MSK PROTOCOL COVER SHEET

A Phase II Study of the BRAF Inhibitor, Vemurafenib, in Patients with Relapsed or Refractory Hairy Cell Leukemia

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Title: A phase II trial of the BRAF Inhibitor, Vemurafenib, in patients with relapsed or refractory hairy cell leukemia (HCL)

Objectives: To determine the efficacy of vemurafenib as assessed by overall response rates after three months of treatment in patients with relapsed or refractory HCL.

Patient Population: Patients with HCL who are refractory to or intolerant of purine analogs, who have relapsed disease within 2 years of purine analog-based therapy, or who have ≥ 2 relapses will be eligible for the trial.

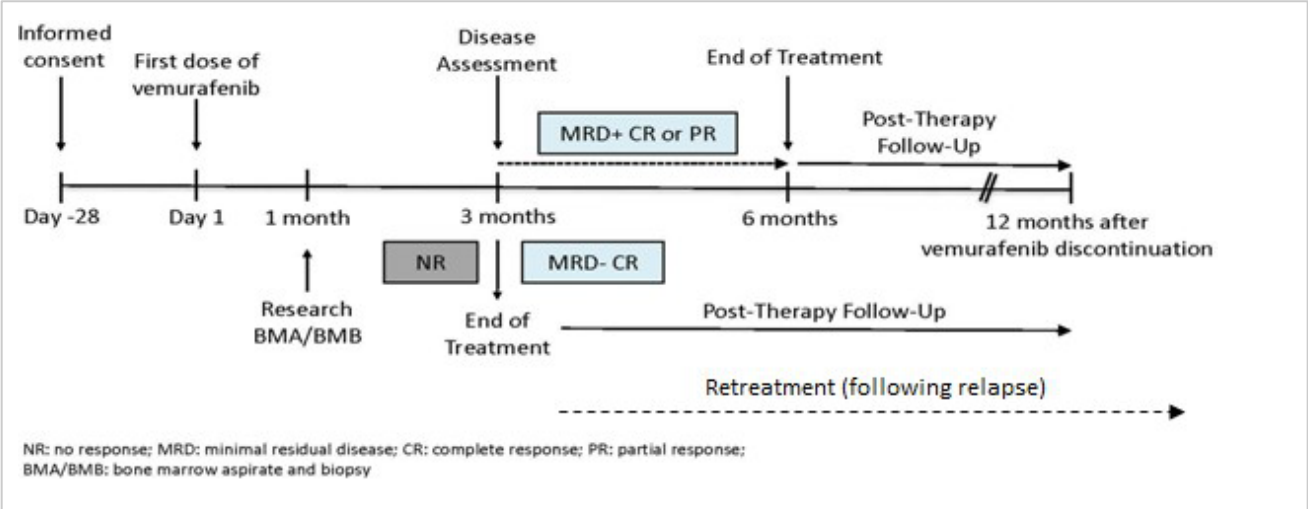
Study Design: This is a multi-center, open label, single arm, phase II trial of the oral BRAF inhibitor, vemurafenib. A Simon mini-max two-stage design will be employed to assess the efficacy of vemurafenib. In the first stage of the protocol, 19 patients will be treated. If 3 or fewer responses (CR or PR) are seen among the first 19 patients, the study will be closed for lack of efficacy. If at least 4 patients respond to the treatment, then an additional 17 patients will be accrued to the second stage. At the end of the trial, if 11 or more patients have responded out of the 36 patients then the drug will be considered worthy of further investigation.

Treatment Plan: Eligible patients will receive vemurafenib at a dose of 960mg orally twice daily (b.i.d.) continuously in cycles of 4 weeks (28 days). A bone marrow aspirate and/or biopsy will be performed after the first cycle for research purposes only. After the completion of the third cycle, a repeat bone marrow aspirate and/or biopsy will be performed for assessment of response and evaluation of minimal residual disease (MRD). Following the third cycle assessments, patients who achieve complete response (CR) with detectable MRD or partial response (PR) may continue with vemurafenib for up to 3 additional cycles at the treating physician's discretion (Cycles 4-6). Patients who achieve CR without MRD will be observed as part of post-treatment followup, and may be re-treated with vemurafenib after relapse (as per below). Patients who achieve no response (NR) after the initial 3 cycles of vemurafenib will be removed from the study.

After patients discontinue vemurafenib, they will be followed every 3 months as part of post-treatment followup for a total of 12 months. Patients who previously experienced CR, PR (either hematologic or MRD) or clinical benefit, but who subsequently relapse after ending treatment may be retreated with Vemurafenib until disease progression or at the treating physician's discretion. Patients who are re-treated will follow the treatment/evaluation plan as outlined in Table 3 (see Section 10). A bone marrow aspirate and/or biopsy may be performed for assessment of response at the end of the third re-treatment cycle or during a subsequent re-treatment cycle when clinically indicated.

In case of certain defined toxicities, dose reductions by 50% (480mg b.i.d.) or interruptions of up to 15 days are permitted. If additional dose reduction is required, vemurafenib may be reduced to 240mg oral b.i.d.

Time to Completion: As of August 17th 2016, this protocol is closed to accrual as target accrual was met.



2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective

To determine the efficacy of vemurafenib as assessed by overall response rates (complete response (CR) and partial response (PR)) after three months of treatment

Secondary Objectives

1. To assess the safety and tolerability of vemurafenib in patients with HCL
2. To assess the efficacy of vemurafenib based on time to response, duration of response, and kinetics of minimal residual disease (MRD) response assessed by immunohistochemistry
3. To determine the progression-free and overall survival of HCL patients treated with vemurafenib
4. To characterize molecular profiling of HCL by high throughput next generation sequencing using Raindance multiplex PCR and Ilumina next generation sequencing
5. To assess the pharmacodynamics of vemurafenib via measurement of BRAF downstream targets (MEK, p-MEK, ERK, p-ERK) from the peripheral blood or bone marrow aspirate samples, and by examining the MAPK, PI3K and JAK-STAT signaling pathways using Cell Biosciences NanoPro 1000 technology
6. To evaluate biomarkers that may be relevant to explain primary or acquired resistance to vemurafenib as assessed by additional BRAF mutations, reactivation of MAPK pathways, activation of alternative signaling pathways (e.g. PI3K and STAT)

3.0 BACKGROUND AND RATIONALE

3.1 Hairy Cell Leukemia

Hairy cell leukemia (HCL) is a chronic B-cell lymphoproliferative disorder that is characterized by marked splenomegaly, progressive pancytopenia, and infiltration of leukemic B cells in the bone marrow, spleen, and liver. Despite the usually indolent course of HCL, most patients require therapy when cytopenias become life-threatening or when they develop symptomatic splenomegaly.

3.2 Treatment of Newly Diagnosed HCL

Currently, the standard first-line treatment of HCL is based on purine analogs, either pentostatin or cladribine as a single agent, which can induce complete response (CR) and partial response (PR) in 80-90% and 10-20% of treated patients, respectively[1]. However, despite the high percentage of patients achieving CR and PR, approximately 30-40% of patients (more patients with PR than CR) will relapse after the initial treatment with either pentostatin or 2-chlorodeoxyadenosine (2-CdA) with the median time to relapse ranging from 10.5 to 42 months[1-5]. The propensity for relapse may be related to the extent of residual disease reported to be present in 50-100% of patients in CR following the initial therapy with purine analogs[6-8], suggesting that most patients, if not all, will relapse if given sufficient time.

3.3 Treatment of refractory and relapsed HCL

For patients who fail to respond to the initial purine analog therapy or who have relapsed disease within 1-2 years of purine analogs, there is currently no standard treatment options and they do not respond well to a second course of purine analog therapy. In patients who have relapsed disease following the initial therapy with purine analogs, CRs can be achieved with repeated courses of purine analogs, and the anticipated response to subsequent lines of therapy can be judged by the duration and quality of the initial response. If there was an initial remission of short duration (e.g. < 2 years), then repeat administration of the original therapy is less likely to result in a longer second remission[9]. Several long-term follow-up studies report the CR and PR rates of 52-62% and 26-30%, respectively, in patients treated with another cycle of purine analogs at the 1st relapse[2,3,10]. However, the ability to attain CR and its duration decline with each subsequent line of purine analog-based therapy[1,4,11]. Due to the limited number of patients with HCL, the outcome information on patients with ≥ 2 relapses are scarce and only reported in a limited number of patients. Three largest studies conducted in patients with HCL include only 10 – 34 patients at 2nd relapse and even less patients at 3rd relapse, and no information is available on patients with > 3 relapses[1,4,11]. In these studies, CR rates ranging of 50-60% have been reported. However, due to such a small sample size, it is unclear whether these high responses rates accurately represent a response rate expected in these patients. Furthermore, the relapsed patients included in these previous published reports are highly selected patient population with a long duration of response to previous purine analog treatments with a median time to 2nd and 3rd relapse ranging from 32 to 70 months. Therefore, the response rates in patients with a short duration of response to the previous purine analog treatments remains unknown. Lastly, there is no evidence to suggest that repeated courses of purine analogs or other alternative therapies offer any survival benefit in these patients, but may cause treatment-related bone marrow injury and prolonged immunodeficiency with successively shorter remission duration.

3.4 Limitations of Current Therapeutic Approach in HCL

Although retreatment with purine analogs is associated with a high response rate, approximately 50% of patients will continue to relapse after each line of treatment requiring further therapy, subjecting these patients to cumulative side effects of purine analogs including prolonged myelosuppression with increased susceptibility to viral and fungal infections[12,13] and a small trend toward an increased risk of secondary malignancies[14-16]. While the latter risk is controversial, the excess frequency of secondary malignancies was reported to be 1.88 in one series[10]. In a 2014 patient follow-up from the National Cancer Institute (NCI), a small trend toward an increased risk for second cancers was also noted (observed/expected ratio of 1.63 for patients who were treated with 2-CdA). However, other studies fail to show an increased

risk for secondary malignancies, although some of them noted an increased risk of lymphoid malignancies[15-17].

More importantly, the relapse-free survival (RFS) curves in HCL patients treated with purine analogs do not appear to reach a plateau, and as high as 11.5% of patients become refractory to this class of agents when treated at 2nd or higher relapses[11]. In fact, all the long-term studies published to date have observed no plateau in the progression-free survival (PFS) curve after follow-up close to 14 years, suggesting that late relapse do occur and purine analogues are not likely curative[3].

Since neither purine analogs can cure the disease as monotherapy and due to associated prolonged immune suppression (particularly among older patients) and increased risk of secondary malignancies, there is an urgent need for novel targeted and potentially curative therapies for patients with HCL who have failed or who have multiply relapsed disease.

3.5 BRAF as a Therapeutic Target in HCL

A recent exome sequencing study of HCL has identified BRAF a potential therapeutic target[18]. The BRAF protein is part of the RAS-RAF-MAPK signaling pathway, which plays a major role in regulating cell survival, proliferation, and differentiation[19]. BRAF mutations constitutively activate the MEK-ERK pathway, leading to enhanced cell proliferation, survival, and ultimately, neoplastic transformation[20]. Activation of the MAPK pathway in HCL has previously been described by several investigators, who reported constitutively activated ERK[21], providing a survival signal for the leukemic hairy cells[22].

BRAF inhibition is an attractive therapeutic target for HCL for several reasons: 1) BRAF V600E mutation is present in 100% of HCL patients, and not found in other B cell lymphoproliferative disorders[23-26]; 2) BRAF mutation is present in the entire tumor-cell clone in virtually all patients; 3) BRAF mutations become undetectable at remission but re-appears at relapse[23-25]; and 4) treatment of primary HCL cells with the BRAF inhibitor vemurafenib markedly inhibited the activation of signaling downstream of BRAF (MEK and ERK) at a very low drug concentrations (≤1 μM)[18]. Previous clinical trials with Vemurafenib in patients with metastatic melanoma reported that concentrations of approximately 80 μM can be safely achieved with 960mg twice daily oral dosing[27].
These data implicate the BRAF V600E mutation in the pathogenesis of HCL, and provides a strong rationale for targeting BRAF in patients with HCL. BRAF inhibition in HCL may not only represent the first targeted therapeutic approach, but also an attractive therapy for patients with suboptimal response to purine analogs as well as for patients with repeated relapses and with unacceptable toxic effects of purine analogs.

3.6 BRAF Inhibitor, Vemurafenib: Clinical Data in Melanoma

The BRAF inhibitor, vemurafenib (previously known as PLX4032 and RO5185426), has been extensively studied both in preclinical models and in clinical trials. *In vitro* studies have demonstrated that PLX4032 selectively inhibits the growth of tumor cells expressing BRAF V600E mutation by inhibiting ERK signaling only in mutant BRAF tumor cells, thus achieving a broader therapeutic index without causing toxicity resulting from the inhibition of ERK signaling in normal cells[28]. This is in contrast to MAPK/ERK (MEK) inhibitors that inhibit ERK phosphorylation in both normal and tumor cells[29,30]. The anti-tumor efficacy of PLX4032 was also demonstrated in several *in vivo* studies using tumor xenograft models of BRAF V600E mutant melanoma with partial or complete tumor regressions and improved animal survival with no significant toxicity[31].

Based on these preclinical data, several clinical trials have been conducted in patients with metastatic melanoma where approximately 50% of patients carry the BRAF V600E mutation. In a phase I trial, the maximum tolerated dose of 960mg twice daily was established, and frequent tumor regressions were observed[27]. Notably, the analysis of paired tumor biopsies (at baseline and at day 15 of PLX4032 treatment) revealed a strong correlation between a decrease in phosphorylated ERK and a clinical response, suggesting that PLX4032 inhibited the MAP kinase pathway (at 960mg twice daily dosing level) and the need to obtain effective ERK signaling inhibition for significant tumor response[27,31]. In a phase II trial involving patients with previously treated metastatic melanoma harboring the BRAF V600E mutation, a response rate of 53% was observed with a median duration of response of 6.7 months[32]. More recently, the results from a randomized, multicenter phase III trial was published, demonstrating a remarkable activity in patients with BRAF-mutated metastatic melanoma with a response rate of 48% (compared to 5% in patients treated with standard chemotherapy dacarbazine) and a relative reduction of 63% in the risk of death[33]. Common adverse events noted in these trials with vemurafenib in melanoma patients included arthralgia, rash, fatigue, alopecia, keratoacanthoma, photosensitivity, nausea, diarrhea and squamous-cell carcinoma, but with very little hematologic toxicity[27,33].

3.7 BRAF Inhibitor, Vemurafenib: Clinical Data in HCL

A group of investigators at Heidelberg University Hospital in Germany have recently reported the striking therapeutic activity of vemurafenib in one patient with refractory HCL[34]. According to the authors, a patient with HCL and massive splenomegaly and pancytopenia, who was refractory to three lines of purine analogue-based treatment, received vemurafenib for 2 months. Within 2 days of treatment, the patient's spleen decreased in size and his leukocytes and platelet counts began to rise. By day 43 of therapy, a CR was achieved as assessed by bone marrow biopsy showing an absence of disease with complete resolution of splenomegaly. While very preliminary, this report suggests the BRAF V600E allele as a driver mutation in HCL and validates mutant BRAF as a therapeutic target in HCL.

3.8 Rationale for Dose Selection

Selection of the dose of vemurafenib is based on the clinical efficacy and safety observed at the MTD of 960mg twice daily in the phase I, II and III studies in melanoma patients. At this clinical dose, it is associated with suppression of pERK in biopsy specimens and consistent with exposures in preclinical models that were associated with anti-tumor activity. The same dose and administration schedule was used in a patient with refractory HCL mentioned above. Although the patient was started at a lower dose initially, the dose was quickly titrated up to 960mg twice daily with no reported toxicity[34].

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

We propose a single arm, multi-center, open-label, phase II study of vemurafenib in patients with HCL who are resistant to or intolerant of purine analogs, who have relapsed disease within 2 years of purine analog-based therapy, or who have ≥ 2 relapses. A Simon mini-max two-stage design will be employed to assess the efficacy of Vemurafenib after three months of treatment. In the first stage of the protocol, 19 patients will be treated. If 3 or fewer responses (CR or PR) are seen among the first 19 patients, the study will be closed for lack of efficacy. If at least 4 patients respond to the treatment, then an additional 17 patients will be accrued to

the second stage. At the end of the trial, if 11 or more patients have responded out of the 36 patients then the drug will be considered worthy of further investigation.

4.2 Intervention

Eligible patients will receive vemurafenib at a dose of 960mg orally b.i.d. continuously in cycles of 4 weeks (28 days). A bone marrow aspirate and/or biopsy will be performed after the first cycle for research purposes only. After the completion of the third cycle, a repeat bone marrow aspirate and/or biopsy will be performed for assessment of response and evaluation of minimal residual disease (MRD). Following the third cycle assessments, patients who achieve complete response (CR) with detectable MRD or partial response (PR) may continue with vemurafenib for up to 3 additional cycles at the treating physician's discretion (Cycles 4-6). Patients who achieve CR without MRD will be observed as part of post-treatment followup, and may be re-treated with vemurafenib after relapse (as per below). Patients who achieve no response (NR) after the initial 3 cycles of vemurafenib will be removed from the study.

After patients discontinue vemurafenib, they will be followed every 3 months as part of post-treatment followup for a total of 12 months. Patients who previously experienced CR, PR (either hematologic or MRD) or clinical benefit, but who subsequently relapse after ending treatment may be retreated with Vemurafenib until disease progression or at the treating physician's discretion. Patients who are re-treated will follow the treatment/evaluation plan as outlined in Table 3 (see Section 10). A bone marrow aspirate and/or biopsy may be performed for assessment of response at the end of the third re-treatment cycle or during a subsequent re-treatment cycle when clinically indicated.

In case of certain defined toxicities, dose reductions by 50% (480mg b.i.d.) or interruptions of up to 15 days are permitted. If additional dose reduction is required, vemurafenib may be reduced to 240mg oral b.i.d.

BRAF inhibition is an attractive therapeutic target for HCL for several reasons: 1) BRAF V600E mutation is present in 100% of HCL patients, and not found in other B cell lymphoproliferative disorders[23-26]; 2) BRAF mutation is present in the entire tumor-cell clone in virtually all patients; 3) BRAF mutations become undetectable at remission but re-appears at relapse[23-25]; and 4) treatment of primary HCL cells with the BRAF inhibitor vemurafenib markedly inhibited the activation of signaling downstream of BRAF (MEK and ERK) at a very low drug concentrations (≤1 μM)[18]. Therefore, BRAF inhibition in HCL may not only represent the first targeted therapeutic approach, but also an attractive therapy for patients with suboptimal response to purine analogs as well as for patients with repeated relapses and with unacceptable toxic effects of purine analogs. Furthermore, there are several limitations with the current standard of care therapies (*i.e.* purine analogs) for patients with relapsed HCL, including 1) neither 2-CdA nor pentostatin is curative; 2) the use of purine analogs is associated with prolonged immune suppression and potentially increased risk of secondary malignancies; and 3) the ability to attain CR, which is critical to achieve longer PFS and DFS, decline with each subsequent line of purine analog-based therapy[1,3,5,35,36].

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Description: Vemurafenib, also known as PLX4032 and RO5185426, will be labeled in compliance with Good Manufacturing Procedures (GMP). The drug label will include: the contents, protocol

number, batch number, and storage conditions, as well as any required statements that the drug is: "For Investigational Use Only." The drug will be labeled as "RO5185426."

Drug Supply and Distribution: Vemurafenib is manufactured and distributed by Genentech.

How Supplied: Each bottle of oral study treatment of vemurafenib contains a total of 120 tablets that are 240 mg each. Patients should be instructed to administer 4 tablets in morning and 4 tablets in evening (total daily dose of 1920mg [960mg b.i.d.]). If a dose is missed, it can be taken up to 4 hours prior to the next dose to maintain the twice daily regimen. Both doses should not be taken at the same time. All missed doses should be recorded in the patient diary.

Storage: Vemurafenib will be stored at the clinical site under recommended storage conditions: "Do Not Store above 25 C" as indicated on the study drug label. Patients will be requested to store the drug at the recommended storage conditions noted on the label out of reach of children or other cohabitants.

Assessment of Compliance: Accountability and patient compliance will be assessed by maintaining adequate "drug dispensing" and return records. A dosing diary will be given to patients to record the time, date, and number of tablets administered on days vemurafenib is dosed outside of clinic and will assist study centers in measuring patient compliance with vemurafenib treatment administration.

Approximately, a 4-week supply of Vemurafenib will be given to the patients on day 1 of each dosing cycle. The drugs may be shipped to patients, one month supply at a time. Patients should be instructed not to open a new bottle until the previous bottle has been finished. Patients are asked to return all used and unused drug supply of vemurafenib for reconciliation (whether bottles are emptied or unused) at their scheduled clinic visits. Study drug should not be crushed, chewed or dissolved.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

1. ≥ 18 years of age
2. Histologically confirmed classical HCL with one of the following:
   - Intolerance to purine analogs or considered to be poor candidates for purine analog-based therapy
   - Failure to achieve any response (CR or PR) to the initial purine analog-based therapy
   - Relapse ≤ 2 years of purine analog-based therapy
   - ≥ 2 relapses

   Histologic confirmation of diagnosis will be performed at MSKCC or a participating site.
3. Patients who meet the standard treatment initiation criteria, as defined by ANC ≤1.0, Hgb ≤ 10.0 or PLT ≤100K
4. ECOG performance status of 0-2
5. Acceptable pre-study organ function during screening as defined as: Total bilirubin ≤ 1.5 times the upper limit of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5x ULN, and serum creatinine ≤ 1.5x ULN
6. Electrocardiogram (ECG) without evidence of clinically significant ventricular arrhythmias or ischemia as determined by the investigator and a rate-corrected QT interval (QT_c, Bazett's formula) of < 480 msec.

7. For women of childbearing potential, agreement to the use of two acceptable methods of contraception, including one barrier method, during the study and for 6 months after discontinuation of vemurafenib
8. For men with female partners of childbearing potential, agreement to use a latex condom and to advise their female partner to use an additional method of contraception during the study and for 6 months after discontinuation of vemurafenib
9. Negative serum pregnancy test within 7 days of commencement of treatment in premenopausal women.
10. Agreement not to donate blood or blood products during the study and for at least 6 months after discontinuation of vemurafenib; for male partners, agreement not to donate sperm during the study and for at least 6 months after discontinuation of vemurafenib
11. Ability to understand and willingness to sign a written informed consent document. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.

6.2 Subject Exclusion Criteria

1. Pregnant or breast-feeding
2. Have had chemotherapy (including purine analogs, rituximab, and other investigational agents) within six weeks prior to entering the study
3. Major surgery within 4 weeks prior to entering the study
4. Invasive malignancy within the past 2 years prior to first study drug administration, except for adequately treated (with curative intent) basal or squamous cell carcinoma, melanoma, in situ carcinoma of the cervix, in situ ductal adenocarcinoma of the breast, in situ prostate cancer, or limited stage bladder cancer or other cancers from which the patient has been disease-free for at least 2 years
5. Refractory nausea or vomiting, malabsorption, external biliary shunt, or history of any type of gastrointestinal surgery that would preclude adequate absorption of study drug
6. Prior treatment with MEK or BRAF inhibitors
7. Active HIV, hepatitis B and hepatitis C
8. Patients with HCL variant (as defined by absence of expression of CD25 or absence of BRAF V600E mutation)

7.0 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). Patient recruitment will occur in medical oncology clinics or the inpatient service of the Leukemia Service at MSKCC. Investigators will screen the patient's medical records of suitable research study participants and discuss the study and their potential for enrolling in the research study. Similar recruitment procedures will be followed at collaborating institutions. It is expected that each of the participating sites will enroll 5-7 patients each over a 2-year period.

Participating site recruitment will be conducted as outlined within the protocol. Any participating sites that require a limited waiver must obtain it from their site IRB/PB via a separate protocol addendum or request. It is the responsibility of the MSK staff to confirm participating data collection sites have a limited waiver approved by their local IRB(s)/PBs.

8.0 PRETREATMENT EVALUATION

The following assessments must be performed prior to treatment start:

Within 4 Weeks of Study Start:

- A complete history and physical exam including general ophthalmologic examination for any signs of conjunctiva inflammation and regular constrictions of pupils
- Head and neck examination: visual inspection of the oral mucosa and lymph node palpation
- ECG
- Laboratory studies: CBC with differential and platelets, smear review, Comprehensive Metabolic Panel (albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], and sodium), phosphorus, uric acid, LDH, PT/PTT, HIV, Hepatitis B and C testing
- CT chest
- CT abdomen in patients with intact spleen
- Bone marrow aspirate for histology, cytogenetics, immunophenotyping by flow cytometry, and a bone marrow biopsy. If bone marrow aspirate cannot be obtained, peripheral blood samples will be tested for cytogenetics and immunophenotyping by flow cytometry.
- Full skin assessment by a dermatologist or equivalent trained skin cancer expert
- Research blood or bone marrow aspirate (if obtained) analysis (please see Section 10.3 for details of the study)

Within 7 Days of Study Start:

- Serum pregnancy test for women of child-bearing potential

9.0 TREATMENT/INTERVENTION PLAN

9.1 Administration of Vemurafenib

Patients will receive vemurafenib at a dose of 960mg orally b.i.d. continuously in cycles of 4 weeks (28 days) as outpatient. A bone marrow aspirate and/or biopsy will be performed after the first cycle for research purposes only. After the completion of the third cycle, a repeat bone marrow aspirate and/or biopsy will be performed for assessment of response and evaluation of MRD. Following the third cycle assessments, patients who achieve complete response (CR) with detectable MRD or partial response (PR) may continue with vemurafenib for up to 3 additional cycles at the treating physician's discretion (Cycles 4-6). Patients who achieve CR without MRD will be observed as part of post-treatment followup, and may be re-treated with vemurafenib after relapse (as per below). Patients who achieve no response (NR) after the initial 3 cycles of vemurafenib will be removed from the study.

After patients discontinue vemurafenib, they will be followed every 3 months as part of post-treatment followup for a total of 12 months. Patients who previously experienced CR, PR (either hematologic or MRD) or clinical benefit, but who subsequently relapse after ending treatment may be retreated with Vemurafenib until disease progression or at the treating physician's discretion. Patients who are re-treated will follow the treatment/evaluation plan as outlined in Table 3 (see Section 10). A bone marrow aspirate and/or biopsy may be performed for assessment of response at the end of the third re-treatment cycle or during a subsequent re-treatment cycle when clinically indicated.

Patients who achieve no response after the initial 3 cycles of vemurafenib will be removed from the study. In case of certain defined toxicities, dose reductions by 50% (480mg b.i.d.) or interruptions of up to 15 days are permitted. If additional dose reductions are required, vemurafenib may be reduced to 240mg oral b.i.d.

9.2 Dose Modifications

Management of Symptomatic Drug Reactions: Symptomatic drug reactions (*e.g.* arthralgia, fatigue, rash) may require temporary interruptions and/or dose reduction of vemurafenib treatment. Arthralgia is one of the common side effects of the drug, and can be first managed with prednisone 5-10mg daily before dose reduction is attempted. When dose reduction is needed, initial dose reduction to 480mg b.i.d. is recommended based on individual safety and tolerability data from the trials in melanoma patients. If additional dose reduction is required or the drug is interrupted for up to 15 days, vemurafenib may be reduced to 240mg b.i.d. Dose escalation after dose reduction is generally not recommended unless under special circumstances (*i.e.* increased likelihood of clinical benefit for the dose increase and no safety concern). This should be done after discussion with the the principal investigator of the study (Dr. Jae Park). Dose increase above 960mg b.i.d. will NOT be allowed.

Management of QT_c Prolongation: Special consideration must be taken with any patient on study with an increase in QT_C >500ms or change from baseline >60ms. If QT_C exceeds 500 ms or the change from baseline is > 60ms on ECG (measured in triplicate), vemurafenib treatment should be temporarily interrupted. When QT_C decreases to < 500ms, re-initiation of vemurafenib treatment may occur and patients should be dose reduced by one dose level. Permanent discontinuation of vemurafenib treatment is recommended if QT_C increase meets both criteria of >500ms and >60ms change from pre-treatment values of if QT_C >500ms or change from baseline >60ms is observed on 2 prior independent occurrences.

Management of Grade 1-4 Non-Hematologic Toxicities: For any grade 1 and tolerable grade 2-3 toxicities, patients may continue full dose. For any intolerable grade 2-3 toxicities, dosing will be interrupted until resolution to grade 1 or less and dose reductions to 480mg b.i.d. are required, except for arthralgia in which case prednisone 5-10mg daily can be attempted first before the study drug dose reduction. If additional dose reduction is required, investigators can further reduce the dose to 240mg b.i.d. On the third appearance of any grade 2 or grade 3 adverse events despite two dose reductions, it is recommended that patients discontinue vemurafenib. For any grade 4 toxicities, patients should discontinue study treatment or, based on investigator judgment, interrupt until resolution to grade 1 or less with dose reduction to 240mg b.i.d. upon restarting study drug. Dose escalation after dose reduction is generally not recommended unless under special circumstances (*i.e.* increased likelihood of clinical benefit for the dose increase and no safety concern). It is recommended that patients permanently discontinue vemurafenib for a second occurrence of any grade 4 toxicities.

Prolonged Drug Interruptions: If a patient's study dose has been interrupted for >15 days, the patient will be considered to have discontinued from the study. If the patient is still benefiting from treatment and an interruption greater than 15 days deemed necessary by the investigator, the length of the requested interruption should be discussed with the principal investigator of the study (Dr. Jae Park). Restarting vemurafenib treatment after discontinuation of drug is permitted during the re-treatment phase if the investigator deems there is a clinical benefit for re-starting drug and there are no safety concerns.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 Clinic Visits

Outpatient clinic visits will occur weekly during the Cycle 1 (Days 1, 8, 15, 22), and on Day 1 of subsequent 28-day cycle (*i.e.* monthly, days 29, 57, 85, etc.). A +/- 4 day window will be allowed for completion of scheduled clinic visits. Please refer to the **Table 1** below for details of routine tests to be performed during the clinic visits. As specified in **Table 1**, some of the blood tests and assessments can be obtained locally if the patient has an established local oncologist.

10.2 Disease Response Assessment

Disease response assessment will be performed after the completion of Cycle 3, and will involve CBC with diff and platelets, a bone marrow aspirate and/or biopsy (flow cytometry, cytogenetics, IHC), and CT Abdomen (CT Abdomen is applicable only if splenomegaly was present on screening the CT abdomen). MRD analysis will be performed on bone marrow biopsy specimens as assessed by IHC for anti-CD20, DBA 44 and anti-CD45RO[6,37,38]. If patients receive additional cycles of therapy (*i.e.* Cycles 4, 5 and 6), the above disease response assessment will occur within 2 weeks of the last therapy.

10.3 Research Tests

The following research tests will be performed at the time points indicated in **Table 1**. Bone marrow aspirate samples will be collected in an EDTA-containing syringe (3-5ml) and peripheral blood samples will be collected in either green top or purple top tubes (10ml). At each specified time point (Table 1), 3 green or purple top tubes of peripheral blood samples will be collected. These samples can be collected locally if the patient has an established local oncologist and only after discussing with the study PI. The collected samples will be delivered to the Abdel-Wahab's laboratory in Zuckerman 519 at Memorial Sloan-Kettering Cancer Center.

BRAF Mutation Analysis: Peripheral blood and/or bone marrow aspirate samples from pre-treatment and post-treatment at specified time points will be assessed for BRAF V600E mutation by allele-specific PCR of genomic DNA followed by conventional agarose-gel electrophoresis[24] and/or by quantitative real-time allele-specific PCR in complimentary DNA (cDNA)[26].

Pharmacodynamic (PD) Studies: Peripheral blood and/or bone marrow aspirate samples from pre-treatment and post-treatment at specified time points will be assessed by Western Blot or by phospho-flow for the downstream targets of BRAF (MEK, pMEK, ERK, pERK) to assess the on-target effect of the Vemurafenib. In addition, signaling studies using Cell Biosciences NanoPro 1000 technology will be performed on the same samples, which will allow us to obtain accurate, quantitative signaling on the entire MAPK, PI3K, and JAK-STAT pathways before and after treatment on sorted circulating hairy cells.

***For MSKCC Patients ONLY:** Additional research blood samples for the above mentioned pharmacodynamic studies will be collected in patients who receive their treatment at MSKCC. These additional time points include 2-4 hours and 24 hours after the first dose of vemurafenib. 24-hour blood sample can be collected locally if the patient has an established local oncologist and only after discussing with the MSKCC PI.

Molecular Characterization of HCL: Peripheral blood and/or bone marrow aspirate samples from pre-treatment and post-treatment at specified time points will be analyzed by high throughput next generation sequencing using the Raindance multiplex PCR platform and Illumina next generation sequencing to perform comprehensive mutation profiling for BRAF and for 29 additional genes known to be mutated in HCL patient and/or in other chronic B-cell lymphoid malignancies.

Biomarkers for Resistance: The following tests will be performed in all patients at baseline, and in patients who do not achieve CR or PR after completing 3 cycles of therapy, or who progresses after achieving CR or PR.

- Reactivation of MAPK pathways: Increased expression of the other RAF isoforms CRAF and ARAF), and MAPK (MAPK8 or COT) will be analyzed by Western Blot and/or real-time PCR[39,40].
- Secondary BRAF mutations (all 18 BRAF exons) and RAS mutations[40] will be analyzed by bi-directional Sanger sequencing and by Raindance multiplex PCR and Illumina next generation sequencing, respectively.
- Activation of RTKs (*i.e.* PDGFRβ and IGF-IR) will be assessed by Western Blot.
- Cell Biosciences NanoPro 1000 technology will be used to examine quantitative signaling on the entire MAPK, PI3K and JAK-STAT pathways[41].

Table 1: Evaluation on Study

Phase	**Screening**	**Study Visits**											
Cycle		**1**				**2**		**3**		**4**	**5**	**6**	
Day[1]	-28 to -1	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 28+/-4	Day 1[13]	Day 1	Day 1	Day 28+/-4
Informed Consent	X												
History and Physical Exam	X	X				X		X		X	X	X	
Head and Neck Exam[2]	X	X				X					X		
ECG	X	X		X[12]		X		X		X			
Serum Pregnancy Test[3]	X												
Dermatology Exam[4,12]	X					X					X		
CBC w/ diff, Platelets	X	X	X[12]	X[12]	X[12]	X	X[12]	X	X	X	X	X	X
Smear Review	X	X	X[12]	X[12]	X[12]	X		X		X	X	X	
COMP, LDH	X	X				X		X	X	X	X	X	X
Phosphorus, Uric Acid	X	X	X[12]	X[12]	X[12]								
PT/PTT	X												
HIV, Hepatitis B and C	X												
Adverse Events		X				X		X		X	X	X	
Review of Concomitant Medications	X	X				X		X		X	X	X	
CT Chest	X								X[5]				
CT Abdomen	X[6]								X[7]				
Bone Marrow Aspirate and/or Biopsy	X								X				X[8]
Research Tests													
Bone Marrow Aspirate and/or Biopsy	X[9]					X[9]			X[9]				X[8,9]
Peripheral Blood[10]	X	X[11]	X[12]	X[12]	X[12]	X		X	X				X[8]

[1]A +/- 4 day window will be allowed for completion of scheduled clinic visits (i.e. holidays, travel delays, site closures, other reasons, etc.) A +/- 7day window is allowed for Cycle 4 Day 1 to allow the adequate time for bone marrow response evaluation from Cycle 3 Day 28.
[2]Head and neck examination can be performed as part of general physical exam, and consist of visual inspection of the oral mucosa and lymph node palpation.21
[3]In women of child-bearing potential, serum pregnancy test should be obtained within 7 days prior to start of treatment.
[4]A window of +/- 21 days of scheduled visit (with exception of screening) is allowed for completion of these assessments.
[5]CT chest at Cycle 3, Day 28 will be performed if considered clinically indicated at the discretion of treating physicians (e.g. monitoring infection or pulmonary nodules).
[6]CT abdomen at screening will be performed if patient has intact spleen.
[7]CT abdomen at Cycle 3, Day 28 will be performed if splenomegaly present on screening CT abdomen.
[8]Only for those who continue vemurafenib for > 3 cycles.
[9]3-5ml of bone marrow aspirate will be collected in an EDTA-containing syringe.
[10]3 green or purple top tubes (10cc tubes) will be collected for all patients at the specified time-points.
[11]For MSKCC patients only, 3 green/purple top tubes will be collected at 2-4 hours and 24 hours after the first dose of vemurafenib. For patients treated at other centers, only the pre-treatment blood samples will be drawn (3 green top tubes).
[12] This test may be done locally
[13]Cycle 3 Day 28 visit may serve as Cycle 4 Day 1 visit for patients who will continue beyond 3 cycles for high suspicion of residual disease before waiting for BMB result at the treating phsyicain's discretion.

Table 2: Procedures for End of Treatment and Post Treatment Follow Up Visits

Phase	End of Treatment	Post Treatment Follow-Up[1,2]
Time Frame	4 weeks from last treatment dose	Every 3 months post last dose
History and Physical Exam	X	X
Head and Neck Examination		X
Dermatology Evaluation[3, 5]	X	X
CBC w/ diff & Platelets, COMP, LDH	X	X
Survival assessments[4]	X	X

[1]These evaluations will continue up to 12 months after study drug discontinuation.
[2]A +/- 14 day window is allowed for this assessment.
[3]This evaluation may be perfomed locally
[4]Survival assessment will be collected on an ongoing basis and at least every 3 months.
[5]If clinically indicated

Table 3: Re-Treatment Evaluation on Study

Phase	Study Visits									
Cycle	1				2		3		"X"	
Day[1]	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 28+/-4	Day 1	As clinically indicated
History and Physical Exam	X				X		X		X	
Head and Neck Exam[2]	X				X					
ECG	X		X[8]		X		X		X[10]	
Dermatology Exam[3, 8]							X			X
CBC w/ diff, Platelets	X	X[8]	X[8]	X[8]	X	X[8]	X	X	X	
Smear Review	X	X[8]	X[8]	X[8]	X		X		X	
COMP, LDH	X				X		X	X	X	
Phosphorus, Uric Acid	X	X[8]	X[8]	X[8]						
PT/PTT										
HIV, Hepatitis B and C Testing										
Adverse Events	X				X		X		X	
Review of Concomitant Medications	X				X		X		X	
CT Chest								X[4]		
CT Abdomen								X[5]		
Bone Marrow Aspirate and/or Biopsy								X[9]		X[9]
Research Tests										
Bone Marrow Aspirate and/or Biopsy[6]								X[9]		X[9]
Peripheral Blood[7]	X				X		X	X[9]		X[9]

[1]A +/- 4 day window will be allowed for completion of scheduled clinic visits (i.e. holidays, travel delays, site closures, other reasons, etc.)
[2]Head and neck examination can be performed as part of general physical exam, and consist of visual inspection of the oral mucosa and lymph node palpation.
[3]A window of +/- 21 days of scheduled visit is allowed for completion of these assessments.
[4]CT chest at Cycle 3, Day 28 will be performed if considered clinically indicated at the discretion of treating physicians (e.g. monitoring infection or pulmonary nodules).
[5]CT abdomen at Cycle 3, Day 28 will be performed if splenomegaly present on screening CT abdomen.
[6]3-5ml of bone marrow aspirate will be collected in an EDTA-containing syringe.

[7]3 green or purple top tubes (10cc tubes) will be collected for all patients at the specified time-points.
[8]This test may be done locally
[9]The bone marrow aspirate and/or biopsy may be performed for assessment of response at the end of the third retreatment cycle OR during a subsequent re-treatment cycle when clinically indicated. The timing also applies for research samples.
[10]ECGs are to be performed every 3 months after Cycle 3 of Re-Treatment

11.0 TOXICITIES/SIDE EFFECTS

11.1 Expected Side Effects of Vemurafenib

Although vemurafenib has been extensively studied in patients with melanoma in phase I, II and III trials, the side effects in patients with HCL are unknown. Based on clinical experience in patients with melanoma, following adverse events can be expected at the dose of 960mg b.i.d. Guidelines for management of the toxicity are given in Section 9.2.

- Common: rash, photosensitivity, pruritus, palmar-plantar erythrodysesthesia (PPE), cutaneous SCC, fatigue, arthralgia, dry skin, mild hair loss and acute kidney injury
- Uncommon: increased AST, ALT, alkaline phosphatase and bilirubin, fever, nausea, vomiting, diarrhea, anorexia, weight loss, headache, neuropathy, altered taste
- Rare: pancytopenia, pancreatitis, conjunctivitis, pericarditis, renal impairment, dysphagia, arthritis, gastrointestinal polyps, allergic reactions, Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), retinal vein occlusion, Dupuytren's contracture and plantar fibromatosis, Peripheral Edema.

11.2 Assessments of Adverse Events

11.2.1 Adverse Events

An adverse event (AE) is any unfavorable and unintended sign, symptom, or disease temporarily associated with the use of an investigational medicinal product 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 HCL that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions
- 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.

To ensure consistency of AE and SAE (see below in Section 11.2.2) causality assignments, the following general guidelines should be applied:

- **Yes:** There is a plausible temporal relationship between the onset of the AE and administration of vemurafenib 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 vemurafenib; and/or the AE abates or resolves upon discontinuation of vemurafenib or dose reduction and, if applicable, reappears upon re-challenge.
- **No:** Evidence exists that the AE has an etiology other than vemurafenib (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to vemurafenib administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected AEs are those adverse events that are listed or characterized in the Package Insert (P.I.) or current Investigator Brochure (I.B.). Unexpected AEs are those not listed in the P.I. or current I.B. or not identified. This includes AEs for which the specificity of 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.

Toxicity will be graded and recorded using the NCI Common Toxicology Criteria version 4.0. Clinically significant adverse events will be noted and compared to the baseline condition. Adverse events that will be noted will include expected side effects, and any other clinically significant symptom or laboratory value. An assessment will be made concerning the severity of the event, and if the event appears to be related to the study drug. Adverse events, toxicity grading, and attributions will be recorded in the electronic database by the Clinical Research Associate (CRA) after review of the data by the Principal Investigator.

11.2.2 Serious Adverse Events (SAEs) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE. SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following

  - An explanation of how the AE was handled
  - A description of the participant's condition
  - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

For IND/IDE protocols:
The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office

11.2.3 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 28 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.

11.2.4 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

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?"

Specific Instructions for Recording Adverse Events

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

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

b. Deaths
All deaths that occur during the protocol-specified AE reporting period (see Section I), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

c. Preexisting Medical Conditions
A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is

important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

d. Hospitalizations for Medical or Surgical Procedures

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

Hospitalizations for the following reasons do not require reporting:
Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

e. Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v 5 .0) will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated d
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE 5, which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event

d. Grade 4 and 5 events must be reported as serious adverse events

f. Pregnancy

If a female subject becomes pregnant while receiving the Vemurafenib or within 6 months after the last dose of Vemurafenib, or if the female partner of a male study subject becomes pregnant while the study subject is receiving Vemurafenib or within 6 months after the last dose, a report should be completed and expeditiously submitted to 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 study drug should be reported as an SAE.

g. AEs of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
  Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ ULN
  Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with clinical jaundice
- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:
  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected
- Acute Kidney Injury
- Bone Marrow Toxicity
- Cutaneous Squamous Cell Carcinomas
- Gastrointestinal Polyps
- Hypersensitivity and Severe Cutaneous Reactions
- Liver Injury
- New/Second Primary Melanomas
- Non cutaneous Squamous Cell Carcinomas
- Pancreatitis
- Photosensitivity
- Potentiation of Radiation Toxicity
- Progression of RAS Mutant Malignancies
- QT Prolongation
- Retinal Vein Occlusion
- Uveitis
- VII Nerve Paralysis

h. Other Special Situations Reports

The following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech:

- Data related to the Product usage during breastfeeding
- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

i. Product complaints

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

f. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior vemurafenib 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.

11.3 Photosensitivity

Photosensitivity has been reported in approximately 50% of vemurafenib-treated patients in the phase 2 study of metastatic melanoma patients[42]. The majority of cases were mild or moderate in severity. All patients should therefore be advised to avoid sun exposure and/or use sun block and lip balm (minimum of SPF 30, re-applied every 2 to 3 hours) during vemurafenib treatment and for at least 5 to 10 days after study drug discontinuation.

11.4 Ophthalmologic Reactions

In the phase 3 study of 675 metastatic melanoma patients[33], five cases of uveitis have been reported in patients treated with vemurafenib. Treatment with steroid and mydriatic ophthalmic drops may be required to manage uveitis. Patients should be routinely monitored for signs and symptoms of uveitis. Additionally, there were five patients with blurry vision, five patients with iritis and six patients with photophobia. There was one case of retinal vein occlusion in the phase 2 study of 132 metastatic melanoma patients[42].

11.5 Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported in association with vemurafenib and upon re-initiation of treatment. Severe hypersensitivity reactions included generalized rash and erythema or hypotension. In patients who experience a severe hypersensitivity reaction, vemurafenib treatment should be permanently discontinued.

11.6 Dermatologic Reactions

Severe dermatologic reactions have been reported in patients receiving vemurafenib, including one case of Stevens-Johnson syndrome and one case of toxic epidermal necrolysis in the phase 3 study[33]. In patients who experience a severe dermatologic reaction, vemurafenib

treatment should be permanently discontinued.

11.7 Liver Laboratory Abnormalities

Liver laboratory abnormalities have occurred with vemurafenib. Liver enzymes (transaminases and alkaline phosphatase) and bilirubin should be monitored before initiation of treatment and monthly during treatment, or as clinically indicated. Laboratory abnormalities should be managed with dose reduction, treatment interruption, or treatment discontinuation (see Section 9.2 for dose modification instructions).

11.8 Cutaneous Squamous Cell Carcinoma

Cutaneous squamous cell carcinoma (cuSCC) is defined as an AE of special interest. Investigator and patient should perform routine skin examination at least once per cycle (28 days). Suspicious lesions or rashes should be referred to a dermatologist. A dermatologist should perform a full skin exam during screening/baseline, after 4 weeks of treatment, and every 12 weeks thereafter until discontinuation of the drug. Patients who withdrew from the study for any reason will be followed for SCC evaluation for 6 months after study drug discontinuation, start of new antineoplastic therapy, or until death, withdrawal of consent, or lost to follow up, whichever occurs first. Additionally, at baseline, the dermatologist will perform a complete dermatological history of prior medications, non-melanoma skin cancers, including SCC and actinic keratosis and their associated treatments, and risk factors for development of cutaneous malignancies (e.g. radiation therapy, sun exposure, phototherapy, use of tanning beds, genetic conditions, and immunosuppression).

Any lesion at baseline or during treatment that is clinically suspected of representing a cuSCC, basal cell carcinoma, actinic keratosis, primary melanoma, or other skin condition identified by the dermatologist should be completely resected by a dermatologist and submitted for pathologic review. A dose reduction is not indicated for this adverse event.

11.9 Non-Cutaneous Squamous Cell Carcinoma

- Head and neck examination: A thorough head and neck examination to monitor for non-cutaneous SCC, consisting of at least visual inspection of the oral mucosa and lymph node palpation, will be performed by the treating physician during screening/baseline, after 4 weeks of treatment, and every 12 weeks thereafter until a maximum of 6 months after discontinuation of study drug or at the start of new antineoplastic therapy, death, withdrawal of consent, or lost to follow up whichever occurs first.

- Chest CT scans: A chest CT scan will be performed during screening/baseline (up to 28 days prior to start of treatment) and, if considered clinically indicated at the discretion of treating physicians, at Cycle 3 Day 28.

11.10 Cardiac Toxicity

Data from the phase II trial indicate that some patients treated with vemurafenib 960mg twice a day developed mild QTc prolongation. The largest mean QTc change from baseline was 15.1 milliseconds (msec). One patient on study had a QTc change of >60 msec. Two patients (1.5%) developed QTc prolongation >500 msec. No ventricular arrhythmias have been reported to date.

The following recommendations have been developed to minimize the risk of arrhythmias on study:

- Avoid combination with other agents with known potential to lead to QTc prolongation.
- ECG should be monitored on day 1 prior to the first dose of vemurafenib, pre-dose on day 15 after study drug initiation, every 4 weeks for the next 3 cycles, and every 12 weeks thereafter.
- If QTc interval exceeds 500 msec or the change from baseline is >60 msec, on three separate ECGs, vemurafenib treatment should be temporarily interrupted. The investigator should check electrolytes (K, Mg, and Ca), correct any electrolyte abnormalities prior ot reinstitution of therapy, recheck concomitant medications to insure that non has been implicated in QTc prolongation, and rule out or control other cardiac risk factors (i.e. ischemia). Monitor ECG weekly until QTc decreases to < 500 msec and reinitiate treatment at once reduced level from 960 mg b.i.d. to 480 mg b.i.d.
- Vemurafenib should be permanently discontinued if a QTc increase meets both criteria of > 500 msec and > 60 msec change from pre-treatment values or if QTc > 500 msec or change from baseline > 60 msec is observed on two separate occasions.

11.11 Renal and Urinary Toxicity

A review of the Roche safety database (with an estimated exposure to vemurafenib of 28,809 patients) in May 2015 concluded that acute kidney injury is an adverse drug reaction (ADR) in patients treated with vemurafenib. This was based on 145 AKI cases with some evidence of vemurafenib causality, of which 102 cases were assessed to have strong evidence. The cases ranged within a broad spectrum, majority were mild (> 1-1.5 x ULN) to moderate (> 1.5 – 3 x ULN) creatinine elevations, that appear to be reversible in nature. There were 3 cases of biopsy-proven interstitial nephritis, 4 cases of biopsy-proven tubular injury/acute tubular necrosis (ATN), and 20 cases presented with DRESS or DRESS-like symptoms.

11.12 Reproductive Risk

The teratogenic potential of vemurafenib has not been investigated. However, women who are pregnant or nursing will be excluded from this study. Women of childbearing potential, including those who have had a tubal ligation, are required to have a negative serum pregnancy test within 7 days prior to start of treatment. Women of childbearing potential are required to use two effective methods of contraception (including one barrier method) during the study and for 6 months after discontinuation of vemurafenib. Male patients (including those who have undergone vasectomy) with female partners of childbearing potential should use a latex condom during any sexual contact and should advise their partners to use an additional method of contraception during the study and for at least 6 months after discontinuation of vemurafenib.

11.13 Acute Kidney Injury

Incidence rate on the Phase III Study (NO25026) was 10% among patients who received vemurafenib versus 1.4% who received dacarbazine. Approximately 40% patients receiving vemurafenib developed creatinine elevations at some point in the study compared to patients receiving dacarbazine (6%).

11.14 Potential for Drug-Drug Interaction

11.14.1 Effects of Vemurafenib on Drug Metabolizing Enzymes

Vemurafenib is a moderate CYP1A2 inhibitor, a weak CYP2D6 inhibitor, and a CYP3A4 inducer. Co-administration of vemurafenib increased the AUC of caffeine (CYP1A2 substrate)

2.6-fold and increased the AUC of dextromethorphan (CYP2D6 substrate) by 47%, while it decreased the AUC of midazolam (CYP3A4 substrate) by 39%. Concomitant use of vemurafenib with agents with narrow therapeutic windows that are metabolized by CYP1A2, CYP2D6 and CYP3A4 is not recommended as vemurafenib may alter their concentrations. If coadministration cannot be avoided, exercise caution and consider a dose reduction of the concomitant CYP1A2 and CYP2D6 substrate drug. Co-administration of vemurafenib resulted in an 18% increase in AUC of S-warfarin (CYP2C9 substrate). Exercise caution and consider additional INR monitoring when vemurafenib is used concomitantly with warfarin.

11.14.2 Drugs that Inhibit or Induce CYP3A4

Vemurafenib is a substrate of CYP3A4, and therefore, concomitant administration of strong CYP3A4 inhibitors or inducers may alter vemurafenib concentrations. Strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) and inducers (e.g. phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) should be used with caution when co-administered with vemurafenib.

Appendix A includes a non-exhaustive list of typical examples of CYP1A2 and CYP2C9 substrates and CYP3A4 inducers and inhibitors.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Response will be determined by the Consensus Resolution response criteria[43].

Complete Response (CR)

- A morphological absence of hairy cells in the blood and bone marrow
- A normalization of any organomegaly and cytopenias

Partial response (PR)

- A normalization of cytopenias
- Circulating hairy cells ≤5% of lymphocytes
- ≥50% reduction in organomegaly and bone marrow hairy cells.

All other responses are considered as no response (NR)

Relapse after CR

- Reappearance of hairy cells in the blood or bone marrow
- Development of cytopenias and/or organomegaly on physical examination

Relapse after PR

- >50% increase of residual disease

13.0 CRITERIA FOR REMOVAL FROM STUDY

- Ineligibility (at the pretreatment evaluation) of the patient as defined in the inclusion/exclusion criteria
- Unacceptable toxicity (as defined in Section 11.0)
- Disease progression requiring alternate therapy (will still be followed for survival)
- Significant protocol violation

- Non-compliance of the patient
- Refusal of the patient to continue treatment and/or observation
- Unrelated medical illness or complication that increase the risk of protocol therapy to unacceptable levels
- Decision by the Investigator that termination is in the patient's best medical interest
- Lost to follow-up
- Death of the patient

14.0 BIOSTATISTICS

The primary objective of this phase II trial is to determine the overall response rate after therapy with the BRAF inhibitor, Vemurafenib, in patients with relapsed and refractory HCL. The outcome is determined as the overall response by three months. Currently, there is no standard treatment for these patients.

We propose a single arm, multi-center, open-label, phase II study of Vemurafenib in patients with HCL who are resistant to or intolerant of purine analogs, who have relapsed disease within 2 years of purine analog-based therapy, or who have ≥ 2 relapses. A Simon's mini-max two-stage design will be employed to assess the efficacy of Vemurafenib. Without a standard of care for these relapsed or refractory patients, there is no well-estimated historical benchmark to base the response rates for this trial. However, an observed response rate of at least 20% would provide sufficient evidence that vemurafenib should be further investigated in this patient population. Therefore, this study is designed such that a 20% overall response rate (PR or better) by three months would not be considered promising, while a 40% response rate would be considered promising..

In the first stage of the study, 19 patients will be treated. If 3 or fewer responses are seen among the first 19 patients, the study will be closed for lack of efficacy. If at least 4 patients respond to the treatment, then an additional 17 patients will be accrued to the second stage. At the end of the trial, if 11 or more patients have responded out of the 36 patients then the drug will be considered worthy of further investigation. The Type I and Type II errors are both 0.10. Safety and tolerability data of the intervention will be tabulated across all study subjects.

In addition to the primary outcome, there are a number of secondary objectives for this trial. Kaplan-Meier methodology will be used to estimate the time to response, duration of response, and progression-free and overall survival. Throughout the study, MRD will be evaluated to determine whether individuals who achieved CR have residual disease by IHC.

High throughput next generation sequencing will explore the mutation profile for BRAF and 29 additional genes at baseline and after three treatment cycles. These binary data will be descriptively reviewed by treatment response.

Pre- and post-treatment peripheral blood or bone marrow samples will be assessed by Western Blot and/or phospho-flow cytometry for downstream targets of BRAF (MEK, pMEK, ERK, pERK). These binary pre/post data will be tabulated across the sample to describe the pharmacodynamics of the intervention. The data will also be compared to a new assay developed by the Abdel-Wahab lab.

The final secondary objective will explore various biomarkers at baseline to investigate whether any are more frequently observed in individuals who are refractory or resistant to vemurafenib. These biomarkers will additionally be obtained in patients who are refractory to vemurafenib

after three cycles of treatment or in patients who relapse after vemurafenib. The biomarkers are described in Section 10.3.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

All participants must be registered through CTMS.

15.2 Randomization

There is no randomization in this trial.

16.0 DATA MANAGEMENT ISSUES

This is a multicenter trial that will be coordinated by the Multicenter Core group at MSKCC. A Clinical Research Associate (CRA) will be assigned to the study. The responsibilities of the CRA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team. The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluation and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated. Additionally, monthly teleconferences including principal investigators and/or their designees from all sites will be held to expedite the review of toxicity and efficacy data.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled ""Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials."

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. At a departmental/PI level there exists procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Deputy Physician-in-Chief, Clinical Research.

The degree of monitoring required will be determined based on level of risk and documented.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

- MSK Investigator Initiated Trials (IITs; MSK as sponsor)
- External studies where MSK is the data coordinating center
- Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participant/or by the end of the year one if no accruals and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.

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17.0 PROTECTION OF HUMAN SUBJECTS

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with others at the time of study publication.

17.2 Serious Adverse Event (SAE) Reporting

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported. Please refer to section 11.2.2 for more detail information.

17.2.2 SAE Reporting to Genentech (MSKCC STAFF ONLY)

MSK will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation reports, AESIs and Product Complaints with an AE where the patient has been exposed to Vemurafenib. The completed MedWatch form should be sent to the Genentech contact specified below.

Fax: 650-238-6067

Email: usds_aereporting-d@gene.com

All Product Complaints without an AE should call via:

PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)

Transmission of these reports (initial and follow-up) will be either electronically via email or by fax and within the timelines specified below:

- **Serious Adverse Drug Reactions (SADRs)**
  Serious AE reports that are related to the Product or where the causality is assessed as unknown or not provided shall be transmitted to Roche within fifteen (15) calendar days of the awareness date.
- **Other SAEs**
  Serious AE reports that are unrelated to the Product shall be transmitted to Roche within thirty (30) calendar days of the awareness date.

- **Special Situation Reports**

- **Pregnancy reports**
  While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy (including pregnancy occurring in the partner of a male study subject), where the fetus may have been exposed to the Product, shall be transmitted to Roche within thirty (30) calendar days of the awareness date. Pregnancies will be followed-up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.
  Pregnancies in Female Partners of Male Patients
  Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 moths after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to Genentech within thirty (30) calendar days of the awareness date.

  Other Special Situation Reports, as defined above, shall be transmitted to Roche within thirty (30) calendar days of the awareness date.

- **Product Complaints**
  All Product Complaints (with or without an AE) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

- **AESIs**
  AESIs requiring expedited reporting (related or possibly related to Roche product or where the causality is assessed as unknown or not provided) shall be forwarded to Roche within fifteen (15) calendar days of the awareness date. Others (non-related to Roche product) shall be sent within thirty (30) calendar days.

Case Transmission Verification of Single Case Reports

MSK agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via MSK emailing Genentech a Quarterly line-listing documenting single case reports sent by MSK to Genentech in the preceding quarter.
The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by MSK to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630

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 emailed to Genentech at: Genentech Drug Safety CTV mail box: ctvist_drugsafety@gene.com

Final study report:

MSK will forward a copy of the Final Study Report to Genentech upon completion of the Study.

STUDY CLOSE-OUT

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

[Bina Machchhar - machchhb@gene.com]

And to Genentech Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com

QUERIES

Queries related to the Study will be answered byMSK. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Product. MSK agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

SAFETY CRISIS MANAGEMENT

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.

The Parties agree that Genentech shall have the final say and control over safety crisis management issues relating to the Product. MSK agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech.

COMPLIANCE WITH PHARMACOVIGILANCE AGREEMENT / AUDIT

The Parties shall follow their own procedures for adherence to AE reporting timelines.
Each Party shall monitor and, as applicable, request feedback from the other Party regarding AE report timeliness in accordance with its own procedures. The Parties agree to provide written responses in a timely manner to inquiries from the other Party regarding AE reports received outside the agreed upon Agreement timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this Agreement, both Parties agree to conduct ad hoc or institute a regular joint meeting to address the issue.

In case of concerns related to non-compliance of processes, other than exchange timelines, with this Agreement, the Parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant Party to

solve the non-compliance issues and inform the other Party of the corrective and preventative actions taken.

Upon justified request, given sufficient notice of no less than sixty (60) calendar days, an audit under the provisions of this Agreement can be requested by either Party. The Parties will then discuss and agree in good faith upon the audit scope, agenda and execution of the audit. The requesting Party will bear the cost of the audit.

17.3 Reporting to Regulatory Authorities, Ethics Committees and Investigators

MSK, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the Study to the Regulatory Authorities (FDA) where it has filed a clinical trial approval, in compliance with local regulations.

MSK, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the study to the EMA through Eudravigilance Clinical Trial Module (EVCTM), where applicable.

17.3.2 Reporting Requirements for IND Holders

For Investigator-Initiated 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 Vemurafenib. An unexpected adverse event is one that is not already described in the Vemurafenib 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 Vemurafenib. 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: 650-238-6067
Email: usds_aereporting-d@gene.com

And MSK will be responsible for the distribution of safety information to Site IRB:

All Product Complaints without an AE should call via:

PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)

18.0 INFORMED CONSENT PROCEDURES

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

The consent form will include the following:

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

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

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

19.0 REFERENCES

19.0 REFERENCES

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20.0 APPENDICES

Appendix A: Impact of Vemurafenib on Concomitant Medications

Appendix B: ECOG Performance Status

Appendix C: Medication Diary for Vemurafenib

Appendix D: Multicenter Addendum for Participating Sites

Appendix E: Genentech Safety reporting Fax cover sheet

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET

Genentech Supported Research

AE / SAE FAX No: (650) 238-6067

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

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

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

SAE or Safety Reporting questions, contact Genentech Drug Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET