Phase 2B single-site, open-label, nonrandomized study evaluating the efficacy of oral vismodegib in various histologic subtypes (infiltrative/morpheaform, nodular and superficial) of high risk and/or locally advanced basal cell carcinoma

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1. BACKGROUND INFORMATION

1.1 INTRODUCTION

Basal cell carcinoma (BCC) is the most common type of skin cancer, with almost 3 million cases diagnosed each year in the United States. (Skin Cancer Foundation 2011, Rogers et al 2010) The incidence of BCC is increasing 10% each year worldwide and its prevalence is expected to equal that of all other cancers combined in the near future. (Madan et al 2010)

Though extremely rare, some patients have progressive mutilating metastatic BCC (mBCC) or locally advanced BCC (laBCC), which can be fatal. Most BCCs are not life-threatening, but they are still quite morbid as they commonly occur on the head and neck. Some BCC lesions grow very quickly and are associated with poorer outcomes. Features of these 'high risk' BCC (hrBCC) lesions were defined by the National Comprehensive Cancer Network (NCCN) and this hrBCC cohort was highlighted as one of particular concern. (See Appendix 1, NCCN 2011). Since hrBCC tumors are much more common, they actually represent a much bigger public health problem than mBCC or laBCC.

Due to its superior cure rate, Mohs micrographic surgery (MMS) is widely accepted as the gold standard for treatment for the majority of BCC tumors, especially laBCC and hrBCC. (Mikhail and Mohs 1993, NCCN 2011) Even with the utilization of the Mohs tissue preservation technique, surgery can be quite extensive resulting in significant disfigurement, depending on the size and anatomic location of the lesion.

While size of tumor is a predictive factor of patient outcomes, visual examination can frequently be deceiving and local microscopic invasion may be much more extensive than initially thought. In some cases, tumor seen at the skin surface may only represent one fifth of its microscopic spread. (Batra and Kelley 2004) Since many tumors exhibit significant subclinical extension, the resulting surgical defect after tumor clearance can be considerably larger than the presenting lesion, often necessitating complex, costly, and time-consuming repairs, compromising the final cosmetic appearance or function.

Adjuvant therapies aiding in the removal of primary or recurrent tumors could lessen the risk of cosmetic disfigurement by decreasing tumor burden prior to surgery. Topical therapies, such as imiquimod, have been investigated in the past for this purpose. They are not widely used due to concern that the variable penetration of topical therapy may lead to noncontiguous response, leading the clinician to incorrectly believe that the tumor has been completely cleared. (Harting et al 2007) An oral agent, that hypothetically would be distributed to the tumor uniformly, may be better suited for neoadjuvant treatment of BCC prior to surgery. In fact, in selected lesions, oral treatment could possibly even lead to complete eradication of tumor tissue, thereby eliminating the need for surgery altogether. Vismodegib is an orally delivered small Hedgehog pathway inhibitor (HPI) that shows promise in the management of BCC. Vismodegib was granted priority review and was recently approved by the U. S. Food and Drug Administration 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.

1.2 RATIONALE

Vismodegib has been shown to have an anti-tumor effect on BCC in preclinical and clinical studies. It exerts its effect by blocking the Hedgehog (Hh) pathway directly, disrupting the development of cancers that are due to PTCH mutations or SMO mutations, like those seen in the majority of BCCs. (Lorusso et al 2011, Von Hoff et al 2009) An estimated 90% of BCC tumors have mutations in the Hh signaling pathway, either an inactivation of the PTCH mutation (loss-of function mutation) or an activation of the SMO15 mutation (gain of function), that disrupt normal signaling between cells and lead to a proliferation of basal cells and the development of BCC. (Rubin and De Sauvage 2006, Hopper and Scott 2006) For this reason, inhibiting the Hh signaling pathway has been identified as a therapeutic target in the treatment of BCC.

Though many BCCs possess the same mutation in the Hh pathway, BCC is a very heterogeneous tumor type when considering all of the known histologic subtypes. Twenty-three subtypes of BCC have been recorded in the literature, but for practical purposes these have been combined and three subtypes (infiltrative/morpheaform, nodular and superficial) are used clinically. (Sexton et al 1990, Wade and Ackerman 1978, Rippey 1998) The most common type of BCC is nodular (70%). (Weedon 2009, Mosterd et al 2011) Superficial subtypes comprise around 10-15% of BCCs. About 10-15% of BCCs are categorized as infiltrative/morpheaform subtype for clinical management and considered to be an "aggressive" subtype of BCC. Infiltrative BCCs and morpheaform BCC have different appearances histologically, but are considered together for management due to their similar aggressive clinical course.

Histologic features are well known to impact tumor biologic behavior and response to treatment. Treatment options for BCC are often curative when considering clinical and histologic features, the latter a more powerful prognostic factor with laBCCs and hrBCCs. (Walling et al 2004) For example, it is well recognized that infiltrative/morpheaform tumors are associated with increased rates of recurrence and poorer prognosis since their tumor characteristics make it difficult to obtain clear margins during surgery. (Walling et al 2004) These BCC subtypes frequently have tumor nests outside of the tumor bulk. During surgery, tumor remnants may go undetected by conventional means and continue to grow. If a histological response to vismodegib in aggressive subtypes can be demonstrated pre-operatively, clinicians may possess greater confidence that all tumor nests have been eradicated and clear margins have been obtained during surgery, leading to improved patient outcomes. Conversely, superficial BCCs are considered to have non-aggressive tumor behavior and are also more likely than other subtypes to be located on the low-risk locations of the trunk and extremities. (Weedon 2009) These tumors, which typically undergo simple excisions, nonetheless can require significant circumferential margins of normal tissue to ensure complete removal, again impacting cosmesis, function and or cost.

It is unknown if BCC histologic subtype impacts tumor response to vismodegib. Data from previous studies, where inclusion was open to all subtypes of basal cell skin cancer, is predominantly based on nodular subtype. Most currently recruiting studies investigating vismodegib in BCC do not specify a tumor subtype for inclusion, but if one is specified for inclusion, it is nodular subtype only. (ClinicalTrials.gov Identifier NCT01201915) No previous or ongoing studies have stipulated inclusion of other histological subtypes of BCC.

The goal of this study is to identify the cohorts of patients that will most likely benefit from treatment with vismodegib. In the new era of cancer therapeutics, matching treatment modality with specific tumor features contributes to better patient outcomes. This investigation will assist in providing a greater understanding of the efficacy of vismodegib in BCCs of aggressive subtypes and of other histologic subtypes. This study may provide better guidance for targeted, individualized information about a patient's unique tumor biology and optimize management of BCCs in our patients.

1.3 POTENTIAL RISKS AND BENEFITS

The safety, preliminary efficacy, and pharmacokinetics of vismodegib in mBCC and laBCC were assessed in an open-label, multicenter, two-stage Phase I trial. Patients with solid tumors refractory to standard therapy were treated until disease progression, intolerable toxicities, or withdrawal from the study. Thirty-three patients with mBCC or laBCC were included in analysis and followed over a 20-month period. Assessment using the RECIST criteria version 1.0 was completed if tumors had radiologically measurable disease. Otherwise, pre-defined clinical response measures were employed. An overall response rate of 58% was observed. (Von Hoff et al 2009) The most common response, in 17 of 33 cases, was partial response. Complete response was seen in 2 cases. Stable disease was observed in 12 cases. (Von Hoff et al 2009) No dose-limiting toxic events or grade 5 events were observed with a single grade 4 adverse event (asymptomatic hyponatremia) reported. The more significant and frequent adverse events were GI related with dysgeusia and muscle spasm reported.

Further evidence of the efficacy of vismodegib in the treatment of BCC was shown in the pivotal ERIVANCE trial, a Phase II single-arm, non-randomized trial of single-agent vismodegib at 150 mg/day to progression or intolerance with 104 patients enrolled: (33 mBCC, 71 LA BCC). The study met its primary endpoint overall response rate (ORR) by an independent review facility (IRF) and showed shrinkage of tumors in a pre-defined percentage of patients[8]. A preliminary safety assessment showed the most common adverse events were consistent with previous experience with vismodegib. The most common adverse events were muscle spasms, hair loss, altered taste sensation, weight loss, fatigue, nausea, decreased appetite and diarrhea. A detailed safety assessment is ongoing.

Therapy with vismodegib has the potential to significantly decrease morbidity of the patients' BCC either through complete clearance of tumor or by substantially decreasing the morbidity of surgery. Though BCC expected to respond favorably to treatment with vismodegib, surgical excision by MMS will occur within 6 months of initial consultation; this study will not adversely affect the current standard of care in the management of BCC in non-responders.

In a recent Phase 2 trial, vismodegib was also reported to slow the development of BCCs in patients with Basal Cell Nevus Syndrome (BCNS), a rare genetic disorder which causes patients to develop hundreds of large BCCs. (Tang et al 2011). Further studies are needed, but vismodegib may slow the progression of BCC in patients without BCNS.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVES

- To compare the efficacy of vismodegib in various histologic subtypes of high risk and/or locally advanced basal cell skin cancer

2.2 SECONDARY OBJECTIVES

- To evaluate the onset of efficacy of vismodegib during 24 weeks of treatment in various histologic subtypes of high risk and/or locally advanced basal cell skin cancer

- To evaluate the safety and tolerability of vismodegib over 24 weeks of treatment in subjects with high risk and/or locally advanced basal cell skin cancer

- To evaluate patient reported outcome (PRO) measures during 24 weeks of treatment with vismodegib in subjects with high risk and/or locally advanced basal cell skin cancer

3. STUDY DESIGN

This is a Phase 2B two-site, open-label, nonrandomized 24-week study of the efficacy and safety of vismodegib (150 mg PO daily) in subjects with high risk and/or locally advanced basal cell carcinoma. A total of 36 subjects with infiltrative/morpheaform, nodular, or superficial BCC will be enrolled in the study. Each subtype group will have a minimum of 10 subjects. No group will have more than 16 subjects.

At Treatment Initiation Visit (Baseline/Day 1), eligible subjects will begin a 24-week treatment regimen with vismodegib 150 mg daily. Clinical assessments will be performed every 4 weeks during treatment. Intra-treatment tissue histopathologic evaluation will be conducted at Week 12. Subjects will be eligible to discontinue treatment early and enter the Observation period if there is no histologic evidence of tumor on Week 12 pathology specimens. Post-treatment histopathologic evaluation will be performed at Week 24 (End of Treatment visit). Subjects will be eligible to enter the Observation period in lieu of surgery if their target lesion displays complete histologic response on biopsy specimens obtained at Week 24 visit. For subjects with histologic evidence of disease on pathology at Week 24 visit, surgical excision or Mohs surgery on the target lesion will be performed within 4 weeks of the last dose of study drug. Patient Reported Outcomes (PRO) data will be collected at baseline visit, during treatment, end of treatment/early termination visit, surgical visit, and study exit (post-surgery) visit, and at first Observation period visit (when applicable) Safety assessments including adverse event (AE) monitoring and concomitant medications will be performed at each visit.

The rationale for using 24-week treatment schedule was based on previous data from pilot studies. Data from a previous trial of 33 subjects with advanced BCC, demonstrated that 94% (17/18) of responders responded by 24-weeks. (Von Hoff et al 2009) In non-responders, treatment beyond 24 weeks may unnecessarily endanger the patient and allow their basal cell skin cancer to progress potentially negatively affecting clinical outcome.

4. SUBJECT SELECTION

A total of 36 subjects with histologically-confirmed basal cell skin cancer who meet all eligibility criteria will be enrolled. Patients with mBCC will be excluded.

4.1 INCLUSION CRITERIA

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and data informed consent document indicating that the subject (or legally acceptable representative) has been informed of all pertinent aspects of the trial.
2. Subjects who are willing to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
3. Be 18 years of age or older at the time of informed consent.
4. Has one or more clinically suspicious lesions for BCC at Pre-Study screening Visit that is/has:
    a. a diameter ≥ 6 mm if located on the "mask areas" of face (central face, eyelids, eyebrows, periorbital, nose lips [cutaneous and vermillion], chin, mandible, preauricular and postauricular skin/sulci, temple, ear), genitalia, hands, or feet (See Appendix 2 for Figure of "mask areas" of face)
    b. a diameter ≥ 10 mm if located on cheeks, forehead, scalp, or neck
    c. a diameter ≥ 20 mm if located on trunk and extremities

    or has a lesion suspicious for locally advanced BCC defined as a lesion that:
    a. is ≥ 10 mm,
    b. has recurred following surgery or surgical resection would result in substantial deformity, and
    c. has been deemed not appropriate for radiation.

5. Have a histologically-confirmed BCC prior to first dose of study drug at Treatment Initiation Visit (Baseline/Day 1).
6. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less at Baseline/Day 1 visit. (See Appendix 3, ECOG Performance Status)
7. Males and females must agree that they have no desire or plan to conceive children in the future
8. Female of reproductive potential must use 2 effective methods to avoid pregnancy during therapy and for 9 months after completing therapy. Effective methods must be used for 1 month before initiating therapy.
9. Male patients must use effective measures to avoid pregnancy in their partner at all times, even after vasectomy, during treatment and for 3 months after the last dose.
10. Agreement not to donate blood or blood products during the study and for 9 months after the last dose.
11. Subjects with Basal Cell Nevus Syndrome are eligible for enrollment.

4.2 EXCLUSION CRITERIA

Subjects presenting with any of the following will not be included in the study:

1. Women who are pregnant or lactating, or planning pregnancy while enrolled in the study.
2. History of prior treatment with vismodegib or any Hh Pathway Inhibitor
3. Have evidence of clinically significant and unstable diseases or conditions such as cardiovascular, immunosuppressive, hematologic, hepatic, neurologic, renal, endocrine, collagen-vascular, or gastrointestinal abnormalities. Subjects with clinically stable chronic medical conditions including, but not limited to, controlled hypertension, diabetes mellitus type II, hypercholesterolemia, or osteoarthritis, will be allowed to enter the study.
4. Have any dermatological disease at treatment site that the investigator thinks may be exacerbated by treatment with vismodegib or cause difficulty with examination (e.g., psoriasis, eczema).
5. The target lesion identified at Pre-study Screening visit has been determined to be mBCC by radiological assessment prior to first dose of study drug.
6. Inability or unwillingness to swallow capsules.
7. Have a history of infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged to be clinically significant by the investigator within 4 weeks prior to first dose of study drug.
8. Have a history of infection requiring antimicrobial therapy within 2 weeks prior to first dose of study drug.
9. Have a history of alcohol of substance abuse, unless in full remission for greater than 6 months prior to first dose of study drug
10. Known to be infected with human immunodeficiency virus (HIV), hepatitis B or hepatitis C viruses.
11. Participation in other study using an investigational or experimental therapy or procedure within 4 weeks or 5 half-lives (whichever is longer) before the study begins and/or during study participation. Subjects cannot participate in studies of other investigational or experimental therapies or procedures at any time during their participation in this study.
12. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
13. Subjects who are investigational site staff members or subjects who are Sponsor employees directly involved in the conduct of the trial.
14. A subject who, in the opinion of the investigator or sponsor, will be uncooperative or unable to comply with study procedures.
15. Subjects (male and female) who desire to conceive in the future

5. INFORMED CONSENT

Prior to entering the study, the investigator or designated assistant will explain to each subject or legally acceptable representative, the nature of the study, its purpose, procedures, expected duration, and the benefits and risks involved in study participation.

Alternative therapies for treatment of BCC (e.g. surgical excision, Mohs surgery, radiation therapy, imiquimod topical treatment, 5-fluorouracil topical therapy, electrodessication and curettage, cryotherapy and photodynamic therapy) will be discussed with the subject. Subjects will be informed that declining to participate or withdrawal after enrollment in trial will in no way affect the management or care of the patient.

Each subject will be given an information and consent document and the opportunity to ask questions; and will be informed of his/her right to withdraw from the study at any time without prejudice. After this explanation and before any study-specific procedures have been performed, the subject, or legally acceptable representative, will voluntarily sign and date an informed consent statement. Prior to participation in the study, the subject or his/her legally acceptable representative should receive a copy of the written informed consent form and any other written information provided to the subject. (See Appendix 4 for information on required elements of informed consent.)

6. STUDY METHODOLOGY

6.1 STUDY PROCEDURES

The following sections describe in detail all study procedures. A flow chart of study procedures is presented at the end of the protocol (Appendix 6).

6.1.1 Pre-study Screening visit

Subjects will be screened within 4 Weeks (+/-3 days) prior to the Treatment Initiation (Baseline/Day 1) visit to confirm that they meet the entrance criteria for the study. The study investigator or sub-investigator will discuss with each subject the nature of the study, its requirements, and its restrictions. Written informed consent must be obtained prior to performance of any protocol-specific procedures.

The following procedures will be performed at Pre-study Screening visit, within 4 weeks prior to Treatment Initiation (Baseline/Day 1, Visit 2) visit

- Confirmation of inclusion criteria, excluding histologic confirmation of basal cell skin cancer of target lesion.
- Identification of skin lesion(s) clinically suspicious for basal cell skin cancer.
- Recording of medical history. (Medical history is defined as a disease or syndrome that is ongoing at or stopped before Informed Consent.)

- Recording of history of alcohol and drug use, smoking status (current smoker, current heavy smoker >20 cigarettes per day), and average weekly alcohol consumption (units/week), where a unit contains 12 g of pure alcohol, an amount equivalent to that contained in 5 oz (a glass or 148 mL) of wine, 12 oz (355 mL) of beer, or 1.5 oz (44 mL) of 90 proof of spirits. (The intent is to monitor the subject's alcohol consumption during the study to determine if it has impact on the efficacy, disease state and any co-morbidities. It is the PI's discretion to determine acceptable levels of consumption or abuse. Alcohol and/or substance abuse are exclusionary.)
- Recording of current medications and all other drugs (including non-prescription drugs, vitamins, and dietary supplements) taken within 4 weeks prior to Screening.
- Complete physical examination including full-body skin exam.
    - Physical examination includes: height, weight, general appearance, skin (other than primary diagnosis), HEENT (head, eyes, ears, nose and throat), heart (auscultation), lungs (auscultation), abdomen (palpation and auscultation), lower extremities (peripheral edema), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes.
- Vital signs [blood pressure (BP); heart or pulse rate; and oral, tympanic, or temporal temperature].
- Males are reminded that they must use effective measures to avoid pregnancy in their partner at all times, even after vasectomy, for 3 months after the last dose.
- Females are reminded that they must use 2 effective methods to avoid pregnancy for 1 month prior to start of study medication, during therapy, and for 9 months after completing therapy.
- For women who do not want to conceive in the future but are still women of childbearing potential:
    - Two negative pregnancy tests with a sensitivity of at least 25 mIU/mL at least 19 days apart
    - For patients with regular menstrual cycles, the second pregnancy test should be done during the first 5 days of the menstrual period immediately preceding the beginning of therapy and after the patient has used 2 effective measures to avoid pregnancy for 1 month.
    - For patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding, the second pregnancy test must be done immediately preceding the beginning of therapy and after the patient has used 2 effective measures to avoid pregnancy for 1 month.
- Laboratory evaluation at baseline to evaluate abnormalities in hematocrit/platelet counts, renal or hepatic function and electrolytes.

6.1.1.1 Target lesion selection

- If multiple lesions are deemed to be suspicious for basal cell skin cancer on visual inspection, up to 4 lesions will be considered for investigation and designated "potential target lesions". Potential target lesion(s) will be selected at clinician discretion using clinical and dermoscopic findings and in consideration of patient preference.
- Measurement pre- and post-biopsy and high resolution digital photography of potential target lesion(s).

- Template map drawing of clinically evident tumor margins and local landmarks using a permanent marker on a clear plastic overlay.
- To confirm diagnosis of BCC and to designate histologic subtype, up to three representative 2-mm or three representative 3-mm punch biopsies will be performed on each potential target lesion.
    - Skin biopsies performed at Pre-study Screening visit will comprise no more than 10% of visible lesion surface area.
    - Skin biopsies must be performed at least 1 mm from peripheral margin of visible lesion.
- Biopsy of each potential target lesion will be performed in area that clinically appears to be thickest by inspection at palpation. If the potential target lesion appears to be homogenous, the biopsy will be performed at the center of the lesion.
- Post-biopsy pre-treatment lesion area will also be recorded and template drawn.

6.1.2 Treatment Initiation Visit (Baseline/Day 1)

The objective of this visit is to ensure that subjects who will enter the study continue to meet all inclusion and exclusion criteria and to perform baseline evaluations of the biopsy-confirmed BCC target lesion site.

For subjects with >1 histologically-confirmed BCC identified at Pre-study Screening Visit, target lesion assignment for primary endpoint analysis is described in Section 9.2.1 Target lesion assignment.

The study visit should occur within 4 weeks of Pre-study Screening visit.

The following procedures will be performed at Treatment Initiation Visit (Baseline/Day 1) after confirmation that the subject has met all inclusion criteria and has no exclusion criteria present:

- Assessment of any changes (deletions, additions, or dose modifications) to medications.
- Complete physical examination including general appearance, skin exam, and visual inspection of target lesion.
- Vital signs (BP; heart or pulse rate; and oral, tympanic, or temporal temperature).
- Weight and height measurements.
- Urine pregnancy test (α--hCG) for women who are of childbearing potential.
  Photography and measurement of target lesion(s) with ruler visible in photographic field
- Template map drawing of clinically evident tumor margins and local landmarks using a permanent marker on a clear plastic overlay.
- Complete an evaluation of target tumor, including:
- Tumor measurement/dimensions Photograph target lesion
- Adverse Event (AE) Monitoring.
- Subjects will complete the Patient Reported Outcomes (PRO) questionnaire: SKINDEX-16 to obtain baseline information. (Appendix 6)
- Dispense study drug bottles.
- Provide appropriate training and specific written instructions for study drug (capsules) self-administer by subject.

- Observe subject administer first dose of study drug (on Day 1 only)
- Review subject diary and instructions on completion for daily dosing/drug accountability. The subject will be instructed to begin data diary recording at home.
- Reminder to use effective measures to avoid pregnancy
- Subject will be a given written instructions for adverse event monitoring, measures to avoid pregnancy and avoiding of blood production products (Appendix 7.)

6.1.2 **Interval Visits**

The objectives of these interval visits are to provide a systematic and objective evaluation of the target tumor, and to monitor subject safety while ensuring continued compliance with study procedures. Every attempt should be made to have individual subject assessments performed by the same physician (investigator or equally qualified physician listed on FDA form 1572), preferably on the same day of the week for each visit.

The following procedures will be performed at all visits during treatment:

- Assessment of any changes (deletions, additions, or dose modifications) to medications.
- Complete physical examination including general appearance, skin exam, and visual inspection of target lesion(s).
- Vital signs (BP; heart or pulse rate; and oral, tympanic, or temporal temperature).
- Weight and height measurements.
- Urine pregnancy test (α--hCG) only for women who are of childbearing potential.
- laboratory evaluation to evaluate abnormalities in hematocrit/platelet counts, renal or hepatic function and electrolytes if deemed necessary by the investigator.
- Photography and measurement of target lesion with ruler visible in photographic field
- Template map drawing of clinically evident tumor margins and local landmarks using a permanent marker on a clear plastic overlay.
- Adverse Event (AE) Monitoring.
- Review subject dosing dairy and conduct accountability of used and unused study drug returned by the subject to determine study drug dosing regimen compliance.
- Collect unused study drug and re-dispense study drug
- Observe subject administer doses of study drug and document in the dosing diary.
- Clinical Response Evaluation by investigator (See below Section 6.2.2, Clinical response evaluation of target lesion for instructions)
- Reminder to use effective measures to avoid pregnancy
- Remind subjects to bring all unused drug supplies with them to their next scheduled visit.

Week 8, 16, and 24, Surgery Visit, Study Exit Visit (Post-Surgery Visit): PRO questionnaires will be performed by the subject (SKINDEX-16 and Functional Assessment of Cancer Therapy – General (FACT-G). (Appendix 7 and 9.)

At week 12, Intra-treatment tissue histopathologic evaluation will be performed to assess histologic response. For subjects with apparent clinical complete response at Week 12 and no histologic evidence of disease is observed, subjects will enter the observation period and be followed clinically every 3 months up to one year (See Appendix 5, Figure 3 for more

information). Sample diagrams demonstrating the sites of screening biopsies and Week 12 biopsies for a tumor is seen in Section 6.1.3.

6.1.3 Intra-treatment Tissue Histopathologic Evaluation

All subjects will undergo intra-treatment Tissue Histopathologic Evaluation at Week 12 visit. For lesions that display complete clinical response, histologic presence or absence of tumor on biopsy determines whether or not the subject is eligible to end treatment early and enter the Observation period (See Appendix 5 , Figure 3). Subjects with clinical partial response or stable disease at Week 12 visit will continue treatment for the full duration of 24 week regardless of pathology on sampling biopsy (See Appendix 5, Figure 2).

Tumors Exhibiting Complete Clinical Response
For lesions that the investigator has determined to show complete clinical response at Week 12 visit, sampling biopsy will be performed at the farthest edge(s) of pre-biopsy lesion compared to location of initial punch biopsy/biopsies at Pre-study Screening Visit (See Figure 1 A). Up to three 2-mm or three 3-mm punch biopsies will be performed on the area of tumor clearance at Week 12 when possible. Tumor biopsies may comprise no more than 10% of visible lesion seen at screening visit.

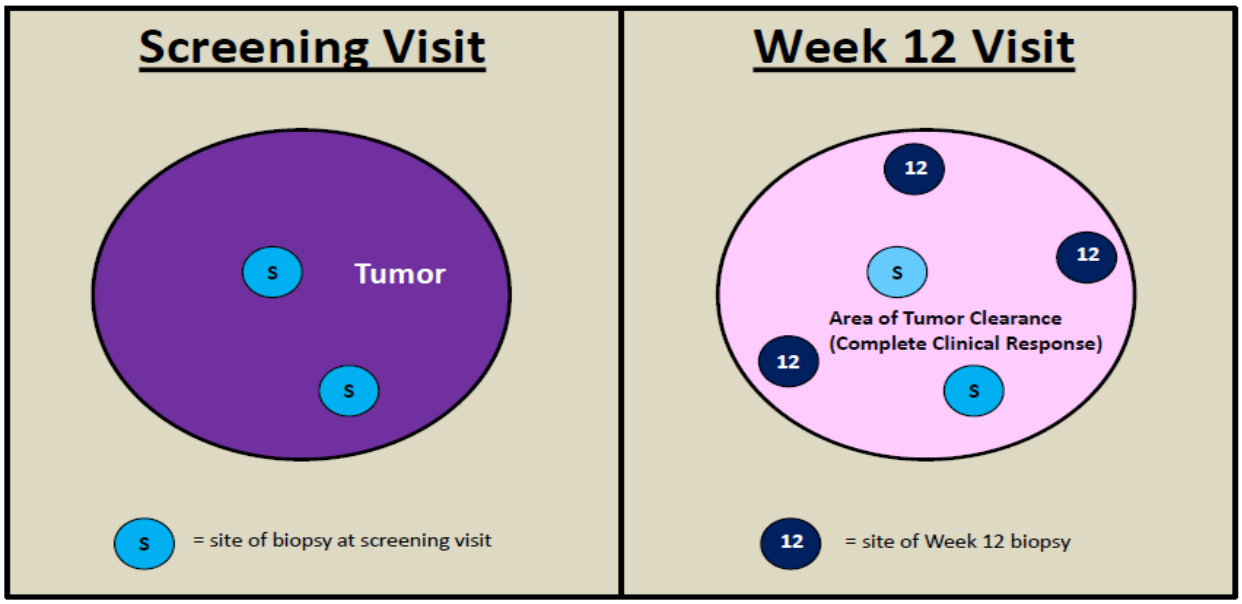

Figure 1. Site of Week 12 biopsies for tumors with exhibiting complete clinical response.

For lesions that display partial clinical response or stable disease by clinical response evaluation, "Residual Tumor Assessment" and "Area of Tumor Clearance Assessment" will be performed (See Figure 2.).

Residual Tumor Assessment

A single 2-mm or 3-mm punch biopsy or up to three 2-mm or three 3-mm sampling punch biopsies will be performed on the residual tumor.

- Biopsy must be performed in area not previously biopsied.
- Biopsy of residual tumor should be performed at least 1 mm from the peripheral margin of visible or palpable lesion
- Tumor biopsies performed at Week 12 visit will comprise no more than 10% of visible lesion surface area.

Area of Tumor Clearance Assessment

Up to three 2-mm or three 3-mm punch biopsies will be performed on the area of tumor clearance at Week 12 when possible.

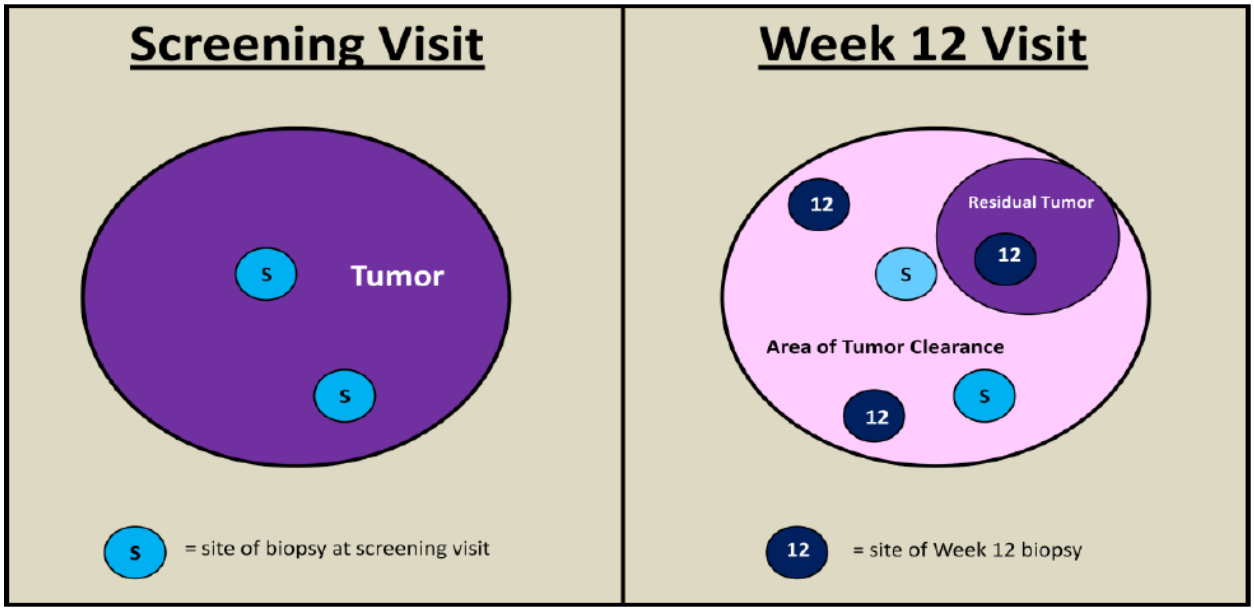

Figure 2. Site of Biopsies at Pre-study Screening Visit and Week 12 visit for tumors exhibiting clinical partial response or stable disease.

6.1.4 End of Treatment visit (Week 24)

Any unused study drug will be collected.

After 24 weeks of treatment, all subjects will undergo sampling biopsy/biopsies. If residual histologic disease is detected, surgical excision will be performed within 4 weeks of last dose of study drug. If no histologic evidence of disease is observed, subjects will enter the observation period and be followed clinically every 3 months up to one year. (See Appendix 5, Figure 1 and Figure 2.)

Biopsies at Week 24 visit will be performed in similar manner as performed at the Week 12 visit.

For lesions that the investigator has determined to show complete clinical response at Week 24 visit, sampling biopsy will be performed at the farthest edge(s) of pre-biopsy lesion compared to location of initial punch biopsy/biopsies at Pre-study Screening Visit and sites of biopsies performed at Week 24 visit (See Figure 3). Up to three 2-mm or three 3-mm punch biopsies will be performed on the area of tumor clearance at Week 24 when possible. Tumor biopsies may comprise no more than 10% of visible lesion seen at screening visit.

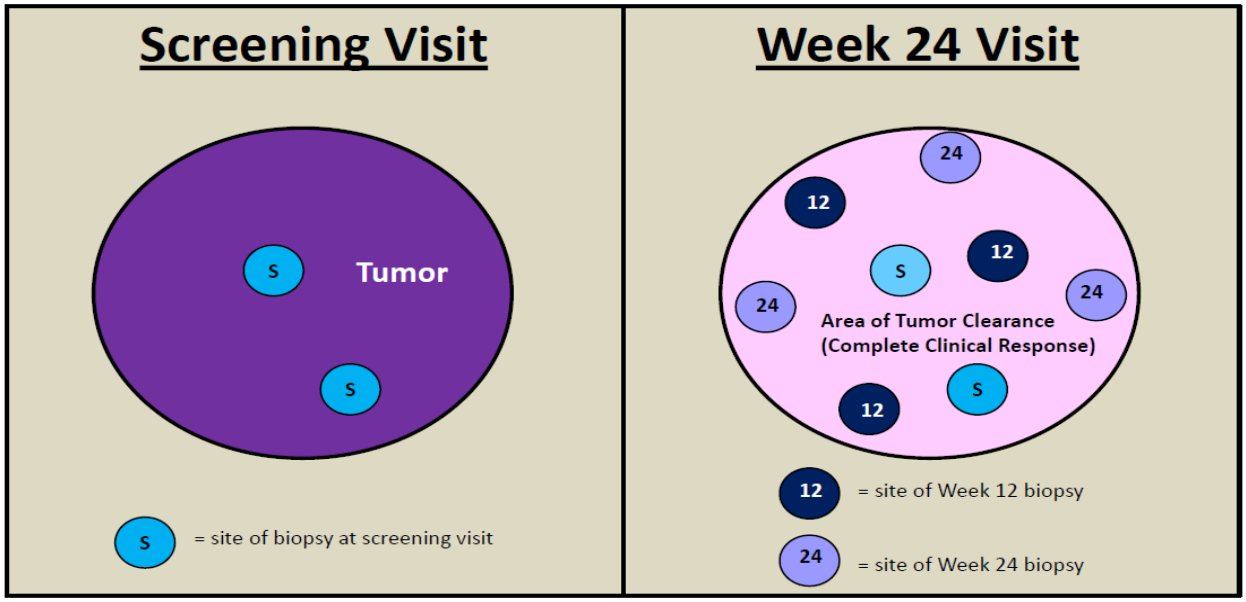

Figure 3. Site of biopsies for tumors displaying clinical complete response at Week 24 visit.

For lesions that display partial clinical response or stable disease by clinical response evaluation, "Residual Tumor Assessment" and "Area of Tumor Clearance Assessment" will be performed (See Figure 4)

Residual Tumor Assessment

A single 2-mm or 3-mm punch biopsy or up to three 2-mm or three 3-mm sampling punch biopsies will be performed on the residual tumor.

- Biopsy must be performed in area not previously biopsied.
- Biopsy of residual tumor should be performed at least 1 mm from the peripheral margin of visible or palpable lesion
- Tumor biopsies performed at Week 24 visit will comprise no more than 10% of visible lesion surface area.

Area of Tumor Clearance Assessment

Up to three 2-mm or three 3-mm punch biopsies will be performed on the area of tumor clearance at Week 24 when possible.

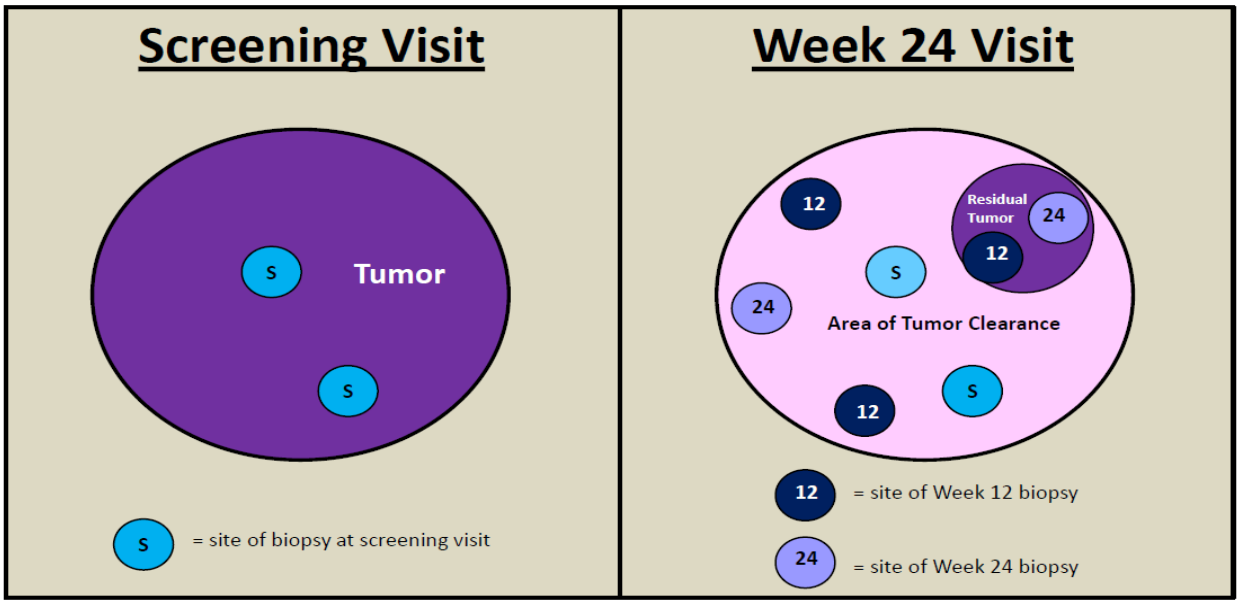

Figure 4. Site of biopsies for tumors that display partial response or stable disease at Week 24 visit.

6.1.5 Early Termination

If a subject discontinues from the study early (due to patient decision to discontinue or disease progression), the study procedures will be completed as described for Week 24.

6.1.6 Surgery visit

Subjects that are found to have histologic evidence of disease on biopsies performed at Week 24 visit will undergo surgical excision. This visit should be scheduled to occur with 4 weeks of last dose of study drug and will be performed as standard of care treatment.

For lesions that display clinical partial response or stable disease and that show histologic evidence of disease on sampling biopsy at Week 24 visit, residual visible or palpable tumor of target lesion will be removed using the standard Slow Mohs micrographic surgery, margin-controlled excision with rush permanent sections. Two types of specimens will be surgically removed at the time of surgical excision. First, the area of known BCC will be excised and will include the pre-biopsy area. This specimen will be labeled the tumor "debulking" specimen.

Second, marginal tissue will be excised in an attempt to completely remove the tumor until clear surgical margins are obtained, providing the patient the known standard of care. This tissue will be labeled "tumor margins" specimen. Peripheral and deep margins will be examined and recorded if positive or negative. If either peripheral or deep margins is positive, additional surgical excisions will be done in the Mohs tissue orientation fashion until no tumor cells are observed and surgical margins are deemed negative, as is standard of care. In the event that only superficial BCC (sBCC) remains at the surgical margin, it will be at the discretion of the managing physician if further surgery, an alternative treatment modality, or observation will occur.

For lesions that were deemed by investigator to exhibit complete clinical response at week 24 visit, but were found to have residual disease on the sampling biopsy at week 24 visit, the debulking specimen will include area of known BCC as seen on histology.

6.1.7 Study Exit Visit (Post-Surgery Visit)

This study visit should be scheduled to occur within 4 weeks of surgical excision or Mohs surgery, performed as standard of care treatment.

The following procedures will be performed:

- Assessment of any changes (deletions, additions, or dose modifications) to medications (noting exclusions, restrictions, and prohibited medications)
- Complete physical examination including general appearance, skin exam, and visual inspection of surgical site of target lesion(s).
- Vital signs (BP; heart or pulse rate; and oral, tympanic, or temporal temperature).
- Weight and high measurements.
- Urine pregnancy test (α-hCG) only for women who are of childbearing potential.
- Surgical site photography
- Adverse Event (AE) Monitoring.

6.1.8 Observation period

All subjects will be followed for the observation period of 1 year after discontinuation of study medication.

During the observation period the subjects will followed every 3 months for 1 year after last dose.

The following study procedures during observation period:

- Assessment of any changes (deletions, additions, or dose modifications) to medications.
- Complete physical examination including general appearance, skin exam, and visual inspection of target lesion(s) area.
- Vital signs (BP; heart or pulse rate; and oral, tympanic, or temporal temperature).
- Weight and height measurements.
- Urine pregnancy test (α--hCG) only for women who are of childbearing potential for visits within 7 months of last dose of study drug.
- Photography and measurement of target lesion area
- Adverse Event (AE) Monitoring.
- Reminder to use effective measures to avoid pregnancy (for women who are of child bearing potential for visits within 7 months of last dose of study drug).
- PRO questionnaires will be performed by the subject (SKINDEX-16 and Functional Assessment of Cancer Therapy – General (FACT-G) at first visit during Observation period (3 months after discontinuing treatment).

If a subject is noted to have a recurrence of target lesion or new lesions suspicious for BCCs on any part of the body, biopsy will be performed to confirm diagnosis. If pathology is consistent with basal cell carcinoma, the subject will exit the Observation period and all treatment options

will be discussed with the subject. If Mohs micrographic surgery is determined to be the best therapeutic option, surgical excision and study procedures will be performed as described in Section 6.1.6.

Subjects who underwent surgical excision of the target lesion may elect to be followed by phone contact every 3 months to provide information on the status of the surgical site and occurrence of any adverse events.

6.2 METHODS OF ASSESSMENT

6.2.1 Measurement of Target Tumor

At the treatment initiation visit, the baseline size of the target tumor will be determined by measuring the 2 largest perpendicular diameters of the target tumor. Target tumor size will be measured at each visit

6.2.2 Clinical response evaluation of target lesion

Measurements of longest length and perpendicular diameter of target lesion(s) will be recorded at each interval visit and compared template map drawn treatment initiation visit.

Complete response will be defined as the disappearance of a palpable or visible tumor.

Partial response will be defined as a reduction of more than 50% in the diameter of a palpable or visible tumor.

Stable disease will be defined as no change in diameter of palpable or visible tumor or a reduction of up to 50% in the diameter of a palpable or visible tumor.

Disease progression will be defined as increase of 20% in either perpendicular diameter of a palpable or visible tumor.

6.2.3 Measurement of Wound Size

Wound size will be measured post-excision to all subjects.

6.2.4 Photographs of Target Tumor

Photographs of the target tumor will aid in tracking the changes in the tumor. Photographs of the target tumor should be taken at the pre-study screening visit before and after biopsy, at the treatment initiation visit, at each interval visit, at the Mohs surgery visit, and at study exit visits.

6.3 HISTOPATHOLOGIC EVALUATION

6.3.1 Histologic Subtype Definitions

Histologic subtypes will be assigned according to the standard classification into infiltrative/morpheaform, nodular, or subtypes (Sexton et al, 1990.) Tumors with more than one subtype (i.e. "mixed" subtype) will be categorized by the most aggressive subtype. The tumor subtypes will also be recorded by their percentage comprising the BCC tumor.

Histologic subtypes will be defined as Table 1.

Histologic subtype	Definition
Nodular (70%)	Large and small, well-circumscribed nests of basaloid cells in the dermis, accompanied by slit-like retraction from surrounding stroma
Superficial (10-15%)	Proliferation of atypical basaloid cells parallel and superficially confined to the epidermis with slit-like retraction of the palisaded basal cells from subjacent stroma
Morpheaform (5-10%)	One to two cells thick columns of basaloid cells enmeshed in a dense collagenized stroma containing proplastic fibroblasts. The tumors are poorly demarcated, showing widespread invasion of the reticular dermis and penetration in the subcutaneous tissue
Infiltrative (5-10%)	Irregularly sized and shaped nests of tumor cells with sharp angulation of their peripheral contours and occasional foci of slit-like retraction; frequently fibrotic stroma with plumb desmoplastic stromal fibroblasts.

Table 1. Histologic classification of BCC (Adopted from Mosterd et al 2011.)

6.3.2 Pre-study Screening Visit biopsy specimens

Biopsy specimens will be processed by Saint Louis University Department of Dermatology's Dermatopathology Laboratory for hematoxylin and eosin (H&E) assessment and immunohistochemical staining. Histologic assessment will be performed by a board-certified Dermatopathologist. If pathology of the target lesion does not demonstrate basal cell skin cancer, the subject will be excluded from the study.

Breslow depth or "invasion index" of deepest basal cell skin cancer cells will be recorded. This may include small nests of cells outside of the bulk of the tumor.

The thickness of the tumor will be measured from below the stratum corneum to the bottom of the deepest tumor nest using an ocular micrometer (Pierre Verniers method) to the precision of 0.1 mm. Tumor thickness and investigation of disease-free deep margin will be defined as at least 0.1 mm of tumor-free tissue.

If more than one sampling biopsy was performed on a target lesion, the most aggressive subtype and the depth of the deepest tumor cells on any biopsy will be recorded.

In tumors with multiple subtypes, a diagram will be created to denote areas of each histological subtype to determine anatomic location of cells of different subtypes and depth of tumor cells of different histological subtype**.**

Photography of pathologic slide will be performed.

Immunohistochemical evaluation of tumor tissue will also be performed in order to estimate the cellular density and composition of the pre-treatment lesion.

6.3.3 Week 12 and Week 24 Visit biopsy specimens

- Week 12 and Week 24 biopsy specimens will be processed and examined in the manner outlined for biopsies performed during the screening visits.

- **Residual tumor**
  - Evidence of any histologic change in residual tumor tissue compared to pre-treatment biopsy specimens
  - Estimate of changes in cellular density and composition compared to screening visit

- **Area of Tumor Clearance**
  - Assessment of histologic clearance in areas of apparent clinical tumor clearance

Additional immunohistochemical staining with anticytokeratin (AE1/AE3) and Ber-EP4 will be performed to delineate tumor from inflammation when necessary.

6.3.4 Surgical Excision specimen

Pathologic evaluation of "debulking" specimen and "tumor margins" specimen will be performed in the manner of the biopsy and Week 12 specimens. Breslow depth of area this measurement will be used to determine quantitative histological response of deepest part of lesion. Histopathologic subtype(s) will be recorded, and comment made as to tissue location of each subtype noted. Photography of surgical specimens will also be performed. In a manner as performed on biopsy specimen, diagram will be created to include tracing of different areas of histological subtype. Depth of deepest tumor cells will be recorded. A percentage estimate will be determined as to the histologic subtypes of the majority of tumor cells within the surgical specimen.

FUTURE USE OF BLOOD, TISSUE OR DATA

The investigator will request permission from subjects to allow tissue to be used in the future for research purposes. Subjects may decline future use of tissue. The specimens taken during the tissue collection as specified for this research study include the sample to be used in the future. No extra tissue will be taken for future research purposes.

The tissue may be used to further evaluate Basal Cell Skin Cancer. All tissue specimens will be labeled with a study ID code, and study assigned pathology number. The investigator will maintain a list of the participants and code numbers in a locked file with access limited to the study team.

The investigator may share the tissue (with code only) with other researchers at Saint Louis University and at other research centers. Other investigators will not have access to identifying information.

All specimens will be kept indefinitely, and will be maintained in the Biospecimens Accessioning and Processing (BAP) Core Lab at Mayo Clinic Florida. .

6.4 INTERCURRENT DISEASE TREATMENT AND CONCOMITANT MEDICATIONS

6.4.1 Intercurrent Disease Treatment

Subjects who develop additional tumors during the study may receive conventional forms of treatment for the non-target tumors during the treatment and follow-up periods if the following criteria are met:

- The tumor(s) are sufficiently distal from the target tumor to prevent interference with the target tumor (at least 5 cm)
- The treatment is not listed in Exclusion Criteria
- The treatment will not affect the target lesion(s)

6.4.2 Concomitant Medications

The investigator will record any medications given in treatment of AEs on the appropriate CRF page. Any medication taken by the subject during the course of the study should also be recorded on this form. Local anesthetics used for pre-study biopsies and target tumor excisions need not be recorded. Over-the-counter medicinal products (dietary supplements, herbal medications, etc) should also be recorded. Data recorded will include name of the medication, dose, unit, frequency, route, indication, and start and stop dates.

6.5 SUBJECT COMMITMENT TO STUDY

The duration of each subject's participation in the study will be approximately 28 weeks. Subjects will be expected to visit the clinic for 10 scheduled study visits. Up to 12 (three sampling biopsies on 4 possible target lesions) will be performed at the pre-study screening visit, 12 punch biopsies at Week 12 visit and a complete Mohs excision may be performed at the target tumor site at the Mohs procedure visit within 4 weeks after the end-of-treatment visit. Subjects are expected to adhere to daily administration of medication during 24 weeks of treatment and take appropriate measures to avoid pregnancy and avoid donation of blood up to 9 months after last dose.

6.6 SUBJECT WITHDRAWAL OR DISCONTINUATION

6.6.1 Subject Stopping Criteria

The following objective measures have been defined as subject stopping criteria. If a subject presents with any of these characteristics, treatment with vismodegib will be stopped before 24 weeks:

1) Pregnancy
2) 20% increase in target lesion tumor size

6.6.2 Other Withdrawal or Discontinuations

Subjects may withdraw themselves or have the investigator withdraw them from the study at any time without prejudice to their future medical care. Any subject who does not comply with the inclusion/exclusion criteria will be withdrawn from further participation in the study. Subjects may also be discontinued if the investigator has determined that the subject has AEs of severe intensity or duration to warrant discontinuation. If a subject discontinues due to AE, the subject will be followed until the AE has resolved.

Any subject who receives study medications or placebo must complete EOT procedures including the Mohs surgical excision, and the investigator must complete the end-of-study Subject Status form.

The investigator is encouraged to carefully select subjects who are likely to complete all study procedures.

6.7 TREATING OVERDOSE

Overdose is unexpected due to the dose level administered with oral administration. There is no information on overdosage in humans. In clinical trials, vismodegib capsule was administered at 540 mg orally once daily; exposure did not increase between 150 mg and 540 mg daily.

6.8 PREGNANCY

Vismodegib is teratogenic. As clinical studies of vismodegib have not been conducted in pregnant humans, subjects who become pregnant during the study must inform the investigator immediately of their pregnancy, and agree to provide follow-up information regarding the outcome of the pregnancy. In addition, there is the unknown potential irreversible affect on fertility with data showed in earlier studies of amenorrhea. Subjects (male and female) who desire to conceive in the future are excluded from the study.

Females of reproductive potential must use effective measures to avoid pregnancy during therapy and for 1 month prior to the start of the study medication, and for 9 months after completing therapy. Male patients must use effective measures to avoid pregnancy in their partner, even after vasectomy, during sexual intercourse with females during treatment and for 3 months after the last dose to avoid exposing a pregnant partner and the unborn fetus to vismodegib. Vismodegib is contraindicated in nursing mothers during treatment and for 9 months after the last dose. In addition, subjects will be instructed not to donate blood or blood products while on treatment and for 9 months after the last dose of vismodegib.

The anticipated pregnancy prevention program includes the following measures for women of childbearing potential:

a) two negative pregnancy tests with a sensitivity of at least 25 mIU/mL at least 19 days apart prior to starting study medication. For patients with regular menstrual cycles, the second pregnancy test should be done during the first 5 days of the menstrual period immediately preceding the beginning of therapy and after the patient has used 2 forms of contraception for 1 month. For patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding, the second pregnancy test must be done immediately preceding the beginning of therapy and after the patient has used 2 forms of contraception for 1 month.

b) Urine pregnancy test at each visit.

c) Female patients must use 2 effective methods to avoid pregnancy for 1 month prior to start of study medication, during therapy, and for 9 months after completing therapy.

Male patients must use effective measures to avoid pregnancy in their partner at all times, even after vasectomy, for 3 months after the last dose(condom with spermicide is the effective method of contraception per approved labeling for vismodegib).

a) Study medication will NOT be dispensed at each visit until the results of pregnancy have been reviewed by the study investigator.
b) Reminder to use effective measures to avoid pregnancy will be performed throughout the study treatment for both men and women

Female patients do not have to follow the aforementioned measures to avoid pregnancy IF they agree to abide to the following conditions:

- have stopped having their period for 12 months in a row (menopause) and their doctor says they are in menopause or clinically fit the criteria for menopause
- had both of their ovaries or uterus taken out by surgery
- their ovaries do not work and they cannot get pregnant (confirmed by their doctor)

7. REPORTING OF ADVERSE EVENTS

7.1 ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to study drug, all events of death, and any study specific issue of concern.

7.1.1 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 period, 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.

7.1.2 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).

7.2 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 FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

7.2.1 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 study treatment and ends 30 days 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. Any subject who has an adverse event deemed related to the study treatment in this trial, will be followed until reversibility is established. This may occur after study completion at the subject's regular clinic follow-up visits.

7.2.2 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through general skin 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 study drug, 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 study drug; and/or the AE abates or resolves upon discontinuation of study drug or dose reduction and, if applicable, reappears upon re-challenge.

No

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

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

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

7.3 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

7.3.1 Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should 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?"

7.3.2 Specific Instructions for Recording Adverse Events

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

7.3.2.1 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 ok to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

7.3.2.2 Deaths

All deaths that occur during the protocol-specified AE reporting period 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".

7.3.2.3 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").

7.3.2.4 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.

7.3.2.5 Pregnancy

If a female subject becomes pregnant while receiving investigational therapy or within 9 months after the last dose of VISMODEGIB, a report should be completed and expeditiously submitted to the Genentech, Inc. 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.

7.3.2.6 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.

7.3.2.7 Reconciliation of Study Drug Supply

Investigators should conduct reconciliation for the product. Genentech and the 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 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.

7.3.2.8 SAE Reporting

Investigators must report all SAEs to Genentech within the timelines described below. The completed Medwatch/case report should be faxed immediately upon completion to Genentech Drug Safety at:

(650) 225-4682
OR
(650) 225-5288

- Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.
- Serious AE reports that are related to study drug will be transmitted to Genentech within fifteen (15) calendar days of the Awareness Date.
- Serious AE reports that are unrelated to study drug 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 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, at most, on a quarterly report to Genentech.

Note: Investigators should also report events to their IRB as required.

7.3.3 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 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 each investigational product 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/Safety/MedWatch/HowToReport/DownloadForms/default.htm

7.3.4 Additional Reporting Requirements for IND Holders

For Investigator-Sponsored IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report:
The 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 study drug. An unexpected adverse event is one that is not already described in the study drug Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

15 Calendar Day Written Report:
The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of study drug. An unexpected adverse event is one that is not already described in the study drug investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a Medwatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

FDA fax number for IND Safety Reports:
Fax: 1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech Drug Safety: Fax: (650) 225-4682 or (650) 225-5288

And to the Site IRB:

Saint Louis University
Institutional Review Board
3556 Caroline Street
Caroline Building C110
St. Louis, MO 63104
Phone: 314-977-7744
Fax: 314-977-7730

For questions related to safety reporting, please contact Genentech Drug Safety:
Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-5288

IND Annual Reports
All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. Copies of such reports should be faxed to Genentech Drug Safety: Fax: (650) 225-4682 or (650) 225-5288

7.4 Data Safety Monitoring Plan

Due to the potential risk of adverse side effects, patients will be monitored closely during the study period as described in protocol Section 6, 7.1, 7.2 and section 12.7. Study participants will be able to contact one of the study physicians at any time with questions and concerns. All adverse events will be recorded, scored for severity and for relationship to the study as described in Section 7.3. Adverse event data will be reviewed periodically by the study team. All serious and unexpected adverse events will be reported to the IRB and regulatory authority as described in Section 7.3.

8. MATERIALS AND SUPPLIES

8.1 STUDY DRUG

Study drugs will be provided by Genentech or a designated facility working under contract for Genentech to Saint Louis University, Department of Dermatology.

Study drug should be taken at approximately the same time each day, with or without food. Capsules must be swallowed whole and must not be opened under any circumstances. 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 instructed to bring all unused capsules to each study visit for assessment of compliance.

Sufficient drug supplies for 36 subjects will be packaged, and labeled. Drug supplies will be numbered in sequential order. The study center should assign study drug in sequential order. The remaining supplies will be made available should additional subjects or study centers be required to reach the enrollment goal of 36 total subjects.

Small, resealable plastic bags will be given to each subject for returning used and opened medication to the clinic. Resealable bags will be dispensed at the same time medication is dispensed.

At the Treatment Initiation Visit (Baseline/Day 1), and at the monthly interval, the study center will dispense a bottle of study drug to be used until the next interval visit at which drug will be dispensed.

At each time medication is dispensed:

- Dispense a resealable plastic bag
- Write the date dispensed on both sides of the 2-part label, located on the carton
- Affix the detachable portion of the 2-part label to the appropriate CRF page

All medication, both used and unused will be destroyed according to standard operating procedure at Saint Louis University at the completion of the study.

8.2 STUDY DRUG LABELING

Clinical supplies will be labeled with the following minimum information:

- Protocol ID Number
- Investigator Name
- Drug name (or description)
- Drug strength
- Dosage form
- Quantity per container
- Instructions for use
- Keep out of the reach of children
- Storage conditions

- Expiration date
- Investigational drug caution statement(s)
- Subject number
- Date dispensed (to be written in)
- Subject initials (to be written in)

Each time study drug is dispensed, study center personnel should write the date the drug is dispensed and the subject initials on both the permanent and detachable labels of the bottle. The study center should also complete the Drug Inventory Form each time study drug is dispensed.

8.3 STUDY DRUG INVENTORY AND STORAGE

The investigator will take the following actions with regard to study drugs in concurrence with international regulatory requirements.

1. Upon receipt of clinical study materials the investigator or designated individual on the study team will check the details of the supplies and document receipt on invoice and DAR.
2. The investigator will keep study drugs in a locked and secure storage facility, accessible only to those individuals authorized by the investigator to dispense this study drug. All study drug will be stored separately from any other medications.
3. The investigator or designee will maintain a temperature log to ensure that study drug is stored at manufacturer recommended room-temperature at all times.
4. The investigator or designated individual will maintain an inventory. This will include the description and quantity of study drug received during the course of this study, as well as a record of the materials that are dispensed and returned (how much, to whom, and when). This inventory record shall indicate the quantity and description of all study drugs on hand at any time during the course of the study.
5. At the conclusion or termination of this study, the investigator agrees to conduct a final drug supply inventory, to record the results of this inventory and destroy all remaining study drug on site by IDS.
6. The investigator agrees not to supply study drug to any person except study personnel and subjects in this study.

9. DATA ANALYSIS AND STATISTICAL PROCEDURES

9.1 SAMPLE SIZE DETERMINATION

This is a pilot study to investigate efficacy of vismodegib in different histologic subtypes of BCCs. A total of 36 subjects will be enrolled into the study. The sample size for this study was selected to allow a sufficient number of subjects of histologic subtypes other than nodular BCC, the most common subtype presenting in clinical practices. Superficial BCC and infiltrative/morpheaform subtypes have similar presentation rates. The enrollment method provides assurances that that evaluable data will be available for at least 36 subjects across three subtype groups: infiltrative/morpheaform, superficial, and nodular. Refer to Section 9.2 for details on subgroup type assignment. A sample size of 16 in the nodular group yields a 95% confidence interval of 54%-96% for an observed partial response rate. The nodular group is

included as part of the pilot study, in part, to assess the overall viability of the study. It is important to note that response rate of approximately 75% is anticipated in the nodular group, based on the published literature; the sample size of 16 the nodular group is sufficient to detect this level of efficacy. A sample size of 10 for the infiltrative/morpheaform and superficial BCC groups yields a 95% confidence interval of 10%-70%. Although the confidence intervals are wide, the sample sizes are sufficient to detect a response rate greater the null rate (0%), the expected efficacy level if the treatment had no effect in these histologic subtypes.

9.2 SUBJECT SUB-GROUP ASSIGNMENT

A total of 36 subjects with infiltrative/morpheaform, nodular, or superficial BCC will be enrolled in the study. For patients with multiple BCC lesions, one "target lesion" will be identified and used for subject sub-group assignment for the purposes of enrollment and followed for primary endpoint analysis. For scientific purposes, data from BCC tumors other than "target lesion" will also be collected. The lesion(s) biopsied at Screening Visit will be reviewed and each subject will be assigned to a subtype group as detailed below and in Figure 5.

Step 1. Infiltrative/morpheaform subtype lesion will be given priority in subject sub-group assignment.

Step 2. If a potential subject does not have a possible target lesion that is infiltrative/morpheaform subtype and has a superficial BCC, then the subject will be assigned to the superficial BCC subtype group.

Step 3. If no infiltrative/morpheaform BCC or superficial BCC are identified, then nodular BCC will be eligible for enrollment.

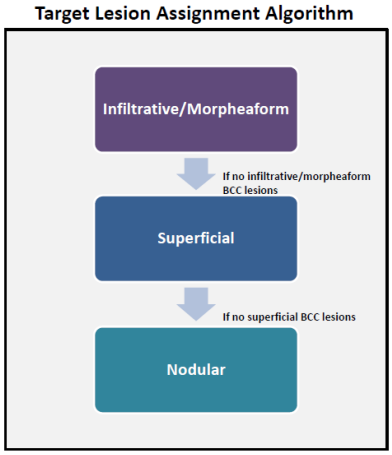

Figure 5. Target Lesion Assignment Algorithm

If there are two lesions that may be eligible for target lesion assignment based on histologic subtype, then the lesion with larger clinical dimensions will be designated the "target lesion". See Appendix 10, Target Lesion Assignment Examples for more information.

This "Target Lesion Assignment Algorithm" will continue in this fashion until any two of the subtype groups reaches 26. This is to ensure that each subgroup has at least 10 subjects. At this point, subjects enrolled must have at least 1 BCC of the remaining subtype group.

9.3 PARAMETERS TO BE MEASURED:

9.3.1 Primary Endpoints

Efficacy of vismodegib in treatment of target lesion(s) by clinical and histologic response evaluation.

9.3.1.1 Clinical Response

- Comparison of number of target lesions in each of the following groups:
  - Complete response, partial response, stable disease, or disease progression as defined above

- Overall response rate and best overall response rate
- Comparison of maximum diameter and lesion area of target lesion(s) post-biopsy and at End of Treatment visit
- Comparison of dimensions of tumor within "debulking" specimen at surgery visit with dimensions of pre-biopsy tumor

9.3.1.2 **Histologic response (at Week 12 and Week 24/Surgical Visit)**

- **Residual tumor**
  - Evidence of any histologic change in residual tumor tissue compared to pre-treatment biopsy specimens
  - Estimate of changes in cellular density and composition at Week 12 and Week 24/Surgical Visit

- **Area of Tumor Clearance**
  - Assessment of histologic clearance in areas of apparent clinical tumor clearance at Week 12 and Week 24, and/or Surgical Visit

- Comparison of deepest "invasion index" on biopsy specimen, at Week 12 biopsy, and "debulking" specimen or "tumor margins" specimen" at Surgery visit
- Histologic subtypes observed on pathologic specimens (Screening visit and Week 12 and Surgical excision specimen) Location and depth of specific tumor cells of each histologic subtype on biopsy, week 12 biopsy, and Surgical excision specimens
- Percentage of each histologic subtype in tumor specimen on biopsy, Week 12 biopsy and surgical excision specimens

9.3.2 **Secondary Endpoints**

9.3.2.1 **Onset of efficacy**

- Onset of efficacy during 24 weeks of treatment by clinical and histologic response
  - Histologic response measured at 12 weeks and after 24 weeks of treatment
- Interval to best overall response during 24 weeks of treatment by clinical response

9.3.2.2 **Safety and Tolerability**

Monitoring of adverse effects, onset of specific adverse effects and adverse effects that lead to early termination of treatment.

9.3.2.3 **Patient Reported Outcomes/Quality of Life**

Evaluation of patient reported outcome (PRO) measures before, during 24 weeks of treatment with vismodegib through SKINDEX-16 and FACT-G questionnaires. (See Appendix VI and VIII.)

9.3.3 **Efficacy Analysis**

9.3.3.1 **Analysis of Primary Endpoints**

9.3.3.1.1 Clinical Response

Comparison of dimensions of tumor within debulk specimen at surgery visit with dimensions of post-biopsy tumor as drawn on template at screening visit will be assessed by a t-test for independent samples.

Sub-group analyses by histologic subtype will be conducted by demographic factors including: gender, race, and anatomic location of target lesion will also assessed for any independent association with clinical response. Statistical significance was defined by alpha 0.05. All analysis was performed using SPSS (PASW) version 18.

Analysis of the following subgroups will be performed:

- Nonaggressive subtypes vs. Aggressive subtypes
- Clinical subtypes (infiltrative/morpheaform, nodular, and superficial)

9.3.3.1.2 Histologic response

Chi-square analysis will be performed to assess histologic response of residual tumor and area of tumor clearance for all tumors and by histologic subtype.

Comparison of the "invasion index" on biopsy specimen and excision specimen will be assessed by a t-test for independent samples.

Histologic subtypes observed on biopsy specimen and excision specimen will be depicted in a frequency table and proportions of each histologic subtype will be compared using a t-test for dependent samples.

Size estimate of tumor based on biopsy specimen to actual size of tumor specimen on day of surgical excision or Mohs surgery will be assessed by a t-test for independent samples.

Location and depth of specific tumor cells of each histological subtype on biopsy and surgical specimen.

9.3.3.2 Analysis of Secondary Endpoints

9.3.3.2.1 Onset of Efficacy

For each target lesion, interval to clinical response and best overall response will be recorded and a histogram depicting response to treatment will be created. For subjects who discontinue treatment early due to disease progression or personal preference, interval of treatment will be recorded.

9.3.3.2.2 Safety and Tolerability

Graded adverse events (number and percent) will be reported according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.0). (See Appendix X.) Adverse events that lead to early discontinuation of treatment will also be tabulated.

Percentage of patients able to complete 24-week treatment regimen will be recorded. For patients that are unable to complete 24-week treatment regimen, average and median time of treatment will be assessed.

9.3.3.2.3 Patient Reported Outcomes

Quality of life (QoL) during study participation and patient impression of adverse effect tolerability will be assessed.

QoL will be assessed using patient reported outcomes (PRO) questionnaires at Baseline, Week 8, Week 16, and Week 24 study visit/End of treatment visit using the following validated measures:

- FACT-G (v. 4), Functional Assessment of Cancer Therapy-General (Appendix VIII)
- Skindex-16, a quality-of-life measure for patients with skin disease (Appendix VI.)

9.4 SAFETY ANALYSES

All safety measures will be analyzed using the ITT data set. For all statistical tests, an overall test will be done first to compare the safety measures among all groups

9.4.1 Adverse Events

Adverse events will be summarized by using the NCI Common Terminology criteria for AE, version 4 (Appendix IX). The incidence of AEs (percent of subjects reporting the AE at least once). A separate tabulation of incidences will display only AEs coded as "probably" or "possibly" related to treatment.

9.4.2 Vital Signs and Dermatological Examination Data

Dermatological Examination findings and vital signs will be tabulated. Any clinically significant changes in either will be discussed in the study report.

10. DATA SECURITY & CONFIDENTIALITY PLAN

Clinical data will be collected at the time of enrollment from the patient's medical record.

Data will be entered into the study electronic database. The Study Coordinator will also use hard copy forms as worksheets. The paper worksheets will be retained at the Dermatology Clinic in a locked file cabinet within a locked office until the study is complete and all study analyses and publications have been accomplished. These paper worksheets will be subject to site safety monitoring reviews.

The data elements obtained and recorded when a patient is enrolled into the study are described in section 11 of the protocol.

When the subject is enrolled in the study, a study number will be automatically provided. The research team will recode the dates of enrollment and birth to calculate the subject's age, in days, and the resulting analytical database fulfills the definition of a de-identified database according to HIPAA definitions.

10.1 HARD-COPY DATA FORMS

The investigators have a dedicated, locked research room within the Dermatology offices, and the building has 24 hour on-site security guards. Data forms will include the aforementioned data points, and will be kept in research binders in a locked cabinet.

10.2 ELECTRONIC DATA

User authentication is maintained with user/group domain-level security, centralized to desktop computers that are password-protected. There will be no transfer of data over public networks. The de-identified electronic database, which contains raw research data will also be pass-word protected and maintained on the Saint Louis University Dermatology department's secured server. Once the data is ready for analyses, it will be coded and locked. Analytical files will contain no identifiers and will contain accumulated data for report of findings.

10.3 CONFIDENTIALITY SECURITY PLAN

The investigators and research staff are fully committed to the security and confidentiality of all data collected this study. All personnel involved in this study have signed confidentiality agreements concerning all data encountered in the study clinic. All personnel involved with this study have completed Human Subjects Protection and HIPAA education.

11. FINAL STUDY REPORT

A final study report will be prepared by the Principal Investigator at Saint Louis University, Department of Dermatology.

12. ADMINISTRATIVE PROCEDURES

12.1 ETHICAL APPROVAL

An IRB should safeguard the rights, safety, and well being of all study subjects. The investigator is responsible for providing the IRB with all necessary documents for review. This may include the following:

- Study protocol/amendment(s)
- Written subject information/informed consent form and updates
- Subject recruitment procedures (e.g., advertisements)
- Investigator brochure/product information
- Information about payments and compensation available to subjects
- Investigator's current curriculum vitae and/or other documentation evidencing qualifications

This study will only be undertaken when full approval has been obtained from the appropriate IRB and a copy of the approval is received by Genentech. The approval letter or notice by the IRB must contain:

- Name and address of IRB
- Date of meeting
- Sufficient information to identify the version of both the protocol and subject information/informed consent documents
- Sufficient information to identify all other documents reviewed

The investigator must submit all subsequent protocol amendments to IRB for approval, according to local practice. The IRB should also be notified of any administrative changes made to the protocol.

12.2 REGULATORY APPROVAL

This study requires application to the FDA for approval under the Investigational New Drug (IND) -application.

12.3 STUDY PERSONNEL

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated significant study-related duties. In addition, he/she should maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on study related documentation, including CRFs.

12.4 PARTICIPANT COMPENSATION AND ESEARCH-RELATED COSTS:

There will be no cost for procedures that are a result of study participation while in the trial. Procedures (skin biopsies and surgical excision) that are standard of care will be billed to the patient's insurance company. Compensation for subject time and inconvenience is $30 for each study visit. If all 10 scheduled visits are kept, a subject will receive a total of $300. A prorated amount will be provided for subjects who do not complete every study visit. Payment will be issued 4-6 weeks after study completion or study termination.

12.5 PRESTUDY DOCUMENTATION REQUIREMENTS

Before shipment of study drug, the investigator must provide Genentech with the following documents:

1. Final version of this protocol including any amendments in place before study initiation.
2. Curriculum vitae or other statement of qualification of the principal investigator. The minimum information to be included is name, address, appointment, qualifications, and previous and current work experience.
3. IRB approval letter.
4. Signed and dated contract and/or research agreement between Genentech and the investigator.

12.6 COMPLETION AND RETURN OF CASE REPORT FORMS

The investigator is responsible for the quality of the data recorded in the CRF. The data recorded should be a complete and accurate account of the subject's record collected during the study.

The investigator and study monitor will identify any data that will be recorded directly on the CRF and considered as source data (i.e., no prior written or electronic record of the data).
All CRF entries should be made in black ink for duplication purposes. The investigator must review all entries for completeness and correctness. When changes or corrections are made on any CRF, the investigator or authorized persons must draw a single line through the error then initial and date the correction as well as stating the reason for the error, except when due to a transcription error. The original entry should not be obscured.

The investigator agrees to complete and sign CRFs in a timely fashion after completion of each subject and make them available to the study monitor for full inspection. In addition, any data queries prepared after the original CRFs have been completed should be answered promptly.

Before acceptance, the clinical monitor will review the CRFs for completeness and adherence to the protocol.

12.7 STUDY MONITORING

The study will be monitored by qualified personnel from the Department of Dermatology at the Saint Louis University. A data monitoring plan will be developed prior to study initiation.

The investigator or designated person should adhere to regulatory requirements and institutional policies for research records documentation and agree, as a minimum requirement, to record the following information in the subject source notes:

- Protocol ID number, brief description or title of study
- Statement that subject has given written consent
- All visit dates
- All AEs
- All concomitant medications
- Primary efficacy details (as defined by the protocol)

Source data verification will be performed by the clinical monitor at each monitoring visit.

12.8 QUALITY ASSURANCE PROCEDURES

Quality assurance activities undertaken during this study include monitoring and source data validation by the study monitor (see Section 13.6).

12.9 AMENDMENT TO PROTOCOL

The investigator will not amend this protocol unless agreed upon in advance by Genentech. Approval of the amendment by the IRB must be obtained before implementation, with 2 exceptions:

1. When necessary to eliminate apparent immediate hazard to the subject.
2. When the change involves logistical or administrative aspects of the study.

12.10 DEPARTURE FROM PROTOCOL FOR INDIVIDUAL SUBJECTS

Deviations from a written protocol for individual subjects are inherent to clinical research and can be categorized as either departure from protocol or minor deviations. A "Departure From Protocol" is a deviation of such magnitude as to affect the evaluability of the subject or to potentially compromise the statistical analysis. A departure is usually an emergency or other circumstance that requires a decision be made as to whether the subject should be withdrawn from the study. When a protocol departure or suspected departure occurs; it will be only for that subject. The investigator will contact the study monitor or medical monitor by telephone to report the departure. In the event they are not available, the following emergency number is in operation at all times:

Saint Louis University Hospital
(on-call Dermatology Resident)
314-577-8000

The investigator must complete a "Departure From Protocol" CRF entry for each departure.

Minor deviations address procedural issues that do not affect subjects' adherence to protocol requirements to the extent it could compromise their continued participation in the study, or the results of the study. Minor deviations observed for a specific subject, or involving several subjects, must be recorded as a comment on the appropriate CRF page(s) for each involved subject.

12.11 RECORDS OF STUDY

The investigator should retain essential documents until at least 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Genentech.

Records to be retained by the investigator include, but are not restricted to the following:

- Signed and dated study protocol and amendments
- Investigator's brochure and any updates
- Investigator agreement, including financial agreement
- Signed and dated informed consent documents
- Copy of all versions of subject information documents (as appropriate)
- Application(s) to IRB
- Copy of approved advertisements
- IRB approval letter(s)
- IRB composition
- Curriculum vitae of all study personnel
- Pre-study and Follow-up Financial Disclosure Forms
- Clinical laboratory normal ranges and any updates
- Clinical and/or pathology laboratory accreditation certificate or certification of established quality control (QC) and/or external QA or other validations
- Instructions on handling study supplies and study related material (if not included in protocol)
- Details of study material/supplies shipment dates, batch numbers, method of shipping, etc
- Treatment allocation
- Study Initiation monitoring report
- CRFs and source data and primary records upon which they are based
- Serious AE reports
- Notification by Genentech and/or investigator to regulatory authorities/IRB of serious AEs including causality assessments
- Report on any interim reviews done

- Subject identification log
- Subject screening/enrollment log
- Drug accountability logs
- Signature log of persons authorized to make entries and/or corrections on CRFs
- Records of any retained samples (if applicable)
- Interim/Final report(s) to the IRB (as appropriate)
- Signed, final study report (if applicable)
- Manuscript/publications of the study
- Correspondence relating to the study monitor (if different from sponsor)
- Correspondence with the study sponsor
- Correspondence with the IRB

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14. APPENDICES

APPENDIX 1: NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES) BASAL CELL AND SQUAMOUS CELL SKIN CANCERS

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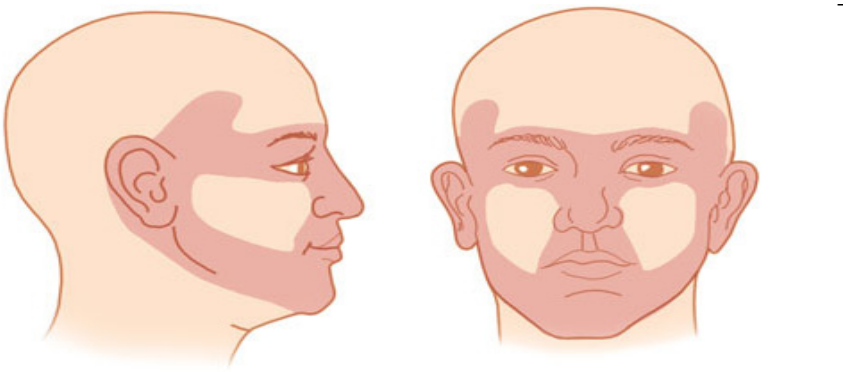
14.1 APPENDIX 1: NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES) BASAL CELL AND SQUAMOUS CELL SKIN CANCERS

http://www.nccn.org/professionals/physician_gls/pdf/nmsc.pdf

14.2 APPENDIX 2: 'MASK AREAS' OF FACE: HIGH RISK ANATOMIC AREAS



Source: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ: *Fitzpatrick's Dermatology in General Medicine*, 7th Edition: http://www.accessmedicine.com

14.3 APPENDIX 3: EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

http://ecog.dfci.harvard.edu/general/perf_stat.html

14.4 APPENDIX 4: REQUIRED ELEMENTS OF INFORMED CONSENT

The Informed Consent must address the following information in simple language, easily understood, and translated when appropriate:

1. Statement that the study involves research.
2. Purpose(s) of the research.
3. Expected duration of subject's participation.
4. Procedures to be followed and identification of any procedures which are experimental.
5. Reasonable foreseeable risks or discomforts to the subject.
    - Risks/discomfort from study procedures Foreseeable risks associated with vismodegib, which include AEs listed in the Investigator's Brochure or package insert
6. Benefits to the subject or to others which may reasonably be expected from the research, including amount and stipulations of monetary compensation.
7. Appropriate alternative procedures or courses of treatment, if any that might be advantageous to the subject.
8. Extent to which confidentiality of records identifying the subject will be maintained.
    - Possibility that representatives of Genentech and the FDA may inspect the records
    - Information on the confidential follow-up form will be held and treated with strict confidentiality, and will be used only in the event that long-term follow-up is needed
9. Compensation and medical treatment available if injury occurs.
   "Genentech will pay medical expenses due to any medical problems caused by vismodegib as specified in the protocol. However one of the risks that you assume by participating in this study is the possibility that the study drug will not be effective for you and will not treat or improve the condition for which you sought treatment. If you suffer from any medical problems from the failure of vismodegib to effectively treat or improve your condition, Genentech will not pay your medical expenses unless another successful treatment was specifically discontinued for this study."
10. Whom to contact for answers to pertinent questions about the research and research subject's rights.
11. Whom to contact in the event of research-related injury to the subject.
12. Participation is voluntary.
    - Refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled
    - Subject may discontinue participation at any time without penalty or loss of benefits to which subject is otherwise entitled

ADDITIONAL ELEMENTS OF INFORMED CONSENT

When appropriate, one or more of the following elements of information shall also be provided to each subject:

13. Particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject may become pregnant) which are currently unforeseeable.
14. Anticipated circumstances under which subject's participation may be terminated by the investigator without regard to subject's consent.
15. Additional costs to the subject that may result from participation in the research.
16. Consequences of subject's decision to withdraw, and procedures for orderly termination by the subject.
17. Significant new findings developed during the course of the research, which may relate to the subject's willingness to continue participation, will be provided to the subject.
18. Approximate number of subjects involved in the study.

14.5 APPENDIX 5: TREATMENT ALGORITHMS

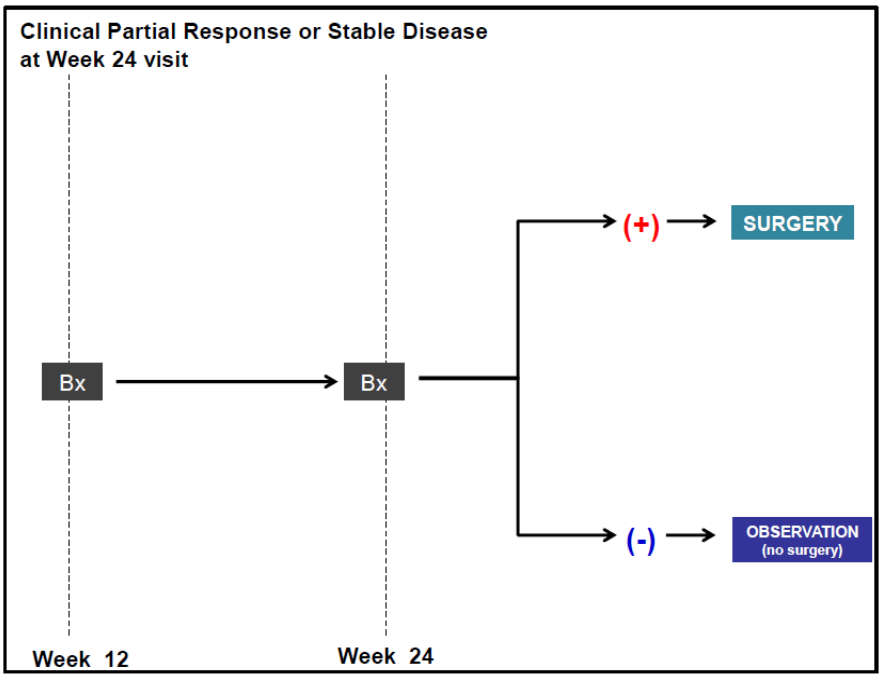


Figure 1.

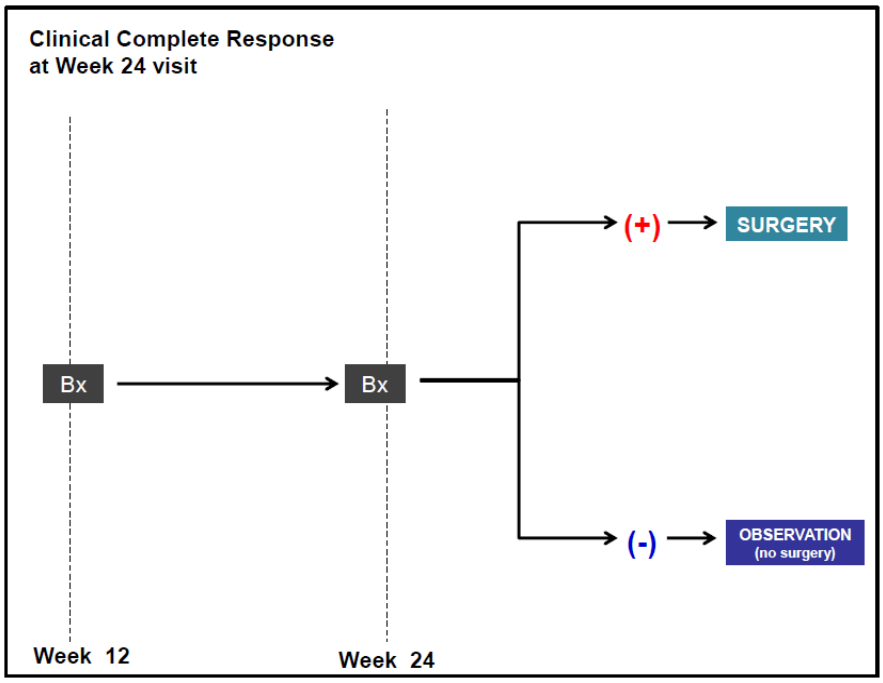


Figure 2.

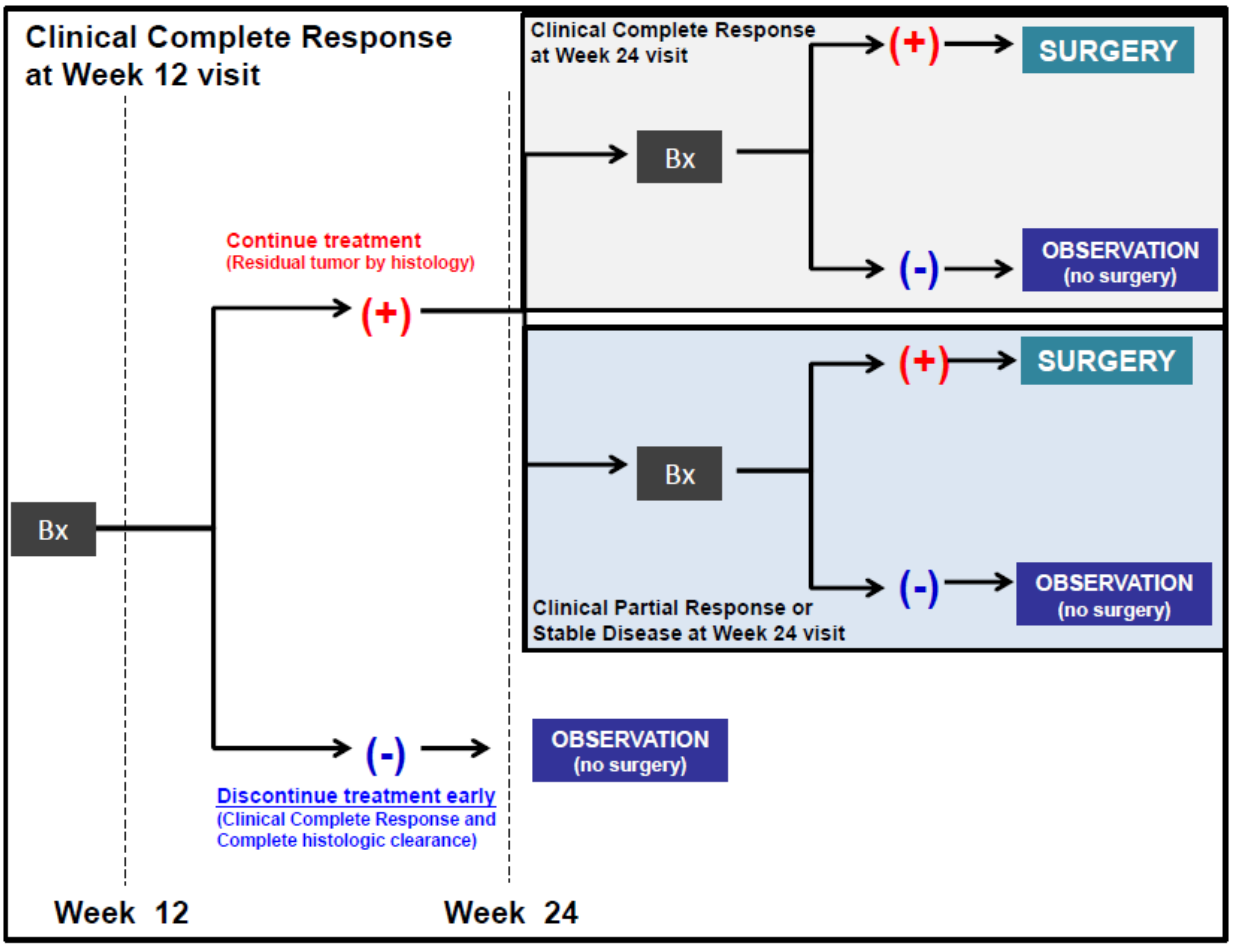

Clinical Complete Response at Week 12 visit
Clinical Complete Response at Week 24 visit
(+)
SURGERY
Bx
(-)
OBSERVATION (no surgery)
Continue treatment
(Residual tumor by histology)
(+)
(+)
SURGERY
Bx
Bx
(-)
OBSERVATION (no surgery)
Clinical Partial Response or Stable Disease at Week 24 visit
(-)
OBSERVATION (no surgery)
Discontinue treatment early
(Clinical Complete Response and Complete histologic clearance)
Week 12
Week 24

Figure 3.

14.6 APPENDIX 6: STUDY PROCEDURES FLOWCHART

Subjects with partial response or stable disease after 24 weeks of treatment and undergo surgical excision within 4 weeks of last dose of study drug.

	Pre-study Screening Visit	Treatment Initiation Visit	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Study Exit Visit[3]
	Day 0	Baseline / Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Surgery Visit	30 days after surgery
Procedure										
Sign & Date Informed Consent	X									
Collect Medical History	X									
Review InclusionExclusion Criteria	X	X								
Review Concomitant medications	X	X	X	X	X	X	X	X	X	X
Review Adverse Events (AEs)		X	X	X	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X
Height, weight	X	X	X	X	X	X	X	X	X	X
Target lesion identification	X									
Lesion measurement (pre-biopsy)	X									
Lesion measurement (post-biopsy)	X									
Lesion photography	X	X	X	X	X	X	X	X	X	
Tumor margins and local landmarks map	X	X	X	X	X	X	X	X	X	
Lesion punch biopsy/biopsies	X				X					
Urine Pregnancy Test	X[1]	X	X	X	X	X	X	X	X	X
CMP/CBC Tests	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Patient reported outcome questionnaires		X		X		X		X	X	X
Review subject diary			X	X	X	X	X	X	X	
Study drug instructions		X	X	X	X	X	X			
Reminder to use effective measures to avoid pregnancy	X	X	X	X	X	X	X	X	X	X
Administer study drug		X	X	X	X	X	X			
Pathological Evaluation (H&E)	X				X				X	
Immunohistochemical Evaluation	X				X				X	
Pathologic Slide Photography	X				X				X	
Breslow depth ("invasion index")	X				X				X	
Perform Mohs Surgery on target lesion(s)									X	
Assess/treat post-surgical tumor area										X
Assess Adverse Events (AEs)		X	X	X	X	X	X	X	X	X

Subjects with complete clinical response and complete histologic response at Week 24

	Pre-study Screening Visit	Treatment Initiation Visit	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Observation Visit 1	Observation Visit 2	Observation Visit 3	Observation Visit 4
	Day 0	Baseline / Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 36	Week 48	Week 60	Week 72
Description												
Informed Consent	X											
Medical History	X											
Inclusion/Exclusion	X											
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Height, weight	X	X	X	X	X	X	X	X	X	X	X	X
Target lesion identification	X											
Lesion measurement (pre-biopsy)	X											
Lesion measurement (post-biopsy)	X											
Lesion photography	X	X	X	X	X	X	X	X	X	X	X	X
Tumor margins and local landmarks map	X	X	X	X	X	X	X	X	X	X	X	X
Lesion punch biopsy/biopsies	X				X							
Urine Pregnancy Test	X[1]	X	X	X	X	X	X	X	X	X		
CMP?CBC Tests	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]				
Patient reported outcome questionnaires		X		X		X		X	X			
Review subject diary			X	X	X	X	X	X				
Study drug instructions		X	X	X	X	X	X					
Reminder to use effective measures to avoid pregnancy	X	X	X	X	X	X	X	X	X	X		
Administer study drug		X	X	X	X	X	X	X				
Adverse Events (AE) monitoring - PI and Oncologist		X	X	X	X	X	X	X	X	X	X	X

Subjects with complete clinical response and complete histologic response at Week 12 visit

	Pre-study Screening Visit	Treatment Initiation Visit	Visit 2	Visit 3	Visit 4	Observation Visit 1	Observation Visit 2	Observation Visit 3	Observation Visit 4
	Day 0	Baseline / Day 1	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60
Description									
Informed Consent	X								
Medical History	X								
Inclusion/Exclusion	X								
Concomitant medications	X	X	X	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X
Height, weight	X	X	X	X	X	X	X	X	X
Target lesion identification	X								
Lesion measurement (pre-biopsy)	X								
Lesion measurement (post-biopsy)	X								
Lesion photography	X	X	X	X	X	X	X	X	X
Tumor margins and local landmarks map	X	X	X	X	X	X	X	X	X
Lesion punch biopsy/biopsies	X				X				
Urine Pregnancy Test	X[1]	X	X	X	X	X	X	X	X
CMP?CBC Tests	X	X[2]	X[2]	X[2]	X[2]				
Patient reported outcome questionnaires		X		X		X			
Review subject diary			X	X	X				
Study drug instructions		X	X	X	X				
Reminder to use effective measures to avoid pregnancy	X	X	X	X	X	X	X		
Administer study drug		X	X	X	X				
Adverse Events (AE) monitoring - PI and Oncologist		X	X	X	X	X	X	X	X

1. Two negative pregnancy tests with a sensitivity of at least 25 mIU/mL prior to starting medication. These tests must be at least 19 days apart. For patients with regular menstrual cycles, the second pregnancy test should be done during the first 5 days of the menstrual period immediately preceding the beginning of therapy and after the patient has used 2 forms of contraception for 1 month. For patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding, the second pregnancy test must be done immediately preceding the beginning of therapy and after the patient has used 2 forms of contraception for 1 month.
2. Repeat testing after screening test is at the discretion of the investigator as clinically determined
3. Post surgical subjects will be offered observational follow up as office visits or telephone visits

14.7 APPENDIX 7: SKINDEX-16

http://www.proqolid.org/instruments/skindex_skindex_skindex_29_skindex_16

14.8 APPENDIX 8: INSTRUCTIONS FOR STUDY PARTICIPANTS

Thank you for participating in this study. We appreciate it. Please see below for instructions during your study participation.

USE OF STUDY MEDICATION

1. Do not share your study medication with any other person; it was prescribed only for you.
2. If you take any other drugs during this study, you should tell the study nurse or doctor. They will need to know the name of the drug, how much you took, how often you took it, why you took it, and when you started and stopped taking it.
3. Some drugs are not allowed at all during the study. The study nurse or doctor will discuss these drugs with you. If you have any questions about whether or not you can take a certain drug, please contact the study staff.
4. Take your study medication at approximately the same time each day, with or without food. Capsules must be swallowed whole and must not be opened under any circumstances. If you miss a dose inform your study doctor and do not to take or make up that dose. Resume your study medication at the next scheduled dose.
5. Please record the days and time that you take the medication in the dosing diary that we have given you. It is important for this to be accurate, so if you miss some doses, please record this truthfully.
6. **As part of your participation in the trial, you have agreed to adhere to the measures below to avoid pregnancy below and to avoid blood or blood product donation until _____ .**

   (13 months after Today's date _____, 9 months after expected last dose of vismodegib)

   - **Females of reproductive potential** must use **2 effective methods to avoid pregnancy** 1 month prior to starting the medication, during therapy, **and for 9 months after completing therapy**.
   - **Male patients must use effective measures to avoid pregnancy in their partner**, even after vasectomy, during treatment and for 9 months after the last dose.

7. If you suspect that you (or your partner) are pregnant, please call the study site immediately.
8. If you have any new health problems, new medications, surgeries or procedures, please contact the study staff. Please sign a medical records release form and have your treating physician send us a copy of your medical records. We will need to record this information in our files.

Please call us if you have any questions. Thank you again!

14.9 APPENDIX 9: FACT-G (VERSION 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy.....	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends.....	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness.....	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support).....	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, Please answer the following question. If you prefer not to answer it, please mark this box and go to the nextection.* ☐					
GS7	I am satisfied with my sex life.....	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

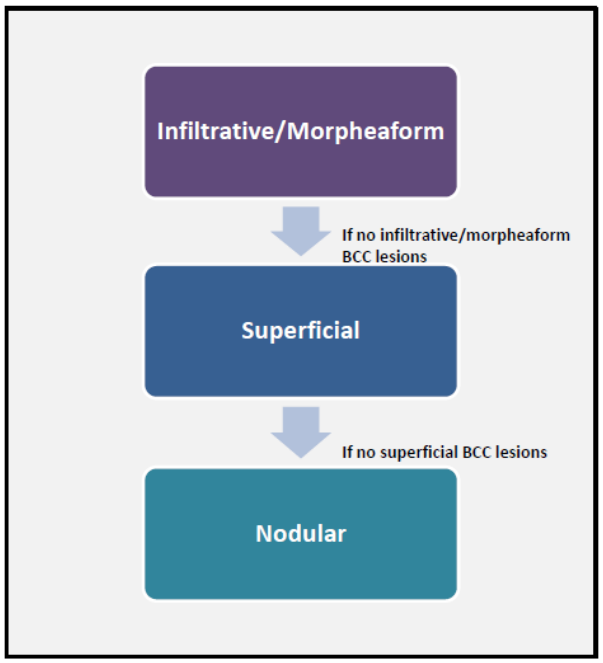
14.10 APPENDIX 10: TARGET LESION ASSIGNMENT EXAMPLES

If a patient has multiple BCC tumors, target lesion assignment will be based on histology using algorithm in Figure 2.

Histology is the primary consideration for "target lesion assignment." Histology trumps size. Size is only considered if there are two lesions that may be eligible for target lesion assignment based on histologic subtype. In this case, the lesion with larger clinical dimensions will be designated the "target lesion".

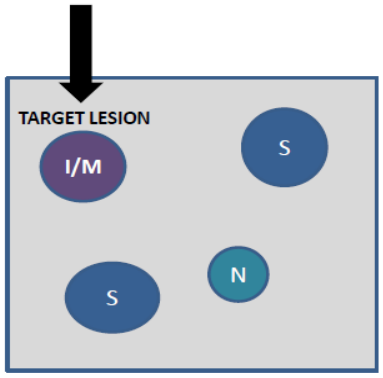
See Example 1 and Example 2 for more details.

Target Lesion Assignment Algorithm



Example 1: Subject with 4 BCC tumors

- 1 infiltrative/morpheaform BCC
- 2 superficial BCCs
- 1 nodular BCC

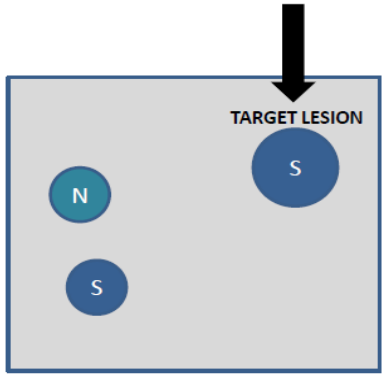


Target lesion: Infiltrative/Morpheaform BCC

Explanation: Lesions of infiltrative/morpheaform subtype given preference. Histology is first consideration for "Target lesion assignment".

Example 2: Subject with 3 BCC tumors

- 2 superficial BCCs
- 1 nodular BCC



Target lesion: Superficial BCC with larger clinical dimensions

Explanation: No infiltrative/morpheaform subtype lesions. Two superficial BCC lesions eligible based on histology. Larger of two superficial BCC lesions selected for "target lesion" assignment.

14.11 APPENDIX 11. NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) V.4

http://evs.nci.nih.gov/ftp1/CTCAE/About.html