in the neck.

Measurable disease is not required, but all disease will be carefully evaluated using Response Evaluation Criteria in Solid tumors (RECIST) criteria.

Inclusion criteria

- Histologically or cytologically confirmed diagnosis of squamous cell or poorly differentiated carcinomas, or lymphoepithelioma
- No prior or radiotherapy
- Prior surgical therapy will consist only of incisional or excisional biopsy, and organ sparing procedures such as debulking of airway compromising tumors or neck dissection in a patient with an existing or unknown (T_x) primary tumor
- Performance status of ≥ 60%
- Intact organ and bone marrow function

Investigational product, dosage and mode of administration

ZD1839 (*IRESSA*®) 500 mg by mouth (PO) daily

Chemotherapy agents, doses, mode of administration

Optional Induction chemotherapy:	Carboplatin and paclitaxel combination will be administered for 2 cycles of 4 weeks duration each. Chemoradiotherapy will begin 1-2 weeks after the last dose.
Paclitaxel:	100 mg/m^2 in 500 ml of dextrose 5% in water (D5W) over 3 hours (on days 1, 8, and 15)
Carboplatin:	Start after completion of paclitaxel on Day 1 AUC 6 (creatinine clearance [CC] + 25). Administer in 100 ml of normal saline (NS) over 30 minutes after completion of paclitaxel.

No therapy on Day 22. Resume chemotherapy for cycle 2 on Day 29.

Concomitant chemoradiotherapy:

ZD1839:	500mg PO QD from day 1 of cycle 1 of chemoradiotherapy, uninterrupted until disease progression, patient intolerance, patient withdrawal or study closure Chemotherapy should be administered during all 5 weeks of radiotherapy.
Day 0 (Sunday):	
P.M.:	Start hydroxyurea at 500 mg PO q 12 hours × 6 days (11 doses). The first daily dose of hydroxyurea on Days 1 through 5 is given 2 hours prior to the first fraction of daily radiotherapy.
6:00 P.M.:	Start continuous infusion of 5-fluorouracil at 600 mg/m^2/day × 5 days (120 hours).
Days 1 through 5:	Radiation therapy is administered twice daily at 150 cGy per fraction.
Days 6 through 14 of each cycle:	No chemoradiotherapy.

Chemoradiotherapy cycles are repeated every 14 days until the completion of radiotherapy.

ZD1839 will be administered from day 1 to 14 of every chemoradiotherapy cycle.

Duration of treatment

8 weeks induction chemotherapy
10 weeks chemoradiation

Number of patients expected per year

40 (85 total)

Number of patients expected to be enrolled each month

3-4

Statistical analysis

This study wishes to explore the frequency of complete and partial clinical response rates of the whole regimen among advanced stage patients, to estimate the impact of concurrent chemoradiotherapy with ZD1839 and adjuvant ZD1839 monotherapy on pattern of failure, and to estimate the survival curve for these patients following treatment. Accordingly, the primary endpoint will be complete response (complete response [CR]). Secondary endpoints will be time to progression (TTP), incidence of second primary tumors, and survival. Pattern of failure will be described as locoregional, distant, or both. In addition to summarizing response rates, investigators will calculate time to progression and survival time using Kaplan-Meier product limit curves. A retrospective comparison at similar time points will be made to the prior patients treated on Protocol 9502.

Table 1: Pre-therapy and induction checklist

Item	Pre-therapy	Week 1 induction	Week 2 induction	Week 3 induction	Week 4 induction	Week 5 induction	Week 6 induction	Week 7 induction	Week 8 induction
Inclusion/exclusion criteria	X								
History and physical	X	X	X	X	X (optional week 4)	X	X	X	X
Informed consent	X								
Panendoscopy[1]	X								
Tumor map	X								
Dental assessment	X								
Swallowing assessment	X								
Performance status	X								
Concomitant medication[2]	X	X	X	X	X	X	X	X	X
Adverse event		X	X	X	X	X	X	X	X
Head and neck CT/MRI[3]	X								
Chest CT	X								
Bone scan[4]	X								

Table 1: Pre-therapy and induction checklist (cont.)

Pregnancy test	X								
Hematology[5]	X	X	X	X	X	X	X	X	X
Biochemistry[6]	X[7]	X	X	X	X	X	X	X	X
Creatinine Clearance[8]	X								
Paclitaxel		X	X	X		X	X	X	
Carboplatin		X				X			
Research Blood Samples	X[9]								

1 Biopsy will be done within 6 weeks of starting therapy.
2 Document use of concomitant medication.
3 The same procedure should be done throughout therapy and follow-up.
4 If clinically indicated.
5 CBC, differential, and platelet count twice weekly.
6 Comprehensive metabolic profile (magnesium if clinically indicated).
7 Should include TSH.
8 Obtain 24-hour urine for calculation. Alternately, can be calculated using formula (see section 6.1.2). Recalculate if serum creatine or weight change > 30%.
9 1-7cc lavender top tube.

CBC = complete blood count; CT = computed tomography; MRI = magnetic resonance imaging; EGFR = epidermal growth factor receptor; TSH = thyroid stimulating hormone.

Table 2: Concomitant chemoradiotherapy

Item	Pre-CRT	Cycle 1[1]	Cycle 2	Cycle 3	Cycle 4	Cycle 5[2]	30-day follow-up
History and physical	X	X	X	X	X	X	X
Adverse event	X	X	X	X	X	X	X
Head and neck CT/MRI[3]	X						X
Chest CT	X						X
Hematology[4]	X	X	X	X	X	X	X
Biochemistry[5]	X	X	X	X	X	X	X
ZD1839[8]		X	X	X	X	X	
5 FU		X	X	X	X	X	
Hydroxyurea		X	X	X	X	X	
Radiotherapy[6]		X	X	X	X	X	
Dental assessment							X
Swallowing assessment	X						X
Biopsy							X[7]

1 Each cycle is 2 weeks long. See section 6.1.3.
2 Some patients may have only 4 cycles total.
3 The same procedure should be done throughout therapy and follow-up
4 CBC, differential, and platelet count twice weekly
5 Comprehensive metabolic profile (with magnesium if indicated) twice weekly.
6 Radiotherapy is given twice daily.
7 Within 8 weeks of completing chemoradiotherapy
8 Start on day 1 of cycle 1 and continue, uninterrupted, until completion of radiotherapy. Given PO, once daily, 500mg.

Table 3: Follow-up

Item	2-month visit	3-month visit	4-month visit	5-month visit	6-month visit	9-month visit	12-month visit/Follow-Up[4]
History and physical	X	X	X	X	X	X	X

Adverse events	X	X	X	X	X	X	X
Quality of life					X		X[5]
Hematology	X	X	X	X	X	X	X
Biochemistry[1]	X	X	X	X	X[2]	X[2]	X[2]
Head and neck CT/MRI[3]		X			X	X (optional)	X
Chest CT		X			X	X (optional)	X

1 Comprehensive profile
2 Should include TSH.
3 The same procedure should be done throughout therapy and follow-up (will be repeated every 3-4 months for 2 years, then yearly).
4 Frequency of follow-up beyond 12 months is left to the investigator although patients must be evaluated clinically and radiographically at a minimum of every 6 months until 3 years post-therapy.
5 And annually for 5 years.

CT = computed tomography; MRI = magnetic resonance imaging; TSH = thyroid stimulating hormone

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1 INTRODUCTION

Investigators should be familiar with the Investigator Brochure (IB).

1.1 Background

1.1.1 Head and Neck Cancer

Approximately 40,000 new cases of head and neck cancer are diagnosed annually in the United States (1). Of these patients, two-thirds present with locoregionally advanced disease (American Joint Committee on Caner [AJCC] stage III or IV) and one-third with early stage disease (AJCC stage I or II). At presentation, 10% of patients may be found to have involvement of distant organs, most commonly the lung. In addition, 20% of patients will develop clinically detected distant metastases over the course of their disease. In autopsy series up to 50% of patients with head and neck cancer are found to have metastases (2, 3). It is likely that with improvements in the rate of locoregional control, the risk of distant failure will become predominant, and that systemic therapy, if efficacious, will have a major impact on outcome. Approximately 95% of all head and neck malignancies are squamous cell carcinomas and this histological type is the focus of this review and study protocol. Also, it should be noted that even though head and neck malignancies are usually examined in one group, they represent a heterogeneous group of diseases, with variability in biologic behavior and natural history, prognosis, and considerations in management. Disease sites such as the hypopharynx and the base of tongue have a worse prognosis compared to the larynx or nasopharynx (4), and may require more aggressive treatment strategies. The vast majority of head and neck malignancies can be attributed to the use of tobacco and alcohol. These carcinogens are synergistic, and may damage the entire aerodigestive epithelium. Due to their frequent history of exposure to tobacco and alcohol, patients with head and neck cancer are in high risk for other comorbidities associated with tobacco and alcohol, such as coronary artery disease, chronic obstructive pulmonary disease, and liver disease (5). In addition, they are at high risk for the development of second primary tumors, synchronous or metachronous, that may involve the head and neck region as well as other organs, predominantly the lung (6).

1.1.2 Locoregionally Advanced Disease (AJCC Stages III and IV)

For patients with resectable locally advanced head and neck cancer (AJCC stage III or IV), surgery and postoperative radiation have been traditionally considered the mainstay of treatment, whereas radiation therapy alone has been offered to patients with unresectable tumors. It is important to recognize that the distinction between resectable and unresectable disease lacks clear definition. With the exception of a few widely accepted signs of unresectability, such as involvement of the carotid artery, in most cases the assessment is subjective and relates to the experience of the surgeon and the

availability of reconstructive strategies. Despite aggressive locoregional treatment with surgical resection and postoperative radiotherapy, locoregionally advanced disease has a poor prognosis with 5-year survival of less than 30% (5). The most common site of failure remains locoregional, whereas distant failure occurs in 20-30% of patients (7).

1.1.3 Chemotherapy for Locoregionally Advanced Disease

The addition of chemotherapy to the overall treatment plan in patients with locoregionally advanced head and neck cancer has been studied intensively. Research strategies, generally, have included the use of induction (neoadjuvant) or adjuvant chemotherapy, as well as concomitant chemotherapy and radiation. The primary goal of such research is to improve local control and survival. Given the anatomic location of the disease and the frequently aggressive surgical approaches used, the use of less extensive surgery (and the preservation of organ function) is an important secondary treatment goal. Concomitant chemoradiotherapy has led to improved disease-free and overall survival in randomized clinical trials and also allows for organ preservation.

1.1.4 Concomitant Chemotherapy with Fluorouracil, Hydroxyurea and Once-daily Radiotherapy (FHX)

In 1986, we initiated the clinical investigation of the interaction of 5-FU, hydroxyurea and radiotherapy (FHX). Both chemotherapy agents have known systemic activity and thus can be postulated to contribute to systemic and locoregional control of head and neck cancer (5). In addition, hydroxyurea modulates the activity of 5-FU by depleting cellular pools of deoxyuridine monophosphate (dUMP) and facilitating binding of the 5-FU metabolite 5-FdUMP to its target enzyme thymidylate synthase (8). Finally, both agents have been shown to act as radiation enhancers *in vitro* and *in vivo* (9, 10).

An intermittent schedule of chemoradiotherapy was used (one week on, one week off) based on the previous experience of Byfield et al. with single-agent 5-FU (11). The recommended dose of 5-FU 800 mg/m^2/day was administered as a 5-day continuous infusion. The maximal tolerated dose of hydroxyurea was 1000 mg administered orally every 12 hours for a total of 11 doses beginning 6 to 12 hours prior to the 5-FU infusion with one daily dose preceding radiotherapy by 2 hours (12). These doses resulted in moderate to severe mucositis and mild to moderate myelosuppression. Radiotherapy was administered once daily at 180 to 200 cGy. Five days of treatment were followed by a 9-day rest period to allow for recovery from toxicities (week on/week off). Response rates exceeded 90%. Only 3 of 19 patients without prior local therapy developed locoregional recurrence. This high locoregional activity of the FHX combination has been confirmed by other investigators (13-15).

More recently, the FHX regimen was one of the arms of a 3-arm phase II randomized trial conducted by the RTOG (9703) in patients with stage III and IV head and neck cancer (13). Regimens compared included cisplatin (10mg/m^2) and 5-FU (400mg/m^2) with 70 Gy/7 weeks of consecutive daily radiation (XCF), cisplatin (20mg/m^2) and

paclitaxel (30mg/m^2) with 70 Gy/7 weeks consecutive daily therapy (XCT), or daily hydroxyurea (1 g PO twice daily [BID]) and 5-FU (800 mg/m^2) with 70 Gy/13 weeks radiation (alternating week schedule) (FHX). Toxicity and survival were not statistically different among the 3 arms. Estimated 1- and 2-year survival rates were 72% and 60% for XCF, 87% and 65% for FHX, and 80% and 67% for XCT, respectively. The survival rates on all three arms were superior to a historic control of radiotherapy and cisplatin (two year survival rate 46%). The pattern of failure showed predominant locoregional failure pattern for all three arms. Therefore, conventional radiotherapy with concomitant chemotherapy given in consecutive weeks or a protracted course yielded acceptable patient toxicity and response rates. Thus, FHX is a feasible regimen in a national cooperative group setting with encouraging tumor control results. In the past decade, the FHX regimen has been the basis for the development of combined modality strategies by our group in an attempt to improve locoregional control and survival of previously untreated patients with locoregionally advanced head and neck cancer (Table 4).

Table 4 Summarized results with Phase II trials with C-FHX and T-FHX

	CFHX {KIES, 2001 #9}	TFHX **(120H){VOKES, 2000 #574)**	TFHX **(1H) {ROSEN, 2001 #439}**
UNIVERSITY OF CHICAGO PROTOCOL NUMBER	6950	7929	8626
N	76	64	90
STAGE IV	93%	97%	96%
*PROGRESSION-FREE SURVIVAL	72%	63%	62%
*LOCAL CONTROL	92%	86%	84%
*SYSTEMIC CONTROL	83%	79%	79%
*OVERALL SURVIVAL	55%	64%	59%
GR 3/4 NEUTROPENIA	41/39	30/5	28/7
GR 3/4 THROMBOCYTOPENIA	25/53	1/0	1/1
GR 3/4 MUCOSITIS	48/12	56/28	69/12
REFERENCE	17	18	19
*3 YEAR DATA			

1.1.5 Current "Platform" Regimen: Induction Carboplatin and Paclitaxel Followed by intensive chemoradiotherapy

Our most recent clinical trials for patients with locoregionally advanced disease in the Chicago Oral Cancer Center Network has continued to use the T-FHX regimen as previously defined. Despite the high locoregional control and high survival rates, three problems were identified: distant failure emerged as the predominant site of failure, mucositis, was often severe, and sometimes resulted in long-term functional impairment, and toxicities related to chemotherapy (specifically neuropathy and myelosuppression) often resulted in dose reduction and patient impairment. To address the first goal, we added induction chemotherapy to precede concomitant chemoradiotherapy. In designing the induction chemotherapy regimen, we selected the combination of carboplatin and paclitaxel, a regimen that is well tolerated and that would not result in mucositis or dermatitis as significant toxicity to avoid overlapping toxicities with the subsequent administration of T-FHX.

We also addressed the second goal of reducing toxicity and improving functional performance. The exceedingly high local and regional control rates observed in all T-FHX studies suggested that a careful attempt to reduce the radiation therapy field sizes to minimize long-term treatment sequelae would be feasible.

The results of this trial involving 69 patients revealed that response to induction chemotherapy to be PR 52% and CR 35%. Symptomatically, there was a significant reduction in mouth and throat pain. The most common grade 3 or 4 toxicity was neutropenia (36%) while 33% of patients experienced neuropathy. Best response following completion of T-FHX was CR in 83%. Toxicities of T-FHX consisted of grade 3 or 4 mucositis (74% and 2%), and dermatitis (47% and 14%). At a median follow up of 28 months, locoregional or systemic disease progression have each been noted in five patients. The overall three year progression-free survival is 80% (95% confidence interval (CI): 71%-90%) and the two and three year overall survival rates are 77% (95% CI: 66%-87%) and 70%, (95% CI: 59%-82%), respectively. At 12 months, 5 patients were completely feeding tube dependent (patients who died without disease progression were censored from the PFS analysis).

1.2 1.2 ZD1839

1.2.1 Efficacy

In two Phase II randomized trials (IDEAL 1 and 2), pretreated non-small-cell lung cancer (NSCLC) patients received ZD1839 250 or 500 mg/day. IDEAL 1 patients (n=210) were recruited across Europe, Australia, South Africa and Japan and had received 1 or 2 prior chemotherapy regimens (1 platinum-based), while IDEAL 2 recruited patients in the US (n=216) who had been given □□2 regimens (including platinum and docetaxel). In IDEAL 1, the response rate (RR) was 18.4 and 19.0%, and disease control rate (DCR =responses plus stable disease) was 54.4 and 51.4%, in

patients who received 250 and 500 mg/day ZD1839, respectively. Symptom improvement, measured by the LCS component of the FACT-L and lasting at least four or more weeks occurred in 40.3% for the 250-mg/day group and 37.0% for the 500-mg/day group. Median survival for the IDEAL-1 population receiving ZD1839 as second or third-line therapy was not calculable with the 4-month minimum follow-up at the time of trial closure.

In IDEAL 2, the RR was 11.8 and 8.8%, and DCR was 42.2 and 36.0%, in patients who received 250 and 500 mg/day, respectively. Symptom improvement, as measured by the LCS component of the FACT-L and lasting at least 4 or more weeks occurred in 43.1% for the 250 mg/day group and 35.1% for the 500 mg/day group. Median survival for the IDEAL-2 population receiving ZD1839 as third-line or greater therapy was 6 months.

Symptom-Improvement was associated with objective tumor response and survival in the IDEAL 1 and 2 trials. Tumor responses occurred in patients predominantly with adenocarcinoma histology but responses have been observed in all histologies and irrespective of the number of previous chemotherapy regimens.

In addition to the efficacy findings, quality of life (QOL) improvement was seen in a significant proportion of patients and was consistent with disease-related symptom improvement, which reflects the lack of significant therapy-related toxicity observed.

1.2.2 Signal Transduction and ZD1839

ZD1839 is a signal transduction inhibitor of EGFR tyrosine kinase, and it has been developed as an oral antitumor agent.

Epidermal growth factor receptor is characteristic of a large family of growth factor receptor tyrosine kinases that share a common structure composed of an extracellular ligand binding domain, a short transmembrane domain, and an intracellular domain that has tyrosine kinase activity. Binding of the cognate ligand, for example, epidermal growth factor (EGF) or transforming growth factor a (TGFa) to the extracellular domain of EGFR initiates a signal transduction cascade that can influence many aspects of tumor cell biology, including growth, survival, metastasis, and angiogenesis, as well as tumor cell sensitivity to chemotherapeutic and radiotherapeutic drugs. Tyrosine phosphorylation provides docking sites on the EGFR for recruitment of proteins that are either direct substrates for EGFR-mediated phosphorylation or adaptor proteins that link the receptor to a cascade of “downstream” biochemical reactions, for example, the ras-raf-MAPK-fos pathway, which drives tumor cell proliferation (16).

1.2.3 ZD1839 Pre-clinical Experience

Key preclinical features of ZD1839 include high tolerability and the ability to delay growth and at higher doses to cause regression in human non-small cell lung cancer (NSCLC) and a wide range of other tumor xenografts (see the ZD8139 Investigator's Brochure [IB] for details).

1.2.4 Animal Data

In preclinical toxicity studies the no-effect dose level after administration of ZD1839 for up to 1 month is 2 mg/kg per day; over a 6-month period it is 1 mg/kg per day. In the 1-month studies, a dose of 40 mg/kg per day produced pathological changes in the ovaries of rats and in the eyes, kidneys, and skin of both rats and dogs. Similar changes were detected in the 6-month studies, and, in addition, minimal/mild hepatocellular necrosis was also detected with increased levels of circulating plasma liver enzymes. These effects showed signs of partial or full reversibility after drug withdrawal. There was evidence of reduced fertility in the female rat at the 20-mg/kg per day dosage as well as slight maternal and fetotoxicity in the rabbit. These changes were all attributed to the pharmacological effects of ZD1839 on EGF-dependent tissues. Reversible abnormalities of atrioventricular conduction were also seen in the dog at the 40-mg/kg per day dosage in the 1-month study and at the 15-mg/kg per day dosage in the 6-month study. Data for dog Purkinje fibers indicate that ZD1839 has a modest potential to affect repolarization and hence prolong QT at high plasma concentrations. There is some evidence for *in vivo* effects; however, these were not clear even at the highest dose tested.

1.2.5 Clinical Data

1.2.5.1 Clinical Pharmacokinetics

ZD1839 is extensively distributed (volume of distribution approximately 1400l), rapidly cleared (514 ml/minute), and has a mean elimination half-life of 48 hours in cancer patients. Plasma protein binding is approximately 90%. Following oral administration, absorption is moderately slow (maximum plasma concentrations typically occur between 3 and 7 hours after administration of the dose), and the mean terminal half-life is 41 hours. The absolute bioavailability of the 250-mg tablet is approximately 60%. The effect of food on the absorption of ZD1839 (35% increase in area under the concentration-time curve [AUC]) is not considered clinically relevant, but sustained elevation of gastric pH above 5 results in a 47% reduction in relative bioavailability. Administration once daily results in 2- to 8-fold accumulation, with steady state plasma concentrations achieved by Days 7 to 10. At steady state, circulating plasma concentrations are typically maintained within a 2- to 3-fold range across the dosing interval. Population pharmacokinetic data from two phase II studies in patients with advanced NSCLC showed the mean steady state trough concentration following a 250-mg dose was 261 ng/ml (95% continuous infusion [CI]: 88.0 to 774 ng/ml), with

interpatient variability of 56% and intrapatient variability of 21% to 30%. No clinically relevant demographic or pathophysiological covariates were identified, but there was a correlation between trough concentration and the incidence of diarrhea and rash.

The majority of a radiolabeled ZD1839 dose was excreted in the feces as parent compound plus metabolites, while less than 4% of the dose was recovered in the urine. At least three sites of biotransformation were identified; resulting in the production of five identified circulating metabolites, one of which is present at concentrations similar to those of parent compound. None of the identified metabolites is thought to contribute significantly to the overall pharmacological activity of ZD1839. ZD1839 does not induce any major cytochrome P450 enzymes, and is itself metabolized by CYP3A4. Interaction studies in healthy subjects demonstrated that ZD1839 AUC (250-mg dose) was increased by approximately 80% in the presence of itraconazole, a potent CYP3A4 inhibitor, an increase that may be clinically relevant because adverse experiences are related to dose and exposure.

Coadministration with rifampicin, a potent CYP3A4 inducer, resulted in an 83% reduction in ZD1839 AUC. Thus, coadministration with other CYP3A4 inducers (e.g., phenytoin, carbamazepine, barbiturates, or St. John's Wort) may potentially reduce efficacy.

In vitro data showed that ZD1839 has inhibitory potential against CYP2D6, but an interaction study with metoprolol, a CYP2D6 substrate, demonstrated only a small effect on ZD1839 with metoprolol exposure. The change is not considered clinically relevant and suggests little potential for interactions with drugs metabolized by this P450.

1.2.5.2 Phase II Efficacy in Squamous Cell Carcinoma of the Head and Neck

A recently completed trial in patients with recurrent or metastatic squamous cell carcinoma of the head and neck confirmed single agent activity of ZD1839 in this population. This trial, performed through the University of Chicago Phase II Consortium demonstrated an 11% response rate with an 8.1 month median overall survival (17).

A second trial at the University of Chicago evaluated the efficacy of ZD1839 at a dose of 250m PO daily in patients with recurrent and metastatic disease. At this dose the observed response rate was only 1.4% with a 1.8 month progression-free survival. These data suggest that, at least in the setting of recurrent/metastatic SCCHN, the appropriate dose should be 500mg daily.

1.2.5.3 Phase I-II Tolerability

Patients given ZD1839 250 mg/day or similar doses frequently had drug-related gastrointestinal disturbances (mainly diarrhea; sometimes associated with dehydration)

and skin reactions (rash, acne, dry skin, and pruritus). The majority of drug-related adverse events were mild (Common Toxicity Criteria [CTC] grade 1) and noncumulative, and rarely led to withdrawal of ZD1839 therapy.

No additional safety concerns were raised for subpopulations of men or women, the elderly, ethnic groups, patients with renal impairment, or patients with mild-to-moderate hepatic impairment. Few specific drug-drug interactions were identified that could impact on the safety of ZD1839.

Recent data suggest an incidence of interstitial lung disease (ILD) in lung cancer patients taking ZD1839 with an incidence of approximately 0.27%. This is less than that reported to occur with other cancer treatments. However, these events are medically significant and up to 40% of cases have possibly had an associated fatal outcome. It is suggested that NSCLC may in itself predispose patients to ILD, however supportive epidemiological data of this type is not readily available. The data from the placebo-controlled combination trials is also supportive of the hypothesis that there is not a significant association between Iressa and ILD events or symptoms. However, there is the possibility that a causal relationship could exist.

To date, gefitinib or ZD1839, has been administered to over 42,000 people worldwide. Interstitial lung disease in patients treated with ZD1839 is uncommon, with a worldwide incidence of less than 1%, which is comparable to that reported with other lung cancer therapies. Interstitial lung disease had a fatal outcome, whether deemed ZD1839-related or not, in approximately 0.1% **in this medically complex group** of the over 42,000 patients receiving ZD1839.

The occurrence of pulmonary toxicity and interstitial lung disease was similar across all treatment arms in the first-line NSCLC combination chemotherapy (INTACT) trials, which were placebo-controlled first-line trials in over 2000 patients with non-small cell lung cancer who received either gemcitabine and cisplatin +/- ZD1839 or carboplatin and paclitaxel +/- ZD1839.

1.2.5.4 ZD1839 in Combination with Chemotherapy

A pilot phase I trial using a standard dose of paclitaxel and carboplatin in newly diagnosed patients with advanced NSCLC has completed recruitment. This trial examined the safety and pharmacokinetics of two dose levels of ZD1839 (250 mg and 500 mg) given concurrently with chemotherapy. Twenty-two patients have been included. No dose-limiting toxicities (DLTs) were reported in either the 250- or 500-mg dose levels of ZD1839. Another pilot Phase I trial is also underway involving two doses of ZD1839 given concurrently with gemcitabine and cisplatin, and an additional trial involving ZD1839 with Navelbine and Navelbine and cisplatin is scheduled to start recruitment.

A pilot Phase I trial (Miller) to demonstrate the safety of ZD1839 in combination with carboplatin and paclitaxel in previously untreated advanced NSCLC has completed recruitment. The trial examined the tolerability of ZD1839 given intermittently or continuously in combination with carboplatin and paclitaxel. Twenty-five patients were included in the trial. The trial showed that ZD1839 given either intermittently or continuously combined with carboplatin and paclitaxel was well tolerated, and no novel increased or cumulative toxicity had been observed. The data showed no evidence of clinically significant drug-drug interactions; they also showed the concurrent administration of ZD1839 does not affect the systemic exposure of either carboplatin or paclitaxel.

A pilot phase I trial (18) to determine the feasibility of combining ZD1839 with 5-FU and leucovorin (LV) and to determine the pharmacokinetics of the combination in patients with advanced colorectal cancer (aCRC) has completed recruitment. The trial examined the tolerability of ZD1839 administered on either an intermittent or a continuous schedule with 5-FU and LV. Twenty-six patients entered the study. Results showed that a dose-limiting toxicity (DLT) of diarrhea occurred in patients given the 500-mg dose of ZD1839 using the intermittent schedule; however, DLT was not seen in patients given the 500-mg dose of ZD1839 using the continuous schedule. Continuous oral administration of ZD1839 at doses up to 500 mg daily in combination with the dose and schedule of 5-FU/LV used in this study is generally well tolerated in patients with aCRC. No significant increase or severity of diarrhea or skin toxicity beyond that seen with 5-FU/LV was observed.

Two large trials have been completed in chemo-naïve patients with stage III and IV non-small cell lung cancer. Patients were randomized to receive ZD1839 250 mg daily, ZD1839 500 mg daily, or placebo in combination with platinum-based chemotherapy regimens. The chemotherapies given in these first-line trials were gemcitabine and cis-platinum (N=1093) or carboplatin and paclitaxel (N=1037). The addition of ZD1839, did not demonstrate any increase in tumor response rates, time to progression, or overall survival beyond that of chemotherapy alone.

1.2.5.5 ZD1839 in Combination with Radiotherapy

Several preclinical studies have demonstrated the efficacy and radiosensitizing ability of ZD1839 (19-22) in cell lines and xenograft models. Phase I studies of ZD1839 in combination with radiation therapy are underway in human subjects and have thus far not encountered significant interactive toxicities. Furthermore, a published phase I trial of a monoclonal antibody directed against EGFR, cetuximab, in combination with radiotherapy in head and neck cancer patients concluded that administering the two modalities simultaneously was safe and did not require dose reduction of either the agent or radiotherapy (23).

ZD1839 in combination with radiation and in combination with chemoradiation is currently being investigated in clinical trials. There is one trial with sufficient numbers

of patients enrolled to discuss safety data, a CALG-B trial led by Dr. Neal Ready. CALG-B trial number 30106 is a phase I/II trial of ZD1839 with induction paclitaxel and carboplatin followed by either radiation (stratum one) or concomitant radiation (stratum two) with weekly paclitaxel and carboplatin in stage III NSCLC. The total dose of radiation is 66 Gray given over 5-6 weeks; 4400 Gray with 2200 cGy "boost" dose to the primary tumor. The CALG-B trial enrolls two strata of stage III NSCLC patients, stratum one consists of performance status 2 patients and the stratum two consists of performance 0-1 patients. Stratum one has not yet completed recruitment to the phase I portion of the trial. Stratum two has completed enrollment in the phase I portion of the trial with 6 patients, who have been followed through completion of their induction chemotherapy with ZD1839 and carboplatin, paclitaxel, ZD 1839 and radiation therapy. The phase I safety portion of this trial, for good performance status patients, has been completed concluding that addition of ZD1839 to carboplatin, paclitaxel, and radiation is feasible. There is no change in the toxicities observed with chemo-radiation and the phase II portion of the trial has been opened. (Personal communication with Dr. Ready).

1.3 Quality of Life

1.3.1 Background

Oral cancer affects cosmesis and critical areas of functioning including eating, speaking and socializing, all of which have profound effect on quality of life (24-29). The impact occurs as a function of both disease and treatment. The consequences are both immediate and long term, and have psychosocial as well as functional implications.

Psychosocial and QoL issues related to surgery are obvious (both disfigurement and changes in levels of functioning) and were the first issues to be studied in head and neck cancer QoL (30-32). New treatment protocols involving less surgery and highly toxic therapies pose new questions. These regimens are specifically designed to minimize surgery and accompanying impairment. However, they rely on intensive radiotherapy and concomitant chemoradiotherapy, which have significant immediate, delayed, and potentially long-term side effects, which also may profoundly influence QoL. While traditional endpoints (e.g., response, time to failure, overall survival) are undeniably critical considerations, assessment of the patient's QoL including, patient satisfaction, the ability to function in key areas, and carry on daily activities, is an important component in the determination of the success of treatment.

1.3.2 Previous Work/Preliminary Data

Quality of life is comprised of multiple components, one of which is functional status. The measurement of functional status in oral cancer patients demands attention to the unique issues presented by this disease and its treatment. In an effort to meet the need for a simple, practical performance scale for this patient group, investigators developed a new Performance Status Scale for Head and Neck Cancer Patients (PSS-HN) (33-35). The scale is simple and practical. It is composed of three sub-scales measuring the

areas of eating, speaking and eating in public. These are the primary areas of disability in this population, yet are not addressed by standard measures of global functioning. The scale has been employed in a number of studies and selected, relevant data are presented here.

After initial validation of the PSS-HN, investigators at University of Chicago have employed this performance measure in combination with multi-dimensional QoL measures to assess outcome in head and neck cancer patients undergoing organ preserving, concomitant chemoradiotherapy protocols. The first study examined performance and QoL outcomes in patients at least 1 year post-completion of an organ-preserving concomitant chemoradiotherapy protocol. Assessment included a semi-structured interview and standardized measures of performance status (PSS-HN), residual side effects (McMaster Radiotherapy Questionnaire) (36), quality of life (FACT-H&N) (37), mood (Profile of Mood States) (38) and depression (CESD) (39). Forty-seven stage II-IV patients, with no evidence of disease were entered. The greatest functional impairment was inability to eat a normal diet: only 14% of the sample were eating normal solid foods; an additional 18% were eating a normal diet with increased liquid intake, and 50% were eating soft foods at best. By logistic regression, inability to eat solid foods was best predicted by disease site, with patients with oropharyngeal cancer (versus all other sites) being four times more likely to be unable to eat solid foods. No additional predictive information was provided by: stage of disease, organ preservation surgery, radiation dose, time since treatment, size of tumor, use of feeding tube or side effect severity during treatment. Decreased QoL and clinically significant depression were found in approximately one quarter of the group, and were not related to problems eating or eating in public. Very few patients had any speech disturbance. While other contributing factors were suggested (e.g., past problems with alcohol, residual side effects, disease site), no clear set of predictor variables has yet emerged (40).

Quality of life has been included, prospectively, in recent phase II studies of intensive chemoradiotherapy. Data from our stage IV cisplatin, BID radiation protocol (6950), the first to include comprehensive QOL assessment, highlight the toxicities of these therapy regimens and the need for inclusion of targeted QoL assessment.

Data are available on the 64 patients enrolled at University of Chicago and Northwestern with follow-up on surviving patients through 4 years. As presented below, pre-treatment problem with eating, swallowing, and pain were seen in over one third of patients. Functional impairment increased during treatment, persisted through 6 months with gradual recovery over the next few years with patients returning to baseline levels in many areas. Dry mouth remained the most persistent symptom.

Table 5 Performance outcome

Performance Outcome	Pre-Rx	On-Rx	6 Mos.	12 Mos.	2-4 Yrs.

Diet (≤ 50: soft food or liquids only)	42%	98%	90%	82%	41%
Eating in Public (≤ 50: discomfort)	26%	N/A	72%	64%	44%
Moderate-Severe Sequelae					
Dry mouth	17%	51%	63%	58%	52%
Sticky saliva	25%	75%	49%	34%	24%
Swallowing	33%	57%	37%	26%	27%
Pain	30%	49%	29%	24%	18%
Tasting	8%	40%	32%	32%	21%

Rx = treatment.

We are currently compiling comparable data from a recently closed, similar protocol in which paclitaxel replaced cisplatin during chemoradiotherapy. We expect to see slightly less acute toxicity with the paclitaxel regimen. Again patients continue to be followed to evaluate long- term effects. Inclusion of QoL assessment in the current study will enable us to assess the impact on QoL, performance, and functional outcome, of adding induction chemotherapy to our established chemoradiotherapy regimen.

1.3.3 Quality of Life Objectives

The proposed regimen aims to improve survival and minimize distant metastases while minimizing performance and QoL deficits. Thus, QoL and performance are important treatment endpoints. The objective is to describe these dimensions prospectively, pretreatment, through treatment, to long-term follow-up. Specific aims are to

- document patient's experience of treatment effects
- evaluate changes in QoL and performance as a function of induction chemotherapy alone
- determine extensiveness and persistence of QoL and function-related treatment effects
- describe the pattern, timing and extent of recovery of function and QoL

1.4 Study Proposal and Rationale

Investigations at the Chicago Oral Cancer Center have demonstrated that patients with locally advanced head and neck cancer can have high survival, time to progression, and organ preservation rates following therapy with carboplatin/paclitaxel and T-FHX chemoradiotherapy. ZD1839 is an exciting novel agent; it has single agent activity and mild toxicities. Recently released phase III data in non-small cell lung cancer suggest that

addition of ZD1839 to chemotherapy may not increase activity of chemotherapy alone. However, conflicting data exist for a monoclonal EGFR antibody (cetuximab) added to cisplatin in head and neck cancer demonstrating a non-statistically significant advantage to EGFR blockade (41). This discrepancy may be agent or disease site dependent. Nevertheless, use of ZD1839 with radiotherapy is well supported by preclinical experience, the cetuximab/radiotherapy experience, and as a targeted agent may be more a more selective and less toxic radiation enhancer than paclitaxel. Furthermore, use of ZD1839, as a maintenance agent is likely to be tolerable with the potential to decrease failure rates and appearance of second malignancies.

We therefore propose to incorporate into our standard program an agent from a promising new class of cancer therapy that targets an important pathway required for tumor growth: ZD1839, an inhibitor of EGFR-tyrosine kinase. ZD1839 will be given after induction therapy, with concurrent chemoradiotherapy replacing a previously used cytotoxic (paclitaxel) and then will be continued as maintenance therapy following completion of FHX chemoradiotherapy for 2 years or until disease progression, unacceptable toxicity, or withdrawal from study since its systemic activity may prevent the regrowth of micrometastatic disease.

In light of data supporting the use of 500mg of ZD1839 in SCCHN, the current protocol will administer this dose concurrently with chemoradiotherapy. In addition, as preliminary results administering maintenance therapy in locally advanced non-small cell lung cancer have not proven efficacious with respect to survival, the 500mg dose will not be continued beyond chemoradiotherapy.

2 TRIAL SCHEMA

OVERVIEW

SCREENING/BIOPSY

↓

OPTIONAL INDUCTION CHEMOTHERAPY
(DURATION 8 WEEKS)

Paclitaxel 100mg/ m^2 in 500 ml D5W over 3 hours IV (Days 1, 8, and 15)
+ Carboplatin (start after completion of paclitaxel on Day 1)
AUC 6 (CC +25) administered in 100 ml NS over 30 min IV after completion of paclitaxel
No paclitaxel or carboplatin on Day 22.
Resume chemotherapy for cycle 2 on Day 29 (two cycles of 4 weeks duration).
Chemoradiotherapy will begin 1 – 2 weeks after the last dose.

↓

CONCOMITANT CHEMORADIATION
(DURATION 10 WEEKS)

Chemotherapy should be administered during all 5 weeks of radiotherapy.
ZD1839 500mg QD PO continuous administration begins on day 1 cycle 1 of chemoradiotherapy and continues into maintenance.

EACH CYCLE:
Day 0 (Sunday):
P.M.: Start hydroxyurea at 500 mg PO q 12 hours x 6 days (11 doses).
The first daily dose of hydroxyurea on Days 1 – 5 is given 2 hours prior to the first fraction of daily radiotherapy.
6:00 P.M.: Start continuous IV infusion of 5-fluorouracil 600 mg/m^2/day × 5 days (120 Hours).
Days 1 – 5: RT 150 Gy (twice daily)
Days 6 – 12: No chemoradiotherapy
Chemoradiotherapy cycles are repeated every 14 days until completion of radiotherapy.

↓

Node dissection and surgery as necessary

↓

FOLLOW-UP

3 INCLUSION CRITERIA

1. Histologically or cytologically confirmed diagnosis of squamous cell or poorly differentiated carcinomas, or lymphoepithelioma of the nasopharynx

2. Age 18 years or older

3. Patients with AJCC (6^{th} edition, 2002) stage III or IV head and neck cancer

4. Patients with AJCC (6^{th} edition, 2002) stage IV head and neck cancer presenting with cervical lymph node metastasis of an unknown primary (i.e., TxN2 or TxN3) are also eligible.

5. Prior to entry in the study, the resectability and alternative treatment options for each patient will be determined by a team composed of a head and neck surgeon, a radiation oncologist, and a medical oncologist. Stage determination, optimal local treatment, and its timing according to this protocol will be determined at this evaluation. Each patient will be classified as having resectable or unresectable disease. The unequivocal demonstration of distant metastasis (M_1) confers ineligibility.

6. Unidimensionally measurable disease (based on RECIST) is desirable but not strictly required. Individuals who are disease free at baseline after excisional biopsy or node dissection will be considered not evaluable for response assessment but are eligible.

7. No prior or radiotherapy

8. Prior surgical therapy will consist only of incisional or excisional biopsy and organ-sparing procedures such as debulking of airway-compromising tumors or neck dissection in a patient with an unknown primary tumor.

9. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 (Karnofsky ≥ 60%)

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

absolute neutrophil count (ANC)	≥ 1,500/μl
platelets	≥ 100,000/μl
total bilirubin	within normal institutional limits
aspartate aminotransferase (AST, SGOT)/ alanine aminotransferase (ALT, SGPT)	≤ 2.5 × institutional upper limit of normal
alkaline phosphatase	≤ 2 × upper limit of normal
creatinine	within normal institutional limits

11. Informed consent must be obtained from all patients prior to beginning therapy. Patients should have the ability to understand and the willingness to sign a written informed consent document.

4 EXCLUSION CRITERIA

1. Unequivocal demonstration of metastatic disease (i.e. M_1 disease).

2. Known severe hypersensitivity to ZD1839 or any of the excipients of this product

3. Any coexisting malignancy that would increase risk of toxicity, interfere with interpretation of toxicity, or is associated with a median survival of less than 24 months.

4. Concomitant use of phenytoin, carbamazepine, barbiturates, rifampin, phenobarbital, or St. John's Wort.

5. Treatment with an investigational drug within 30 days before Day 1 of trial treatment

6. Incomplete healing from previous surgery

7. Pregnancy or breast feeding (women of child-bearing potential). Patients should be advised to use effective contraception as appropriate.

8. History of allergic reactions attributed to compounds of similar chemical or biologic composition to paclitaxel, Cremaphor EL, carboplatin, 5 FU, or hydroxyurea

9. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure (CHF), unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

10. Patients with clinically significant pulmonary dysfunction, cardiomyopathy, or any history of clinically significant CHF are excluded. The exclusion of patients with active coronary artery disease will be at the discretion of the attending physician.

11. Patients must have no uncontrolled active infection other than that not curable without treatment of their cancer.

12. No patients with severe baseline neurologic deficits (> grade II neuropathy) will be treated with induction chemotherapy.

13. Any evidence of clinically active interstitial lung disease (patients with chronic stable radiographic changes who are asymptomatic need not be excluded)

5 CRITERIA FOR DISCONTINUATION/WITHDRAWAL OF INFORMED CONSENT

Patients may be discontinued from trial treatment and assessments at any time, at the discretion of the investigator(s). Specific reasons for discontinuing a patient from this trial are

- objective progression of disease
- patient lost to follow-up (i.e., dropouts)
- adverse events
- protocol non-compliance
- withdrawal of consent

If the reason for withdrawal from the trial is the death of the patient, the two options for categorizing withdrawal are either progressive disease or an adverse event (AE; more than one AE may be documented as a reason for withdrawal). Only one event will be captured as the cause of death. Note that death is an outcome and not an AE.

All deaths that occur within the trial period or within 30 days after administration of the last dose of trial drug must be reported to AstraZeneca primarily for the purposes of serious adverse event (SAE) reporting; however, deaths due unequivocally to progression are not SAEs.

All subjects who have new or worsening CTC grade 3 or 4 laboratory values at the time of withdrawal must have further tests performed and the results recorded appropriately until the lab values have returned to CTC grade 1 or 2, unless these values are not likely to improve because of the underlying disease. In these cases, the investigators must record their opinions in the subject's medical records. Laboratory abnormalities should **not** be reported as adverse events unless any criterion for a SAE is fulfilled, the laboratory abnormality causes the subject to discontinue from the study, or the investigator insists the abnormality should be reported as an AE.

At withdrawal 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 subject's underlying disease.

After withdrawal from treatment, subjects must be followed up for all existing and new AEs for 30 calendar days after the last dose of trial drug. All new AEs occurring during that period must be reported to AstraZeneca and all study-related toxicities and SAEs must be followed up for resolution where possible.

6 TREATMENT PLAN

6.1 Agent Administration

Induction chemotherapy and maintenance therapy will be administered on an outpatient basis and chemoradiotherapy will be administered on an inpatient basis. Expected AEs and appropriate dose modifications for ZD1839, carboplatin, paclitaxel, 5-FU, hydroxyurea, and radiation are described in sections 8 and 9. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

6.1.1 Pre-therapy Checklist (all pre-therapy evaluations should be conducted within 4 weeks of starting therapy unless otherwise indicated)

- Inclusion/exclusion criteria
- Informed consent
- Dental consultation (within 8 weeks of starting radiotherapy)
- Speech and swallow consultation
- Panendoscopy with biopsy and tumor map (within 6 weeks of starting therapy)
- Radiographic studies (CT or MRI of the head and neck, CT chest, bone scan [if indicated], within four weeks of starting therapy) N.B.: a bone scan is not required prior to therapy unless the investigator feels there is a clinical indication or suspicion of bone metastases.
- Complete blood count (CBC), complete metabolic profile (within 2 weeks of starting therapy).

6.1.2 Induction Therapy

The administration of induction chemotherapy in this trial is at the discretion of the investigator. Patients who have not received prior chemotherapy should be offered induction chemotherapy as specified below.

Carboplatin and paclitaxel combination will be administered IV for two cycles of 4 weeks duration each. Chemoradiation will begin 1 – 2 weeks after the last dose. Dose delays and dose modifications should take place as in section 9. **In no case should the six doses of induction paclitaxel be given over a period exceeding nine (9) weeks.**

Paclitaxel: 100 mg/m^2 in 500 ml of D5W IV over 3 hours (on Days 1, 8, 15)

Carboplatin: Start after completion of paclitaxel on Day 1, AUC 6 (CC + 25). Administer in 100 ml of NS IV over 30 minutes after completion of paclitaxel. No therapy on Day 22. Resume chemotherapy for cycle 2 on Day 29.

A 24-hour urine collection for measurement of CC is recommended, but is not mandatory. A baseline on creatinine level should be drawn within 1 week prior to starting chemotherapy. The carboplatin dose will remain unchanged on the second cycle unless the serum creatinine increases by > 25%. In this event, a CC should be recalculated for the second cycle. No changes will be made for decreases in serum creatinine.

When necessary, calculated CC should be determined as follows:

$$\frac{(140 - \text{age}) \times \text{weight (in kg)}}{72 \times \text{creatinine (mg/dL)}} \; (\times 0.85 \text{ in females}) \; (\times 1.0 \text{ in males})$$

Note: The body weight should be ideal body weight for patients whose actual body weight is greater than their ideal body weight (IBW), based on the following formula:

Males IBW = 50 kg + 2.3 × height in inches over 5 feet
Female IBW = 45.5 kg + 2.3 × height in inches over 5 feet

Antiemetics: ondansetron hydrochloride (Zofran®), dolasetron mesylate (Anzemet®), or granisetron hydrochloride (Kytril®) prior to paclitaxel on Day 1. The use of antiemetics when paclitaxel is administered alone is not routinely required and is at the discretion of the investigator.

Pre-medications: dexamethasone sodium phosphate injection (Decadron®) 20 mg IV 1 hour prior to paclitaxel
diphenhydramine hydrochloride injection (Benadryl®) 25 mg IV push to be given 1/2 hour prior to paclitaxel

Hydration: At the discretion of the investigator.

6.1.3 Concomitant Chemoradiotherapy

Chemotherapy should be administered during all 5 weeks of radiotherapy. If less than 3 days of radiation therapy (RT) are required during Week 5, chemotherapy may be omitted.

Day 0 (Sunday)

P.M.:	start hydroxyurea at 500 mg PO q 12 hours × 6 days (11 doses). The first daily dose of hydroxyurea on Days 1 – 5 is given 2 hours prior to the first fraction of daily radiotherapy.
6:00 P.M.:	start continuous IV infusion of 5-FU at 600 mg/m^2/day × 5 days (120 hours).
Day 1 – 5	Radiation therapy is administered twice daily at 150 cGy per fraction.
Days 6 – 12:	No chemoradiotherapy.
For each cycle:	Administer 5 μg/kg subcutaneously (SQ) of G-CSF daily, beginning on Day 6 through Day 12 at a minimum of 12 hours after completion of 5-FU in patients who develop grade 3 neutropenia or who have neutropenia ≥ grade 2 on Day 0 of any cycle. In these patients, G-CSF will be utilized in all subsequent cycles. GM-CSF can be substituted at the discretion of the investigator.

Chemoradiotherapy cycles are repeated every 14 days until the completion of radiotherapy.

ZD1839 will be administered continuously at 500mg QD PO (preferably in the morning) during radiotherapy from day 1 of cycle 1 until discontinuation criteria are met during maintenance therapy.

If radiation esophagitis or pneumonitis or other radiation-related toxicities develop during radiation and necessitate interruption of radiation therapy, then ZD1839 treatment should be held and not re-started during radiation therapy. Every effort should be made to complete the full prescribed course of radiation therapy as soon as these toxicities have resolved sufficiently to proceed.

6.1.4 Maintenance Therapy

Adjuvant ZD1839 will not be administered at the 500mg dose level. ZD1839 will be discontinued upon completion of radiotherapy.

6.2 Radiotherapy Guidelines

1. All patients will have a complete dental evaluation prior to the start of radiation therapy, ideally prior to the start of chemotherapy.

2. All patients will be simulated prior to the start of treatment with an appropriate immobilization device.

3. Appropriate field sizes will be determined at the time of simulation to treat gross disease and areas of potential microscopic disease.

4. Ideally all patients should undergo CT based treatment planning. Initial field size and arrangement will be at the discretion of the attending radiation oncologist. The optimal field arrangement will be determined based on the treatment planning employed. Either 3-D CT based treatment planning or Intensity Modulated Radiation Treatment (IMRT) techniques will be acceptable. In both instances the physician will attempt to deliver an even dose to the target tissue and minimize doses to normal structures.

5. Initial fields will encompass all known areas of gross tumor as defined by physical exam or diagnostic studies (CT or MRI). The exact field arrangement will depend on whether 3-D conformal or IMRT techniques are used.

6. Blocking will be individualized for each patient. Either custom Cerrobend blocks or multileaf collimator will be acceptable.

7. Each cycle of treatment will consist of 5 consecutive days of radiation with 150 cGy given bid (300 cGy per day and 1500 cGy per week) in conjunction with chemotherapy. There should be a minimum of 6 hours between fractions. All fields will be treated each day. The exceptions will be the supraclavicular and posterior neck fields.

8. The total radiation dose to patients will be determined based on the responses to induction chemotherapy and risk of disease. The disease risk sites will be 1) gross disease, 2) high risk microscopic disease, and 3) low risk microscopic disease. Gross disease is all demonstrated disease based on physical exam and radiographic studies. Low risk microscopic disease is the second echelon of clinically uninvolved nodes.

9. Radiation doses: The dose to gross disease will be 70 to 72 Gy. High-risk microscopic disease will receive 48 to 51 Gy. Low risk microscopic disease will receive 36 to 39 Gy.

10. The dose limit to the spinal cord will vary depending upon the technique used. Attempts should be made to limit the spinal cord dose to < 40 Gy with conventional 3D radiation treatment. Doses should be limited to 46 Gy with IMRT techniques and reduced fraction size to the spinal cord.

6.3 Supportive Care

- Antiemetics will be ordered at the discretion of the attending physician.

- Administration of sucralfate (Carafate®) suspension (1 gm QD swish and swallow on an empty stomach) is recommended during chemoradiation to ameliorate mucositis/esophagitis.

- A double lumen venous access device (e.g., Port-a-Cath®) will be recommended prior to initiation of therapy. Use of a feeding device is recommended for high-risk patients.

- Prior to discharge of the patients after a cycle of chemoradiation, a CBC and platelet count, and determination of serum electrolytes, including blood urea nitrogen (BUN) and creatinine will be performed.

- Patients will be discharged with instructions for oral hygiene (e.g., oral nystatin and viscous lidocaine HCl (Xylocaine®) solution) and replacement drugs for electrolyte imbalances when applicable.

- Use of intravenous home hydration is recommended in patients with inadequate oral intake.

- If Hgb < 10, patients should generally be transfused an amount sufficient to increase Hgb to ≥ 10. The use of erythropoietin is at the discretion of the investigator.

- Treatment-related diarrhea will be managed with high-dose loperamide. The recommended dose of loperamide is 4 mg initially (two capsules) then 2 mg after each loose stool, not to exceed 16 mg daily.

- The use of amifostine during IFHX chemoradiotherapy is not permitted

6.4 Surgical Guidelines

The timing and extent of the surgical procedure remains an individualized decision between the patient and his or her surgeon. Generally, it is expected that patients will undergo concomitant chemoradiotherapy prior to extensive surgery. Simple excision (e.g., transoral laser excision) of the primary lesion may be performed initially if it can be accomplished while preserving organ function. A tumor biopsy will be performed prior to therapy, on day 1 of cycle 2 of chemoradiotherapy, and after completion of chemoradiotherapy (see Tables 1 and 2). Modified or selective neck dissection may also be performed. When these procedures are not performed initially, neck dissection should be performed following concomitant chemoradiotherapy for any residual nodal disease. This may also be performed in patients initially staged N_{2b}, N_{2c} or N_3, even in the absence of macroscopic residual disease (elective node dissection). Surgery at the primary site should be omitted in patients who have achieved biopsy-proven complete response. In patients with pathologically

proven residual disease at the primary site, complete excision of disease should be accomplished. Patients demonstrating progression of disease at any time or disease recurrence should be considered for conventional surgical management.

6.5 Quality of Life Measurements

N.B.: QUALITY OF LIFE MEASURMENTS WILL NOT BE CONDUCTED AT THE 500MG DOSE LEVEL OF ZD1839

Quality of life and performance measures to be used in this protocol include:

1) Performance Status Scale for Head and Neck Cancer Patients (PSS-HN)

2) Functional Assessment of Cancer Therapy - Head and Neck Version 3 (FACT-H&N)

3) Center for Epidemiological Studies – Depression (CES-D)

4) Selected questions from the McMaster University Head and Neck Radiotherapy Questionnaire

Performance Status Scale for Head and Neck Cancer (PSS-HN) (34). The PSS-HN is a clinician rated instrument consisting of three subscales: Normalcy of Diet, Eating in Public, and Understandability of Speech. It has been demonstrated to be reliable and valid in head and neck cancer patients (described in detail in section 1.3.1).

Functional Assessment of Cancer Therapy-Head and Neck Version 3 (FACT-H&N) (37, 42). The FACT-H&N is a multidimensional, self-report QoL instrument specifically designed for use with head and neck cancer patients. The core scale (FACT-G) consists of 27 core items assessing patient well being in four areas: Physical, Social/Family, Emotional, and Functional. The Core scale is supplemented with site-specific modules, of which the head and neck version (12 items) will be employed here.

Center for Epidemiological Studies – Depression (CES – D). The CES – D is a short, 20-item self-report scale measuring depressive symptomatology. It has demonstrated reliability and validity with scores equal to or above 16 considered suggestive of depression (39).

McMaster Radiotherapy Questionnaire (36). This patient self-report instrument (can be clinician administered) quantifies patients' perception of the frequency and severity (troublesomeness) of radiation related side effects.

These will be administered prior to therapy, after induction therapy, during chemoradiotherapy, and at 1, 6, and 12 months after completing the study drugs and then annually for five years.

6.6 Duration of Therapy

In the absence of treatment delays due to adverse events, chemoradiotherapy may continue for 5 cycles or until one of the following criteria applies

- Disease progression,
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study, or general or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

7 IDENTIFICATION OF INVESTIGATIONAL PRODUCT

7.1 ZD1839

Other names: Gefitinib, Iressa.

Mode of action: inhibitor of EGFR tyrosine kinase.

ZD1839 will be supplied to the investigator by AstraZeneca as brown film-coated tablets for use as follows:

Table 6 ZD1839 trial treatment

Treatment	Strength	Description	Daily dose	Tablets per dose
ZD1839[a]	250-mg tablet	Brown, 11mm	250 mg	2

[a] Descriptive information for ZD1839 can be found in the Investigator's Brochure.

Tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each bottle will contain 30 tablets of a single formulation. The tablets will be dispensed to the patient as a 1-month supply in the bottle provided by AstraZeneca.

7.1.1 Management of Interstitial Lung Disease

If the patient develops new pulmonary infiltrates while receiving ZD1839 therapy, consideration of consultation with a pulmonologist is advised. All infectious etiologies and tumor progressions should be excluded as the underlying cause of the

infiltrates. If these infiltrates are thought to be ZD1839 treatment related, the patient should permanently discontinue ZD1839.

7.2 Storage

All investigational products must be kept in a secure place under appropriate storage conditions. All ZD1839 trial treatment will be stored in a lockable storage area, between 20-25°C (68 – 77°F).

7.3 Accountability

It is the investigator's/institution's responsibility to establish a system for handling trial treatments, including investigational medicinal products, so as to ensure that

- Deliveries of such products from AstraZeneca Pharmaceuticals or distribution site are correctly received by a responsible person (e.g., a pharmacist)
- Deliveries are recorded
- Certificates of delivery and return are signed, preferably by the investigator or a pharmacist, and copies are retained
- Trial treatments are handled and stored safely and properly
- Trial treatments are prescribed only by the investigator or subinvestigators named in Form FDA-1572
- ZD1839 supplied for this trial is dispensed to trial patients only in accordance with the protocol
- Subjects must return all unused medication and empty containers to the investigator
- All unused ZD1839 trial treatment and empty bottles at the site or distribution center are destroyed

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed/returned stock. Records of usage should include the identification of the person to whom the trial treatment was dispensed, the quantity and date of dispensing, and unused study treatment returned to the investigator. Any discrepancies must be documented.

7.3.1 Treatment Schedule

ZD1839 treatment will be taken once a day, every day about the same time. It can be taken with or without food.

If a patient forgets to take a dose, the last missed dose should be taken as soon as the patient remembers, as long as it is at least 12 hours before the next dose is due to be taken. The daily treatment schedule will be resumed the next day.

This protocol will be closed 28 months after the last patient is enrolled. At that time, patients will continue to be followed for survival. AstraZeneca reserves the right to suspend drug supply for new patients if recruitment does not meet the protocoled target. In this event, drug supply for patients already receiving ZD1839 will be continued for 28 months after the suspension date, as long as they are eligible to remain on-study. Once the protocol is completed (or suspended), ZD1839 has been approved, and is available commercially; patients who are continuing to receive clinical benefit from ZD1839 therapy will obtain ZD1839 via insurance or through the AstraZeneca Assistance program (if required criteria are met).

7.3.2 ZD1839 Dose Interruption

Dose interruptions should be the first approach to managing toxicity. Repeat dose interruptions are allowed as required.

7.4 Non-hematopoietic Toxicity

In the event of CTC grade 3 or 4 non-hematopoietic AE(s) that the investigator considers due to suspected disease progression, re-evaluation of tumor status is indicated, irrespective of scheduled clinic visits.

If any of the following conditions occur, administration of ZD1839 may be interrupted for a maximum of 14 days to allow the AE to resolve or decrease in severity:

- CTC grade 3 or 4 or unacceptable toxicity, e.g., cosmetic effect of grade 2 rash
- No consideration and/or corroborative evidence that the AE is due to progressive disease
- The AE is consistent with previously described ZD1839 toxicity

At a minimum, reassessment of toxicity should be done twice weekly and more frequently if clinically indicated. Once the AE decreases in severity to CTC grade 1, the patient may continue to take the assigned dose of 250-mg daily.

7.5 Skin Toxicity

Patients with poorly tolerated skin toxicity may be successfully managed by providing a brief (up to 14 days) therapy interruption, after which the daily dose of ZD1839 should be reinstated. However, the rash may improve without the need for interrupting therapy with ZD1839. Of note in current trials, many patients were able to resume ZD1839 therapy at the same dose after resolution of rash, and they then had less extensive and/or severe rashes.

7.6 Gastrointestinal (GI) Toxicity

If GI toxicity is not appropriately managed, it may be associated with the development of dehydration.

7.7 Nausea and/or Vomiting

In patients who have emesis and are unable to retain ZD1839, every attempt should be made to obtain control of nausea and vomiting. The dose of ZD1839 may be repeated if emesis occurs within 30 minutes of taking the tablet(s).

7.8 Diarrhea

Diarrhea has been successfully managed with anti-diarrheal agents such as loperamide.

If a grade 4 diarrhea is associated with hemodynamic collapse, the investigator should report it as an SAE and remove patient from trial.

In all cases where the subject is withdrawn due to unusual or unusually severe toxicity considered related to ZD1839, the investigator must report it to AstraZeneca.

7.9 Hypersensitivity to ZD1839

One case of hypersensitivity with hives following the first dose of ZD1839 occurred in phase I trials. This was successfully managed over several months with low-dose daily oral antihistamines while treatment with ZD1839 continued.

7.10 Management of Interstitial Lung Disease

If patients present with an acute worsening or new onset of respiratory symptoms such as dyspnea, cough and fever, ZD1839 should be interrupted and the patient promptly investigated for Interstitial Lung Disease. If Interstitial Lung Disease is confirmed, and is believed to be ZD1839-related, ZD1839 should be permanently discontinued.

If in-field radiation toxicities develop while the patient is receiving radiation therapy and interruption of radiation therapy is necessary, then ZD1839 should be held until and not re-started during radiation therapy. Every effort should be made to complete the full course of radiation therapy, as soon as the acute toxicity has resolved sufficiently to proceed. ZD1839 therapy may be restarted, if appropriate, after the patient has completed radiation therapy and has recovered to a CTC grade 2 or less event.

7.11 Duration of ZD1839 Therapy

Treatment should be discontinued only if disease progression or unacceptable/unmanageable drug-related adverse events occur.

7.12 Guideline for Dispersing Whole ZD1839 Tablets

ZD1839 tablets cannot be crushed. Experimentation has shown that ZD1839 tablets will break up into a fine dispersion within 5 to 7 minutes when they are dropped whole into lukewarm water. There are no known risks to the chemical stability of ZD1839, providing this process occurs immediately before administration to the patient. There may be a risk to ensuring delivery of the whole dose because a certain amount of deposition of powder on the surfaces of the container will occur while the container is being emptied. No information exists concerning bioequivalence of efficacy for non-oral administration of ZD1839.

The following procedure is recommended for administering a dispersed whole tablet to a patient who is unable to swallow:

- Drop the ZD1839 tablet into an appropriate container (ideally glass to help confirm removal of all the dispersed material) containing approximately 1 to 2 ounces (or 50 ml) of lukewarm water.
- Stir the liquid occasionally to ensure complete break-up of the tablet. When the tablet has broken up into a fine dispersion (approximately 5 minutes) it can be administered to or by the patient.
- 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.
- Confirmation that the subject has received the whole dose and that it was administered in this fashion should be included on the subject dispensing record.
- Because no data are available concerning the stability of the dispersed tablet, administration to the patient should occur immediately after dispersion is complete.

7.13 Other Concomitant Treatment

The use of investigational agents other than ZD1839 is not allowed while patients are on this study.

If surgery is considered necessary for the patient, whenever possible, at least 7 days should elapse after the last dose of ZD1839 before surgery is performed. ZD1839 can be resumed on the 7^{th} post-operative day.

Any patients who require ophthalmic surgery during the course of the trial will be temporarily withdrawn. These patients can restart ZD1839 at the discretion of the investigators.

Concomitant use of medications known to affect the conductive system, such as beta-blockers, calcium channel blockers, or digoxin, is allowed under investigator supervision.

No concomitant use of the following drugs is allowed: phenytoin, carbamazepine, rifampicin, phenobarbital or St. John's Wort, as these drugs induce CYP3A4 and may decrease levels of ZD1839.

Coadministration of drugs that cause significant sustained elevations in gastric pH ≥ 5 may reduce plasma concentrations of ZD1839, and therefore may reduce efficacy.

International normalized ratio (INR) elevations, bleeding, or both events have been reported in some patients taking warfarin. Patients taking warfarin should be monitored regularly for changes in prothrombin time (PT) or INR.

Systemic retinoids should not be given because of theoretical concerns about negatively affecting the ZD1839 mechanism of action. Systemic steroids are discouraged for the treatment of skin toxicities. Patients who are taking steroids for reasons other than skin toxicity at trial entry may continue treatment.

For subjects on steroids at the start of the study, the dose of steroids should not be changed without consultation with the Investigator.

Other FDA approved medication that is considered necessary for the patient's safety and well-being may be given at the discretion of the investigator(s).

No additional anti-cancer therapies, other than those specified in this protocol, should be given to patients while on this study.

8 EXPECTED TOXICITIES

8.1 ZD1839

ZD1839 has been well tolerated in phase I and II studies. Diarrhea and a generalized skin rash are the major dose limiting toxicities. The skin rash may improve despite continuation of ZD1839. Diarrhea may lead to dehydration and electrolyte disturbances. Mucositis also developed as DLT in one patent. Other non-dose limiting toxicities that were encountered in phase I or II trials include headache, elevated liver enzymes, skin rash, nausea, vomiting, and fatigue. Symptoms are generally reversible with drug discontinuation. Keratitis (grade 1-2) and dry eyes have been reported in a few subjects. In all cases, the eye changes were managed with either standard treatment (artificial tears or topical corticosteroids) or the discontinuation of study drug. The use of contact lenses while taking ZD1839 is discouraged.

8.2 Paclitaxel

The main toxicities associated with paclitaxel include: electrocardiogram (ECG) abnormalities with bradycardia, heart block, bundle branch block, and ventricular

tachycardia, peripheral neuropathy, myalgias and arthralgias, nausea and vomiting (usually moderate), ischemic colitis, neutropenic enterocolitis, diarrhea, alopecia, and myelosuppression primarily manifesting as neutropenia. Hypersensitivity reactions have occurred, with dyspnea, bronchospasm, hypotension, pancreatitis, hepatic enceph-urticaria, angioedema, sensation of flashing lights, and blurred vision. Abnormalities of liver function tests have occurred as well but are usually mild. The concomitant administration of paclitaxel and radiation to the head and neck will aggravate the local side effects of radiation such as dermatitis, mucositis, and others.

8.3 Carboplatin

Common toxicities include

- Hematologic – myelosuppression
- Gastrointestinal – nausea, vomiting, mucositis, diarrhea
- Neurologic – peripheral and central neuropathy and ototoxicity
- Renal – tubular damage
- Dermatologic – alopecia
- Allergic reactions

It is a known radiation sensitizer and may potentiate side effects of radiation.

8.4 5-Fluorouracil

Common toxicities include:

- Gastrointestinal – diarrhea, mucositis, nausea, and vomiting
- Hematologic – myelosuppression
- Dermatologic – photosensitivity, skin dryness, hand-foot syndrome, increased pigmentation of skin, increased pigmentation of veins used for infusion, nail changes

Less commonly observed toxicities include

- Cardiac – myocardial ischemia, arrhythmias
- Allergic reactions
- Neurologic – acute cerebellar syndrome, disorientation, headache
- Eye – lacrimal duct stenosis, lacrimation, photophobia, and visual changes

5-FU may cause birth defects and should not be used in pregnant women. It is a known radiation sensitizer and may potentiate side effects of radiation.

8.5 Hydroxyurea

Common side effects include:

- Myelosuppression (mainly leukopenia)
- Nausea, vomiting
- Diarrhea or constipation
- Stomatitis

It may aggravate the inflammation of mucous membranes secondary to irradiation.

Less common side effects include:

- Dysuria or impairment of renal tubular function
- Rare neurologic disturbances, e.g., headaches, dizziness, disorientation, hallucination and convulsion.

8.6 Radiation

Radiation to the head and neck will cause skin irritation, dry mucous membranes due to salivary gland dysfunction, mucositis and stomatitis. The concomitant administration of chemotherapy will aggravate these side effects. Long-term side effects include myelitis, osteoradionecrosis, hoarseness, hypothyroidism, and fibrosis of soft tissues.

9 DOSE AND SCHEDULE MODIFICATIONS

9.1 During Induction Chemotherapy

9.1.1 Dose Modification

Table 7 Dose modification

Induction Dose Level	Carboplatin (AUC)	Paclitaxel (mg/m2)
0	6	100
–1	5	80
2	4	70

9.1.2 Hematologic Toxicity

Hematologic toxicity is based on any interval laboratory results within 7 days prior to treatment or on the day of treatment.

Table 8 Hematologic toxicity

ANC/μl		Platelet count/μl	Dose Modification

> 800	And/or	> 50,000	No change, give previous dose
≤ 800	And/or	≤ 50,000	Decrease 1 level*

* Do not treat until ANC > 800 µl and platelet count > 50,000 µl. Retreat when patient recovers at lower dose level. A patient who does not recover within 2 weeks should proceed with concomitant chemoradiotherapy.
ANC = absolute neutrophil count.

9.1.3 Non-hematologic Toxicities

Modification of carboplatin/paclitaxel dosages will occur if the toxicity is considered to be related to study drug. Non-hematologic toxicities will be based on any interval observations between treatments or at the time of each dose.

9.1.4 Motor and/or Sensory Neuropathy

Table 9 Motor and sensory neuropathy

Neuro-sensory/Motor	**Paclitaxel**	**Carboplatin**
Grade 0 – 1	No change	No change
Grade 2	Decrease 1 dose level	Decrease 1 dose level
Grade 3 or greater	Off study	Off study

9.1.5 Fatigue, Arthralgia, Myalgias

Table 10 Fatigue, arthralgia, myalgias

Arthralgia, Myalgia	**Paclitaxel**	**Carboplatin**
Grade 0 – 1 (normal, mild)	No change	No change
Grade 2 (decrease in ability to move)	No change	No change
Grade 3 (disabled)	Hold until ≤ grade 2 (moderate), then decrease 1 dose level	No change

9.1.6 Hepatic Dysfunction

Table 11 Hepatic dysfunction

Bilirubin (mg/dL)	Paclitaxel	Carboplatin
< 1.5	No change	No change
1.5 – 2.0	Decrease 1 dose level	No change
> 2.0	Hold until ≤ 2.0, then decrease 1 dose level	No change

9.2 ZD1839 Dose Modifications During Chemoradiotherapy Therapy

N.B.: Since experience with administration of ZD1839 with radiotherapy is limited, a toxicity analysis will be performed after 12 patients complete therapy. If greater than 5 patients require dose reductions, a review of the treatment protocol will take place to determine if the toxicities are related to ZD1839 administration. Accrual will continue during this review but will be suspended if the protocol requires amendment.

If radiation esophagitis or pneumonitis or other radiation-related toxicities develop during radiation and necessitate interruption of radiation therapy, then ZD1839 treatment should be held and not re-started during radiation therapy. Every effort should be made to complete the full prescribed course of radiation therapy as soon as these toxicities have resolved sufficiently to proceed.

9.2.1 Diarrhea and Skin Rash

Grade 1 – 2 diarrhea and skin rash do not require temporary discontinuation of treatment, as these toxicities may improve despite continued treatment with ZD1839. Diarrhea should be treated with high-dose loperamide (see section 6.3).

For grade 3 – 4 skin rashes felt to be secondary to ZD1839 (i.e. typical acneiform rash, outside of radiation field) and diarrhea or grade 2 skin rashes secondary to ZD1839 and diarrhea that are unacceptable to the patient for symptomatic reasons, ZD1839 should be temporarily held (< 2 weeks) until resolution and subsequently re-started at 250 mg. If symptomatic grade 2 skin rash or diarrhea recur after re-instituting treatment and require a second temporary discontinuation, treatment should be held until resolution to ≤ grade 1 and re-instituted at 250 mg.

For grade 3 and 4 diarrhea or skin rash felt to be secondary to ZD1839, treatment will be held until the patient has been reevaluated at least weekly until it resolves to ≤ grade 1. Treatment will then be re-instituted at 250 mg.

9.2.2 Other Toxicities

For any other grade 2 toxicity that is medically concerning (e.g., prolonged pulmonary toxicity), treatment may be held until resolution.

For any other grade 3 and 4 toxicity, or for grade 2 toxicity that may be attributed to ZD1839 and it is medically concerning, treatment will be discontinued and the patient reevaluated at least weekly until resolution to ≤ grade 1. Treatment will then be re-instituted at 250 mg.

Patients with unresolved toxicity after 3 weeks should be taken off study.

9.3 Dose Modifications during Concomitant Chemoradiotherapy

9.3.1 Myelosuppression

For absolute neutrophil count (ANC) of 500/μl to 1,000/μl or platelet count of 50,000/μl to 74,000/μl on Day 0 – 5 of each cycle, decrease hydroxyurea to 50% of full dose. On subsequent cycles, a reduced starting dose of hydroxyurea may be used.

For ANC of ≤ 500/μl or platelet count ≤ 50,000/μl on Day 0 – 5 of any cycle, omit hydroxyurea, and administer 600 mg/m^2/day of 5-FU and radiotherapy only. On subsequent cycles, a reduced starting dose of hydroxyurea by 50% should be used.

In the presence of a persisting fever ≥ 38°C or other clinically apparent infection a cycle can be postponed for 1 week or interrupted (if treatment cycle has already started) if this is necessary in the opinion of the treating medical and radiation oncologists.

9.3.2 Mucositis, Dermatitis, Diarrhea

For grade 4 mucositis, dysphagia, and dermatitis exceeding 7 days duration or persisting on Day 1 of a subsequent cycle, decrease 5-FU to 500 mg/m^2/day.

For grade 4 diarrhea exceeding 7 days duration or persisting on Day 1 of a subsequent cycle, decrease 5-FU to 500 mg/m^2/day. ZD1839 can be temporarily held as described in section 9.2.1.

Doses will not be increased on subsequent cycles.

TREATMENT CYCLES WILL NOT BE DELAYED FOR MUCOSITIS, DYSPHAGIA, DERMATITIS, OR DIARRHEA.

9.3.3 Other Non-hematological Toxicity

Radiotherapy should not be interrupted for non-hematologic toxicity except as in section 9.1.3, or as judged necessary on a case-by-case basis by the treating radiation and medical oncologists.

9.4 For Other Toxicities on Day 0 of Chemoradiotherapy

9.4.1 Hepatotoxicity

Grade 3, 4 – Hold hydroxyurea

9.4.2 Nephrotoxicity

Grade 2 – Give ½ dose hydroxyurea

Grade 3, 4 – Hold hydroxyurea

9.5 ZD1839 Dose Modifications During Maintenance Therapy

N.B.: ZD1839 AT THE 500MG DOSE LEVEL WILL NOT BE CONTINUED AS MAINTENANCE THERPAY. ZD1839 SHOULD BE DISCONTINUED UPON COMPLETION OF RADIOTHERAPY

The same procedures for dose modifications will apply to maintenance therapy as for chemoradiotherapy with the exception that patients can be re-started on ZD1839 after any delay regardless of causality or length of interruption at the discretion of the treating physician. The physician and patient must conclude that the benefits of continuing maintenance therapy outweigh the risks of doing so. Regardless of dose interruptions or delays, maintenance therapy will not last longer than 2 years after the date of completion of chemoradiotherapy.

10 AGENT FORMULATION AND PROCUREMENT

10.1 Paclitaxel

Paclitaxel (Taxol®, Bristol-Myers Squibb, Princeton, NY): supplied in 5 ml vials containing 30 mg of drug (6mg/ml). Side effects are listed in section 8.2.

Drug interactions: There is a potential for interaction with Ketoconazole, which might interfere with paclitaxel metabolism.

Contraindications: Known hypersensitivity to either paclitaxel or Cremaphor EL.

10.2 Carboplatin

Carboplatin (Paraplatin® – NSC#241240): supplied commercially as a sterile lyophilized powder available in single-dose vials containing 50 mg, 150 mg and 450 mg of carboplatin. Each vial contains equal parts by weight of carboplatin and mannitol.

Side effects: listed in section 8.3. Please refer to the package insert for full prescribing information.

Preparation: Immediately before use, the content of each vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP to produce a carboplatin concentration of 10 mg/ml. When prepared as directed, carboplatin solutions are stable for 8 hours at room temperature. Since no antibacterial preservative is contained n the formulation, it is recommended that carboplatin solutions be discarded 8 hours after dilution.

Storage and Stability: Unopened vials of carboplatin are stable for the life indicated on the package when stored at controlled room temperature and protected from light.

Administration: Administer over ½ hour after completing the paclitaxel infusion. The Calvert Equation (Dose=AUC (CC+25) will be used to achieve the desired dose where CC = Wt*(140-age)/72/creatinine (if female use 85%).

10.3 Fluorouracil

5-Fluorouracil (Adria, OH): commercially available as 10 ml ampules containing 500 mg/10 ml. No dilution is necessary for administration, but it may be further diluted in D5W or normal saline. It is stored at room temperature and is stable for 24 hours. It will be administered by intravenous continuous infusion. Toxicities are listed in section 8.4. Please refer to the package insert for full prescribing information.

10.4 Hydroxyurea

Hydroxyurea (Bristol-Myers Squibb, Princeton, NY): commercially available as 500 mg capsules. It is stored at room temperature and will be administered orally. Please refer to the package insert for solution preparation and expected AEs (also given in section 8.5). Please refer to the package insert for full prescribing information.

11 TRIAL MEASUREMENTS

The modified RECIST criteria will be used for this trial for objective tumor response assessment; details are given in Appendix A.

N.B.: THE ONLY CORRELATIVE STUDIES ON THE 500MG ZD1839 DOSE LEVEL WILL BE A PRESTUDY TUMOR BIOPSY AND BLOOD COLLECTION FOR PHARMACOGENOMICS (GENOTYPING).

11.1 EGFR Expression from Samples

11.1.1 Rationale and Reporting of Results

The purpose of the samples is to understand the mechanism of the mode of action of ZD1839, and/or identify a marker to monitor or predict treatment results. The patient will be informed in the patient information sheet on how the samples will be obtained and stored.

11.1.1.1 EGFR signaling

EGFR signaling is transduced via multiple pathways including PI3 kinase/AKT and MAP kinase. These downstream effectors are in turn phosphorylated and are responsible for the intracellular effects of EGFR activation. We plan to study expression of EGFR, AKT, ERK 1/2, and their phosphorylated forms before therapy and during chemoradiotherapy by immunohistochemistry. Biopsies will be obtained in all patients (if possible) and levels of expression will be correlated to response. If inadequate tissue is available for all correlative studies the order of priority is p-ERK, p-AKT, ERK, AKT, EGFR and p-EGFR.

11.1.1.2 EGFR genotyping

The level of EGFR expression is predominantly regulated by the abundance of its mRNA (Merlino GT-1, 2). The transcription initiation of EGFR gene derives from multiple initiation sites within a GC rich promoter region (Ishii S). The first intron of EGFR has been shown to regulate gene transcription, and it contains a CA dinucleotide repeat sequence that is highly polymorphic and is located in proximity to a transcriptional enhancer element (Chrysogelos SA, Maekawa T, Haley JD). Repeat lengths vary from 14 to 21 in the population; with the most common alleles contain 16 (42%), 18 (20%), and 20 (26%) repeats (Chi DD). Gebhardt and colleagues have recently reported an inverse correlation between the number of CA repeats present and the EGFR gene transcriptional activity over a 5-fold range (Gebhardt F).

The role of inter-individual genetic variability on disposition, toxicity and efficacy of many anticancer agents is also increasingly being recognized. Understanding and recognizing consequences of genetic polymorphisms of potential therapeutic targets and/or drug metabolizing enzymes earlier in development of new agents may enhance the efficacy and minimize the toxicity of these agents. Hence, identifying genetic determinants responsible for inter-individual variability of drug response will be of paramount importance in development of such targeted

therapeutic agents. This study seeks to discover whether polymorphisms in the first intron of the EGFR gene are related to response or toxicity.

11.1.1.3 Tumor Biopsies

On-study biopsies should be collected and prepared according to section 11.1.2a. A total of three on-study biopsies may be performed throughout the trial if possible, before induction chemotherapy, during chemoradiation, and after chemoradiation. Patients may refuse to undergo biopsy and still participate in the trial. The first and third biopsies are for clinical, as well as research purposes and will help determine histology and pathologic response, respectively.

11.1.1.4 Exploratory Serum and Plasma Markers

Both angiogenesis and hypoxia have been linked with outcome in head and neck cancer. In addition, preclinical data has revealed that ZD1839 may have antiangiogenic activities. Blood samples will be collected from patients before study entry, after induction chemotherapy, at the beginning of cycle 2 of chemoradiotherapy (to coincide with the biopsy), and after completion of chemoradiotherapy. These samples will be analyzed for quantitative determination of VEGF and PAI-1 levels using commercially available ELISA kits.

Any remaining samples and test samples such as stained slides will be retained at the testing laboratory until completion of the trial. Stained slides used in the development of diagnostics kits will be retained at the University of Chicago. Permission for future research will be sought from the relevant International Ethics Committee (IEC)/ International Review Boards (IRB), and patients may be contacted again for informed consent.

It is not proposed that the analysis of results from a specific patient are made available routinely to either the patient or the treating physician; however, group results from this trial will be published. The patient will be informed of this in the patient information sheet.

The tumor samples collected in this trial, the results of any testing, and any patents, diagnostic tests, drugs, and biological products developed directly or indirectly as a result of this trial, as well as any information derived directly or indirectly from those samples, are the sole property AstraZeneca (and its successors, licensees and assigns). The patient has no right to this property or to any share of any profits that may be earned directly or indirectly as a result of this trial. The patient will be informed of this in the patient informed consent.

11.1.2 Sample Management

a) Collection of Tumor Slides or Tumor Blocks

Every effort should be made to obtain biopsies that contain cells representative of the tumor. The specimen should contain sufficient non-necrotic tumor tissue. Biopsies during study will be performed on an outpatient basis [unless the patient is undergoing an operative procedure (ie panendoscopy) as part of standard evaluation] under local anesthesia using an 18-guage core biopsy needle to obtain a total tissue length of at least 2 cm. These tissues should be frozen at -80°C according to protocol.

For freezing tissues, you will need O.C.T. embedding compound (Baxter), plastic tissue molds (Baxter), 2-methylbutane (Sigma), dry ice, a hemostat or other clamping device, and a metal or plastic 1 L container.

- Label the mold with proper tissue identification and fill partly with O.C.T.
- If freezing unfixed tissue, dab it on a towel to remove any fluid, and immediately place in tissue mold with O.C.T. and continue with protocol
- Choose the best orientation for the tissue to be frozen in, and let it settle to the bottom. Note that the bottom of the mold is where cutting will begin.
- Add more O.C.T. on top of tissue to cover it completely and fill the mold.
- Fill the plastic or metal container half way with 2-methylbutane.
- Add several small pieces of dry ice and wait a few moments for the temperature to drop to -40°C.
- Grasp the edge of the mold with the hemostat and dip into 2-methylbutane. Note that you should NOT submerge yet. Dip only the most bottom part of the plastic mold.
- The O.C.T. will begin to turn white as it freezes
- When all of the O.C.T. is frozen, drop the mold into the cold 2-methylbutane to freeze thoroughly (~5 min)
- Remove the mold from the freezing liquid, wrap the mold in foil, label it, and immediately store at -80°C.

b) Blood Collection for Correlative Studies

11.1.2.b.i Genotyping

Blood samples will be collected from patients in a 7 cc lavender top tube. Samples should be collected prior to therapy with ZD1839. They will be analyzed for EGFR genotyping. Note that this blood samples can be collected at any time as genotype is not expected to change.

11.1.2.b.ii VEGF and PAI-1

Blood samples will be collected from patients in 7 cc green top tubes. Samples will be collected prior to therapy, after induction therapy, on day 1 of cycle 2 of chemoradiotherapy, and after chemoradiotherapy. These will be analyzed for VEGF and PAI-1.

11.1.3 Sample Preparation and Shipment Instructions

The shipment of all human samples (blood, tissue) must comply with appropriate regulations as specified by the carrier. At a minimum, all frozen tissue and blood samples must be packaged in dry ice within two containers with absorbent material between containers to control any spill or leakage. The outer container must be puncture resistant (e.g., cardboard mail tube, corrugated cardboard box). A biohazard sticker must be affixed to both the inner and outer containers. All samples must be accompanied by a sample transmission form and shipped to:

Dr. Mark Lingen (773-702-5548, email: MLINGEN@UCHOSPITALS.EDU)

University of Chicago
FMI Dock/Lab Supply
5830 S. Ellis Ave
Room G-02
Chicago, IL 60637

Attn: Rifat Hasina

All of the participating institutions outside of the University of Chicago will be provided with a University of Chicago Federal Express Account assigned to this study.

Biopsy samples that are obtained at the University of Chicago Medical Center should be forwarded directly to the Translational Research Laboratory in J652.

Each sample must be accompanied with a list containing the following information:

Treating Physician Information
Patient name, ID number, date of birth, sex
Diagnosis
Day started on clinical protocol
Site of biopsy
Date and time of biopsy

On arrival, each sample will be assigned a Study Number. All subsequent handling of the tissue samples will be blinded to the investigators performing various tests, except for the clinical pathologists.

Only biopsy samples determined by the pathologist to contain tumor will be subjected to immunohistochemical analysis.

For all histochemical studies, samples will be marked only by an assigned study number. Patient name, diagnosis and other information will be unknown to the laboratory/clinical investigators involved and will be revealed only after studies are completed for further data analysis and statistics.

The samples collected for genotyping will be stored on ice and transported on the same day (labeled with patient name) to the University of Chicago (see above). A laboratory accession number will be assigned to the sample and the patient name will be removed. Information regarding specimen identification, protocol number, and date of blood draw will be indicated on a requisition form. Samples will be stored at –80°C for no more than 5 days for optimal DNA isolation. DNA extraction will be performed using commercial DNA isolation kits, such as Puregene™ (Gentra Systems, Inc., Minneapolis, MN). Genotyping for EGFR will be performed according to methods optimized in Dr. Mark Ratain's laboratory. The two primers that will be used are:

sAVH3F: 5'-Fam-GTTTGAAGAATTTGAGCCAACC-3'

sAVH3R: 5'-TTCTTCTGCACATTGGCAC-3'

One μl of sample will be loaded on ABI 3700 DNA sequencer, genotyped using GeneScan™ and Genotyper® software.

11.1.4 Immunohistochemistry

Tissues will be fixed in 4% paraformaldehyde and sectioned in 4 – 8 μ slices. Slides will be incubated with 1% hydrogen peroxide for endogenous peroxidase blocking. Slides will be incubated with 5% normal horse serum, avidin, then biotin labeling solutions. The slides will be incubated with the primary antibody overnight at 4°C. All primary antibodies are commercially available for use in immunohistochemistry. The slides will be incubated with species-appropriate biotinylated secondary antibody in

protein blocking solution for one hour at room temperature. Avidin/biotin complex will be applied. Slides will be developed with diaminobenzidine (DAB), counterstained with hematoxylin, dehydrated, and mounted. Slides will be interpreted by Dr. Wendy Recant using a four point scoring system. This protocol may be modified to improve antigen retrieval and staining.

11.1.5 ELISA

Samples will be analyzed for plasma VEGF (R&D systems) and serum PAI-1 (Biopool International) using commercially available ELISA kits.

12 MEASUREMENT OF EFFECT

12.1 Definitions

Response and progression will be evaluated in this study using the new international criteria proposed by the RECIST Committee (43). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

12.1.1 Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques (CT, MRI, x-ray) or as ≥ 10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

12.1.2 12.1.2 Non-measurable Disease

All other lesions or sites of disease, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

12.1.3 Target Lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total representative of all involved organs should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated 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 by which to characterize the objective tumor response.

12.1.4 Non-target Lesions

All other lesions or sites of disease should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required but the presence or absence of each should be noted throughout follow-up.

12.2 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment. Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. Given the nature of locoregional failure after prior irradiation characteristic of head and neck cancer, these areas are considered as progression of disease and will be included. If doubt exists on appropriate scans, then biopsy will be necessary to measure disease.

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 antitumor effect of a treatment.

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

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI. These techniques 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 tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound. When the primary endpoint of the study is objective response evaluation, ultrasound should not be used to measure tumor lesions. It is,

however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy, Laparoscopy. The use 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 be available only at some centers. Therefore, the use 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.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific additional criteria for standardized usage of prostate-specific antigen (PSA) and CA-125 response in support of clinical trials are being developed.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., 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.

12.3 Response Criteria

12.3.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

12.3.2 Evaluation of Non-target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level

Incomplete Response/ Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Although a clear progression of "non-target" lesions only is exceptional, in such circumstances the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the review panel (or study chair).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

12.3.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until assessment 6-8 weeks after chemoradiotherapy. Pathologic response will take precedence over clinical or radiographic response. If there is discordance between clinical and radiographic response then clinical response will take precedence. The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see section 12.4).

Table 12 Lesions

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	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; PD = progressive disease; PR = partial response; SD = stable disease.

Note:

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

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

12.4 Confirmatory Measurement/Duration of Response

12.4.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed at least 12 weeks after the criteria for response are first met (this does not apply for induction therapy in this protocol).

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

12.5 Progression-Free and Overall Survival

Progression-free (time to progression): From the date of registration to the date of progressive disease or death

Overall survival time: From the date of registration to the date of death or date of last patient contact if censored

12.6 Response Review

Independent review of imaging studies will take place under the following circumstances

- Patients felt to have a complete response
- Patients felt to have a partial response
- Cases of prolonged stable disease, as selected by the primary investigator.

An experienced radiologist with no affiliation to the present study will review the films. Images will be free of extraneous marks whenever possible.

13 ADVERSE EVENTS

13.1 Definitions

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

13.2 Adverse Events

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

Any events that are unequivocally due to progression of disease should not be reported as an adverse event.

If any of the above events occurs, information will be required as to if it is an event possibly due to adverse effect of the study drug or an infection possibly caused with the study drug.

13.3 Serious Averse Events

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

- Results in death
- Is immediately life-threatening

- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

Any event or hospitalization unequivocally due to progression of disease should not be reported as a serious adverse event.

The causality of SAEs (i.e., 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 the drug?"

13.3.1 Other significant adverse event (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 subject from study treatment, will be classified as OAEs. Examples of these are marked hematological 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.

13.4 Recording of Adverse Events

All AEs should be documented. 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[s]). AEs will also be graded according to the NCI CTC, and changes documented.

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 medicinal product and the AE.

13.4.1 Abnormal laboratory values/vital signs

The reporting of laboratory /vital signs abnormalities as both laboratory findings and adverse events should be avoided. They should not be reported unless any criterion for a SAE is fulfilled, the laboratory /vital signs abnormalities causes the subject to discontinue from the study, or the investigator insists the abnormality should be reported as an AE. If an abnormal laboratory value /vital sign is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated laboratory result/vital sign should be considered additional information that must be collected on the relevant CRF.

Any new conditions reported during the study will be documented as an AE. Only those findings that are in addition to the condition being treated will be documented as AE. Conditions that are considered by the investigator to be unequivocally disease-related will not be documented as AEs.

Any detrimental change in a patient's condition, subsequent to his or her entering the trial and during the 30-day follow-up period after the final treatment, should be considered an AE. The development of a new cancer should be regarded as an AE. New cancers are those that are not the primary reason for the administration of the trial treatment and have been identified after the patient's inclusion in this clinical trial.

13.5 Lack of Efficacy

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

13.6 Skin Adverse Events

A variety of agents can be used to manage skin rashes. These include mild-to-moderate strength steroid creams, topical or systemic antibiotics, topical or systemic antihistamines, and occasionally retinoid creams.

There is no standard, known, or established treatment proven effective for drug-related skin rashes or changes due to ZD1839. Most commonly, a pustular rash has been observed, which frequently improves even though the same dose of ZD1839 therapy is continued uninterrupted. The need for oral or topical antibiotics is a clinical decision of the investigator and should be preceded by a culture of affected areas and, if indicated, a dermatology consultation. Oral retinoids should not be given because of theoretical concerns about negatively affecting the ZD1839 mechanism of action. Oral steroids are also strongly discouraged.

13.7 Gastrointestinal Adverse Events

Diarrhea can be debilitating and on rare occasions is potentially life threatening. Guidelines developed by an American Society of Clinical Oncology (ASCO) panel for treating chemotherapy-induced diarrhea are abstracted below (44).

Pharmacological approaches include the following:

- Loperamide administered as an initial 4-mg dose followed by 2-mg doses every 4 hours. This dose and regimen are moderately effective.

- Clonidine, nonsteroidal anti-inflammatory drugs, and the serotonin antagonist cryoheptadine have been shown to be effective in controlling diarrhea associated with inflammation of the bowel.

The synthetic octapeptide octreotide has been shown to be effective in the control of diarrhea induced by fluoropyrimidine-based chemotherapy regimens when administered as an escalating dose by continuous infusion or subcutaneous injection. Octreotide can be administered at doses ranging from 100 micrograms twice daily to 500 micrograms 3 times daily, with a maximum-tolerated dose of 2000 micrograms 3 times daily in a 5-day regimen.

13.8 Pregnancy

Should a pregnancy occur, it must be reported in accordance with the following procedures:

Pregnancy itself is not regarded as an AE unless there is a suspicion that the trial treatment under investigation 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 trial.

All reports of congenital abnormalities or 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.

13.9 Reporting of Serious Adverse Events

Federal and Manufacturer Reporting Guidelines

Investigators and other site personnel must inform the **FDA, via a Medwatch form**, of any SAE that occurs during the course of the study. The PI must also fax a copy of the **Medwatch report to AstraZeneca** at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

Send by way of fax to: 302-886-7483
Attention: IRESSA® IIT Safety Representative

Follow-up information on SAEs must also be reported by the investigator to AstraZeneca and the FDA 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 and the FDA within the FDA's regulatory timelines.

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

13.9.1 University of Chicago Reporting Guidelines

Participating institutions must report serious adverse events to their own IRBs and the Cancer Clinical Trials Office (CCTO) at the University of Chicago who will in turn submit AE reports to the protocol chair for review. These AE reports will then be submitted to the University of Chicago IRB and circulated to all participating institutions. A copy will be forwarded to the appropriate research nurse.

Within 24 hours of knowledge of Serious Adverse Event

If the reaction requires reporting, it should be called to the CCTO (773-834-0357) within 24 hours (or next business day) when the investigator/research study nurse becomes aware of the event.

The following information is required when calling in the event:

- Name and Telephone Number of Reporter
- Patient Initials
- Patient Medical Record Number
- IRB Protocol Number
- PI of Study
- Treating Physician
- Date of Event
- Description of Event (including grade of the event and if the event required hospitalization)

An email will be sent to the research nurse, treating physician and PI of the study informing that the SAE notification has been received.

Within 5 working days of knowledge of Serious Adverse Event

A completed MedWatch must be sent to the CCTO (fax number (773) 702-8855) within **5 working days of event occurrence**. If the event occurred at the University of Chicago, the University of Chicago's IRB Adverse Event Form must also be filled out. The UC IRB Serious and Unexpected Adverse Event form is available on-line at: HTTP://ORS/IRB/AESERIOUS.PDF. The UC IRB Fatal/Life-Threatening Event form is available on-line at: HTTP://ORS/IRB/AEFATAL.PDF.. This form must be typed. Once the

forms are completed, the PI will then review, sign and place folder in the QA coordinator's box.

Once the appropriate SAE documents have been received, the CCTO will submit these to the IRB and a copy will be forwarded to the appropriate research nurse. Copies will also be sent to participating institutions.

13.10 Handling Unresolved SAEs and AEs at Completion or Withdrawal

All trial treatment-related toxicities and SAEs must be followed until resolution, unless, in the investigator's opinion, the condition is unlikely to resolve because of the patient's underlying disease.

13.11 Data Safety and Monitoring

Data Safety and Monitoring will occur at the weekly University of Chicago section meetings, which are lead by senior level medical oncologists. At each meeting, all active studies will be reviewed for safety and progress toward completion. Toxicities and adverse events will be reviewed at each meeting and a Data Safety and Monitoring form will be completed for each protocol and signed by either the principal investigator, the chairman of the section or by his designate if the chairman is not available.

14 STATISTICAL CONSIDERATIONS

14.1 Study Design and Primary Endpoints

A comprehensive statistical analysis plan (SAP) will be produced prior to locking of the database.

The primary objective of this study is to test whether the new treatment regimen with ZD1839 is at least as effective as previous standard regimen, which has complete response rate of 80%. The study will be conducted as a single arm, two-stage, non-inferiority phase II trial. The primary endpoint for this study is the complete response rate achieved 1 month after chemoradiotherapy. A two-stage design will be used to explore the activity of ZD1839 added to concurrent chemoradiotherapy. A sample size of 59 patients will be sufficient to detect a 15% lower response rate than standard treatment.

During the first stage, 25 patients will be recruited, and the study will be terminated if ≤ 16 complete responses are observed after completing chemoradiotherapy among those evaluable. Otherwise an additional 34 patients will be recruited for a total of 59 patients overall. If 45 or more responses are observed at the end of the study, we shall conclude the new treatment is not inferior to the standard treatment.

14.2 Sample Size Determination

With a total sample size of 59 in this design, the probability of falsely rejecting the null hypothesis is at most 0.05 (one-sided alpha=0.05) and the probability of correctly rejecting the null hypothesis if the alternative hypothesis is true is at least 0.80 (power = 80%). In addition, the false negative rate in the first stage is less than 0.05.

14.3 Accrual Rate and Study Duration

To account for patients with non-measurable disease an inflation factor of 10% will be applied to the sample size, resulting in a total of 65 patients to be accrued. It is anticipated that 3 – 4 patients per month can be accrued, for a total accrual period of 18 months. Response assessment and correlative marker analysis will proceed upon completion of the regimen by all patients (approximately 4 – 6 weeks after the last patient is enrolled).

Subsequent to these analyses, follow-up to obtain TTP, time to site-specific failure, and total survival will continue. Minimum follow-up of 12 months will be required to provide adequate precision for estimates of time-to-event endpoints. Follow-up will be maintained for the remainder of patients' lifetimes to obtain further information on long-term disease course and mortality.

14.4 Evaluation of Response and Cohorts to be Analyzed

All patients included in the study will be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible (intent-to-treat population). Criteria described in Appendix A will be used to assign each patient to one of the following response categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

All patients who have met the eligibility criteria will be included in the main analysis of the response rate. Patients in response categories 4 – 9 will be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration will not result in exclusion from the analysis of the response rate.

14.5 Analytic Methods

14.5.1 Primary Analyses

Primary analysis of response will consist of estimation of complete response as described in section 12.3. Exact confidence limits on response rate will be computed with the use of the binomial distribution.

14.5.2 Secondary Endpoints and Analyses

Overall survival and progression-free survival (PFS) will be calculated using the Kaplan-Meier estimator. Median survival times and their associated 95% confidence intervals will also be calculated. Patient and disease characteristics prior to treatment as well as surgical intervention will be evaluated as potential prognostic factors using Cox proportional hazards models. In addition to the overall analyses we will stratify by whether patients received surgery or not and evaluate the extent to which the addition of surgery affects outcomes and quality of life (see below).

All observed toxicities will be recorded and summarized using appropriate descriptive statistics including mean, standard deviation, median, range and frequency counts.

Descriptive statistics will be compiled for assessments of QoL and performance outcomes at pre-therapy, after induction therapy, and several points after chemoradiotherapy as described in section 6.5. Patterns of change over time in QoL subscale scores and performance assessments will be evaluated using paired and longitudinal data analysis methods.

Performance data will be used to classify patient status at some fixed follow-up time (e.g., six months or one year post therapy) into binary outcome categories, such as ability to eat solid foods (yes/no). Logistic regression modeling will be used to identify factors predictive of these outcomes.

A certain degree of patient attrition from the QoL study, due to patient mortality and other factors, is assumed. Characteristics of individuals with missing data will be evaluated to identify imbalance in baseline characteristics. In the absence of apparent systematic loss, data will be analyzed assuming that the observations are missing at random. In the case of evidence for systematic patterns of missing data ("informative" missingness), alternative strategies for analyzing such data, depending on the pattern will be investigated.

Adverse events will be summarized using counts and proportions, in order to determine the tolerability of the treatment combination.

14.5.3 Analysis of Exploratory endpoints

Molecular correlative markers, including p-ERK, p-AKT, ERK, AKT, EGFR, p-EGFR, genotyping, plasma VEGF, and serum PAI-1 will be analyzed using simple paired data methods (paired t-test or Wilcoxon signed-rank test, as appropriate) for changes between pre-therapy and during chemoradiotherapy (when applicable). Logistic regression will be used to determine if those patients showing marker changes indicative of ZD1839 activity experience superior clinical response.

15 TRIAL MANAGEMENT

15.1 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.

15.2 Audits and Inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an IRB may visit the center to perform audits or inspections, including source data verification. The purpose of an AstraZeneca audit or inspection is to examine all trial related activities and documents systematically and independently to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), 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.

15.3 Changes to the Protocol

If it is necessary for the trial protocol to be amended, the amendment or a new version of the trial protocol must be reported to and approved by the IRB. If a protocol amendment requires a change to a particular center's Written Informed Consent Form, then the IRB must be notified. Approval of the revised Written Informed Consent Form by the IRB is required before the revised form is used.

AstraZeneca's willingness to supply study drug is predicated upon the review of the protocol. The investigator agrees to provide prior written notice to AstraZeneca of any modifications to the protocol or informed consent form.

15.4 Ethics

The principal investigator(s) is also responsible for providing the IRB with reports of any SAEs from any other trial conducted with the investigational product.

15.5 Ethical Conduct of the Trial

The trial will be performed in accordance with GCP.

15.6 Procedures in Case of Overdose

There is currently no known antidote for ZD1839. The treatment of AEs associated with overdose should be supportive and for the underlying adverse symptoms. To date, no patient has experienced an overdose with ZD1839.

Information on overdoses that do not result in AEs should be forwarded to AstraZeneca. This will then be reported to AstraZeneca Drug Safety in accordance with procedures defined for non-SAEs.

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Appendix A
Objective tumor response criteria (RECIST)

1 INTRODUCTION

The introduction explores the definitions, assumptions, and purposes of tumor **response criteria**. Below, guidelines that are offered may lead to more uniform reporting of outcomes of clinical trials. Note that, although single investigational agents are discussed, the principles are the same for drug combinations, non-investigational agents, or approaches that do not involve drugs.

Tumor **response** associated with the administration of anticancer agents can be evaluated for at least three important purposes that are conceptually distinct:

- Tumor **response** as a prospective end point in early clinical trials. In this situation, objective tumor **response** is employed to determine whether the agent/regimen demonstrates sufficiently encouraging results to warrant further testing. These trials are typically phase II trials of investigational agents/regimens (*see* appendix section 1.2), and it is for use in this precise context that these guidelines have been developed.

- Tumor **response** as a prospective end point in more definitive clinical trials designed to provide an estimate of benefit for a specific cohort of patients. These trials are often randomized comparative trials or single-arm comparisons of combinations of agents with historical control subjects. In this setting, objective tumor **response** is used as a surrogate end point for other measures of clinical benefit, including time-to-event (death or disease progression) and symptom control (*see* appendix section 1.3).

- Tumor **response** as a guide for the clinician and patient or study subject in decisions about continuation of current therapy. This purpose is applicable both to clinical trials and to routine practice (*see* appendix section 1.1), but use in the context of decisions regarding continuation of therapy is not the primary focus of this document.

However, in day-to-day usage, the distinction among these uses of the term "tumor **response**" can easily be missed, unless an effort is made to be explicit. When these differences are ignored, inappropriate methodology may be used and incorrect conclusions may result.

1.1 Response Outcomes in Daily Clinical Practice of Oncology

The evaluation of tumor **response** in the daily clinical practice of oncology may not be performed according to predefined **criteria**. It may, rather, be based on a subjective medical judgment that results from clinical and laboratory data that are used to assess the treatment benefit for the patient. The defined **criteria** developed further in this document are not necessarily applicable or complete in such a context. It might be appropriate to

make a distinction between "clinical improvement" and "objective tumor **response**" in routine patient management outside the context of a clinical trial.

1.2 Response Outcomes in Uncontrolled Trials as a Guide to Further Testing of a New Therapy

"Observed **response** rate" is often employed in single-arm studies as a "screen" for new anticancer agents that warrant further testing. Related outcomes, such as **response** duration or proportion of patients with complete **response**s, are sometimes employed in a similar fashion. The use of a **response** rate in this way is not encumbered by an implied assumption about the therapeutic benefit of such **response**s but rather implies some degree of biologic antitumor activity of the investigated agent.

For certain types of agents (i.e., cytotoxic drugs and hormones), experience has demonstrated that objective antitumor **response** observed at a rate higher than would have been expected to occur spontaneously can be useful in selecting anticancer agents for further study. Some agents selected in this way have eventually proven to be clinically useful. Furthermore, **criteria** for "screening" new agents in this way can be modified by accumulated experience and eventually validated in terms of the efficiency by which agents so screened are shown to be of clinical value by later, more definitive, trials.

In most circumstances, however, a new agent achieving a **response** rate determined *a priori* to be sufficiently interesting to warrant further testing may not prove to be an effective treatment for the studied disease in subsequent randomized phase III trials. Random variables and selection biases, both known and unknown, can have an overwhelming effect in small, uncontrolled trials. These trials are an efficient and economic step for initial evaluation of the activity of a new agent or combination in a given disease setting. However, many such trials are performed, and the proportion that will provide false-positive results is necessarily substantial. In many circumstances, it would be appropriate to perform a second small confirmatory trial before initiating large resource-intensive phase III trials.

Sometimes, several new therapeutic approaches are studied in a randomized phase II trial. The purpose of randomization in this setting, as in phase III studies, is to minimize the impact of random imbalances in prognostic variables. However, randomized phase II studies are, by definition, not intended to provide an adequately powered comparison between arms (regimens). Rather, the goal is simply to identify one or more arms for further testing, and the sample size is chosen so to provide reasonable confidence that a truly inferior arm is not likely to be selected. Therefore, reporting the results of such randomized phase II trials should not imply statistical comparisons between treatment arms.

1.3 Response Outcomes in Clinical Trials as a Surrogate for Palliative Effect

1.3.1 Use in Nonrandomized Clinical Trials

The only circumstance in which objective **response**s in a nonrandomized trial can permit a tentative assumption of a palliative effect (i.e., beyond a purely clinical measure of benefit) is when there is an actual or implied comparison with historical series of similar patients. This assumption is strongest when the prospectively determined statistical analysis plan provides for matching of relevant prognostic variables between case subjects and a defined series of control subjects. Otherwise, there must be, at the very least, prospectively determined statistical **criteria** that provide a very strong justification for assumptions about the **response** rate that would have been expected in the appropriate "control" population (untreated or treated with conventional therapy, as fits the clinical setting). However, even under these circumstances, a high rate of observed objective **response** does not constitute proof or confirmation of clinical therapeutic benefit. Because of unavoidable and nonquantifiable biases inherent in nonrandomized trials, proof of benefit still requires eventual confirmation in a prospectively randomized, controlled trial of adequate size. The appropriate end points of therapeutic benefit for such a trial are survival, progression-free survival, or symptom control (including quality of life).

1.3.2 Use in Randomized Trials

Even in the context of prospectively randomized phase III comparative trials, "observed **response** rate" should not be the sole, or major, end point. The trial should be large enough that differences in **response** rate can be validated by association with more definitive end points reflecting therapeutic benefit, such as survival, progression-free survival, reduction in symptoms, or improvement (or maintenance) of quality of life.

2 MEASURABILITY OF TUMOR LESIONS AT BASELINE

2.1 Definitions

At baseline, tumor lesions will be categorized as follows: measurable (lesions that can be accurately measured in at least one dimension [longest diameter to be recorded] as $\geq$20 mm with conventional techniques or as $\geq$10 mm with spiral CT scan [*see* appendix section 2.2]) or nonmeasurable (all other lesions, including small lesions [longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan] and truly nonmeasurable lesions).

The term "evaluable" in reference to measurability is not recommended and will not be used because it does not provide additional meaning or accuracy.

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

Lesions considered to be truly nonmeasurable 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, and cystic lesions.

(*Note:* Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable, and the conditions under which such lesions should be considered must be defined in the protocol when appropriate.)

2.2 Specifications by Methods of Measurements

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 antitumor effect of a treatment.

2.2.1 Clinical Examination

Clinically detected lesions will be considered measurable only when they are superficial (e.g., skin nodules and 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.

2.2.2 Chest X-ray

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

2.2.3 CT and MRI

CT and MRI are the best currently available and most reproducible methods for measuring target lesions selected for **response** assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed by use of a 5-mm contiguous reconstruction algorithm. This specification applies to the tumors of the chest, abdomen, and pelvis, while head and neck tumors and those of the extremities usually require specific protocols.

2.2.4 Ultrasound

When the primary end point of the study is objective **response** evaluation, ultrasound should not be used to measure tumor lesions that are clinically not easily accessible. It may be used as a possible alternative to clinical measurements for superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

2.2.5 Endoscopy and Laparoscopy

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

2.2.6 Tumor Markers

Tumor markers alone cannot be used to assess **response**. However, if markers are initially above the upper normal limit, they must return to normal levels for a patient to be considered in complete clinical **response** when all tumor lesions have disappeared. Specific additional **criteria** for standardized usage of prostate-specific antigen and CA (cancer antigen) 125 **response** in support of clinical trials are being validated.

2.2.7 Cytology and Histology

Cytologic and histologic techniques can be used to differentiate between partial **response** and complete **response** in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met **criteria** for **response** or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between **response** or stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). New techniques to better establish objective tumor **response** will be integrated into these **criteria** when they are fully validated to be used in the context of tumor **response** evaluation.

3 TUMOR RESPONSE EVALUATION

3.1 Baseline Evaluation

3.1.1 Assessment of Overall Tumor Burden and Measurable Disease

To assess objective **response**, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. Only patients with measurable disease at baseline should be included in protocols where objective tumor **response** is the primary end point. Measurable disease is defined by the presence of at least one measurable lesion (as defined in appendix section 2.1). If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

3.1.2 Baseline Documentation of "Target" and "Nontarget" Lesions

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

All other lesions (or sites of disease) should be identified as nontarget lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

3.2 Response Criteria

3.2.1 Evaluation of Target Lesions

This section provides the definitions of the **criteria** used to determine objective tumor **response** for target lesions. The **criteria** have been adapted from the original WHO Handbook, taking into account the measurement of the longest diameter only for all target lesions: complete **response** — the disappearance of all target lesions; partial **response** — at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter; progressive disease — at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions; stable disease — neither sufficient shrinkage to qualify for partial **response** nor

sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

3.2.2 Evaluation of Nontarget Lesions

This section provides the definitions of the **criteria** used to determine the objective tumor **response** for nontarget lesions: complete **response** — the disappearance of all nontarget lesions and normalization of tumor marker level; incomplete **response/**stable disease — the persistence of one or more nontarget lesion(s) and/or the maintenance of tumor marker level above the normal limits; and progressive disease — the appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions.

(*Note:* Although a clear progression of "nontarget" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later by the review panel [or study chair]).

3.2.3 Evaluation of Best Overall Response

The best overall **response** is the best **response** recorded from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best **response** assignment will depend on the achievement of both measurement and confirmation **criteria** (*see* appendix section 3.3.1). Appendix Table 1 provides overall **response**s for all possible combinations of tumor **response**s in target and nontarget lesions with or without the appearance of new lesions.

(*Notes:*

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

- Conditions that may define early progression, early death, and inevaluability are study specific and should be clearly defined in each protocol (depending on treatment duration and treatment periodicity).

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

3.2.4 Frequency of Tumor Re-evaluation

Frequency of tumor re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up of every other cycle (i.e., 6 to 8 weeks) seems a reasonable norm. Smaller or greater time intervals than these could be justified in specific regimens or circumstances.

After the end of the treatment, the need for repetitive tumor evaluations depends on whether the phase II trial has, as a goal, the **response** rate or the time-to an event (disease progression/death). If time to an event is the main end point of the study, then routine re-evaluation is warranted of those patients who went off the study for reasons other than the expected event at frequencies to be determined by the protocol. Intervals between evaluations twice as long as on study are often used, but no strict rule can be made.

Appendix Table 1 Overall responses for all possible combinations of tumor responses in target and nontarget lesions with or without the appearance of new lesions

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	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; PD = progressive disease; PR = partial response; SD = stable disease.
See text for more details.

3.3 Confirmatory Measurement/Duration of Response

3.3.1 Confirmation

The main goal of confirmation of objective **response** in clinical trials is to avoid overestimating the **response** rate observed. This aspect of **response** evaluation is particularly important in nonrandomized trials where **response** is the primary end point. In this setting, to be assigned a status of partial **response** or complete **response**, changes in

tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the **criteria** for **response** are first met. Longer intervals as determined by the study protocol may also be appropriate.

In the case of stable disease, measurements must have met the stable disease **criteria** at least once after study entry at a minimum interval (in general, not less than 6 to 8 weeks) that is defined in the study protocol (*see* appendix section 3.3.3).

(*Note:* Repeat studies to confirm changes in tumor size may not always be feasible or may not be part of the standard practice in protocols where progression-free survival and overall survival are the key end points. In such cases, patients will not have "confirmed **response**." This distinction should be made clear when reporting the outcome of such studies.)

3.3.2 Duration of Overall Response

The duration of overall **response** is measured from the time that measurement **criteria** are met for complete **response** or partial **response** (whichever status is recorded first) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall complete **response** is measured from the time measurement **criteria** are first met for complete **response** until the first date that recurrent disease is objectively documented.

3.3.3 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the **criteria** for disease progression are met (taking as reference the smallest measurements recorded since the treatment started). The clinical relevance of the duration of stable disease varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of stable disease. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

(*Note:* The duration of **response** or stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency that should take into account many parameters, including disease types and stages, treatment periodicity, and standard practice. However, these limitations to the precision of the measured end point should be taken into account if comparisons among trials are to be made.)

3.4 Progression-free Survival/Time to Progression

This document focuses primarily on the use of objective **response** end points. In some circumstances (e.g., brain tumors or investigation of noncytoreductive anticancer agents), **response** evaluation may not be the optimal method to assess the potential anticancer activity of new agents/regimens. In such cases, progression-free survival/time to progression (PFS/TTP) can be considered valuable alternatives to provide an initial estimate of biologic effect of new agents that may work by a noncytotoxic mechanism. It is clear though that, in an uncontrolled trial proposing to utilize progression-free survival/time to progression, it will be necessary to document with care the basis for estimating what magnitude of progression-free survival/time to progression would be expected in the absence of a treatment effect. It is also recommended that the analysis be quite conservative in recognition of the likelihood of confounding biases, e.g., with regard to selection and ascertainment. Uncontrolled trials using progression-free survival or time to progression as a primary end point should be considered on a case-by-case basis, and the methodology to be applied should be thoroughly described in the protocol.

4 RESPONSE REVIEW

For trials where the **response** rate is the primary end point, it is strongly recommended that all **response**s be reviewed by an expert or experts independent of the study at the study's completion. Simultaneous review of the patients' files and radiologic images is the best approach.

(*Note:* When a review of the radiologic images is to take place, it is also recommended that images be free of marks that might obscure the lesions or bias the evaluation of the reviewer[s]).

5 REPORTING OF RESULTS

All patients included in the study must be assessed for **response** to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete **response**, 2) partial **response**, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). (*Note:* By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.)

All of the patients who met the eligibility **criteria** should be included in the main analysis of the **response** rate. Patients in **response** categories 4 – 9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the **response** rate. Precise definitions for categories 4 – 9 will be protocol specific.

All conclusions should be based on all eligible patients.

Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should be provided.

6 RESPONSE EVALUATION IN RANDOMIZED PHASE III TRIALS

Response evaluation in phase III trials may be an indicator of the relative antitumor activity of the treatments evaluated but may usually not solely predict the real therapeutic benefit for the population studied. If objective **response** is selected as a primary end point for a phase III study (only in circumstances where a direct relationship between objective tumor **response** and a real therapeutic benefit can be unambiguously demonstrated for the population studied), the same **criteria** as those applicable to phase II trials (RECIST guidelines) should be used.

On the other hand, some of the guidelines presented in this special article might not be required in trials, such as phase III trials in which objective **response** is *not* the primary end point. For example, in such trials, it might not be necessary to measure as many as 10 target lesions or to confirm **response** with a follow-up assessment after 4 weeks or more. Protocols should be written clearly with respect to planned **response** evaluation and whether confirmation is required so as to avoid *post-hoc* decisions affecting patient evaluability.

Appendix B
Forms to accompany laboratory samples

Protocol 12019

The University of Chicago

Tissue and Blood Sample Collection Form

Clinician/Research Nurse: Please Fill Out

Tissue Samples

Patient Name or Initials: _____ UC MR # (if applicable): _____

Patient Protocol ID #: **12019-** _____ Date Tissue Obtained: _____

Institution: _____ Attending Physician: _____

Site of Biopsy: _____ Site of Primary Tumor: _____

Pre/Post Therapy (Please circle)

Did Surgical Pathology receive tissue for diagnosis? **Yes** **No**

Contact Person's Phone Number and email address at Affiliate:

Blood Samples

		date drawn	time	date shipped	
Pre-Therapy:	2 green top/plasma				(batched on dry ice)
	1 purple top/DNA				(fresh on ice pack)
Post-Induction:	2 green top/plasma				(batched on dry ice)
Cycle 2 Day 1:	2 green top/plasma				(batched on dry ice)
Post-Chemo:	2 green top/plasma				(batched on dry ice)

Researcher: Please Fill Out

Date Samples received: _____ Data entered into Database: **Yes** **No**

Name of Data Manager informed: _____ Date Informed:_____

Location in –80C freezer **UC 0 -**

Approximate size and number of tissue: _____

Notes:

Questions or Problems? ***Please contact:***

Dr. Rifat Hasina, University of Chicago, 5841 S Maryland, MC 3083, Chicago, IL 60637

Phone ***773-834-9814 or 773-702-0119*****, Pager** ***773-753-1880-9747*** **email:** ***rhasina@bsd.uchicago.edu***

SHIPPING DIRECTIONS

All shipments must contain a completed Sample Identification form.

Prior to shipment please email **both** of the following persons the FedEX bill number:

Rifat Hasina: RHASINA@BSD.UCHICAGO.EDU
Shannon Delaney: SDELANEY@MEDICINE.BSD.UCHICAGO.EDU

Tissue Samples need to be shipped on **dry ice**; may be batched at institution and shipped with Plasma samples to the below address:

Dr. Rifat Hasina
c/o Dr. Mark Lingen
University of Chicago
FMI Dock/Lab Supply
5830 S. Ellis Ave
Room G-02
Chicago, IL 60637
Phone: 773-834-9814

Plasma Sample need to be shipped on **dry ice**; may be batched at institution and shipped with Tissue Samples to:

Dr. Rifat Hasina
c/o Dr. Mark Lingen
University of Chicago
FMI Dock/Lab Supply
5830 S. Ellis Ave
Room G-02
Chicago, IL 60637
Phone: 773-834-9814

***Purple Tubes** for DNA need to be sent on **ice packs** overnight to:

Dr. Rifat Hasina
c/o Dr. Mark Lingen
University of Chicago
FMI Dock/Lab Supply
5830 S. Ellis Ave
Room G-02
Chicago, IL 60637
Phone: 773-834-9814

* **Please draw purple tubes on Monday, Tuesday or Wednesday only.**