UCSF Helen Diller Family Comprehensive Cancer Center

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A PHASE II STUDY OF RADIATION THERAPY AND VISMODEGIB, FOR THE TREATMENT OF LOCALLY ADVANCED BASAL CELL CARCINOMA OF THE HEAD AND NECK

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Protocol Signature Page

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1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Institutional Review Board (IRB), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable IRB requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with IRB policies, Federal, state and local laws and regulations.

UCSF Principal Investigator / Study Chair

_____
Printed Name

_____ _____
Signature Date

Participating Site(s)

San Francisco General Hospital [redacted]

Memorial Sloan-Kettering Center [redacted]

Principal Investigator **Site**

_____ _____
Printed Name

_____ _____
Signature Date

Abstract

Title	A Phase II Study of Radiation Therapy and Vismodegib, for the Treatment of Locally Advanced Basal Cell Carcinoma of the Head and Neck
Patient population	Patients with locally advanced basal cell carcinoma in the head and neck, who are ineligible for surgical resection and are planned for definitive intent radiation therapy.
Rationale for Study	Vismodegib is a proven effective means for treating locally advanced and metastatic BCC. Radiotherapy for advanced, unresectable BCC can be effective as well, but ultimate success rates can remain limited for complex, unresectable tumors, either due to anatomic or technical factors. Vismodegib alone produces high response rates in BCC but is unlikely to sustain permanent eradication of very advanced tumors. This study is designed to assess the safety and demonstrate the efficacy of a combined approach using radiation therapy after induction and concurrent systemic administration of vismodegib, which may increase the rates of complete response and sustained local control in patients with locally advanced BCC. This population was chosen for study based on unmet medical need and evidence of efficacy observed in earlier studies of vismodegib in advanced BCC. At this point in time, despite the clear success of vismodegib in treating BCC, there is no guidance about how to integrate this treatment with other curative-intent therapies.
Primary Objective	To determine local-regional control rate at 12 months from protocol therapy completion, defined as complete or partial response, with absence of progressive disease within the irradiated planning tumor volumes (PTV) for patients with locally advanced basal cell carcinoma in the head and neck.
Secondary Objectives	• To estimate of the probability of PFS, with failure defined as any disease recurrence or death due to any cause, and OS with the duration for each measured from the time of first treatment with vismodegib to 12 months after completion of study treatment. • To evaluate toxicity during the drug-alone and combined-modality components of the protocol regimen during treatment. This will be assessed by: 1) The number and attribution of all adverse events, (including vital signs, physical findings, and clinical laboratory results, CTCAE, v 4.0) in patients who receive any amount of study drug and radiation therapy. 2) The proportion of any adverse events (CTCAE, v. 4.0) assessed to be definitely, probably, or possibly related to vismodegib or its combination with radiation therapy. 3) The proportion of patients experiencing Grade 4-5 adverse events assessed to be definitely, probably, or possibly related to the induction or concurrent treatment components of the protocol regimen (that is not definitely related to disease progression). • To evaluate initial toxicity during the 3 months immediately after completion of protocol therapy. • To estimate the feasibility of administering concurrent vismodegib with radiation therapy determined by the proportion of patients discontinuing treatment due to toxicity during the concurrent administration of vismodegib and radiation therapy (<75% of planned radiation therapy delivered). • To evaluate the response rate (as per RECIST version 1.1) of the primary site and regionally involved areas following all treatment components at 3 months after the completion of protocol therapy. • To estimate the clinical response to vismodegib and radiation therapy determined by the proportion of patients with a decrease of BCC within the irradiated planning tumor volumes (PTVs, see Section 5.0 for definition) in patients who complete combined therapy.

Study Design	This is a single arm, multi-centered Phase II clinical trial to assess the safety and demonstrate the efficacy of a combined modality approach using radiation therapy after induction and concurrently with systemic administration of vismodegib, which may increase the rates of complete response and sustained local control in patients with locally advanced BCC.
Number of patients	24 evaluable patients who complete at least 75% of protocol-mandated radiotherapy.
Duration of Therapy	Patients will receive treatment for approximately 21 weeks.
Duration of Follow up	Follow-up visits will occur at 3, 6, & 12 months (+/- 2 weeks) post End of Treatment visit. Survival follow-up information may be collected via telephone calls and/or at clinic visits every 3 months for 12 months.
Duration of study	The study will reach completion 3-4 years from the time the study opens to accrual.
Study Drugs	Vismodegib capsules (150 mg QD PO) will be taken orally (whole). Patients will be instructed to swallow one capsule once a day (preferably at the same time each day) 7 days/week, with or without food, with about 1 cup (240 mL) of water. Capsules must be swallowed whole; they must not be opened, chewed, broken, or crushed under any circumstances.
Safety Assessments	The study will use the CTCAE v 4.0 for reporting of non-hematologic adverse events and modified criteria for hematologic adverse events. Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to vismodegib, all events of death, and any study specific issue of concern. The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 12 months following the last administration of study treatment or study discontinuation/termination, whichever is earlier.
Efficacy Assessments	Measurable lesions are those that can be accurately measured in at least one dimension as ≥20mm with CT or MRI scan or on color photographs. Patients will undergo tumor assessments per RECIST version 1.1 tumor response criteria outlined below. No central review of imaging data will be required due to the visual clarity in identifying the lesions and the consistent method of assessment to be used by all participating sites. Prior radiation therapy is acceptable but there cannot be major overlap of the previously irradiated tissues with the new radiation treatment volumes anticipated to be delivered for the purposes of this protocol, in such a way that curative intent with radiation cannot be met. Furthermore, the total dose from all radiation delivered and expected to be delivered should not exceed the suggested dose constraints given for normal structures. To ensure a valid comparison of tumor data and uniformity in the assessment of tumor response and disease progression, the following procedures should be implemented: - The same local physician should perform all physical tumor assessment evaluations for an individual patient. Radiologic interpretation should be performed by designated faculty members with experience in describing skin lesions. - All lesions (target and non-target) identified at baseline will be reassessed according to the imaging schedule provided in Table 6-1. The same method of evaluation (either CT scan or MRI), and/or color photography in the case of skin lesions, if feasible, must be used from baseline until the end of the study.

List of Abbreviations

AE	adverse event
ADR	adverse drug reaction
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BUN	blood urea nitrogen
BCC	Basal Cell Carcinoma
CBC	complete blood cell (count)
CR	complete response
CRC	Clinical Research Coordinator
CRF	case report form
CT	computerized tomography
CTCEA	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
CTV	Clinical Target Volume
DFS	disease-free survival
DLT	dose limiting toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
FCBP	female of childbearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCT	hematocrit
HDFCCC	Helen Diller Family Comprehensive Cancer Center
ICH	International Conference on Harmonization
IND	investigational new drug application
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
laBCC	Locally advanced Basal Cell Carcinoma
LDH	lactate dehydrogenase
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute

List of Abbreviations

PFS	Progression-free survival
PD	disease progression
PO	*Per os* (by mouth, orally)
PR	partial response
PRC	Protocol Review Committee (UCSF)
PRV	planning risk volumes
PTV	planning tumor volume
QD	once daily
RBC	red blood cell (count)
SD	stable disease
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
ULN	upper limit of normal
WBC	white blood cell (count)

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1 Introduction

1.1 Background on Indication

1.1.1 Advanced Basal Cell Carcinoma

Basal Cell Carcinoma (BCC) is the most common malignancy in people; of the more than 1 million cases of non-melanoma skin cancers reported in the United States in 2007, approximately 80% are BCC (American Cancer Society 2007). Almost all of these cases are small BCCs that can be effectively treated by dermatologists using several surgical modalities. However, in a subset of patients, invasion of the BCC into subcutaneous structures can occur. In some cases, this results from neglect of indolent BCCs, whereas in other cases, patients may develop particularly aggressive BCCs that recur and progress despite standard surgical treatment. If further surgical resection is not possible, there are many types of non-surgical treatment, although no one clear standard of care exists.

Although radiation therapy may be used for either palliative or curative intent, its use may be limited by the proximity of the tumor to nearby radiation-sensitive structures, as well as prior interventions and/or cumulative radiation dosage. Locally advanced BCC (laBCC) can be associated with significant morbidity as the result of chronic pain, risk of bacterial infection and sepsis, bleeding/oozing, and compromise of function, resulting from invasion of structures such as the ear, nose, and eye. In some cases, invasion can progress to involve critical organs such as the meninges, brain, and spinal cord, resulting in death (Cohen et al. 2000; Korvarik et al. 2005). In such cases, comprehensive radiation may become very technically challenging or pose risks to the patient's function.

Metastatic BCC (mBCC) is extremely rare. BCC has an overall reported metastasis rate ranging from .0028% to 0.55%, but most believe the true metastasis rate to be significantly less than 0.1% (Wadhera et al. 2006). A total of approximately 300 cases of mBCC have been reported in the literature. The most common sites of metastasis are the lymph nodes, lung, bone, liver, other viscera, and soft tissue (Snow et al. 1994). Once metastasis is detected, survival can be short for some patients, but a range of 8 to 14 months has been reported by some investigators, and individual patients have been reported to live for as many as 25 years (von Domarus and Stevens 1984; Lo et al. 1991; Spates et al.2003). For treatment of distant metastasis, there is anecdotal use of chemotherapeutic agents such as platinum compounds (Pfeiffer et al. 1990). There is also vismodegib, an orally administered, systemically targeted agent recently approved for use in treatment-refractory BCC (Sekulic 2012).

1.1.2 Basal Cell Carcinoma and Surgery

Standard surgical excision is the preferred method for removal of most small and well defined BCCs. When a standard surgical margin is applied (usually 4 mm or more), a high cure rate can be achieved. A weakness of standard surgical excision is the high recurrence rate of BCC of the face, especially around eyelids, nose, and facial structures. On the face, or for recurrent BCC, surgical margins must be assured with controlled processing via complete circumferential peripheral and deep margin assessment.

Most standard excisions are evaluated by a standard bread loafing method of processing. This method has a high "false negative" rate due to the random sampling of the tumor. It is likely that less than 5% of the surgical margin is examined, as each slice of tissue is only 6 micrometers thick, about 3 to 4 serial slices are obtained per section, and only about 3 to 4 sections are obtained per specimen. Usually, if a 4 mm free surgical margin is obtained around a small tumor (less than 6mm), or a wider 6 mm free surgical margin is obtained around a larger tumor (greater than 6mm), the cure rate is very high, at 95% or better. For cosmetic reasons, many doctors take only very small surgical margins 1–2 mm especially when facial tumor is being removed. A pathology report from such a case indicating "margins free of residual tumor," often is inaccurate, and there are recurrence rates of up to 38%.

Mohs micrographic surgery (Mohs) is an outpatient procedure in which the tumor is surgically excised and then immediately examined under a microscope. It has the highest cure rate of 97% to 99.8% in some reports. The base and edges of the tumor are microscopically examined to verify sufficient margins before the surgical repair of the site. If the margins are insufficient, more tissue is removed from the patient until the margins are sufficient.

Extensive BCC that involves central facial structures, the base of skull, or specialized sensory organs requires oncologically oriented head and neck surgical resection with advance planning for reconstruction. If complete surgical removal of the tumor is not possible, there is no clear standard of care to treat these lesions. In these unresectable cases, radiotherapy, either for palliative or definitive intent, can play a major role in this setting. If treatment with radiotherapy is not possible due to surrounding radiation-sensitive organs or contraindicating medical conditions, treatment with vismodegib has recently been FDA-approved for use.

1.1.3 Basal Cell Carcinoma and Radiation Therapy

Radiation therapy is appropriate for all forms of BCC, and adequate doses will frequently eradicate the disease. Although radiotherapy is often used in older patients who are not candidates for surgery, it is also used in cases where surgical excision will be extremely disfiguring or difficult to reconstruct (such as the anterior portions of the nose, nostril rims, lips, or eyelids). Longer and more extended fractionation schedules are associated with fewer long-term complications to the normal tissue supporting the tumor.

Radiotherapy is also delivered with curative intent if a surgical excision has been done incompletely or if the pathology report following surgery suggests a high risk of recurrence, such as if significant nerve involvement by tumor has been demonstrated. Some tumors are deemed unresectable at the outset and definitive radiotherapy is the only remaining standard option.

Cure rates resulting from radiotherapy in this setting are difficult to determine due to the historical heterogeneity of treatment approaches and the lengthy natural history of the disease. However, certain prognostic factors are known to predispose for worse outcome, either due to bone invasion, gross perineural invasion, or adjacency or invasion of a critical anatomic structure, which limits the amount of radiotherapy dose that can be delivered to the tumor. The presence of bone or soft tissue invasion or gross perineural spread is associated with lower rates of success resulting from radiation therapy treatment. Cure rates can be low for extremely invasive tumors that are difficult to encompass properly with radiotherapy. Usually, invasive tumors that have recurred or remain persistent after radiation therapy are treated with surgery and/or vismodegib, and not with reirradiation.

1.1.4 Basal Cell Carcinoma and Chemotherapy

Some superficial BCC respond to local therapy with 5-fluorouracil, a chemotherapy agent. Topical treatment with 5% Imiquimod cream, with five applications per week for six weeks, has a reported 70-90% success rate at reducing, or even removing, the BCC. Both Imiquimod and 5-fluorouracil have received FDA approval for the treatment of superficial BCC. Off-label use of imiquimod on invasive BCC has been reported. Neither of these therapies is penetrating enough for deeply invasive BCC.

Topical chemotherapy may be used following Mohs surgery to eliminate residual superficial BCC after the invasive portion is removed. Some advocate the use of imiquimod prior to Mohs surgery to remove the superficial component of the cancer and reduce the size of the ultimate surgical defect required for removal of the cancer. These experimental procedures likely will result in better cure rate than one modality alone, but are not the standard of care.

Locally advanced or deeply invasive BCC are not treated with chemotherapy and no real standard exists for the use of systemically administered agents in this setting, although vismodegib can be considered if other standard therapies do not apply.

1.1.5 Hedgehog signaling pathway

The Hedgehog (Hh) signaling pathway presents a novel and potentially beneficial target for cancer therapy. Hh signaling regulates epithelial and mesenchymal interactions in a variety of tissues during mammalian embryogenesis (Ingham and McMahon 2001). The Hh ligand in the extracellular space binds to Patched (PTCH1), a 12-pass transmembrane receptor on the surface of cells. Hh binding relieves the inhibitory effect of PTCH1 on Smoothened (SMO), a 7-pass transmembrane domain protein and a member of the G-protein coupled receptor superfamily. Signal transduction by SMO then leads to the activation and nuclear localization of GLI1 transcription factors and induction of Hh target genes, many of which are involved in proliferation and survival, as well as angiogenesis.

A role for aberrant Hh signaling in cancer was initially discovered in patients with Gorlin syndrome, a rare genetic disorder associated with predisposition to BCC, medulloblastoma, and rhabdomyosarcoma. In these patients, mutations in the PTCH1 gene lead to ligand-independent activation of SMO and constitutive activity of the Hh pathway (Johnson et al. 1996). Recent molecular and genetic studies have demonstrated that the majority of sporadic human BCCs also have mutations in the Hh signaling pathway, resulting in aberrant activation of the pathway and uncontrolled proliferation of basal cells (Galilani et al. 1966; Aszterbaum et al. 1998). Two mutations commonly found in BCC result from either the inactivation of the PTCH1 receptor or the activation of SMO protein (Xie et al. 1998). Both have the same functional consequence, i.e., the uncontrolled activation of the Hh signaling pathway in the absence of the Hh protein. High levels of Hh target genes, such as GLI1 and PTCH1, are found in nearly all cases of human BCC examined (Dahmane et al. 1997; Unden et al. 1997), suggesting that activation of this pathway is a causal even in the initiation of tumor formation. These data suggest that blocking the Hh signaling pathway at the level or downstream of SMO may provide a therapeutic benefit in the treatment of BCC (Williams et al. 2003).

The feasibility of blocking Hh signaling in vivo was first demonstrated as a result of teratogenic phenomena occurring in lambs with mothers that had ingested a particular forage plant, Veratrum californicum (Binns et al 1963). Cyclopamine, a steroid alkaloid isolated from this plant, was shown to induce midline deformities, including cyclopia, by blocking SMO signaling in the developing lamb fetuses (Chen et al. 2002). Cyclopamine has proven to be valuable as a tool compound to confirm the importance of Hh signaling in a subset of malignancies, such as slowing the growth of pancreatic cancer xenografts and blocking the metastatic potential of prostate cancer cells in mice (Thayer et al. 2003; Karhadkar et al. 2004).

1.2 Background on Vismodegib

Vismodegib is a small-molecule antagonist of the Hh signal pathway with a molecular weight of 421.30 g/mol. The International Union of Pure and Applied Chemistry name for vismodegib is 2-chloro-N-(4-chloro-3-pyridin-2-yl-phenyl)-4-methanesulfonyl-benzamide.

Vismodegib, the molecule to be evaluated in this Phase II study, has oral bioavailability and potent anti-tumor activity in a variety of primary human tumor xenografts and tumor cell line xenograft models (see the vismodegib Investigator Brochure and the U.S. package insert for further details).

1.2.1 Pharmacokinetics and Drug Metabolism (Safety)

As part of a phase I trial for patients with any advanced or metastatic solid malignancy, 33 patients with metastatic or locally advanced BCC were randomized to receive oral vismodegib 150mg/day (17 patients), 270mg/day (15 patients), and 540mg/day (one patient). Pharmacokinetic data were obtained by a unique schedule of administration of the first dose at day 1, followed by a second dose at day 8 with daily dosing thereafter. Subsequent expansion cohorts included additional patients who received daily oral vismodegib at either 150mg/day or 270mg/day.

The half life of the drug on a daily dosing schedule was 10-14 days and maximal drug concentration after a single dose was the same in the 270 and 540 mg cohorts. Steady state serum levels were the same in all three dose cohorts, indicating pharmacodynamic futility at doses higher than 150 mg/day on this schedule (Molckovsky J Hem Oncol 2008).

Of the 33 patients with BCC, 19 had an objective response to vismodegib for an overall response rate of 58%. Two of these patients had a complete response, and 17 had a partial response. Of the remaining patients, only four had progression of disease, and 10 patients remained stable.

Dose-limiting toxicities (DLTs) were not seen with vismodegib; prevalent adverse events included grade 1-2 dysgeusia and grade 1-2 alopecia. Reversible Grade 3 fatigue and asymptomatic hyponatremia were reported beyond the DLT window. Although disease stabilization has been previously seen in some patients with malignancies other than BCC, all major responses seen to date in the clinical trial setting have been in patients with advanced BCC (Lorusso, Clinical Cancer Research 2011).

1.2.2 Clinical Experience of Vismodegib

The oral small-molecule hedgehog inhibitor vismodegib has provided promising results in treatment of advanced BCC. Abnormal signaling in the Hh pathway is implicated in more than 90 percent of sporadic BCC cases due to loss-of-function mutations in at least one allele of PTCH1, and an additional 10% have activating mutations in the downstream SMO protein.

Results of a larger phase II trial offer additional positive evidence for the hedgehog inhibitor. The Erivance trial was an international, single-arm, multi-center, two-cohort, open-label study that enrolled 104 patients with advanced BCC, including locally advanced BCC (laBCC, n=71) and metastatic BCC (mBCC, n=33) (Sekulic 2012a). laBCC patients had lesions that were inappropriate for surgery and for which radiotherapy was unsuccessful or contraindicated. These patients were either deemed inoperable, or it was judged that surgery would result in substantial deformity. mBCC was defined as BCC that had spread to other parts of the body, including the lymph nodes, lung, bones and/or internal organs. Subjects received 150 mg vismodegib orally, once daily, until disease progression or intolerable toxicity.

The primary endpoint of overall response rate was 43 percent in the laBCC cohort, and 30 percent in mBCC, as assessed by strict independent review. Based on the secondary endpoint of clinical study investigators' assessments, the overall response rate for laBCC was 60 percent and for mBCC, it was 46 percent. The median duration of progression-free survival by independent review was 9.5 months for both metastatic and locally advanced BCC patients and 11.3 months by investigators' assessments.

In 73 percent of patients, vismodegib was shown to shrink tumors, heal visible lesions, or prevent tumor growth. The most common adverse events included muscle spasms, hair loss, altered taste sensation, weight loss, fatigue, nausea, decreased appetite and diarrhea. Serious adverse events were reported in 26 patients (25 percent), but these were considered after review to be related to vismodegib in only four subjects (four percent). Although fatal events were reported over the course of the study in seven patients (seven per

cent), none were considered by investigators to be related to treatment with vismodegib. These events included death from an unknown cause (in 3 patients) and hypovolemic shock, myocardial infarction, meningeal disease, and ischemic stroke (in 1 patient each). A review of these events suggested no definite pattern, and these 7 patients had clinically significant risk factors or coexisting conditions at baseline. Pre-existing diseases or symptoms, primarily cardiac conditions, were most likely related to the presumed causes of death (Sekulic 2012b).

1.3 Rationale for the Proposed Study

Vismodegib is a proven effective means for treating locally advanced and metastatic BCC. Radiotherapy for advanced, unresectable BCC can be effective as well, but ultimate success rates can remain limited for complex, unresectable tumors, either due to anatomic or technical factors. Vismodegib alone produces high response rates in BCC but is unlikely to sustain permanent eradication of very advanced tumors. This study is designed to assess the safety and demonstrate the efficacy of a combined approach using radiation therapy after induction and concurrent systemic administration of vismodegib, which may increase the rates of complete response and sustained local control in patients with locally advanced BCC.

Preclinical evidence indicates a role for vismodegib in combination with radiation therapy. In a number of solid tumor types, the Hh signaling pathway has been implicated in therapeutic resistance to both chemotherapy and radiation therapy. A leading hypothesis is that the Hh signaling pathway may mediate therapeutic resistance via a paracrine effect on stromal and endothelial components of tumor. This resistance mechanism, which has been observed in parallel to upregulation of PTCH1 and GLI1, has been implicated in adenocarcinoma models of pancreas and colon cancer (Yauch 2008), as well as in radiation resistance of hepatocellular carcinoma cells (Chen 2011). GLI1 has been implicated independently in impairment of radiation-induced checkpoint activation (Leonard 2008). In non-small cell lung cancer, a recent study demonstrated a lack of radiation sensitization for in vitro cultures but did show radiation sensitization by Hh antagonists in vivo, indicating the influence of a paracrine effect; this effect was confirmed by genetic analysis showing downregulation of PTCH1 in mouse stromal cells by Hh antagonist (Zeng 2012). Hh signaling has also been implicated in human tumor survival following chemoradiation therapy for esophageal cancers. One study found upregulated PTCH1 expression in xenografts and residual tumors after chemoradiation, and additional clonogenic assays demonstrated increased radiosensitization with Hh inhibition (Sims-Mourtada 2006). A second esophageal cancer study found that expression of PTCH1 and GLI1 predicted for a lack of complete pathologic response (Ajani 2011). Thus, there is growing interest in the possibility of a synergistic effect that might be achieved from the combination of radiation therapy with paracrine-mediated stromal effects of Hh antagonist.

The advanced BCC population was chosen for study based on unmet medical need and evidence of efficacy observed in earlier studies of vismodegib in advanced BCC. At this point in time, despite the clear success of vismodegib in treating BCC, there is no guidance about how to integrate this treatment with other curative-intent therapies.

2 Objectives of the Study

2.1 Primary

- To determine local-regional control rate at 12 months from protocol therapy completion, defined as complete or partial response, with absence of progressive disease (PD) within the irradiated planning tumor volumes (PTV) for patients with locally advanced basal cell carcinoma in the head and neck.

2.2 Secondary

- To estimate of the probability of progression free survival (PFS), with failure defined as any disease recurrence or death due to any cause, and overall survival (OS) with the duration for each measured from the time of first treatment with vismodegib to 12 months after completion of study treatment.
- To evaluate toxicity during the drug-alone and combined-modality components of the protocol regimen during treatment. This will be assessed by

  - The number and attribution of all adverse events, (including vital signs, physical findings, and clinical laboratory results, CTCAE, v 4.0) in patients who receive any amount of study drug and radiation therapy.
  - The proportion of any adverse events (CTCAE, v. 4.0) assessed to be definitely, probably, or possibly related to vismodegib or its combination with radiation therapy.
  - The proportion of patients experiencing Grade 4-5 adverse events assessed to be definitely, probably, or possibly related to the induction or concurrent treatment components of the protocol regimen (that is not definitely related to disease progression).
- To evaluate initial toxicity during the 3 months immediately after completion of protocol therapy.
- To estimate the feasibility of administering concurrent vismodegib with radiation therapy determined by the proportion of patients discontinuing treatment due to toxicity during the concurrent administration of vismodegib and radiation therapy (<75% of planned radiation therapy delivered)
- To evaluate the response rate (as per RECIST) at completion of protocol therapy of the primary site and regionally involved areas in subjects with measurable disease prior to initiation of therapy at 3 months after the completion of protocol therapy.
- To evaluate the clinical response to vismodegib and radiation therapy determined by the proportion of patients with a decrease of BCC within the irradiated planning tumor volumes (PTVs) in patients who complete the combined therapy.

2.3 Endpoints

2.3.1 Primary Endpoints

- The proportion of patients with local-regional control rate at 12 months from protocol therapy completion, defined as complete or partial response, with absence of PD within the irradiated PTV.

2.3.2 Secondary Endpoints

- Estimate of the probability of PFS, with failure defined as any disease recurrence or death due to any cause, and OS with each duration measured from the time of first treatment with vismodegib to 12 months after completion of study treatment.
- The number and attribution of all adverse events, (including vital signs, physical findings, and clinical laboratory results, CTCAE, v 4.0) in patients who receive any amount of study drug and radiation therapy at any point during protocol therapy or during the followup period.
- The proportion of any adverse events (CTCAE, v. 4.0) assessed to be definitely, probably, or possibly related to vismodegib or its combination with radiation therapy at any point during protocol therapy or during the followup period.
- The proportion of patients experiencing Grade 4-5 adverse events assessed to be definitely, probably, or possibly related to the induction or concurrent treatment components of the protocol regimen (that is not definitely related to disease progression) at any point during protocol therapy or during the followup period.
- The proportion of patients discontinuing treatment due to toxicity during the concurrent administration of vismodegib and radiation therapy (<75% of planned radiation therapy delivered).
- Response rate (as per RECIST) of the primary site and regionally involved areas following all treatment components at 3 months after the completion of protocol therapy.

- Proportion of patients with a decrease of BCC within the irradiated planning tumor volumes (PTV) in patients who complete initial combined therapy, indicating a clinical response to vismodegib and radiation therapy.

3 Study Design

3.1 Characteristics

This is a single arm, multi-centered Phase II clinical trial to assess the safety and demonstrate the efficacy of a combined approach using radiation therapy after induction and concurrently with systemic administration of vismodegib, which may increase the rates of complete response and sustained local control in patients with locally advanced BCC.

3.2 Number of Subjects

Required Sample Size: 24 evaluable patients who complete at least 75% of protocol-mandated radiotherapy. Patients who withdraw consent, drop out of the study before starting radiation therapy or before completing 75% of protocol treatment without grade ≥3 toxicity will be replaced. Any patient receiving any study drug will be included in the analysis of toxicity.

3.3 Eligibility Criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

3.3.1 Inclusion Criteria

1. Patients with locally advanced BCC of the head and neck, consisting of at least one histologically or cytologically confirmed lesion ≥ 20 mm in longest diameter that is considered to be inoperable or to have a medical contraindication to surgery, in the opinion of a Mohs dermatologic surgeon, head and neck surgeon, or plastic surgeon. Locally advanced disease is considered to include involved lymph nodes of the neck. A patient with regionally involved lymph nodes in the neck is considered eligible. The patient should be considered a candidate for radiotherapy and should not have medical contraindications to receipt of radiation therapy.

   If a patient has distant metastatic spread of BCC (e.g., spread to distant areas outside the regional lymph nodes, clearly non contiguous areas of bone involvement, or distant metastasis to lung, brain, or other visceral organs), the patient should be considered as having distant metastasis and is not eligible.

   Note: All lesions that the investigator proposes to follow as target lesions during the course of the study must have previously been histologically confirmed as BCC.

   Acceptable contraindications to surgery include:

   - BCC that has recurred in the same location after two or more surgical procedures and successful curative resection is deemed unlikely
   - Complete surgical resection is not possible or is deemed excessively morbid (e.g. invasion into cranial nerves or skull base, proximity to brain, spinal canal, or orbit)

- Anticipated substantial morbidity and/or major deformity from surgery (e.g. removal of a major facial structure, such as nose, ear, eyelid, eye, or jaw; or requirement for upper limb amputation)
- Medical contraindication to surgery
- Patient refusal of surgery due to anticipated morbidity
- Other conditions considered to be contraindicating must be discussed with Data Coordinator before enrolling the patient.

2. Prior radiation therapy is acceptable but there cannot be major overlap of the previously irradiated tissues with the new radiation treatment volumes anticipated to be delivered for the purposes of this protocol, in such a way that curative intent with radiation cannot be met. Furthermore, the total dose from all radiation delivered and expected to be delivered should not exceed the suggested dose constraints given for normal structures (see Section 5.2.7).

3. Zubrod Performance Status 0-2

4. Age ≥18 years of age

5. Adequate bone marrow and organ function defined as follows:

<u>Adequate bone marrow function:</u>	
leukocytes	> 3,000/mcL
absolute neutrophil count	≥1000 cells/mm^3
platelets	≥75,000 cells/mm^3
hemoglobin	≥ 8.5 g/dl (recommended cutoff subject to judgment of medical oncologist), but cannot be transfusion dependent
<u>Adequate hepatic function:</u>	
total bilirubin	≤ 1.5x institutional ULN or within 3x the ULN for patients with Gilbert disease
AST(SGOT)	< 3 X institutional upper limit of normal
ALT(SGPT)	< 3 X institutional upper limit of normal
<u>Adequate renal function:</u>	
creatinine	within normal institutional limits
OR	
creatinine clearance	> 60 mL/min/1.73 m2 for patients with creatinine levels above institutional normal

6. Agreement not to donate blood or blood products during the study and for 24 months after discontinuation of vismodegib.

7. For male patients, agreement not to donate sperm during the study and for 3 months after the final dose of vismodegib. Male patients must use condoms at all times, even after a vasectomy, during sexual intercourse with pregnant partners or female partners of reproductive potential during treatment with vismodegib. Vismodegib is present in semen. It is not known if the amount of vismodegib in semen can cause embryo-fetal harm.

8. Verify the pregnancy status of females of reproductive potential within 7 days prior to initiating vismodegib. For women of childbearing potential, a negative pregnancy test within 7 days prior to commencement of dosing is required. Women of reproductive potential are required to use two forms of acceptable contraception (including one acceptable barrier method with spermicide) during therapy and for 24 months after completing therapy. Acceptable forms of primary contraception include the following: Combination hormonal contraceptives, subcutaneous hormonal implant, hormonal patch, hormonal contraceptives (levonorgestre-releasing intrauterine system, medroxyprogesterone acetate depot), tubal sterilization, vasectomy, and intrauterine device (IUD). Acceptable forms of barrier contraception include the following: any male condom (with spermicide) or diaphragm (with spermicide).

3.3.2 Exclusion Criteria

1. Patients with distant metastasis (e.g. spread to distant areas outside the regional lymph nodes, clearly non contiguous areas of bone involvement, or distant metastasis to lung, brain, liver or other visceral organs) are ineligible.

2. Patients with nevoid BCC syndrome (Gorlin syndrome) should not enroll in this study.

3. A patient with a known other malignancy is eligible if there is a negligible risk for disease progression or death within one year, there is no active ongoing treatment for this malignancy, and the malignancy and/or any anticipated future treatments would not interfere with protocol-mandated evaluations at 1 year.

4. Prior vismodegib or other antagonists of the Hh pathway;

5. Concurrent non-protocol-specified anti-tumor therapy (e.g., chemotherapy, other targeted therapy, topical therapy such as 5-Fluorouracil or imiquimod, radiation therapy, surgery, or photodynamic therapy.

    - For patients with multiple cutaneous BCCs at baseline that are not designated by the investigator as target lesions, treatment of these non-target BCCs with surgery may be permitted but must be discussed with Data Coordinator prior to any surgical procedure.

6. Recent (within 4 weeks of Registration), current, or planned participation in another experimental drug study.

7. Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields in such a way that curative intent with radiation cannot be met

8. Inability or unwillingness to swallow capsules; Patients with any condition that may impair the ability to swallow or absorb oral medications/investigational product including:

    - any lesion, whether induced by tumor, radiation or other conditions, which makes it difficult to swallow capsules or pills;
    - prior surgical procedures affecting absorption including, but not limited to major resection of stomach or small bowel;
    - active peptic ulcer disease;
    - malabsorption syndrome

9. Pregnant or lactating women. Patients who are unable or are unwilling to adhere to the required contraceptive methods are excluded from the study.

    - Women of reproductive potential are required to use two forms of acceptable contraception (including one acceptable barrier method with spermicide) during

therapy and for 24 months after completing therapy. Acceptable forms of primary contraception include the following: Combination hormonal contraceptives, subcutaneous hormonal implant, hormonal patch, hormonal contraceptives (levonorgestre-releasing intrauterine system, medroxyprogesterone acetate depot), tubal sterilisation, vasectomy and intrauterine device (IUD). Acceptable forms of barrier contraception include the following: Any male condom (with spermicide) or diaphragm (with spermicide).

- Women should not breastfeed a baby while on this study, or for 24 months after completing therapy.
- Male patients must use condoms at all times, even after a vasectomy, during sexual intercourse with female partners of reproductive potential during treatment with vismodegib and for 2 months after the last dose to avoid exposing a pregnant partner and unborn fetus to vismodegib.

10. Life expectancy of <1 year

11. Patients with widespread superficial multifocal BCC who are considered unresectable due to breadth of involvement and do not have a single definable area of disease amenable to radiation therapy targeting.

    Note: If an area including one or more lesions is definable for radiation therapy targeting, the patient may be eligible for treatment on study using the designated target lesion(s) identified by the investigator.

12. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection or psychiatric illness/social situations that would limit compliance with study requirements;

13. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or that might affect interpretation of the results of the study or renders the patient at high risk form treatment complications

14. HIV-positive patients on combination antiretroviral therapy, because of the potential for pharmacokinetic interactions with vismodegib;

3.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for approximately 21 weeks or until:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patients decides to withdraw from the study
- Significant patient non-compliance with protocol
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

3.5 Duration of Follow Up

Patients will be followed for 12 months after completion of all protocol therapy, or until death, whichever occurs first. Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related adverse events to Grade 2 or lower.

3.6 Study Timeline

3.6.1 Primary Completion

It is estimated that study accrual will be completed within 12-18 months of the time at which the study is opened for enrollment. It is estimated that primary outcome measure will be determined approximately 3 years after the study is opened for enrollment.

Study Completion

It is estimated that study completion will occur within 3-4 years of the time from when the study is open for enrollment.

4 Study Drugs

4.1 Description, Supply and Storage of Investigational Drugs

4.1.1 Vismodegib

Vismodegib capsules will be taken orally (whole). Patients receive vismodegib on an outpatient basis. Patients are instructed to swallow one capsule once a day (preferably at the same time each day) 7 days/week, with or without food, with about 1 cup (240 mL) of water. Capsules must be swallowed whole; they must not be opened, chewed, broken, or crushed under any circumstances. It is preferable that vismodegib be taken prior to radiation therapy throughout the treatment course. If a patient misses a dose (e.g., due to emesis), he or she should be instructed not to take or make up that dose and to resume dosing with the next scheduled dose. Missed doses will not be made up.

Patients will be asked to document daily vismodegib on a pill diary during pre-radiation treatment and concurrent treatment, which will be collected by the institution as source documentation. Institutions will submit a (DP) form at the end of both induction treatment and concurrent treatment.

Classification

Inhibitor of the hedgehog (Hh) signaling pathway

Mechanism of Action

Vismodegib is a more potent novel and specific synthetic oral hedgehog pathway inhibitor with an IC50 of 3 nM. Vismodegib targets the Hedgehog signaling pathway, blocking the activities of the Hedgehog-ligand cell surface receptors PTCH and/or SMO and suppressing Hedgehog signaling. The Hedgehog signaling pathway plays an important role in tissue growth and repair; aberrant constitutive activation of Hedgehog pathway signaling and uncontrolled cellular proliferation may be associated with mutations in the Hedgehog-ligand cell surface receptors PTCH and SMO. Vismodegib also inhibits ABCG2, Pgp, and MRP1-important ABC transporters associated with multidrug resistance.

Metabolism

Greater than 98% of the total circulating drug-related components are the parent drug. Metabolic pathways of vismodegib in humans include oxidation, glucuronidation, and pyridine ring cleavage. The two most abundant oxidative metabolites recovered in feces are produced *in vitro* by recombinant CYP2C9 and CYP3A4/5.

Contraindications

None per product insert.

Availability

Each vismodegib capsule has a pink opaque body and a grey opaque cap with “150 mg” printed on the capsule body and “VISMO” printed on the capsule cap in black ink. Vismodegib capsules are available in bottles of 28 capsules (NDC 50242-140-01).

Storage and handling

Drug storage will be in the site pharmacy, according to institutional guidelines. Store at room temperature 15°C to 30°C (59°F to 86°F).

Side Effects

Though no specific concomitant medications are prohibited during this study (other than concomitant anti-tumor therapies), vismodegib may potentially affect the pharmacokinetics of other drugs by altering their metabolism. In addition, metabolic inducers could possibly modify the pharmacokinetics of vismodegib. Therefore, concomitant medications should be used with care, and the risk benefit profile of each agent should be taken in to consideration.

Identified Risks (excerpted from IB, version 6.0, dated 01-25-2012)

The safety of vismodegib has been evaluated in 138 laBCC patients from four open-label, single-arm Phase I and II clinical studies. One hundred thirty-eight laBCC patients received at least one 150 mg dose of vismodegib monotherapy. Doses > 150 mg did not result in higher plasma concentrations in patients administered doses > 150 mg and have been included in analyses. In general, the observed safety profile was consistent between mBCC and locally advanced BCC patients as described below.

Adverse reactions are presented by MedDRA System Organ Class and absolute frequency in Table 16. Frequencies are defined as:

- Very common: ≥ 1/10
- Common: <1/10 to ≥ 1/100
- Uncommon: <1/100 to ≥1/1000

Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. Frequency categories do not account for other factors such as varying study duration, pre-existing conditions or baseline patient characteristics. ADR frequency categories are assigned based on clinical trial experience and may not reflect the frequency of adverse events occurring during normal clinical practice.

Table 16 Adverse Drug Reactions Occurring in Patients Treated with Vismodegib in Clinical Trials

MedDRA System Organ Class	Very Common	Common	Uncommon
Gastrointestinal disorders	Nausea Diarrhoea Constipation Vomiting	Abdominal pain	Nausea (Grade 3) Diarrhoea (Grade 3)
General disorders and administration site conditions	Fatigue	Fatigue (Grade 3)	
Investigations	Weight decreased	Weight decreased (Grade 3)	Weight decreased (Grade 4)
Metabolism and nutrition disorders	Decreased appetite	Dehydration (Grade 1–3) Decreased appetite (Grade 3)	
Musculoskeletal and connective tissue disorders	Muscle spasms Arthralgias	Musculoskeletal pain	
Nervous system disorders	Dysgeusia Ageusia	Hypogeusia	
Reproductive system and breast disorders	Amenorrhea*		
Skin and subcutaneous tissue disorders	Alopecia		

* In clinical trials, a total of 3 of 10 pre-menopausal women developed amenorrhea while receiving vismodegib.

All reporting is based on adverse events of all grades using NCI - CTCAE v3.0 except where noted.

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

Complete and updated adverse event information is available in the Investigational Drug Brochure and/or product package insert.

4.2 Radiation Therapy

The administration of radiation therapy is outlined in section 5.2.

There will be expected radiation related toxicities; very likely toxicities are mucositis, mouth dryness or changes in taste and/or smell that may be permanent, thick saliva, hoarseness, tanning or redness and/or irritation of the skin in the head and neck area being treated with radiation, ear pain and/or pressure, fatigue, weight loss, permanent hair loss in the area treated with radiation (face, chin, neck), and hypersensitivity of teeth and/or loss of teeth or cavities in the teeth, if strict dental care is not followed.

Serious but less likely toxicities are decreases in function of the thyroid gland that may require thyroid replacement therapy; serious damage to the spinal cord, nerves in the neck, jawbone, larynx, skin, or other parts of the head and neck that may require surgical intervention and may

be life threatening; temporary pain or scarring around nerves in the shoulder that could cause numbness and/or weakness; breathing problems; difficulty with swallowing and eating, possibility of inhaling food and/or liquids into the lungs which could result in pneumonia; serious ear infections and/or hearing loss; damage to the spinal cord leading to permanent weakness and/or symptoms like a stroke; loss of hearing; and decreased vision.

In general, the anticipated toxicities from the combination of vismodegib and radiation therapy should not be overlapping in a synergistic fashion with the possible exception of wound healing. It is possible that the side effects of radiation therapy which are related to wound healing may be intensified in the presence of vismodegib. In the absence of any further surgical procedures given after the combined therapy, it is not expected that there should be serious additional toxicity related to wound healing over that expected from a typical standard-of-care radiation therapy course, although these types of effects will be tracked carefully as part of this study protocol.

4.3 Drug Accountability

The Investigational Pharmacist will manage drug accountability records. Drug will be shipped for assigned study patients only. Drug from one patient cannot be transferred to another patient even if that patient is on protocol.

4.4 Drug Ordering

Study investigators will obtain vismodegib directly from pharmaceutical company as study supply. Participating sites will receive drug shipments directly from Genentech.

4.5 Packaging and Labeling of Study Drugs

Drugs will be packaged and labeled per institutional standards, adhering to applicable local and federal laws.

4.6 Reconciliation

The Sponsor-Investigator agrees to conduct reconciliation for the product. Genentech and the Sponsor-Investigator will agree to the reconciliation periodicity and format, but agree at minimum to exchange monthly line listings of cases received by the other party. If discrepancies are identified, the Sponsor-Investigator and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

5 Treatment Plan

5.1 Dosage and Administration: Vismodegib

Treatment will be administered on an outpatient basis. Patients will take vismodegib 150 mg orally (QD PO). Prior to Radiation Treatment, patients will take vismodegib (150 mg/day) for approximately 12 weeks, then for 1-14. days as required until the start of radiation therapy. If there is an unforeseen delay in starting the radiation therapy after the induction phase, an additional 1-2 weeks of treatment with vismodegib may be given after contacting and getting the consent of the Principal Investigator. During radiation treatment, vismodegib (150mg/day) concurrent treatment will be given on the same day as the first fraction of radiation therapy and will continue daily through the completion of radiation treatment. The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff approximately every four weeks (Week 5, 9, 13-15, 18, and at the end of drug treatment) .

Table 5.1 Regimen Description

Study Drug	Dose	Route	Schedule
Vismodegib	150 mg	Oral	Induction Phase (12 weeks) End of Induction / Re-Evaluation (2 weeks)
			Radiation Treatment (7 weeks)

5.2 Dosage and Administration: Radiation Therapy

5.2.1 Three-dimensional conformal radiation therapy

For three-dimensional conformal radiation therapy, the PTV1 (CTV1 + margin) will receive 6600-7000 cGy in 33-35 fractions, with the final prescribed dose decided per discretion of the prescribing investigator, and the PTV2 (CTV2 + margin) will receive 5000 cGy in 25 fractions.

The PTV1 should encompass any area of disease visible or palpable at post-induction restaging and any areas involved on the initial imaging prior to induction, even if the area has responded to the drug. The PTV2 should encompass any areas of elective coverage deemed necessary, such as the regional lymph node drainage basins.

Treatment will be delivered once daily, 5 fractions per week, over 7 weeks. After the initial 25 fractions for treatment of the PTV2, a reduced field will be given encompassing only PTV1. If PTV2 is not required, then PTV1 will be treated for the entire course of radiation.

The reported doses for PTV1 and PTV2 shall include the prescription dose as well as the maximum point dose (maximum dose encompassing 0.1 cc volume) for that PTV, % PTV receiving > 110% and 115% for that PTV and the PTV receiving < 93% of the prescribed dose for that PTV, and the mean dose for that PTV.

All plans shall be normalized such that 95% of the volume of each PTV is covered by the prescription isodose surface. To avoid a minor variation:

- No more than 20% of PTV1 will receive 110% of the prescription dose and no more than 5% of PTV1 will receive 115% of the prescription dose.
- No more than 1% of any distinct PTV should receive <93% of its prescribed dose.

5.2.2 Intensity modulated radiation therapy

IMRT is particularly encouraged for tumors involving the skull base or which lie in close approximation to critical structures such as the eye, brain, or spinal cord.

For intensity modulated radiation therapy, the PTV2 (CTV2 + margin), if deemed necessary by the investigator, will receive 5000 cGy in 25 fractions and the PTV1 (CTV1 + margin) will receive 6600-7000 cGy in 33-35 fractions (maximum total dose to be at discretion of the investigator). The PTV1 should encompass any anatomic areas involved by disease that remain visible or palpable at post-induction restaging and any anatomic areas involved on the initial imaging prior to induction, even if the area has exhibited response to the drug. The PTV2 should encompass any areas of elective coverage deemed necessary, such as the regional lymph node drainage basins.

Treatment will be delivered once daily, at a rate of 5 fractions per week, over 7 weeks. There are two options for radiation treatment planning, either employing a field reduction and boost at

the end of treatment, or a simultaneous integrated boost with all PTVs being treated simultaneously.

For the sequential boost approach: After the initial 25 fractions for treatment of the PTV2, a reduced field will be given encompassing only PTV1. For this approach, two separate plans are required, the first encompassing the entirety of the 5000 cGy volume, with a boost plan to encompass the smaller volume which will be treated for an additional 1600-2000 cGy.

For the simultaneous integrated boost approach: Alternatively, a simultaneous integrated boost plan can be used in which the PTV1 receives 6600-7000 cGy in 33-35 fractions, but the PTV2 is to be treated in the same plan for all 33-35 fractions. For this approach, the PTV2 dose should be increased to 5400-5600 cGy given in 33-35 fractions, to account for the more extended fractionation schema.

The reported doses for PTV1 and PTV2 shall include the prescription dose as well as the maximum point dose (maximum dose encompassing 0.1 cc volume) for that PTV, % PTV receiving > 110% and 115% for that PTV and the PTV receiving < 93% of the prescribed dose for that PTV, and the mean dose for that PTV.

All plans shall be normalized such that 95% of the volume of each PTV is covered by the prescription isodose surface. To avoid a minor variation:

- No more than 20% of PTV1 will receive 110% of the prescription dose and no more than 5% of PTV1 will receive 115% of the prescription dose.
- No more than 1% of any distinct PTV should receive <93% of its prescribed dose.

5.2.3 Technical Factors

5.2.3.1 External Beam Equipment and Beam Delivery Methods

Megavoltage equipment capable of delivering static modulation with a multileaf collimator or dynamic intensity modulation (using a multileaf collimator or tomotherapy) is required. Volumetric arc delivery techniques can be used.

5.2.4 Treatment Planning, Imaging and Localization Requirements

The immobilization device should include the body area of the primary tumor volume and any grossly involved, regional nodal volumes to be treated with radiation therapy. It is strongly encouraged that the participating centers include the entire head, neck, and shoulders in the immobilization. Accuracy of patient set-up should be ensured with verification using on-board imaging, either portal films or conebeam CT, at least twice per week of treatment.

Treatment planning CT scans will be required to define gross target volume(s) and clinical target volume(s). The treatment planning CT scan should be acquired with the patient in the same position and using the same immobilization device as for treatment.

All tissues to be irradiated must be included in the CT scan. CT scan slice thickness should be no more than 0.3 cm through the entirety of the region that contains the primary target volumes. The regions above and below the target volume may be scanned with 0.5 cm slice thickness, although 0.3 cm slice thickness is preferred.

The GTV and CTV and normal tissues must be outlined on all CT slices in which the structures exist.

5.2.5 Treatment Planning/Target Volumes

The definition of volumes will be in accordance with the 1993 ICRU Report #50, but the dose reporting and prescription are specified in Sections 5.2.

The Gross Tumor Volume (GTV) is defined as all known gross disease determined from imaging studies at presentation, clinical information, and physical examination findings. The GTV should encompass any area of disease visible or palpable at post-induction restaging and any areas involved on the initial imaging prior to induction, even if the area has responded to the drug. Grossly positive lymph nodes are defined as any lymph nodes > 1 cm in shortest dimension or nodes with a necrotic center. It is strongly encouraged that the radiation oncologist outline the radiologic extent of the primary tumor and any involved nodes along with a radiologist. Whenever possible, it is recommended that the diagnostic-quality images be fused to the planning CT scan image dataset to more accurately define the GTV as it existed prior to induction with vismodegib. To further subdivide the GTV, gross disease at the primary site may be designated as GTV-P and clinically involved gross lymph nodes may be designated GTV-N. In situations where the patient underwent surgical biopsy or surgery prior to radiation therapy, the GTV is defined as the residual gross disease thought to remain following the surgery.

The Clinical Target Volume (CTV): See Sections 5.2 for delineation details.

For patients without complete surgical resection: In terms of the GTV (GTV-P and GTV-N), a margin of 5 mm should be given circumferentially around the GTV (GTV-P and GTV-N) and this volume will be called the CTV1 (CTV1-P and CTV1-N). This margin can be reduced to as low as 1 mm for tumors in close proximity to critical structures, e.g., tumors next to the spinal cord or brain.

For regions deemed to be at high risk for microscopic disease, the treating radiation oncologist should delineate all potential routes of spread for primary and nodal GTVs. This is known as CTV for subclinical disease or CTV2. Delineation and treatment of CTV2 is optional and based on the judgment of the study investigators.

For patients who have undergone a prior surgical resection: CTV2 should include all of the original sites of gross disease at the primary disease site and any grossly involved but resected lymph nodes (e.g the post-operative bed). A CTV1 should be delineated if a region has had surgery but still contains residual gross disease.

To further define the subclinical region at risk for microscopic spread at the primary disease site, CTV2-P includes CTV1-P + at least 3 mm margin. This margin can be reduced to as low as 1 mm for tumors in close proximity to critical structures, e.g., tumors next to the spinal cord or brain. At the discretion of the treating physician, elective nodal regions considered to be at high risk can be covered in CTV2 when indicated.

Note: Thus, if CTV-2 is delineated and treated, the outermost boundary of CTV2-P should usually be 8 mm from the GTV-P. In regions near the spinal cord or other sensitive or critical structures, the total margin between GTV-P and CTV2-P can be as low as 2 mm.

A separate Planning Target Volume (PTV) will provide a margin around the CTV's to compensate for the variabilities of treatment set up and internal organ motion. A minimum of 3 mm around the CTV's is required in all directions to define each respective PTV (PTV1, PTV2). Careful consideration should be made when defining the superior and inferior margins in three dimensions. Note that at any given point, the margin from the GTV to the PTV1 should usually be at least 8 mm and to the PTV2 should usually be at least 11 mm. The exception is when the tumor is close to the spinal cord or other sensitive structures where CTV margins may be reduced as described; for these cases, the PTV may be set as equal to the CTV to ensure avoidance of critical neural structures. In these exceptionally difficult cases, the total expansion from the GTV to the PTV1 could be as low as 1 mm and to the PTV2 could be as low as 2 mm. Margins may be reduced to these absolute minima just around the anatomic areas of greatest risk; expansion to the larger standard margins is encouraged wherever possible.

The treatment plan used for each patient will be based on an analysis of the volumetric dose, including dose-volume histogram (DVH) analyses of the PTVs and critical normal structures. An

"inverse" planning process using computerized optimization should be used. The treatment aim will be the delivery of radiation to the PTVs and the exclusion of non-involved tissue.

5.2.6 Critical Structures

Critical Normal Structures

Surrounding critical normal structures, including spinal cord, brain, brainstem, orbits, chiasm and optic nerves, cochlea, parotid glands, submandibular glands, skin, oral cavity, mandible, brachial plexus, esophagus and glottic larynx should be outlined.

Physicians should assist the planner in identifying the critical normal structures. If planning risk volumes (PRVs) are used, the spinal cord PRV will be defined as a three-dimensional margin at least 4 mm larger than the spinal cord to ensure that the PRV margin is at least 4 mm from any portion of the spinal cord. The normal tissues will be contoured and considered as solid organs. The tissue within the skin surface and outside all other critical normal structures and PTVs is designated as unspecified tissue.

DVH's must be generated for all critical normal structures, any corresponding PRVs, and the unspecified tissues. Institutions that use PRVs must clearly define them as such.

Unspecified tissue outside the targets: No more than 8cc of unspecified tissue can receive greater than 6600 cGy or more and no more than 1cc of unspecified tissue can receive 7000 cGy or more. Participants are strongly encouraged to remain within these limits. The treating physician is encouraged to call the Principal Investigator should questions arise.

The method used for tissue heterogeneity calculations shall be recorded. The dose prescription is to be based on a dose distribution corrected for heterogeneities.

5.2.7 Planning Goals: Normal Structures

These dose objectives are recommendations. An effort should be made to stay within the normal tissue dose guidelines stipulated in this protocol.

- Spinal Cord: The PRV should not exceed 48 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). The spinal cord PRV should not exceed 50 Gy to any volume in excess of 0.01 cc. This PRV should be given the highest priority.
- Brainstem: The PRVbrainstem should not exceed 56 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). In treatment planning, the PRVbrainstem should be given less priority than the PRVcord but more priority than other critical structures.
- Optic chiasm, optic nerves, and globe: The PRV should not exceed 54 Gy to any volume in excess of 0.01 cc. Every effort should be made to keep the dose as low as possible in these areas.
- Parotid glands: Mean dose < 2600 cGy should be achieved in at least one gland, or at least 20 cc of the combined volume of both parotid glands will receive < 2000 cGy, or at least 50% of one gland will receive < 3000 cGy. Every effort should be made to achieve the lowest mean doses as possible without compromising tumor coverage.
- Submandibular glands and oral cavity: Reduce the dose as much as possible, preferably with a mean dose < 3900 cGy. If, at the discretion of the treating physician, level I region of the neck must be covered, there is no need to constrain the submandibular glands.
- Mandible: Reduce the dose as much as possible. It is recognized that portions of the mandible will overlap the CTVs and/or PTVs but hot spots within the mandible should be avoided. It is recommended that maximum dose within the mandible be < 6600 cGy.

5.2.8 Planning Priorities

Critical normal structure constraints followed by the prescription goals are the most important planning priorities. The priorities in addressing the protocol aims and constraints will be in the following order: 1) Critical Normal Structure Constraints (Section 5.2.6); 2) Dose Specifications (Section 5.2); 3) Planning Goals: Salivary glands (Section 5.2.7); 4) Planning Goals: Other normal structures (Section 5.2.7).

5.3 Dose Modifications and Dosing Delays

There are no planned dose reductions of vismodegib.

Treatment with vismodegib may be interrupted for up to 4 weeks for evaluation of an intolerable toxicity finding. In addition, treatment with vismodegib may be interrupted for up to 4 weeks if a patient becomes temporarily unable to swallow capsules or is in need of an unrelated surgical procedure which does not require disenrollment from the study. Any other proposed reasons for interruption of treatment should be discussed in advance with the Principal Investigator. If the patient resumes drug, administration will start at the point in the protocol at which was interrupted and the total durations of days of drug given to the patient should equal those specified in the protocol.

Radiation therapy should not be halted if at all possible and any radiation delays are to be stringently avoided, even if drug administration is interrupted. If radiation therapy treatments are interrupted for any reason, including holidays or mechanical breakdown, the missed treatments are to be addended to the end of the treatment course, such that the total radiation dosage and days of radiation therapy given to the patient should equal those specified in the protocol.

If either vismodegib or radiation treatment has been held for more than 28 days to allow for resolution of an adverse event, the treating physician should contact the Study Chair to review the subject's condition prior to resuming the patient's treatment, except for delays due to hypertension. As a patient progresses from one treatment to another (i.e., pre-radiation therapy, radiation therapy, post radiation therapy), the patient should remain at the SAME DOSE LEVEL.

5.3.1 Intolerable Toxicity Requiring Discontinuation of Vismodegib

Intolerable toxicities are defined as new (not present at baseline) Grade 3 or 4 adverse events considered related to vismodegib that are likely to be life-threatening or irreversible, and when in the opinion of the investigator, the risk outweighs the benefit of continued treatment.

The following adverse events are not considered intolerable:

- Grade 3 or 4 events that in the opinion of the investigator are more likely related to ongoing or recent procedures or concomitant medications other than vismodegib
- Hematologic or metabolic/chemistry laboratory abnormalities that are found on routine testing and are not considered clinically significant
- Musculoskeletal abnormalities, skin ulceration, fracture, debridement or wound care, and dental or periodontal disease related to underlying medical conditions
- Nausea, vomiting, or diarrhea that is adequately controlled after optimization of medical management.
- Grade 3 infection that is transient and treatable or manageable
- Grade 3 sterility
- Asymptomatic thromboembolism found incidentally on imaging and managed with anti-coagulation therapy

Patients with an asymptomatic or tolerable severe adverse event may continue to receive study drug, provided that the adverse event is manageable and the patient and the investigator agree that continued study participation is acceptable.

5.4 Monitoring and Toxicity Management

Each patient receiving vismodegib will be evaluable for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical findings, performance status evaluations, Skindex-16 survey responses and spontaneous reports of adverse events reported to the investigator by patients.

Each patient will be assessed periodically for the development of any toxicity as outlined in Section 6 Study Procedures and Observations. Toxicity will be assessed according to the NCI CTCAE v4.0. Dose adjustments will be made according to the system showing the greatest degree of toxicity.

5.5 Other Therapy

5.5.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

After the 12 month follow-up period has ended following completion of combination therapy, patients may receive standard-of-care treatment for recurrence or for other skin cancers. These therapies may include vismodegib.

5.5.2 Non-permitted Supportive Therapy

The patient's medications will be evaluated within 4 weeks prior to treatment (see Section 6.1.1.1) to assess any medication that affects CYP3A4.

Certain medications act through the CYP450 system. Strong inhibitors of CYP3A4 such as ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole may increase vismodegib concentrations and are generally prohibited although, if absolutely necessary, they may be administered with caution. Grapefruit juice is also an inhibitor of CYP450. CYP3A4 inducers such as rifampin may decrease vismodegib concentrations and therefore are strictly prohibited. Caution should be used when strong inhibitors and/or inducers of CYP2D6 are co-administered with vismodegib. Concomitant use of vismodegib with agent with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6 or CYP2C8 should be avoided. In addition, the use of St. John's Wart is not recommended.

Vismodegib, 150 mg once daily, has no effect on CYP2C9, CYP1A2 or CYP2C19 in vivo although it does in vitro. Therefore, therapeutic doses of warfarin, a substrate of CYP2C9, and omeprazole, a substrate of CYP2C19 are permitted. Caffeine, a substrate of CYP1A2, is also permitted. A list of medications that should be used with caution during this trial of vismodegib can be found in Appendix 5. Comprehensive lists of agents that could affect vismodegib through the cytochrome P450 system can be found in Appendix 5. No drugs are specifically prohibited but caution is recommended for these agents.

Amifostine or other intravenously administered supportive systemic therapies are not allowed due to the unknown interaction of these compounds with vismodegib.

5.6 Compliance Criteria

Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Treatment breaks, if necessary, should ideally not exceed five treatment days at a time and ten treatment days total. Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and not for social or logistical reasons. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

Institutions are encouraged to generate treatment that fall within the dose limits defining the per protocol category. For those target to critical structures geometries that are more challenging, some variation from the specified protocol dose limits is acceptable.

6 Study Procedures and Observations

6.1 Schedule of Procedures and Observations

The study-specific assessments are detailed in this section and outlined in Section 6 Schedule of Study Procedures and Assessments. Screening assessments must be performed within 28 days prior to the first dose of investigational product unless otherwise noted. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. All on-study visit procedures are allowed **a window of ± 3 days** unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All patients who are consented will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

6.1.1 Pretreatment Period

6.1.1.1 Screening Assessments

The Screening procedures and assessments must be completed within 14 days of the Day 1 Visit unless otherwise noted.

- Physical examination - The initial complete physical examination should include evaluation of the head, eyes, ears, nose and throat (HEENT); cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Height and weight will also be recorded.
- Vital signs
- Complete medical history – can be done within 28 days of Day 1
- Baseline conditions assessment
- Documentation of disease assessment - Assessments should include an evaluation of all sites of disease. Patients will undergo tumor assessments per RECIST version 1.1 tumor response criteria. Can be done within 28 days of Day 1
- Performance status
- Skindex-16 questionnaire
- History of prior treatments and any residual toxicity relating to prior treatment
- Baseline medications taken within 28 days of Day 1

- Laboratory assessments
    - Hematology (hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent and absolute differential count [neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, other cells])
    - Serum chemistries (sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, alkaline phosphatase, magnesium, total bilirubin, albumin, total protein, ALT, AST, and as clinically indicated; LDH, and phosphorus)
    - Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening, within 7 days of Day 1.
        - Urine or serum pregnancy tests will be performed every 4 weeks at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
    - Urinalysis
- Imaging (CT or MRI) of primary tumor region and any involved regional lymph nodes for tumor assessment. Can be done within 28 days of Day 1
    - Note: The CT scan with contrast or an MRI with gadolinium must be done unless medically contraindicated. The MRI or CT scan must encompass the skull base and/or upper mediastinum if those areas are involved. If locally advanced BCC lesions with a RECIST-measurable component are identified, the same imaging modality used at baseline must be used throughout the study.
- Chest x-ray or chest CT scan, or CT of chest and abdomen – can be done within 28 days of Day 1
- For externally visible tumors
    - Bidimensional measurements of externally visible tumor dimension
    - Description of the lesion at baseline
    - Digital photography of target lesion(s)
    - Tumor biopsy for pathologic diagnosis - can be done within 360 days prior to Day 1

The following pre-treatment evaluations/interventions are not required but are highly recommended:

- PET/CT scan for patients with suspected metastatic disease
- Brain MRI for patients with disease located at or near the skull base
- Biopsy confirmation of suspected involved regional nodes (fine needle aspiration is acceptable);
- For patients with head and neck cancers who will have treatment-related risk to salivary function, pre-radiotherapy dental evaluation is strongly recommended

6.1.2 Treatment Period

6.1.2.1 Study Procedures, Week 5 and 9 (Induction Phase)

- Physical examination including weight
- Vital signs
- Performance status
- Evaluation of adverse events
- Concomitant medications

- Skindex-16 survey
- Laboratory assessments
    - Hematology
    - Serum chemistries
- Urine or serum pregnancy tests at weeks 5 and 9 - if a woman of childbearing age

6.1.2.2 Study Procedures, Week 13-14 (End of Induction)

Within 14 days after completion of induction vismodegib therapy, patients must have a re-evaluation to determine if there has been disease progression prior to starting concurrent treatment. Patients whose disease has progressed will no longer continue on study.

- Physical examination including weight
- Vital signs
- Performance status
- Evaluation of adverse events
- Concomitant medications
- Skindex-16 survey
- Laboratory assessments
    - Hematology
    - Serum chemistries
- Urine or serum pregnancy tests - if a woman of childbearing age
- Disease assessment
- Imaging (CT or MRI) of head and neck for tumor assessment
- CT chest or chest x-ray – if clinically indicated
- For externally visible tumors
    - Bidimensional measurements of externally visible tumor dimension
    - Standardized digital photography of target lesion(s)

6.1.2.3 Study Procedures, Week 15-21 (Radiation Therapy)

Three-dimensional conformal therapy is required for this study. IMRT is allowed as deemed appropriate and is highly encouraged for very advanced disease presentations.

Following conclusion of induction drug therapy and completion of re-evaluation procedures, radiation should start within 1 to 14 days after completion of induction vismodegib, unless there is an unforeseen delay. During the re-evaluation interval, vismodegib will continue to be given daily until radiation therapy starts. Radiation therapy is anticipated to last approximately 7 weeks depending on the prescription dose chosen by the study investigator.

Note: If there is an unforeseen delay in starting the radiation therapy, an additional 1-2 weeks of treatment with vismodegib may be given after contacting and getting the consent of the Principal Investigator. If there is a delay over 4 weeks in initiation of radiation therapy, investigators should consider removal of the patient from the protocol.

While receiving radiation therapy, patients will have limited physical exams, evaluation of adverse events, and assessment of concomitant medications weekly. At week 18 only, patients will have urinalysis, pregnancy test, and laboratory assessments (hematology and serum chemistries). The drug diary will be collected at week 18.

Radiation therapy will be 66-70 Gy in 33-35 fractions over 7 weeks as prescribed in Section 5.2. See section 5 for Radiation Therapy treatment planning, imaging, and localization requirements.

6.1.3 End-of-Treatment Study Procedures

To be completed within 8 – 12 weeks of the last dose of study drug.

- Physical examination including weight
- Vital signs
- Performance status
- Evaluation of adverse events
- Concomitant medications
- Skindex-16 survey
- Laboratory assessments
    - Hematology
    - Serum chemistries
- Urine or serum pregnancy tests within 4 weeks after completion of radiation therapy - if a woman of childbearing age
- Disease assessment
- Imaging (CT or MRI) of head and neck for tumor assessment
- CT chest or chest x-ray – if clinically indicated
- For externally visible tumors
    - Bidimensional measurements of externally visible tumor dimension
    - Digital photography of target lesion(s)
    - Description of the lesion
    - Tumor biopsy – as needed to confirm progression

    If biopsy results are confirmatory of persistent cancer, the patient may be offered salvage surgery as indicated. This would result in discontinuation from the study. Post-salvage follow-up may be conducted by UCSF investigators with separate consent by the patient.

6.1.4 Post-treatment/Follow Up Visits

Patients will be followed at 3, 6, and 12 months (+/- 2 weeks) after the End of Treatment visit or until disease progression. The following procedures will be performed at the Follow-Up Visit(s):

- Evaluation of clinical response or deterioration
- Physical examination including weight
- Vital signs
- Performance Status
- Evaluation of adverse events
- Concomitant medications
- Skindex-16 survey
- Laboratory assessments
    - Hematology

  - Serum chemistries
- Urine or serum pregnancy tests - if a woman of childbearing age – at 3 and 6 month visits only
- Disease assessment
- Imaging (CT or MRI) of head and neck for tumor assessment
- CT chest or chest x-ray – if clinically indicated
- For externally visible tumors
  - Bidimensional measurements of externally visible tumor dimension
  - Digital photography of target lesion(s)
  - Description of the lesion
  - Tumor biopsy - to confirm progression

6.1.5 Long Term/Survival Follow-up Procedures

The study team will follow patients for survival outcome via telephone calls or medical record requests approximately every 3 months for 12 months, until death or loss to follow-up, whichever occurs first. Additional, survival follow-up information may be collected via telephone calls and/or at clinic visits every 3 months for 12 months. Follow-up may consist of at least a telephone contact with the patient, a family member, or physician to inquire about the patient's survival status.

If/when a subject begins a new type of non-protocol treatment for laBCC or mBCC, long-term follow up may cease. Subjects will continue to be followed if they have not recurred local-regionally within the original treated PTV. If they have a BCC in a non-treated separate location, or if metastatic disease occurs, subjects will continue to be followed for the local-regional disease control outcomes. Subjects would be taken off protocol if they have any form of non-protocol treatment affecting the primary local or nodal site that was originally treated or if they receive vismodegib or other Hedgehog inhibitor or chemotherapy outside of original protocol parameters. Patients off study protocol who need to have vismodegib will not have drug provided by the study.

6.1.6 Discontinuation of Therapy

The Investigator will withdraw a patient whenever continued participation is no longer in the patient's best interests. Reasons for withdrawing a patient include, but are not limited to, disease progression inside the PTV or at distant sites at any point, the occurrence of an adverse event or a concurrent illness, excessive delay in protocol treatment (greater than 4 weeks), a patient's request to end participation, a patient's non-compliance or simply significant uncertainty on the part of the Investigator that continued participation is prudent. There may also be administrative reasons to terminate participation, such as concern about a patient's compliance with the prescribed treatment regimen.

Table 6.1 Schedule of Study Procedures and Assessments

All evaluations have a window of +/- 3 days unless noted otherwise below.

Period/ Procedure	Screening		Induction		End of Induction (Re-Evaluation)	Concurrent Therapy							End of Treatment	Follow-up visits [1]
Study Week/Visit Week	**-28 to -1**	**-14 to -1**	**5**	**9**	**13-14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**29-33**	
Informed consent	X													
Assignment of patient ID number		X												
Baseline conditions		X												
AE assessment [2]		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X	X	X
Treatment/Drug Administration														
Vismodegib			Daily (150 mg/day)											
Radiation Therapy						Daily (5 fractions/week)								
Clinical procedures														
Physical exam [3]		X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs [4]		X	X	X	X								X	X
Medical history	X													
Disease assessment	X				X								X	X
Performance status		X	X	X	X								X	X
Biopsy	X[5]													
Skindex-16 Survey		X	X	X	X								X	X
Digital photographs [5]		X			X								X	X
Tumor measurements [5]		X			X								X	X
Fine Needle Biopsy [6]		X												
Dental evaluation [6]		X												
Laboratory procedures														
Hematology [7]		X	X	X	X				X				X	X
Blood chemistry [8]		X	X	X	X				X				X	X

Table 6.1 Schedule of Study Procedures and Assessments

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Study Week/Visit Week	**-28 to -1**	**-14 to -1**	**5**	**9**	**13-14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**29-33**	
Pregnancy test (HCG)		X[11]	X	X	X				X				X	X[11]
Urinalysis		X							X					
Imaging procedures														
Imaging (CT or MRI) [6,9]	X				X								X	X
Chest x-ray, CT Chest, or PET/CT [6,10]	X				X								X	X

1. Follow-up visits will occur at 3, 6, & 12 months (+/- 2 weeks)post EOT. Patients with documented disease progression within the irradiated PTV will be removed from study treatment. Survival follow-up information may be collected via telephone calls and/or at clinic visits every 3 months for 12 months.
2. The reporting period for adverse events (AEs) and serious adverse events (SAEs) will begin at the time of enrollment and continues until 90 days after the last dose of vismodegib. During screening, only SAEs related to protocol-mandated procedures should be reported. At the end of the study period, any patient with an ongoing AE or SAE will be followed until the event resolves, the investigator assesses the event as stable, or the patient is lost to follow-up.
3. A complete physical exam includes evaluation of the head, eyes, ears, nose and throat; cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Exam includes height (at screening only) and weight.
4. Vital signs include pulse, systolic and diastolic blood pressure while the patient is in a seated position, respiratory rate, and temperature.
5. For externally visible tumors. Can be done up to 180 days prior to day 1. Additional biopsy after screening will only be to confirm progression.
6. Dental evaluation, fine needle biopsy, Brain MRI, and PET/CT are highly recommended but not required at screening.
7. Hematology consists of hemoglobin, hematocrit, platelet count, red blood cell (RBC) count, white blood cell (WBC) count, and percent or absolute differential count (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells).
8. Serum chemistry includes glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, magnesium, chloride, bicarbonate (if routinely performed on venous blood samples), calcium, total protein, albumin, total bilirubin, alkaline phosphatase, AST, and ALT, and as clinically indicated; LDH, and phosphorus
9. The CT scan with contrast or an MRI with gadolinium must be done unless medically contraindicated. The MRI or CT scan must encompass the skull base and/or upper mediastinum if those areas are involved. If locally advanced BCC lesions with a RECIST-measurable component are identified, the same imaging modality used at baseline must be used throughout the study.
10. Locally advanced BCC patients should have a CT of the chest and abdomen at baseline to assess for possible metastatic disease or other significant abnormalities. Abdominal imaging must cover the liver and adrenal glands; therefore, separate abdominal imaging is not required if these areas are covered by a chest CT scan. If this scan shows no significant findings at baseline, it does not need to be repeated for tumor assessment.
11. No need to repeat Week 1 if screening test is within 1 week prior. Pregnancy testing at 3 months and 6 months Follow-Up visits only.

6.2 Usage of Concurrent/Concomitant Medications

Though no specific concomitant medications are prohibited during this study (other than concomitant anti-tumor therapies), vismodegib may potentially affect the pharmacokinetics of other drugs by altering their metabolism. In addition, metabolic inducers could possibly modify the pharmacokinetics of vismodegib. Therefore, concomitant medications should be used with care, and the risk benefit profile of each agent should be taken in to consideration.

Vismodegib inhibits CYP2C8, CYP2C9, and CYP2C19 drug metabolism enzymes in vitro at clinically relevant concentrations. Caution should be exercised and dose reduction of the concomitant substrate drug should be considered when dosing vismodegib concurrently with medications with narrow therapeutic windows that are substrates of CYP2C8, CYP2C9, and CYP2C19, because their concentrations may become elevated and their effects increased or prolonged.

Vismodegib did not significantly inhibit CYP3A4 at clinically relevant concentrations in vitro; however, the clinical impact of vismodegib on substrates of CYP3A4 is unknown. Vismodegib is a substrate of CYP3A4; however, the in vitro metabolic conversion of vismodegib is low. Effects of CYP inducers (i.e, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, St John's wort, and troglitazone) on clinical concentrations of vismodegib are unknown; it is possible that these drugs could reduce concentrations of vismodegib. Likewise, the effects of strong inhibitors of CYP3A4 (i.e., clarithromycin, erythromycin, itraconazole, ketoconazole, nefazodone, telithromycin) on vismodegib clinical concentrations are unknown; it is possible that these drugs could increase the concentrations of vismodegib. Use of these drugs should be documented.

The table in Appendix 5 lists substrate drugs in columns under the designation of specific cytochrome P450 isoforms. A drug appears in a column if there is published evidence that it is metabolized, to a clinically relevant degree by that isoform or in the FDA table of in vivo substrates for study. This is not necessarily a complete list; other medications may also interact with vismodegib.

7 Reporting and Documentation of Results

Measurable lesions are those that can be accurately measured in at least one dimension as ≥20mm with CT or MRI scan or on color photographs. Patients will undergo tumor assessments per RECIST tumor response criteria outlined below. No central review of imaging data will be required due to the visual clarity in identifying the lesions and the consistent method of assessment to be used by all participating sites.

Prior radiation therapy is acceptable but there cannot be major overlap of the previously irradiated tissues with the new radiation treatment volumes anticipated to be delivered for the purposes of this protocol, in such a way that curative intent with radiation cannot be met. Furthermore, the total dose from all radiation delivered and expected to be delivered should not exceed the suggested dose constraints given for normal structures.

To ensure a valid comparison of tumor data and uniformity in the assessment of tumor response and disease progression, the following procedures should be implemented.

The same local physician should perform all physical tumor assessment evaluations for an individual patient. Radiologic interpretation should be performed by designated faculty members with experience in describing skin lesions.

All lesions (target and non-target) identified at baseline will be reassessed according to the imaging schedule provided in Table 6-1. The same method of evaluation (either CT scan or

MRI), and/or color photography in the case of skin lesions, if feasible, must be used from baseline until the end of the study.

7.1 Evaluation of Efficacy (or Activity)

A new cutaneous BCC will be considered as progressive local-regional disease (locally or regionally relapsed) if the lesion is > 5 mm, within the PTVs, and can be clearly documented as not being previously present. The new lesion should be biopsied but will be considered as PD unless confirmed on biopsy not to be consistent with BCC. If the new cutaneous lesion is not biopsied or the histology is inconclusive, it should be considered to be BCC and indicative of PD. Significant enlargement of a cutaneous BCC that was present at baseline should also be considered as PD.

If imaging shows a high likelihood of distant metastases (investigators are highly encouraged to contact one of the Principal Investigators with any questions in this matter), ongoing protocol-prescribed therapy may be terminated based on evaluation of potential clinical benefits versus risks to the patient, as assessed by the study investigator. The patient may still be eligible for follow-up, per stipulations in section 6.1.5. New distant metastatic lesions should be biopsied if possible and will be considered as PD unless confirmed on biopsy not to be consistent with BCC. If the new metastatic lesion is not biopsied or the histology is inconclusive, it should be considered to be indicative of PD.

Note: Information about patients who have progressed on study and been removed from study may be voluntarily submitted at the discretion of the treating investigator (see Section 6.1.5).

7.2 Antitumor Effect – Solid Tumors

Response and progression in this study will be evaluated using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3):205-216, 2000]. Assessments should include an evaluation of all sites of disease. Patients will undergo tumor assessments per RECIST tumor response criteria. Screening digital photographs of visible portions of the lesions may be taken any time from the start of screening until just prior to dosing on Day 1. Tumor measurements will be performed measuring the maximal diameter as the maximal extent of tumor plus any adjacent or underlying ulceration. Any tumors which were included in the original assessment as either a primary involved site or involved regional lymph node must be measured.

7.2.1.1 Definitions

Evaluable for toxicity

All patients receiving any study drug will be evaluable for toxicity from the time of their first treatment with the study drug.

Evaluable for objective response

Only those patients who have measurable disease present at baseline, have completed at least 75% of protocol-mandated radiotherapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of induction therapy will also be considered evaluable.)

7.2.1.2 Disease Parameters

Measurable disease

Measurable disease is defined as lesions (or tumors) that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of 10mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10mm), 10mm caliper measurement by clinical exam (when superficial), and/or 20mm by chest X-ray (if clearly defined and surrounded by aerated lung).

Tumor measurements will be performed measuring the maximal diameter as the maximal extent of tumor plus any adjacent or underlying ulceration. All tumor measurements will be recorded in millimeters or decimal fractions of centimeters. Previously irradiated lesions are considered non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Target lesions

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

Non-measurable disease

Non-measurable disease is all other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan). Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques are all non-measurable.

7.2.1.3 Methods for Evaluation of Measurable Disease

All measurements will be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations will be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

The same method of assessment and the same technique will be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Conventional CT and MRI

CT or MRI scans will be performed of the primary tumor site and any regionally involved nodal regions. These imaging studies will be performed with contrast (iodinated or gadolinium) unless medically contraindicated. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis.

7.2.1.4 Response Criteria

Evaluation of Target Lesions

Complete Response (CR)

Disappearance of all target lesions in the irradiated PTV, determined by two separate observations conducted not less than 4 weeks apart. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be "0" if there are target nodes). There can be no appearance of new lesions in irradiated PTV.

Partial Response (PR)

At least a 30% decrease in the sum of the longest diameter (LD) of target lesions in the irradiated PTV, taking as reference the baseline sum LD. There can be no appearance of new lesions in irradiated PTV.

Progressive Disease (PD)

At least a 20% increase in the sum of the SLD of target lesions, taking as reference the smallest sum SLD recorded since the treatment started and minimum 5 mm increase over the nadir, or the appearance of one or more new lesions in the irradiated PTV.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 7.1 Response Criteria

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires
CR	CR	No	CR	> 4 weeks confirmation
CR	Non-CR/ Non-PD	No	PR	> 4 weeks confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once > 4 weeks from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. These circumstances should be discussed with the Principal Investigators.

Duration of Response

Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or PD is objectively

documented (taking as reference for PD the smallest measurements recorded since the treatment started).

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

Duration of stable disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death due to any cause.

7.3 Assessment of Failure Patterns

Local or Regional Relapse

Relapse is defined as reappearance of tumor after complete response. If possible, relapse should be confirmed by biopsy.

Local or Regional Progression

Progression is defined as an estimated increase in the size of the tumor (product of the perpendicular diameters of the two largest dimensions) of greater than 20%, taking as reference the smallest value of all previous measurements or appearance of new areas of malignant disease. This should be compared to radiology reassessment done after the completion of radiation therapy.

Distant Metastasis Progression

Progression of a distant metastasis (e.g. lung, bone, brain, liver) is defined as an estimated increase in the size of the tumor (product of the perpendicular diameters of the two largest dimensions) of greater than 20%, taking as reference the smallest value of all previous measurements or appearance of new areas of malignant disease. This should be compared to radiology reassessment done after the completion of radiation therapy.

7.4 Evaluation of Safety

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE v4.0 for reporting of non-hematologic adverse events and modified criteria for hematologic adverse events. Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to vismodegib, all events of death, and any study specific issue of concern.

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. The Study Chair is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 1 year following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

7.5 Definitions of Adverse Events

7.5.1 Adverse Event

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an adverse event (can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with locally advanced BCC of the head and neck that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).

If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.

Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

7.5.2 Adverse reaction

An adverse reaction is defined as any adverse event caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

7.5.2.1 Suspected

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, “reasonable possibility” indicates that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

7.5.2.2 Unexpected

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

“Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

Some adverse events are listed in the Investigator Brochure as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the ACE inhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes.

7.5.2.3 Serious

An adverse event or suspected adverse reaction is considered *serious* if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.5.2.4 Life-threatening

An adverse event or suspected adverse reaction is considered *life-threatening* if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.6 Recording of an Adverse Event

All grade 3 and above adverse events will be entered into OnCore®, whether or not the event is believed to be associated with use of the study drug. Data about these events and their severity will be recorded using the NCI CTCAE v4.0.

The Investigator will assign attribution of the possible association of the event with use of the investigational drug, and this information will be entered into OnCore® using the classification system listed below:

Relationship	Attribution	Description
Unrelated to investigational drug/intervention	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely	The AE *is doubtfully related* to the intervention
Related to investigational drug/intervention	Possible	The AE *may be related* to the intervention
	Probable	The AE *is likely related* to the intervention
	Definite	The AE *is clearly related* to the intervention

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE v 4.0. When specific adverse events are not listed in the CTCAE v 4.0 they will be graded by the Investigator as *none*, *mild*, *moderate* or *severe* according to the following grades and definitions:

Grade 0 No AE (or within normal limits)

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2 Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

7.7 Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For selected adverse events for which administration of the investigational drug was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

7.8 Adverse Events Monitoring

All adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, as noted above.

The Investigator will assess all adverse events and determine reportability requirements to the UCSF Data and Safety Monitoring Committee (DSMC) and UCSF's Institutional Review Board (IRB); and, when the study is conducted under an Investigational New Drug Application (IND), to the Food and Drug Administration (FDA) if it meets the FDA reporting criteria..

All adverse events entered into OnCore® will be reviewed by the Helen Diller Family Comprehensive Cancer Center Site Committee on a weekly basis. The Site Committee will review and discuss at each weekly meeting the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

In addition, all adverse events and suspected adverse reactions considered "serious," entered into OnCore® will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings which take place every six (6) weeks. For a detailed description of the Data and Safety Monitoring Plan for a Multicenter Study refer to Appendix 9.

7.9 Expedited Reporting

Participating sites reporting to Study Chair

In addition to complying with all applicable regulatory reporting laws and regulations, each site will report the following information in writing to the Sponsor-Investigator within one business day of the Investigator's awareness of occurrence:

- All SAEs
- Reports of pregnancy exposure (pregnancy encompasses the entire course of pregnancy and delivery, perinatal and neonatal outcomes, even if there were no abnormal findings; both maternal and paternal exposure is collected);
- Reports of lactation exposure;
- Overdose (with or without an SAE);
- Abuse (use for non-clinical reasons with or without an SAE);
- Inadvertent or accidental exposure; and
- Follow-up information regarding any of the above.
- The participating investigator should include his or her assessment of the causal relationship between each SAE and the study treatment.

Death from any cause while a patient is receiving protocol treatment and up to 30 days after the end of protocol must be telephoned and reported within ten days of discovery. Death related to surgery, regardless of the interval from surgery, must be reported by telephone within 10 days of discovery.

Reports will include the cover page provided, and reference the Protocol Number.

A copy of the report should be sent to the coordinating center CRC at UCSF. Information will be provided.

Reporting to the Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Reporting to UCSF Committee on Human Research (Institutional Review Board)

The Principal Investigator must report events meeting the UCSF IRB definition of "Unanticipated Problem" (UP) within 10 business days of his/her awareness of the event.

Reporting to Genentech or Roche

Study investigators must report all SAEs to Genentech or Roche within the timelines described below. The completed IND Safety Reports submitted to the FDA/Medwatch/case report should

be faxed immediately upon completion to Genentech Drug Safety at:

- Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.
- If a female subject becomes pregnant while receiving the study drug or within 24months after the last dose of study drug, a report should be completed and expeditiously submitted to the Genentech. If a male subject receiving study drug (or within 3 month after the last dose of study drug) impregnates a female partner, then the female partner will be requested to provide informed consented to permit a report of the pregnancy to be completed and expeditiously submitted to Genentech.

  Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the vismodegib should be reported as an SAE.

  Additional information on any vismodegib-exposed pregnancy and infant will be requested by Roche Drug Safety at specific timepoints (i.e., after having received the initial report, at the end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant's life).
- Serious AE reports that are related to the vismodegib and AEs of Special Interest (AESI) (regardless of causality) will be transmitted to Genentech within fifteen (15) calendar days of the Awareness Date.
- Serious AE reports that are unrelated to the vismodegib will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.
- Additional Reporting Requirements to Genentech include the following:
  - Any reports of pregnancy following the start of administration with the vismodegib will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.
  - All Non-serious Adverse Events originating from the Study will be forwarded in a quarterly report Genentech.
  - All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech.

Refer to Appendix 11 for Genentech safety reporting fax cover sheet.

Study Close-Out

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

8 Statistical Considerations and Evaluation of Results

8.1 Study Design

This is a single arm, multi-center, phase II study evaluating the safety and efficacy of treating locally advanced and metastatic BCC patients with vismodegib alone followed by concurrent vismodegib with radiation therapy for a total of 21 weeks. After completing protocol therapy patients will be followed for 12 months. The primary efficacy study outcome measure is the proportion of patients with local-regional control at 12 months after completing protocol therapy.

8.2 Study Endpoints

Primary Endpoint:

- The proportion of patients with local-regional control at 12 months from protocol therapy completion, defined as complete or partial response, with absence of PD (see section 7.2) within the irradiated PTV.

Secondary Endpoints:

- Estimate of the probability of PFS and OS 12 months after protocol therapy completion. PFS is measured until disease recurrence or death due to any cause, whichever occurs first.
- Number and attribution of all adverse events (including vital signs, physical findings, and clinical laboratory results, CTCAE, v 4.0) in patients who receive any amount of study drug and radiation therapy.
- For each toxicity, the maximum occurring grade will be tabulated for each patient. The results will be summarized by toxicities observed during vismodegib treatment alone, during concurrent vismodegib with radiation therapy, for 3 months immediately following the completion of protocol therapy and for up to 12 months after completion of protocol therapy. The focus will be on the proportion of patients experiencing ≥grade 3 toxicity during each of these intervals.
- Proportion of patients experiencing Grade 4-5 adverse events assessed to be definitely, probably, or possibly related to the induction or concurrent treatment components of the protocol regimen (that is not definitely related to disease progression).
- Proportion of patients discontinuing treatment due to toxicity during the concurrent administration of vismodegib and radiation therapy. For this endpoint, discontinuation is defined as < 75% of planned radiation therapy delivered.
- Response rate per RECIST criteria in patients who complete initial combined therapy of the primary site and regionally involved areas in subjects with measurable disease prior to initiation of therapy at 3 months after completion of protocol therapy.
- Proportion of patients with a decrease of BCC within the irradiated PTV after completing all protocol therapy to estimate clinical response to vismodegib and radiation therapy.

8.3 Determination of Sample Size and Accrual Rate

8.3.1 Sample Size and Power Estimate

The sample size for this single-arm phase II study is based upon the anticipated degree of improvement in the primary clinical hypothesis (i.e. local-regional control rate) at 12 months after completing all protocol treatment. The null hypothesis is that 60% of patients treated may achieve local-regional control after treatment on the study. Patients treated for advanced-stage

nonmelanomatous skin cancers typically achieve 50-60% local-regional control with radiation therapy alone. The alternative hypothesis is that 80% of the patients will obtain local-regional control at 12 months from the end of protocol therapy. This goal for local-regional control is justifiable as the current study includes radiation therapy, which is known to be effective against advanced BCC, in combination with vismodegib, also known to have high efficacy against BCC when administered alone.

Sample Size Justification: With accrual of 24 evaluable patients, this test will have 81% power to detect an increase in the overall proportion of patients achieving local-regional control assuming a directional level of significance of 0.10 based upon a one sample exact binomial test. It is anticipated that accrual will be completed in 12-18 months, with each patient treated for approximately 5.5 months and then followed for 12 months after completing protocol therapy. The total study duration is expected to be about 3 years.

8.3.2 Replacement Policy

Patients who drop-out before starting radiation therapy will be replaced. In addition, patients who come off study before completing at least 75% of radiation therapy given concurrently with vismodegib without grade ≥3 toxicity will be replaced. The frequency of each of these events will be reported and reasons for replacement reviewed.

8.3.3 Accrual estimates

The multi-center study expects to accrue 1-2 patients per month over a 2 year period. The UCSF radiation oncology program sees approximately 15 patients with locally advanced BCC of the head and neck per year. Approximately 8 patients have inoperable carcinomas or have a medical contraindication to surgery. UCSF will accrue 5-6 patients per year for a total of approximately 10 patients.

8.4 Interim Analysis for Safety and Stopping Rules

An interim analysis for safety will be performed once 5 patients have been treated on study and completed all drug and radiation-based protocol therapy. This will occur approximately 7-8 months after the start of accrual assuming 2 patients are enrolled per month and protocol therapy is completed in about 5.5 months. After the fifth patient completes radiation therapy, accrual will be temporarily stopped in order to perform this interim analysis. Thus no additional patients will start radiation therapy during the evaluation interval that overlaps with the treatment period for patients included in the interim analysis. During the conduct of this study, toxicity will also be evaluated weekly so that any unacceptable toxicity can be identified early. If there is no reason to stop accrual (as defined below), the remainder of the 19 patients will be recruited.

Stopping rules: Acceptable occurrence of toxicity is defined as the discontinuation of treatment in ≤40% of patients (2 of 5 patients who discontinue protocol treatment, having completed <75% of planned radiation therapy) and the proportion of patients with grade 4-5 toxicity is ≤20%.

Accrual of the final 19 patients will be determined by the results of the interim analysis.

8.5 Analyses Plans

Data will be summarized with respect to demographic and baseline characteristics and safety observations and measurements. The assessment of safety will include calculation of all specified study endpoints (see section 8.2) and will be based mainly on the frequency and attribution of adverse events, the frequency of discontinuation of treatment due to toxicity during concurrent vismodegib plus radiation therapy, and the proportion of patients experiencing Grade

3 or higher AEs related to the treatment components. Adverse events will be summarized by presenting the number and percentage of patients having any adverse event. Any other information collected (e.g. severity or relatedness to study medication) will be listed as appropriate. Toxicities will be tabulated by maximum grade occurring and organ system using the NCI Common Toxicity Criteria version 4.1 during each of 4 protocol stages (vismodegib alone, in combination with radiation therapy, during the immediate 3 months following completion of protocol therapy and then up to 12 months of follow-up after completing treatment).

To evaluate the primary protocol aim the proportion of patients with local-regional control (LRC), those with a CR or PR as defined by RECIST criteria, at 12 months after completing protocol therapy will be calculated and presented with 95% confidence intervals. As a most conservative estimate of disease control any patient beginning concurrent vismodegib and radiation therapy who is removed from study prior to completion of at least 75% of radiation therapy without a documented complete or partial response will be considered as a local-regional failure. To test the primary study hypothesis the observed proportion with LRC will be compared with the null hypothesis of 60% using a one sample test of a binomial proportion.

The secondary clinical aims of the duration of progression free survival (PFS) and overall survival (OS) will be measured from the start of protocol therapy until death due to any cause or until the first evidence of any disease progression, or death, respectively. Point estimates (e.g. median, percent PFS at 12 months) with 95% confidence intervals will be calculated using the Kaplan-Meier product limit method to summarize results. Based upon RECIST criteria, the proportion of patients responding in the primary site and regionally involved areas at 3 months after completing protocol therapy will be determined and presented with 95% confidence intervals. The proportion of patients achieving any decrease in BCC within the boundaries of the treated radiation PTV area will be determined and presented with a 95% confidence interval. In addition, the proportion of patients who start concurrent vismodegib and radition therapy and receive at least 75% of the planned radiation therapy will be determined and presented with a 95% confidence interval to summarize the feasibility of administering concomitant therapy.

8.5.1 Analysis Population

The statistical analysis of efficacy will include all patients completing the initial treatment with vismodegib alone and start the concurrent vismodegib with radiation therapy. Anyone who receives any vismodegib with radiation therapy will be included in the assessment of efficacy. As the most conservative approach, any patient removed from study prior to completion of at least 75% of radiation therapy without a documented complete or partial response will be considered as a case of local-regional failure.

Failure is defined as a lack of local-regional control within the boundaries of the treated radiation PTV area within the 12 month follow-up period.

8.6 Evaluation of Safety

The analyses of safety will be performed for all patients having received at least one dose of study drug. The study will use the NCI CTCAE v4.0.

9 Study Management

9.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all

applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

9.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF IRB (UCSF Institutional Review Board). Prior to obtaining IRB approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

9.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

9.4 Changes in the Protocol

Once the protocol has been approved by the UCSF IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five (5) working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

9.5 Handling and Documentation of Clinical Supplies

The UCSF Principal Investigator and each participating site will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The Principal Investigator shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the Principal Investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

9.6 Case Report Forms (CRFs)

The Principal Investigator and/or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Study Chair, the Trial Statistician, and the Protocol Project Manager.

Each participating site will complete study specific CRFs for safety monitoring and data analysis. Each site will enter the study data into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The participating site's Clinical Research Coordinator (CRC) will complete the CRFs; the Investigator will review and approve the completed CRFs – this process must be completed within 3 business days of the visit. Study data from the participating site will be reported and reviewed in aggregate with data from patients enrolled at the coordinating center, UCSF. All source documentation and CTMS data will be available for review/monitoring as needed.

9.7 Modality Review

The Principal Investigator will perform a Quality Assurance Review of all patients in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Appendix 8. The scoring mechanism is: Per Protocol/Acceptable Variation, Not Per Protocol, and Not Evaluable. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

The Principal Investigator will perform a Quality Assurance Review after complete data for the first 4 cases enrolled has been received. The Principal Investigator will perform the next review after complete data for the next 4 cases enrolled. The final cases will be reviewed within 3

months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received, whichever occurs first.

9.8 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered "serious". The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 9 Data and Safety Monitoring Plan for additional information.

9.9 Multicenter communication

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate, at minimum, quarterly conference calls with the participating sites or more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

- Enrollment information
- Adverse events (i.e. new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

9.10 Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it

is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

9.11 Coordinating Center Documentation of Distribution

It is the responsibility of the Study Chair to maintain adequate files documenting the distribution of study documents as well as their receipt (when possible). The HDFCCC recommends that the Study Chair maintain a correspondence file and log for each segment of distribution (e.g., FDA, drug manufacturer, participating sites, etc.).

Correspondence file: should contain copies (paper or electronic) of all protocol versions, cover letters, amendment outlines (summary of changes), etc., along with distribution documentation and (when available) documentation of receipt.

Correspondence log: should be a brief list of all documents distributed including the date sent, recipient(s), and (if available) a tracking number and date received.

At a minimum, the Study Chair must keep documentation of when and to whom the protocol, its updates and safety information are distributed.

9.12 Regulatory Documentation

Prior to implementing this protocol at UCSF HDFCCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the UCSF Institutional Review Board (IRB). Prior to implementing this protocol at the participating sites, approval for the UCSF IRB approved protocol must be obtained from the participating site's IRB.

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

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB'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 training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals

Upon receipt of the required documents, UCSF HDFCCC will formally contact the site and grant permission to proceed with enrollment. See Appendix 10 for submission information.

10 Protection of Human Subjects

10.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the

subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

10.2 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

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Appendices

Appendix 1 Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed < 50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

Appendix 2 AJCC Staging System for Cutaneous Carcinoma

PRIMARY TUMOR (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor 2 cm or less in greatest dimension with less than two high risk features**
T2 Tumor greater than 2 cm in greatest dimension or Tumor any size with two or more high risk features**
T3 Tumor with invasion of maxilla, orbit, or temporal bone
T4 Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base
* Excludes cutaneous carcinoma of the eyelid.
**High Risk Features for the Primary Tumor (T) Staging :
Depth/Invasion: >2 mm thickness, Clark level Ñ IV, Perineural invasion
Anatomic Location: Primary site ear, Primary site hair-bearing lip
Differentiation: Poorly differentiated or undifferentiated

REGIONAL LYMPH NODES (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2 Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3 Metastasis in a lymph node, more than 6 cm in greatest dimension

DISTANT METASTASIS (M)

M0 No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1 Distant metastasis

ANATOMIC STAGE/PROGNOSTIC GROUPS

Group T N M
0 Tis N0 M0
I T1 N0 M0
II T2 N0 M0
III T3 N0 M0
T1 N1 M0
T2 N1 M0
T3 N1 M0
IV T1 N2 M0
T2 N2 M0
T3 N2 M0

T Any N3 M0
T4 N Any M0
T Any N Any M1

Appendix 3 RTOG/EORTC Late Radiation Morbidity Scoring Scheme

RTOG/EORTC Late Radiation Morbidity Scoring Scheme

ORGAN TISSUE	0	GRADE 1	GRADE 2	GRADE 3	GRADE 4	5
SKIN	None	Slight atrophy; Pigmentation change; Some hair loss	Patch atrophy; Moderate telangiectasia; Total hair loss	Marked atrophy; Gross telangiectasia	Ulceration	**DEATH DIRECTLY RELATED**
SUBCUTANEOUS TISSUE	None	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; Slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; Field contracture > 10% linear measurement	Necrosis	
MUCOUS MEMBRANE	None	Slight atrophy and dryness	Moderate atrophy and telangiectasia; Little mucous	Marked atrophy with complete dryness; Severe telangiectasia	Ulceration	
SALIVARY GLANDS	None	Slight dryness of mouth; Good response on stimulation	Moderate dryness of mouth; Poor response on stimulation	Complete dryness of mouth; No response on stimulation	Fibrosis	
SPINAL CORD	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono, para quadriplegia	
BRAIN	None	Mild headache; Slight lethargy	Moderate headache; Great lethargy	Severe headaches; Severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis; Coma	
EYE	None	Asymptomatic cataract; Minor corneal ulceration or keratitis	Symptomatic cataract; Moderate corneal ulceration; Minor retinopathy or glaucoma	Severe keratitis; Severe retinopathy or detachment Severe glaucoma	Panopthalmitis/ Blindness	
LARYNX	None	Hoarseness; Slight arytenoid edema	Moderate arytenoid edema; Chondritis	Severe edema; Severe chondritis	Necrosis	
LUNG	None	Asymptomatic or mild symptoms (dry cough); Slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough); Low grade fever; Patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis; Dense radiographic changes	Severe respiratory insufficiency/co ntinuous O2/Assisted ventilation	
HEART	None	Asymptomatic or mild symptoms; Transient T wave inversion & ST	Moderate angina on effort; Mild pericarditis; Normal heart size; Persistent abnormal T wave and ST	Severe angina; Pericardial effusion; Constrictive pericarditis; Moderate	Tamponade/Sev ere heart failure/Severe constrictive	

		Changes; Sinus tachycardia >110 (at rest)	changes ; Low ORS	heart failure; Cardiac enlargement; EKG abnormalities	pericarditis	**LATED**
ESOPHAGUS	None	Mild fibrosis; Slight difficulty in swallowing solids; No pain on swallowing	Unable to take solid food normally; Swallowing semi-solid food; Dilation may be indicated	Severe fibrosis; Able to swallow only liquids; May have pain on swallowing Dilation required	Necrosis/Perforation Fistula	
SMALL/LARGE INTESTINE	None	Mild diarrhea; Mild cramping; Bowel movement 5 times daily Slight rectal discharge or bleeding	Moderate diarrhea and colic; Bowel movement >5 times daily; Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/Perforation Fistula	**TO**
LIVER	None	Mild lassitude; Nausea, dyspepsia; Slightly abnormal liver function	Moderate symptoms; Some abnormal liver; function tests; Serum albumin normal	Disabling hepatitic insufficiency; Liver function tests grossly abnormal; Low albumin; Edema or ascites	Necrosis/Hepatic coma or encephalopathy	**RADIATION**
KIDNEY	None	Transient albuminuria; No hypertension; Mild impairment of renal function; Urea 25-35 mg%;Creatinine 1.5-2.0 mg%; Creatinine clearance > 75%	Persistent moderate albuminuria (2+); Mild hypertension; No related anemia; Moderate impairment of renal function; Urea > 36-60mg% Creatinine clearance (50-74%)	Severe albuminuria; Severe hypertension Persistent anemia (< 10%); Severe renal failure; Urea >60 mg% Creatinine >4.0 mg% Creatinine clearance < 50%	Malignant hypotension; Uremic coma/Urea > 100%	
BLADDER	None	Slight epithelial atrophy; Minor telangiectasia (microscopic hematuria)	Moderate frequency; Generalized telangiectasia; Intermittent macroscopic hematuria	Severe frequency & dysuria Severe generalized Telangiectasia (often with petechiae); Frequent hematuria; Reduction in bladder capacity (< 150 cc)	Necrosis/Contracted bladder (capacity < 100 cc); Severe hemorrhagic cystitis	**EFFECTS**
BONE	None	Asymptomatic; No growth retardation; Reduced bone Density	Moderate pain or tenderness; Growth retardation; Irregular bone sclerosis	Severe pain or tenderness; Complete arrest of bone growth; Dense bone sclerosis	Necrosis/Spontaneous fracture	
JOINT	None	Mild joint stiffness; Slight limitation of movement	Moderate stiffness; Intermittent or moderate joint pain; Moderate limitation of movement	Severe joint stiffness; Pain with severe limitation of movement	Necrosis/Complete fixation	

Appendix 4 Management of Dental Problems in Irradiated Patients

Dental Care for Irradiated Patients Goals for a dental care program include:

1. To reduce incidence of bone necrosis.
2. To reduce incidence of irradiation caries.
3. To allow proper fitting of dentures following treatment.

Pre-irradiation Care and Procedures The patients may be grouped into four groups in accordance with the problems they present prior to irradiation.

Group 1

Includes edentulous patients. They may require surgical removal of any symptomatic cysts, infected retained root tips, or alveolar hyperplasia. These patients require hygiene instruction and precautionary instruction about trauma with premature use of a prosthesis.

Group 2

Includes those with poor dental hygiene, including those patients whose teeth are beyond repair by ordinary dental procedure, those with generalized oral sepsis, those with generalized periodontal disease, and those with chronic periapical abscesses or granulomas.

Procedures performed on this group include removal of all remaining teeth prior to irradiation with primary closure and surgical preparation of the alveolar ridges to laterally support a prosthesis. There should be antibiotic coverage during the healing stage and adequate time prior to the start of radiation therapy. These patients need complete hygiene instruction and precautionary instruction about premature use of a prosthesis.

Group 3

Includes those in whom dental condition is fair, including those patients whose teeth are restored, ordinary dental procedures, periodontal pockets are less than 3 mm deep, carious lesions are not in proximity to the pulp, and no more than 20 restorable carious lesions are present. X-ray examinations show at least 1/2 of the bone still present around root surfaces. These patients require removal of any teeth that are non-salvageable in accordance with the above and restorations of the remaining teeth as required. The patients are instructed for dental prophylaxis and the patients utilize custom-made fluoride carriers.

Group 4

Includes those in whom dental hygiene is good. This includes patients who do not have severe malocclusion in whom few carious lesions are present. Carious lesions are not in close proximity to the pulp and are correctable by conventional methods. These patients require periodontal evaluation and dental prophylaxis training, restorations as needed, no extractions prior to radiation therapy, and fitting for custom carriers.

Extraction of Teeth: If extraction of teeth is necessary prior to radiation therapy, the bone must be contoured so that closure at the extraction site is possible. All loose spicules and sharp projections must be removed. The approximation of the gingival tissue must be such that the

closure is neither too loose nor too tight. At least 10 days are required for adequate healing prior to initiation of therapy.

Causative Factors: The major causative factors appear to be the reduction of the amount of saliva and secondarily, reduced pH in the mouth. This occurs following high dose radiation to the major salivary glands using parallel opposed fields. The decay process usually occurs in the first year following radiation therapy. It tends to occur more quickly in teeth which have a large amount of root cementum exposed to those teeth with large amounts of plaque formation present. Doses of radiation in excess of 20 Gy to salivary tissue place the teeth at risk.

Preventive Program: The rationale behind the use of fluoride treatments is to make the tooth surfaces less susceptible to the decay process. This is accomplished by a combination of increasing fluoride concentration on the tooth surface and by the effect of fluoride on the plaque and flora that are present in the oral cavity. Adequate results are obtained by: 1) cleansing the teeth thoroughly, followed by a good home care dental prophylaxis program, 2) construction of fluoride carriers, custom-made mouth guards, which provide local application of fluoride solution to the gingiva and tooth surfaces. Fluoride carriers are made individually with the use of casts. Material used for making a mouth guard is "Sta-Guard" plastic used in conjunction with vacutrole unit produced by Jelrus Technical Products, Corp., both of which are available through local dental supply. This material is molded to the cast impression and allowed to harden. The patients are instructed to cleanse their teeth prior to placement of the carrier. It is then worn in place for 5 minutes each day. The patients are instructed to rinse their mouths thoroughly following the use of the carrier. This will be continued for an indefinite period of time. Close follow-up is necessary.

Results: In the 5-1/2 year program at the M.D. Anderson Hospital beginning in 1966, a study of 304 patients shows that the incidence of necrosis of the jaw was reduced to approximately 21% compared to 37% prior to initiation of the study. Groups 3 and 4 patients randomized with and without fluoride treatment showed reduction in radiation carries from 67% to 34% among Group 3 patients, and from 65% to 22% among Group 4 patients.

Failure to Control Decay: Management of failure to control radiation decay includes silver fillings with continued use of fluoride treatments. If the decay process is sufficiently advanced that a filling will no longer stay in place, these teeth are merely smoothed so that there will be no sharp, irritating edges. The mere existence of such a decayed tooth is not necessarily reason for extraction, for it must be remembered that extraction could lead to complications such as bone necrosis.

Pulp exposure resulting from the decay process can usually be handled by use of antibiotics and/or root-canal therapy.

Hypersensitivity of Teeth: Occasionally, a patient will exhibit extreme sensitivity of the teeth secondary to diminished amounts of saliva. This has been shown to be reduced in incidence with the fluoride treatments. Should this problem become manifest, increasing the fluoride treatment to 10 to 15 minutes 3 times a day is recommended.

Infections: Infections occurring in patients under or after radiation therapy are best managed conservatively with good oral hygiene, irrigation and flushing procedures, and systemic antibiotics.

Bone Necrosis: The patients receiving radiation therapy to a high dose to the head and neck region have increased susceptibility to bone necrosis for several reasons including: impairment of normal metabolism, increased susceptibility to infection and severely limited repair process.

Bone necrosis occurs most often after dental or oral surgery in patients who have been previously radiated. Conservative management should be tried first, though in more aggressive lesions a more radical approach may ultimately be necessary.

Appendix 5 Medications with Potential to Interact with Vismodegib

Vismodegib inhibits CYP2C8, CYP2C9, and CYP2C19 drug metabolism enzymes in vitro at clinically relevant concentrations. Caution should be exercised and dose reduction of the concomitant substrate drug should be considered when dosing vismodegib concurrently with medications with narrow therapeutic windows that are substrates of CYP2C8, CYP2C9, and CYP2C19, because their concentrations may become elevated and their effects increased or prolonged.

Vismodegib did not significantly inhibit CYP3A4 at clinically relevant concentrations in vitro; however, the clinical impact of vismodegib on substrates of CYP3A4 is unknown. Vismodegib is a substrate of CYP3A4; however, the in vitro metabolic conversion of vismodegib is low. Effects of CYP inducers (i.e., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, St John's wort, and troglitazone) on clinical concentrations of vismodegib are unknown; it is possible that these drugs could reduce concentrations of vismodegib. Likewise, the effects of strong inhibitors of CYP3A4 (i.e., clarithromycin, erythromycin, itraconazole, ketoconazole, nefazodone, telithromycin) on vismodegib clinical concentrations are unknown; it is possible that these drugs could increase the concentrations of vismodegib.

Use of these drugs with vismodegib should be documented. The table below lists substrate drugs in columns under the designation of specific cytochrome P450 isoforms. A drug appears in a column if there is published evidence that it is metabolized, to a clinically relevant degree by that isoform (Flockhart) or in the FDA table of in vivo substrates for study. This is not necessarily a complete list; other medications may also interact with vismodegib.

2C8 Miscellaneous:	2C9 NSAIDs:	2C19 Proton Pump Inhibitors:
repaglinide rosiglitazone	Diclofenac Ibuprofen piroxicam naproxen celecoxib Oral Hypoglycemic Agents: glipizide tolbutamide Angiotensin II Blockers: irbesartan losartan NOT candesartan NOT valsartan Miscellaneous: fluvastatin phenytoin sulfamethoxazole tamoxifen torsemide warfarin	omeprazole lansoprazole pantoprazole rabeprazole esoprazole Anti-epileptics: diazepam phenytoin phenobarbitone Miscellaneous: amitriptyline clomipramine clopidogrel cyclophosphamide progesterone

Reference: Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction; Table. Indiana University School of Medicine (2007); http://medicine.iupui.edu/flockhart/clinlist.htm

FDA Drug Development and Drug Interactions: Table of Substrates; Inhibitors and Inducers (May 2006). http://www.fda.gov/cder/drug/drugInteractions/tableSubstrates.htm#classSub

Appendix 6 Skindex-16 Survey

Skindex16
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THESE QUESTIONS CONCERN THE SKIN CONDITION WHICH HAS BOTHERED YOU THE MOST DURING THE PAST WEEK

During the past week, how often have you been bothered by:	Never Bothered ↓						Always Bothered ↓
1. Your skin condition **itching**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
2. Your skin condition **burning or stinging**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
3. Your skin condition **hurting**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
4. Your skin condition **being irritated**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
5. The **persistence / reoccurrence** of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
6. **Worry** about your skin condition (For example: that it will spread, get worse, scar, be unpredictable, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
7. The **appearance** of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
8. **Frustration** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
9. **Embarrassment** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
10. **Being annoyed** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
11. **Feeling depressed** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
12. The effects of your skin condition on your **interactions with others** (For example: interactions with family, friends, close relationships, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
13. The effects of your skin condition on your **desire to be with people**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
14. Your skin condition making it hard to **show affection**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
15. The effects of your skin condition on your **daily activities**.	☐0	☐1	☐2	☐3	☐4	☐5	☐6
16. Your skin condition making it hard to **work or do what you enjoy**	☐0	☐1	☐2	☐3	☐4	☐5	☐6

Skindex16
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SKINDEX 16 SCORING

SCALE	ITEMS
Symptoms	1-2-3-4
Emotion	5-6-7-8-9-10-11
Functioning	12-13-14-15-16

Item scores transformed to 0 – 100 scale.
Scale Score: Average of items in given scale

Appendix 7 Digital Photographic Procedures For Serial Photographic Documentation Of Basal Cell Carcinoma

Views

- Close-up view with millimeter scale of the target area of the basal cell carcinoma(BCC): two each
- Global view of the target BCC area: two each

Procedures

In these clinical photographs for the duration of the study, the only variable allowed to change is the skin condition itself. Therefore, anything extraneous to the condition (furniture, etc.) is to be eliminated from the photographic field, starting at the entry visit through the final visit. The necessity of good end-of-study photographs should be stressed to patients to ensure their cooperation. Lighting, framing, exposure, and reproduction ratios must be held constant. In the end, the images should read like a time-lapse movie. Any doubt as to the correctness of the photographic technique should result in an immediate re-shoot.

Each photographic session includes an exposure series of:

a. Patient ID, which will include the following legible information in black indelible ink (two exposures):

   Date

   Center name

   Patient's study ID number

   Photographer's initials

b. Close-up view of patient's target BCC area(s), consisting of one individual BCC lesion (two exposures)

c. Global view of patient's target BCC area(s), consisting of up to two individual BCC lesions (two exposures)

Appendix 8 Data Submission

Participating sites must submit the following data components.

- Within 2 weeks of study entry, the following documents must be submitted to the coordinating center
    - Demographic Form (A5)
    - Initial Evaluation Form (I1)
    - Pathology Report (P1)
- At the completion of preradiotherapy component and at the completion of concurrent therapy component: Treatment Form (TF) and Pill Diary (DP) 3 months from the start of treatment, after restaging imaging and before starting post-radiation therapy: Initial Follow-up Form (F0)
- After the F0, q 12 weeks for 1 year, all subsequent follow up with patient will be done by UCSF per section 6.1.5

Dosimetry Data Submission

Hard copy isodose distributions for total dose plan

DVH printouts showing doses to critical structures

Summary printout of entire plan, including summary table of contour names, with contour (region) volume, and the Min, Mean and Max dose to the regions of interest.

Data should be submitted to:

[redacted]

Appendix 9 Data and Safety Monitoring Plan* for a Multicenter Institutional Study

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of subject data
- Review of suspected adverse reactions considered "serious"
- Monthly monitoring (depending on study accrual)
- Minimum of a yearly regulatory audit

Monitoring and Reporting Guidelines

All institutional Phase 2 or 3 therapeutic studies are designated with a moderate risk assessment. The data is monitored every six months, with twenty percent of the subjects monitored (or at least three subjects if the calculated value is less than three).

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate quarterly conference calls with the participating sites to communicate the review of adverse events, safety data, and other study matters.

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and subject safety and discuss each subject's treatment at monthly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

Multicenter communication

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate, at minimum, monthly conference calls with the participating sites at the completion of each cohort or more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

- Enrollment information
- Adverse events (i.e. new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The DSMC will be responsible for monitoring all data entered in OnCore® at the UCSF Coordinating Center and the participating sites. The data (i.e. copies of source documents) from the participating sites will be sent electronically or faxed over to the UCSF Coordinating Center prior to the monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol, patient safety, and to verify data entry.

Adverse Event Review and Monitoring

Adverse Event Monitoring

All Grade 3-5 Adverse Events, whether or not unexpected, and whether or not considered to be associated with the use of study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Site Committee meetings. All clinically significant adverse events must be reported to the UCSF Coordinating Center by the participating sites within 10 business days of becoming aware of the event or during the next scheduled quarterly conference call, whichever is sooner. The UCSF Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s) from the UCSF Coordinating Center and the participating sites.

In addition, all suspected adverse reactions considered "serious" must be entered in OnCore® and reported to the UCSF Coordinating Center within 1 business day. The suspected adverse reactions considered "serious" will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at the DSMC meeting, which take place every six (6) weeks.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify the DSMC Chair or qualified alternate within 1 business day of this notification. The contact may be by phone or e-mail.

Increase in Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert), the Study Chair at the UCSF Coordinating Center is responsible for notifying the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day via e-mail. The DSMC must receive a formal letter within 10 business days and the IRB must be notified.

Data and Safety Monitoring Committee Contacts:

DSMC Chair:
Phone:
Email:
Address:

[redacted]

DSMC Monitors

[redacted]

* DSMP approved by NCI 09/February2012

Appendix 10 UCSF Policy/Procedure for Required Regulatory Documents for a UCSF Multicenter Investigator-Initiated Oncology Clinical Trials with an Investigator held Investigational New Drug (IND)

Purpose

This policy defines the required Regulatory Documents for Single Site and Multicenter Investigator Initiated Oncology Clinical Trials at the Helen Diller Family Comprehensive Cancer Center (HDFCCC) where the Principal Investigator (PI) holds the IND.

Background

The International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines define Essential Regulatory Documents as those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of data produced. These documents serve to demonstrate compliance with standards of GCP and with all applicable regulatory requirements. Filing essential documents in a timely manner can greatly assist in the successful reconscilimanagement of a clinical trial.

The Regulatory Documents will consist of electronic files in both iMedRIS and OnCore®, as well as paper files in the Regulatory Binders for both the Coordinating Site and the Participating Site(s) in the HDFCCC Investigator Initiated Oncology Clinical Trials.

Procedures

1. HDFCCC Essential Regulatory Documents

Documents Filed in iMedRIS:

- IRB approvals for initial submission of application, all modifications, and continuing annual renewals
- Current and prior approved protocol versions with signed protocol signature page(s)
- Institutional Review Board (IRB) approval letters and Informed Consent Form(s) (ICF)
- Current and prior versions of the Investigator Brochure (IB).
- Serious Adverse Event Reporting
- Protocol Violations and Single Patient Exception (SPE) Reports to IRB with supporting fax documentation

Documents Filed in OnCore®:

- Package Insert (if the study drug is commercial) or Investigator Brochure
- Protocol Review Committee (PRC) approved protocols, protocol amendments and Summary of Changes (SOC)
- Patient handouts
- Screening/enrollment log
- Data and Safety Monitoring Committee (DSMC) monitoring reports
- DSMC dose escalation approvals with study status summary forms
- OnCore® Case Report Form (CRF) completion manual

Documents Filed in Regulatory Binder:

- Completed Food and Drug Administration (FDA) 1572 document with Principal Investigator's signature
- For all Principal Investigators and Sub-Investigators listed on the FDA 1572, will need Financial Disclosure Forms, CVs, MD Licenses, Drug Enforcement Agency (DEA) Licenses, and Staff Training Documents (i.e. Collaborative Institute Training Initiative (CITI), etc.)
- Site Initiation Visit (SIV) minutes and correspondence with participating site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center
- Serious Adverse Event (SAE) reports to IRB and sponsor.
- MedWatch reporting to FDA and sponsor
- Delegation of Authority Form
- Drug Destruction Standard Operating Procedure (SOP)
- For all laboratories listed on the FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges

2. Additional Essential Documents for Multicenter Trials for the Coordinating Center (filed in Regulatory Binder or OnCore)

- Institutional Review Board (IRB) approval letters, IRB roster, Informed Consent Form (ICF), and Health Insurance Portability and Accountability Act (HIPAA) Consent Form for the Participating Site(s)
- For all Principal Investigators and Sub-Investigators listed on the 1572 at the Participating Site(s) – Financial Disclosure Forms, CVs, MD Licenses, and Staff Training documents (i.e. Collaborative Institute Training Initiative (CITI), etc.) (for Investigational New Drug Application
- Site Initiation Visit (SIV) minutes and correspondence with Participating Site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center for the Participating Site(s)
- Protocol Violations and Single Patient Exception (SPE) reports to IRB with supporting fax documentation for Participating Site(s)
- Drug Destruction Standard Operating Procedure (SOP) for the Participating Site(s)
- Data and Safety Monitoring Committee (DSMC) monitoring reports for the Participating Site(s)
- For all laboratories listed on FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges for the Participating Site(s)
- Copy of the Data and Safety Monitoring Plan (DSMP) Monitoring Plan for all participating site(s) in Multicenter studies or Contract Research Organization (CRO) Monitoring Plan (if an outside CRO is used for the study)
- Serious Adverse Event (SAE) forms submitted to both the IRB and the sponsor for the Participating Site(s)

3 Required Regulatory Documents for Sub-sites Participating in a UCSF Investigator Initiated Multicenter Trial (Checklist)

Directions:

1) Fax the documents listed below to the UCSF Coordinating center [redacted] *or*

2) Scan the documents and upload to OnCore® and create a Note to File for the on-site Regulatory binder to indicate where these documents may be found

1572

☐ PI and Sub investigators:

CV and Medical license

Financial disclosure form

NIH or CITI human subject protection training certification

☐ Laboratories

CLIA and CAP

CV of Lab Director and Lab Licenses

Laboratory reference ranges

Local Institutional Review Board

☐ IRB Approval letter

☐ Reviewed/Approved documents

- Protocol version date: _____
- Informed consent version date: _____
- Investigator Brochure version date: _____
- HIPAA

☐ Current IRB Roster

Other

☐ Delegation of Authority Log

- Include NIH or CITI human subject protection training certificates or GCP training certification

☐ Pharmacy

- Drug destruction SOP and Policy

☐ Protocol signature page

☐ Executed sub contract

27.apr.2012

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SAFETY REPORTING FAX COVER SHEET

Genentech Supported Research

AE / SAE FAX No: [redacted]

Alternate Fax No: [redacted]

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[ ]-[ ]-[ ]

SAE or Safety Reporting questions, contact Genentech Safety: [redacted]

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET.

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