Memorial Sloan-Kettering Cancer Center
IRB Protocol

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A phase II trial of external beam radiation therapy and cetuximab followed by irinotecan and cetuximab for children and young adults with newly diagnosed diffuse pontine tumors and high-grade astrocytomas (POE08-01)

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

In this protocol entitled "A phase II trial of external beam radiation therapy and cetuximab followed by irinotecan and cetuximab for children and young adults with newly diagnosed diffuse pontine tumors and high-grade astrocytomas", patients will be enrolled after maximal safe neurosurgical resection (HGA patients) or radiological diagnosis (diffuse pontine tumor patients). They will then receive protocol-prescribed therapy:

- External beam radiation therapy (5940 cGy in 180 cGy fractions) with weekly cetuximab (250 mg/m^2/dose).
- 4-8 week rest
- 10 cycles of irinotecan (16 mg/m^2/day x 5 consecutive days x 2 weeks) with weekly cetuximab (250 mg/m^2/dose) at about 21 day intervals

Research biological evaluations will be performed in consenting patients as an optional portion of the study.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary objectives:

1. To determine the proportion of patients with high-grade astrocytoma and diffuse pontine tumors achieving one year progression free survival.
2. To determine the safety of cetuximab administered weekly in conjunction with involved field external beam radiation therapy for diffuse pontine tumors and high-grade astrocytomas.

Secondary objectives:

1. To estimate the response rate, time to progression, and overall survival in 2 cohorts of patients (diffuse intrinsic pontine tumors, high-grade astrocytomas) treated on this protocol.
2. To explore whether there are any potential associations between primary tumor tissue molecular markers and tumor response.
3. To identify CSF protein markers that might indicate the presence of a brain tumor, to validate proteomic methodology by correlating protein and ELISA measurements of known proteins implicated in angiogenesis and tumor progression (VEGF, bFGF, SPARC, attractin), and to explore whether there are any potential associations between histology (grade) with protein and ELISA measurements of those proteins.
4. To investigate whether the rash associated with cetuximab is secondary to an inflammatory pathway initiated and mediated by the action of cetuximab on host cells.

3.0 BACKGROUND AND RATIONALE

3.1 DIFFUSE INTRINSIC PONTINE TUMORS

Diffuse intrinsic pontine tumors remain one of the most difficult challenges in pediatric oncology. While the prognosis for children with most forms of cancer has steadily improved over time, the dismal prognosis for children with diffuse intrinsic pontine tumors has not yet been altered.

Patients with typical diffuse pontine tumors usually present with a short history of signs or symptoms, and physical examination at presentation typically reveals abducens palsy among other neurological findings. MRI scan reveals infiltrative expansion of the pons, typically with high signal on T2 weighted images, little or no enhancement, and no significant exophytic component. Envelopment of the basilar artery is commonly present [Cancer 2000, 89:1569-1576].

About 30,000 to 40,000 children worldwide develop brain tumors each year [Childs Nerv Syst 1999, 15:758-763]. Data from 1990 to 1999 from the population-based German Childhood Cancer Registry reveal that 1 of 2,500 children will be diagnosed with a central nervous system tumor within the first 15 years of life [Cancer 2001, 92:3155-3164], with brain stem tumors representing 13.8% of the total. Primary pons and brain stem tumors make up 10.7% of the central nervous system tumors. Assuming that most of those represent diffuse pontine tumors, we can estimate that about 1 of 23,000 children will develop a diffuse pontine tumor by the age of 15 years.

While rare, diffuse pontine tumors represent a significant portion of the deaths due to childhood cancer. The German registry included 16,826 pediatric oncology patients enrolled over a 10 year period. If we assume that 75% of the children were cured, then about 4,200 children died of all forms of cancer. There were 351 patients with brain stem and pontine tumors. If we assume that 90% of those died (as would be expected based on current data), then this group represents about 8% of the total deaths due to childhood cancer, a number that far exceeds its proportional representation in the distribution of pediatric cancer diagnoses.

3.2 RADIATION THERAPY IS VERY RARELY CURATIVE FOR DIFFUSE INTRINSIC PONTINE TUMORS

External beam radiation therapy is the standard therapy for diffuse pontine tumors, but several cooperative group (POG and CCG) trials published in the early 1990's indicated that only approximately 10% of patients achieve 3-year survival despite dose-escalation as high as 7800 cGy via hyperfractionation.

POG 9239 was a phase III trial of conventional radiation therapy versus hyperfractionated radiation therapy in children with newly diagnosed diffuse intrinsic brainstem tumors [Int J Radiat Oncol Biol Phys 1999, 43:959-964]. Conventionally treated patients received 5400 cGy in

180 cGy daily fractions, while patients on the experimental arm received 7020 cGy in 117 cGy fractions administered twice daily. Two year survival rates were 7.1% and 6.7%, respectively (p=0.65). One year event-free survival was approximately 10%.

Accelerated fractionation (conventional fraction doses administered twice daily, resulting in a shorter total treatment duration) was studied in the United Kingdom. While the treatment was tolerable, it was also associated with very poor survival [Int J Radiat Oncol Biol Phys 1997, 38:925-929].

3.3 CHEMOTHERAPY HAS NOT BEEN EFFECTIVE FOR DIFFUSE INTRINSIC PONTINE TUMORS

Conventional-dose chemotherapy (usually administered in conjunction with external beam radiation therapy) has not been proved to be effective for diffuse pontine tumors. CCG 9941 was a randomized phase II trial of 2 intensive pre-radiation chemotherapy regimens for children with newly diagnosed diffuse pontine tumors [J Clin Oncol 2002, 20:3431-3437]. Thirty-two patients received regimen A: vincristine (1.5 mg/m2), carboplatin (600 mg/m2/day x 2) and etoposide (167 mg/m2/day x 3). Thirty-one received regimen B: vincristine (1.5 mg/m2), cisplatin (100 mg/m2), cyclophosphamide (1500 mg/m2/day x 2) and etoposide (167 mg/m2/day x 3). Regimen A resulted in a 10% (+/- 5%) objective response rate (≥ 25% decrease in 2-dimensional tumor size) while regimen B resulted in a 19% (+/- 8%) objective response rate. All patients then received hyperfractionated radiation therapy (7200 cGy) and 2-year event-free survival for the entire group was only 6%. These results were not considered to be superior to the historical results with radiation therapy alone. Additionally, high-dose thiotepa-based chemotherapy regimens with stem cell rescue explored by MSKCC/CCG [J Neurooncol 1998, 37:67-73] and French [Cancer 2000, 88:685-692] investigators have similarly not been effective for diffuse pontine tumors.

A variety of agents have been used in conjunction with radiation therapy, often as putative radiation sensitizers, including high-dose tamoxifen [J Clin Oncol 2000, 18:1246-1253], topotecan [Neurooncol 2003, 5:8-13], and etanidazole [Int J Radiat Oncol Biol Phys 2003, 55:1182-1185]. None has yet been demonstrated to be superior to radiation therapy alone, and there is some evidence that the combined use of external beam radiation therapy and radiosensitizers may actually be worse than radiation therapy alone. POG investigators non-randomly compared patients with diffuse pontine tumors treated with hyperfractionated radiation therapy alone (7020 cGy) on POG 8495 with those treated with the same radiation therapy plus concurrent cisplatin on POG 9239. A strong trend towards inferior 1-year survival amongst patients treated with combined therapy was noted [Int J Radiat Oncol Biol Phys 2000, 47:561-564].

3.4 NON-PONTINE HIGH-GRADE ASTROCYTOMAS ALSO HAVE A DISMAL PROGNOSIS

While surgery is often an additional treatment modality available for pediatric patients with non-pontine high-grade astrocytomas, their prognosis also remains very poor. The current standard of care is maximal safe surgical resection, involved-field radiation therapy, and chemotherapy. The largest published pediatric trial to date (CCG-945) compared vincristine, lomustine and

prednisone to the "eight-in-one" chemotherapy regimen in 185 children diagnosed with high-grade astrocytomas between 1985 to 1990 [J Clin Oncol 1995; 13:112-123]. There was no difference in progression-free survival between the two regimens. Overall, patients with AA had a 5-year progression-free survival of 28% versus 16% for patients with GBM. Patients with a gross total resection (> 90%) fared better than did those with less radical surgery (5-year progression-free survival for patients with AA, 42% vs 14%, respectively; for patients with GBM, 27% vs 4%). Thus, perhaps apart from those who had gross total resection, the prognosis for children with newly diagnosed high-grade astrocytomas was very poor. COG ACNS 0126 subsequently treated children with newly diagnosed high-grade astrocytomas with post-operative external beam radiation therapy and concurrent daily temozolomide (90 mg/m2/day x 42), followed by post-RT temozolomide (200 mg/m2/day x 5 per cycle, for ten 28 day cycles). The results have not yet been published, but the preliminary results have been presented on multiple occasions and they do not appear superior to the historical results seen in CCG-945. One year EFS for patients with AA and GBM was 31% +/- 8% and 36% +/- 7%, respectively [ISPNO 2006 abstract TMZ-02, p 57].

3.5 CETUXIMAB

Cetuximab is a human/mouse chimerized antibody of the IgG_1 subclass. It is composed of the F_v regions of a murine anti-EGFR antibody (M225) which human IgG_1 heavy and kappa light chain constant regions and has an approximate molecular weight of 152 kDa. Cetuximab is produced in mammalian (murine myeloma) cell culture and blocks binding of EGF and TGFα to the EGFR and inhibits ligand-induced activation. In addition, cetuximab binding stimulates EGFR internalization, effectively removing the receptor from the cell surface for interaction with ligand. In 2004 the FDA approved cetuximab to be used in combination with irinotecan in adult patients with metastatic colorectal cancer who had failed a prior irinotecan-containing regimen, or as a single agent in patients intolerant to irinotecan.

3.6 CETUXIMAB WITH EXTERNAL BEAM RADIATION THERAPY

The combination of cetuximab and external beam radiation therapy has not previously been investigated in pediatric patients. However, this combination has been determined to be tolerable [J Clin Oncol 2001; 19:3234-3243] and effective in adults with head and neck cancer. A phase III trial comparing RT to RT + cetuximab revealed the addition of cetuximab was associated with improved locoregional control, decreased mortality, and was not associated with increased RT-associated side effects [N Engl J Med 2006; 354:567-578].

3.7 CETUXIMAB FOR BRAIN TUMORS

Clinical data are not yet available regarding cetuximab for brain tumors in either adults or children, with the exception of data discussed below in Section 3.9. Pre-clinical work with an EGFR-amplified glioblastoma multiforme cell line implanted into the flanks or intra-cranially in nude mice yielded encouraging results. Animals treated with cetuximab achieved a significant increase in median survival versus the control animals. Radiation therapy was noted to augment the effect of cetuximab [Neurosurgery 2005; 56:155-162].

Limited information is available regarding the biology of diffuse intrinsic pontine tumors because they are usually diagnosed radiographically and a biopsy is not performed. However, a series of 28 samples (18 obtained via biopsy, 10 via autopsy) was studied and the results suggested that EGFR signaling is worthy of study as a therapeutic target [Clin Cancer Res 2003; 9:3620-3624]. Similarly, while EGFR amplification has been infrequently found in pediatric high-grade astrocytomas, increased expression has been frequently found and targeting EGFR has been suggested as a novel strategy worthy of investigation [Clin Cancer Res 1999; 5:1786-1792].

3.8 IRINOTECAN IS ACTIVE VERSUS PEDIATRIC HIGH-GRADE ASTROCYTOMAS

Duke investigators performed a phase II study of irinotecan (125 mg/m2/dose IV weekly x 4 weeks, followed by a 2 week rest) in children with high-risk malignant brain tumors [Neurooncol 2002; 4:102-108]. Responses (complete + partial) were seen in 4 of 9 patients with high-grade astrocytomas, but none of the 5 with recurrent diffuse intrinsic pontine tumors. However, a POG phase I study of irinotecan (30-65 mg/m2/dose IV x 5 days every 21 days) included 3 patients with brainstem gliomas and 1 achieved stable disease [Clin Cancer Res 2001; 7:32-37].

The effectiveness of irinotecan is known to be schedule-dependent, and St Jude investigators have suggested that the most effective regimen is likely to be 20 mg/m2/dose IV daily x 5 days x 2 weeks, every 3 weeks, based on strong pharmacologic and pharmacokinetic data [J Clin Oncol 1999; 17:1815-1824].

3.9 POETIC PHASE I CETUXIMAB-IRINOTECAN EXPERIENCE

POETIC performed the first pediatric phase I study of the irinotecan and cetuximab combination (CA225085), which was also the initial experience using cetuximab in pediatric oncology patients and in patients with primary tumors of the central nervous system. The preliminary results of this study were presented at the 2007 meeting of the American Society of Clinical Oncology (ASCO) and help justify the exploration of this combination in patients with newly diagnosed disease.

Thirty-five heavily pre-treated patients with refractory solid tumors were enrolled, including 16 patients with high-grade, refractory astrocytomas or progressive brainstem gliomas. Weekly cetuximab was escalated in 3 sequential dose levels: 75, 150 or 250 mg/m^2/dose weekly; irinotecan was given at 16 or 20 mg/m2/day over 1 hour (daily x 5) for two weeks, every 21 days. Patients were treated in two age cohorts (ages 1-12 years = Group A, and 13-18 years = Group B). Pharmacokinetic analyses showed linearity, with similar t1/2, clearance, and volume of distribution between the groups. Irinotecan-related DLT in 2/6 patients in Group A/dose 2 necessitated dose de-escalation from 20 mg/m^2/dose to 16 mg/m^2/dose. Three patients experienced Grade 3 hypersensitivity infusion reaction and were discontinued. A patient with an EGFR-negative high-grade glioma (dose level 1) achieved a >70% reduction in tumor size and remains on study for 22+ months. A patient with ependymoma experienced a confirmed partial response (PR) and continues on treatment for more than 12 cycles. Nine patients received >4 cycles of therapy. Sixteen patients had a best response of stable disease or PR (mean 17 wks, range 5-66+ wks) for an overall clinical benefit rate of 45%. The authors concluded that the combination of cetuximab and irinotecan is well-tolerated over multiple repeat cycles without

cumulative toxicity in children with refractory CNS and non-CNS solid tumors and that promising preliminary anti-cancer activity was observed in a variety of pediatric solid tumors, including high-grade and refractory tumors of the central nervous system.

3.10 CORRELATION OF MOLECULAR MARKERS & TUMOR RESPONSE TO THERAPY (Project leaders: Dr. Nicholas Foreman & Andrew Donson, University of Colorado Health Sciences Center, Denver, CO)

While cetuximab has been approved for the treatment of metastatic colorectal cancer and head and neck cancer, and has shown promise in treating a number of other solid tumors either as a single agent or in combination with other treatments, EGFR over-expression was found to be non-predictive for cetuximab response [Mol Cancer Ther 2006; 5:104-113]. The over-expression of EGFR has, therefore, not been used as an inclusion criterion in clinical trials of cetuximab. Consequently, there is interest in alternative predictors of response to cetuximab. These molecular predictors could be used to select patients who may have a better response to cetuximab whilst sparing those patients who will not respond to ineffective therapy.

The laboratory investigations described in Section 10.1 will be performed using tumor specimens from patients enrolled in this trial in order to identify predictive markers for response to this regimen. Cetuximab, in combination with RT and/or irinotecan, may prove to be effective in a fraction of the patients treated, and the goal of this objective is to identify a target or targets whose expression pattern predicts treatment response.

3.11 CSF PROTEOMICS (Project leaders: Dr. Anna Janss, Children's Healthcare of Atlanta, Atlanta, GA & Dr. Brian Rood, Children's National Medical Center, Washington, DC)

Current diagnostic and therapeutic monitoring of brain tumor patients are significantly hindered due to limited understanding of brain tumor biology and response to therapy. The majority of CNS tumors cannot be identified or followed by expression of serum or CSF markers. However, if available, such markers would be highly desirable and could be used to:

- Detect minimal residual disease
- Predict response to specific targeted therapies
- Distinguish tumor recurrence from post surgical changes or post-radiation changes on neuroimaging
- Augment current histopathologic classification systems
- Improve current clinical and pathological treatment stratification schemata
- Assess efficacy of and tumor response to specific biologic targeted therapies that may not impact tumor size as a primary tumor endpoint (e.g., small molecule inhibitors or anti-angiogenic strategies)

While such markers would be useful to prognosticate, monitor and treat all CNS tumors, the need is greatest in the care of children with malignant glial tumors, especially diffuse brainstem gliomas. These tumors are infrequently amenable to complete resection due to the eloquence of brain tissue they infiltrate, and extension of neoplastic cells beyond tumor margins identified by radiologists or neurosurgeons. As a result, surgery is often limited to diagnostic biopsy or ventricular decompression. In the case of diffuse intrinsic pontine tumors diagnosis is

radiographic and tumor tissue is not obtained unless neuroimaging features are atypical and/or the diagnosis is in question. This has led to a dearth of pathologic material for scientific examination and limited understanding of the biology of these terminal pediatric brain tumors. While technologic advances in neuro-imaging, neurosurgery, radiation therapy and chemotherapy have improved outcomes for many childhood brain tumors, survival for children with diffuse malignant gliomas has not changed in over 30 years. It is unlikely to improve without elucidation of their biology throughout the clinical course.

CNS biologic material in CSF

Malignant glial tumors tend to disseminate locally along white matter tracts rather than through sub-arachnoid seeding. While autopsy studies have identified such dissemination in over 50% of patients at time of death, mortality and morbidity of malignant glial tumors is most often due to local tumor expansion and resultant brain injury or obstructive hydrocephalus. Thus examination of CSF cytology for these tumors is not standard. Given limitations of identifying tumor cells in the CSF, methodologies that could improve our understanding of CNS tumors of all types, and particularly malignant glial tumors are needed. This would provide a significant improvement in currently available knowledge about the biology of these tumors, and could elucidate potential therapeutic avenues.

Proteomics, a relatively new area of research whereby total protein complement of a tissue compartment is analyzed, has successfully been used to identify novel biomarkers in solid tumors [J Neuropathol Exp Neuro 2003; 62:855-862]. Because proteins are effectors of all cellular functions, their measurement should represent the most direct means of cellular characterization and hence tumor biology. Because cells and their environment exist in an integrated state, it has been possible to interrogate the proteins of extra-cellular compartments to assess the presence and impact of tumor cells. This has been done primarily using serum or plasma to establish a method of screening for the presence of low stage tumors.

An analogous extra-cellular compartment for use in brain tumors would be cerebrospinal fluid (CSF). It circulates throughout the CNS and exchanges proteins with the extra-cellular fluid of the brain and spinal cord. CSF is continuously created and reabsorbed, providing a real time steady state proteome. Unlike serum, which contains a highly complex protein mixture ranging from very low abundance proteins in the 10-30 pg/mL range to very abundant proteins in the 35-55 mg/mL range, CSF contains a less complex protein mixture [Proteomics 2005; 5:32223-3225]. Therefore, the CSF is more likely to contain higher relative concentrations of tumor-specific proteins (higher signal to noise ratio) than serum. Taken together this makes CSF and attractive alternative to serum for detection of brain tumor related biomarkers.

Unlike leukemia and many solid tumors outside the CNS, where serial biopsies are readily performed, tumors of the CNS are not easily accessible other than at the time of initial or repeat resection or biopsy. While studies on these samples provide important findings regarding tumor biology, serial analyses during treatment are not reasonable. By contrast, the CSF of tumor patients can be more readily sampled in most pediatric patients. With the development of proteomic technology, investigation of tumor related signals at the time of diagnosis through treatment, and then in remission and/or at the time of recurrence or progression is possible.

While CSF for seeding tumors is readily available and routinely obtained for cytology, the systematic evaluation of the proteins within these samples could be of considerable scientific importance. In addition to identifying potential makers of disease or response to therapy, the glycosylation and phosphorylation status of many proteins can also be evaluated. Studies in tumor tissue show that such information reveals activity of different enzymes that correlate with treatment response [N Engl J Med 2005; 353:2012-2024, N Engl J Med 2005; 352:997-1003] or progression of leptomeningeal metastases [Neurooncol 2006; 8:127-136].

Proteomics

CSF proteomics has been applied to many neurological disorders including Alzheimer's disease, amyotrophic lateral sclerosis, multiple sclerosis, acute brain injury and Creutzfeldt-Jakob disease [Int J Neuropsychopharmacol 2001; 4:93-102]. Reports of its use in neuro-oncology are limited, but demonstrate the potential of this technology to effectively identify tumor biomarkers. One study used two dimensional polyacrylamide (2-D) gel electrophoresis to measure the relative quantities of two pre-selected markers, N-Myc and l-CaD, in the CSF of brain tumor patients [J Neuropathol Exp Neuro 2003; 62:855-862]. Another used ELISA of CSF to identify Ostopontin as predictive of AT/RT and correlated with response to therapy [Am J Clin Pathol 2005; 123:297-304]. CSF proteomics using 2-D gel electrophoresis in combination with mass spectroscopy and cleavable isotope Coded Affinity Tag (cICAT) was used to evaluate 60 samples of CSF and tumor cyst fluid taken from adults with brain tumors and non-neoplastic controls. These techniques were used to find a panel of proteins differentially expressed in lower vs. higher-grade gliomas. Findings were confirmed using Western Blot analysis probing for eight selected proteins based on implied role in gliomagenesis and availability of antibodies. This report, which has been accepted for publication pending revisions, identified 21 potential CSF biomarkers for astrocytoma.

As mentioned above, there is evidence that a significant number of brainstem tumors and gliomas of low and high grade disseminate through the subarachnoid space. The presence of leptomeningeal dissemination of glial tumors is significant because it demonstrates that glial tumor cells have access to the CSF space, and thus, proteins secreted from these tumors have the ability to access the CSF space and may be detected by CSF proteomics.

Proteins involved in angiogenesis

The role of angiogenesis and neovascularization in tumor progression and migration is well established for malignant glial tumors [Anticancer Res 1997; 17:4747-4753, Brain Pathol 2005; 15:342-363]. A large number of cytokines have been identified that up regulate angiogenesis and are balanced by natural inhibitors of this process. Putrefaction of this balance of stimulators and inhibitors increases vascularity and promotes tumor growth. In fact, factors that regulate angiogenesis have been identified and correlate with the degree of malignancy in both non-CNS and CNS tumors [Adv Anat Pathol 2002; 9:24-36, Neurooncol 2005; 7:134-153]. The presence of abnormal neovascular structures is a diagnostic criterion for malignant gliomas and the aberrant regulation of angiogenic cascades is well documented in malignant glial tumors in both adults and children. While angiogenic regulatory molecules act locally within the tumor vascular bed, these molecules are routinely identified in urine and blood, but can also be identified in the CSF [Neurosurgery 2004; 55:562-567]. Improving our understanding of the angiogenic profile in pediatric malignant gliomas may allow better selection of targeted drugs that specifically inhibit

this process. VEGF and bFGF are two integral ligands in the angiogenic cascade and will be studied in this objective.

Proteins involved in tumor growth and migration

Tumor progression is the result of growth and migration facilitated by a complex interplay of mitogenic triggers and proteins that regulate integrity of CNS architecture. While these proteins are important in development and regeneration of the brain, they can be manipulated to promote expansion of tumor and infiltration of neoplastic cells.

Secreted protein with acidic and cysteine rich domains (SPARC), also known as osteonectin is a glycoprotein mitogen found in low levels in normal tissue. Its production is increased in malignant gliomas [J Neurooncol 2002; 60:213-226], and it has been identified in the CSF of adults with glial tumors (grades II-IV).

Attractin is a cell adhesion and guidance protein that exists in both a secreted and transmembrane form due to alternative splicing [Adv Ex Med Biol 2000; 477:173-185]. The transmembrane form (200 kDa) is implicated in axonal regeneration and maintenance of normal CNS architecture because it is upregulated in the former condition and its absence results in juvenile neurodegeneration [Proc Natl Acad Sci USA 2001; 98:559-564]. In contrast, secreted attractin (175 kDa) can interfere with neuronal differentiation by regulation of the neuronal extra-cellular matrix [J Neuropathol Exp Neurol 2002; 61:767-777]. Interestingly, secreted attractin is normally absent in the CSF, but was selectively elevated in the CSF of adults with malignant gliomas by both western blot and proteomic analysis.

As part of this objective, we will study attractin and SPARC levels in the CSF of children with malignant glial tumors and diffuse intrinsic brainstem gliomas to determine if the observation in adults can be generalized to pediatrics, and to evaluate their potential as biomarkers or therapeutic targets.

3.12 ANALYSIS OF SERUM INFLAMMATORY CYTOKINE LEVELS IN PATIENTS TREATED WITH CETUXIMAB: BIOLOGICAL CORRELATIVE STUDIES ON CUTANEOUS MANIFESTATIONS AND DRUG ACTIVITY

(Project leader: Dr. Aru Narendran, Alberta Children's Hospital, Calgary, Alberta)

EGFR inhibitors are generally well tolerated but frequently cause signs of skin toxicity [Ann Oncol 2005; 16:1425-33]. A number of recent reports have suggested a correlation between the acneiform eruption and EGFR inhibitor antitumour activity [J Clin Oncol 2004; 22:1201–1208]. Consequently, there is an ongoing interest in the use of skin side effects as a surrogate marker for pharmacodynamic effects of EGFR inhibitors and about a 'dose-to-rash' strategy to titrate the EGFR inhibitor dose in individual patients to a level that causes detectable skin rash [Clin Cancer Res 2003; 9:2389–2390]. Steroids per se are not appreciably effective and are not used as routine treatment for the rash in patients receiving EGFR targeted agents [Ann Oncol 2005; 16:1425-33]. However, as shown previously, EGFR directed therapies may affect the immune system more directly as well, by unblocking cutaneous chemokine production resulting in an inflammatory type reaction [Am J Pathol 2003; 163:303–312]. We hypothesize that the evaluation of serum levels of inflammatory cytokines in patients who develop the characteristic rash would provide

an effective means of biological correlative analysis during this study. Based on published literature, we have selected approximately 40 cytokines that have been shown to be associated with inflammatory processes involving the skin (Table 1). Antibodies to these molecules have been validated for their ability to detect serum levels of these cytokines and are commercially available in an array format (Ray Biotech, Norcross, GA). The experimental design using cytokine antibody arrays to detect inflammatory cytokines during treatment is described in section 10.3.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

This is a 2-group parallel (high-grade astrocytoma, diffuse pontine tumor), single stage study investigating cetuximab in conjunction with external beam radiation therapy, followed by cetuximab and irinotecan in pediatric and young adult patients. Optional exploratory components of the study include (1) correlation of tumor molecular markers with outcome, (2) CSF proteomics, and (3) assay of serum cytokine levels in patients who develop a cetuximab-associated rash.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 CETUXIMAB

Cetuximab is an anti-EGFR human-to-murine chimeric antibody. Cetuximab is expressed in SP2/0 myeloma cell line, grown in large scale cell culture bioreactors and purified to a high level purity using several purification steps including protein A chromatography, ion exchange chromatography, low pH treatment and nanofiltration. Cetuximab is not known to be a vesicant.

Supplier/How Supplied: Bristol-Myers Squibb (BMS) will supply cetuximab free of charge to the patient. The product is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small amount of easily visible, white, amorphous cetuximab particulates. Each single-use 50-mL vial contains 100 mg of cetuximab at a concentration of 2 mg/mL and is formulated in a preservative-free solution containing 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.42mg/mL sodium phosphate monobasic monohydrate, and water for injection, USP.

Packaging and Labeling: Cetuximab for injection will be supplied by BMS in single-use, ready-to-use 50-mL vials containing 2 mg/mL of product.

Handling and Dispensing of Cetuximab: Cetuximab must be dispensed only from official study sites by authorized personnel according to local regulations. Cetuximab should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that study drug is only dispensed to study patients.

Storage Requirement/Stability: Store vials under refrigeration at 2 C to 8 C (36 F to 46 F). DO NOT FREEZE. Increased particulate formation may occur at temperatures at or below 0 C. This product contains no preservatives. Preparations of cetuximab in infusion containers are chemically and physically stable for up to 12 hours at 2 C to 8 C (36 F to 46 F) or up to 8 hours

at controlled room temperature (20 C to 25 C; 68 F to 77 F). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2 to 8 C. Discard any unused portion of the vial.

Preparation and Administration: Cetuximab must not be administered as an IV push or bolus.

Cetuximab must be administered with the use of a low protein binding 0.2 or 0.22-micrometer in-line filter.

Cetuximab is supplied as a 50-mL, single-use vial containing 100 mg of cetuximab at a concentration of 2 mg/mL in phosphate buffered saline. The solution should be clear and colorless and may contain a small amount of easily visible white amorphous cetuximab particulates. DO NOT SHAKE OR DILUTE.

Cetuximab can be administered via infusion pump or syringe pump.

Infusion Pump:

- Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike or other appropriate transfer device may be used).
- Fill cetuximab into a sterile evacuated container or bag such as glass containers, polyolefin bags (eg, Baxter Intravia), ethylene vinyl acetate bags (eg, Baxter Clintec), DEHP plasticized PVC bags (eg, Abbott Lifecare), or PVC bags.
- Repeat procedure until the calculated volume has been put in to the container. Use a new needle for each vial.
- Administer through a low protein binding 0.2 or 0.22-micrometer in-line filter (placed as proximal to the patient as practical).
- Affix the infusion line and prime it with cetuximab before starting the infusion.
- Maximum infusion rate should not exceed 5 mL/min.
- Use 0.9% saline solution to flush line at the end of infusion.

Syringe Pump:

- Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike may be used).
- Place the syringe into the syringe driver of a syringe pump and set the rate.
- Administer through a low protein binding 0.2 or 0.22-micrometer in-line filter rated for syringe pump use (placed as proximal to the patient as practical).
- Connect the infusion line and start the infusion after priming the line with cetuximab.
- Repeat procedure until the calculated volume has been infused.
- Use a new needle and filter for each vial.

- Maximum infusion rate should not exceed 5 mL/min.
- Use 0.9% saline solution to flush line at the end of infusion.

Cetuximab should be piggybacked to the patient's infusion line.

Following the cetuximab infusion, a 1-hour observation period is recommended.

Safety Precautions: Appropriate mask, protective clothing, eye protection, gloves, and Class II vertical-laminar-airflow safety cabinets are recommended during preparation and handling. Opened vials must be disposed of at the investigational center as chemotherapy or biohazardous waste provided documented procedures for destruction are in place. Otherwise, opened vials must be returned to BMS for disposal. For questions regarding cetuximab destruction please contact BMS at 1-800-743-9224.

Cetuximab therapy should be used with caution in patients with known hypersensitivity to cetuximab, murine proteins, or any component of this product.

It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving cetuximab as sunlight can exacerbate any skin reactions that may occur.

Cetuximab Records at Investigational Site(s): It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number.
- Dates and initials of person responsible for each investigational product inventory entry/movement.
- Amount dispensed to and returned by each patient, including unique patient identifiers.
- Amount transferred to another area for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).
- Amount returned to Sponsor.

BMS will provide forms to facilitate inventory control if the staff at the investigational site does not have an established system that meets these requirements.

Drug Ordering and Accountability: Following submission and approval of the required regulatory documents, a supply of cetuximab may be ordered from BMS. Investigators must complete a Drug Request Form and email it to (cetuximab.drug@bms.com).

Keep in mind that you will need 4-6 vials for weekly maintenance doses, dependent on patient's BSA. Cetuximab is shipped in quantities of 24. Allow 5 business days for shipment of drug from BMS receipt of the C225 (Cetuximab) Clinical Supply Shipment Request form. Drug is protocol specific, but not patient specific.

All product will be shipped via Federal Express in a temperature-controlled container. Shipments will be made from BMS on Monday through Thursday for delivery onsite Tuesday through Friday. There will be no weekend or holiday delivery of drugs. Please contact BMS at cetuximab.drug@bms.com if you have questions or cannot send the form electronically.

It is possible that sites may have more than one cetuximab clinical study ongoing at the same time. It is imperative that only product designated for this protocol number be utilized for this study. To help segregate product for this study from other investigational or marketed product, stickers bearing the protocol number will be provided and should be affixed to the front of the outer carton just above the company names so as not to obscure any marking.

Inside each shipping container, a disposable electronic unit (TagAlert™) to ensure the product has remained at the appropriate temperature during shipping may be included. This unit may be attached to an information card. The LCD display will show "OK" (indicating no alarm has been triggered) or a black bar and the number(s) 1-4 (indicating an alarm/alarms have been triggered). Should an alarm be triggered, follow the instructions on the attached information card. Display results should be recorded on the packing list. For questions regarding drug requisitioning or shipment contact Bristol-Myers Squibb at cetuximab.drug@bms.com.

Important Reorder Instructions: Reorders should be emailed directly to BMS using cetuximab.drug@bms.com for shipment within 5 days. When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose (~4-6 for weekly doses, dependent on patient's BSA), and that shipments may take 5 business days from BMS receipt of request. Cetuximab is shipped in quantities of 24. Drug is not patient specific. Be sure to check with your pharmacy regarding existing investigational stock to assure optimal use of drug on hand.

Receipt of Drug Shipment: Study drug shipments may include a TagAlert™ unit and attached information card (see above for description) and a clinical supply packing list (CSPL). If included, the pharmacist/study personnel responsible for the clinical study product will need to indicate the condition of the shipment, record the TagAlert™ results, and sign the CSPL in the designated areas. The pharmacist/study personnel will keep a photocopy for the site's records, and return the original to BMS, using the enclosed, pre-addressed envelope. The TagAlert™ unit can be discarded after the reading is recorded on the CSPL.

Drug Destruction and Return: At the end of an infusion for an individual patient, any remaining study drug should be destroyed at the site according to the institution's policy for drug destruction. At the completion of the study, all unused study drugs will also be destroyed at the site as per institutional policy for drug destruction. Please maintain appropriate records of the disposal, including dates and quantities. If approved procedures are not in place, please contact Bristol-Myers Squibb at cetuximab.drug@bms.com for assistance.

Drug Inventory Records: It is the responsibility of the Investigator to ensure that a current record of study drug disposition is maintained at each study site where the study drug is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines.

5.2 IRINOTECAN

Route of administration: Intravenous

Supplier: Commercially available

Formulation: 100 mg single use vial (20 mg/ml; 5 ml vials)

Storage: Store vials at room temperature. Do not freeze.

Stability: Refrigerated – infusions prepared in D_5W are stable for 48 hours.
Room temperature – infusions prepared in D_5W are stable for 24 hours.

Preparation: Investigators should use the approved package insert for complete preparation and administration information.

- Must be diluted prior to infusion in Dextrose in D5W. Solutions prepared in Sodium Chloride 0.9% should not be refrigerated.
- Final concentration range from 0.12 to 2.8 mg/ml.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 SUBJECT INCLUSION CRITERIA

- Patients must have either (1) histologic proof of a high-grade astrocytoma reviewed by a POETIC institutional pathologist or (2) a radiological diagnosis via MRI scan of a typical diffuse pontine tumor made by a POETIC institutional neuroradiologist. Patients with a radiological diagnosis via MRI scan of a typical diffuse pontine tumor will be enrolled on the diffuse pontine tumor arm of the study regardless of histology in cases that are biopsied. Note: For collaborating non-POETIC institutions, the reviews may be done by an institutional pathologist/neuroradiologist.

- Patients must begin study prescribed therapy within 42 days of neurosurgical resection or biopsy of the tumor (high-grade astrocytoma patients) or radiological diagnosis (diffuse pontine tumor patients).

- Age ≥ 3-years and < 22-years-old.

- Brain MRI (and any other studies done according to clinical indications) must not show any definitive evidence of leptomeningeal or extra-neural metastases.

- Patients must have adequate hematopoietic function as defined by:

  ANC ≥ 1000/μL and platelet count ≥ 100,000/μL

- Patients must have adequate organ function as defined by:

  Hepatic: total bilirubin < 1.5 mg/dl, AST ≤ 2.5 x the upper limit of normal.

  Renal: serum creatinine ≤ 1.5 x the upper limit of normal for age, or calculated creatinine clearance or nuclear GFR ≥ 70 ml/min/1.73 m^2.

- Performance status ≥ 50 (Lansky for children ≤ 16 years of age, Karnofsky for patients > 16 years of age). Both performance scales are available in Appendix 1.

- The patient, or for minors, a parent or legal guardian, must give informed written consent indicating they are aware of the investigational nature of this study.

6.2 SUBJECT EXCLUSION CRITERIA

- Evidence of leptomeningeal or extra-neural metastatic disease.

- Prior radiation therapy or chemotherapy

- Pregnancy, mothers unwilling to refrain from breast-feeding, and sexually mature patients unwilling to practice an effective form of birth control

- Other significant concomitant medical illnesses that would compromise the patient's ability to receive all prescribed study therapy.

- Prior therapy which specifically and directly targets the EGFR pathway.

- Prior severe infusion reaction to a monoclonal antibody.

- Significant history of uncontrolled cardiac disease; i.e., uncontrolled hypertension, unstable angina, recent myocardial infarction (within prior 6 months), uncontrolled congestive heart failure, and cardiomyopathy with decreased ejection fraction.

- Patients with known Gilbert's Syndrome.

7.0 RECRUITMENT PLAN

Patients will be offered the opportunity to participate in this trial if they meet all eligibility criteria. There will be no discrimination against females or minorities. Informed consent will be obtained from the patient, or if they are non-emancipated minors, their parent or legal guardian. Consent will be obtained by an investigator authorized to obtain consent. Patients will not receive any payment for their participation in this study.

7.1 Patients or their parent/legal guardian will be required to sign a statement of informed consent indicating the investigational nature of this study.

7.2 The investigators listed on the cover page and their qualified designees at each institution as listed on the FDA 1572 for this study may obtain consent and care for the patients according to good clinical practice and protocol guidelines.

7.3 One to three copies of the informed consent will be signed and dated by the patient, parent or the patient's legally authorized representative and by the physician obtaining informed consent, as per institutional guidelines. If institutional guidelines mandate that only one original copy is signed, the following sentences will refer to photocopies of the original. One copy will be given to the patient/parent/legal guardian to be retained for their personal records. One copy will be maintained on file at the Data and Coordinating Center. The third copy will be confidentially maintained by the participating institution.

7.4 A note will be placed in the medical record documenting that informed consent was obtained for this study, and that the patient and/or his/her parents, to the degree of their understanding, acknowledge and accept the risk of participation in this study.

7.5 Written consent must be documented on the appropriate consent form approved by the Institutional Review Board at the respective POETIC center. Attainment of the written consent must be verified by the Data and Coordinating Center (or equivalent entity) of the participating institution prior to entry on study. A copy of the consent form, along with the eligibility checklist, and Health Insurance Portability and Accountability Agreement (HIPAA) must be submitted to the Clinical Trials Office at the Data and Coordinating Center prior to enrollment of any subject on this study. Verification of subject enrollment on this study will be sent by FAX or email the participating center immediately on receipt of the required documents.

Every effort will be made to include women, children of both sexes and minorities in the study population for this trial. No patient will be excluded from participation in this trial on the basis of gender, ethnicity, or race. Review of accrual to past pediatric multicenter studies of new agents demonstrates the accrual of both genders and all NIH-identified ethnicities to such studies. The small number of patients entered into this trial will obviate any analysis of variation in toxicity profile or response rate with gender or ethnicity.

Data from the institutions participating in this trial have been reviewed with respect to enrollment of patients of different races and genders. It is anticipated that enrollment of the current study will follow the same pattern.

Institution	Number of Patients	White Non-Hispanic	Black Non-Hispanic	Hispanic (%)	Other (%)

		(%)	(%)		
MSKCC	147	61.0	19.0	15.0	5.0
UAHSC	40	35.0	3.0	53.0	9.0
JHMC	77	73.0	21.0	1.0	5.0
UCHSC	154	75.0	0.0	20.0	5.0
MDACC	146	60.0	5.0	29.0	6.0
VMC	116	83.0	15.0	1.0	1.0
UF	93	81.5	16.5	0.8	0.8
PCH	137	65.7	< 0.1	27.7	6.5
CHOA	276	60.5	27.2	9.4	2.9

8.0 PRETREATMENT EVALUATION

- Review of the pathology by a POETIC institutional pathologist (not required for patients with unbiopsied diffuse pontine tumors) Note: For collaborating non-POETIC institutions, the review may be done by an institutional pathologist
- Pre-operative brain MRI with/without contrast
- Post-operative brain MRI with/without contrast (high-grade astrocytoma patients only)
- Complete blood count
- Liver function tests: Total bilirubin, AST
- Renal function tests: Creatinine (Creatinine clearance or nuclear GFR study if serum creatinine > 1.5 x upper limit of normal for age)
- For females of child-bearing potential: Urine or serum pregnancy test according to local institutional standards
- All of these pre-treatment evaluations (other than pathology review, pregnancy testing, and the pre-operative brain MRI with/without contrast) must be performed ≤ 30 days before registration onto study. Pregnancy testing must be performed ≤ 14 days before registration.
- Physical exam

Appendix 2 also provides a summary of these pre-treatment evaluations

9.0 TREATMENT/INTERVENTION PLAN

Patients will receive 2 phases of therapy, as described below.

9.1.0 FIRST PHASE: RADIATION THERAPY & CETUXIMAB

Cetuximab will be given at 250 mg/m2/weekly for 6 doses. On days when both the radiation therapy and cetuximab are administered, there is no mandated order of administration or timing between the 2 treatments. Regardless of the order of administration, it is important to note that the patient should be carefully monitored for signs of anaphylaxis for at least 1 hour following completion of the infusion in an appropriate area with readily available resuscitation equipment and medications (as per protocol section 9.1.2). Patients will be treated for about 6 ½ weeks during this phase (33 daily fractions of radiation therapy and 6 weekly doses of cetuximab).

Cetuximab is to be given every 7 days (+/- 2 days). Cetuximab does not need to be given on Day 1 of each week.

The dose of cetuximab will be rounded off to the nearest 10 mg.

There will be no dose modification of the radiation therapy for toxicity. For dose modifications of cetuximab see section 9.3 below.

9.1.1 RADIATION THERAPY GUIDELINES

Technique:
All radiotherapy techniques are permitted including 3D conformal, IMRT and proton therapy. Lateral fields may be used for diffuse pontine tumors though 3D target definition is recommended.

Dose and volume:
All tumors will be treated to 5940 cGy in 33 once daily 180 cGy fractions.

The initial PTV for high-grade gliomas will be determined by adding a 2 cm margin to the area of T1 enhancement (GTV) based on the pre-operative MRI scan. For non-enhancing tumors, the MRI sequence that best defines the extent of disease should be used. A conedown to the post-operative tumor bed, including any residual disease plus a 1cm margin is allowed at 5400 cGy.

The GTV for diffuse pontine tumors will consist of the tumor best demonstrated on MRI. The MRI sequence that best defines the extent of disease should be used. A 1 cm margin is added in all directions to determine the PTV.

Volumes and doses may be modified as necessary to prevent overdosing of critical normal tissues such as spinal cord and optic chiasm, based on institutional practices.

The dose and source will be documented in the Case Report Forms.

Radiation must be performed at a POETIC institution or at a designated academic or professional partner institution, according to standard institutional practice for patients on clinical trials. Radiation may not be performed at a local or private facility that is not a partner for academic purposes.

9.1.2 CETUXIMAB ADMINISTRATION

Strong consideration should be given to antihistamine premedication prior to cetuximab to try to reduce the risk of a hypersensitivity reaction. Diphenhydramine (1 mg/kg IV or orally) is recommended.

Cetuximab will be administered as an intravenous infusion over about 60 minutes +/- 10 minutes, and must be administered at a POETIC institution. The infusion rate should not exceed 10 mg/minute (5 ml/minute). Patients should be carefully monitored for signs of anaphylaxis for at least 1 hour following completion of the infusion in an appropriate area with readily available resuscitation equipment and medications.

9.2 SECOND PHASE: IRINOTECAN & CETUXIMAB

Between 28 and 56 days after completion of radiation therapy (based on the discretion of the investigator and resolution of compromising radiation-induced toxicities) patients will begin irinotecan and cetuximab. To begin this phase of therapy, the ANC must be $\geq$ 1000/mcl, the platelet count $\geq$ 100,000/mcl, and the total bilirubin $\leq$ 2.0 mg/dL. Patients who cannot begin the second phase of therapy within 56 days will be considered study failures and will be removed from the study and not replaced.

Irinotecan will be administered at a dose of 16 mg/m^2/day IV over about 60 minutes +/- 10 minutes x 5 consecutive days x 2 weeks every 21 days. Cetuximab will be administered at a dose of 250 mg/m^2/dose IV over 60 minutes +/- 10 minutes weekly x 3 weeks per cycle (see section 9.12 for administration instructions). The dose of cetuximab will be rounded off to the nearest 10 mg and the dose of irinotecan to the nearest 1 mg. These doses of irinotecan and cetuximab were determined to be safe and tolerable in the POETIC phase I study (CA225085). On days when both irinotecan and cetuximab are administered, the cetuximab will be administered first and the irinotecan infusion will begin about 60 minutes following completion of the cetuximab infusion. Cetuximab is to be given every 7 days (+/- 2 days). Cetuximab does not need to be given on Day 1 of each week.

Subsequent cycles of irinotecan will begin 21 days following the start of the previous cycle if the ANC is $\geq$ 1000/mcl, the platelet count is $\geq$ 100,000/mcl, and there has been adequate resolution of any other toxicity. If adequate recovery has not taken place by day 21, the start of the cycle will be delayed until sufficient recovery. If the cycle must start more than 28 days following the start of the prior cycle the dose modification section below should be consulted. Patients are intended to receive 10 cycles unless a criterion for removal from study is met (section 13.0). However, for patients whose disease remains stable or better at the completion of 10 cycles,

therapy may be continued at the discretion of the patient and physician until a criterion for removal from the study is met.

The cetuximab must be administered at a POETIC center, but the irinotecan may be administered at another center or via homecare if such a regimen is more convenient for the patient. In such cases, adequate documentation must be sent to the Data and Coordinating Center at MSKCC in a timely fashion and in compliance with all study guidelines and requirements. Local institutions will be responsible for securing all documentation as required on the Case Report Forms regarding irinotecan administration.

9.3 CHEMOTHERAPY/BIOLOGIC DOSE MODIFICATION RULES

9.3.1 CETUXIMAB

Management of Infusion Reactions

Severe infusion reactions require the immediate interruption of cetuximab therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Patients should be carefully observed until the complete resolution of all signs and symptoms.

In previous clinical trials, mild to moderate infusion reactions were managed by slowing the infusion rate of cetuximab and by continued use of antihistamine pre-medications (eg, diphenhydramine) in subsequent doses. If the patient experiences a mild or moderate (Grade 1 or 2) infusion reaction, the infusion rate should be permanently reduced by 50%. For grade 1 or 2 reactions manifesting only as delayed drug fever, see paragraph below. Cetuximab should be immediately and permanently discontinued in patients who experience severe (Grade 3 or 4) infusion reactions.

Treatment of Isolated Drug Fever

In the event of isolated drug fever, the investigator must use clinical judgment to determine if the fever is related to the study drug or to an infectious etiology.

If a patient experiences isolated drug fever, for the next dose, pre treat with acetaminophen or non-steroidal anti-inflammatory agent (investigator discretion), repeat antipyretic dose 6 and 12 hours after cetuximab infusion. The infusion rate will remain unchanged for future doses.

If a patient experiences recurrent isolated drug fever following premedication and post-dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be 50% of previous rate. If fever recurs following infusion rate change, the investigator should assess the patient's level of discomfort with the event and use clinical judgment to determine if the patient should receive further cetuximab.

Management of Pulmonary Toxicity

In the event of acute onset (grade ≥ 2) or worsening pulmonary symptoms which are not thought to be related to underlying cancer, cetuximab therapy should be interrupted and a prompt investigation of these symptoms should occur. Cetuximab retreatment should not occur until

these symptoms have resolved to grade 1. If interstitial lung disease is confirmed, cetuximab should be discontinued and the patient should be treated appropriately.

Management of rash

Cetuximab Dose Modification Guidelines

Grade 3 Acneform Rash/ desquamation	**Cetuximab**	**Outcome**	**Cetuximab Dose Modification**
1st occurrence	Delay infusion 1 to 2 weeks	Improvement	Continue at 250 mg/m^2
		No Improvement	Discontinue cetuximab
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce Dose Level -1
		No Improvement	Discontinue cetuximab
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce to Dose Level -2
		No Improvement	Discontinue cetuximab
4th occurrence	Discontinue cetuximab		

Cetuximab Dose Levels

	Weekly Cetuximab dose
Starting dose	250 mg/m^2
Dose Level -1	200 mg/m^2
Dose Level -2	150 mg/m^2

Cetuximab in Combination with Radiation Therapy

Cetuximab in combination with radiation therapy should be used with caution in patients with a history of coronary artery disease, congestive heart failure, and arrhythmias. Although the etiology of these events is unknown, close monitoring of serum electrolytes, including serum magnesium, potassium, and calcium, during and after cetuximab therapy is recommended.

Management of Hypomagnesemia

Hypomagnesemia has been reported with Cetuximab when administered as a single agent and in combination with multiple different chemotherapeutic regimens. The incidence of hypomagnesemia (both overall and severe [NCI CTC grades 3 & 4]) is increased in patients receiving chemotherapy and Cetuximab as compared with those receiving chemotherapy alone based on controlled clinical trials. Patients receiving Cetuximab therapy should be monitored for hypomagnesemia. Magnesium repletion may be necessary based on clinical judgment.

9.3.2 IRINOTECAN

- GI Toxicity: Grades 3 or 4 despite maximal medical management will mandate a dose reduction by 2 mg/m^2/day.
- Hepatic impairment: Irinotecan should not be administered if the total bilirubin is > 2 mg/dL. It may be restarted if the total bilirubin falls to ≤ 2 mg/dL.
- If a cycle cannot start by day 28 due to hematopoietic toxicity (ANC < 1000 and/or platelet count < 100,000), the dose of irinotecan should be reduced by 2 mg/m^2/day.

9.4 SUPPORTIVE CARE

Clinical judgment may be used to alter the following guidelines without being a protocol violation:

<u>During all phases of therapy</u>

Anti-emetics may be used.

Filgrastim (G-CSF) may be used according to institutional practice and/or ASCO guidelines.

Patients developing dermatologic toxicities while receiving cetuximab should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Dose modifications of any future cetuximab infusions should be instituted in case of severe (grade 3) acneform rash/desquamation (section 9.3.1). Treatment with topical and/or oral antibiotics should be considered; topical corticosteroids are not recommended. If a patient experiences severe acneform rash/ desquamation, cetuximab treatment adjustments should be made according to the table above (section 9.3.1). In patients with mild and moderate skin toxicity, treatment should continue without dose modification.

<u>During the second phase of therapy (while patients are receiving irinotecan)</u>

Anti-convulsants: Enzyme-inducing anti-convulsants (phenytoin, phenobarbital, carbamazepine) should be avoided. Patients who require an anti-convulsant should be treated with a non-enzyme inducing anti-convulsant for a minimum of 4 half-lives of the anti-convulsant agent prior to starting treatment with irinotecan. Documentation of this should be included on the Concomitant Medication form in the Case Report Forms.

Diarrhea: Prophylaxis with an oral cephalosporin (such as cefixime 8 mg/kg/day, maximum 400 mg/day) may be used [J Clin Oncol 2006; 24:563-570]. For early onset diarrhea (during irinotecan infusion or shortly after the infusion), consider atropine (0.01 mg/kg, maximum 0.4 mg) and octreotide. For later onset diarrhea, consider prompt use of loperamide, and consider octreotide if that does not adequately control diarrhea. Suggested loperamide (1 caplet = 2 mg, 1 teaspoon = 5 ml = 1 mg) dosing follows:

- Patients > 43 kg: Take 4 teaspoons or 2 caplets after the 1st loose bowel movement followed by 2 teaspoons or 1 caplet every 2 hours. During the night the patient may take 2 caplets every 4 hours rather than 1 caplet every 2 hours.
- Patients > 30 to 43 kg: Take 2 teaspoons or 1 caplet after the 1st loose bowel movement followed by 1 teaspoon or ½ caplet every 2 hours. During the night the patient may take 1 caplet every 4 hours rather than ½ caplet every 2 hours.
- Patients > 20 to 30 kg: Take 2 teaspoons or 1 caplet after the 1st loose bowel movement followed by 1 teaspoon or ½ caplet every 3 hours. During the night the patient may take 1 caplet every 4 hours rather than ½ caplet every 3 hours.
- Patients > 10 to 20 kg: Take 1 teaspoon after the 1st loose bowel movement followed by 1 teaspoon every 3 hours. During the night the patient may take 1 teaspoon every 4 hours rather than every 3 hours.
- Patients 8 to 10 kg: Take 1 teaspoon after the 1st loose bowel movement followed by ½ teaspoon every 3 hours. During the night the patient may take ¾ teaspoon every 4 hours rather than every 3 hours.

Pneumocystis carinii (PCP) prophylaxis: Patients should receive PCP prophylaxis, according to any standard regimen chosen by the attending pediatric oncologist in agreement with local standard practices, and an individual patient's medication compatibility profile and compliance determination.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

The mandated observations are summarized in Appendix 2.

<u>During the first phase of therapy (Radiation therapy with cetuximab)</u>
Physical exams will be performed and potassium, calcium, and magnesium levels will be obtained once a week, prior to each cetuximab infusion.

CBC and other laboratory work will be obtained as clinically indicated.

<u>During the second phase of therapy (irinotecan with cetuximab)</u>
Physical exams will be performed and a CBC, potassium, calcium, magnesium, total bilirubin, AST, and creatinine will be obtained prior to each cycle. Laboratory work during a cycle will be obtained as clinically indicated.

Assessment of tumor status via brain MRI will be performed about 3 weeks after completing RT (pre-cycle 1 chemotherapy), then during every 3rd cycle of irinotecan-cetuximab (during cycles 3, 6, and 9).

<u>Following completion of therapy</u>
For patients who complete protocol therapy and remain on study progression-free, MRI scans of the brain will be performed at about 3, 6, 9, 12, 18, 24, 30, 36, and 42 months post-completion of therapy or until the patient has been removed from the study. Subsequent scans will be performed at the clinician's discretion and are not mandated by this protocol, but are recommended approximately annually.

Mandated evaluations including lab work and MRI scans may be performed at other (non-POETIC) centers if deemed clinically indicated as long as they are submitted to the POETIC investigator in a timely fashion.

10.1 TUMOR TISSUE ANALYSES

Analysis of EGFR and associated molecules HER2 and HER3 expression

Although over-expression of EGFR was not shown to be predictive for cetuximab response in previous studies, it cannot be assumed that it will not be predictive in pediatric patients with high-grade glial tumors. We will therefore screen tumor samples for EGFR gene amplification, and EGFR protein over-expression. HER2 and HER3 heterodimerize with EGFR to affect EGFR activity, and HER2 has previously shown some value in predicting cetuximab response. We will therefore study HER2 and HER3 gene amplification and over-expression in tumor specimens. Both procedures will be performed on paraffin sections of tumor (5 micron thickness). To ensure consistency of results between specimens received from different institutions we recommend a standardized fixation procedure, but this is a guideline only and institutional practices may be substituted. Tissue samples will be dissected to a thickness of no greater than 5 mm and fixed in 10% NBF 24-48 hours. Samples will then be transferred to 70% ethanol where they can remain indefinitely with no deterioration of antigen. All subsequent experimentation will be performed at a single institution, the University of Colorado Denver (UCD), to ensure consistency of results.

Gene amplification will be assessed using fluorescence in-situ hybridization (FISH). This procedure requires fifteen paraffin sections per tumor sample. FISH will be performed at the University of Colorado Cancer Center DNA Core facility, managed by Dr Leila Garcia. This core facility has relevant experience in that it has performed standardized FDA approved FISH analysis of EGFR, HER2 and HER3 in previous cetuximab lung cancer clinical trials.

Gene over-expression will be assessed using immunohistochemistry (IHC). IHC will be performed by IHCtech (www.ihctech.net), an IHC dedicated facility located on the UCHSC campus that routinely performs standardized staining for EGFR and HER2 in clinical samples.

Analysis of surrogate biomarkers predictive for cetuximab and RT or irinotecan response

To identify surrogate predictors of response to cetuximab and RT or irinotecan, we will perform a global gene analysis of tumor specimens using microarray technology. We will generate gene expression profiles for 50,000 genes for each patient's tumor, and then compare the profiles of those patients who responded to treatment against those who did not respond. This analysis may provide a small number of genes whose expression, or lack thereof, accurately predicts response to therapy. The Pediatric Neuro-oncology Laboratory at UCHSC has performed similar analyses in the identification of prognostic genes for ependymoma recurrence [J Neuro-Oncol 2006; 78:41-46]. Cetuximab-predictive genes identified using gene-expression microarrays would be validated by Western blot analysis and IHC. For microarray and Western blot analyses we would require at least 6 mm3 of tumor tissue, snap frozen in liquid nitrogen at the time of surgery. This would provide a sufficient quantity and quality of RNA and protein to perform the proposed analyses. Fifteen paraffin sections will be required for IHC validation of specific microarray results.

Analysis of MGMT expression

MGMT promoter methylation status has been shown to influence both survival and response to therapy in pediatric glioblastoma multiforme [Pediatr Blood Cancer 2006; 48:403-407]. MGMT methylation status of patients enrolled in this clinical trial will be studied. This procedure requires 1 microgram of DNA, preferably obtained from snap frozen tumor, but also retrievable from paraffin embedded material. In addition, MGMT expression will be measured by IHC.

Data Analysis

Data obtained by FISH, IHC, microarray analysis and MGMT methylation analysis will be analyzed to identify therapeutic response correlates. The biological data can be correlated to response both to the RT-cetuximab and irinotecan-cetuximab as response data to both modalities will be potentially evaluable on this study. These data will help to elucidate the anti-tumor mechanisms of cetuximab in high-grade gliomas of childhood. Correlates of response may also help to select patients with high-grade astrocytomas for treatment with cetuximab in future clinical trials.

The data obtained from these studies directly on high grade gliomas will be correlated with the CSF proteomics data (described below). This will hopefully provide additional insight into the biology of the diffuse pontine gliomas, which is clearly lacking in the literature at this time.

Table of material requirements

Submission of paraffin material is mandatory for high-grade gliomas outside the pons and optional for diffuse pontine gliomas. Submission of the number of paraffin section below is encouraged, but patients will not be excluded from the study if fewer samples or less material are available. Submission of frozen tumor material is strongly encouraged, but not mandatory for study participation.

Analysis	**Technique**	**Tissue requirement per patient**
EGFR, HER2, HER3 gene amplification	FISH	12 paraffin sections (5 micron thickness)
EGFR, HER2, HER3 protein overexpression	IHC	
Microarray gene expression analysis and subsequent Western blot analysis	Affymetrix U133+2 microarray analysis and Western blot	6 mm^3 of tumor snap frozen immediately at resection
IHC analysis subsequent to microarray results	IHC	3 paraffin sections (5 micron thickness)
MGMT methylation analysis	Methylation specific PCR	2 mm^3 of tumor snap frozen immediately after resection

Specimen collection

These samples should be forwarded via FedEx, Monday through Thursday to the following address:

Attn: Andrew Donson
UCD, Pediatrics
Bldg RC1, Rm P18-4402F
12800 E 19th Ave
Aurora CO 80010-7174

No weekend deliveries are permitted. Sites should contact 303-724-4012 to notify of shipment.

10.2 CSF PROTEOMICS

Patient specimens

Participation in this component of the study is optional. Patients excluded from this biological study will include those in whom procurement of CSF is deemed unsafe by the attending physician and in those participants whose family declines the evaluation.

CSF will be obtained prior to initiation of any post-operative radiation therapy or cetuximab. CSF will be obtained via lumbar puncture, ventricular or cisternal sample at the time of flow diversion or aspiration of an external ventricular drain or surgical procedure. In patients where more than one site of CSF fluid has been accessed, analysis from each site will be undertaken when possible.

CSF cytology will be evaluated for presence of tumor cells by an institutional pathologist using standard methods. Approximately 3 ml of CSF will be requested for proteomic analysis. After acquisition, the CSF should be kept on wet ice or in a 4 degree refrigerator until processing. Processing should be performed within 6 hours of sample acquisition. The CSF will be spun at 400-500 g for 10 minutes to remove cellular contaminants. The first 2 ml of CSF supernatant will be aliquoted into four 500 mcl units (taking care to leave the cellular pellet behind) and frozen at -20 to -80 degrees Celsius to be used for proteomic analysis. Each tube must be labeled with the POETIC patient accession number, the sample type and the time it was drawn.

If sample is insufficient for both laboratories priority is to send sample to Dr. Hathout
Sample collection and shipping dates must be documented in the clinical research core. These samples should be forwarded via FedEx, Monday through Thursday. No weekend deliveries are permitted. Sites should contact Yetrib Hathout, PhD, at 202-476-3136 to notify of shipment. All CSF biologic samples should be shipped on dry ice, along with a completed biologic specimen transmittal form to:

Attention: Yetrib Hathout, PhD
CRI, Room 5700
111 Michigan Avenue, NW
Washington, DC 20010
Phone: 202-476-3136
Email: YHathout@cnmcresearch.org

The remaining 1 ml of CSF will be aliquoted in 200 mcl units and frozen at -20 to -80 degrees Celsius to be evaluated for cytokines. Each tube must be labeled with the POETIC patient

accession number, the sample type, site from where the sample was obtained, and the time it was drawn.

These samples should be forwarded on dry ice via FedEx, Monday through Thursday to the following address:

Attn: Andrew Donson
UCD, Pediatrics
Bldg RC1, Rm P18-4402F
12800 E 19th Ave
Aurora CO 80010-7174

No weekend deliveries are permitted. Sites should contact 303-724-4012 to notify of shipment.

Laboratory analysis

a. Proteomic Biomarker Evaluation

Criteria for a successful proteomic methodology for identification of a usable biomarker include high throughput, reproducibility and toleration of real world collection and shipping conditions. In addition, such methods must be able to identify differentially expressed proteins in an unsupervised manner as well as provide information about specific proteins of interest. Currently, there is not a single mature technology available to meet all these criteria. Therefore, a combined approach will be employed in this exploratory study to attempt to fit all of these characteristics and improve the body of knowledge about the utility of these strategies.

All these approaches will require concentration and desalting of the samples. Proteins can be precipitated using 15% trichloracetic acid, re-suspended in denaturing buffer and stored at -20 to -80 degrees Celsius until the time of analysis.

The first component of the proteomic approach will employ 2-D gel electrophoresis to separated proteins in two dimensions according to their size and charge. The gels are then stained with Gelsoft coomasie stain (Bio-Rad) and then scanned by a high resolution scanner. Relative spot positions and intensities are quantitated by pixel reading software (PDQuest and Ludesi). Individual spots are normalized to total signal [Proteomics 2003; 3:1962-1979]. Individual proteins that are found to be differentially expressed between groups will be subjected to in-gel trypsin digestion. Published work at Children's National Medical Center with this methodology has successfully fractionated CSF derived proteins and identified differentially expressed proteins in white matter disease [Clin Chem 2005; 51:2031-2042].

The second approach employed will be label free quantification. MS-based proteome profiling is a powerful method by which a large number of proteins across large sets of complex samples can be identified. The main obstacle in protein profiling is to distinguish ('labels') proteins (at the peptide level) that are originated from different samples. New and emerging techniques such as stable isotope labeling (SILAC, iTRAQ, ^{18}O) are either expensive (iTRAQ, SILAC) or unstable (^{18}O). With the improvement of liquid chromatography (LC) as well as mass spectrometry (MS) techniques, the new trend in proteome profiling is label-free methodology. The idea behind this

method is first to generate reliable and reproducible LC-MS runs using trypsin digested proteins from CSF samples. In order to accommodate minor discrepancies between subsequent runs, each sample will be spiked with a known amount of non-native protein. Peaks generated by this protein will be used for internal normalization, as well as for normalization across sample sets. Given that peptides elute and behave similarly between different runs, peak heights (at MS or MS/MS stage) representing peptides can be extracted, calculated, and normalized to the internal (spiked) standard. From these data, differential protein expression can be calculated across inter/intra sample populations to identify potential biomarkers.

b. ELISA for confirmation/correlation of target proteins

CSF samples will be evaluated for expression of specific secreted proteins implicated in tumor progression, migration and response to therapy. These target proteins, described above, have well-characterized, commercially available antibodies including VEGF, dFGF, attractin, SPARC and EGF.

10.3 SERUM ANALYSIS OF INFLAMMATORY CYTOKINE LEVELS

Participation in this component of the study is optional.

Experimental design

Sera will be collected before the first dose of cetuximab and at the time of the development of the characteristic skin rash and at its distinct stages of progression. A scoring system will provide a standardized evaluation of the rash (Table 1).

Table 1. Simplified classification of acneiform eruption caused by EGFR inhibitors

NCI CTCAE v3.0			
Rash/desquamation			
Grade 1	Grade 2	Grade 3	Grade 4
Lesions without symptoms	Lesions with symptoms < 50% body surface	Lesions with symptoms ≥ 50% body surface	Exfoliative, ulcerative or bullous erythroderma
Rash: acne/acneform			
Grade 1	Grade 2	Grade 3	Grade 4
Intervention not indicated	Intervention indicated	Pain, disfigurement, ulceration or desquamation	-

Using a sensitive antibody array technique, the presence of approximately 40 separate cytokines (Table 2) will be detected and quantified as described previously [Anal Biochem 2001; 294:55-62, http://www.raybiotech.com/principle.asp?m=6]. Briefly, blood will be collected at specified times and sera will be incubated with cytokine arrays that contain capture antibodies. Commercially available normal human sera will be used as additional control. Following three washing steps to remove unbound proteins, enzyme labeled detection antibodies will be added and the arrays will be developed using conventional ECL reagents. The resulting X-ray films will be scanned and analyzed by digital image processing. Significant changes will be validated by ELISA or Western blot analysis. Data will be analyzed using GraphPad Prism version 3.00 statistical software (GraphPad Software, San Diego, CA). Changes more than a standard deviation seen in normal sera will be considered significant. Correlative analysis will be carried out with clinical parameters indicated in the protocol.

EOTAXIN	GCSF	GM-CSF	ICAM-1	IFN-g	I-309	IL-1[a]	IL-1b
IL-2	IL-3	IL-4	IL-6	IL-6sR	IL-7	IL-8	IL-10
IL-11	IL-12	p40	p70	IL-13	IL-15	IL-16	IL-17
IP-10	MCP-1	MCP-2	M-CSF	MIG	MIP-1a	MIP-1b	MIP-1d
MIP-1d	RANTES	TGF-b1	TNF-a	TNF-b	sTNFRI	sTNFRII	PDGF-BB
TIMP-2							

Table 2. Inflammation related cytokines to be analyzed in the sera of patients who develop rash during treatment on protocol.

Timing of sample collections

Blood will be collected from patients prior to the first dose of cetuximab in the phase I portion of the study as a control. Sera will also be collected from patients who do not develop rash prior to the first 4 cycles of irinotecan and cetuximab in the Phase II portion of the study. If a patient develops a rash at any point during the Phase I portion of the study or during cycles 1-3 of the Phase II portion of the study they are not to be considered a control subject anymore and are not to have any further pre-cycles 1-4 blood samples taken. Additional samples will be drawn when there is an incremental increase in the severity score of the rash (see guidelines, Table 1). Specific information regarding the rash will be collected based on the key clinical features and classification of dermatologic adverse reactions of EGFR targeted agents described by Agero et al [J Am Acad Dermatol 2006; 55:657-670]. To minimize patient inconvenience, blood draws will be done to coincide with other routine blood draws or IV access.

Sample collection, processing and transport

Collect 1 ml of blood and allow for clotting on ice or in a refrigerator for approximately 15- 30 minutes. Separate and collect the serum, preferably in an Eppendorf microcentrifuge tube. If micro centrifuge tubes are not available, any cloudy plastic tube can be used. Sera will be separated from the clot by centrifugation (1,200 RPM for 5 minutes), transferred to an Eppendorf tube and stored frozen in a -20 C freezer until shipment.

Ship sera on dry ice by next day delivery. Send samples only on Monday through Thursday. Public holidays in Canada can be found in: http://www.pch.gc.ca/progs/cpsc-ccsp/jfa-ha/index_e.cfm

The following information should be included with each sample:, Site ID, study number, study time point, date and time of collection. Please attach 3 copies of the completed customs form below **on the outside of your shipment box. Shipments with less then 3 customs forms and are not located on the outside of the box will not be considered for shipment.** Please send an email notification of the shipment including the tracking number to the following addresses: a.narendran@ucalgary.ca, Janice.Hamilton@calgaryhealthregion.ca

Laboratory personnel will be available to answer questions regarding this process by phone at all times as indicated in the sample processing form.

Information for Customs Canada Form
Date:

Description: Human sera, Research use only, non-living, not known to be infectious, non-radioactive, no commercial value.

Country of Origin: USA

Transport/ Packaging: ICE/Dry Ice

From: Insert "Your name, Address, Telephone number"

To: Dr. Aru Narendran
Alberta Cancer Research Institute
HRIC Lab 2a34
3280 Hospital Drive NW
Calgary, Alberta, T2N 4Z6
CANADA Tel: (403) 210-6402
Pager: (403) 955-7211 request #2700

11.0 TOXICITIES/SIDE EFFECTS

Toxicities will be assessed via the NCI Common Terminology Criteria for Adverse Events (CTCAE, version 3.0, http://ctep.cancer.gov/forms/CTCAEv3.pdf). All toxicities, grades 1-4, will be recorded in both phases of the protocol until 30 days after the last dose of cetuximab.
Any patients consented after the memo sent to participating sites dated December 15, 2010 need to have all grades toxicities collected

The most common side effects expected are alopecia (likely), nausea and vomiting due to RT and/or chemotherapy (likely), myelosuppression (blood product transfusions and need for

hospitalization for fever and neutropenia both possible), infertility (possible), and second malignancies due to RT and/or chemotherapy (unlikely, but very severe should one occur).

Possible risks also include unexpected side effects from the addition of cetuximab to the external beam radiation therapy and chemotherapy.

11.1 RADIATION THERAPY

Acute toxicities: Nausea with or without emesis is an anticipated side effect of radiation therapy and may be treated with antiemetic medications. Fatigue may occur. Patients generally have transient focal alopecia in the radiation field and may have permanent epilation in some regions. Skin erythema is expected but is rarely severe. Temporary xerostomia and dysphagia may occur. Standard supportive care according to institutional guidelines will be delivered in an attempt to ameliorate any of these relevant effects.

Late effects: Common late effects of radiation, depending on the field of radiation, include neurocognitive dysfunction, growth impairment, hearing loss, and endocrine dysfunction (hypothalamic/pituitary, thyroid, and gonadal). Rare but severe late effects may include secondary malignancies (approximately 5%) and necrosis of central nervous system tissue, including brainstem (approximately 1-2%).

11.2 CETUXIMAB

Anticipated Adverse Events (all data in this section 11.2 provided by Bristol-Myers Squibb)
Please see updated Investigators brochure dated 10/21/2010

Squamous Cell Cancer of the Head and Neck
Except where indicated, the data described below reflect exposure to cetuximab in 208 patients with locally or regionally advanced SCCHN who received cetuximab in combination with radiation and as monotherapy in 103 patients with recurrent or metastatic SCCHN. Of the 103 patients receiving cetuximab monotherapy, 53 continued to a second phase with the combination of cetuximab plus chemotherapy. Patients receiving cetuximab plus radiation therapy received a median of 8 doses (range 1-11 infusions). The population had a median age of 56; 81% were male and 84% Caucasian. Patients receiving cetuximab monotherapy, received a median of 11 doses (range 1-45 infusions). The population had a median age of 57; 82% were male and 100% Caucasian. The most serious adverse reactions associated with cetuximab in combination with radiation therapy in patients with head and neck cancer were:

- Infusion reaction (3%)
- Cardiopulmonary arrest (2%)
- Dermatologic toxicity (2.5%)
- Mucositis (6%)
- Radiation dermatitis (3%)
- Confusion (2%)
- Diarrhea (2%)

Fourteen (7%) patients receiving cetuximab plus radiation therapy and 5 (5%) patients receiving cetuximab monotherapy, discontinued treatment primarily because of adverse events.

The most common adverse events seen in 208 patients receiving cetuximab in combination with radiation therapy were acneform rash (87%), mucositis (86%), radiation dermatitis (86%), weight loss (84%), xerostomia (72%), dysphagia (65%), asthenia (56%), nausea (49%), constipation (35%), and vomiting (29%).

The most common adverse events seen in 103 patients receiving cetuximab monotherapy were acneform rash (76%), asthenia (45%), pain (28%), fever (27%), and weight loss (27%).

The data in the table below are based on the experience of 208 patients with locoregionally advanced SCCHN treated with cetuximab plus radiation therapy compared to 212 patients treated with radiation therapy alone [Cetuximab package insert. ImClone Systems Incorporated and Bristol-Myers Squibb Company 2006. ER-B0001-03-06].

Incidence of selected adverse events (≥10%) in patients with loco-regionally advanced SCCHN

	Cetuximab plus Radiation (n=208)		Radiation Therapy Alone (n=212)	
Body System	Grades 1 – 4	Grades 3 and 4	Grades 1 – 4	Grades 3 and 4
Preferred Term	% of Patients			
Body as a Whole				
Asthenia/Malaise	56	4	48	5
Fever[1]	29	1	13	<1
Headache	19	<1	8	<1
Infusion Reaction[2]	15	3	2	0
Infection	13	1	9	1
Chills[1]	16	0	5	0
Digestive				
Mucositis/Stomatitis	93	56	94	52
Xerostomia	72	5	71	3
Dysphagia	65	26	63	30
Nausea	49	2	37	2

Constipation	35	5	30	5
Vomiting	29	2	23	4
Anorexia	27	2	23	2
Diarrhea	19	2	13	1
Dyspepsia	14	0	9	1
Metabolic/Nutritional				
Weight Loss	84	11	72	7
Dehydration	25	6	19	8
Respiratory				
Pharyngitis	26	3	19	4
Cough Increased	20	<1	19	0
Skin/Appendages				
Acneform Rash[3]	87	17	10	1
Radiation Dermatitis	86	23	90	18
Application Site Reaction	18	0	12	1
Pruritus	16	0	4	0

[1] Includes cases also reported as infusion reactions

[2] Infusion reaction is defined as any event described at any time during the clinical study as “allergic reaction” or “anaphylactoid reaction” or any event on the first day of dosing described as “allergic reaction”, “anaphylactoid reaction”, “fever”, “chills”, “chills and fever” or “dyspnia”.

[3] Acneform rash as defined as any event described as “acne”, “rash” , “maculopapular rash” , “pustular rash”, “dry skin” or “exfoliative dermatitis”.

Late Radiation Toxicity

The overall incidence of late radiation toxicities (any grade) was higher in cetuximab in combination with radiation therapy compared with radiation therapy alone. The following sites were affected: salivary glands (65% versus 56%), larynx (52% versus 36%), subcutaneous tissue (49% versus 45%), mucous membrane (48% versus 39%), esophagus (44% versus 35%), skin (42% versus 33%), brain (11% versus 9%), lung (11% versus 8%), spinal cord (4% versus 3%), and bone (4% versus 5%). The incidence of Grade 3 or 4 late radiation toxicities were generally similar between the radiation therapy alone and the cetuximab plus radiation treatment groups.

Colorectal Cancer

Except where indicated, the data described below reflect exposure to cetuximab in 774 patients with advanced metastatic colorectal cancer. Cetuximab was studied in combination with irinotecan (n=354) or as monotherapy (n=420). Patients receiving cetuximab plus irinotecan received a median of 12 doses [with 88/354 (25%) treated for over 6 months], and patients receiving cetuximab monotherapy received a median of 7 doses [with 36/420 (9%) treated for over 6 months]. The population had a median age of 59 and was 59% male and 91% Caucasian. The range of dosing for patients receiving cetuximab plus irinotecan was 1-84 infusions, and the range of dosing for patients receiving cetuximab monotherapy was 1-63 infusions.

The most **serious adverse reactions** associated with cetuximab were:

- Infusion reaction (3%)
- Dermatologic toxicity (1%)
- Interstitial lung disease (0.4%)
- Fever (5%)
- Sepsis (3%)
- Kidney failure (2%)
- Pulmonary embolus (1%)
- Dehydration (5%) in patients receiving cetuximab plus irinotecan, 2% in patients receiving cetuximab monotherapy
- Diarrhea (6%) in patients receiving cetuximab plus irinotecan, 0.2% in patients receiving cetuximab monotherapy

Thirty-seven (10%) patients receiving cetuximab plus irinotecan and 17 (4%) patients receiving cetuximab monotherapy discontinued treatment primarily because of adverse events.

The most common adverse events seen in 354 patients receiving cetuximab plus irinotecan were acneform rash (88%), asthenia/malaise (73%), diarrhea (72%), nausea (55%), abdominal pain (45%), and vomiting (41%).

The most common adverse events seen in 420 patients receiving cetuximab monotherapy were acneform rash (90%), asthenia/malaise (48%), nausea (29%), fever (27%), constipation (26%), abdominal pain (26%), headache (26%), and diarrhea (25%).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Data in patients with advanced colorectal carcinoma in the table below are based on the experience of 354 patients treated with cetuximab plus irinotecan and 420 patients treated with cetuximab monotherapy.

Infusion Reactions

Severe infusion reactions occurred with the administration of cetuximab in approximately 3%

Incidence of Adverse Events (≥10%) in Patients with Advanced Colorectal Carcinoma

Body System Preferred Term[1]	Cetuximab plus Irinotecan (n=354)		Cetuximab Monotherapy (n=420)	
	Grades 1 - 4	Grades 3 and 4	Grades 1 – 4	Grades 3 and 4
	% of Patients			
Body as a Whole				
Asthenia/Malaise[2]	73	16	48	10
Abdominal Pain	45	8	26	9
Fever[3]	34	4	27	<1
Pain	23	6	17	5
Infusion Reaction[4]	19	3	21	2
Infection	16	1	14	1
Back Pain	16	3	10	2
Headache	14	2	26	2
Digestive				
Diarrhea	72	22	25	2
Nausea	55	6	29	2
Vomiting	41	7	25	3
Anorexia	36	4	23	2
Constipation	30	2	26	2
Stomatitis	26	2	10	<1
Dyspepsia	14	0	6	0
Hematic/Lymphatic				
Leukopenia	25	17	<1	0
Anemia	16	5	9	3
Metabolic/Nutritional				
Weight Loss	21	0	7	1
Peripheral Edema	16	1	10	1
Dehydration	15	6	10	3
Nervous				
Insomnia	12	0	10	<1
Depression	10	0	7	0
Respiratory				
Dyspnea[3]	23	2	17	7
Cough Increased	20	0	11	1
Skin/Appendages				
Acneform Rash[5]	88	14	90	8
Alopecia	21	0	4	0
Skin Disorder	15	1	4	0
Nail Disorder	12	<1	16	<1
Pruritus	10	1	11	<1
Conjunctivitis	14	1	7	<1

[1] Adverse events that occurred (toxicity Grades 1 through 4) in ≥10% of patients with refractory colorectal carcinoma treated with cetuximab plus irinotecan or in ≥10% of patients with refractory colorectal carcinoma treated with cetuximab monotherapy.

[2] Asthenia/malaise is defined as any event described as “asthenia”, “malaise”, or “somnolence”.

[3] Includes cases reported as infusion reaction.

[4] Infusion reaction is defined as any event described at any time during the clinical study as “allergic reaction” or “anaphylactoid reaction”, or any event occurring on the first day of dosing described as “allergic reaction”, “anaphylactoid reaction”, “fever”, “chills”, “chills and fever” or “dyspnea”.

[5] Acneform rash is defined as any event described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis”.

(46/1485) of patients, rarely with fatal outcome (<1 in 1000). Approximately 90% of severe infusion reactions were associated with the first infusion of cetuximab despite the use of prophylactic antihistamines. These reactions were characterized by the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, hypotension, and/or cardiac arrest. Caution must be exercised with every cetuximab infusion, as there were patients who experienced their first severe infusion reaction during later infusions. A 1-hour observation period is recommended following the cetuximab infusion. Longer observation periods may be required in patients who experience infusion reactions.

A 20-mg test dose was administered intravenously over 10 minutes prior to the initial dose to all patients in earlier studies. The test dose did not reliably identify patients at risk for severe allergic reactions.

In the Southeastern region of the United States a higher number of infusion-related anaphylactic reactions to cetuximab have been reported in adult studies than in other areas of the United States [J Clin Oncol 2007, 25:3644-3648 and N Engl J Med 2008, 358:1109-1117].

Pulmonary Toxicity

Interstitial lung disease (ILD) was reported in 3 of 774 (<0.5%) patients with advanced colorectal cancer and in 1 of 796 patients with head and neck cancer receiving cetuximab. Among these four cases, interstitial pneumonitis with non-cardiogenic pulmonary edema resulting in death was reported in one patient with colon cancer. In two of the remaining cases, the patients had pre-existing fibrotic lung disease and experienced an acute exacerbation of their disease while receiving cetuximab in combination with irinotecan. The onset of symptoms occurred between the fourth and eleventh doses of treatment in all reported cases. In the event of acute onset or worsening pulmonary symptoms, cetuximab therapy should be interrupted and a prompt investigation of these symptoms should occur. If ILD is confirmed, cetuximab should be discontinued and the patient should be treated appropriately [Cetuximab package insert. ImClone Systems Incorporated and Bristol-Myers Squibb Company 2006. ER-B0001-03-06].

Dermatologic Toxicity

In cynomolgus monkeys, cetuximab, when administered at doses of approximately 0.4 to 4 times the weekly human exposure (based on total body surface area), resulted in dermatologic findings, including inflammation at the injection site and desquamation of the external integument.[1] At the highest dose level, the epithelial mucosa of the nasal passage, esophagus, and tongue were similarly affected, and degenerative changes in the renal tubular epithelium occurred. Deaths due to sepsis were observed in 50% (5/10) of the animals at the highest dose level beginning after approximately 13 weeks of treatment.

In clinical studies of cetuximab, dermatologic toxicities, including acneform rash, skin drying and fissuring, and inflammatory and infectious sequelae (eg, blepharitis, cheilitis, cellulitis, cyst) were reported. In patients with advanced colorectal cancer, acneform rash was reported in 89% (686/774) of all treated patients, and was severe (Grade 3 or 4) in 11% (84/774) of these patients. Subsequent to the development of severe dermatologic toxicities, complications including *S. aureus* sepsis and abscesses requiring incision and drainage were reported.

Non-suppurative acneform rash described as "acne", "rash", "maculopapular rash", "pustular rash", "dry skin", or "exfoliative dermatitis" was observed in patients receiving cetuximab plus irinotecan or cetuximab monotherapy. One or more of the dermatological adverse events were reported in 88% (14% Grade 3) of patients receiving cetuximab plus irinotecan and in 90% (8% Grade 3) of patients receiving cetuximab monotherapy. Acneform rash most commonly occurred on the face, upper chest, and back, but could extend to the extremities and was characterized by multiple follicular- or pustular-appearing lesions. Skin drying and fissuring were common in some instances, and were associated with inflammatory and infectious sequelae (eg, blepharitis, cellulitis, cyst). Two cases of *S. aureus* sepsis were reported. The onset of acneform rash was generally within the first two weeks of therapy. Although in a majority of the patients the event resolved following cessation of treatment, in nearly half of the cases, the event continued beyond 28 days.

A related nail disorder, occurring in 14% of patients (0.4% Grade 3), was characterized as a paronychial inflammation with associated swelling of the lateral nail folds of the toes and fingers, with the great toes and thumbs as the most commonly affected digits.

Cetuximab Use With Radiation Therapy

The safety of cetuximab in combination with radiation therapy and Cisplatin has not been established. Death and serious cardiotoxicity were observed in a 21 patient single-arm study of patients with locally advanced squamous cell cancer of the head and neck. Patients received cetuximab, delayed, accelerated (concomitant boost) fractionation radiation therapy and Cisplatin (100 mg/m^2) [Cetuximab package insert. ImClone Systems Incorporated and Bristol-Myers Squibb Company 2006. ER-B0001-03-06].

In a randomized, controlled trial in patients with squamous cell carcinoma of the head and neck (SCCHN), cardiopulmonary arrest and/or sudden death occurred in 4/208 patients (2%) treated with radiation therapy and cetuximab as compared to none of 212 patients treated with radiation therapy alone. Three patients with prior history of coronary artery disease died at home, with myocardial infarction as the presumed cause of death. One of these patients had arrhythmia and one had congestive heart failure. Death occurred 27, 32, and 43 days after the last dose of cetuximab. One patient with no prior history of coronary artery disease died one day after the last dose of cetuximab.

Electrolyte Depletion

In 244 patients evaluated in ongoing, controlled clinical trials, the incidence of hypomagnesemia, both overall and severe, was increased in patients receiving cetuximab alone or in combination with chemotherapy as opposed to those receiving best supportive care or chemotherapy alone. Approximately one-half of these patients receiving cetuximab experienced hypomagnesemia and 10-15% experienced severe hypomagnesemia[1].

Cardiac Toxicity

Cardiac arrest and / or sudden death occurred in 2% (4/208) of patients with squamous cell carcinoma of the head and neck treated with radiation therapy and cetuximab as compared to none of 212 patients treated with radiation therapy alone. Fatal events occurred within 1 to 43 days after the last Cetuximab treatment. Cetuximab in combination with radiation therapy should be used with caution in head and neck cancer patients with known coronary artery disease,

congestive heart failure, and arrhythmias. Although the etiology of these events is unknown, close monitoring of serum electrolyte, including serum magnesium, potassium and calcium, during and after Cetuximab therapy is recommended.

11.3 IRINOTECAN

Common
Dermatologic: Alopecia
Hematologic: Drug-induced eosinophilia

Serious
Gastrointestinal: Diarrhea, Nausea and Vomiting
Hematologic: Leukopenia, Neutropenia, Thrombocytopenia, Lymphopenia
Hepatic: Decreased liver function
Respiratory: Interstitial lung disease

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The study's primary aim is to increase the proportion of patients achieving 1-year progression-free survival. Progression-free is defined as lack of unequivocal tumor progression or treatment-associated death. Unequivocal tumor progression will be determined (usually via brain MRI) by a POETIC institutional radiologist. If radiological studies suggest possible, but not unequivocal progression, the patient may remain on study until unequivocal progression has been determined. In select cases biopsy may be necessary to distinguish tumor recurrence from radiation effect.

In this study, we will compare the product of 2-dimensional measures of the tumor on the baseline and follow-up MRI scans. Modified Macdonald criteria will be used [J Clin Oncol 1990; 8:1277-1280]. Responses will be defined as:

Complete response: Complete resolution of all tumor.

Partial response: ≥ 50% decrease in the 2-dimensional size of the tumor.

Stable disease: < 50% decrease to < 25% increase in the 2-dimensional size of the tumor.

Progressive disease: (1) ≥ 25% increase in the 2-dimensional size of the tumor, or (2) any new tumor focus, or (3) worsening neurological status that cannot be explained by any other cause associated with increase in tumor size (but < 25%).

Determination of favorable responses will be made via comparison to the baseline MRI, while determination of progressive disease will be via comparison to the nadir

13.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

13.1 Criteria for Removal from Protocol Therapy

- Tumor recurs or progresses
- Second malignancy
- Intolerable toxicity occurs
- Unable to start the second phase of therapy (irinotecan and cetuximab) within 56 days of completion of RT
- The patient is significantly non-compliant with the treatment plan
- The patient withdraws consent for protocol-prescribed therapy
- Completion of protocol-prescribed therapy

13.2 Off study criteria

- Death occurs
- Withdrawal of consent for any further data submission

14.0 BIOSTATISTICS

14.1 DEFINITION OF ENDPOINTS

The primary endpoint of this study is progression free survival at one year. Progression will be measured from initiation of therapy until first documented progression of disease. Death or the unlikely event of loss to follow-up, within one year will also be counted as progression. Those who are alive and progression free one year after initiation of therapy will be considered treatment successes for the evaluation of the primary endpoint.

Response is considered as a secondary endpoint. All patients who have initiated therapy will be evaluated for response. Only patients who were declared ineligible and removed prior to receiving any treatment will be excluded.

14.1.1 DIFFUSE PONTINE TUMORS

For this group of patients the goal is to effectively discriminate between progression free survival rates at one year of $\leq$ 10% and $\geq$ 30% using a single stage design.

The progression free proportion is deemed unacceptable if it is lower than 10% and is promising if greater than 30%. The null hypothesis that the proportion progression free at one year (p) is less than or equal to 0.10 (H0: $p \leq 0.10$) will be tested against the alternative hypothesis that p is greater than or equal to 0.30 (H1: $p \geq 0.30$). For this group of tumors, we will accrue 25 patients. If 6 or more are alive and progression free at one year, the treatment will be declared effective and worthy of further testing. If 5 or fewer are alive and progression free at one year, then this group of the trial will be declared to have a negative result. This design yields $\geq$ 80% probability of a positive result if the true percentage of patients alive and progression free at one year is $\geq$ 30% (80% power). It yields $\geq$ 95% probability of a negative result if the true percentage is $\leq$ 10% (5% type I error).

14.1.2 HIGH-GRADE ASTROCYTOMAS

For this group of patients the goal is to effectively discriminate between progression free survival rates at one year of $\leq$ 35% and $\geq$ 60%, using a single stage design.

The progression free proportion is deemed unacceptable if it is lower than 35% and is promising if greater than 60%. The null hypothesis that the proportion progression free at one year (p) is less than or equal to 0.35 (H0: $p \leq 0.35$) will be tested against the alternative hypothesis that p is greater than or equal to 0.60 (H1: $p \geq 0.60$). For this group of tumors, we will accrue 26 patients. If 14 or more are alive and progression free at one year, the treatment will be declared effective and worthy of further testing. If 13 or fewer are alive and progression free at one year, then this group of the trial will be declared to have a negative result. This design yields ≥ 80% probability of a positive result if the true percentage of patients alive and progression free at one year is ≥ 60% (80% power). It yields ≥ 95% probability of a negative result if the true percentage is ≤ 35% (5% type I error).

14.2 EARLY STOPPING RULE FOR TOXICITY

In order to confirm the safety of the radiation therapy and cetuximab component of this regimen, patients will continuously be monitored for excessive toxicity and early stopping rules for toxicity will be employed. Unacceptable toxicity is defined as any grade 4 or higher non-hematological toxicity (with the exception of diarrhea, infection, electrolyte abnormalities, nausea and vomiting, hypersensitivity reactions, and neurological dysfunction clearly due to tumor rather than treatment) that does not resolve to less than or equal to grade 2 within 7 days. Stopping rules and the corresponding power calculations are provided in the table below.

# failures/toxicities need to stop the study	Projected probability of failure/toxicity in the populations	Probability of study completion (based on projection)
2 in the first 6 patients 3 in the first 15 patients 4 in the first 26 patients 5 in the first 50 patients 6 in all 51 patients	0.05	.90
	0.09	.60
	0.15	0.17

14.3 SECONDARY BIOLOGICAL AIMS

14.3.1 Progression free and overall survival will be calculated using the methods of Kaplan and Meier, separately for the diffuse pontine and high-grade groups. The response rates will be provided along with their 95% confidence intervals for all patients receiving any study medication or radiation.

14.3.2 It is not known how many patients will agree to participate in the components of the study involving (1) correlation of molecular markers and tumor response to therapy, (2) CSF proteomics, and (3) serum inflammatory cytokine levels. These endpoints are exploratory in nature and any analyses will be purely descriptive. Continuous endpoints will be summarized using medians and ranges, categorical data will be tabulated. Changes in measurements will be given in terms of percent change from baseline and change in absolute value.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 RESEARCH PARTICIPANT REGISTRATION

All patients must be centrally registered by the Data and Coordinating Center, at Memorial Sloan-Kettering Cancer Center. Registrations will be handled by the RSA at the Pediatrics Clinical Trials Office at MSKCC. The contact telephone number is 646-888-5714 or 646-888-5715 and the fax number is 646-888-5726. Registrations will occur between 9:00 am and 5:00 pm Eastern Standard Time (EST), Monday through Friday and will include review of the signed consent form, HIPAA research authorization form, eligibility checklist, eligibility source documentation and Patient Enrollment form. The RSA will also verify, via a FAX copy, that the written informed consent is obtained and dated prior to subject entry on the study.

The participating sites must contact the Research Study Assistant (RSA) at the Data and Coordinating Center to reserve a slot on the protocol when a patient is being considered for a trial. To begin a registration the participating site must fax the signed consent form and HIPAA research authorization to the RSA within 48 hours of the patient signing consent. To complete the registration, the completed eligibility checklist, patient eligibility source documentation and the Patient Enrollment form must be faxed to the RSA at MSKCC prior to protocol treatment or any research tests. Registrations must be faxed to the Clinical Trials Office and the Research Study Assistant (RSA) at MSKCC will verify eligibility and complete the registration with the PPR Office.

Once eligibility has been established and the participant is registered, the participant will be assigned an MSKCC Clinical Research Database (CRDB) number (protocol participant number). This number is unique to the participant and must be written on all data and correspondence for the participant. This protocol participant number will be relayed back to study staff at the registering site via e-mail and will serve as the enrollment confirmation. The participating site must not begin treatment until receiving this email from the Data and Coordinating Center.

Written consent must be documented on the appropriate consent form and Research Authorization designated and approved by the Institutional Review Board at the institution at which the patient is enrolled. The POETIC Principal Investigators or consenting professionals at their institution

The registration procedure is summarized below.

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the written consent/verbal script and a completed Eligibility Checklist must be faxed to PPR.

15.2 RANDOMIZATION

This study is not randomized.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) at the Memorial Sloan-Kettering Cancer Center will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problems and prioritization. In addition, coordination between the RSA and Research Staff at the participating POETIC institutions is necessary in order for a complete process. The Clinical Research Coordinator (CRC) will also be responsible for being the liaison among all staff involved including the principal investigators, attending physicians and nurses.

Case report forms will be drafted in a standard format and will be provided to each participating institution by the Data and Coordinating Center. Required study tools for each protocol including correlative studies, vital signs, drug administration and protocol evaluations will also be provided to each participating institution by the Data and Coordinating Center. Case report forms, study tools and source documentation are required to be submitted to the Data and Coordinating Center on a weekly basis.

The data collected for this study will be entered into a secure database by the MSKCC RSA. Data will be collected, stored, and monitored at an institutional level via the Clinical Research Database (CRDB) system. Data will be provided from CRDB to protocol-defined sponsors (CTEP, FDA, etc.) as required, through the Data Management Resource Division, a division of the Office of Clinical Research.

Source documentation will be available to support the computerized patient record and must be submitted with the case report forms and required study tools. Case report forms will not be considered source documentation. Variables that will be recorded include the patient's birth date, date of diagnosis, date of study entry and histologic diagnosis. The results of the pretreatment and end of therapy evaluations, including the extent of disease evaluation (history, physical examination and imaging studies), baseline laboratory values, renal and hepatic function, as

defined per protocol, will be recorded. All study related treatment data and concomitant drugs will be recorded. The presence of toxicity at baseline, during and for 30 days after administration of the investigational agent will be monitored and recorded. The results of the extent of disease evaluation (history, physical examination and imaging studies) following each course of treatment will be recorded. The patient's disease status and last follow-up will be recorded. If disease progresses or recurs, the results of the repeat extent of disease evaluation will be recorded.

Research staff will be assigned at each POETIC center. Lead research personnel will be identified at each site. Their responsibilities will include maintaining file documentation of data for the clinical trial, pharmacokinetic or other biologic correlative study collection and analysis as outlined in this study, for each patient enrolled on study. They will also be responsible for maintaining a regulatory binder for each protocol. The designated research staff will also be responsible for submitting the data on a weekly basis by fax or mail to the RSA at MSKCC. Case report forms and required study tools along with supporting source documentation should be faxed or mailed to:

Pediatric Clinical Trials Office
Memorial Sloan-Kettering Cancer Center
405 Lexington Avenue, Room 3-512
New York, NY 10174
Telephone: 646-888-5714/5715
Fax: 646-888-5726

The protocol will be conducted as a single research study effort and data from each participating institution will be included in the analysis of results.

The Protocol Chair will be responsible for the conduct of the study, and the monitoring of the progress and will review all case report forms from each participating institution.

Initial Protocol Submission

Prior to implementing this protocol at MSKCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSKCC IRB/PB. Prior to implementing this protocol at the participating centers, approval must be obtained from the participating center's Local IRB of Record.

The following documents must be provided to MSKCC before the participating site can be initiated and begin enrolling participants:

- Local IRB of Record approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Local IRB of Record membership
- Local IRB of Record's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification and HIPAA training for investigators and key staff members
- Signed and dated FDA Related Forms 1572/1571 (if applicable)

- Lab Certifications and Reference Ranges for each lab listed on the 1572

Protocol Amendments/Status Changes

Each change to the protocol must be organized and documented by the Data and Coordinating Center. The Protocol Chair at the lead institution will submit the amendment locally for approval. After approval at the lead institution, the Data and Coordinating Center will distribute the amendment to the participating institutions, for approval by their local IRB within 60 days of the amendment date. The participating sites will ensure that documentation for all IRB approved amendments are sent to the Data and Coordinating Center and are maintained in the regulatory binder. This documentation will include the IRB approval letter referencing the protocol version date and amendment number, IRB approved protocol, IRB approved appendices and IRB approved consent forms.

The amendment will be written so that no other institution will need to reformat the information but can simply copy and distribute. An amendment memo as well as highlighted and clean copies of the protocol, appendices and consent forms will be distributed to the participating sites. The consent form will be a sample that may be edited in order to adhere to local IRB guidelines. The amendment must be submitted at each site to the IRB for review and approval before patients can be enrolled on the study and within 90 days of the amendment version date. The amendment number and version date will also be displayed on each amendment.

Additional IRB Correspondence

Annual re-approval

Annual re-approval from the participating center's Local IRB of Record must be submitted to MSKCC at the time re-approval is granted. The most current approved version of the consent form should also be submitted to MSKCC at that time. Failure to submit the re-approval will result in suspension of accrual privileges.

Deviations and Violations

If a deviation from the protocol is proposed for a potential or existing participant at a participating site, approval from the MSKCC IRB/PB is required prior to the action. Please be sure to inform the DCC as soon as possible to ensure IRB approval.

For protocol violations that are reported after they occur, the participating site should report to MSKCC as soon as possible. The MSKCC PI will in turn report the violation to the MSKCC IRB/PB.

Participating sites should report deviations and violations to the Local IRB of Record as they occur. Approvals/acknowledgments from the Local IRB of Record for protocol deviations and violations should be submitted to MSKCC as received.

Other correspondence

Participating sites should submit other correspondence to their local IRB of Record according to local guidelines, and submit copies of that correspondence to MSKCC.

16.1 QUALITY ASSURANCE

This will be a central responsibility of the Data and Coordinating Center and it will be achieved by frequent review, constant oversight and input from objective advisors. Each project will maintain a steering committee that will meet in conference call on a weekly basis to critically review the scientific progress of the clinical trial. The steering committee will include the principal investigators, research staff and the biostatistical support team under the direction of the lead biostatistician.

Monitoring visits will be conducted by the Clinical Research Coordinator (CRC) from the Data and Coordinating Center as needed. During this visit, the CRC will:

- Review regulatory binders for protocol documentation;
- Ensure that case report forms are source data verified according to the monitoring plan;
- Verify drug accountability is complete and accurate;
- Verify compliance to GCPs, ICH guidelines, FDA regulations, and applicable SOPs.

Internal audits will be conducted by the Data and Coordinating Center. Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Data and Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. Each site is responsible for having all source documents, research records, all IRB approval documents, Drug Accountability Record Forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

16.2 DATA AND SAFETY MONITORING

The Data and Safety Monitoring Committee (DSMC) at Memorial Sloan-Kettering Cancer Center will be responsible for monitoring the data safety of the protocol. The DSMC meets quarterly, and will review data from respective trials on a semi-annual basis. A copy of the MSKCC Data and Safety Monitoring policy document has been distributed to local sites and is on file at the Data and Coordinating Center.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/clinicaltrials/conducting/dsm-guidelines. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://mskweb2.mskcc.org/irb/index.htm. The Data and Safety Monitoring Committee (DSMC) monitors all Phase I and II clinical trials and reports to the Research Council and Institutional Review Board.

17.0 PROTECTION OF HUMAN SUBJECTS

All of the patients on this study will be children, adolescents, and young adults. Patients of both sexes and all ethnic backgrounds are eligible for the study. Participation will be voluntary. The

hypothesized potential benefits include superior event-free survival. Alternatives include external beam radiation therapy alone or in conjunction with other chemotherapy regimens, including, but not limited to (1) temozolomide, (2) vincristine and lomustine, or other investigational protocols.

Patients are responsible for all costs of their care including (but not limited to) physician visits, hospitalizations, medications (except for cetuximab), MRI scans, and laboratory work (except for the optional research biology studies performed on blood, tumor tissue and CSF). Cetuximab will be supplied by Bristol Myers-Squibb in collaboration with Imclone Systems Incorporated, via a research and development agreement. The costs of all research-only related studies will be covered by the study and participating institutions' research support.

Patient confidentiality will be protected, but records may be reviewed by appropriate staff of the Memorial Sloan-Kettering Cancer Center, the participating institutions, and representatives from the FDA, Bristol Myers-Squibb, and Imclone Systems Incorporated.

17.1 PRIVACY

All institutional, local, federal, FDA, and NCI requirements for human subjects research must be met. This study will be carried out in compliance with the regulations of the Health Insurance Portability and Accountability Act (HIPAA). Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Data and Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site. The Data and Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.

The risks and benefits of participation in this study will be reviewed with the patient and/or parent/legal guardian.

Enrollment on this study is on a voluntary basis and every effort will be made to maintain privacy and confidentiality. The patient's records will be confidential. Only authorized individuals or agencies may inspect the records. No identifying information will be used in reports or publications resulting from this study.

17.2 SERIOUS ADVERSE EVENT (SAE) REPORTING

The Protocol Chair is responsible for monitoring the safety of patients who enroll in the study. All AEs and SAEs occurring after any administration of the study drug regardless of drug attribution will be followed to the end of the study including 30 days after the last administration of study drug, as well as any SAEs designated possibly, probably or definitely related to treatment that occur greater than 30 days.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be used for adverse event and serious adverse event reporting. All participating sites should have access to a copy of the CTCAE version 3.0. A copy of the CTCAE version 3.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/reporting/ctc.html).

The Protocol Chair is required to report all adverse events that occur during the clinical study starting with the first dose of study drug throughout 30 days of stopping the investigational agent, must be reported to the appropriate protocol-defined study sponsors. Serious adverse events must be reported either by telephone or in person to the Protocol Chair, Data and Coordinating Center and local IRB within 24 hours of knowledge of their occurrence. A written SAE report including source documentation must be sent to the Protocol Chairman and Data and Coordinating Center within another 3 calendar days, using the Serious Adverse Event case report form.

Additionally, the Protocol Chair is responsible for submitting follow-up reports for all SAEs regarding the patient's subsequent course until the SAE has resolved or until the patient's condition stabilizes (in the case of persistent impairment), or the patient dies.

A serious adverse event (SAE) is any adverse drug experience that occurs at any dose that results in any of the following outcomes:

- Death
- Life-threatening adverse drug experience
- Requires inpatient hospitalization or prolongation of existing hospitalization
- For the purpose of this study, hospitalizations for protocol-scheduled procedures, blood product transfusions, or for social reasons (ie, awaiting transport home) will not be considered SAEs
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Requires medical or surgical intervention to prevent one of the outcomes listed above

Reporting Requirements for Adverse Events That Occur on Treatment and Within 30 Days[1] of the Last Dose of Study Drug **(Please see section 17.2.1 for exception to the table)**

	Grade 1	Grade 2		Grade 2		Grade 3		Grade 3		Grades 4 & 5
	Unexpected and Expected with or with-out hospitalization	Unexpected		Expected		Unexpected		Expected		Unexpected and Expected
		With Hospitalization	without Hospitalization	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	
Unrelated Unlikely	Not Required	SAE Report Required	Not Required	SAE Report Required	Not Required	SAE Report Required	Not Required	SAE Report Required	Not Required	SAE Report Required
Possible Probable Definite	Not Required	SAE Report Required	SAE Report Required	SAE Report Required	Not Required	SAE Report Required	SAE Report Required	SAE Report Required	Not Required	SAE Report Required

[1] Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of study treatment require an SAE report as follows:

- **Grade 3 unexpected events with hospitalization or prolongation of hospitalization**
- **Grade 4 unexpected events**
- **Grade 5 expected events and unexpected events**

Initial notification for all SAEs must include:

- Grade of event
- Date of event
- A brief description of the event
- Attribution to the investigational agent
- Patient Status

Relationship of any adverse event to study drug should use the following criteria:

- Definite - The adverse event *is clearly related* to
- Probable - The adverse event *is likely related* to
- Possible - The adverse event *may be related* to
- Unlikely - The adverse event *is doubtfully related* to
- Unrelated - The adverse event *is clearly NOT related* to

SAEs must be reported within 24 hours by phone or e-mail to:

- Data and Coordinating Center
- Lead Principal Investigator of the protocol / Protocol Chair
- Local IRB

SAE contact information for the Data and Coordinating Center is listed below:

Memorial Sloan-Kettering Cancer Center
Pediatric Clinical Trials Office
405 Lexington Avenue, Room 3-512

New York, NY 10174
Telephone: 646-888-5714/5715
Fax: 646-888-5726

Contact information for the Primary Investigator is listed below:

Primary Investigator
Ira Dunkel, MD
Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, NY 10065
Telephone (212) 639-2153
Fax (212) 717-3239
E-mail: dunkeli@mskcc.org

In the event of an AE, appropriate medical and supportive care will be administered. All efforts will be made to minimize the side effects and to support the patient until the toxicity resolves.

- Adverse events classified as "serious" require expeditious handling and reporting to BMS to comply with regulatory requirements.
- All serious AEs whether related or unrelated to investigational product, must be immediately reported to the Data and Coordinating Center by confirmed facsimile transmission. If only limited information is initially available, follow-up reports are required. The original SAE form must be kept on file at the study site.

  All SAEs should simultaneously be faxed or emailed to Data and Coordinating Center (see above) who will submit the information to Bristol-Myers Squibb at:

  Global Pharmacovigilance & Epidemiology
  Bristol-Myers Squibb Company
  Fax Number: 609-818-3804
  Email: WorldWide.Safety@bms.com

- Collection of complete information concerning SAEs is extremely important. Full descriptions of each event will be followed by BMS. Thus, follow-up information which becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report.
- An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. For reporting purposes, BMS considers an overdose, regardless of adverse outcome, as an important medical event (see Serious Adverse Events).
- In BMS supported trials, all SAEs must be collected which occur within 30 days of discontinuation of dosing or completion of the patient's participation in the study if the last scheduled visit occurs at a later time. In addition, the Investigator should notify BMS of any

SAE that may occur after this time period which they believe to be certainly, probably or possibly related to investigational product.

17.2.1 AGENT-SPECIFIC EXPECTED ADVERSE EVENTS LIST

The list below guides the investigator in determining which AEs require expedited reporting. Those AEs that do not require expedited reporting are reported in routine study data submissions.

Hospitalization for the following expected events and toxicities will not be considered serious adverse events (SAE) and will not require reporting to the Institutional Review/Ethics Boards:

- Therapy administration
- Fever and neutropenia
- Central venous catheter-associated infection
- Possible septicemia
- Vomiting and/or dehydration
- Diarrhea

Similarly, non-life threatening grade 3 and 4 toxicities clearly attributed to the external beam radiation therapy and/or chemotherapy will not be reported as SAE's. However, life-threatening infections or other life-threatening side effects will be considered SAE's and will be promptly reported.

17.2.2 SERIOUS ADVERSE EVENT (SAE) REPORTING

SAE Reporting (This section pertains to guidelines for Memorial Sloan-Kettering only)

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org containing the following information:

Fields populated from the CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title
- Concomitant medication

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE

- The intervention
- Detailed text that includes the following information:
  - An explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
  - If an amendment will need to be made to the protocol and/or consent form

The PI's signature and the date it was signed are required on the completed report.

18.0 INFORMED CONSENT PROCEDURES

Regulatory agencies have issued regulations to provide protection for human patients in clinical investigations and to describe the general requirements for informed consent.

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care under applicable regulations. In addition, the investigator should be aware that some regulations require that he/she permit regulatory agencies to conduct inspections and review records pertaining to this clinical investigation.

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

18.1 RESEARCH AUTHORIZATION

Procedures for obtaining Research Authorization: Before any protocol-specific procedures are carried out, investigators and/or designated staff will fully explain the details of the protocol, study procedures, and the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must sign the Research Authorization component of the informed consent form. The Research Authorization requires a separate set of signatures from the patient. The original signed documents will become part of the patient's medical record, and each patient will receive a copy of the signed documents.

19.0 APPENDICES

Appendix 1: Performance scales

Appendix 2: Table of mandated observations