PROTOCOL

STUDY TITLE:	VISmodegib for ORbital and periocular Basal cell carcinoma (VISORB).
STUDY DRUG:	ERIVEDGE® (vismodegib)

SUPPORT PROVIDED BY: Genentech, Inc.

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1. INTRODUCTION

Basal cell carcinoma (BCCA) is the most common human cancer, and frequently affects facial structures. While rarely fatal, facial BCCA can be disfiguring and expensive to treat. Treatment of facial BCCA typically includes Mohs micrographic surgery followed by plastic reconstructive surgery. Success rates of treatment for non-metastatic BCCA that is limited to skin can approach 99%. However, deeply invasive BCCA can involve vital organs, such as the eye or lacrimal drainage system, requiring aggressive surgical interventions that often compromise organ function. Hence, there is a critical need for improved treatments of invasive BCCA in the face.

Vismodegib is a small, orally administrable molecule that functions as an antagonist of the smoothened receptor (SMO), which is part of the hedgehog signaling pathway. Vismodegib (Erivedge, Genentech), was recently approved by the Food and Drug Administration (FDA) for treatment of recurrent, locally advanced or metastatic BCCA. Its primary indication in these cases is organ preservation. Initial results from clinical usage have been very promising. However, it remains to be determined whether use of vismodegib in treating locally advanced periocular or orbital BCCA would increase the chance of preserving visual function. Furthermore, chronic use of vismodegib is associated with side effects, such as muscle spasms, weight loss, hair loss, fatigue, and loss of appetite. Some side effects, such as muscle spasms, can be functionally debilitating. Recent reports have suggested that vismodegib treatment for orbital BCCA may facilitate globe preservation even if surgery is eventually required (Kahana, Worden and Elner, JAMA Ophthalmol, 2013). **The goal of this study is to test whether treatment with vismodegib for periocular and orbital BCCA is associated with preservation of a functioning globe and lacrimal apparatus.** Recruitment will be limited to patients who meet the standard criteria for vismodegib treatment of locally advanced periocular/orbital BCCA, for whom vismodegib has the potential to be organ-preserving.

1.1 Disease Background

Background on Basal Cell Carcinoma

Basal cell carcinoma (BCC) is the most common human cancer, affecting approximately 750,000 Americans per year (Epstein 2008). Based on rapidly rising tumor incidence rates, it is estimated that almost 1 in 3 Caucasians born in the United States after 1994 will develop a BCC during their lifetime (Miller and Weinstock 1994). Like other skin cancers, BCC risk is correlated inversely with the degree of skin pigmentation and positively with exposure to ultraviolet or ionizing radiation. In states near

the equator, such as Hawaii, BCC incidence is approaching 3-fold that of states in the Midwest, such as Minnesota.

BCC incidence also varies globally. The highest rates of skin cancer occur in South Africa and Australia, areas that receive high amounts of UV radiation (Marks et al. 1989). Australia has a trend toward increasing BCC incidence, whereas Finland has a low reported incidence that is approximately one quarter that in Minnesota; nonetheless, BCC incidence in Finland appears to be increasing, especially among young women. A study from the Netherlands found that high socioeconomic status was associated with increased incidence of BCC among men, suggesting that BCC is changing from a disease of the poor to a disease of the rich, at least in northern Europe (van Hattem et al. 2009).

BCCs are generally treated by local excision, which in many cases is associated with scarring and potential disfigurement. Until recently, there has been no reliable medical (non-surgical) therapy for BCC, particularly for advanced forms of the disease.

1.2 The Hedgehog Signaling Pathway and Basal Cell Carcinoma Pathogenesis

The vast majority of cases of BCC occur sporadically. However, a rare autosomal dominant inherited condition has been identified – Gorlin syndrome (also known as basal cell nevus syndrome [BCNS] or nevoid basal cell carcinoma syndrome) – in which individuals develop many BCCs (tens to thousands) from a relatively early age (Gorlin 1987; Online Mendelian Inheritance in Man 2012). The mutant gene in Gorlin syndrome has been mapped using genetic linkage studies to human chromosome 9q22 and, subsequently, to the Patched 1 (PTCH1) gene (Gailani et al. 1992; Hahn et al. 1996). PTCH1 is a member of the Hedgehog (Hh) signaling pathway, a critical regulator of both cellular growth and differentiation during embryonic development (Caro and Low 2010).

The Hh pathway operates in both time- and position-dependent mechanisms to allow developing tissues to attain their correct size, location, and cellular content (Caro and Low 2010). The pathway was originally identified in the fruit fly *Drosophila melanogaster*, where mutations in the Hh gene gave rise to embryos covered in spiky processes, suggesting the “hedgehog” name. In fruit flies, as well as humans, signaling in the pathway is initiated by the hydrophobic secreted Hh protein, which binds to PTCH1, a 12-transmembrane domain protein located on the cell membrane. This binding releases inhibition of the Smoothened (SMO) protein, a 7-transmembrane G-protein-coupled-like receptor located on the membrane of intracellular endosomes. Activated SMO, in turn, transmits a signal via interacting proteins, leading to

activation of the Gli family of zinc finger transcription factors. In patients with Gorlin syndrome, loss of function of PTCH1 constitutively turns on the Hh pathway by allowing SMO to constitutively activate its downstream targets, thereby leading to the high incidence of BCCs.

Subsequent studies have shown that approximately 90% of sporadic BCCs also have *de novo* mutations in PTCH1, whereas the remaining 10% have activating mutations in SMO that prevent inhibition by normal PTCH1 protein (Epstein 2008; Scales and de Sauvage 2009). Thus, a common genetic basis exists for the sporadic and syndrome-associated forms of BCC, suggesting both may be amenable to treatment with inhibitors of the Hh pathway.

The feasibility of blocking Hh signaling in vivo was first demonstrated in studies of teratogenic phenomena that were observed in lambs born of ewes that had ingested the forage plant, *Veratrum californicum* (Binns et al. 1963). The active agent in the plant was shown to be cyclopamine, a steroidal alkaloid that induces midline deformities, including cyclopia, which blocks *SMO* signaling in the developing lamb fetus (Chen et al. 2002).

Cyclopamine has proven to be a valuable tool to confirm the importance of Hh signaling in a subset of malignancies. One study, for instance, showed that chronic oral administration of cyclopamine reduced the development of UVB-induced BCCs in the skin of Ptch1 (+/-) mice, an animal model for Gorlin syndrome, by approximately 67% (Athar et al. 2004). Another study found that 25% of small-cell lung cancers expressed elevated levels of Hh ligand and *GLI1* and that cyclopamine inhibited the growth of SCLC cell lines in culture (Watkins et al. 2003). Similarly, systemic cyclopamine treatment slowed the growth of pancreatic cancer xenografts and blocked the metastatic potential of prostate cancer cells in mice (Thayer et al. 2003; Karhadkar et al. 2004). Finally, activation of Hh signaling in some types of extracutaneous tumors has been shown to be due to tumor cell expression and secretion of Hh ligand and subsequent activation of the pathway in stromal cells, which leads to secondary growth stimulation of the tumor cells by stromally-expressed cytokines (Yauch et al. 2008).

1.3 Clinical Experience, Vismodegib Safety and Efficacy

Background on Vismodegib

Vismodegib is a small molecule inhibitor of SMO developed by Genentech, Inc. for the treatment of tumors in which the Hh signaling pathway appears to contribute to the development and maintenance of tumorigenesis. Vismodegib, a systemic Hh pathway antagonist, has been shown to have 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 US package insert for further details).

1.3.1 Malignancies with Mutation Driven Hh Pathway Signaling

1.3.1.1 Basal Cell Carcinoma

Phase I Study SHH3925g - Safety and Pharmacokinetics Assessment

A Phase I, company-sponsored clinical trial (SHH3925g) assessed the safety and pharmacokinetics (PK) of vismodegib and responses of metastatic or locally advanced BCC to the drug (Von Hoff et al. 2009). Thirty-three patients with metastatic or locally advanced BCC received oral vismodegib at one of three doses: 17 patients received 150 mg per day, 15 patients received 270 mg per day, and 1 patient received 540 mg per day (median duration of treatment was 9.8 months). Of the 33 patients, 18 had an objective response to vismodegib, according to assessment on imaging (7 patients), physical examination (10 patients), or both (1 patient). Of the patients who had a response (see Table 1), 2 had complete responses (CRs) and 16 had partial responses (PRs). The other 15 patients had either stable disease (11 patients) or progressive disease (4 patients). Eight Grade 3 adverse events (AEs) that were deemed to be possibly related to the study drug were reported in 6 patients (see Table 2), including fatigue (4 AEs), hyponatremia (2 AEs), muscle spasm (1 AE), and atrial fibrillation (1 AE). One patient withdrew from the study because of AEs.

Table 1: SHH3925g Phase I Efficacy Results

	aBCC (n=33)
Objective response, n (%)	18 (54.5%)
Complete response, n (%)	2 (6.1%)
Partial response, n (%)	16 (48.5%)
Stable disease, n (%)	11 (33.3%)
Progressive disease, n (%)	4 (12.1%)

Table 2: SHH3925g Phase I Adverse Events in Patients With aBCC (n=33)

Clinical Event	Grade 2	Grade 3	Grade 4
	Number of Patients With Event		
Fatigue	0	4	0
Hyponatremia	0	2	1
Muscle spasm	3	1	0
Atrial fibrillation	0	1	0
Dysgeusia	2	n/a	n/a
Anorexia	2	0	0
Weight loss	2	2	0
Dyspepsia	1	0	0
Dyspnea	0	2	0
Aspiration	0	1	0
Back pain	0	1	0
Corneal abrasion	0	1	0
Dehydration	0	1	0
Keratitis	0	1	0
Lymphopenia	0	1	0
Pneumonia	0	1	0
Urinary tract infection	0	1	0
Electrocardiographic event (prolonged QT interval)	0	1	0

Phase II Study ERIVANCE (SHH4476g) in Metastatic and Locally Advanced Basal Cell Carcinoma

A multicenter, international, two-cohort, nonrandomized, pivotal, Phase II, company-sponsored study (SHH4476g) enrolled patients with metastatic BCC and those with locally advanced BCC who had inoperable disease or for whom surgery was inappropriate (because of multiple recurrences and a low likelihood of surgical cure, or substantial anticipated disfigurement) (Sekulic et al. 2012). In 33 patients with metastatic BCC (see Table 3), the independently assessed response rate was 30% (95% confidence interval [CI], 16 to 48; p=0.001). In 63 patients with locally advanced BCC (see Table 4), the independently assessed response rate was 43% (95% CI, 31 to 56; p<0.001), with complete responses in 13 patients (21%). The median duration of response was 7.6 months in both cohorts at the time of data cutoff. Muscle spasms, alopecia, dysgeusia, weight loss, and fatigue occurred in more than 30% of patients, whereas serious adverse events

(SAEs) were reported in 25% of patients. Seven deaths due to AEs were reported and none of the deaths were related to vismodegib.

Based on the results of this pivotal trial, vismodegib was approved on January 30, 2012 by the United States Food and Drug Administration (US FDA) for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation. (Erivedge [package insert] 2013).

Table 3: Efficacy Results from Primary Analysis

	Metastatic BCC (n=33)		**Locally Advanced BCC** (n=63)	
	IRF (1°)	**INV (2°)**	**IRF (1°)**	**INV (2°)**
Response ORR	10 (30%)	15 (45%)	27 (43%)	38 (60%)
95% CI	(16%, 48%)	(28%, 62%)	(30%, 56%)	(47%, 72%)
***P* value**	0.001		**<0.001**	
SD	21 (64%)	15 (45%)	24 (38%)	15 (24%)
PD	1 (3%)	2 (6%)	8 (13%)	6 (10%)
Unevaluable/ missing	1 (3%)	1 (3%)	4 (6%)	4 (6%)
Median DoR, mos	7.6	12.9	7.6	7.6

Table 4: ERIVANCE Investigator Assessed Efficacy at the18-Month Update

Investigator Assessed (INV)	**mBCC** (n = 33)	**laBCC** (n = 63)	**Total** (n = 96)
ORR, n (%) [95% CI]	16 (48.5) [30.8-66.2]	38 (60.3) [47.2-71.7]	54 (56.3) [45.7-66.4]
Complete response	0	20	20
Partial response	16	18	34
Stable disease	14	15	29
Progressive disease	2	6	8
Median duration of response, months, (95% CI)	(n = 16) 14.7 (5.6-17.0)	(n = 38) 20.3 (9.0-NE)	(n = 54) 16.8 (9.5-NE)
Median PFS, months, (95% CI)	9.3 (7.4-16.6)	12.9 (10.2-31.4)	12.8 (9.5-18.0)
Median OS, months, (95% CI)	30.9 (18.1-NE)	NE (NE-NE)	NE (NE-NE)
1-Year survival rate, % (95% CI)	78.7 (64.7-92.7)	93.1 (86.6-99.6)	NA

Table 5: ERIVANCE Safety Results at the 18-Month Update

	Metastatic BCC (n = 33)	**Locally Advanced BCC** (n = 71)
All AE	33 (100%)	71 (100%)
Grade 3-5 Adverse Event	14 (42.4%)	40 (56.4%)
Grade 5 Adverse Event[§]	1 (3%)	6 (8.5%)
Serious Adverse Events	8 (24.2%)	28 (39.4%)
Adv. Events Leading To Treatment Discontinuation	5 (15.2%)	16 (22.5%)

[§] No new deaths on study since the primary data analysis. Fatal events included: Death of unknown cause (n=3), acute myocardial infarction (n=1), ischemic stroke (n=1), meningeal disorder (n=1), and hypovolemic shock (n=1). In all cases, clinically significant risk factors or comorbid conditions were present at baseline. Relationship between study drug and event is unknown.

Table 6: Most Frequent Treatment Emergent Adverse Events (>10% of patients) at the 18-Month Update

Adverse Event, n (%)	**NCI CTCAE Grade, (N = 104)**					
	Total	**1**	**2**	**3**	**4**	**5**
Any adverse events	**104 (100.0)**	**11 (10.6)**	**38 (36.5)**	**34 (32.7)**	**13 (12.5)**	**7 (6.7)**
Muscle spasms	74 (71.2)	49 (47.1)	19 (18.3)	6 (5.8)	0	0
Alopecia	68 (65.4)	48 (46.2)	20 (19.2)	n/a	n/a	n/a
Dysgeusia	57 (54.8)	31 (29.8)	26 (25.0)	n/a	n/a	n/a
Weight decreased	53 (51.0)	29 (27.9)	17 (16.3)	7 (6.7)	n/a	n/a
Fatigue	44 (42.3)	32 (30.8)	7 (6.7)	4 (3.8)	1 (1.0)	0
Nausea	34 (32.7)	25 (24.0)	9 (8.7)	0	0	0
Decreased appetite	28 (26.9)	18 (17.3)	7 (6.7)	3 (2.9)	0	0
Diarrhea	28 (26.9)	20 (19.2)	5 (4.8)	3 (2.9)	0	0
Constipation	20 (19.2)	14 (13.5)	6 (5.8)	0	0	0
Cough	20 (19.2)	16 (15.4)	4 (3.8)	0	0	0
Vomiting	18 (17.3)	15 (14.4)	3 (2.9)	0	0	0

Adverse Event, n (%)	NCI CTCAE Grade, (N = 104)					
	Total	1	2	3	4	5
Arthralgia	17 (16.3)	12 (11.5)	4 (3.8)	1 (1.0)	0	0
Headache	15 (14.4)	12 (11.5)	3 (2.9)	0	0	0
Nasopharyngitis	13 (12.5)	11 (10.6)	2 (1.9)	0	0	0
Squamous cell carcinoma	12 (11.5)	3 (2.9)	5 (4.8)	3 (2.9)	0	0
Ageusia	12 (11.5)	8 (7.7)	4 (3.8)	n/a	n/a	n/a
Hypogeusia	11 (10.6)	10 (9.6)	1 (1.0)	n/a	n/a	n/a

Expanded Access Study (SHH4811g) in Advanced BCC

An open-label, single-arm, multicenter, expanded access study (SHH4811g) of an oral repeating dose of vismodegib was conducted in patients with locally advanced or metastatic BCC, who are otherwise without satisfactory treatment options. Safety of vismodegib and objective response in patients with measurable disease (RECIST v1.0) were assessed (Weiss G, et al. Poster, ESMO 2012). The study has been completed following FDA approval and commercial availability of vismodegib.

Among 95 efficacy evaluable patients (56 patients with laBCC and 39 patients with mBCC) at the time of final analysis data cutoff date of 23 April 2012 the observed objective response rates (see Table 7) were 46.4% (95% CI, 33.0%, 60.3%) for patients with laBCC (n = 56) and 30.8% (95% CI, 17.0%, 47.6%) for patients with mBCC (n = 39). Complete response, partial response and stable disease were observed in 10.7%, 35.7%, and 48.2%, respectively, of patients with laBCC; no patients in this cohort exhibited PD as best response. For patients with mBCC, complete response, partial response and stable disease rates observed were 5.1%, 25.6%, and 51.3%, respectively. 7.7% of patients in this cohort exhibited PD as best response. Among patients with laBCC who responded the median and mean times to response were 2.6 months and 3.5 months, respectively; and among patients with mBCC who responded the median and mean times to response were 2.6 months and 3.8 months, respectively.

As of the final analysis data cutoff date of 23 April 2012, 116 of 119 safety evaluable patients (97.5%) experienced at least one adverse event (22 SAEs total, see Table 8). Adverse events that had the highest reported occurrences (≥ 20%) in 119 safety evaluable patients were: muscle spasms (84 patients; 70.6%), dysgeusia (84 patients; 70.6%), alopecia (69 patients; 58.0%), and diarrhea (30 patients; 25.2%). Only one of 22 SAEs (4.5%) was assessed as being related to treatment with vismodegib: a Grade 3 muscle spasm, reported

in 1 patient. There have been three deaths among 119 safety-evaluable patients (2.5%); 2 assessed as unrelated to study drug, and 1 patient with PD.

Table 7: EAP SHH4811g Overall Response (RECIST) at Study Termination

	laBCC (n=56)	mBCC (n=39)
Objective response, n (%)	26 (46.4)	12 (30.8)
(95% CI)	(32.4-59.3)	(17.0-47.6)
Complete response, n (%)	6 (10.7)	2 (5.1)
Partial response, n (%)	20 (35.7)	10 (25.6)
Stable disease, n (%)	27 (48.2)	20 (51.3)
Progressive disease, n (%)	0	3 (7.7)
Unevaluable/missing, n (%)	3 (5.4)	4 (10.3)
Median time to response (range), months[a]	2.6 (1.0-11.0)	2.6 (1.4-12.6)

Table 8: SHH4811g Vismodegib Expanded Access Study Common Treatment-Emergent Adverse Events

TEAEs (n=120)	Median Time to AE Onset, Days (95% CI)*	All AEs, n (%)	Gr 1, n (%)	Gr 2, n (%)	Gr 3, n (%)	Gr 4, n (%)	Gr 5, n (%)
Muscle spasms	37 (28-44)	84 (70.0)	63 (52.5)	19 (15.8)	2 (1.7)	–	–
Dysgeusia	41 (30-51)	84 (70.0)	68 (56.7)	16 (13.3)	n/a	n/a	n/a
Alopecia	87 (74-104)	69 (57.5)	57 (47.5)	12 (10.0)	n/a	n/a	n/a
Diarrhea	38 (22-116)	30 (25.0)	23 (19.2)	5 (4.2)	1 (0.8)	1 (0.8)	–
Nausea	30 (11-130)	23 (19.2)	19 (15.8)	4 (3.3)	–	–	–
Fatigue	42 (16-120)	23 (19.2)	14 (11.7)	8 (6.7)	1 (0.8)	–	–
Weight decreased	175 (114-293)	19 (15.8)	12 (10.0)	7 (5.8)	–	–	–

*For those patients experiencing the TEAE

Phase II BCNS Study (SHH4685s)

The anti–BCC efficacy of vismodegib was tested in a randomized, double-blinded, placebo-controlled, Investigator-sponsored trial in Gorlin syndrome (BCNS) patients with surgically eligible BCCs (Tang et al. 2012). Forty-one patients were randomized 2:1 to receive oral vismodegib (n=26) or placebo (n=15). After a mean follow up of 8 months (range, 1 to 15 months), the per-patient rate of new surgically eligible BCCs (SEBs) was lower with vismodegib than with placebo (2 vs. 29 cases per group per year, p<0.001), as was the size (percent change from baseline in the sum of the longest diameter) of existing clinically significant BCCs (–65% vs. –11%, p=0.003). In some patients, all BCCs clinically regressed. No tumors progressed during treatment with vismodegib. Patients receiving vismodegib routinely had Grade 1 or 2 AEs of loss of taste, muscle cramps, hair loss, and weight loss. Overall, 54% of patients (14 of 26) receiving vismodegib discontinued drug treatment due to AEs. At 1 month, vismodegib use had reduced the Hh pathway's target-gene expression in BCC cells by 90% (p<0.001) and diminished tumor-cell proliferation, but apoptosis was not affected. No residual BCC was detectable in 83% of biopsy samples taken from sites of clinically regressed BCCs. At the second pre-specified interim analysis, a data safety and monitoring board concluded that the pre-determined threshold for a significant difference between the two groups had been reached (p<0.0113), and the treatment with placebo in this arm was terminated.

See the Vismodegib Investigator Brochure and the US package insert for additional details on nonclinical and clinical studies on vismodegib.

Table 9: Phase II BCNS Study (SHH4685s) Adverse Events Reported in ≥10% of Patients

Grade 1 or 2 AEs, n (%)	Vismodegib (n=26)	Placebo (n=15)	*P* Value
Taste disturbance, n	22 (85)	1 (7)	<0.001
Muscle cramps	21 (81)	0 (0)	<0.001
Hair loss	16 (62)	1 (7)	0.004
>5% weight decrease	11 (42)	0 (0)	0.003
GI upset	5 (19)	1 (7)	0.14
Acne	3 (12)	1 (7)	0.60

Phase II STEVIE (MO25616) Safety Study

Study MO25616 is an ongoing Phase II open-label, single-arm, multicenter (ex-U.S.) study of vismodegib in patients with locally aBCC or mBCC who are otherwise without satisfactory treatment options. The primary objective is to assess the safety of vismodegib in patients with locally aBCCor mBCC. Secondary objectives are to assess the overall response (according to RECIST Version 1.1) in those patients with measurable disease as permitted by local regulatory requirement and to assess other efficacy parameters such as time to response, duration of response, PFS, and overall survival (OS).

All patients receive 150 mg vismodegib orally (PO) daily (QD)until investigator-assessed progression of disease (PD), unmanageable toxicities, or withdrawal from study (investigator/patient request).

As of 6 November 2013, a total of 1228 patients have been enrolled into the study. Results of an interim analysis, when a total of 501 patients could be followed for 1 year, are presented below.

As of the cutoff date of 6 November 2013, safety data were available for 500 patients (469 with locally aBCC and 31 with mBCC) with followup information for at least 3 months after treatment. Overall, 492 of 500 safety-evaluable patients (98.4%) experienced at least one AE. The most frequently reported AEs, regardless of relationship to study drug, in descending order of frequency, were: muscle spasms (63.2%), alopecia (61.0%), dysgeusia (53.8%), weight decreased (32.4%), asthenia (28.2%), decreased appetite (25.4%), and ageusia (22.4%).

As of 6 November 2013, 210 of 500 safety-evaluable patients (42.0%) experienced Grade 3−5 treatment-emergent adverse events (TEAEs). Of 500 patients, 165 patients (33.0%) experienced a Grade 3 AE, 24 patients (4.8%) experienced a Grade 4 AE, and 21 patients (4.2%) experienced a Grade 5 AE. All of the Grade 5 AEs were considered by investigator to be unrelated to treatment with vismodegib except for cardio-respiratory arrest and myocardial infarction.

Of the 500 patients, 107 (21.4%) experienced SAEs. The most common events were in the following system organ classes: infections and infestations, 30 patients (6.0%); neoplasms (benign, malignant, and unspecified, including cysts and polyps), 16 patients (3.2%); general disorders and administration site conditions, 12 patients (2.4%); nervous system disorders, 12 patients (2.4%); cardiac disorders, 11 patients (2.2%); injury, poisoning and procedural complications, 10 patients (2.0%); and metabolism and nutrition disorders, 10 patients (2.0%).

As of 6 November 2013, there have been 29 deaths among 500 safety-evaluable patients. The causes of death were PD in 4 patients, AE in 20 patients, and 5 patients with “other” as cause of death. Most patient deaths were considered unrelated to treatment with vismodegib. Two

deaths (cardiopulmonary arrest and cardiac infarction) were assessed by the investigator as related to vismodegib; however, both patients had significant risk factors and comorbidities. Both events were considered by the investigator to be related because of the temporal relationship between the onset of the event and administration of vismodegib; therefore, an association could not be excluded.

As of 6 November 2013, 400 of 500 patients (80%) treated during Study MO25616 had discontinued study drug. Reasons for discontinuation of study drug included: AE (178 patients, 35.6%); progression of disease (70 patients, 14.0%); patient request (62 patients, 12.4%); death (10 patients, 2.8%); investigator request (14 patients, 2.8%); lost to follow-up (4 patients, 0.8%); and other (62 patients, 12.4%).

The majority of patients (98.2%) in Study MO25616 (STEVIE) experienced TEAEs. The most common ($>$20%) TEAEs included muscle spasm (63.2 %), alopecia (61.0%), dysgeusia (53.8%), weight decreased (32.4%), asthenia (28.2%), decreased appetite (25.4%), and ageusia (22.4%). Twenty-four (4.8%) Grade 4 events and 21 (4.2%) Grade 5 events were reported. Two of the deaths were considered related to vismodegib treatment (cardio-respiratory arrest and myocardial infarction). There were 107 (21.4%) patients who reported SAEs. Common SAEs that were reported in $\geq$1% of patients were pneumonia (1.8%, n$=$9), general physical health deterioration (1.4%, n$=$7), and dehydration (1.0%, n$=$5).

Interim results of the STEVIE study demonstrate that vismodegib is generally well tolerated in a patient population that is representative of patients treated in routine clinical practice, with a safety profile consistent with that previously observed in other vismodegib studies. Investigator-assessed response rates are consistent with those reported in the ERIVANCE study and confirm high rates of tumor control.

As the trial is ongoing, efficacy analyses will be presented at final analysis.

Phase II Operable Basal Cell Carcinoma (SHH4812g) Study

The ability of vismodegib to induce complete histological clearance (CHC) of BCC tumors, an important step in assessing the role of the drug in the setting of smaller resectable lesions, was examined in a single-arm, 3-cohort, Phase II study (Sofen et al. 2015). Patients in the trial were required to have one clinically operable, nodular BCC lesion on the scalp (0.5 - 2.0 cm maximum diameter) or in the "cape" area (chest, shoulders, or upper back; 1.0 - 3.0 cm maximum diameter). The nodular BCC required a positive biopsy that was limited to ≤ 25% of the target lesion. After 12 weeks of oral vismodegib (150 mg QD), patients were assessed clinically and then underwent excision of the target tumor site for pathologic assessment of residual carcinoma, followed by re-excision of the tumor site for margin assessment using standard Mohs techniques.

Efficacy objectives for CHC were not met in this study. The CHC rates were 42% (10/24) in Cohort 1, 16% (4/25) in Cohort 2, and 44% (11/25) in Cohort 3; these clearance rates were not statistically significant (p-values of 0.8463, 0.9668, and 0.7878, respectively). The low response rate in Cohort 2 (4 [16%] of 25 patients) indicates a lack of durable response. Investigator-assessed clinical response (CR and PR) did not correlate with CHC. Time to complete clinical clearance in patients in Cohorts 1 (10 patients), 2 (9 patients), and 3 (18 patients) with investigator-assessed CR, the time to first CR was 59.5 days (95% CI: 28.0 □ 80.0 days), 84.0 days (95% CI: 27.0 □ 120.0 days), and 60.0 days (95% CI: 55.0 □ 86.0 days), respectively.

No new safety signals were noted for patients in this study after dosing with vismodegib 150 mg QD PO. No deaths occurred during this study. The safety profile of vismodegib 150 mg QD was similar among the 3 cohorts. The data generally showed reversibility of muscle spasms, dysgeusia, and ageusia 6 to 12 weeks after drug discontinuation, and reversibility of delayed-onset alopecia in most patients during the 24-week follow-up period in Cohort 2.

Efficacy objectives for CHC were not met in this study.

1.3.1.2 Medulloblastoma

Data from a phase II clinical trial evaluated vismodegib treatment at 150 mg QD in adult patients with medulloblastoma that was recurrent after or progressive while receiving standard care (n=40) [Gajjar et al 2013, Asklund et al 2013]. Patients were stratified by histologic subtypes based on immunohistochemical (IHC) analysis into three strata: non-SHH group, SHH group, and indeterminate group. The primary endpoint was objective response rate as assessed by RECIST using independent review. Responses must be sustained at least 8 weeks. The study met its primary endpoint of sustained objective response, with 3/20 patients in SHH group exhibiting sustained responses. Secondary efficacy endpoints were consistent with the primary endpoint. Grade 3-4 TEAEs reported were lymphocytopenia, thromboembolic event, syncope, back pain, myalgia, seizure, and hypophosphatemia.

1.3.2 Malignancies with Ligand Driven Hh Signaling

1.3.2.1 Colorectal Cancer

A randomized phase II clinical trial evaluated addition of vismodegib or placebo to standard chemotherapy (mFOLFOX-6 or FOLFIRI) plus bevacizumab in patients with untreated metastatic colorectal cancer (n=199;Berlin et al 2013). Choice of chemotherapy regimen was based on investigator decision. The primary endpoint was improvement in progression-free survival (PFS). The study failed to meet its primary

endpoint of improved PFS vs. chemotherapy + placebo (hazard ratio 1.25 [90%, CI 0.89 -1.76], p =0.28) Secondary efficacy endpoints were consistent with the primary endpoint. The TEAEs (all grades) that differed in frequency by 10% or more vs. placebo were vomiting, asthenia, weight loss, decreased appetite, dehydration, muscle spasms, and dysgeusia. Grade 3-5 TEAEs that differed in frequency by 5% or more vs. placebo were fatigue, nausea, asthenia, mucositis, peripheral sensory neuropathy, weight loss, decreased appetite, and dehydration.

1.3.2.2 Ovarian Cancer

A randomized phase II clinical trial evaluated the use vismodegib or placebo as maintenance treatment for patients with ovarian cancer in second or third complete remission (n=104;Kaye et al 2012). The primary endpoint was improvement of PFS. The study failed to meet its primary endpoint of improved PFS vs. placebo (hazard ratio0.79 95%CI 0.46-1.35, p=0.39). TEAEs occurring in greater than 10% of vismodegib treated patients were dysgeusia/ageusia, muscle spasms, alopecia, nausea, fatigue, constipation, abdominal pain, decrease appetite, upper abdominal pain, arthralgia, vomiting and hypomagnesemia.

1.3.2.3 Pancreatic Cancer

A randomized phase II clinical trial evaluated addition of vismodegib or placebo to standard chemotherapy (gemcitabine) in patients with untreated metastatic pancreatic cancer (n=106;Catenacci et al 2013). The primary endpoint was improvement in progression-free survival. The study failed to meet its primary endpoint of improved PFS vs. chemotherapy + placebo (HR = 0.81 95%CI 0.54 - 1.21, p=0.3) Secondary efficacy endpoints were consistent with the primary endpoint. The frequency of Grade ¾ TEAEs reported vs. placebo (V/P) were neutropenia (32%/28%), hyponatremia (4%/15%), fatigue (13%/8%), hyperglycemia (23%/19%), elevated alanine aminotransferase (ALT; 13%/9%). TEAEs that differed in frequency by 10% or more vs. placebo were vomiting, asthenia, weight loss, decreased appetite and dehydration.

1.3.2.4 Glioblastoma Multiforme

A phase II clinical trial evaluated vismodegib treatment at 150 mg QD in patients with glioblastoma multiforme that was recurrent after or progressive while receiving standard treatment (n=40;Sloan et al 2012). The primary endpoint was improvement in PFS at 6 months. The study failed to meet its primary endpoint of improved PFS at 6 months (median PFS 1.8 months 95%CI 1.40 - 1.9 months) Secondary efficacy endpoints were consistent with the primary endpoint. TEAE reported were abdominal infection, abdominal pain, atrial flutter, fatigue, hypophosphatemia, lymphocytopenia, and thrombocytopenia (1 patient each).

1.3.2.5 Gastric Cancer

A randomized phase II clinical trial evaluated addition of vismodegib or placebo to chemotherapy (mFOLFOX-6) in patients with untreated metastatic gastric cancer (n=124;Cohen et al 2013). The primary endpoint was improvement in PFS. The study ailed to meet its primary endpoint of improved PFS vs. chemotherapy + placebo (hazard ratio 1.03 95%CI 0.69 - 1.55, p=0.64) Secondary efficacy endpoints were consistent with the primary endpoint. No significant differences in the rates of common grade ¾ TEAEs (≥ 5% incidence) were observed between the vismodegib and placebo arms. The rates of grade ½ TEAEs were comparable with no significant differences except for a higher incidence of dysgeusia in the vismodegib arm (42%/16%, p=0.003).

1.3.2.6 Small Cell Lung Cancer

A randomized phase II clinical trial evaluated addition of vismodegib or cixutumumab (IMC-A12) to standard chemotherapy (Cisplatin/Etoposide) in patients with untreated extensive stage SCLC (n=155;Belani et al 2013). The primary endpoint was improvement in PFS. The study failed to meet its primary endpoint of improved PFS vs. cisplatin/etoposide chemotherapy (hazard ratio 1.32, p=0.21) Secondary efficacy endpoints were consistent with the primary endpoint. Grade ¾ TEAEs reported (chemotherapy alone vs. chemotherapy+vismodegib) included anemia (25%/ 9%), febrile neutropenia (15%/13%), neutropenia (48%/47%), thrombocytopenia (22%/6%), leukopenia (46%/41%), nausea (11%/11%), vomiting (9%/6%), hyperglycemia (2%/2%), muscle weakness (4%/0%), and renal dysfunction (6%/0%)

1.4 Background for Other Study Drugs

There are no other study drugs.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary goal of this project is to determine whether treatment with vismodegib of patients with locally advanced or recurrent orbital and/or periocular BCCA will be associated with good ophthalmic outcomes, as measured using a novel Visual Assessment Weighted Score (Table 15). The primary objective emphasizes globe preservation and maintenance of visual acuity, and a score of 21 or greater (out of 50) will be considered a good outcome.

2.2 Secondary Objectives

The secondary goals of this project are (1) to assess individual parts of the composite Visual Assessment Weighted Score to independently assess vision and lacrimal function after treatment, (2) to correlate visual function

to location and size of tumor over the course of treatment, (3) to identify histologic characteristics of periocular BCCA that correlate with tumor response, and (4) to characterize molecular markers that may identify opportunities for developing adjunct treatment approaches for recalcitrant tumors. An additional objective (5) is to characterize and validate the Visual Assessment Score for use in future investigations of orbital disorders.

3. STUDY PROTOCOL

3.1 Description of the Study

In order to assess the potential of vismodegib to improve the vision- and lacrimal-related morbidities associated with orbital and periocular BCCA, this study will follow patients with globe-threatening orbital and lacrimal-threatening periocular BCCA treated with vismodegib as standard of care. The study will be prospective, open label, non-randomized, and will determine visual and lacrimal function of treated patients.

Basic Protocol (see flow chart at the end of the section):

ELIGIBILITY AND ENROLLMENT

1) Patients will be enrolled based on Eligibility Criteria, Section 4.1, at which time a pre-treatment visual assessment score will be obtained as a baseline (Table 14).
2) Enrollment will include Informed Consent and Baseline blood tests.
3) Enrollment will be performed by the PI, Co-I, or qualified designee.

Table 14: Pre-treatment Visual Assessment Score:
(This score provides a non-weighted baseline that will be used for testing the consistency and internal validity of the Post-treatment Visual Assessment Score (Secondary Objective #5).)

VA in affected eye of at least 20/200	0/1
Ocular Motility intact	0/1
No diplopia	0/1
Binocularity (Fusion) +/- prism	0/1
Normal tear lake, No complaint of persistent tearing	0/1
Intact lacrimal system by probing/irrigation (both canaliculi to NLD)	0/1
Patient assessment of visual function on the affected side (Poor, Fair, Good)	0/1/2
Score Maximum	**8**

ONGOING TREATMENT (See Appendix 4, Schedule of Assessments)

4) Vismodegib treatment initiated by Co-I (FW) per standards of care, within 3 months of medical oncology screening visit.
    a. Formal enrollment will occur at the time of initiation of vismodegib treatment.
    b. Side effects and any adverse events will be assessed and documented at the time of each medical exam.
    c. Medical exams (by Medical Oncologist or qualified designee) will occur at the following time points following initiation of treatment: one, three, six, nine and twelve months. Subjects who complete the study prior to the 1-year term (see section 4.7) will no longer be required to undergo medical oncology exams as part of the study. (See Appendix 4, Table 16, Schedule of Assessments).
    d. Blood draws for biomarker analysis will be performed at screening and 6-month intervals (+/- 1 month) for 1 year or at time of early discontinuation of vismodegib.

RESPONSE ASSESSMENT

5) Assess response by ophthalmic exam at 3 month intervals or at time of early discontinuation of vismodegib (by treating physician or qualified designee), + MRI or CT with contrast at 5 and once in the timeframe from 9-12 months (+/- 1 month) and clinical photography.
6) Treatment response will be determined per Response Evaluation Criteria in Solid Tumors (**RECIST)** protocol, using clinical measurements and/or tumor imaging measurements (determined by treating physician):
    i. Complete response (CR) = complete disappearance of tumor
    ii. Partial response (PR) = at least 30% decrease in largest diameter
    iii. Progressive disease (PD) = at least 20% increase in largest diameter
    iv. Stable disease (SD) = neither PR nor PD
7) Determination of whether the tumor is progressing (PD) vs. responding (SD, PR or CR) will be done at regular intervals (3 months), until 1 year after initiation of vismodegib treatment. Following the 1 year mark, patients will continue to be followed per SOC.

OUTCOME ASSESSMENT

8) The **PRIMARY OUTCOME** will be determined by analyzing visual function per **Table 15** at 1 year following initiation of vismodegib treatment or at 2 months +/- 1 month following surgery, whichever is longer (i.e. final assessment may be extended up to 15 months following initiation of vismodegib). **A weighted score of at least 21 out of possible 50 would constitute a successful treatment outcome.**

9) **SECONDARY OUTCOMES will be assessed via subgroup analysis:**
    a. If the tumor progresses (PD) while on vismodegib treatment, then treating physician may discontinue vismodegib and offer surgical resection or debulking per SOC → **OUTCOME #1 (Progressive Disease)**.
    b. If patient refuses surgical option, then continue monitoring patient.
    c. Patients with stable or shrinking tumors (CR, PR or SD) will be considered "**Responders**."
    d. If the tumor responds within the first year of treatment and patient tolerates side effects (per patient), CONTINUE vismodegib therapy and monitoring until the end of the study → **OUTCOME #2 (SD, PR or CR and <u>good</u> tolerance)**
    e. If patient reports subjectively <u>intolerable</u> side effects (per patient), then discontinue vismodegib, and treating physician can offer surgical resection or debulking → **OUTCOME #3 (SD, PR or CR and <u>poor</u> tolerance).**
    f. If patient refuses surgical options, continue monitoring.
    g. A treatment break, or "drug holiday" will <u>not</u> be offered as an option as part of this study.
    h. If treatment with vismodegib is stopped but the patient later decides to restart vismodegib, then the patient's exam findings at termination of treatment will be used for assessing the primary outcome. The patient can continue to be followed as part of the study, and additional exam findings can be used for secondary outcome assessment.

EVALUATION

10) VA, diplopia, motility, and tearing are assessed at each office visit (Visual Assessment Weighted Score see **Table 15**).
11) Patients undergoing surgery will have their specimen assessed histologically for the presence of tumor, and used for comparison to baseline biopsy.
    a. The presence of tumor at the surgical margin will be determined by the pathologist. Absence of tumor at the surgical margin will lead to a presumptive cure.
12) The **primary outcome** will be the Visual Assessment Weighted Score (Table 15) at 1 year following initiation of vismodegib or 2 (+/- 1) months after tumor excision/debulking surgery, whichever is longer.

Table 15: Follow-up Visual Assessment Weighted Score:

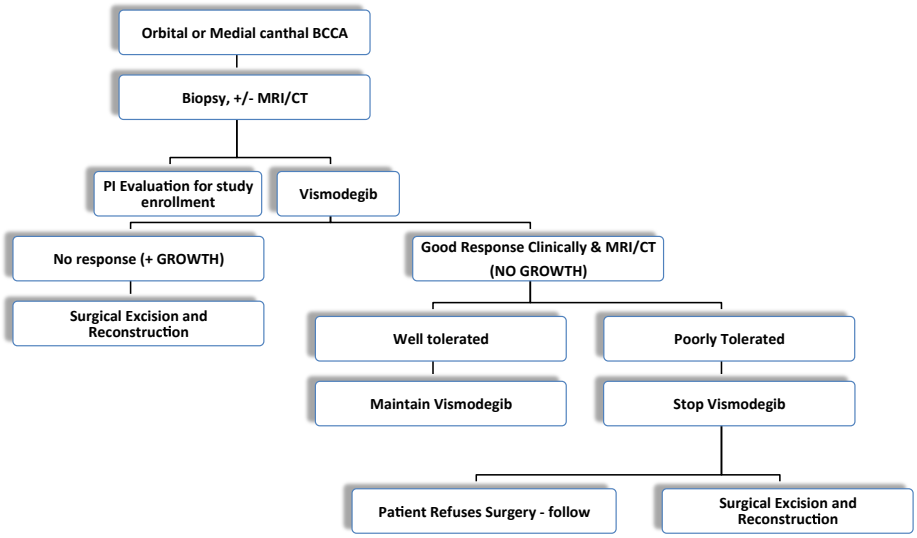
	Score (0=No; 1=Yes)	Max Weighted score
Intact globe (no enucleation or evisceration)	0/1	20
VA within 4 Snellen lines of baseline VA or better	0/1	5
VA at 20/200 or better	0/1	5
No binocular diplopia in primary gaze	0/1	2
Fusion (Fly) +/- prism	0/1	2
No symptomatic tearing	0/1	3
Intact lacrimal system by probing/irrigation (either canaliculus to NLD)	0/1	3
Patient pleased with visual function (Poor, Fair, Good)	0/1/2	5
Total possible:	**9**	**50**

Because there are no validated measures for assessing the success of treating orbital disease, a new, non-validated measure must be used. The Visual Assessment Weighted Score (VAWS) was developed for the purpose of this study. It is made up of standard ophthalmic exam points, as well as a subjective assessment of tearing and overall patient satisfaction. Because it is a composite score, weighting is used to emphasize visual acuity and an intact globe.

BASIC RESEARCH ARM

13) Concomitant with the clinical arm of the study, a basic research arm will be performed to analyze the tumor specimens using histologic, immunohistochemical and molecular techniques.
    a. All patients will have a pre-treatment biopsy specimen. Adequacy of the biopsy specimen for laboratory investigation will not be a criterion for inclusion or exclusion from the study.
    b. For those patients who have an adequate biopsy specimen, the characteristics of the specimen will be analyzed and matched with treatment outcome.
    c. For patients who undergo surgery following initiation of vismodegib treatment - failure (outcome #1) or intolerance of side effect (outcome #3) - the pre- and post-treatment characteristics of the tumor within the surgical specimens will be analyzed and compared.

d. All patients will have blood drawn at initiation of therapy and at 6 month intervals for 1 year or at time of early discontinuation of vismodegib. One 5 ml red top tube and two 10 ml purple top (EDTA) tubes will be drawn, in this order, for each interval. Blood will be drawn at the Kellogg Eye Center and processed in Dr. Kahana's laboratory. Serum and blood will be barcoded and stored in a -80 freezer for marker and genetic analysis and correlation with histo-pathologic findings.



See **Table 16** (Appendix 4) for a Schedule of Assessments.

3.2 Rationale for Study Design

Hypothesis: Treatment of orbital and periocular BCCA with oral vismodegib facilitates globe-sparing treatment of orbital BCCA, and lacrimal apparatus-sparing treatment of medial canthal BCCA.

This is a prospective study that will follow the interventional standard of care use of vismodegib in patients with locally advanced BCCA that threatens the globe or lacrimal drainage system (see flow chart), and utilize a laboratory approach to identify predictors of disease severity, progression and response to treatment.

3.3 Outcome Measures

Primary Outcome Measure:

Determined by analyzing visual function per **Table 15** at completion of the study. **A weighted score of at least 21 out of possible 50 would constitute a successful treatment outcome.**

Secondary Outcome Measures:

Visual function measures collected numerically at 3-month intervals will be correlated with size of tumor and timing of surgery (if any).

In addition, a laboratory basic research protocol will utilize histologic and molecular analyses of the tumors, as outlined below. The **aim of the basic research protocol is to characterize the tumor response to vismodegib treatment in order to determine the biology of tumor shrinkage/fibrosis, determine whether compensatory pro-oncogenic pathways are induced by treatment, and to identify potential markers that correlate with good treatment response.** The specific aims are:

1) **Aim 1:** Histologically assess the cellular characteristics and extent of residual tumor and its relationship to:
    a. Vascular supply
    b. Lymphatic vessels
    c. Nerves
    d. Leukocytes

    Hypothesis: the response to vismodegib is unevenly distributed, and is anatomically driven by the vascular bed, watershed zones, and the presence of tumor-clearing leukocytes.

Using histologic and immunohistochemical techniques, the tumor will be assessed from pre-treatment biopsy specimens as well as post-treatment specimens. Micro-anatomical techniques, including high-resolution tile scanning of multiple sections, and immunofluorescence techniques, will be used to develop a reproducible system that will measure capillary and tumor cell densities, to develop possible predictors of vismodegib resistance based on tumor anatomy. When possible (per tissue availability), transmission electron microscopy will be used to characterize the cellular and stromal response to vismodegib treatment.

2) **Aim 2:** Develop a profile of biomarkers within the tumors before and after treatment.

    Hypothesis: inhibition of hedgehog signaling with vismodegib alters the biology of other signaling pathways, which can lead to opportunities for multi-modal treatment synergies for resistant tumors, as well as identify risk factors for resistant tumors.

Utilizing immunofluorescence and confocal microscopy techniques, each tumor will be profiled for expression of a comprehensive set of ligands and receptors of the above-mentioned pathways. Using laser microdissection

(LMD) and quantitative PCR technology (qPCR), specific regions within tumors will be profiled and compared within and between tumors for expression of ligand-receptor pairs before and after vismodegib treatment, along with the presence of mutations within genes that are known to bypass or confer resistance to hedgehog pathway inhibition. Expression of cancer stem cell markers will also be assessed via qPCR, in both tumor and in blood samples from patients before and after vismodegib treatment, to identify possible serum markers for tumor sensitivity and response. Collaborators include Prof. Andrzej Dlugosz, University of Michigan, and Frederic de Sauvage, Genentech, Inc.

3.4 Safety Plan

Patients will be evaluated at regular clinic visits for the duration of the study participation

Specific potential safety issues for this trial are outlined below.

Please refer to the Vismodegib Investigator Brochure for a detailed description of the safety profile of vismodegib.

See Section 5.1 (Assessment of Safety) for complete details of the safety evaluation for this study.

3.5 Compliance with Laws and Regulations

This study will be conducted in accordance with current U.S. Food and Drug Administration (FDA) Good Clinical Practices (GCPs), and local ethical and legal requirements.

4. MATERIALS AND METHODS

4.1 Subject Selection

INCLUSION CRITERIA AND ENROLLMENT PROCESS

1) Adult patients over 18 years of age with locally advanced or recurrent **orbital** or **periorbital** BCCA, or a **medial canthal** BCCA that threatens the lacrimal drainage system, as noted by clinical exam, Clinical photography, CT or MRI imaging and positive biopsy, and who do not have a contraindication to either surgical or vismodegib treatment.
    a. Treating physician to assess whether the patient is a candidate for vismodegib treatment.
2) Clinical assessment score per **Table 14** will be obtained, at baseline.
3) Medical Oncology screening evaluation performed to assess medical indication/contra-indication to vismodegib treatment.

4) PI (AK) to review the exam findings, photos and imaging study and determine whether the patient meets inclusion criteria in the study, based on BCCA size, location of tumor, and clinical assessment score.

    a. Orbital invasion or impending invasion by BCCA

    b. Medial canthal BCCA within 7 mm of lacrimal apparatus

5) Adequate liver function, renal function and hematocrit.

6) Male patients must agree to use condoms for sexual intercourse with female partners of reproductive potential at all times, even after a vasectomy, during treatment with vismodegib and for 3 months after the last dose to avoid exposing a pregnant partner and unborn fetus to vismodegib (see Appendix 2).

7) Male patients must agree not to donate sperm during the study and for 3 months after discontinuation of vismodegib

8) Agreement not to donate blood or blood products during the study and for 7 months after discontinuation of vismodegib.

9) Patient will be approached for enrolling in the study by the PI, treating physician or a designee. Informed consent will be obtained by the PI, Co-I or a qualified designee.

10) If the patient consents to enroll, then blood will be drawn and stored for biomarker analysis.

EXCLUSION CRITERIA

Patients will be excluded from the study based on the following criteria:

- Inability or unwillingness to swallow capsules
- Inability or unwillingness to comply with study procedures and protocol
- Pregnant, lactating or breast feeding women
- Women of childbearing potential.
- Uncontrolled medical illnesses
- Age under 18 years
- Dementia or significantly altered mental status that would prohibit the understanding or rendering of informed consent and compliance with the requirements of this protocol.

4.2 Method of Treatment Assignment

Treatment will be determined by the treating physicians in accordance with SOC. The PI will determine eligibility for the study and be the final arbiter for inclusion of patients. There will be no randomization.

4.3 Study Treatment

The study treatment will follow SOC protocol for BCCA that threatens the eye or lacrimal apparatus. The study aims to enroll 50 patients over 3 years and follow each patient for 1 year.

Vismodegib Dosage

Vismodegib is 150 mg taken QD PO until disease progression or until unacceptable toxicity. Vismodegib may be taken with or without food.

- **Swallow capsules whole**
- **Do not open or crush capsules**
- **If a dose of vismodegib is missed, do not make up that dose; resume dosing with the next scheduled dose.**

Vismodegib Dose and Schedule Modifications

Vismodegib dose modifications and schedule modifications during the study are not recommended due to the pharmacokinetic characteristics of the drug (see Vismodegib Investigator Brochure v9, Section 5.9.3). Briefly, vismodegib's pharmacokinetic profile is a result of high affinity, reversible binding to Alpha-1 acid Glycoprotein (AAG) and binding to albumin, in addition to solubility limited absorption and slow metabolic elimination properties (Graham 2011). Initiation of less frequent administration schedules than the approved dose and schedule of vismodegib of 150 mg orally once daily, (i.e. 150 mg three times weekly [TIW] or 150 mg once weekly [QW] dosing), was associated with marked decrease in the pharmacologically active unbound fraction.

Unbound steady-state vismodegib concentrations were 60% and 85% lower for the TIW and QW dose groups, respectively, relative to the QD dose group (LoRusso et al. 2011b). Such decreases may be associated with loss of vismodegib activity based on findings from nonclinical models. Integrated PK/pharmacodynamic modeling of vismodegib in xenograft models has revealed a steep relationship between pathway modulation (GLI1 inhibition) and anti-tumor effect, suggesting that even small reductions in exposure could lead to dramatic loss in vismodegib activity (see Vismodegib Investigator's Brochure v9, Section 4.1.2.8)

Dose reduction of vismodegib is not permitted as there is only a 150-mg capsule strength available. Capsules should not be opened or crushed. If

a treatment interruption occurs, and it is determined that vismodegib will be re-started, the original dose will be maintained

Vismodegib Overdosage

There is no information on overdosage in humans. In clinical trials, ERIVEDGE capsule was administered at 540 mg QD; exposure did not increase between 150 mg and 540 mg daily.

Vismodegib Clinical Formulation and Storage

For the clinical studies, hard gelatin capsules containing 150 mg vismodegib are available. The 150-mg vismodegib drug product is a hard gelatin capsule formulation for oral administration. The capsule fill consists of vismodegib and the following excipients: microcrystalline cellulose PH101, lactose monohydrate, sodium lauryl sulfate, povidone K29/32, sodium starch glycolate, talc, magnesium stearate, and purified water. All of these excipients are compendial (USP/NF-EP) grade. The capsule shell consists of gelatin, red iron oxide, black iron oxide, and titanium dioxide. A compendial-grade black printing ink may be used.

Vismodegib capsules should be stored in the recommended storage conditions at15°C−30°C. Information on the shelf life of the capsules is provided on the label.

4.4 Concomitant and Excluded Therapy

Drugs that Inhibit or Induce Drug Metabolizing Enzymes

Vismodegib elimination involves multiple pathways. Vismodegib is predominantly excreted as an unchanged drug. Several minor metabolites are produced by multiple CYP enzymes. Although vismodegib is a substrate of CYP2C9 and CYP3A4 *in vitro*, CYP inhibition is not predicted to alter vismodegib systemic exposure since similar steady-state plasma vismodegib concentrations were observed in patients in clinical trials concomitantly treated with CYP3A4 inducers (i.e., carbamazepine, modafinil, and phenobarbital) and those concomitantly treated with CYP3A4 inhibitors (i.e., erythromycin and, fluconazole).

Drugs that Inhibit Drug Transport Systems

In vitro studies indicate that vismodegib is a substrate of the efflux transporter P-glycoprotein (P-gp). When ERIVEDGE is coadministered with drugs that inhibit P-gp (e.g. clarithromycin, erythromycin, azithromycin), systemic exposure of vismodegib and incidence of AE of ERIVEDGE may be increased.

Drugs that Affect Gastric pH

Drugs that alter the pH of the upper gastrointestinal (GI) tract (e.g., proton pump inhibitors, H2-receptor antagonists, antacids) may alter the solubility

of vismodegib and reduce its bioavailability. However, no formal clinical study has been conducted to evaluate the effect of gastric pH altering agents on the systemic exposure of vismodegib. Increasing the dose of ERIVEDGE when coadministered with such agents is not likely to compensate for the loss of exposure. When ERIVEDGE is coadministered with a proton pump inhibitor, H2-receptor antagonist or antacid, systemic exposure of vismodegib may be decreased and the effect on efficacy of ERIVEDGE is unknown.

Effects of Vismodegib on Other Drugs

Results of a drug-drug interaction study conducted in cancer patients demonstrated that the systemic exposure of rosiglitazone (a CYP2C8 substrate) or oral contraceptives (ethinyl estradiol and norethindrone) is not altered when either drug is co-administered with vismodegib.

In vitro studies indicate that vismodegib is an inhibitor of CYP2C8, CYP2C9, CYP2C19 and the transporter BCRP. Vismodegib does not induce CYP1A2, CYP2B6, or CYP3A4/5 in human hepatocytes.

4.5 Study Assessments

Assessments during Treatment

- **Pregnancy test:** All women of childbearing potential (including those who have had a tubal ligation) will be excluded from this study. This will have no bearing on their eligibility for treatment with vismodegib per SOC by their treating physician.

Ophthalmologic Exam Follow-Up Assessments

At month 3 and every 3 months a standard oculoplastic eye exam to assess visual function (see Table 15). The tumor size will be measured in two coordinates using a metric ruler at each clinic visit. This will be performed by the treating physician or a trained designee.

MRI or CT with contrast and clinical photographs will be obtained prior to the onset of treatment (per SOC). Clinical photographs will be obtained at subsequent clinic visits (every 3 months), and a follow up MRI or CT will be obtained at 5 and 9-12 months (+/- 1 month) after initiation of vismodegib therapy to assess tumor response/progression, and additionally at the discretion of the treating physician (per SOC).

Progression of disease, per ophthalmic/oculoplastic evaluation, will result in offering the patient a surgical approach. Patients will continue to be followed for the duration of the study period irrespective of vismodegib treatment status. If progression of disease is suspected by the Medical Oncology team, then an urgent ophthalmic evaluation will be obtained within 2 weeks or less.

Patients will be followed for 1 year after initiation of vismodegib treatment, or 1 month (+/- 1 month) following surgery.

4.6 Discontinuation of Protocol-Specified Therapy

Protocol-specified therapy may be discontinued for any of the following reasons:

- Patient election to discontinue study participation (for any reason)
- Patient election to refuse treatment (for any reason)
- Treating physician's judgment

4.7 Subject Discontinuation

All subjects who enroll in the study will be followed for 1 year, -1/+3 months, at which point their study participation will be deemed completed. If patients undergo tumor resection surgery prior to completion of the study, they will be given their final study evaluation within 1 month after the surgery, at which time their enrollment will be deemed completed. Subjects who discontinue vismodegib prior to the end of the 1-year study period, do not restart vismodegib within 30 days, and refuse surgery, will be deemed to have completed the study and their evaluation within 1 month of treatment discontinuation will be considered their exit time point and primary end point. Subjects who decide to resume vismodegib will be able to reenroll to complete the 1-year trial period.

Subjects who discontinue vismodegib before completing the 1-year study will return for evaluation by Ophthalmology within the first month post-operatively, at which point the final evaluation will be completed and their study enrollment will be deemed complete.

Completion of a final Ophthalmology evaluation and Visual Assessment Score will constitute a subject's completion of the study if so deemed by the PI.

See Table 16.

4.8 Study Discontinuation

The Principal Investigator has the right to terminate this study at any time. Reasons for terminating the study may include the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory

4.9 Statistical Methods

Number of referrals to PI, number of eligible participants, and number of enrollees will be used to monitor accrual. AEs and SAEs will be documented for all enrollees. All enrollees will be included in an intent-to-treat analysis. Pre-post tumor comparisons will be made among enrollees with both samples.

The study will use an exact binomial one-sided test to provide statistical measures to the outcomes.

Analysis

Treatment outcome (Visual Function Score; Table 15) will be measured overall (primary endpoint). The **primary** outcome will be the assessment of the visual system using a weighted assessment scale per Table 15. A weighted score of 21 or more (out of possible 50) constitutes a successful outcome.

Exact binomial one-sided tests will be used to compare success rate of the primary outcome (Visual Function Score, Table 15) to 30% (a literature- and practice-based estimate of the loss of visual and lacrimal function after treatment of locally advanced periocular/orbital BCCA). If the true success rate is 50%, the study will have 90% power to reject the null hypothsis (p=0.3) in favor of the alternative (p>0.3) at alpha=0.05.

Secondary endpoints will utilize the three treatment modality groups:

- #1: treatment stopped due to non-response (per RECIST);
- #2: treatment continued for a full year with good response and good tolerance
- #3: treatment stopped due to poor tolerance in spite of good response;

Secondary outcomes will utilize the actual numerical values obtained during the assessment over time to correlate visual function with tumor size (measured at each visit and/or via MRI/CT imaging). The secondary outcome measures will assess each part of the composite visual assessment score to determine changes in vision and lacrimal function following vismodegib treatment.

Histologic characteristics and molecular markers to be studied for the secondary objective include HMW keratin, proliferation markers such as Ki67, hedgehog and Wnt pathway markers. These will be summarized overall, by treatment modalities, and by outcome groups (e.g., Good or Poor Visual or Lacrimal Function). No other subgroup analyses are planned. **Please see page 20, BASIC RESEARCH ARM.**

Safety Analysis

AEs and SAEs will be tabulated among all enrollees.

Missing Data

Pre-treatment data will be reviewed prior to enrollment to ensure that all the required elements are documented. Incomplete post-treatment data will be completed via subsequent clinical exam and/or telephone interview.

Determination of Sample Size

- *Endpoints used*

  The endpoint used for determining sample size was a Visual Assessment Weighted Score of at least 21 (out of possible 50).

- *Methodology used*

  The exact binomial one-sided test with n=50 has 90% power to reject the null hypothesis p=0.3 in favor of the alternative p=0.5 at alpha=0.05.

A recruitment assessment will be performed at the 2 and 3 year time points (out of 4 years), in order to assess recruitment. The goal of the study is to enroll 50 patients over 3 years, or 16-17 patients per year. After year 1, if recruitment drops below a minimum 12 patients (or at least one per month on average) then the study will be adjusted by (1) extending the trial beyond 3 years of recruitment, and/or (2) extending patient recruitment to outside medical institutions. After year 2, if recruitment is greater than 20 but below 30 patients, then the trial will be extended by 1 year. If recruitment is below 20 patients at the end of year 2 then the trial will be both extended by 1 year and patient recruitment extended to outside institutions.

4.10 Data Quality Assurance

Accurate, consistent, and reliable data will be ensured through the use of standard practices and procedures.

5. REPORTING OF ADVERSE EVENTS

5.1 Assessment of Safety

This study will be monitored in accordance with the NCI approved University of Michigan Rogel Cancer Center Data and Safety Monitoring Plan.

The study team will meet quarterly or more frequently depending on the activity of the protocol. The discussion will include matters related to the safety of study participants (SAE/UaP reporting), validity and integrity of the data, enrollment rate relative to expectations, characteristics of

participants, retention of participants, adherence to the protocol (potential or real protocol deviations) and data completeness. At these regular meetings, the protocol specific Data and Safety Monitoring Report form will be completed and signed by the Principal Investigator or by one of the co-investigators.

Data and Safety Monitoring Reports will be submitted to the University of Michigan Rogel Cancer Center Data and Safety Monitoring Committee (DSMC) on a quarterly basis for independent review.

Specification of Safety Variables

Safety assessments will consist of monitoring and reporting AEs and SAEs per protocol. This includes all events of death, and any study specific issue of concern.

Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting including signs or symptoms associated with basal cell carcinoma 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.

Serious Adverse Events

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.

- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

5.2 Methods and Timing for Assessing AND Recording Safety Variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the appropriate IRB(s), in accordance with CFR 312.32 (IND Safety Reports).

Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of vismodegib treatment and ends 30 days following the last administration of vismodegib or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of vismodegib, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to vismodegib; and/or the AE abates or resolves upon discontinuation of vismodegib or dose reduction and, if applicable, reappears upon re-challenge

No

Evidence exists that the AE has an etiology other than vismodegib (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to vismodegib administration (e.g., cancer diagnosed 2 days after first dose of vismodegib).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator's Brochure.

Unexpected adverse events are those not listed in the Package Insert or current Investigator's Brochure (or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the Package Insert or current Investigator's Brochure. For example, under this definition, hepatic necrosis would be unexpected if the Package Insert or Investigator's Brochure only referred to elevated hepatic enzymes or hepatitis.

5.3 Procedures for Eliciting, Recording, and Reporting Adverse Events

Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation timepoints will be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 5.2.1), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the

single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

e. Pregnancy

Women of child bearing potential are not eligible to participate in the study. 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 study drug 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).

f. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior vismodegib exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

g. Reconciliation

The Sponsor agrees to conduct reconciliation for the product. Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange quarterly line listings of cases received by the other party. If discrepancies are identified, the Sponsor 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. The sponsor shall receive reconciliation guidance documents within the "Activation Package."

MEDWATCH 3500a REPORTING GUIDELINES

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to vismodegib, and suspect medication.

Follow-up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted

(The patient identifiers are important so that the new information is added to the correct initial report).

- Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom and adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm

5.4 Safety Reporting Requirements for IND Exempt Studies

Postmarketing 15-Day "Alert Report":
The Sponsor-Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is **unexpected and assessed by the investigator to be possibly related to the use of vismodegib**. An unexpected adverse event is one that is not already described in the Investigator Brochure. Such reports are to be submitted to the FDA (2 copies) at the following address: Central Document Room, 12229 Wilkins Avenue, Rockville, MD 20852.

All Postmarketing 15-Day "Alert Reports" submitted to the FDA by the Sponsor-Investigator must also be faxed to Genentech at: (650) 225-4682 or (650) 225-4630.

5.5 Study Close-Out

At the close of the study, all the patient data will be entered into a repository for 7 years, and then destroyed. All biological data, including tissue and blood samples, will be stored indefinitely for patient care purposes and future analysis as needed. A research report will be prepared by the PI and submitted for publication as well as to the funding agencies. Any study report by the Sponsor-Investigator should be copied to Genentech. Additionally, any literature articles that are a result of the study should be sent to Genentech.

6. RETENTION OF RECORDS

U.S. FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, subject records, consent forms, laboratory test

results, and medication inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of vismodegib. All state and local laws for retention of records also apply.

For studies conducted outside the United States under a U.S. IND, the Principal Investigator must comply with the record retention requirements set forth in the U.S. FDA IND regulations and the relevant national and local health authorities, whichever is longer.

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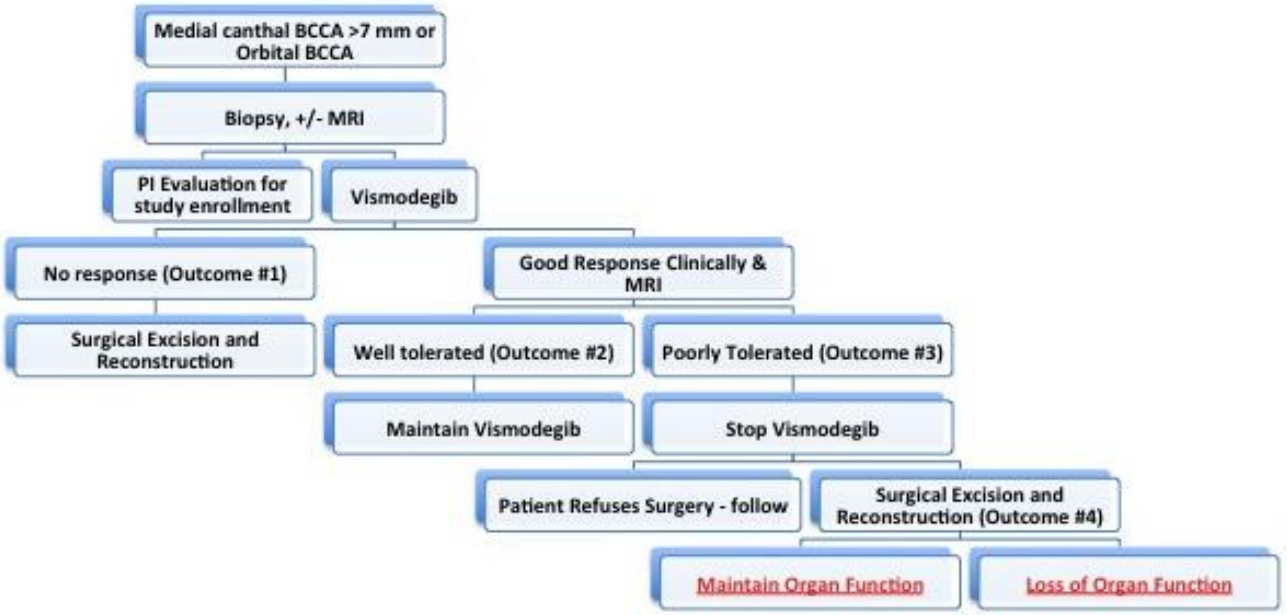
APPENDICES

APPENDIX 1 Study Flowchart



APPENDIX 2: Definition of Women of Non-Childbearing Potential

Female patients who meet at least one of the following criteria are defined as women of **non-childbearing** potential:

- ≥ 50 years old and naturally amenorrheic for ≥ 1 year
- Permanent premature ovarian failure confirmed by specialist gynecologist
- Previous bilateral salpingo-oophorectomy and/or hysterectomy
- XY karyotype, Turner's syndrome, or uterine agenesis

Female patients who do not meet at least one of the above criteria are defined as women of **childbearing** potential, and will be excluded from this study.

Children of both genders will be excluded from this study, which includes pre-menstrual as well as post-menarche girls.

Women of **childbearing** potential who are excluded from this study will still be eligible to receive vismodegib per FDA-approved indications and standard of care.

APPENDIX 3: Material Safety Data Sheet (MSDS)

The current Material Safety Data Sheet (MSDS) for ERIVEDGE® Capsules (150 mg) is available at:

http://www.gene.com/download/pdf/ErivedgeCapsules150mgMSDS.pdf

The information in this safety data sheet is based on current scientific knowledge. It should not be taken as expressing or implying any warranty concerning product characteristics.

APPENDIX 4

Table 16: Schedule of Assessments

	Screen	Initiation of Vismodegib	Assessments (+/- 1 month[10])													
Study Visit (months)			1	2	3	4	5	6	7	8	9	10	11	12, -1/ +3 months (or 1 month post-op following surgery)[12]	Withdrawal of vismodegib for surgical treatment (+/- 1 month)	Early withdrawal of vismodegib
Informed Consent	x															
Demographics	x															
Medical History[1]	x															
Medical Exam[2,]	x	x	x		x[10]			X[10]			X[10]			X[10]	X[10]	X[10]
Ophthalmic oculoplastic exam[3]	x				x			x			X			x	x	x
Standard clinical photos	x				x			x			x			x	x	x
Visual Assessment Score (pre)[4]	x															
Visual Assessment Score (post)[5]					x			x			x			x	x	x
Biopsy for histologic diagnoses/evaluation	x															
MRI or CT scan[6]	x						x				X[13]			x	X[11]	X[11]
CBC/Chemistry Labs[7]	x				x			x			x			x	x	x
Biomarker Draw	x							x						x	x	x
Response Evaluation[8]					x			x			x			x	x	x
AE assessment[9]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Footnotes:

1. Medical history including smoking history. Assessed by Ophthalmology team.
2. Medical exam assessed by Med Onc team. 3 month supply of medication will be provided at the time of each standard 3-month visit.
3. Ophthalmic exam should include visual acuity, slit lamp exam, eye motility and tearing. Assessed by Ophthalmology team.
4. See Table 14 in the protocol. Assessed by Ophthalmology team.
5. See Table 15 in the protocol. Assessed by Ophthalmology team.
6. Additional MRI/CT will be for tumor measurements and assessments. Assessed by Ophthalmology team.
7. CBC/Chemistry lab tests per Med-Onc team for SOC.
8. Assessed by Ophthalmology team.
9. Assessed by Med-Onc team.
10. Visits may be scheduled more frequently per Med-Onc or Ophthalmology team discretion. Last medical exam will occur prior to surgery. Remaining medication and diary should be returned to Ophthalmology.
11. Per the discretion of the Ophthalmologist.
12. Subjects will be followed for 1 year or until surgery followed by one month post-operative evaluation.
13. 9-12 month window for CT-MRI imaging, as determined by the treating physician.

APPENDIX 5

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET
Genentech Supported Research

AE / SAE FAX No: (650) 225-4682

Alternate Fax No: (650) 225-4630

Genentech Study Number	ML29160
Principal Investigator	Alon Kahana, MD, PhD
Site Name	Kellogg Eye Center/University of Michigan
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: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET