A PHASE I/II STUDY OF AN ORAL EPIDERMAL GROWTH FACTOR RECEPTOR
TYROSINE KINASE INHIBITOR (EGFR-TKI), ZD 1839 (IRESSA), [NSC# 715055] WITH
RADIATION THERAPY IN GLIOBLASTOMA MULTIFORME

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A PHASE I/II STUDY OF AN ORAL EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE KINASE INHIBITOR (EGFR-TKI), ZD 1839 (IRESSA), [NSC# 715055] WITH RADIATION THERAPY IN GLIOBLASTOMA MULTIFORME

SCHEMA

PHASE I COMPONENT

<table>
<thead>
<tr>
<th>S</th>
<th>ZD1839 daily dose during RT</th>
<th>Radiotherapy: 2.0 Gy daily, 5 days/week for 6 weeks for a total dose of 60 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>Arm 1: 250 mg</td>
<td>Followed by 500 mg ZD 1839 daily for 18 months or until evidence of disease progression.</td>
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<td>Arm 2: 500 mg</td>
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<td>Arm 3: 750 mg</td>
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PHASE II COMPONENT

<table>
<thead>
<tr>
<th>S</th>
<th>ZD1839 daily dose during RT</th>
<th>Radiotherapy: 2.0 Gy daily, 5 days/week for 6 weeks for a total dose of 60 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>Arm 6: MTD dose from Phase I</td>
<td>Followed by 500 mg ZD 1839 daily for 18 months or until evidence of disease progression.</td>
</tr>
<tr>
<td></td>
<td>Arm 7: MTD dose from Phase I</td>
<td></td>
</tr>
</tbody>
</table>

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1 See Section 13.3.2 for dose escalation details.
2 ZD 1839 should begin one week prior to radiotherapy (See Section 7.1.1).
3 Patients taking enzyme-inducing anticonvulsant drugs (See Section 7.1.1) at the time of registration
4 With dose escalation to 750 mg permitted, if tolerated, in the EIACD patient population only

ELIGIBILITY (See Section 3.0 for details) [11/15/02]

- Histopathologically confirmed glioblastoma multiforme (with areas of necrosis)
- The tumor must be supratentorial in location

(continued on next page)
- Radiotherapy must begin ≤ five weeks after surgery, and Iressa must begin one week prior to radiotherapy.
- Estimated survival of at least 8 weeks
- Zubrod Performance Scale of 0-1
- Hgb ≥ 10 gm, absolute neutrophil count ≥ 1500, platelets ≥ 100,000, BUN ≤ 25, Creatinine ≤ 1.5, Bilirubin ≤ 2.0, SGPT or SGOT ≤ 2 x normal range
- No recurrent or multifocal malignant gliomas
- No prior radiation therapy to head or neck area (except for T1 glottic tumors)
- No prior chemotherapy or radiosensitizer for cancers of head or neck region
- No active connective tissue disorders, such as lupus or scleroderma
- No major medical illnesses or psychiatric impairments
- No malignancy (within the past three years) except non-melanomatous skin cancer or carcinoma in situ of the cervix or bladder
- Patients with known Acquired Immune Deficiency (AIDS) are excluded, as regimens with ZD 1839 may pose a safety risk related to excess toxicity or interference with anti-viral effectiveness.
- Patients with known multiple sclerosis are excluded, as these patients may have decreased tolerance for radiation therapy to the brain.
- No pregnant or lactating women, due to possible adverse effects on the developing fetus or infant due to study drug.
- Patients cannot be treated on any other clinical protocols within 30 days prior to study entry or during participation in the study.
- Patients must consent to submission of their tissue/serum.
- Patients must sign study-specific consent form prior to registration.

**Required Sample Size:**

**Phase I:**
- maximum of 18 EIACD patients and 12 non-EIACD patients

**Phase II:** 140

**Study Total 140-158**
1. Does the patient have histologically confirmed supratentorial glioblastoma multiforme? 

2. Has the patient recovered from the effects of surgery, post-operative infection, or other complications? 

3. Has a diagnostic contrast enhanced MRI or CT of the head been performed pre-operatively? 

4. Has a diagnostic contrast enhanced MRI or CT of the head been performed post-operatively? 
   - If no, did the patient have only a stereotactic biopsy performed? 

5. Do the patient’s laboratory values meet the criteria in Section 3.1.9? 

6. Has the patient received any prior radiotherapy to the head and neck (T1 glottic tumors excluded) or any chemotherapy or radiosensitizer for any reason? 

7. Is the patient known to have Acquired Immune Deficiency Syndrome? 

8. Has the patient had prior malignancies, except for non-melanomatus skin cancers, or carcinoma in-situ of uterus, cervix or bladder? 
   - If yes, has the patient been disease free for ≥ 3 years? 

9. Does the patient have any detected metastases below the tentorium or beyond the cranial vault? 

10. Is the patient’s Zubrod 0-1? 

11. Does the patient have an estimated survival of at least 8 weeks? 

12. Does the patient have any major medical or psychiatric illness which, in the investigator’s opinion, will prevent administration or completion of the protocol therapy? 

13. Is the patient known to have multiple sclerosis? 

14. Is the patient pregnant or lactating? 

15. Has the patient been treated on any other clinical protocols within 30 days prior to study entry or is treatment on other protocols planned during participation in the study? 

16. Has the patient consented to submission of his/her tissue/serum? 

17. Will radiotherapy begin ≤ 5 weeks after surgery, and Iressa begin 1 week prior to radiotherapy?

(continued on next page)
The following questions will be asked at Study Registration:

1. Name of institutional person registering this case?

2. Has the Eligibility Checklist (above) been completed?

3. Is the patient eligible for this study?

4. Date the study-specific Consent Form was signed? (must be prior to study entry)

5. Patient’s Initials (Last, First) [Initials only effective 2/2002]

6. Verifying Physician

7. Patient’s ID Number

8. Date of Birth

9. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)

10. Race

11. Gender

12. Patient’s Country of Residence

13. Zip Code (U.S. Residents)

14. Patient’s Insurance Status

15. Will any component of the patient’s care be given at a military or VA facility?

16. Treatment Start Date

17. Medical Oncologist

18. Is the patient taking an enzyme-inducing anticonvulsant?

If yes, specify the anticonvulsant the patient is taking.

19. Will the patient receive IMRT?

20. Tissue/blood kept for cancer research?

21. Tissue/blood kept for medical research?

(continued on next page)
RTOG Institution # 
RTOG 0211  ELIGIBILITY CHECK (10/4/02)
Case #

___________(N/Y)  22.  Allow contact for future research?

___________(Y)  23.  Tissue/blood for research in current study?

______  24.  Treatment Assignment

The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by______________________________  Date  ___________________________
1.0 INTRODUCTION

1.1 Glioblastoma Multiforme (GBM) Prognosis

Results with current methods of treatment for GBM have been disappointing. The combination of surgical resection, radiation therapy, and chemotherapy produces a median survival of less than one year.\(^1,2\) Surgery and radiation have probably reached maximal effectiveness. Chemotherapy has the potential to improve survival, but significant increase has been marginal using either intravenous or intra-arterial administration of conventional agents.\(^1,2\)

1.2 GBM Molecular Biology

Astrocytomas, the most common primary human CNS tumor, are histopathologically classified into four increasing grades of malignancy (I-IV), which differ in their prognosis and molecular profiles. At least two molecular pathways have been proposed leading to the most malignant, and unfortunately, the most common grade IV astrocytoma, also known as or GBM, with a 9-12 month median survival rate.\(^3,7\) One group of “Primary GBMs,” usually presenting de-novo in the elderly, present with molecular aberrations involving amplifications of epidermal growth factor receptor (EGF-R) and loss of genetic material on chromosome 10.\(^8,10\) The prevalence of genetic changes associated with the lower grade astrocytomas (I/II) are much less in these primary GBMs, compared to the “Secondary GBMs,” which arise from progression of the lower grades to the more malignant forms (grade III-Anaplastic Astrocytomas (AA); IV-GBM), and are more common in younger GBM patients. For example, mutations and LOH at the p53 loci (17p) are observed in two-thirds of lower grade astrocytomas (grades I, II) but in only approximately one third of GBMs.\(^11,15\)

Both primary and secondary GBMs carry two molecular signatures which are common to GBMs and not found in lower grade astrocytomas. One is amplification of EGF-R on chromosome 7, found in about 40% of GBMs.\(^16,24\) The majority of these GBMs also harbor mutated EGF-Rs, the most common of which found in 17-25% of all GBMs is the constitutively activated EGF-RvIII.\(^25,38\) The second molecular signature is loss of the entire chromosome or several regions on chromosome 10, prevalent in 60-95% of all GBMs, with the PTEN/MMAC1 tumor suppressor gene (TSG) being at least one of relevant TSGs in that region in GBMs.\(^8,10\) Mutations in PTEN/MMAC1 are found in 25-30% of GBMs, though when examined at the level of protein expression, the gene it is absent in about 75% of the tumors.

1.3 Aberrant Expression and Activation of EGF-Rs in Malignant Astrocytomas

Analysis of several growth factors and their cognate receptor tyrosine kinases has led to the hypothesis that these factors contribute to the growth of astrocytomas.\(^6\) Inhibitors of these growth factor receptors, such as platelet derived growth factor receptors (PDGF-R), vascular endothelial growth factor receptors (VEGF-R) and EGF-R has demonstrated anti-tumor effect in experimental paradigms, and in the case of PDGF-R, led to a current phase II/III clinical trial. As mentioned above, amplification and mutations of EGF-R are a common molecular signature of GBMs\(^6,16-25\), with experimental evidence that inhibition of EGF-R leads to decreased astrocyte proliferation in vitro and in vivo.\(^6,26-29\) The most common mutant variant of EGF-R in GBMs is the truncated EGFRvIII (140kDa), found in approximately 17-25% of all GBMs.\(^20,29\) EGFRvIII results from variable intragenic deletions in the 5’ region of wt-EGFR involving exons 2-7, with subsequent coercive splicing that deletes 801 bases, a region that encodes amino acids\(^6,273\) of wt-EGFRs extracellular domain. This process results in a novel glycine splice site, with the C-terminal of the protein translated in frame. On a structural basis, EGFRvIII lacks most of the extracellular subdomain I and a considerable portion of subdomain II. Subdomain III is the major ligand-binding domain, while subdomains II and IV are homologous cysteine-rich domains involved in intramolecular interactions. Despite the physical presence of subdomain III, EGFRvIII has been shown to be incapable of binding EGF or TGF, though it is constitutively activated/phosphorylated. Another ~40% of GBMs (plus other cancers) also express EGFRvIII without gene amplification or intragenic deletions; hence, as many as two thirds of all GBMs express EGFRvIII at the protein level.

Expression of the constitutively activated EGF-RvIII in experimental paradigms has demonstrated that it provides both an in vitro and in vivo growth advantage; however, whether it is a relevant prognosticator in patients with GBMs is unclear. The molecular-clinical correlation studies in GBMs to date have examined amplification of wt-EGFR, with conflicting results with respect to
Work by Guha, et al.\textsuperscript{25} measuring expression of EGFRvIII in 16 GBMs by RT-PCR demonstrated the ability of EGFRvIII specific antibodies to detect those GBMs harboring this mutant EGF-R, and also, in this small cohort, that it was a negative prognosticator. Whether the molecular makeup of a GBM is composed of amplified and mutated EGF-Rs is not only of potential prognostic importance, but of potential therapeutic relevance. Small molecule inhibitors targeting EGF-R, or its tyrosine kinase activating enzyme, are an active area of drug discovery.

1.4 Receptor Tyrosine-Kinase Inhibitors as a Novel Class of Antineoplastic Agents

Two major signaling pathways without primary oncogenic activating mutations, p21-ras and PI3Kinase, are postulated to be of relevance in growth of malignant astrocytomas. Previous publications demonstrate that activation of p21-ras is a key mitogenic signaling pathway in GBMs\textsuperscript{41,42}, resulting in elevation of activated phosphorylated MAPKinase, one of the major downstream effectors of p21-ras. Activated MAPKinase can be measured directly by a kinase assay on frozen specimen, or also by phospho-specific MAPKinase antibodies by western or IHC analysis, as demonstrated by a study on breast cancers, as well as human astrocytoma surgical specimens in Guha’s laboratory. In addition to proliferation, activated p21-ras regulates angiogenic signals mediated by VEGF in GBMs under normoxic and the biologically relevant hypoxic conditions, a major growth regulator in these highly angiogenic tumors.\textsuperscript{43-46} Oncogenic mutations of p21-ras or loss of ras-GAPs (GTPase activating proteins) are not found in sporadic GBMs, leading us to postulate that it is activated secondary to growth promoting signals from aberrantly expressed receptors such as EGF-R and EGF-RvIII. The critical role of p21-ras in astrocyte transformation is also supported by the fact that individuals with neurofibromatosis-1 (NF1) develop astrocytomas at an increased frequency. The NF1 gene product, neurofibromin, functions as a negative regulator of p21-ras, or ras-GAP.\textsuperscript{47-49} Loss of neurofibromin in astrocytes in NF1 patients leads to increased p21-ras activity associated with astrocytoma formation, with resultant activation of MAPKinase and PI3-Kinase pathway (as detected by phosphorylated akt/PKB) on western blot analysis. PI3-Kinase can be activated in a p21-ras dependent fashion, by binding of the p110 catalytic subunit directly on activated p21-ras-GTP. In addition, through the binding of the regulatory p85 subunit to SH2 binding sites on activated receptors, PI3-Kinase can also be activated in a p21-ras independent fashion.

The recent results of transgenic mouse GBM models from Guha’s laboratory are additional demonstration of the importance of p21-ras activation in the pathogenesis of malignant astrocytomas. In these mice, GBMs with pathological and molecular similarities to human GBMs were derived with astrocyte specific expression of oncogenic activated p21-ras. The GBMs in these mice also overexpressed EGF-R though they did not express EGF-RvIII, lost PTEN/MMAC1, overexpressed MDM2 and CDK4, lost p16 and p19, similar to the molecular characteristics of human GBMs.

Agents such as ZD 1839, aimed at inhibiting signal transduction, are currently under clinical investigation. EGFR tyrosine kinase is activated by a variety of ligands when they bind to the external domain. Activation causes EGFR itself and a number of cellular substrates to become phosphorylated on tyrosine residues.\textsuperscript{50} There is now considerable evidence that EGFR is overexpressed in an extensive range of human cancers including GBM.

1.5 ZD 1839 Experience

1.5.1 Glioblastoma Multiforme (GBM) as a Candidate for TKI Therapy

Rationale: Oncogenic Ras mutations lock Ras in its activated GTP-bound form, resulting in malignant transformation. Unlike most other human solid tumors, glioblastoma multiforme (GBM) do not harbor such oncogenic Ras mutations. As a result, virtually all FTI studies have ignored these tumors. However, while they lack oncogenic Ras mutations, GBMs are characterized by the overexpression of ligand-dependent and -independent growth factor receptors. Recent studies have demonstrated that receptor-induced Ras activation is a common feature of GBMs and their derived cell lines, regulating both proliferative and angiogenic signals in these tumors. Thus, while TKIs were initially designed to target tumors characterized by the presence of oncogenic Ras mutations, we have postulated that the presence of receptor-induced Ras activation would lend GBM to be growth inhibited by TKIs.
Efficacy of Earlier FTIs Against GBM Cells: GBM-derived established cell lines have been studied in three separate studies, and have provided cell culture evidence to support the use of FTIs in patients with GBMs. The early peptidomimetic FTI L-739,749 has been shown to inhibit the growth of established U87 glioma cell lines, as well as U118 cells expressing the frequently-expressed constitutively-phosphorylated Epidermal Growth Factor Receptor variant EGFRvIII.\textsuperscript{51} Independent studies have demonstrated similar efficacy by the peptidomimetic FTI FTI-276 against U87 cells in culture and when inoculated in nude mice. Most recently, it has been shown that the peptidomimetic FTI L-744,832 inhibits the proliferation of a panel of six glioma cell lines, with IC\textsubscript{50} ranging from 5.3 µM to 17.4 µM.\textsuperscript{52} Furthermore, this agent exerts its therapeutic effect through a combination of effects: (1) inhibition of cell cycle progression through the G1-S checkpoint; (2) inhibition of cell cycle progression through the G2-M checkpoint; (3) induction of apoptosis; and (4) inhibition of angiogenesis through reduced secretion of the potent angiogenic factor Vascular Endothelial Growth Factor (VEGF).\textsuperscript{53} These various studies thus provide proof-of-principle evidence that FTIs as a class are capable of inhibiting the growth of established astrocytoma cells in culture and when implanted in nude mice. It is therefore logical to expand this research to TKIs. These findings thus demonstrate that astrocytomas are appropriate targets for treatment with these novel molecularly-targeted agents.

1.5.2 Pre-clinical Evidence for Anti-Tumor Efficacy by ZD 1839

ZD 1839 is an oral, specific, and potent inhibitor of EGFR associated tyrosine kinase. Key preclinical features of this compound include high tolerability and ability to delay growth and, at higher doses, the ability to cause regression in human NSCLC and a wide range of other tumor xenografts.

Animal Pharmacokinetics: The major route of excretion for ZD 1839 and its metabolites is via the bile. ZD 1839 is extensively metabolized to a number of components, extensively distributed outside the central compartment, and rapidly cleared. Bioavailability following oral dosing is approximately 50%. Exposure to ZD 1839 increases approximately proportionally with dose. The plasma concentration-time profile data shows evidence of prolonged absorption occurring at the highest doses.

Animal Toxicology: ZD 1839 showed no genotoxic potential \textit{in-vitro}. The no-effect dose level after administration of ZD 1839 for up to 1 month is 10 mg/kg per day; at 6 months it is 1 mg/kg per day. The predominant and consistent form of toxicity was epithelial and included inflammation of eyelids, folliculitis, and degeneration of hair follicles. The findings at the lowest tested dose level were similar to those in the top and intermediate dose levels when given for longer but were less severe and had a lower incidence. Reversible ocular changes included granular/rough appearance to the cornea and corneal translucency without ulceration. Irreversible corneal opacities were seen only in the dog at the highest dose given chronically for 6 months. Renal papillary necrosis was seen in 7 out of 20 rats given 40 mg/kg/day for one month, and 1 out of 6 dogs given the same dose for a month. In addition, ECG recordings revealed a PR interval increase in 2 out of 12 dogs, with large variations between the individual PR interval measurements. A second-degree atrio-ventricular block occurred in one instance; ECG findings returned to normal when therapy was discontinued. The ophthalmologic, renal, and skin changes were considered to be related to the pharmacological activity of ZD 1839. Cardiac change was considered a possible effect of ZD 1839. Biochemical or hematological abnormalities included increased white blood cells, decreased red cells, reduced plasma albumin, increased plasma liver enzymes (alkaline phosphatase [ALP], alanine transaminase [ALT], and aspartate transaminase [AST]). They were generally reversible on discontinuation of the drug. The ovaries showed a reduction in the number of corporal lutea.

\textsuperscript{12/29/04} As part of this continuing nonclinical safety evaluation of ZD 1839, AstraZeneca completed the in-life part and necropsy of a 104-week oral carcinogenicity study in rats at doses of 1, 5, and 10 mg/kg/day. The necropsy and histopathological results revealed an increased incidence of benign liver tumors and mesenteric lymph node hemangiosarcomas.
A statistically significant increase in the incidence of hepatocellular adenomas in both male and female rats at 10 mg/kg/day was noted. Other findings included increased numbers of eosinophilic liver cell foci, increased pigment deposits, and decreased bile duct hyperplasia at this same dose level. In addition, a statistically significant increase in the incidence of hemangiosarcoma in the mesenteric lymph nodes was reported in female rats at the 10-mg/kg/day dose level. There was no evidence that either the benign liver cell tumor or mesenteric lymph node hemangiosarcoma was the cause of death of any study animal. Pharmacokinetic studies indicate that exposures achieved in rats given 10 mg/kg/day dose could be achieved in some patients treated with ZD1839 250 mg daily.

1.5.3 ZD 1839 as a Radiosensitizer

The effects of ZD 1839 in combination with radiotherapy have been explored in several cell lines, including non small cell lung cancer and glioblastoma.\textsuperscript{54} Using the combination index-isobologram equation, the interactions were deemed to be additive or synergistic, primarily for cell lines with moderate to high EGFR expression, providing preliminary observational data to hypothesize that tumors overexpressing EGFR may demonstrate enhanced radioresponsiveness in the presence of specific anti-EGFR therapeutic approaches.

1.5.4 ZD 1839 Clinical Experience to Date

**Clinical Pharmacokinetics:** In healthy volunteers oral ZD 1839 is well absorbed, with an absolute bioavailability of about 60%, and has been shown to be both extensively distributed outside the central compartment and rapidly cleared. Absorption is moderately slow with plasma concentrations typically reaching a maximum at between 3 to 7 hours after dosing. Beyond the peak, the concentrations decline in a biphasic manner, with a terminal half-life of between 10 and 83 hours. Exposure has shown up to a 20-fold range at the same dose level and was not dose proportional over the dose range 50 to 500 mg with a greater than expected increase in exposure in some volunteers at the highest dose. However, the maximum degree of non-proportionality observed was only about 2 fold. On multiple dosing (utilizing a double dose on day 1), the exposure increased 1.3 to 2.8 fold with steady state achieved between day three and five. In the fed state, there was a small reduction in exposure that is not considered to be clinically significant. The major route of elimination for ZD 1839 and its metabolites is via the faecal route (<4% of a radiolabeled dose was excreted via the urinary route).

In cancer patients, there was up to an eleven-fold range in exposure observed within a dose group. Despite this exposure, the group did show an increase with dose across the dose range studied of 50 to 700 mg. The terminal half-life in cancer patients ranged from 27 to 85 hours. Steady state was achieved within the first week of dosing with the variability in steady state trough concentrations within an individual patient being typically 4 to 35%.

The metabolism of ZD 1839 has not yet been elucidated although \textit{in vitro} data indicated the involvement of the cytochrome P450 CYP3A4. A trial in healthy volunteers, who received a low dose, 50 mg, of ZD 1839 alone and in combination with itraconazole (\textit{a potent CYP3A4 inhibitor}), demonstrated that the mean AUC for ZD 1839 was increased by only 30% in the presence of itraconazole. However, the combination of a single dose of 500 mg ZD 1839 with rifampicin, a potent CYP 3A4 inducer, resulted in a six-fold reduction in mean AUC to ZD 1839, which was considered to be clinically significant. Enzyme-inducing anticonvulsant drugs (\textit{EIACDs}) also may act to enhance clearance of ZD 1839. Therefore, in phase I of this study, the MTD of ZD 1839 will be evaluated separately for patients on EIACDs compared to all others.

**ZD 1839 Phase I Tolerability:** As of December 2000, nearly 300 cancer patients have received oral ZD 1839 in five separate phase I trials. The doses tested range from 50 mg to 1000 mg. In each trial, expanded patient number cohorts have received escalating doses of ZD 1839. In the absence of symptomatic disease progression, patients could continue to receive the same dose and schedule of ZD 1839; almost 400 total patient months observation are currently available.

In three phase I trials, dose-limiting toxicity of diarrhea has occurred; in one trial in which 64 patients received ZD 1839 daily for 14 days followed by no therapy for 14 days, at escalating doses, non-bloody, non mucoid, CTC grade 3 diarrheal toxicity was observed at the 700-mg dose level. The two largest phase I trials, in which ZD 1839 is given daily without interruption,
have a combined total of 142 enrolled patients, and recently completed enrollment at the highest planned dose level of 1000 mg. At this 1000-mg dose level, CTC grade 3 diarrheal dose-limiting toxicity has been reported in four patients. Full toxicity evaluation of this dose level is ongoing. A picture of increasing intolerability resulting in the inability to deliver planned daily therapy has emerged at doses of or greater than 600 mg. At the 600 mg dose level, therapy interruptions and dose reductions occurred in 3 out of 20 patients due to CTC grade 3 skin rash (1 patient) or diarrheal toxicity (2 patients), in the first or second month. At the 800-mg dose level, 6 out of 20 patients have been removed from the trial in the first or second month for a variety of reasons, including CTC grade 3 diarrhea (4 patients), transient CTC grade 3 transaminase elevation (1 patient), and CTC grade 4 fatigue (1 patient).

In Japan, a phase I study in patients with solid tumors is ongoing; four to six patients per dose level (31 patients in total) have been enrolled. The CTC grade 3 adverse reactions are elevation of AST and ALT in 2 patients (1 at 225 mg, 1 at 525 mg). At the 700 mg dose level, CTC grade 3 diarrhea and transaminase elevation were dose limiting.

In these phase I trials, consistently observed, dose-related, mechanism-based toxicity has been common and confined to the skin and gastrointestinal system; rare hepatic enzyme elevation has also occurred. Skin toxicity consists mainly of a CTC grade 1-2 pustular rash on an erythematous base; gastrointestinal toxicity consists mainly of CTC grade 1-2 loose or watery, intermittent, non-bloody, non-mucoid stools, occasionally with nausea or isolated episodes of emesis. Overall, the frequency of skin or diarrheal toxicity is greater in the continuous daily dosing schedule compared to the 14-day intermittent schedule (48% versus 35% for skin, and 44% versus 31% for diarrhea, respectively). The majority of patients with rash at higher doses also experienced diarrhea. Skin, gastrointestinal, and the rare hepatic toxicity rapidly reverse with drug discontinuation and/or symptomatic support.

Consistent or drug related hematopoietic, renal, and corneal toxicity have not occurred. Uveitis occurred in one patient. In two continuous monotherapy trials, 8.2% of the patients experienced mild, transient adverse events related to the eye which were considered to be possibly related to trial therapy (e.g., transient redness or itchiness). Four cases of reversible corneal erosion have been reported after patients reported to their physicians that they had symptoms of pain or discomfort (accompanied by hyperemia in 2 of the cases). Three of these cases were directly related to aberrant eyelash growth and one to a possible ocular foreign body. In 3 of the 4 patients, the condition reversed within one week. In the fourth patient, the condition resolved within one week of the aberrant eyelash being detected. These adverse events happened with long-term dosing (3 to 7 months) at higher doses (400, 600, and 800 mg). All but one of the patient deaths were considered by investigators as due to disease progression. One patient’s death was considered by investigators as possibly drug related; however, at autopsy a large, fatal pulmonary embolus was found.

Phase I ZD 1839 Anti-Tumor Effect in Solid Tumors: From the phase I trials, in 70 patients with various advanced, recurrent, previously pre-treated tumors who received ZD 1839 alone at doses ranging from 150 mg to 800 mg, clinically significant disease stabilization was observed. In some cases of NSCLC, head and neck, and prostate cancer, objective, measurable, partial responses, or significant evaluable tumor reduction often accompanied by rapid symptom relief has been observed. Significant, confirmed radiographic antitumor response was evident in 9 patients: 3 patients (225 mg, 400 mg, and 700 mg) had a significant regression of non-measurable, evaluable disease lasting 8.5 months and ongoing, 3.5 months and 6 months and ongoing, respectively, and 6 patients (150 mg, 300 mg, 400 mg, 525 mg, and 700 mg) showed partial responses for 9 months and ongoing, 10 months and ongoing, and 7 months, respectively. Overall, more than 11% of patients in phase I trials had stable or improved disease for at least 3 months with a median duration of 4 months (range 3 to 10 months and ongoing).

2.0 OBJECTIVES
2.1 To identify the maximum tolerated dose of ZD 1839 when given concurrently with cranial radiotherapy;
To determine if ZD 1839, given orally on a daily basis starting at the time of conventional RT, may improve the overall survival of adults with newly-diagnosed supratentorial glioblastoma multiforme, compared with historical controls, stratifying by EGFR status;

To determine, in a multi-institutional setting, the feasibility and toxicity of prescribing ZD 1839;

A secondary objective is whether ZD 1839 also improves progression-free survival in these patients.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria (11/15/02)

3.1.1 Histopathologically confirmed glioblastoma multiforme (with areas of necrosis);

3.1.2 Diagnosis must be made by surgical biopsy or excision;

3.1.3 The tumor must be supratentorial in location;

3.1.4 The patient must have recovered from the effects of surgery, post-operative infection, or other complications before study entry;

3.1.5 Radiotherapy must begin ≤ five weeks after surgery, and Iressa must begin one week prior to radiotherapy;

3.1.6 Patients must have an estimated survival of at least 8 weeks;

3.1.7 Zubrod Performance Status of 0-1;

3.1.8 A diagnostic contrast-enhanced MRI or CT scan must be performed preoperatively and postoperatively prior to the initiation of radiotherapy. Preoperative and postoperative scans must be the same type.

3.1.8.1 Patients diagnosed only by stereotactic biopsy do not require the postoperative scan.

3.1.8.2 Patients unable to undergo MR imaging because of non-compatible devices can be enrolled, provided pre and postoperative CT scans are obtained and are of sufficient quality.

3.1.9 Hematologic, renal, and hepatic status should be documented. If anemia is present to the extent that the hemoglobin is less than 10 grams and the hematocrit is less than 30%, then correction by transfusion is indicated before entry into the study.

Hematologic: Hemoglobin ≥ 10 grams

Absolute neutrophil count ≥ 1500 (ANC) per mm³

Platelets ≥ 100,000 per mm³

Renal: BUN ≤ 25 mg

Creatinine ≤ 1.5 mg

Hepatic: Bilirubin ≤ 2.0 mg

SGPT or SGOT ≤ 2x normal range

3.1.10 Patients must consent to submission of their tissue/serum (See Sections 10.0 and 13.4.2).

3.1.11 The patient must sign a study-specific informed consent prior to study entry. If the patient’s mental status precludes his/her giving informed consent, written informed consent may be given by the responsible family member.

3.2 Conditions for Patient Ineligibility (11/15/02)

3.2.1 Recurrent or multifocal malignant gliomas;

3.2.2 Metastases detected below the tentorium or beyond the cranial vault;

3.2.3 Major medical illnesses or psychiatric impairments which, in the investigator's opinion, will prevent administration or completion of protocol therapy;

3.2.4 Previous radiotherapy to the head or neck (except for T1 glottic cancer), resulting in overlap of radiation fields;

3.2.5 Active connective tissue disorders, such as lupus or scleroderma which, in the opinion of the treating physician, may put the patient at high risk for radiation toxicity;

3.2.6 Previous malignancies, except for non-melanomatosus skin cancers and carcinoma in situ of the uterine cervix or bladder, unless disease-free for ≥ 3 years;

3.2.7 Prior chemotherapy or radiosensitizers for cancers of the head and neck region;

3.2.8 Patients with known Acquired Immune Deficiency (AIDS); Patients with AIDS require complex therapeutic regimens. The pharmacokinetic interactions of these regimens with ZD 1839 are unknown and therefore, pose a safety risk related to excess toxicity or interference with anti-viral effectiveness;
3.2.9 Patients with known multiple sclerosis, as these patients may have decreased tolerance for radiation therapy to the brain;
3.2.10 Pregnant or lactating women, due to possible adverse effects on the developing fetus or infant due to study drug;
3.2.11 Patients treated on any other clinical protocols within 30 days prior to study entry or during participation in the study.

4.0 PRETREATMENT EVALUATION

4.1 Mandatory Studies

4.1.1 Complete history and general physical examination
4.1.2 Radiological assessments: chest X-ray; contrast-enhanced MRI or CT scan performed preoperatively and postoperatively prior to the initiation of radiotherapy (mandatory for eligibility). The postoperative scan is not required if the patient was diagnosed by stereotactic biopsy.
4.1.3 CBC with differential, platelet count, BUN, serum creatinine, bilirubin, and SGOT or SGPT; serum concentration of CYP34A substrates (anticonvulsant levels)
4.1.4 Steroid doses must be documented.
4.1.5 Detailed neurological examination and Mini-Mental Status Exam (MMSE) immediately prior to beginning protocol treatment course; request a forms pack from RTOG Headquarters in advance.
4.1.6 Pregnancy test (in patients in whom conception is possible); a serum pregnancy test must be done within 24 hours before starting ZD 1839.

5.0 REGISTRATION PROCEDURES

5.1 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated Checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

6.0 RADIATION THERAPY

6.1 Dose Definition and Schedule (11/15/02)

Radiotherapy must begin within 5 weeks after surgery. One treatment of 2.0 Gy will be given daily, 5 days per week, (over six weeks) for a total of 60.0 Gy. All portals shall be treated during each treatment session. Doses are specified as the target dose, which shall be to the center of the target volume. For the following portal arrangements the target dose shall be specified as follows:

6.1.1 For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams.
6.1.2 For an arrangement of two or more intersecting beams: at the intersection of the central ray of the beams.
6.1.3 For complete rotation or arc therapy: in the plane of rotation at the center of rotation.
6.1.4 Treatment with a single beam is not acceptable due to unacceptable tumor dose inhomogeneity.
6.1.5 The technique of using two opposing co-axial unequally weighted fields is not recommended due to unacceptable hot spots and unacceptable dose inhomogeneity. However, if this technique is utilized, the dose shall be specified at the center of the target area.
6.1.6 Other or complex treatment arrangements: at the center of the target volume.

6.2 Physical Factors

Treatment shall be delivered with Cobalt 60 beams or megavoltage machines of energy ranging up to and including 10 MV photons. Selection of the appropriate photon energy(ies) should be based on optimizing the RT dose distribution within the target volume and minimizing dose to non-target normal tissue. Photon energies > 10 MV should be utilized only in dual energy beam arrangements using at least one beam with energy < 10 MV. Source skin distance for SSD techniques or source axis distance for SAD techniques must be at least 80 cm. Source sizes must
be no more than 2 cm in Cobalt 60 machines. For Cobalt 60 machines, secondary collimation is required. Electron, particle or implant boost is not permissible.

6.3 Localization, Simulation, and Immobilization

The patient shall be treated in the supine or other appropriate position for the location of the lesion. A head-holding device that is transparent to x-rays must ensure adequate immobilization during therapy and ensure reproducibility. The target volume for both the initial volume and the conedown volume shall be based on the preoperative CT/MRI. The initial target volume shall include the contrast-enhancing lesion and surrounding edema (if it exists) demonstrated on CT/MRI plus a 2.0 centimeter margin. If no surrounding edema is present, the initial target volume should include the contrast-enhancing lesion plus a 2.5 centimeter margin.

This initial target volume will be treated to 46.0 Gy in 23 fractions, 2.0 Gy per fraction. After 46 Gy, the conedown target volume should include the contrast-enhancing lesion (without edema) on the pre-surgery CT/MRI scan plus a 2.5 centimeter margin. The conedown volume will be treated to an additional 14.0 Gy in 7 fractions, 2.0 Gy per fraction. This will bring the total target dose to 60 Gy in 30 fractions.

6.4 Treatment Planning

Treatment plans may include opposed lateral fields, a wedge pair of fields, rotation, or multiple field techniques. CT/MRI-guided treatment planning is necessary to assure accuracy in the selection of field arrangements.

Isodose distributions for the initial target volume and the conedown target volume are required on all patients, including those treated with parallel opposed fields. A composite plan is required showing the respective target volumes. The inhomogeneity across the target volume shall be kept to a minimum.

The minimum dose to the target volume should be kept within 5% of the dose at the center of the volume. The use of vertex fields requires either a diagram or photograph of treatment position to be submitted to RTOG Headquarters. The maximum dose should be no higher than 5% of the dose at the center of the target volume. A radiograph of the vertex field portal and a DRR (if available) of the same portal also should be submitted to RTOG Headquarters.

6.5 Dose Limitations to Critical Structures

The lens and cervical spine must be shielded from the direct beam at all times. When possible to do without shielding gross tumor, attempts should be made to limit the dose to the optic chiasm to 60 Gy, the retina of at least one eye (but preferably both) to 50 Gy, and the brain stem to 60 Gy. When the optic chiasm must be included in the full dose, there may be a finite unknown risk of developing blindness.

6.6 Documentation Requirements

At the completion of treatment, the following should be forwarded to RTOG Headquarters: daily treatment record, all isodose distributions, simulation and portal films of the large and conedown fields, and the radiotherapy summary per Section 12.1. In addition, CT/MRI documentation must be submitted per Section 12.2.

6.7 Radiation Toxicities (6/16/05, 3/24/10)

6.7.1 Expected toxicities include loss of hair and erythema of the scalp. Reactions in the ear canals and on the ear should be observed and treated symptomatically. If significant increase in reaction of the normal tissue occurs, it should be noted and reported to the Study Chairman.

6.7.2 Both acute and delayed or late reactions to radiotherapy are to be recorded and included in the complete toxicity evaluation. Reaction within 90 days of treatment start date was scored using the revised NCI Common Toxicity Criteria, version 2.0. For reactions appearing or persisting beyond 90 days, refer to the RTOG/EORTC Late Radiation Morbidity Scoring Scheme (Appendix III).

6.7.3 Hematologic toxicities should be rated on a scale of 0-5 as defined in the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) beginning April 1, 2010. The CTEP Active Version of the CTCAE is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Active Version of the CTCAE.

6.7.4 See Section 7.5 for Adverse Event Reporting. (6/29/05)
DRUG THERAPY

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

7.1 Schedule

7.1.1 Phase I (10/4/02)

EIACD patients (Group 1 in Schema): In Arm 1, the dose of ZD 1839 during radiotherapy will be a single 250 mg tablet, to be taken in the a.m., daily, for the entire course of radiotherapy. To ensure ZD 1839 has reached steady-state plasma concentrations, treatment should begin one week prior to the initiation of radiotherapy. This dose will escalate to 500 mg (2 tablets) and 750 mg (3 tablets) in subsequent cohorts of patients (Arms 2 and 3) if acceptable levels of toxicity are observed, as detailed in Section 13.3. Enzyme-inducing anticonvulsants may include Carbamazepine, Phenytoin, Phenobarbital, and/or Primidone. (There may be other drugs that fall into this category: treating physicians should check with their institution pharmacologist if they have concerns/questions.)

Non-EIACD patients (Group 2 in Schema): In Arm 4, the dose of ZD 1839 during radiotherapy will be a single 250 mg tablet, to be taken in the a.m., daily, for the entire course of radiotherapy. To ensure ZD 1839 has reached steady-state plasma concentrations, treatment should begin one week prior to the initiation of radiotherapy. This dose will escalate to 500 mg (2 tablets) in the subsequent cohort of patients (Arm 5), if acceptable levels of toxicity are observed, as detailed in Section 13.3.

Investigators should make every effort to keep patients in the treatment group (“EIACD patients” vs. “all others”) in which they were when they went on study. In the event that a patient must be taken off enzyme-inducing anticonvulsants, i.e., switch from EIACD to non-EIACD or be started on enzyme-inducing anticonvulsants, i.e., switch from non-EIACD to EIACD, the investigator should contact the study chair, Dr. Chakravarti, immediately (617) 726-1548, to discuss further treatment. In addition, the site should contact RTOG Headquarters, Data Management, to report the change in treatment. NOTE: If the 750 mg dose of ZD 1839 (Arm 3) is opened for accrual and a patient receiving enzyme-inducing anticonvulsant is taken off EIACDs, then dose reduction of ZD 1839 may be required for that patient’s safety.

At completion of radiation therapy, all patients will proceed to a maintenance dose of 500 mg p.o. per day. If this dose is tolerated for the first two weeks of maintenance therapy, the dose can be escalated to 750 mg, if tolerated, in the EIACD patient population only. This dose will be continued for 18 months, or until tumor progression or, in the absence of progression, until discontinuation due to toxicity.

Phase II

For both EIACD and non-EIACD patients (Groups 1 and 2), the starting dose of ZD 1839 during radiotherapy will be based on the MTD established in the phase I portion of the study followed by a maintenance dose of 500 mg daily. If this dose is tolerated for the first two weeks of maintenance therapy, the dose can be escalated to 750 mg, if tolerated, in the EIACD patient population only. To ensure ZD 1839 has reached steady-state plasma concentrations, treatment should begin one week prior to the initiation of radiotherapy. Maintenance drug will be continued for 18 months, or until tumor progression or, in the absence of progression, until discontinuation due to toxicity.

If a patient on enzyme-inducing anticonvulsants in either phase I or II is taken off enzyme-inducing anticonvulsants, the patient will continue on study, including continuing Iressa, (unless the patient develops serious toxicities; see Section 7.2.4) and will be considered evaluable in statistical analyses.

7.2 ZD 1839 (NSC# 715055) (11/15/02)

7.2.1 Source and Formulation

ZD 1839 will be provided by CTEP/NCI. It will be supplied to the investigator as brown, film-coated tablets for use; each tablet will be of 250 mg strength (Formulation # F12653).
Descriptive information for ZD 1839 can be found in the Investigator’s Brochure. For U.S. and Canadian centers, tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each carton of trial material will have an investigational-use label permanently affixed to the outside, stating that the drug is to be used only for investigational purposes.

7.2.2 **Storage and Stability**

All investigational products must be kept in a secure place under appropriate storage conditions. For U.S. centers, all trial treatment will be stored in a lockable storage area, between 20-25°C (68-77°F), and protected from light. For Canadian centers, all trial treatment will be stored in a lockable storage area, between 15-30°C (59-86°F), and protected from light.

7.2.3 **Known Toxicities**

See Appendix IV for the Comprehensive Adverse Event and Potential Risks List (CAEPR) for ZD 1839. (1/13/05)(6/16/05).

There have been a total of 12 incidences of CNS hemorrhage reported among patients on NCI sponsored studies of ZD 1839. There have been five reports of CNS hemorrhage of the 48 patients enrolled in the pediatric studies, four events, including one fatality, occurred among 33 patients enrolled on a study of concurrent ZD 1839 and radiation followed by continued ZD 1839 and one event occurred in a patient with ependymoma receiving single agent ZD 1839. There have been 7 patients with CNS hemorrhages into primary or metastatic tumors reported among 1355 patients enrolled in the adult studies. Four adult patients with hemorrhage had gliomas out of a total of 290 patients enrolled in the glioma studies. (9/3/2003)

7.2.4 **Drug Dose Modification (11/15/02, 3/24/10)**

Dose modification of ZD 1839 can be secondary to dose limiting toxicities (DLTs) [see Section 13.3.1] or any other toxicity according to the judgment of the treating physician. Toxicities eliciting dose modification will be treated differently depending on whether they occur during radiotherapy or after the completion of radiotherapy. If these toxicities occur during radiotherapy, ZD 1839 will be temporarily discontinued during radiotherapy, but restarted at the next lower dose level of ZD 1839 during the maintenance phase (post-radiotherapy), as long as the toxicity has resolved to grade 1 or lower. This is the only situation in which dose reduction of ZD 1839 is permitted. For patients receiving 500 mg, the lower dose level will be 250 mg; for those receiving 750 mg, it will be 500 mg. If patients develop toxicity that requires dose modification during the maintenance phase (post-radiotherapy), a drug holiday can be granted, but not to exceed more than 14 days in any 28-day period. Exceptions only will be made for temporary therapy interruption due to drug toxicity or hospitalization. In the event of hospitalization for reasons other than drug toxicity, patients should be directed to continue trial drug at the discretion of their physician. The study chair should be notified immediately of any compliance issues that arise in the course of the trial. If the dose-modifying toxicities have not decreased in severity to grade 1 or lower after the drug holiday, an intermittent dosing schedule of no less than 14 days out of 28 will be permitted. If a patient still experiences dose-modifying toxicities despite drug holiday and intermittent dosing schedule, the patient, if benefiting from treatment, should be referred to the CTEP drug monitor regarding an appropriate dose/schedule; otherwise the patient should stop receiving ZD 1839.

The following toxicities, in addition to any other toxicity as judged by the treating physician, merit temporary discontinuation and, in some cases, subsequent dose-reduction, as described above:

1. Any grade 3 or 4 non-hematopoietic adverse event that the investigator considers consistent with a drug-related toxicity;
2. Any grade 4 hematopoietic adverse event that the investigator considers consistent with a drug-related toxicity;
3. Toxicity requiring treatment interruption of greater than 7 days during radiation should be considered dose limiting.
4. Patients with worsening pulmonary symptoms of new onset or worsening dyspnea, cough, or fever should be promptly evaluated for interstitial pneumonitis and treated as clinically indicated. ZD 1839 should be temporarily discontinued pending diagnosis of
the nature of the pulmonary disorder. ZD 1839 should be permanently discontinued if a diagnosis of interstitial pneumonitis/pneumonia is confirmed and is considered to be related to ZD 1839.

7.3 Accountability and Supply

7.3.1 The Principal Investigator (or authorized designee) at each participating institution may request ZD 1839, from NCI’s Pharmaceutical Management Branch (PMB). PMB policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions unless prior approval from PMB is obtained. Completed Clinical Drug Requests (NIH-986) should be submitted to the PMB by fax (301) 480-4612 or mailed to the Pharmaceutical Management Branch, CTEP, DCTD, NCI, 9000 Rockville Pike, EPN, Rm. 7149, Bethesda, MD 20892.

7.4 Drug Inventory Records

The Investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all drugs received from DCTD, using the NCI Drug Accountability Record Form (see the NCI Investigators Handbook for Procedures for Drug Accountability and Storage).

7.5 Adverse Events (6/16/05, 3/24/10)

Beginning April 1, 2010, this study will utilize the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) for grading of all adverse events. The CTEP Active Version of the CTCAE is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

All adverse events (AEs) as defined in the tables below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site (https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup). Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERS. Sites also can access the RTOG web site (http://www.rtog.org/members/toxicity/main.html) for this information.

7.5.1 Adverse Events (AEs) — RTOG AE PHONE: 215-717-2762 (available 24 hours/day)

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

The following guidelines for reporting adverse events (AEs) apply to all NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported via AdEERS. Use the patient’s case number as the patient ID when reporting via AdEERS. AEs reported using AdEERS also must be reported on the AE case report form (see Section 12.1). NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting may be required. Reporting AEs only fulfills Data Management reporting requirements.

7.5.2 Serious Adverse Events (SAEs) — All SAEs that fit any one of the criteria in the SAE definition below must be reported to RTOG (SAE PHONE: 215-717-2762, available 24 hours/day) within 24 hours of discovery of the event.

Definition of an SAE: Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.
Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE drug experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

Outside of regular business hours (8:30-5:00 EST), leave a message that includes the study/case numbers and the caller’s contact information. A Data Manager will return the call the next business day requesting details of the event and also will inform the caller which type of report is required for that study (5 or 10 day AdEERS). The required report must be completed in AdEERS within 5 or 10 calendar days of the initial phone report, as directed by the Data Manager taking the call. SAEs reported using AdEERS also must be reported on the AE case report form (see Section 12.1).

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported to RTOG via the AE/SAE telephone line within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

All supporting source documentation, if applicable or if being faxed to NCI, must be properly labeled with the study/case numbers and the date of the adverse event and must be faxed to the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. All forms (and supporting source documentation) submitted to RTOG Headquarters must include the RTOG study/case numbers; non-RTOG intergroup study and case numbers must be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient’s case number as the patient ID when reporting via AdEERS.

SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as “expedited reporting NOT required” must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the “NOT Required” assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment. Note: Sites must print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

7.5.3 **Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)**

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the NCI/CTEP Secondary AML/MDS Report Form available at [http://ctep.cancer.gov/forms/index.html](http://ctep.cancer.gov/forms/index.html). The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of a report via the AdEERS system and must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis.

<table>
<thead>
<tr>
<th>RTOG Headquarters</th>
<th>AML/MDS Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>1818 Market Street, Suite 1600</td>
<td>Philadelphia, PA 19103</td>
</tr>
</tbody>
</table>
### 7.5.4 AdEERS Expedited Reporting Requirements

**Phase 1 Trials Utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days\(^1\) of the Last Dose of the Investigational Agent [ZD 1839] on Treatment Arms 1-5 [ZD1839 daily dose during RT]**

<table>
<thead>
<tr>
<th>Phase 1 Trials</th>
<th>Grade 1 Unexpected and Expected</th>
<th>Grade 2 Unexpected</th>
<th>Grade 2 Expected</th>
<th>Grade 3 Unexpected with Hospitalization</th>
<th>Grade 3 without Hospitalization</th>
<th>Grade 3 Expected with Hospitalization</th>
<th>Grade 3 without Hospitalization</th>
<th>Grades 4 &amp; 5(^2) Unexpected and Expected</th>
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<tbody>
<tr>
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<tr>
<td>Possible</td>
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<td>Not Required</td>
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<td>24-Hour; 5 Calendar Days</td>
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<td>10 Calendar Days</td>
</tr>
<tr>
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<td>10 Calendar Days</td>
<td>Not Required</td>
<td>24-Hour; 5 Calendar Days</td>
<td>24-Hour; 5 Calendar Days</td>
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<tr>
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<td>24-Hour; 5 Calendar Days</td>
<td>24-Hour; 5 Calendar Days</td>
<td>24-Hour; 5 Calendar Days</td>
</tr>
</tbody>
</table>

\(^1\) Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:
- AdEERS 24-hour notification followed by complete report within 5 calendar days for:
  - Grade 3 unexpected events with hospitalization or prolongation of hospitalization
  - Grade 4 unexpected events
  - Grade 5 expected events and unexpected events

\(^2\) Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see exceptions below under section entitled “Additional Instructions or Exceptions.”

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**Note:** All deaths on study require both routine and expedited reporting regardless of causality.

**Attribution to treatment or other cause must be provided.** “On study” is defined as during or within 30 days of completing protocol treatment.

- Expedited AE reporting timelines defined:
  - “24 hours; 5 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - “10 calendar days” – A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.

- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

**Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 1 Trials Utilizing an Agent under a CTEP-IND:**

Note: For this study, seizures do not require expedited reporting.
7.5.5 Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days of the Last Dose of the Investigational Agent [ZD 1839] in this Study [Arms 6-7]

<table>
<thead>
<tr>
<th>Grade 1</th>
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<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 3</th>
<th>Grades 4 &amp; 5(^2)</th>
<th>Grades 4 &amp; 5(^2)</th>
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<td>10 Calendar Days</td>
<td>24-Hour; 5 Calendar Days</td>
</tr>
<tr>
<td>Probable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^2\) Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:
- Grade 4 and Grade 5 unexpected events
- AdEERS 10 calendar day report:
- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. “On study” is defined as during or within 30 days of completing protocol treatment.

- Expedited AE reporting timelines defined:
  - “24 hours; 5 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - “10 calendar days” - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP-IND:

Note: For this study, seizures do not require expedited reporting.

7.5.6 This study will be monitored by the Clinical Data Update System (CDUS) version 1.1. Complete cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.
Clinical Trials Agreement

The agent(s) (hereinafter referred to as “Agent[s]”), used in this protocol is/are provided to the NCI under a Clinical Trials Agreement (CTA) between AstraZeneca (hereinafter referred to as “Collaborator(s)”) and the NCI Division of Cancer Treatment, Diagnosis. Therefore, the following obligations/guidelines apply to the use of the Agent(s) in this study:

Agent(s) may not be used outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and should be maintained as such by the investigators.

For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different CTAs, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as “Multi-Party Data.”):

a) NCI must provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI’s participation in the proposed combination protocol.

b) Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

c) Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

d) The NCI encourages investigators to make data from clinical trials fully available to Collaborator(s) for review at the appropriate time (see #5). Clinical trial data developed under a CTA will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate.

e) When a Collaborator wishes to initiate a data request, the request should first be sent the NCI, who will then notify the appropriate investigators (Group Chair for cooperative group studies, or PI for other studies) of Collaborator’s wish to contact them.

f) Any data provided to Collaborator(s) must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

g) Any manuscripts reporting the results of this clinical trial should be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. An additional 30 days may be requested in order to ensure that confidential and proprietary data, in addition to Collaborator(s)’s intellectual property rights, are protected. Copies of abstracts should be provided to Collaborator(s) for courtesy review following submission, but prior to presentation at the meeting or publication in the proceedings. Copies of any manuscript and/or abstract should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Room 7111
Bethesda, Maryland 20892
FAX (301) 402-1584

The Regulatory Affairs Branch will then distribute them to Collaborator(s).
8.0 SURGERY
Not applicable to the study.

9.0 OTHER THERAPY

9.1 Concomitant Therapy

9.1.1 If surgery is considered necessary for the patient, whenever possible at least 7 days should elapse after the last dose of ZD 1839 before surgery is performed. Any patients requiring ophthalmic surgery during the course of the trial should be withdrawn from the study.

9.1.2 Concomitant use of medications known to affect the conductive system, such as beta-blockers, calcium channel blockers, or digoxin, is allowed at physician discretion. Systemic retinoids and herbal medicines or remedies must be discontinued before study entry and are not allowed during the study. Systemic retinoids should not be given because of theoretical concerns about negatively affecting the ZD 1839 mechanism of actions. Systemic steroids are discouraged for the treatment of skin toxicities. Patients who are taking steroids for reasons other than skin toxicity at study entry may continue treatment. The dose of steroids should not be changed without consultation with the study chair.

9.1.3 Patients who are concomitantly taking drug(s) known to induce CytP4503A4, other than EIACDs, must discontinue drug prior to study entry, and such drugs are not allowed during the study. Other medication which is considered necessary for the patient’s safety and well being may be given at the discretion of the treating physician. Administration of all medication (including investigational products) must be recorded in the appropriate sections of the study specific flow sheet (SF).

9.2 Supportive Care

9.2.1 Skin: There is no standard, known, or established proven-effective treatment for drug-related skin rashes or changes due to ZD 1839. Most commonly, a pustular rash has been observed, which frequently improves with same dose of uninterrupted ZD 1839 therapy. 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. Neither oral nor topical retinoids should be given because of the theoretical concerns about negatively affecting the ZD 1839 mechanism of action.

9.2.2 GI: In previous phase I trials, a small number of patients with CTC grade 3 diarrhea have been observed; loperamide administered as an initial 4 mg dose followed by 2 mg doses every 4 hours is moderately effective in treating this toxicity. Anti-emetics may be used for nausea, as necessary.

10.0 PATHOLOGY (6/27/02)

10.1 Submission of Tissue and Serum Samples  (Tissue submission is mandatory for this study; patients must consent to participate in the tissue/serum component of the study, question #1, Appendix IB. Patients are encouraged but not required to respond “yes” to questions 2 and 3.)

10.1.1 Rationale
The purpose of the samples is to understand the mechanism of the mode of action of ZD 1839 and/or identify a marker to monitor or predict treatment results. The samples will not be used for genetic testing, and the patient will be informed in the consent form as to how the samples will be obtained and stored. Any data obtained from analysis of tumor tissue or serum samples will be used for basic science research only, and patient confidentiality will be preserved internally and in any presentations or publications. The samples will be available to scientists within RTOG or at laboratories/research institutes contracted to RTOG, and patient confidentiality will be preserved.

10.1.2 Tissue/Serum Samples to Be Submitted

10.1.2.1 Where possible, every effort should be made to obtain a paraffin block containing a sample of tumor tissue of a minimum size, 2mm x 2mm of tumor tissue. Tissue should have been fixed in 10% buffered formalin for less than 24 hours prior to processing. If the block is not available, 10-15 unstained slides, cut on “plus” slides and containing tumor cells from biopsies should be provided. Blocks and slides should be kept in a covered container at room temperature prior to shipment.
In addition, serum samples will be collected for analysis of steady-state ZD 1839 level in the phase I component. Steady state trough levels will be examined by obtaining a serum sample immediately before ingestion of ZD1839 on the 5th and 10th doses, respectively (1 sample prior to the 5th dose, 1 sample prior to the 10th dose; 2 samples from each patient). Serum samples also will be obtained after the 5th and 10th doses of ZD 1839, respectively; these samples will be collected within 2-4 hours of ZD 1839 ingestion on that day (2 samples from each patient). The samples (a total of 4 from each patient) should be collected in a 10ml green top (heparinized blood), centrifuged with plasma separated; two aliquots should be placed in cryo-vials at -70 C. Samples must be clearly labeled with the patient and study numbers, and the date and time of collection. Samples should be shipped on dry ice with a Specimen Transmittal form to the address in Section 10.2.5; a copy of the Specimen Transmittal form also should be submitted to RTOG headquarters.

10.2 Process
10.2.1 The samples will be tested at the RTOG’s central pathology repository at LDS Hospital in Salt Lake City, Utah, under the supervision of Dr. Elizabeth Hammond. Slides and blocks will be retained at the testing laboratory until destruction.
10.2.2 The following must be provided:
10.2.2.1 Block/slides must be clearly labeled with the pathology identification number that agrees with the pathology report.
10.2.2.2 Pathology report documenting that submitted block or slides contain tumor
10.2.2.3 A Pathology Submission Form must be included and must clearly state that it is being submitted for the RTOG Tissue Bank.
10.2.3 RTOG will reimburse pathologists from submitting institutions $100 per case for tissue samples, if proper materials are submitted. In addition, RTOG will reimburse submitting institutions $150 for serum samples, if proper materials are submitted. RTOG Administration will prepare the proper paperwork and send a check to your institution after confirmation from LDS that they have received the appropriate materials.
10.2.4 Patient consent form should give the Pathology Department authority and responsibility to comply with this request (pathology blocks belong to the patient from whom tissue has been removed).
10.2.5 Materials will be sent to(6/16/05):

LDS Hospital  
Dept. of Pathology  
E.M. Laboratory  
8th Ave & C Street  
Salt Lake City, UT  84143  
(801) 408-5626  
FAX (801) 408-5020  
holly.goold@ihc.com
11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (10/4/02)

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Prior to Therapy</th>
<th>During Radiotherapy</th>
<th>Post RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological Exam</td>
<td>X(^a)</td>
<td>Weekly</td>
<td>X(^c)</td>
</tr>
<tr>
<td>History and Physical</td>
<td>X(^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid Dose Documentation</td>
<td>X(^a)</td>
<td>X</td>
<td>X(^e)</td>
</tr>
<tr>
<td>CBC with differential, Platelets</td>
<td>X(^a)</td>
<td>Weekly(^f)</td>
<td>X(^d)</td>
</tr>
<tr>
<td>BUN, Serum Creatinine, Bilirubin, SGOT or SGPT</td>
<td>X(^a)</td>
<td>Weekly(^f)</td>
<td>X(^d)</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>X(^b)</td>
<td></td>
<td>X(^g)</td>
</tr>
<tr>
<td>Contrast enhanced Brain CT or MRI</td>
<td>X(^h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>X(^i)</td>
<td></td>
<td>X(^j)</td>
</tr>
<tr>
<td>Toxicity Evaluation</td>
<td>Weekly(^k)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum pregnancy test</td>
<td>X(^l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum samples for PK analysis</td>
<td>X(^m)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum concentration of CYP3A4 substrates (anticonvulsant levels)</td>
<td>X(^n)</td>
<td>X(^o)</td>
<td>X(^p)</td>
</tr>
</tbody>
</table>

a. Should be done within 14 days of registration
b. Should be done within 28 days of registration; both preoperatively and postoperatively prior to RT. Postoperative scan not required if patient diagnosis was by stereotactic biopsy only
c. At every follow-up visit once a month
d. Every 8 weeks during drug administration
e. As clinically indicated
f. Every week during drug administration with XRT in the phase I component only
g. Every 12 weeks post-RT
h. For patients in phase I, serum samples for PK analysis will be collected within 2-4 hours after ingesting ZD 1839 on the 5\(^{th}\) and 10\(^{th}\) dose, respectively; in addition, trough levels of ZD1839 will be examined by obtaining serum before ingestion of ZD1839 on the 5\(^{th}\) and 10\(^{th}\) dose, respectively See Section 10.1.2.2.
i. 24 hours prior to starting ZD 1839
j. The patient’s physician should evaluate serum levels of anticonvulsants pretreatment, in the 3\(^{rd}\) week of RT, and 2 weeks post-RT; treatment decisions based on substrate results are at the discretion of the treating physician.

NOTE: It is mandatory that patients are followed with the same study (CT vs. MRI) as the baseline study.

11.2 Evaluation During Study (Phase I component)

11.2.1 A general examination, specifically evaluating toxicities shall be performed once a week during radiation therapy and ZD 1839 administration with XRT.

11.2.2 CBC with differential, platelet count, BUN, serum creatinine, bilirubin, SGOT/SGPT will be obtained weekly during the XRT/ZD 1839 concomitant administration in the phase I component of the study.

11.2.3 The contrast-enhanced CT/MRI of the brain shall be obtained prior to surgery, post-surgery, prior to initiation of ZD 1839 therapy, then every 12 weeks and at the time of neurologic deterioration. Attention is drawn to the occurrence of "early delayed radiation reactions" that occur usually within the first 10 weeks post treatment and last up to 6-8 weeks. These transient adverse signs and symptoms may spontaneously improve without therapy. They are considered to be due to transient demyelination. Caution is, therefore, urged in diagnosing and treating recurrent tumor during the first 2-3 months post irradiation.

11.2.4 While a patient is receiving ZD 1839 in the maintenance phase, monthly (q 4 weeks) evaluations are required and will include at a minimum, a neurologic exam, steroid dose documentation, and
toxicity assessments; blood counts will be obtained every eight weeks; MMSE and imaging assessment will be done every 12 weeks. (10/4/02)

11.3 **Evaluation During Study (Phase II component)**

11.3.1 A general examination, specifically evaluating toxicities, shall be performed once a week during radiation therapy.

11.3.2 The contrast-enhanced CT/MRI of the brain shall be obtained prior to surgery, post-surgery, prior to initiation of ZD 1839 therapy, then every 12 weeks, and at the time of neurologic deterioration. Attention is drawn to the occurrence of "early delayed radiation reactions" that occur usually within the first 10 weeks post treatment and last up to 6-8 weeks. These transient adverse signs and symptoms may spontaneously improve without therapy. They are considered to be due to transient demyelination. Caution is, therefore, urged in diagnosing and treating recurrent tumor during the first 2-3 months post irradiation.

11.3.3 While a patient is receiving ZD 1839 in the maintenance phase, monthly (q 4 weeks) evaluations are required and will include a neurologic exam, steroid dose documentation and toxicity assessments; MMSE status exam and blood counts will be obtained every eight weeks, and imaging assessment every 12 weeks.

11.4 **CT/MRI Review**

The serial CT/MRI shall be examined at the institution by an independent reviewer (i.e. a neuroradiologist who is not a co-investigator on this study and who is not involved in the patient’s care). The evaluation of the scans will be compared to and correlated with the patient's clinical course.

11.5 **Overall Response**

11.5.1 **Complete Response (CR):** shall be defined as the circumstance when the enhancing tumor is no longer seen by neuroimaging, with the patient off all steroids, or on adrenal maintenance only; CR will be coded only if confirmed by a second CT/MR scan performed a minimum of 4 weeks after the initial scan coding a response.

11.5.2 **Partial Response (PR):** Decrease of >50% in the product of two diameters with the patient off all steroids, or on adrenal maintenance only; PR will be coded only if confirmed by a second CT/MR scan performed a minimum of 4 weeks after the initial scan.

11.5.3 **Minor Response (MR):** Decrease in diameter products of < 50% with the patient off all steroids, or on adrenal maintenance only. This will not need a confirmatory scan.

11.5.4 **Stable Disease (SD):** shall be defined as the circumstance when the scan shows no change. Patients should be receiving stable or decreasing doses of steroids. This will not need a confirmatory scan.

11.5.5 **Progression (P):** shall be defined as a > 25% increase in tumor area (two diameters) provided that the patient has not had his/her dose of steroids decreased since the last evaluation period. This will not need a confirmatory scan. A concomitant decrease in steroid dose will rule out a progression designation during the first 2 months after completion of XRT.

11.6 **Instructions For Administration of Mini-Mental Status Examination (MMSE)**

The Mini-Mental Status Exam can be administered by the physician, a nurse, or an assistant trained in the administration of such tools. The person administering the MMSE needs to be sensitive if patients show embarrassment because of their inability to answer the questions. Patients should be assured that this is another way of determining how the treatment is affecting their brain tumor. It also needs to be made clear to the patient that it is very important to obtain this information directly from the patient. The person administering the test should score answers as correct or incorrect; there should be no partial credit given.

11.7 **Criteria for Evaluation of Therapy Effectiveness**

11.7.1 Tumor response and regrowth can frequently be difficult to measure directly. Serial neurological exams and CT/MRI scans may provide a guide to the actual course. Time interval to progression will be measured from registration until deterioration is documented by the individual investigator using these guides. The patient should consistently be followed with the same diagnostic imaging study (CT or MRI).

11.7.2 Overall survival will be measured from registration until death.

11.7.3 The quality of survival will be measured by neurological functional classification and performance status.
11.7.4 Post mortem examination of the cranial contents should be obtained at death whenever possible
to evaluate effects of this therapy on malignant and normal brain tissue.

11.7.5 Toxocities will be measured using the CTC criteria, version 2.0.

11.8 **Ineligible and Inevaluable Patients**

11.8.1 Patients that are registered and retrospectively found to be ineligible for this trial may
discontinue forms submission upon notification of eligibility from HQ. Data until that point,
however, must be submitted to RTOG. These patients will be excluded from all analyses.

11.8.2 Patients that receive no protocol drug will be excluded from all analyses. No data will be
required by RTOG.

12.0 **DATA COLLECTION (10/4/02) (6/16/05)**

12.1 **Summary of Data Submission**

(RTOG, 1818 Market Street, Suite 1600, Philadelphia, PA 19103, Fax: 215/928-0153)

<table>
<thead>
<tr>
<th>Data</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within two weeks of registration</td>
</tr>
<tr>
<td>On-study Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Pretreatment MRI/CT scan (<strong>both pre- and post-surgery</strong>) (C1) and reports (C3)</td>
<td></td>
</tr>
<tr>
<td>Pathology report (P1)</td>
<td></td>
</tr>
<tr>
<td>Mini-Mental Status Exam (MS)</td>
<td></td>
</tr>
<tr>
<td>Specimen Transmittal Form (ST)</td>
<td>Within four weeks of registration</td>
</tr>
<tr>
<td>Radiotherapy Form (T1)</td>
<td>Within one week of completing radiotherapy</td>
</tr>
<tr>
<td>Final Dosimetry Information:</td>
<td></td>
</tr>
<tr>
<td>Daily Treatment Record (T5),</td>
<td></td>
</tr>
<tr>
<td>Isodoses (T6),</td>
<td></td>
</tr>
<tr>
<td>Simulation &amp; Port films of all Fields (TP)</td>
<td></td>
</tr>
<tr>
<td>Protocol Calculation Form (TL)</td>
<td>At 2 &amp; 3 months from treatment start</td>
</tr>
<tr>
<td>Initial Follow-up Form (FS)</td>
<td>Monthly during drug administration (1 month=1 “cycle”)</td>
</tr>
<tr>
<td>Study Specific Flow Sheet (SF)</td>
<td>Every 12 weeks post-RT</td>
</tr>
<tr>
<td>Mini-Mental Status Exam (MS)</td>
<td></td>
</tr>
<tr>
<td>Follow-up Form (F1)</td>
<td>Every month from treatment start, starting with month 4, for the first 18 months; then q 4 months x 1 year; q 6 months x 2 years; then annually. Also at progression/relapse and at death.</td>
</tr>
<tr>
<td>Follow-up MRI/CT scan (C2) and report (C3)</td>
<td>See Section 12.2 for scan submission</td>
</tr>
<tr>
<td>Operative reports (S2), surgical reports (S5)</td>
<td>As applicable</td>
</tr>
<tr>
<td>(for subsequent surgery)</td>
<td></td>
</tr>
<tr>
<td>Autopsy Report (D3)</td>
<td>As applicable</td>
</tr>
</tbody>
</table>

12.2 **CT/MRI Documentation**

The contrast-enhanced MRI/CT taken before surgery and after-surgery-before-radiotherapy begins
must be submitted within two weeks of registration. A MRI/CT must be done at the time of
neurologic deterioration, suggestive of tumor recurrence, and should be submitted. Other causes of
neurological deterioration, such as metabolic imbalance, anticonvulsant or interferon toxicities, should be considered and properly investigated. The patient should consistently be followed with the same diagnostic study. Subsequent scans should be forwarded to RTOG Headquarters.

13.0 STATISTICAL CONSIDERATIONS
13.1 Study Endpoints
13.1.1 Primary Endpoints
- Rate of acute and late toxicities associated with ZD 1839 and standard cranial radiation.
- Overall survival, stratified by EGFR status.

13.1.2 Secondary Endpoint
- Progression-free survival

13.2 Inclusion in analysis
Eligible patients starting protocol drug treatment will be included in the statistical analyses.

13.3 Phase I Component
13.3.1 Evaluation of Acute and Late Toxicity (11/15/02)
The primary objective of this phase of the study is to determine the maximum tolerated dose (MTD) of ZD 1839 combined with cranial radiation, the dose at which no patients develop acute grade 5 toxicity and less than 30% of patients developed acute dose limiting toxicities. A dose limiting toxicity (DLT) is defined as any of the following: any grade 3 or 4 nonhematologic toxicity excluding grade 3 nausea/vomiting, grade 3 fatigue, and grade 3 skin toxicity, as defined in CTC, v. 2 — unless there is evidence of erythema multiforme, or any toxicity requiring i.v. hydration, hospitalization, or an interruption of greater than a total of 7 days during radiation treatment. Acute toxicity is defined to be a toxicity occurring within 90 days from the start of radiotherapy treatment. If at any time a grade 5 toxicity is observed, accrual will be suspended and the Study Chair will review the event. Furthermore, if the cumulative incidence (obtained by time to event analysis), at any time, of combined acute/late DLTs estimates the toxicity rate to be greater than 30% at any dose level, then the Executive Committee will be notified and the committee will determine whether to stop accrual.

13.3.2 Dose Escalation (10/4/02)
This study consists of escalations of 250 mg from the starting dose of 250 mg daily during radiation therapy. EIACD and non-EIACD patients will be evaluated in separate phase I components, with a maximum dose of 750 mg (two escalations) for EIACD patients, and 500 mg (one escalation) for non-EIACD patients. Dose escalation will follow the standard 3+3 design. Due to the expected rapid accrual, all six patients for a dose level will be accrued at once. If none of the first three patients (0/3), or one of the first three and none of the last three (1/3+0/3), experience a DLT, then the next dose will be opened. Otherwise, the current dose level will be considered too toxic. The highest dose achieved with an acceptable level of toxicity will be considered the Maximum Tolerable Dose. Patients starting protocol drug will be evaluable for toxicity.

At a given dose level, the probability of halting dose escalation when the true toxicity is 50% or higher is 83% (power). In addition, if the true DLT rate is instead 15%, there will still be a 19% probability of halting dose escalation at a given dose level (type I error). Note that the patients finally determined to be at the MTD will be included in the phase II component. Maximum size for the phase I component of the study will be 18 EIACD patients and 12 non-EIACD patients.

13.4 Phase II Component
13.4.1 Background
RTOG recursive partitioning analysis (RPA) has found that the survival of malignant glioma patients is highly influenced by prognostic factors (age, histology, mental status, KPS, symptom duration, extent of surgery, neurological class, and RT dose). The RTOG, and many groups in the brain cancer research community, use the RPA classes to stratify patients for study eligibility, treatment assignment at randomization, and for analytic purposes. GBM patients on this study must have a Zubrod score 0-1 (KPS ≥ 70), and therefore will fall into RPA classes III, IV, or V, which historically have a median survival time (MST) of 17.9, 11.1, and 8.9 months, respectively. The RTOG GBM data base contains 1027 RPA class III through V patients, with a distribution of 20%, 49%, 31%, respectively.

13.4.2 Sample Size
The primary objective of this phase of the study is to compare the overall survival, by EGFR status, of these patients to GBM RPA class III-V cases from the RTOG tissue bank which have been evaluated for EGFR expression by immunohistochemistry (Patients will not be distinguished by enzyme-inducing anticonvulsant use). We conservatively expect to have a minimum of 100 tissue bank cases with EGFR over-expression (EGFR+) as determined by immunohistochemistry, to be performed in the laboratory of Dr. Kian Ang at M.D. Anderson Cancer Center. We have no data to allow us to adjust for the effect of EGFR status on survival and will therefore calculate sample size based on the survival of all RPA class III-V patients from the RTOG GBM database. The historical distribution and MST of RPA classes III-V (see previous section) results in an overall MST of 11.1 months for the historical control. Using the Dixon-Simon method of calculating sample size for the comparison of survival against a historical control, a sample size of 84 evaluable RPA class III-V patients followed over 18 months will ensure at least 80% probability of detecting a minimum of 50% improvement in MST compared at the 0.05 level (one-sided) to 100 EGFR+ tissue bank patients.\(^5^7\) Since EGFR+ patients are expected to comprise 60% of accrual, 140 total patients will need to be accrued. In addition, see the following table for equivalent statements regarding power, alpha, and detectable improvement. Eligible patients starting protocol drug will be included in this analysis. Adjusting for a 95% eligibility/evaluability rate results in 140 patients needed in order to accrue 84 eligible EGFR+ patients as determined immunohistochemically. This study is powered for analysis of the EGFR+ patients, but we will also be comparing EGFR- patients to EGFR- tissue bank cases and reporting these results. In summary, the phase II component requires a total sample size of 140 patients (including 6 patients each from the EIACD and non-EIACD phase I components).

<table>
<thead>
<tr>
<th>84 Evaluable EGFR+ Patients</th>
<th>Detectable Improvement (MST)</th>
<th>Alpha (1-sided)</th>
<th>Statistical Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>0.05</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>45%</td>
<td>0.10</td>
<td>86%</td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td>0.10</td>
<td>87%</td>
<td></td>
</tr>
<tr>
<td>35%</td>
<td>0.20</td>
<td>87%</td>
<td></td>
</tr>
</tbody>
</table>

### 13.5 Inclusion of Women and Minorities

In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we make the following observations. The recursive partitioning analysis of the RTOG database for patients entered into glioma trials failed to show any treatment interaction with gender.\(^5^6\) The RTOG found no difference in survival of glioblastoma multiforme patients by race.\(^5^8\) Since there are no publications found to support a possible interaction between different radiation therapy schedule and either gender or race, the sample size will remain the same. A statistical analysis will be performed to examine the possible difference between the genders and among the races.

The projected gender and minority accruals appear below:

<table>
<thead>
<tr>
<th></th>
<th>White, not of Hispanic Origin</th>
<th>Hispanic</th>
<th>Black, not of Hispanic Origin</th>
<th>Native Hawaiian or other Pacific Islander</th>
<th>Asian</th>
<th>American Indian or Alaskan Native</th>
<th>Other/Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
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<td>6</td>
<td>1</td>
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<td>0</td>
<td>95</td>
</tr>
<tr>
<td>Total</td>
<td>128</td>
<td>11</td>
<td>15</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>158</td>
</tr>
</tbody>
</table>
13.6 Patient Accrual

The patient accrual is projected to be 14 cases per month, based upon the monthly accrual for prior RTOG GBM studies. Estimating a 60% rate of patients on enzyme-inducing anticonvulsants, we expect 8 EIACD cases per month for the phase I component, and 6 non-EIACD cases per month. At this rate, the phase I components should complete accrual for each dose level within a month. When both EIACD and non-EIACD patients are accruing to the phase II component, it should take less than 10 months to reach the required total accrual of 140, noting that the 140 includes 12 patients from the phase I components. If the average monthly accrual rate is less than three patients, the study will be re-evaluated with respect to feasibility.

13.7 Analyses Plans

13.7.1 Interim Analyses

Interim reports with statistical analyses are prepared every six months until the initial manuscript reporting the treatment results has been submitted. In general, the interim reports will contain information about:

a) the patient accrual rate with a projected completion date for the accrual phase, and compliance rate of treatment delivery with respect to protocol prescription;

b) the quality of submitted data with respect to timeliness, completeness, and accuracy;

c) the frequency and severity of the toxicities.

Through examining the above items, the statistician and study committee can identify problems with the execution of the study. If necessary, problems will be reported to the RTOG Executive Committee, so that corrective action can be taken.

13.7.2 Analysis for Reporting the Initial Treatment Results

This analysis will be undertaken when each phase II patient has been potentially followed for a minimum of 18 months. The usual components of this analysis are:

a) tabulation of all cases entered, and any excluded from the analysis with reasons for the exclusion;

b) reporting of institutional accrual;

c) distribution of important prognostic baseline variables – (age, KPS, neurologic function, extent of surgery, mental status);

d) observed results with respect to the endpoints described in Section 13.2.

e) Overall survival of patients will be compared to RPA class III-V patients, by EGFR status, from the RTOG tissue bank using a one-sided log-rank test with a significance level of 0.05.
REFERENCES


APPENDIX IA
RTOG 0211

SAMPLE CONSENT FOR RESEARCH STUDY

A PHASE I/II STUDY OF AN ORAL EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE KINASE INHIBITOR (*EGFR-TKI*), ZD 1839 (*IRESSA*), [NSC# 715055] WITH RADIATION THERAPY IN GLIOBLASTOMA MULTIFORME

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. You are being asked to take part in this study because you have a brain tumor called a supratentorial glioblastoma multiforme (GBM).

Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, “Taking Part in Clinical Trials: What Cancer Patients Need to Know,” is available from your doctor.

WHY IS THIS STUDY BEING DONE?

This is a two-part study. The purpose of the study is to find out what effects (good and bad) an investigational drug, ZD 1839, has on patients with your type of brain tumor. Part 1 of the study will find out the highest dose of ZD 1839 that can be safely given with radiation therapy. Groups of patients will receive ZD 1839 in increasing doses between 250-750 mg until at least some of the patients experience severe side effects.

ZD 1839 has been designed to block certain chemical pathways that lead to tumor cell growth. In prior studies with lung cancer patients, ZD 1839 has delayed tumor growth and provided relief of symptoms in some patients.

The second part of this study will find out whether the highest dose of ZD 1839 that can be safely given (determined in Part 1) adds to the activity of radiation therapy.

This research is being done because currently, there is no effective treatment for your type of cancer.
HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

A maximum of 30 people will take part in the first part of this study. About 140 people will take part in the second part of this study.

WHAT IS INVOLVED IN THE STUDY?

The treatment you receive will depend on when you enter the study and if you are taking anti-seizure medicine. Anti-seizure medicine may change the way your body processes the ZD 1839.

Part 1: (10/4/02)

If you are enrolled in Part 1, you will receive radiation therapy once daily, 5 days a week, for six weeks as an outpatient. If you are taking anti-seizure medicine, you also will receive one of three doses of ZD 1839 (250, 500, or 750 mg). If you are not taking anti-seizure medicine, you will receive one of two doses of ZD 1839 (250 or 500 mg). If your anti-seizure medicine needs to be changed during the study, your doctor will discuss with you how those changes might affect the study treatment you receive.

The dose of ZD 1839 will be increased from a starting dose of 250 mg (one tablet) only after the safety at the previous level has been confirmed in several people. You will swallow one, two, or three tablets (depending on the dose you receive) of ZD 1839 in the morning every day during radiation therapy. You will be provided with a pill diary and asked to keep track of your daily doses of ZD 1839. After radiation therapy, you will take 500 mg of ZD 1839 (two tablets) every day. If you tolerate this dose for 2 weeks, your doctor may increase the dose to 750 mg (three tablets). You will take ZD 1839 for 18 months, unless there is evidence that your tumor is growing or you experience severe side effects.

Part 2:

If you are enrolled in Part 2, you will receive radiation therapy once daily, 5 days a week, for six weeks as an outpatient. If you are taking anti-seizure medicine, you will take ZD 1839 in the morning every day during radiation therapy at the dose determined to be safe in Part 1 (250, 500, or 750 mg). If you are not taking anti-seizure medicine, you will take ZD 1839 in the morning every day during radiation therapy at the dose determined to be safe in Part 1 (250 or 500 mg). You will be provided with a pill diary and asked to keep track of your daily doses of ZD 1839. After radiation therapy, you will take 500 mg of ZD 1839 (two tablets) every day. If you tolerate this dose for 2 weeks, your doctor may increase the dose to 750 mg (three tablets). You will take ZD 1839 for 18 months, unless there is evidence your tumor is growing or you experience severe side effects.
The Division of Cancer Treatment and Diagnosis, National Cancer Institute will provide ZD 1839 free of charge for this study.

Before beginning the study, you will have the following tests and procedures:
- Physical examination
- Neurological examination
- Blood tests
- Chest X-ray
- MRI or CT scan (tests to measure tumor size and shape)
- Pregnancy test (for women who can have children)
- A brief questionnaire that will measure your thinking abilities by asking you to answer questions and follow a few directions.

If you take part in this study, you also will have the following tests and procedures: (10/4/02)
- Neurological examination weekly during radiation therapy and after radiation therapy, monthly while taking ZD 1839
- Blood tests weekly during radiation therapy, 2 weeks after radiation therapy, and then monthly while taking ZD 1839
- A brief questionnaire that will measure your thinking abilities by asking you to answer questions and follow a few directions every 3 months after radiation therapy
- MRI or CT scan every 12 weeks after radiation therapy
- Chest X-ray and blood tests as your doctor determines

After 18 months of ZD 1839, follow-up visits with your doctor every 4 months for 1 year, then every 6 months for 2 years, then annually.

Also, you are being asked for your permission to send a small part of the tumor removed by your doctor and samples of your blood to a central office for review and research investigation associated with this protocol.

**HOW LONG WILL I BE IN THE STUDY?**

You will receive radiation therapy to the brain for six weeks. You will take ZD 1839 during your radiation therapy and for 18 months after radiation therapy, unless there is evidence that your tumor is growing or you experience severe side effects. Follow-up visits will continue for the rest of your life according to the above schedule.

Your doctor may decide to take you off this study if it is in your medical best interest, drug supply is insufficient, your condition worsens, or new information becomes available and this information suggests the treatment
will be ineffective or unsafe for you. It is unlikely, but the study may be stopped early due to lack of funding or participation.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

**WHAT ARE THE RISKS OF THE STUDY?**

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the drug or radiation therapy is stopped, but in some cases side effects can be serious or long-lasting or permanent.

**Risks Associated with Radiation Therapy** — The side effects of radiation may be worse when ZD 1839 is taken.

*Very Likely*
- Scalp redness or soreness
- Hair loss
- Dry mouth or altered taste
- Fatigue or sleepiness
- Headaches
- Weakness
- Seizure

*Less Likely*
- Fever, chills, or heavy sweating
- Upset stomach, nausea, and/or vomiting
- Loss of appetite

*Less Likely But Serious*
- Permanent hair loss
- Hearing loss
- Eye injury resulting in blindness
- Mental slowness
- Behavioral changes
- Blood clots
- Severe damage to normal brain tissue that may require additional surgery
Risks Associated with ZD 1839

Serious adverse reactions to ZD 1839 are infrequent. They are seldom severe enough to require discontinuing treatment. The following side effects have been observed:

**Frequent Side Effects (1/13/05)**
The most common side effect is skin rash like pimples, sometimes with redness, which can appear on the face, upper arms, or chest and which can be severe. The rash usually goes away once the drug is stopped, but it often disappears or reduces in severity even when the drug is being continued.

Diarrhea is another common side effect, occurring in up to half of all patients; diarrhea also can be severe. The diarrhea usually can be controlled with a drug called loperamide.

Other known side effects include: tiredness, weakness, dry skin, itching, acne, a scaly rash, dry mouth, muscle pain, and/or inflammation of the eye.

**Infrequent Side Effects (1/13/05)**
Nausea and vomiting are occasional to rare. Anti-nausea medications can be given for this.

Other potential side effects include:
- Change in taste
- Decreased ability to digest milk and/or milk products
- Decreased appetite
- Stomach pain
- Inflammation of the lining of the mouth
- Inflammation of the lining of the digestive tract
- Dry eyes
- Bleeding from the nose
- Hair loss
- Chills
- Weakness
- Dehydration
- Swelling due to fluid accumulation in tissues
- Change in sensation, such as tingling or burning
- Anxiety about the eyes or about exposure to light
- Headache
- Sleepiness
- Depression
- Back pain
- Urinary frequency
• Blood in the urine
• Rapid heartbeat
• Decreased red or white blood cell levels
• Decreased potassium in the blood
• Abnormal kidney function test results, that may indicate kidney damage
• Abnormal liver function test results, that may indicate liver damage
• Nail changes
• Eyelid problems
• Inflammation or ulceration of the cornea
• Problems with the surface of the eye
• Erosion of the cornea
• Eyelash problems
• Eye pain

In a study testing the combination of ZD 1839 (gefitinib, Iressa) and radiation in children with brain tumors (called gliomas), 4 of 33 patients had bleeding into the tumors while receiving ZD 1839 with radiation or while continuing to take ZD 1839 after finishing radiation. At present, while the frequency of bleeding into tumors does not appear to be increased in adults, it is unclear whether the risk of bleeding into cancers in children, into gliomas or into cancers getting radiation is higher with ZD 1839. (9/3/2003)

Rare Side Effects

Rare Side Effects (11/15/02)
ZD 1839 has caused small changes in the electrical activity of the heart in a few animals, but this has not occurred in people. Rarely, abnormalities in the way the liver works have been measured, but these changes have not resulted in liver damage. Temporary changes on the surface of the eye have been seen in 4 people, which did not affect their sight. They had symptoms such as eye discomfort, itching, or slight pain. When they stopped taking ZD 1839, their eyes returned to normal.

Rarely, some patients (less than 1%) taking ZD 1839 get a type of inflammation of the lungs called ‘interstitial lung disorder’ or ‘interstitial pneumonia’. This type of lung disease causes worsening of existing lung problems or causes new lung problems, such as sudden onset of shortness of breath, fever, cough, and/or problems with oxygen getting through the lungs to the blood. In some patients, this lung disease has been fatal. If you should have lung problems such as shortness of breath, cough, and/or fever, you should contact your doctor immediately. ZD 1839 will be stopped until your doctor has identified the cause of these lung problems. If the lung problems are related to ZD 1839, it will not be restarted.

Reproductive Risks
Because the drug in this study can affect an unborn baby or infant, you should not become pregnant or father a baby while on this study. You should not nurse your baby while on this study. Ask your doctor about counseling and more information about preventing pregnancy.

**Additional Risk Information (12/29/04)**

In a study to look at the effects of ZD 1839 taken long term, rats were given ZD 1839 for 2 years. At the end of this time, some rats given the highest dose of ZD 1839 developed non-cancerous liver tumors and some female rats developed a cancer in lymph nodes. These tumors have not been seen in people treated with ZD 1839, and whether these results in rats apply to people is unknown.

**ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with brain tumors in the future.

The benefit of ZD 1839 to patients with brain tumors is unknown. Treatment with radiation and ZD 1839 may keep your brain tumor from growing and may shrink it. This may provide relief from symptoms and improve your quality of life. ZD 1839 may improve control of your brain tumor. However, none of these benefits are guaranteed, and the effects of a combination of radiation and ZD 1839 may be no different or worse than radiation alone.

**WHAT OTHER OPTIONS ARE THERE?**

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) radiation therapy; (2) chemotherapy; (3) surgery; or (4) no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would spread. These treatments could be given either alone or in combination with each other.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments. Please talk to your regular doctor about these and other options.

**WHAT ABOUT CONFIDENTIALITY?**
Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (FDA), the National Cancer Institute (NCI), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study.

WHAT ARE THE COSTS?

The Division of Cancer Treatment and Diagnosis, National Cancer Institute, will provide you with ZD 1839 free of charge for this study. Every effort has been made to ensure adequate supplies of ZD 1839, free of charge, for all participants. If, however, this investigational agent becomes commercially available for brain cancer like yours while you are being treated, there is a possibility that you or your insurance company will be charged for subsequent supplies.

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. If you choose to stop participating in the study, you should first discuss this with your doctor. In order to provide important information that may add to the analysis of the study, he/she may ask your permission to submit follow-up data as it relates to the study. You may accept or refuse this request. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.
We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A Data Safety and Monitoring Board, an independent group of experts, may be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

**WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS? (THIS SECTION MUST BE COMPLETED)**

For information about your disease and research-related injury, you may contact:

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

For information about this study, you may contact:

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

For information about your rights as a research subject, you may contact (OPRR suggests that this person not be the investigator or anyone else directly involved with the research):

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

**WHERE CAN I GET MORE INFORMATION?**

You may call the NCI’s Cancer Information Service at:

1–800–4–CANCER (1–800–422–6237) or TTY: 1–800–332–8615

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (full study plan).

_____________________                  __________________              _________
Patient’s Name               Signature              Date

_____________________                   __________________              _________
Name of Person Obtaining Consent     Signature               Date
CONSENT FORM FOR USE OF TISSUE AND BLOOD FOR RESEARCH

ABOUT USING TISSUE/BLOOD FOR RESEARCH

You have had or will have a biopsy (or surgery) to see if you have cancer. Your doctor has removed or will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will used to plan your care.

In order to participate in the main part of this study, you must agree to allow us to keep some of the tissue that is left over and a small amount of your blood for use in research to learn about, prevent or treat cancer. (You must answer “yes” to question 1 below.)

If you agree, your blood will be drawn prior to taking the 5th and 10th dose of ZD 1839 and within 2-4 hours after taking the 5th and 10th dose of ZD 1839. Four samples of your blood will be sent to a central office to study the level of ZD 1839 in your blood.

We also would like to keep some of the tissue that is left over for future research. You are encouraged but not required to answer “yes” to questions 2, 3, and 4 below. If you agree, your tissue will be kept and may be used in research to learn more about cancer and other diseases.

Your tissue may be helpful for research whether you do or do not have cancer. The research that may be done with your tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an affect on your care.

THINGS TO THINK ABOUT

The choice to let us keep the left over tissue and to use your blood for future research is up to you. **No matter what you decide to do, it will not affect your care.** You will continue to receive high quality treatment and supportive care.

If you decide now that your tissue/blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue/blood and then any tissue/blood that remains
will no longer be used for research; or, you may request that your tissue/blood be returned to you or your designee. Because use of tissue and blood for research is required for this study, if you do change your mind, you will be taken off ZD 1839. You can continue to receive radiation therapy and be followed as part of this study, if you wish.

In the future, people who do research may need to know more about your health. While [treating physician/institution] may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Your tissue will not be used for genetic research (about diseases that are passed on in families).

Your tissue/blood will be used only for research and will not be sold. The research done with your tissue may help to develop new products in the future.

**BENEFITS**

The benefits of research using tissue/blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

**RISKS**

The greatest risk to you is the release of information from your health records. [Treating physician/institution] will protect your records so that your name, address, and phone number will be kept private. The chance that this information will be given to someone else is very small.

**MAKING YOUR CHOICE**

Please read each sentence below and think about your choice. After reading each sentence, circle “Yes” or “No”. **No matter what you decide to do, it will not affect your care.** If you have any questions, please talk to your doctor or nurse, or call our research review board at [IRB’s phone number].

1. My tissue/blood may be used for the research in the current study.

    Yes          No
2. My tissue/blood may be kept for use in research to learn about, prevent or treat cancer.
   Yes  No

3. My tissue/blood may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer’s disease, or heart disease).
   Yes  No

4. Someone from [treating physician/institution] may contact me in the future to ask me to take part in more research.
   Yes  No

Participant statement:
I have read and received a copy of this consent form. I have been given an opportunity discuss the information with my doctor/nurse, and all of my questions/concerns have been answered to my satisfaction. My answers above and my signature below indicate my voluntary participation in this research.

_________________________  ___________________________  ______________
Patient’s Name                           Signature           Date

Witness statement:
I have explained the information in this consent form to the patient and have answered any questions raised. I have witnessed the patient’s signature.

_________________________  ___________________________  ______________
Name of Person Obtaining Consent   Signature           Date
APPENDIX II

KARNOFSKY PERFORMANCE SCALE

100 Normal; no complaints; no evidence of disease
90 Able to carry on normal activity; minor signs or symptoms of disease
80 Normal activity with effort; some sign or symptoms of disease
70 Cares for self; unable to carry on normal activity or do active work
60 Requires occasional assistance, but is able to care for most personal needs
50 Requires considerable assistance and frequent medical care
40 Disabled; requires special care and assistance
30 Severely disabled; hospitalization is indicated, although death not imminent
20 Very sick; hospitalization necessary; active support treatment is necessary
10 Moribund; fatal processes progressing rapidly
0 Dead

ZUBROD PERFORMANCE SCALE

0 Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).
1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).
2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).
3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).
4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).
<table>
<thead>
<tr>
<th>ORGAN TISSUE</th>
<th>GRADE 0</th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3</th>
<th>GRADE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td>Slight</td>
<td>Patch</td>
<td>Marked</td>
<td>Ulceration</td>
</tr>
<tr>
<td>SKIN</td>
<td>None</td>
<td>hair</td>
<td>atrophy; Pigmentation change; Some hair</td>
<td>atrophy; Moderate telangiectasia; Total hair</td>
<td>atrophy; Gross telangiectasia</td>
</tr>
<tr>
<td>SUBCUTANEOUS</td>
<td>None</td>
<td>Slight</td>
<td>Moderate fibrosis but asymptomatic; Slight field contracture;</td>
<td>Severe induration and loss of subcutaneous tissue; Field contracture &amp; 10% linear measurement</td>
<td>Ulceration</td>
</tr>
<tr>
<td>TISSUE</td>
<td>None</td>
<td>induration</td>
<td>&amp; loss of subcutaneous fat</td>
<td>contracture; &lt;10% linear reduction</td>
<td>Necrosis</td>
</tr>
<tr>
<td>MUCOUS</td>
<td>None</td>
<td>Slight</td>
<td>Moderate atrophy and telangiectasia; Little mucous</td>
<td>Marked atrophy with complete dryness;</td>
<td>Ulceration</td>
</tr>
<tr>
<td>MEMBRANE</td>
<td>None</td>
<td>atrophy</td>
<td>&amp; dryness</td>
<td>Severe telangiectasia</td>
<td>Fibrosis</td>
</tr>
<tr>
<td>SALIVARY GLANDS</td>
<td>None</td>
<td>Slight</td>
<td>Dryness of mouth; Good response on stimulation</td>
<td>Complete dryness of mouth; No response on stimulation</td>
<td>Mono, para quadriplegia</td>
</tr>
<tr>
<td>SPINAL CORD</td>
<td>None</td>
<td>Mild</td>
<td>L'Hermitte’s syndrome</td>
<td>Objective neurological findings at or below cord level treated</td>
<td>Seizures or paralysis; Coma</td>
</tr>
<tr>
<td>BRAIN</td>
<td>None</td>
<td>Headache</td>
<td>Headache; Great laryngitis</td>
<td>Severe headaches; Severe CNS dysfunction (partial loss of power or dyskinesia)</td>
<td>Necrosis</td>
</tr>
<tr>
<td>EYE</td>
<td>None</td>
<td>Asymptomatic cataract; Minor corneal ulceration or keratitis</td>
<td>Symptomatic cataract; Moderate corneal ulceration; Minor retinopathy or glaucoma</td>
<td>Severe keratitis; Severe retinopathy or detachment</td>
<td>Panophthalmitis/Blindness</td>
</tr>
<tr>
<td>LARYNX</td>
<td>None</td>
<td>Hoarseness; Slight arytenoid edema</td>
<td>Moderate arytenoid edema; Chondritis</td>
<td>Severe edema; Severe chondritis</td>
<td>Severe respiratory insufficiency/continuous O2/Assisted ventilation</td>
</tr>
<tr>
<td>LUNG</td>
<td>None</td>
<td>Asymptomatic or mild symptoms (dry cough); Slight radiographic appearances</td>
<td>Moderate symptomatic fibrosis or pneumonitis (severe cough); Low grade fever; Patchy radiographic appearances</td>
<td>Severe symptomatic fibrosis or pneumonitis; Dense radiographic changes</td>
<td>Tamponade/Severe heart failure/Severe constriction of pericarditis</td>
</tr>
<tr>
<td>HEART</td>
<td>None</td>
<td>Asymptomatic or mild symptoms; Transient T wave inversion &amp; ST Changes; Sinus tachycardia &gt;110 (at rest)</td>
<td>Moderate angina on effort; Mild pericarditis; Normal heart size; Persistent abnormal T wave and ST changes; Low ORS</td>
<td>Severe angina; Pericardial effusion; Constrictive pericarditis; Moderate heart failure; Cardiac enlargement; EKG abnormalities</td>
<td>Necrosis/Perforation Fistula</td>
</tr>
<tr>
<td>ESOPHAGUS</td>
<td>None</td>
<td>Mild fibrosis; Slight difficulty in swallowing solids; No pain on swallowing</td>
<td>Unable to take solid food normally; Swallowing semi-solid food; Dilation may be indicated</td>
<td>Severe fibrosis; Able to swallow only liquids; May have pain on swallowing Dilation required</td>
<td>Necrosis/Perforation Fistula</td>
</tr>
<tr>
<td>SMALL/LARGE</td>
<td>None</td>
<td>Mild diarrhea; Mild cramping; Bowel movement 5 times daily Slight rectal discharge or bleeding</td>
<td>Moderate diarrhea and colic; Bowel movement &gt;5 times daily; Excessive rectal mucus or intermittent bleeding</td>
<td>Obstruction or bleeding, requiring surgery</td>
<td>Necrosis/Perforation Fistula</td>
</tr>
<tr>
<td>INTESTINE</td>
<td>None</td>
<td>Lassitude; Nausea, dyspepsia; Slightly abnormal liver function</td>
<td>Moderate symptoms; Some abnormal liver function; function tests; Serum albumin normal</td>
<td>Disabling hepatic insufficiency; Liver function tests grossly abnormal; Low albumin; Edema or ascites</td>
<td>Necrosis/Hepatic coma or encephalopathy</td>
</tr>
<tr>
<td>LIVER</td>
<td>None</td>
<td>Anemia; Dyspepsia; Slightly abnormal liver function</td>
<td>Persistent moderate albuminuria (2+); Mild hypertension; No related anemia; Moderate impairment of renal function; Urea &gt;36-60 mg/100 mL Creatinine clearance (50-74%)</td>
<td>Severe albuminuria; Severe hypertension</td>
<td>Malignant hypotension; Uremic coma/Urea &gt; 100%</td>
</tr>
<tr>
<td>KIDNEY</td>
<td>None</td>
<td>Transient albuminuria; No hypertension; Mild impairment of renal function; Urea 25-35 mg% Creatinine 1.5-2.0 mg%; Creatinine clearance &gt; 75%</td>
<td>Persistent moderate albuminuria (2+); Mild hypertension; No related anemia; Moderate impairment of renal function; Urea &gt; 36-60 mg% Creatinine clearance (50-74%)</td>
<td>Severe albuminuria; Severe hypertension</td>
<td>Necrosis/Contracted bladder (capacity &lt; 100 cc); Severe hemorrhagic cystitis</td>
</tr>
<tr>
<td>BLADDER</td>
<td>None</td>
<td>Slight epithelial atrophy; Minor telangiectasia (microscopic hematuria)</td>
<td>Moderate frequency; Generalized telangiectasia; Intermittent macroscopic hematuria</td>
<td>Severe frequency &amp; dysuria Severe generalized Telangiectasia (often with petechiae); Frequent hematuria; Reduction in bladder capacity (&lt; 100 cc)</td>
<td>Severe pain or tenderness; Complete arrest of bone growth; Dense bone sclerosis</td>
</tr>
<tr>
<td>BONE</td>
<td>None</td>
<td>Asymptomatic; No growth retardation; Reduced bone Density</td>
<td>Moderate pain or tenderness; Growth retardation; Irregular bonesclerosis</td>
<td>Severe pain or tenderness; Complete arrest of bone growth</td>
<td>Necrosis/Spontaneous fracture</td>
</tr>
<tr>
<td>JOINT</td>
<td>None</td>
<td>Joint stiffness; Slight limitation of movement</td>
<td>Moderate stiffness; Intermittent or moderate joint pain; Moderate limitation of movement</td>
<td>Severe joint stiffness; Pain with severe limitation of movement</td>
<td>Necrosis/Complete fixation</td>
</tr>
</tbody>
</table>
### APPENDIX IV (1/13/05)(6/16/05)

**Comprehensive Adverse Events and Potential Risks List (CAEPR)**

*for ZD 1839 (715055)*

**Bold** and **italic** text (column three) identifies events that are considered “Expected” and do not require expedited reporting through AdEERS.

**Version 1.0, December 20, 2004**

<table>
<thead>
<tr>
<th>Category (Body System)</th>
<th>Adverse Events with Possible Relationship to ZD 1839 (CTCAE v3.0 Term)</th>
<th>“Expected” Adverse Events (These events do not require expedited reporting through AdEERS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLOOD/BONE MARROW</strong></td>
<td>Neutrophils/granulocytes (ANC/AGC)</td>
<td></td>
</tr>
<tr>
<td><strong>CONSTITUTIONAL SYMPTOMS</strong></td>
<td>Fatigue (asthenia, lethargy, malaise)</td>
<td>Fatigue (asthenia, lethargy, malaise)</td>
</tr>
<tr>
<td><strong>DERMATOLOGY/SKIN</strong></td>
<td>Dry skin, Nail changes, Pruritus/itching, Rash/desquamation, Rash: acne/acneiform</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dry skin</td>
<td>Dry skin</td>
</tr>
<tr>
<td></td>
<td>Nail changes</td>
<td>Nail changes</td>
</tr>
<tr>
<td></td>
<td>Pruritus/itching</td>
<td>Pruritus/itching</td>
</tr>
<tr>
<td></td>
<td>Rash/desquamation</td>
<td>Rash/desquamation</td>
</tr>
<tr>
<td></td>
<td>Rash: acne/acneiform</td>
<td>Rash: acne/acneiform</td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL</strong></td>
<td>Anorexia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dehydration</td>
<td>Dehydration</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td>Dry mouth/salivary gland (xerostomia)</td>
<td>Dry mouth/salivary gland (xerostomia)</td>
</tr>
<tr>
<td></td>
<td>Mucositis/stomatitis (functional/symptomatic) - Select</td>
<td>Mucositis/stomatitis (functional/symptomatic) - Select</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>Vomiting</td>
</tr>
<tr>
<td><strong>HEPATOBILIARY/PANCREAS</strong></td>
<td>Liver dysfunction/failure (clinical)</td>
<td>Liver dysfunction/failure (clinical)</td>
</tr>
<tr>
<td><strong>LYMPHATICS</strong></td>
<td>Edema:limb</td>
<td></td>
</tr>
<tr>
<td><strong>METABOLIC/LABORATORY</strong></td>
<td>ALT, SGPT (serum glutamic pyruvic transaminase)</td>
<td>ALT, SGPT (serum glutamic pyruvic transaminase)</td>
</tr>
<tr>
<td></td>
<td>AST, SGOT (serum glutamic oxaloacetic transaminase)</td>
<td>AST, SGOT (serum glutamic oxaloacetic transaminase)</td>
</tr>
<tr>
<td></td>
<td>Bilirubin (hyperbilirubinemia)</td>
<td>Bilirubin (hyperbilirubinemia)</td>
</tr>
<tr>
<td></td>
<td>Creatinine</td>
<td>Creatinine</td>
</tr>
<tr>
<td><strong>OCULAR/VISUAL</strong></td>
<td>Dry eye syndrome</td>
<td>Dry eye syndrome</td>
</tr>
<tr>
<td></td>
<td>Eyelid dysfunction</td>
<td>Eyelid dysfunction</td>
</tr>
<tr>
<td></td>
<td>Keratitis (corneal inflammation/corneal ulceration)</td>
<td>Keratitis (corneal inflammation/corneal ulceration)</td>
</tr>
<tr>
<td></td>
<td>Ocular surface disease</td>
<td>Ocular surface disease</td>
</tr>
</tbody>
</table>
### APPENDIX IV (cont’d)

<table>
<thead>
<tr>
<th>Ocular/Visual - Other (Corneal erosion/ulcer)</th>
<th>Ocular/Visual - Other (Aberrant eyelash)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular/Visual - Other (Aberrant eyelash)</td>
<td>Uveitis</td>
</tr>
</tbody>
</table>

**PAIN**

<table>
<thead>
<tr>
<th>Pain - abdomen NOS</th>
<th>Pain - eye</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pain - head/headache</td>
</tr>
<tr>
<td></td>
<td>Pain - muscle</td>
</tr>
</tbody>
</table>

| Pneumonitis/pulmonary infiltrates | Pneumonitis/pulmonary infiltrates |

1This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting ADEERSMD@tech-res.com. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

**Also reported on ZD1839 trials but with the relationship to ZD 1839 still undetermined:**

- Allergic reaction
- Allergic rhinitis
- Hemoglobin
- Leukocytes
- Platelets
- Conduction abnormality
- Ventricular tachycardia
- Fibrinogen
- INR in patients taking Warfarin
- Rigors/chills
- Weight loss
- Sudden death
- Alopecia
- Erythema multiforme
- Seborrhea
- Urticaria
- Taste alteration
- CNS hemorrhage
- GI hemorrhage
- Lung hemorrhage
- Nose hemorrhage
- Urinary hemorrhage
- Pancreatitis
- Pneumonia with neutropenia
- Albuminuria
- Hypokalemia
- Hypoproteinemia
- Muscle weakness
- Depression
- Motor neuropathy
- Sensory neuropathy
- Somnolence/depressed level of consciousness
- Blurred vision in patients with corneal abrasions related to ZD 1839
- Corneal ischemia/hemorrhage
- Photophobia
- Renal failure has been seen with diarrhea related to ZD 1839
- Urinary frequency
- Acute vascular leak syndrome

**Animal Data:** The following toxicities have been observed in animal studies with ZD1839:

- Benign liver tumors seen in long-term study
- Mesenteric lymph node hemangiosarcomas seen in Females only in long-term study

**Notes:** ZD 1839 in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.