THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

A Phase I/II Study of Weekly Topotecan and Gefitinib in Patients with Platinum-Resistant Ovarian, Peritoneal, or Fallopian Tube Cancer 2003-0322

Core Protocol Information

Short Title	Weekly Topotecan and Iressa
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Full Title:	A Phase I/II Study of Weekly Topotecan and Gefitinib in Patients with Platinum-Resistant Ovarian, Peritoneal, or Fallopian Tube Cancer
Protocol Type:	Standard Protocol
Protocol Phase:	Phase I/Phase II
Version Status:	Activated -- Closed to new patient entry as of 01/11/2007
Version:	06
Submitted by:	Maria Jung--10/6/2005 1:29:40 PM
OPR Action:	Accepted by: Cimetra R. Cox -- 10/7/2005 8:29:27 AM

Which Committee will review this protocol?

(●) The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

1. To determine the dose limiting toxicity (DLT) and the maximum tolerated dose (MTD) weekly topotecan in combination with standard dose gefitinib in patients with relapsed, platinum-resistant, ovarian, peritoneal or fallopian tube cancers that are EGF-R positive (>/= 1+).
2. To determine the response rate and response duration in this patient population treated with the maximum tolerated dose (MTD) of topotecan administered on a weekly schedule in combination with standard dose gefitinib, given PO daily.

2.0 Background

Ovarian cancer is the leading cause of death from gynecologic malignancy and the fifth leading cause of cancer death in American women. An estimated 25,400 new cases are reported in the United States yearly, and approximately 14,300 women die annually from the disease. [1] Unfortunately, ovarian cancer often is detected only when it has spread throughout the peritoneal cavity. Despite aggressive surgical resection and adjunctive therapy, most patients die in a period of months from malnutrition and small bowel obstruction caused by intraperitoneal tumor. The term mullerian cancer refers to carcinomas arising from organs developmentally derived from mullerian duct epithelium. In this study we restrict the term to epithelial ovarian cancer, fallopian tube cancer and primary surface peritoneal adenocarcinoma. The commonly used staging and histology are similar. In fact in some cases of advanced carcinoma it is not possible to determine the origin of the carcinoma. Most importantly, the treatment is the same. Accordingly, the discussion of epithelial ovarian cancer applies to mullerian carcinoma in general.

A pivotal Gynecologic Oncology Group (GOG) trial published in 1996 introduced paclitaxel into front line therapy in combination with cisplatin. Women with pathologically verified stage III and IV ovarian cancer were included. All patients had sub-optimal tumor reductive surgery. This combination produced a 70% response rate with a progression-free survival of 18 months and a median survival of 38 months compared with a progression-free survival of 13 months and a median survival of 24 months with cisplatin and cyclophosphamide. [2] Carboplatin-based regimes have equivalent activity and are considered the current chemotherapeutic regimen of choice in advanced ovarian cancer. [3] Ovarian cancers are often (70-80%) responsive to platinum-based chemotherapy, most become resistant.

One of the major issues faced by investigators is the optimal treatment of patients with recurrent disease. The disease-free interval is the major predictor of response to second-line treatment or reinduction treatment with platinum agents. Patients may be classified as platinum-resistant (relapse within 6 months) and platinum-sensitive (relapse after 6 months). In a series by Markman et al. [4], the response rate to second-line cisplatinum/carboplatin ranged from 27% for patients with a cisplatin-free interval of 5-12 months to 59% for those with an interval longer than 24 months. Other studies have shown that re-treatment with carboplatin for patients with a disease-free interval less than 6 months will yield a response rate of approximately 13%. [5] Unfortunately, in spite of the best possible chemotherapy, the majority of patients treated will recur within 2 years of treatment and will go on to die of their disease.

Topotecan is a water soluble, semi-synthetic, analogue of camptothecin, and exerts its antitumor activity through its inhibition of topoisomerase-I. Topotecan has received FDA approval for the treatment of relapsed ovarian and small cell lung carcinomas. The dose and schedule of topotecan administration remains under active investigation.

Agents that target topoisomerase-I stabilize a covalent DNA topoisomerase complex, which leads to DNA cleavage. Topoisomerase is also important in DNA transcription and replication. [6] High levels of topoisomerase can be found in tumor tissue with low, as well as high, growth fractions. As the activity of topoisomerase inhibitors is in proportion to the level of the target enzyme, topotecan may be just as effective on slowly dividing tumors as more actively dividing tumors. [7]

Two groups have examined the concentration of topoisomerase I following administration of topotecan.

Using a 72 hour continuous infusion of topotecan, Hammond, et al. [8] demonstrated decreases in topoisomerase I to 40-60% of baseline in two of six patients on day three, with a return to baseline by day seven. When administered on a daily times five regimen, Murren, et al. [9] noted that topoisomerase levels were significantly decreased on days three and five (as compared to baseline) in 62% of 33 cycles of therapy administered. In thirteen patients in this study, seven (54%) demonstrated a greater than 20% decrease in topoisomerase I levels on day one of topotecan therapy. Weekly administration of topotecan may allow for maximal interaction with topoisomerase I and prevent down regulation of the enzyme as a cellular protective mechanism.

Various doses and schedules of topotecan administration have been studied. The FDA approved schedule of 1.5mg/m^2 daily times five every 21 days was developed from work by Rowinsky, et al. [10] where the dose limiting toxicity was determined to be noncummulative neutropenia. This five day regimen requires frequent office visits, and may require colony stimulating factors to mitigate the drug induced neutropenia.

Dose limiting neutropenia has also been noted 24 hour continuous infusion schedules (where the maximal tolerated dose was 10.5mg/m^2) [11] and 30 minute IV bolus infusion (where the maximal tolerated dose was 22.5mg/m^2) once every 21 days. [12] In these studies, neutropenia was non-cummulative and non-hematologic toxicities were mild.

Modifying the schedule of topotecan administration is an approach to resolution of the myelotoxicity issue that has been studied. A weekly schedule appears to be at least as well-tolerated, more convenient and efficacious as the daily x 5 schedule. [12] Homesley, et al, reported 4mg/m2/week as a safe well-tolerated dose of Topotecan in previously treated ovarian cancer patients. Responses were seen at doses as low as 2mg/m^2/week. [13,14]

The epidermal growth factor receptor (EGF-R) is expressed in many types of cancer. Fifty to 70% of epithelial ovarian can
Importantly, over-expression of EGFR has been correlated with poor prognosis features in many cases. While these tumor
chemosensitive to platinum based therapy, chemoresistance often develops. Clinical trials in other sites (lung, pancreas, h
cancers) have found that chemoresistance can be overcome in some patients by blocking the EGF-R. Using either an anti
tyrosine kinase inhibitor, such as gefitinib or tarceva. These agents have been combined with several different chemothera
including taxol, platinum and gemcitabine. The major toxicity is an acniform rash. Gefitinib also can cause diarrhea. None
effect on the chemotherapy toxicities.

Gefitinib (Iressa) is a potent and selective inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase. Activation of the tyrosine kinase catalyses autophoshorylation and subsequent phosphorylation of protein tyrosine residues, which then initiates a cellular signal transduction cascade. Selective Gefitinib inhibition of the EGFR tyrosine kinase results in interruption of mitogenic and anti-apoptotic signals responsible for cellular cancer processes such as proliferation, growth, metastases, angiogenesis, and responsiveness to chemotherapy or radiotherapy.

Preclinical evidence in ovarian cancer supports this concept for this site. Combined antisense to EGF-R with cisplatin in cell culture of ovarian cancer cell lines that express the EGF-R sensitized the cells the effects of cisplatin. In another study, combining an EGF-R tyrosine kinase inhibitor with either cisplatin or carboplatin in cell culture of an ovarian cancer cell line also enhanced chemotherapy activity.

Preclinical evidence also exists to support the combination of an EGF-R TK inhibitor with topotecan. Erlichman, et al, reported synergistic activity of SN38 (a camptothecin) or topotecan with CI1003, a tyrosine kinase inhibitor (not available for clinical trials) in glioblastoma and colon cancer cell lines. Their work found that the TK inhibitor increased the intracellular levels of the camptothecins by decreasing efflux of the drug from the cell.

Taken together, this information supports evaluating the combination of topotecan and an EGF-R antagonist in patients with recurrent ovarian cancer.

3.0 Background Drug Information

TOPOTECAN
Topotecan is an antineoplastic agent. It acts by inhibiting the enzyme topoisomerase I. Double strand DNA damage caused by topotecan cannot be easily repaired by mammalian cells.

DOSING INFORMATION: The usual dose of topotecan in patients with solid tumors is 1.5 milligrams/square meter/day (mg/m^2/day) as a 30-minute intravenous infusion for 5 days every three weeks. The drug has also been given in numerous prolonged infusion schedules (eg, 24 hrs, 21 days). Dose adjustments are indicated in moderate renal impairment.

PHARMACOKINETICS: Topotecan is absorbed orally, although most clinical studies have employed the intravenous route. In vivo, rapid conversion of topotecan (lactone) to the hydroxy acid occurs, although the reverse reaction appears minimal; no other metabolic pathways have been confirmed. The protein binding of total topotecan is approximately 35%, and the steady-state volume of distribution is approximately 90 liters/square meter (L/m(2)) with 30-minute daily infusions. The average urinary excretion of total topotecan is about 45% of the dose administered; total body clearance of topotecan (lactone) has ranged from 40 to 130 L/hour/m(2) with daily 30-minute infusions. Biliary excretion of topotecan may occur. With daily 30-minute infusions for 5 days, the elimination half-life of topotecan is 2 to 3 hours.

STORAGE AND STABILITY: Unopened vials of topotecan hydrochloride are stable prior to expiration date when stored in the original cartons between 20 and 25 degrees Celsius (68 to 77 degrees Fahrenheit) and protected from light. 2. While it is recommended that topotecan be used immediately after reconstitution, the reconstituted solution is stable for up to 24 hours when stored between 20 and 25 degrees Celsius (68 to 77 degrees Fahrenheit) in ambient light. Topotecan infusion solution 0.025 mg/mL and 0.05 mg/mL in 0.9% sodium chloride or 5% glucose was stable for 28 days (over 95% of original topotecan content) when refrigerated or stored at room temperature protected from light

CAUTIONS: Neutropenia is dose-limiting with all administration schedules of topotecan; thrombocytopenia and anemia have also been severe in some studies. Other adverse effects include alopecia, nausea and vomiting, diarrhea, mucositis, headache, fatigue, rash, liver enzyme abnormalities, microscopic hematuria, and proteinuria. Mucositis has been dose-limiting in leukemic patients but not in solid tumor patients. Neutropenic fever has been reported in up to 30% of patients receiving daily 30-minute topotecan infusions. Topotecan has not produced the hemorrhagic cystitis observed with its parent compound camptothecin.

CLINICAL APPLICATIONS: Topotecan is indicated for second-line treatment of refractory small-cell lung cancer or metastatic ovarian cancer, and has demonstrated variable antitumor efficacy in non-small cell lung cancer, prostate cancer, and colorectal cancer.

PREPARATION: Contents of each 4mg vial should be reconstituted with 4ml sterile water for injection, USP, or bacteriostatic water for injection, USP, yielding a l mg/ml solution of topotecan. Further dilution in dextrose 5% in water, or normal saline retains stability for 24 hours at room temperature.

ADMINISTRATION: The diluted solution may be infused via a peripheral or central vein over 30 minutes.

CONTRAINDICATIONS
Breast-feeding
Hypersensitivity to topotecan, irinotecan, or camptothecin
Neutrophil counts of less than 1500 cells/cubic millimeter
Pregnancy

PRECAUTIONS
Bone marrow suppression (mild-to-moderate)

Neutropenia is dose-limiting with all dose schedules
Extravasation associated with only mild local erythema and bruising
Hepatic dysfunction (topotecan may have hepatotoxic potential)
Prior chemotherapy/radiation (possibility of greater myelosuppression)
Renal impairment (dose reductions)

ADVERSE REACTIONS
HEMATOLOGIC EFFECTS: Neutropenia is the main dose-limiting toxicity of topotecan and has been severe in 60% of patients during the first course of treatment. Nadir neutrophil counts have occurred at a median of 11 days. Higher doses of topotecan can be administered with a short infusion every 3 weeks as compared with intermittent or prolonged infusions. THROMBOCYTOPENIA and ANEMIA are also observed, and may be dose-limiting. Anemia may occur in all patient groups with or without renal impairment.

CARDIOVASCULAR EFFECTS: Topotecan does not appear to produce significant cardiotoxic effects. Asymptomatic HYPOTENSION has been reported in up to 15% of patients treated with 30-minute infusions for 5 consecutive days. Deep-vein thrombosis was described in 1 of 20 non-small cell lung cancer patients during treatment with daily 30-minute infusions of topotecan for 5 days. However, other factors may have been contributory or causal.

CENTRAL NERVOUS SYSTEM EFFECTS: HEADACHE has been reported occasionally during or after infusions of topotecan. PERIPHERAL NEUROPATHY or PARESTHESIA has occurred rarely, although a causal relationship is uncertain

FATIGUE: Fatigue has been a frequent complaint with intravenous topotecan, occurring in 54% of patients receiving 21-day infusions, 40% receiving 24-hour infusions every 3 weeks, and up to 70% receiving 30-minute infusions for 5 days every 3 weeks.

ENDOCRINE/METABOLIC: Neutropenic FEVER has been reported in 4% to 33% of cancer patients receiving 30-minute infusions of topotecan for 5 days every 3 weeks. Fever on days of treatment (unrelated to infection) has also been reported with this regimen and with 24-hour continuous infusions. Fever began within minutes to three hours after the first dose of TOPOTECAN and resolved within 24 hours of the last dose. Infection was not documented in these cases. High temperatures ranged from 39.9 to 41.8 degrees Celsius

GASTROINTESTINAL: Nausea, vomiting, and diarrhea are relatively frequent adverse effects of intravenous topotecan in solid tumor patients, but are seldom severe; mucositis is generally infrequent. In patients with acute leukemia, however, mucositis is dose-limiting.

KIDNEY/GENITOURINARY: Occasional increases in serum creatinine, PROTEINURIA, and HEMATURIA have been reported

SKIN: Alopecia has occurred with variable frequency (only rarely to up to 70%) in cancer patients receiving daily 30-minute infusions of topotecan for 5 days every 3 weeks; total hair loss has been reported occasionally. SKIN RASH, typically maculopapular involving the trunk, scalp, and extremities, has been observed in 17% to 25% of cancer patients receiving daily short infusions of topotecan for 5 days every 3 to 4 weeks. Topotecan-induced skin rashes during daily 5-day regimens or 5-day continuous infusion regimens have typically appeared between days 4 and 8, with maximal symptoms around day 10; resolution typically occurs by day 15. Skin rashes have not limited therapy with topotecan.

SEPSIS: Sepsis or FEBRILE NEUTROPENIA has been attributed to topotecan use in 23% of patients; sepsis was fatal in 1%.

DRUG SUPPLY: Commercially available from GalxoSmithKline, Brentford, Middlesex, TW8 9GS

GEFITINIB
Gefitinib is a selective epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor.

DOSING INFORMATION: Given orally. Optimal doses/schedules for the treatment of solid tumors have not been established. The most common dose in available clinical studies has been 250 or 500 milligrams (mg) once daily, alone or combined with cytotoxic agents.

Tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each bottle will contain 100 tablets of a single formulation. The tablets will be dispensed to the patient as a 3-month supply in the bottle provided by AstraZeneca.

Each bottle will be labeled with the statement: "Caution: New Drug - Limited by Federal (or USA) Law to Investigational Use". Instructions stating that the tablets should be taken orally “as directed by your doctor” will be included. Information on the label will indicate the identity and quantity of tablets and storage conditions. There will be blank lines for trial number, patient number, center number, and date dispensed; this information should be recorded by the investigator at the time the bottle is dispensed.

Gefitinib treatment will be taken once a day, every day about the same time. It can be taken with or without food. If the subject forgets to take a dose, they should take the last missed dose as soon as they remember, as long as it is at least 12 hours before the next dose is due.

PHARMACOKINETICS: Peak plasma levels of gefitinib occur 3 to 7 hours following oral administration; a dose of at least 100 mg daily maintains plasma levels above those required in vitro for inhibition of EGF-R kinase, although clinical correlations are lacking. Only small amounts of an oral dose appear unchanged in the urine (less than 1%); biliary excretion appears significant. An elimination half-life 26 to 49 hours has been reported (single or repeat oral dosing).

CAUTIONS: Gefitinib has been generally well-tolerated in cancer patients. Predominant adverse effects are an acne-like skin rash, diarrhea, nausea, vomiting, and mild or moderate myelosuppression.

CLINICAL APPLICATIONS: Once-daily oral gefitinib has exhibited antitumor efficacy in several tumor-types expressing or overexpressing EGF-R, including non-small
cell lung cancer. Results of larger clinical trials are required to address its place in therapy.

CONTRAINDICATIONS: Prior hypersensitivity

PRECAUTIONS: Hepatic insufficiency (pharmacokinetic data are unavailable (potential need for dose adjustment); gefitinib has exhibited hepatotoxic potential; close monitoring of ALT and AST is indicated)
Gastrointestinal disorders (diarrhea is common during gefitinib therapy)
Myelosuppression (potential exacerbation)
Bacterial/viral infection (potential exacerbation)
Pregnancy (animal/human data lacking)
Breastfeeding period (animal/human data lacking)

EFFICACY:
In two Phase II randomized trials (IDEAL 1 and 2), pretreated non-small-cell lung cancer (NSCLC) patients received Gefitinib 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 ³ 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 Gefitinib, respectively. Symptom improvement, measured by the LCS component of the FACT-L and lasting at least 4 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 gefitinib 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 gefitinib 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.

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 gefitinib 250 mg daily, gefitinib 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 gefitinib, did not demonstrate any increase in tumor response rates, time to progression, or overall survival beyond that of chemotherapy alone.

TOLERABILITY:
Patients given Gefitinib 250 mg/day (or similar doses) frequently had drug-related gastrointestinal (GI) disturbances (mainly diarrhea; sometimes associated with dehydration) and skin reactions (rash, acne, dry skin, and pruritus). The majority of drug-related adverse events are mild and non-cumulative, and rarely lead to withdrawal of Gefitinib 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 Gefitinib.

SIDE EFFECTS:
HEMATOLOGIC EFFECTS: ANEMIA (grade 1) has been relatively common in phase I/II studies. NEUTROPENIA and decreases in platelet counts have also been reported with variable frequency.
CENTRAL NERVOUS SYSTEM EFFECTS: FATIGUE has been described by some cancer patients during gefitinib therapy, although this is more likely related to the disease state.
GASTROINTESTINAL EFFECTS: DIARRHEA, NAUSEA, and VOMITING have been relatively common during therapy, occurring in 17% to 45%, 10% to 25%, and 10% to 22% of patients, respectively, in phase I/II studies (various doses). Diarrhea (grade 3) has been dose-limiting, usually at 700 mg daily. Anorexia has occurred in some patients.
HEPATOTOXICITY: Increases in transaminases and alkaline phosphatase have been reported occasionally; some transaminase elevations reached grade 3 and were dose-limiting. Hepatic effects have been reversible. Recent preclinical findings following preliminary results from a carcinogenicity study (Study No. 455921, AstraZeneca Reference No. TC2577) in rats. The results have identified an increased incidence of benign liver tumors and mesenteric lymph node hemangiosarcomas in rats treated with gefitinib, which are suggestive of a possible association with gefitinib treatment. There was no evidence that either the benign liver cell tumor and mesenteric lymph node hemangiosarcomas were the cause of death of any animal on this study and the majority of findings were at end of life examinations.
OCULAR EFFECTS: In patients participating in other trials and receiving gefitinib therapy, there were infrequent reports of reversible corneal erosion, sometimes in association with aberrant eyelash growth. In the event of a patient developing any eye symptoms, patients should be advised to seek medical advice promptly (consultation with an optometrist or ophthalmologist is advised).
DERMATOLOGIC EFFECTS: A characteristic skin RASH has accompanied gefitinib therapy in up to 80% of cancer patients in phase I/II studies, and is the most common adverse effect. Rashes typically

consist of pustular or acne-like lesions with occasional erythema/pruritus, or dry skin; they are usually located on the face, but involve the upper torso at higher doses (eg, 400 or 500 mg daily). Skin rashes are grade 1/2 in severity in most instances, although they have occasionally reached grade 3, requiring withdrawal of therapy. Rashes resolve rapidly upon cessation of treatment.
PULMONARY EFFECTS:To date, Gefitinib has been administered to over 50,000 people worldwide. Interstitial lung disease in patients treated with Gefitinib is uncommon, with a worldwide frequency of less than 1%, which is comparable to that reported with other lung cancer therapies. Interstitial lung disease had a fatal outcome, whether deemed Gefitinib related or not, in approximately 0.24% in this medically complex group of over 50,000 patients receiving Gefitinib. 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 +/- Gefitinib or carboplatin and paclitaxel +/- Gefitinib. Interstitial lung disease (ILD), including interstitial pneumonitis, is a common complication of lung diseases including advanced lung cancer, regardless of treatment. It has been widely observed in clinical trials in which chemotherapy and/or radiotherapy has been used for the treatment of advanced lung cancer. Interstitial Lung Disease, which may be acute in onset, has been observed uncommonly in patients treated with Gefitinib. These patients usually present with a fairly acute onset of dyspnea sometimes associated with cough or low grade fever. This may become quite severe within a short period of time and usually results in hospitalization. Radiological investigations, often including CT scan, frequently show pulmonary infiltrates or interstitial shadowing with ground glass appearance. There is often respiratory distress with arterial oxygen desaturation. Cultures are frequently negative for bacterial growth. In a number of cases, the event has responded to steroid therapy but this is not always so and a significant number of cases have had a fatal outcome.

DRUG SUPPLY: AstraZeneca will supply gefitinib to the investigator as brown, film-coated round shaped 250mg tablets for use as follows: daily po x28 days in conjunction with intravenous topotecan on days 1, 8 and 15.

LABELING: Each carton of study material will have an investigational-use label permanently affixed to the outside, stating that the drug is for clinical study use only and should be kept out of reach of children. Instructions stating that the tablets should be taken as a single dose orally at the same time in the morning will be included.

STORAGE: All investigational products must be kept in a secure place under appropriate storage Conditions. For US centers, all study treatment will be stored in a lockable storage area, between 20-25°C (68-77°F).

ACCOUNTABILITY**:** It is the investigator's responsibility to establish a system for handling study treatments, including investigational products, so as to ensure that:

- Deliveries of such products from AstraZeneca 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
- Study treatments are handled and stored safely and properly
- The drug is to be prescribed only by the investigator or sub-investigators named in Form FDA-1572
- Study treatments are dispensed only to study subjects in accordance with the protocol
- Subjects must return all unused medication and empty containers to the investigator
- All unused gefitinib 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.

GUIDELINE FOR DISPENSING WHOLE GEFITINIB TABLETS: Gefitinib tablets cannot be crushed.

Experimentation has shown that gefitinib tablets will break up into a fine dispersion within 5 to 7 minutes when they are dropped whole into lukewarm water. There are felt to be no risks to the chemical stability of gefitinib providing this process occurs immediately prior to administration by the subject. The only risk is felt to be concerned with ensuring delivery of the whole dose, as a certain amount of deposition of powder on the surfaces of the container will occur while the container is being emptied.
Although bio-equivalence has not yet been formally tested in clinical trials the following procedure is recommended for administering dispersed whole tablets to subjects who are unable to swallow the tablets:

Drop the required number of gefitinib tablets into an appropriate container (ideally glass to help confirm removal of all the dispersed material) containing approximately 1-2 ounces (or 50 mls) of lukewarm water.

Stir the liquid occasionally to ensure complete break-up of the tablet(s). When the tablet has broken up into a fine dispersion (approximately 5 minutes) it can be administered to or by the subject. Administration should occur immediately after dispersion is complete.

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 subject.

Since no data are available concerning the stability of the dispersed tablet, administration to the subject should occur immediately after dispersion is complete.

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.

4.0 Patient Eligibility

Inclusion Criteria

1. Women with platinum-resistant, histologically confirmed epithelial ovarian, fallopian tube or peritoneal cancer. Resistance is defined as:
   Progression of disease during platinum chemotherapy, or
   Progression of disease within 6 months of completing platinum chemotherapy
   Failure to achieve a complete response, with persistent macroscopic disease, after an adequate trial of primary therapy.
2. EGF-R expression must be positive (e.g., 1+ or greater) (See Appendix G. Biomarker Collection and Analysis).
3. Patients with a known hypersensitivity to platinum compounds, who have failed a desensitization regimen, or in the opinion of the investigator, are not good candidates for desensitization, are eligible.
4. Patients must have measurable disease.
5. Unlimited number of prior chemotherapy regimens are allowed.
6. Zubrod performance status $\leq$ 2.
7. Patients must have adequate hepatic, renal, and bone marrow function, defined as serum creatinine $\leq$ 2 mg/dl (estimated creatinine clearance 50 ml/min); total bilirubin $\leq$ 2.0 X the upper limit of normal (ULN); alanine aminotransferase (ALT) $\leq$ 2X ULN; white blood count (WBC) $\geq$ 3,000/mm^3; absolute neutrophil count (ANC) $\geq$ 1,500/mm^3; platelets $\geq$ 100,000/mm^3.
8. At least three weeks must have elapsed from completion of chemotherapy or radiation therapy. Patients may have been on hormone therapy.
9. At least 30 days must have elapsed from completion of treatment with a non-approved or investigational drug.
10. Patients must sign an informed consent indicating that they are aware of the investigational nature of the study, in keeping with the policies of the hospital. The only approved consent is appended to this protocol.
11. Women of childbearing potential must be willing to practice acceptable methods of birth control to

prevent pregnancy.

Exclusion Criteria

1. Patients with borderline or low malignant potential tumors are not eligible.
2. Patients who have had prior therapy with topoisomerase I inhibitors.
3. Patients who are pregnant or lactating.
4. Concurrent chemotherapy, radiation therapy, or surgery (excluding palliative radiation).
5. Concurrent, uncontrolled, medical or psychiatric disorders.
6. Patients with an active infection.
7. Patients with a known hypersensitivity to topotecan or gefitinib.
8. Patients with severe cardiovascular disease (i.e. arrhythmias requiring chronic treatment or congestive heart failure) (NYHA classification III or IV).
9. History of other malignancy (except nonmelanoma skin cancer or carcinoma in situ of the cervix), unless in complete remission and off all therapy for that disease for a minimum of 5 years.
10. Patients with overt psychosis or mental disability or otherwise incompetent to give informed consent.
11. Patients who have had prior anti-EGFR therapy (i.e. Tarceva, Centuximab).
12. Evidence of any other significant clinical disorder or laboratory finding that makes it undesirable for the subject to participate in the trial.
13. Concomitant use of phenytoin, carbamazepine, rifampicin, barbiturates, or St. John's Wort.
14. Any evidence of clinically active interstitial lung disease (patient with chronic stable radiograp

5.0 Treatment Plan

This is a prospective, Phase I/II, open label, dose escalation study designed to evaluate the maximum tolerated dose of topotecan administered in combination with standard dose gefitinib to patients with histologically confirmed, platinum resistant ovarian, fallopian tube, or peritoneal cancer. Response rate and response duration in this patient population will also be studied.

The Phase I portion of the trial will use the standard dose of gefitinib of 250 mg PO QD with an escalation of the topotecan dose. Topotecan 2.0, 3.0, or 4.0 mg/m^2 will be given i.v. on days 1, 8 and 15 of a 28 day cycle. A conventional 3 + 3 algorithm will be used. The 2mg/m^2 dose of topotecan was chosen as a starting dose because there are reported responses to this level when it has been used as a single agent on this schedule. [12]

Cohort 1: Topotecan 2.0mg/m^2 i.v. over 30 min on days 1, 8 and 15 and Gefitinib 250mg p.o. QD x28 days
Cohort 2: Topotecan 3.0mg/m^2 i.v. over 30 min on days 1, 8 and 15 and Gefitinib 250mg p.o. QD x28 days
Cohort 3: Topotecan 4.0mg/m^2 i.v. over 30 min on days 1, 8 and 15 and Gefitinib 250mg p.o. QD x28 days

Definitions:

1. DLT (dose-limiting toxicity): Any Grade 4 hematological toxicity and any $\geq$ Grade 3, treatment related, non-hematologic toxicity (except Grade 3 fatigue lasting < 7days).
2. MTD (maximum tolerated dose): The highest dose level in which we have treated 6 patients with at most 1 experiencing the DLT.

Analysis of the Phase I data will be conducted and the results submitted to the Institutional Review Board prior to proceeding to the Phase II portion of the study.

Phase II

The patients treated at the MTD in the Phase I part of the study will be the first 6 patients in this part of the trial. We will accrue a minimum of 10 patients and a maximum of 40 patients at a rate of 2 patients per month. The primary outcome for this trial is response (CR + PR) rate, which is evaluated at the completion of 8 weeks of treatment.

Dose modifications:
Dose modifications for hematologic and nonhematologic toxicity will be based upon the worst toxicity observed during the previous treatment cycle. The minimum infusion dose of topotecan is 2.0 mg/m^2 /week. After recovery, standard dose adjustments for toxicity should be applied as follows:

1. For ≥ Grade 4 hematologic and ≥ Grade 3, treatment related, nonhematologic toxicity (except fatigue as noted above) the weekly infusion dose of topotecan will be reduced one dose level.
2. For patients experiencing neutropenic complications (febrile neutropenia, documented active infection during neutropenia, etc.), the dose will be decreased two levels. Patients who require dose reductions below the 2.0mg/m^2 dose level will be removed from study.

There will be no dose escalations.

Duration of therapy: Therapy should be continued until progression of disease, patient refusal, or 6 months following documentation of a complete or partial response.

Growth Factors:
Routine prophylactic use of G-CSF, erythropoetin or platelets is not permitted. However, therapeutic use in patients with serious neutropenic, anemic, or thrombocytopenic complications such as sepsis or bleeding may be considered at the investigator's discretion.

Other considerations regarding dose and schedule:
1. No dose shall be given until the absolute neutrophil count is greater than 1,500 and platelet count greater than 100,000.
2. If these criteria are not met for a weekly infusion, the infusion for that week should be eliminated without delay or rescheduling.
3. Failure to recover within two weeks will be cause to remove the patient from study.
4. If these criteria are not met for a new cycle, the cycle will be delayed until recovery for a maximum of two weeks.
5. Gefitinib treatment will be taken once a day, every day about the same time. It can be taken with or without food. If the subject forgets to take a dose, they should take the last missed dose as soon as they remember, as long as it is at least 12 hours before the next dose is due.
6. Subjects must return all unused medication and empty containers to the investigator.

Other concomitant treatment
If surgery is considered necessary for the patient, whenever possible, at least 7 days should elapse after the last dose of Gefitinib before surgery is performed. Treatment may be restarted after adequate wound healing.

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

Concomitant use of CYP3A4 inhibitors, e.g., itraconazole, may result in increased levels of Gefitinib. This exposure may be clinically relevant since adverse experiences are related to dose and exposure.

Co-administration of drugs that cause significant sustained elevations in gastric pH 5 may reduce plasma concentrations of Gefitinib and therefore may reduce efficacy.

Further evaluation of International Normalized Ratio (INR) elevations and/or bleeding events have been

reported in some subjects taking warfarin while also taking Gefitinib. Subjects taking warfarin (Coumadin) should be monitored regularly for changes in their prothrombin time (PT) or INR.

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

The institution of iv and/or oral administration of biphosphonates during the course of the study, if initiated specifically for symptomatic bone metastases, is not permitted.

Other medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the investigator(s). The administration of all concurrent medication must be documented.

Management of skin toxicity
Subjects with poorly tolerated skin toxicity may be successfully managed by providing a brief (up to 14 days) interruption of Gefitinib; the daily dose of Gefitinib should then be reinstated. However, the rash may improve without the need for interrupting therapy with Gefitinib.

A variety of agents can be used to manage skin rashes. These include mild to moderate strength steroid creams, either 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 Gefitinib. Most commonly, a pustular rash has been observed, which frequently improves even though the same dose of Gefitinib 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 Gefitinib mechanism of action. Oral steroids are also strongly discouraged.

Management of GI toxicity
If GI toxicity is not appropriately managed this may be associated with a development of dehydration.

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

Diarrhea
Diarrhea has been successfully managed with anti-diarrheal agents such as loperamide.
Grade 1-2 diarrhea: No specific supportive care is usually needed or indicated`

Grade 3 or 4 diarrhea: If this occurs, and immediate supportive care measures begun, Gefitinib should be discontinued for up to a maximum of 14 days until resolution, or the diarrhea has decreased in severity to grade 1.

Grade 2, 3, or 4 diarrhea with rapidly or precipitously declining absolute neutrophil count (ANC), or at same time as neutropenia, grade 3 or 4: Gefitinib should be discontinued for up to a maximum of 14 days until the ANC is 0.5 x 109/L, or resolution of the diarrhea, or the diarrhea has decreased in severity to grade 1.

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 Gefitinib, the investigator must report it to the sponsor.

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 (Wadler 1998).

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 is moderately effective. Clonidine, non-steroidal 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 three times daily, with a maximum-tolerated dose of 2000 micrograms three times daily in a 5-day regimen.

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

Other Toxicity
For any other grade 3 or 4 toxicity or any clinically significant lower grade toxicity treatment with gefitinib should be interrupted for a maximum of 14 days until the patient recovers completely or the toxicity reverts to grade 1 or to baseline grade.

6.0 Pretreatment evaluation

1. Medical history to include review of systems and concurrent therapies, performance status, including prior cancer history, cancer therapy and residual toxicities from prior therapies.
2. All medications taken within 3 weeks prior to the start of therapy and all concomitant therapy taken during the study (with reasons for therapy use) will be recorded in the medical record.
3. Complete physical examination including vital signs, weight, and pelvic examination.
4. Pretreatment laboratory tests:
   Hematology: CBC, differential and platelet count.
   Coagulation panel: PT and INR for patients on therapeutic coumadin.
   Chemistry: Albumin, total protein, BUN, creatinine, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT, CA-125 and electrolytes. Serum pregnancy test for women of childbearing potential.
5. Pretreatment exams:
   Baseline EKG
   Chest x-ray
   CT of the abdomen and pelvis and/or any other pertinent radiologic evaluation to document disease status. Radiologic exams must be done within 4 weeks of starting therapy

7.0 Evaluation During Study

1. Weekly with CBC, platelet count and differential while on study.
2. CBC, platelet count and differential, chemistries including albumin, total protein, BUN, creatinine, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), LDH, electrolytes, and CA-125 shall be performed prior to each course or as frequently as needed to define drug toxicity.
3. Interim history and physical exam with performance status and weight prior to each course.
4. Assessment of clinically measurable disease (if present) will be recorded before each course.

Imaging studies will be done post cycle 2 and 4 and then every 3rd cycle and at the completion of treatment.

5. At the time a patient is discontinued from protocol participation, medical history, physical exam, performance status, weight, hematology and chemistry (as noted above) and response will be documented. Any ongoing adverse events deemed treatment-related will be followed until resolution.

8.0 Criteria for Response

Assessment of Tumor Response (RECIST):

Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest dimension to be recorded). Each lesion must be at least >/= 20mm when measured by conventional techniques, including palpation and plain x-ray. Lesions must be at least twice the cut thickness when measured by MRI or spiral CT. Ultrasound will not be used to define measurable disease.

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

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

All baseline evaluations of disease status should be performed as close as possible to the start of treatment and never more than 4 weeks before the beginning of therapy.

Best Response:
Measurement of the longest dimension of each lesion size is required for follow-up. Change in the sum of these dimensions affords some estimate of change in tumor size and hence therapeutic efficacy.

All disease must be assessed using the same technique as baseline. Reporting of these changes in an individual case should be in terms of the best response achieved by that case since entering the study.

Complete Response (CR):
Disappearance of all target and non-target lesions and no evidence of new lesions documented by two disease assessments at least 4 weeks apart. Normalization of CA-125, if elevated at baseline, is required.

Partial Response (PR):
At least 30% decrease in sum of the longest dimensions (LD) of all target measurable lesions taking as reference the baseline sum of LD. There can be no unequivocal progression of non-target lesions and no new lesions. Documentation by two disease assessments at least 4 weeks apart is required. In the case where the ONLY target lesion is a solitary pelvic mass measured by physical examination, which is not radiographically measurable, a 50% decrease in the LD is required.

Increasing Disease (defined as ANY of the following):
At least a 20% increase in the sum of LD of target lesions taking as reference the smallest sum LD or the appearance of new lesions within 8 weeks of study entry. Unequivocal progression on existing non-target lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating physician within 8 weeks of study entry is also considered increasing disease. In the case where

the only target lesion is the solitary pelvic mass measured by physical examination, which is not radiographically measurable, a 50% increase is the LD is required. Death due to disease without prior objective documentation of progression. Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression.

Stable disease: Any condition not meeting the above criteria.

Response Duration: Measured from the time of response (not the beginning of treatment) until there is evidence of progressive disease. Time to treatment failure will also be measured in responding patients.

Survival Duration: The survival of patients will be measured from protocol entry.

9.0 Criteria for Removal from the Study

1. The patient has a serious or life-threatening adverse event.
2. Failure to recover from all treatment-related toxicities after 2 week treatment delay.
3. The investigator feels that it is in the best interest of the patient.
4. The patient wishes to withdraw.
5. The patient fails to comply with the dosing, evaluations or other requirements of the study.
6. Disease progression.
7. The development of severe or life threatening hypersensitivity reaction to either topotecan or gefitinib.
8. All patients will be followed for a minimum of one month from the last dose of study drug.
9. Any patient who misses 14 or more days of gefitinib in one cycle will be removed from the study, regardless of the reason.

10.0 Statistical Considerations

Phase I

The Phase I portion of the trial will use the standard dose of gefitinib of 250 mg PO QD with an escalation of the topotecan dose. Topotecan 2.0, 3.0, or 4.0 mg/m^2 will be given i.v. on days 1, 8 and 15 of a 28 day cycle. A conventional 3 + 3 algorithm will be used and is described below:

- enroll 3 patients at the lowest dose level
- proceed to the next higher dose level with a cohort of 3 patients until at least 1 patient experiences the dose-limiting toxicity (DLT)
- if only 1 of 3 patients experiences the DLT at a given dose level, enter 3 additional patients at the current dose level
- if only 1 of 6 patients experiences the DLT at a given dose level, proceed to the next higher dose level with a cohort of 3 patients
- if at least 2 of 3 or 2 of 6 patients experience the DLT at a given dose level, then the MTD has been exceeded
- once the DLT has been exceeded, treat another 3 patients at the previous dose level if there were only 3 patients treated at that dose level

The DLT (dose-limiting toxicity) is defined as any Grade 4 hematological toxicity and any $\geq$ Grade 3 non-hematologic toxicity.

The MTD (maximum tolerated dose) is the highest dose level in which we have treated 6 patients with at most 1 experiencing the DLT.

Since there are only 3 doses to be considered, and since we will have only a maximum of 6 patients at the MTD, the maximum number of patients enrolled in this phase I part of the trial will be 18.

Phase II

This is a phase II activity trial. We will accrue a minimum of 10 patients and a maximum of 40 patients at a rate of 2 patients per month. The primary outcome for this trial is response (CR + PR) rate, which is evaluated within 8 weeks of treatment. Our target response rate is 20%. We will monitor the response rate as patients accrue and are evaluated, and we will stop the trial if we have evidence that the target response rate cannot be met. The patients treated at the MTD in the Phase I part of the study will be the first 6 patients in this part of the trial.

We will stop the trial early if P (response rate $\geq$ 20% | data from the trial) < 0.10. That is, given the outcomes from the patients who have already been evaluated, if we determine that there is less than a 10% chance that the response rate is 20% or more, we will stop the trial. This decision rule gives the following stopping rule. We assume a uniform prior distribution for the response rate. Stop the trial if

[# of patients with response / # of patients evaluated] < 1/10, 2/17, 3/24, 4/31, 5/37

The operating characteristics of this study design are shown in the following table.

Response Rate (CR+PR)	Probability of Stopping Early	Sample Size (Percentile)		
		25th	50th	75th
5%	0.979	10	10	17
10%	0.784	10	17	37
15%	0.480	17	40	40
20%	0.238	40	40	40
25%	0.104	40	40	40
30%	0.044	40	40	40

11.0 Data Management

Protocol Compliance: The attending physician and oncology research nurse must see each patient prior to each cycle of treatment. All required interim and pretreatment data should be available in order to evaluate toxicities, assign grade and make a determination regarding continuing therapy.

Data Entry: Data must be entered into the Protocol Data Management System at the completion of each course of therapy. A brief explanation for required but missing data should be recorded as a comment.

Accuracy of Data Collection: The Study Chairman will be the final arbiter of response or toxicity should a difference of opinion exist.

12.0 Reporting Requirements

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for adverse event reporting. A copy of the CTCAE version 3.0 can be downloaded from the CTEP home page (http:/www.ctep.info.nih.gov/) and is appended to this protocol. Life-threatening toxicities should be reported immediately to the Study Chairman, who in turn must notify the IRB. In addition, serious adverse events (SAE) will be reported to the IRESSA Safety Representative (fax - 302-886-7483). Reporting of adverse reactions is in addition to and does not supplant the reporting of toxicities as part of the results of the clinical trial.

Reporting requirements are defined in Appendix A of this protocol.

Criteria for response and toxicity:

Adverse Event: Any unfavorable or unintended symptom, sign, or disease (including abnormal lab)

temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. Such effects can be intervention related, dose related, route related, patient related, caused by an interaction with another drug.

Serious Adverse Event: Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity – a substantial disruption of a person's ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Eliciting Adverse Event Information: Adverse events will be elicited at each clinic visit during participation in the study. Patients will be given a worksheet to record the occurrence of adverse events throughout the study. All adverse events which are directly observed and all adverse events which are spontaneously reported by the patient are to be documented by the investigator.

Grading/Rating Scale:

1. All adverse events reported during the study will be evaluated and graded on a scale of 0-5. The CTCAE version 3.0 will be used to determine the grade for all toxicities.
2. For any adverse events which are not listed in the CTCAE version 3.0 the following rating system will be used:

Non-NCI Adverse Event Grading Scale

Grade	Description
0	No adverse event (absent) or within normal limits
1	Mild adverse event (minor, no specific medical intervention, asymptomatic laboratory findings only, radiographic findings clinical relevance)
2	Moderate adverse event (minimal intervention, local intervention, non-invasive intervention [packing, cautery])
3	Severe and undesirable adverse event (significant symptoms requiring hospitalization or invasive intervention; transfusio interventional radiological procedure; therapeutic endoscopy or operation
4	Life threatening or disabling adverse event (complicated by acute, life threatening metabolic or cardiovascular complicat circulatory failure, hemmorhage, sepsis. Life-threatening physiologic consequences; need for intensive care or emergen procedure; emergent interventional radiological procedure therapeutic endoscopy or operation
5	Death related to adverse event

Relationship to Study Treatment: The investigator will use the following definitions to assess the relationship of the adverse event to the study treatment:

1. Definite: Adverse event is clearly related to the study treatment.
2. Probable: Adverse event is likely related to the study treatment.
3. Possible: Adverse event may be related to the study treatment.
4. Unlikely: Adverse event is doubtfully related to the study treatment.

5. Not Related: Adverse event is clearly not related to the study treatment.

13.0 Emergency procedures

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.

Procedures in case of overdose
There is currently no known antidote for gefitinib. The treatment of AEs associated with overdose should be supportive for the underlying adverse symptoms. To date, no subject has experienced an overdose with gefitinib.

Doses of study treatment in excess of that specified in the clinical study protocol are considered to be an overdose. Overdose, with or without associated symptoms should be handled in the same way as a SAE and sent to AstraZeneca Drug Safety. Signs or symptoms of an overdose that meet the criteria of serious should be reported as a SAE in the appropriate timeframes and be documented as clinical sequelae to an overdose.

Procedures in case of pregnancy
Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive treatment. All reports of congenital abnormalities/birth defects are SAEs. Elective terminations for medical reasons, and any serious complications of pregnancy (including spontaneous miscarriage) should be reported as SAEs. Elective abortions without complications should not be handled as AEs.

Pregnancy should be reported to AstraZeneca as soon as possible after it has been identified that the subject (or subject's partner) received an AstraZeneca product during pregnancy. It should be sent to AstraZeneca, Drug Safety within 45 days. The outcome of the pregnancy must be sent to AstraZeneca, Drug Safety within AE or SAE timeframes if appropriate. Reports of normal outcomes should be sent within 45days.

The time period for collecting information on the occurrence of a pregnancy is from first administration of study treatment up to and including the follow up period.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality/birth defects) must be followed up and documented (on the pregnancy outcome form) even if the subject was discontinued from the study.

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