MSK PROTOCOL COVER SHEET

Phase II Trial of Single-agent Cobimetinib for Adults with Histiocytic Disorders

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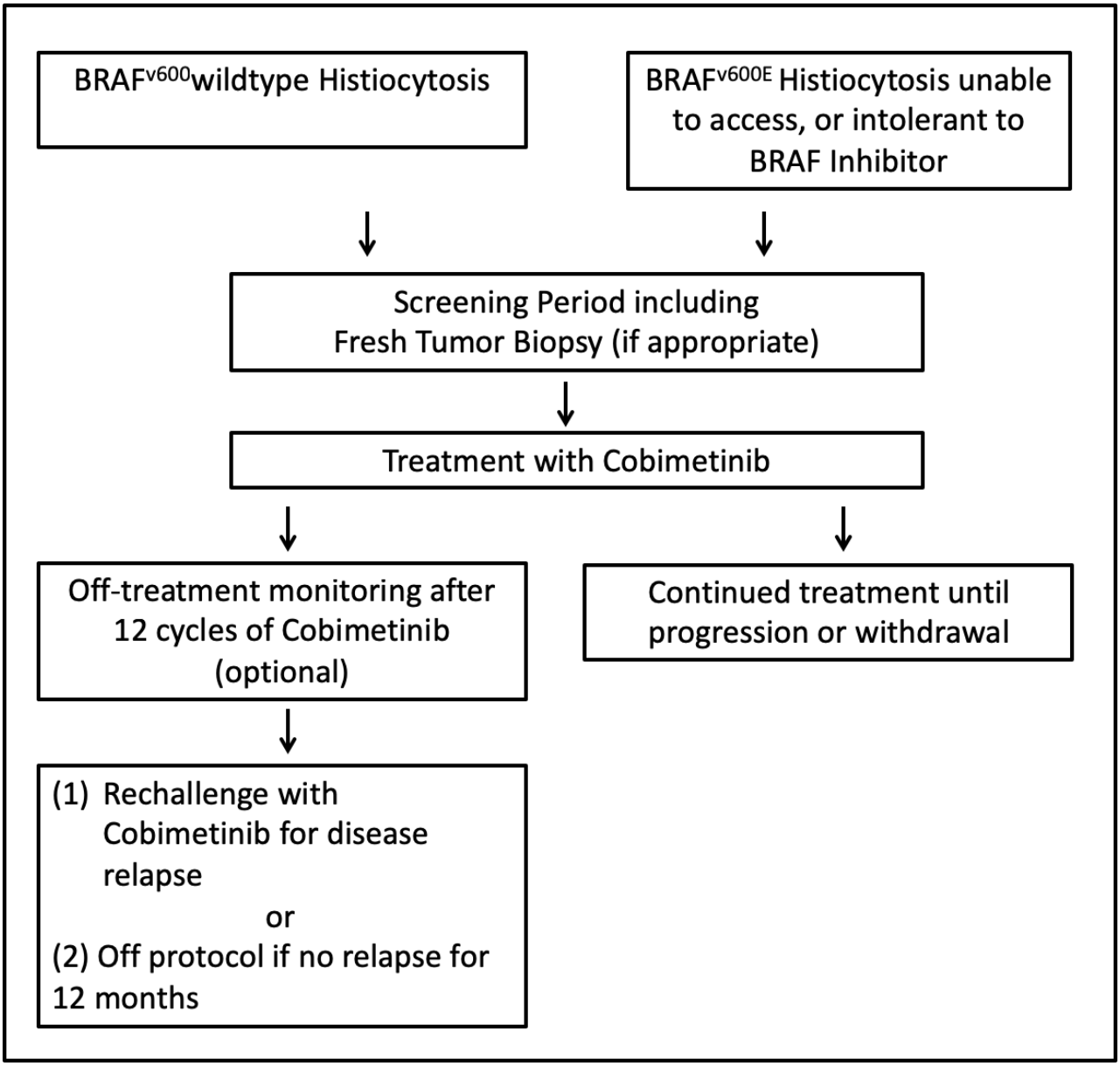
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This trial, "A Phase II Trial of Single-agent Cobimetinib for Adults with Histiocytic Disorders" is an investigator-initiated, multicenter, open-label phase II study exploring the safety and efficacy of monotherapy with Cobimetinib, an oral selective MEK1 inhibitor, in patients with histiocytic disorders including Langerhans Cell Histiocytosis (LCH) and Erdheim-Chester disease (ECD). Genomic studies of LCH and ECD at MSKCC and elsewhere strongly suggest that these disorders are marked by alterations of the MAP kinase pathway including ARAF, BRAF, NRAS, KRAS, and MAK2K1, and our therapeutic trial of Vemurafenib for BRAFV600E-mutant LCH/ECD has demonstrated dramatic and sustained response to single-agent therapy.

55 patients with a confirmed histiocytic disorder (confirmed by examination of biopsy material in the setting of appropriate clinical and radiologic findings) will be enrolled in this study. The trial will consist of a screening period (Day -28 to -1), a treatment period, and end-of-treatment visit occurring when study medication is discontinued for any reasons, a safety-follow-up visit occurring 28 (±5 days) after the last dose of study medication and a survival follow-up period lasting for a minimum of 12 months after enrollment of the last patient or until all patients have died, withdrawn consent or are lost to follow-up (whichever occurs first). Day 1 of the study will be defined as the first day a patient received study medication. One cycle of therapy will be defined as 28 days of treatment. Cobimetinib 60mg will be administered once daily on days 1-21 of each treatment cycle. Treatment will continue until progression, intolerable adverse events, or withdrawal. Patients will have the option to discontinue treatment after 12 cycles and will be monitored for disease relapse for an additional 12 months. In the event that disease relapse occurs within the 12 month monitoring period, patients will restart treatment and continue on study as described below.



2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary Endpoint:

- Best overall response rate according to PET Response Criteria (PRC)

Secondary Endpoints:

- Best overall response rate according to RECIST v1.1 (for the subset of patients with RECIST-measurable disease)
- The following secondary endpoints will be based on response and progression as defined by the PRC:
    a. Time to Progression
    b. Progression-free Survival

c. Duration of Response
d. Clinical benefit rate (for patients with CR, PR, or stable disease)

- Overall Survival
- Safety of Cobimetinib in patients with histiocytosis

Exploratory Endpoints:

- Response as determined by mutational allele burden in plasma cell-free DNA
- Exploratory Quality of life (QOL) and Patient-Reported Outcome (PRO) Responses

3.1 BACKGROUND AND RATIONALE

The systemic histiocytic disorders Erdheim-Chester disease (ECD) and Langerhans cell histiocytosis (LCH) are rare hematologic malignancies with heterogeneous clinical courses and prognoses which share a common primary event: the pathologic accumulation and infiltration of cells of the monocyte/macrophage lineage in affected tissues. Currently there are no approved therapies for these disorders. Recently, a major breakthrough in the management of these disorders was made following the discovery of *BRAF*^{V600} mutations in 50% of LCH and ECD patients (**Figure 1**).(1, 2) Given this important finding, we expeditiously amended an existing multicenter Phase II clinical trial (NCT01524978, PI: Hyman) to initiate treatment of *BRAF*^{V600} mutant histiocytosis patients with Vemurafenib. The responses to Vemurafenib in the first 18 multisystemic *BRAF* mutant histiocytic disorder patients have been unprecedented in both magnitude and durability.(3) Thus far, no patient has developed acquired resistance despite follow-up of more than two years in the longest treated patients. Given the rarity of these disorders, we anticipate that these extraordinary data will be sufficient to support expanded labeling of Vemurafenib for *BRAF*^{V600} mutant ECD/LCH by the regulatory authorities.

As of a data lock performed on June 10th 2014, 18 ECD/LCH patients had enrolled on the MSK-lead international Vemurafenib study (15 at MSKCC, 3 at other sites) – one of the largest collections of adult histiocytosis patients ever enrolled on a prospective clinical trial.(3) Patients were generally heavily pre-treated with a variety of off-label therapies with 50% of patients having received ≥2 prior therapies. All patients were symptomatic from their disease at the time of enrollment and 3 patients had an ECOG performance status of 2. The remarkable preliminary response data are summarized in **Figure 2**. The overall response rate was 40% (95% CI: 16.3-67.7) and the clinical benefit rate was 93.3% (95% CI: 98.1-99.8). No patient discontinued for progressive disease despite a median treatment duration at the time of data lock of 181 days (range, 19-568). Tumor regressions were observed in 92.9% (13/14) of patients assessed for response. With longer follow-up since this data lock, the median treatment duration now exceeds 1 year with no events of disease progression. The median progression free survival and overall survival have not yet been reached.

Figure 3 shows images from 2 representative patients treated on this study. Patient 1 had extensive ECD involving the brain, bones, and retroperitoneum and has had both a partial radiographic response and marked clinical benefit. Importantly, this response has been sustained for 26 months and the patient continues on treatment. Patient 2 has LCH with debilitating cutaneous involvement previously requiring narcotics and resulting in recurrent infection. She achieved both a complete clinical and pathologic response after only 4

weeks of therapy (**Figure 3B**). Her complete pathologic response has been sustained for 24 months and she continues on treatment.

Although Vemurafenib treatment resulted in clear clinical benefit in all *BRAF*^{V600}-mutant ECD/LCH patients, only a proportion achieved RECIST responses as outlined above. Moreover, dramatic improvement in clinical symptoms occurred in all patients regardless of the degree of tumor regression. Because ECD lesions are known to be heavily infiltrated by fibroblasts and other inflammatory cells, we hypothesized that residual lesions might represent post-treatment scarring rather than active malignancy (**Figure 4**). In fact, on-treatment tumor biopsies of persistent lesions from patients on this study have demonstrated fibrous scar without evidence of persistent histocytes. To determine if molecular response to RAF inhibition could instead be used as a non-radiographic surrogate for response, we performed an analysis of the *BRAF*^{V600E} mutation in circulating tumor cfDNA in plasma as well as urine to both identify the *BRAF*^{V600E} mutation and monitor changes with therapy.(4) Importantly, more closely reflecting the improvement in patients' clinical status than CT imaging, *BRAF*^{V600E} allele declined significantly in all patients on Vemurafenib and in some cases the *BRAF*^{V600E} allele became undetectable **(Figure 5A-B)**. Equally important, in one patient where successful Vemurafenib inhibitor therapy was discontinued for toxicity, urinary cfDNA *BRAF*^{V600E} burden subsequently increased in parallel with radiographic evidence of disease recurrence (**Figure 5C**). **Figure 6** demonstrates the results of urinary cfDNA obtained pre-treatment and weekly for the first 2 months following initiation of Vemurafenib during which time the patient had dramatic improvement in her disease related symptoms and PET imaging. These data demonstrate the effect of RAF inhibition on the *BRAF*^{V600E} mutant clone in these patients.

cfDNA analysis also facilitated identification of previously undescribed *KRAS*^{G12S} mutant ECD and dynamically tracked disease burden in patients treated with a variety of therapies.(4) In total, these data indicate that cfDNA *BRAF*V600E mutational analysis in plasma and urine provides a convenient and reliable method of detecting mutational status and may serve as a non-invasive biomarker to monitor response to therapy in LCH/ECD. Although clinical outcomes of *BRAF*^{V600} mutant ECD and LCH patients has been dramatically altered by the use of Vemurafenib, the remaining 50% of histiocytosis patients whose tumors are *BRAF*^{V600}-negative are desperately in need of effective therapies. Recently, *MAP2K1* (MEK1) mutations have been identified in ~30% of pediatric LCH patients and are mutually exclusive with *BRAF*^{V600} mutations.(5, 6) Also, *ARAF* mutations have been found in a small proportion of *BRAF* and *MAP2K1* wildtype cases.(7) Our group has also identified *MAP2K1* and *ARAF* mutations in *BRAF*^{V600} wildtype adult ECD patients, in addition to multiple novel fusion events involving *BRAF*, *ALK*, and *NTRK1* (**Figure 1**). Together, these data strongly suggest that activation of MAP kinase pathway activation is a common downstream event in ECD and LCH, a conclusion supported by studies that have found ERK activation in ECD and LCH lesions regardless of *BRAF* mutational status.(8, 9) Based on these findings, we hypothesize that *BRAF*^{V600}-wildtype systemic histiocytosis patients will be sensitive to therapeutic targeting of the MAP kinase pathway. To this end, we are opening the current study evaluating single agent Cobimetinib, an oral selective MEK1 inhibitor, in adult patients with: 1) *BRAF*^{V600} wildtype ECD/LCH or, 2) *BRAF*^{V600} mutant ECD/LCH intolerant to Vemurafenib therapy.

Although rare malignancies in aggregate, histiocytic disorders comprise an important group of hematologic malignancies with substantial morbidity/mortality and no approved therapies currently. Our international leadership of the Vemurafenib histiocytosis trial, a first for many of these disorders, has rendered MSKCC the top national referral center for histiocytic diseases. Moreover, we are now leading a multinational funded effort to

establish the first global ECD patient registry. These projects have provided an unprecedented opportunity to study histiocytic disorders in both the lab and clinic. Importantly, the remarkable durability of responses to Vemurafenib in this study suggests that the impact of MAP-kinase pathway inhibition on the natural history of histiocytic disorders may be far greater than similar targeted therapies in solid tumors. Our multidisciplinary group of physicians and scientists now plans to extend our work to address the ongoing unmet need for therapies for the 50% of ECD and LCH patients that do not harbor *BRAF*^{V600} mutations.

As demonstrated above, tumor regression as measured by RECIST criteria under-represents the degree of clinical benefit achieved in ECD/LCH patients with RAF targeted therapy (See **Figure 7**). Moreover, the infiltrative nature of ECD means that many patients do not form well circumscribed lesions that meet criteria as RECIST target lesions despite a high burden of disease. To overcome these limitations, we amended the Vemurafenib study to implement a novel PET Response Criteria (PRC) designed in collaboration with Dr. Gary Ulaner of Nuclear Medicine. In the PRC, just as in RECIST, up to 5 target lesions are chosen and response is measured based on the response in these target lesions, measured by SUVmax. SUVmax is highly reproducible, even for lesions with lower FDG-avidity, a significant shortcoming of the previously proposed PERCIST criteria.(10) We have found that metabolic response by PRC accurately reflects clinical benefit, and we anticipate that PRC assessments in this study will allow for the most clinically and pathophysiologically accurate measurement of response to therapy.

In order to identify potential driving oncogenic alterations in *BRAF*^{V600}-wildtype histiocytosis patients as well as to identify any recurrent mutations which might co-exist with *BRAF*^{V600} mutations in ECD/LCH, we performed whole exome sequencing (WES) of prospectively acquired ECD/LCH tissue biopsy specimens from patients referred to MSKCC. WES of 23 patients with ECD/LCH revealed *BRAF*^{V600E} mutations at a similar frequency to previously reported frequencies in LCH and ECD.[2, 3, 4]

Amongst the *BRAF*^{V600E}-wildtype patients, WES demonstrated mutations in multiple genes that are expected to result in activation of MAP kinase signaling. This includes *MAP2K1 (*MEK1*)* mutations in 33% of LCH and 8% of ECD, *ARAF* mutations in 8% of ECD, and *NRAS* mutations in 8% of ECD (**Figure 8**).

The *ARAF* mutation identified occurred in recurrent hot spot in *ARAF* (the S214 residue) and has previously been functionally characterized to activate MAP kinase signaling.(11) Consistent with this, immunohistochemical analysis of this patient's tumor revealed robust ERK phosphorylation (**Figure 9**). Moreover, this mutation has been associated with dramatic responsiveness to RAF inhibition with sorafenib in one prior patient with metastatic lung cancer(11) suggesting that this mutation may have immediate therapeutic implications.

Due to the discovery of a *MAP2K1* mutation in ECD in our WES study, we next performed Sanger sequencing of *MAP2K1* in DNA from archival formalin-fixed paraffin-embedded (FFPE) tissues of histiocytic neoplasms that were known to be *BRAF*-wild type. This identified a mutational frequency of 40% in *BRAF*^{V600E}-wildtype ECD patients (**Figure 10A**). Several of the *MAP2K1* mutations identified here are known activating mutations of *MAP2K1* (e.g. the *MAP2K1*^{K57N} mutation). However, we also identified several recurrent *MAP2K1* point mutations that have never been functionally characterized previously (e.g. the recurrent *MAP2K1*^{S123} and *MAP2K1*^{E144K} mutations) (**Figure 10B**).

In parallel to the above analyses of genomic DNA, we also performed mRNA sequencing (RNA-seq) in a subset of 15 of the above cases that were sequenced by WES. Remarkably, this identified 3 in-frame translocations resulting in an activating kinase fusion in a *BRAF*V600-wildtype ECD patient (**Figure 11**). This included:

1) A *BRAF* translocation resulting in the fusion of exon 1 of *RNF11* to exons 11-18 of *BRAF* (*RNF11-BRAF*).

2) An in-frame *ALK* translocation resulting in the fusion of exons 1-24 of *KIF5B* to exons 19-29 of *ALK* (*KIF5B-ALK*).

3) An in-frame fusion translocating *NTRK1* to *LMNA* (*NTRK1-LMNA*).

In each of these fusion events, the kinase domain is retained suggesting that the translocation event leaves the kinase activity intact but disrupts the normal regulation of kinase activity. We have subsequently validated each of these events through Sanger sequencing of cDNA as well as FISH (**Figure 11**). These represent the first descriptions of activating kinase fusions in histiocytic neoplasms and the first description of a *BRAF* fusion in a hematological malignancy.

In addition to utilizing the RNA-seq data to identify fusion transcripts, we also examined gene expression amongst the patients based on genotype. Unsupervised hierarchical clustering revealed that patients with LCH clustered separately from those with non-Langerhans cell disease (**Figure 12**). However, amongst both sets of diseases, those patients which were not identified to have a kinase mutation had a similar gene expression signature as those which harbored a known kinase alteration (**Figure 13**) suggesting that these tumors all harbor activation of the MAP kinase pathway regardless of the exact kinase alteration identified.

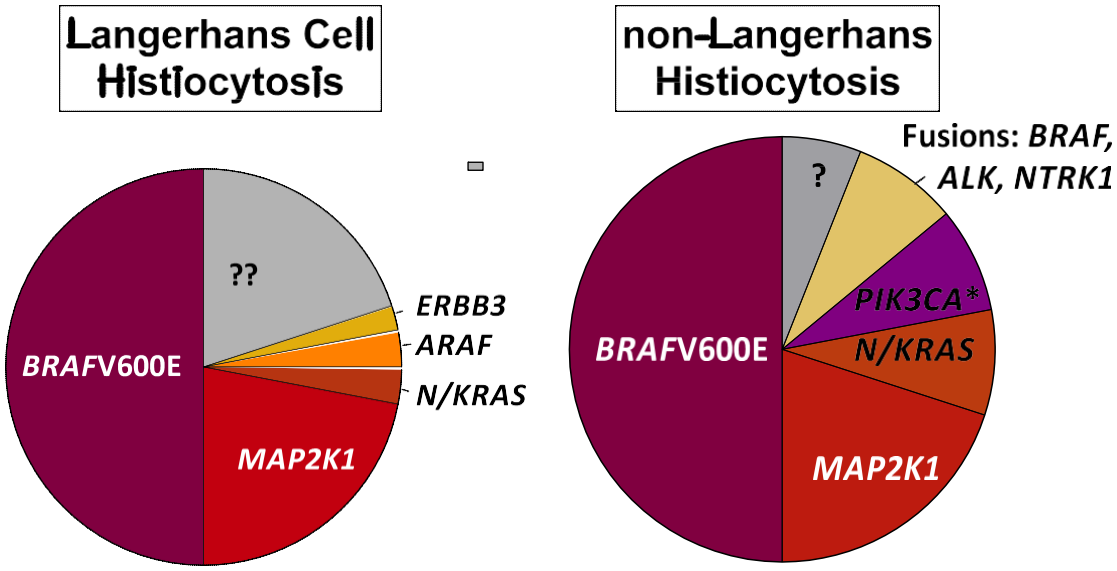
Overall, our preliminary data have identified that (1) therapeutic targeting of kinase alterations has profound therapeutic benefit in patients with systemic histiocytoses and (2) patients not identified to harbor *BRAF*^{V600}-mutations are likely to harbor alternative mutations that confer responsiveness to MAP kinase pathway inhibition. Based on these observations we now plan to test the therapeutic efficacy of MEK inhibition in systemic histiocytosis patients who do not have a *BRAF*^{V600}-mutation or who have the *BRAF*^{V600}-mutation but are intolerant to Vemurafenib. We believe this study represents the next logical and critically needed step in the therapeutic advances for these disorders.

Cobimetinib (GDC-0973, XL518) is a potent and highly selective inhibitor of MEK1 and MEK2, central components of the RAS/RAF pathway. In vitro studies showed that Cobimetinib is a time-dependent inhibitor of CYP3A and a competitive inhibitor of CYP2D6, although in-human studies did not replicate these findings. In vitro studies also show that Cobimetinib is a substrate of CYP3A and UGT2B7. Cobimetinib pharmacokinetics (PK) have been characterized in cancer patients following oral administration after single and multiple dosing in the Phase Ia dose-escalation study (MEK4592g). Stages II and IIA expansion stages further evaluated the safety, potential efficacy, and pharmacodynamic effects of Cobimetinib at the MTDs determined in Stage I and Stage IA in patients with RAS- and RAF-mutant tumors. See Section 5.0 (THERAPEUTIC/DIAGNOSTIC AGENTS) for details on these trials and section 11.0 for summarized toxicity data.

To date, we have treated one patient with ECD with a MEK inhibitor (off label Trametinib) with dramatic clinical response. This 52 year-old man with multisystem ECD was hospitalized for cytopenias, ascites, and renal failure in the setting of refractory disease.

He was previously treated with standard and pegylated interferon as well as anakinra. Trametinib was administered in the hospital and in the two weeks to follow his creatinine lowered to 0.9, ascites stopped accumulating, and his platelets rose above 50,000 for the first time in months. Now 6 weeks after starting Trametinib, platelets are above 100,000 and chemistries remain normal. PET scan demonstrated resolution of known avid abnormalities.

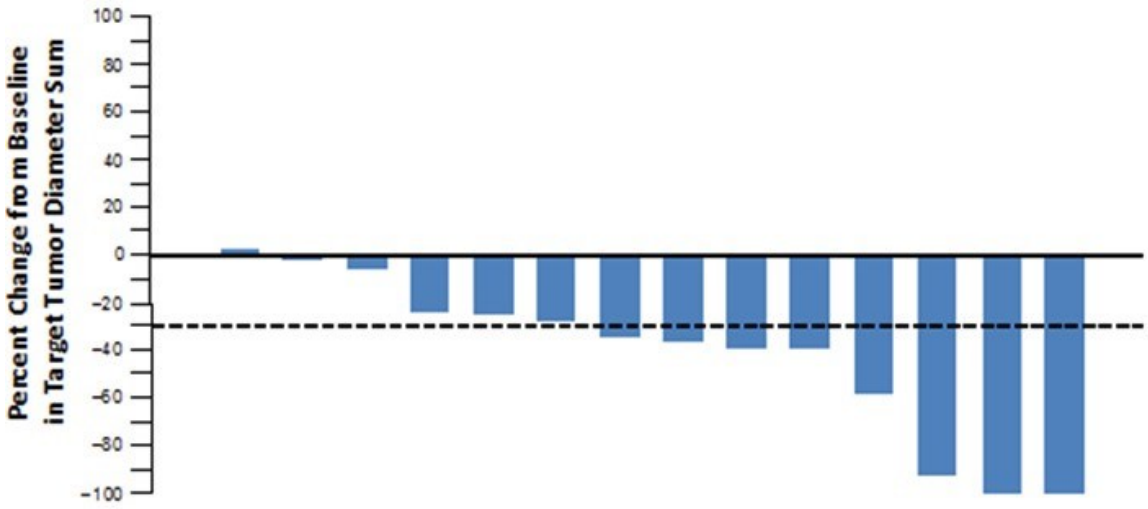
Figure 1: Schematic depiction of the recurrent kinase alterations identified in patients with Langerhans Cell Histiocytosis (LCH) and non-Langerhans Cell Histiocytoses (Erdheim Chester Disease and Juvenile Xanthogranuloma). These data are derived from published data as well as our own unpublished data.



* A proportion of *PIK3CA* mutant patients have concomitant *BRAF*V600E mutations.

Figure 2: Waterfall and Swimmer plots of patients with systemic histiocytoses treated as part of the phase II clinical trial of Vemurafenib for *BRAF*^{V600}-mutant tumors (the VE-Basket Study). (A) Percent change in tumor diameter of sum of target lesions. (B) Time to events by patient and best overall response (confirmed). Bar length for those patients who do not have disease progression (box) or death (circle) represents progression-free survival duration. Purple bars indicate patients who remain on therapy, orange bars those who have discontinued therapy.

a)



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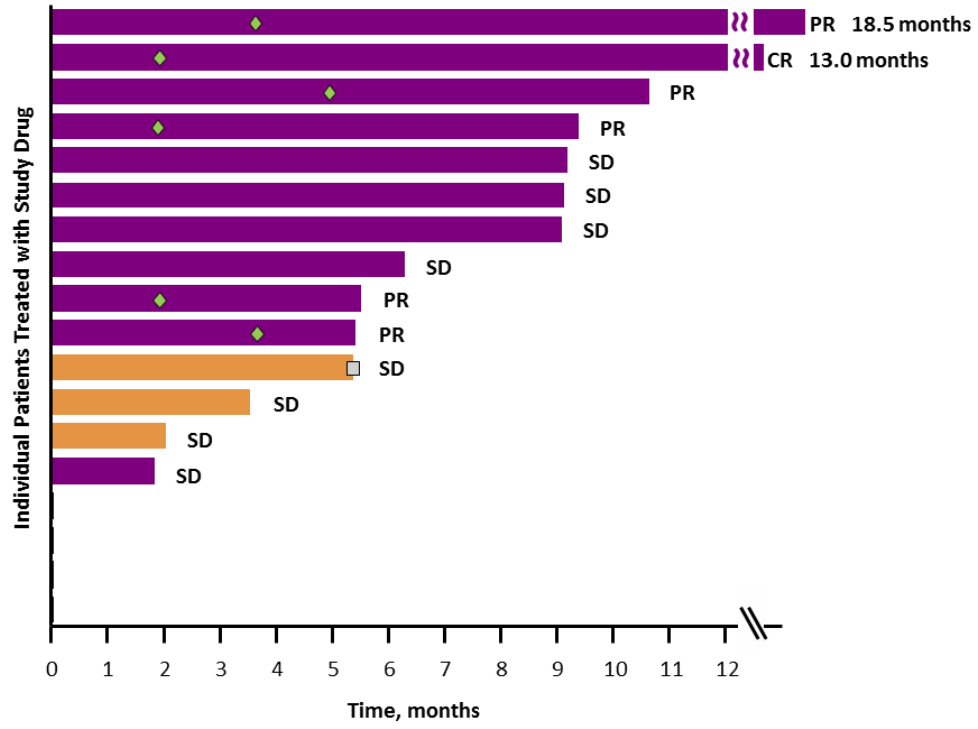


Figure 3: Images of clinical responses to Vemurafenib in patients with *BRAF*^{V600E}-mutant systemic histiocytoses (ECD: Erdheim-Chester Disease; LCH: Langerhans Cell Histiocytosis). (A) MRI images of an ECD patient cerebellar lesions pre-Vemurafenib and then following 2 months of Vemurafenib. (B) Photos of the skin lesions of an LCH patient pre-Vemurafenib and following 4 months of Vemurafenib.

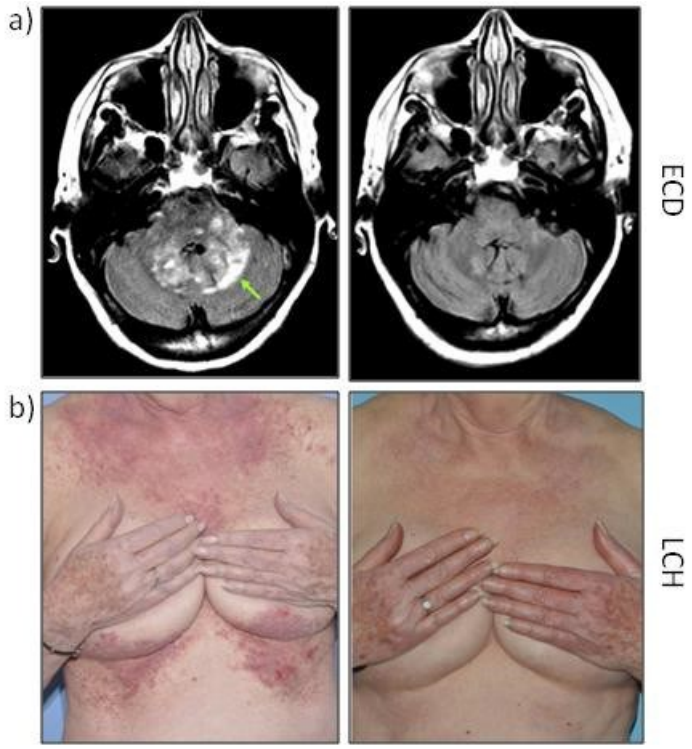


Figure 4: Use of cell-free DNA (cfDNA) analyses to monitor response of *BRAF*V600E-mutant histocytosis patients to Vemurafenib. (A) Comparison of urinary cfDNA *BRAF*V600E allele burden in patients pre-Vemurafenib versus on Vemurafenib. (B) Serial urinary *BRAF*V600E cfDNA measurements in first 7 patients treated with Vemurafenib. (C) FDG-PET scan images (top) along with urinary *BRAF*V600E allele burden pre-Vemurafenib, following 2 months of Vemurafenib, and 3 months after Vemurafenib discontinuation. The PET scan reveals the classic femoral lesions of ECD pretreatment and following Vemurafenib discontinuation.

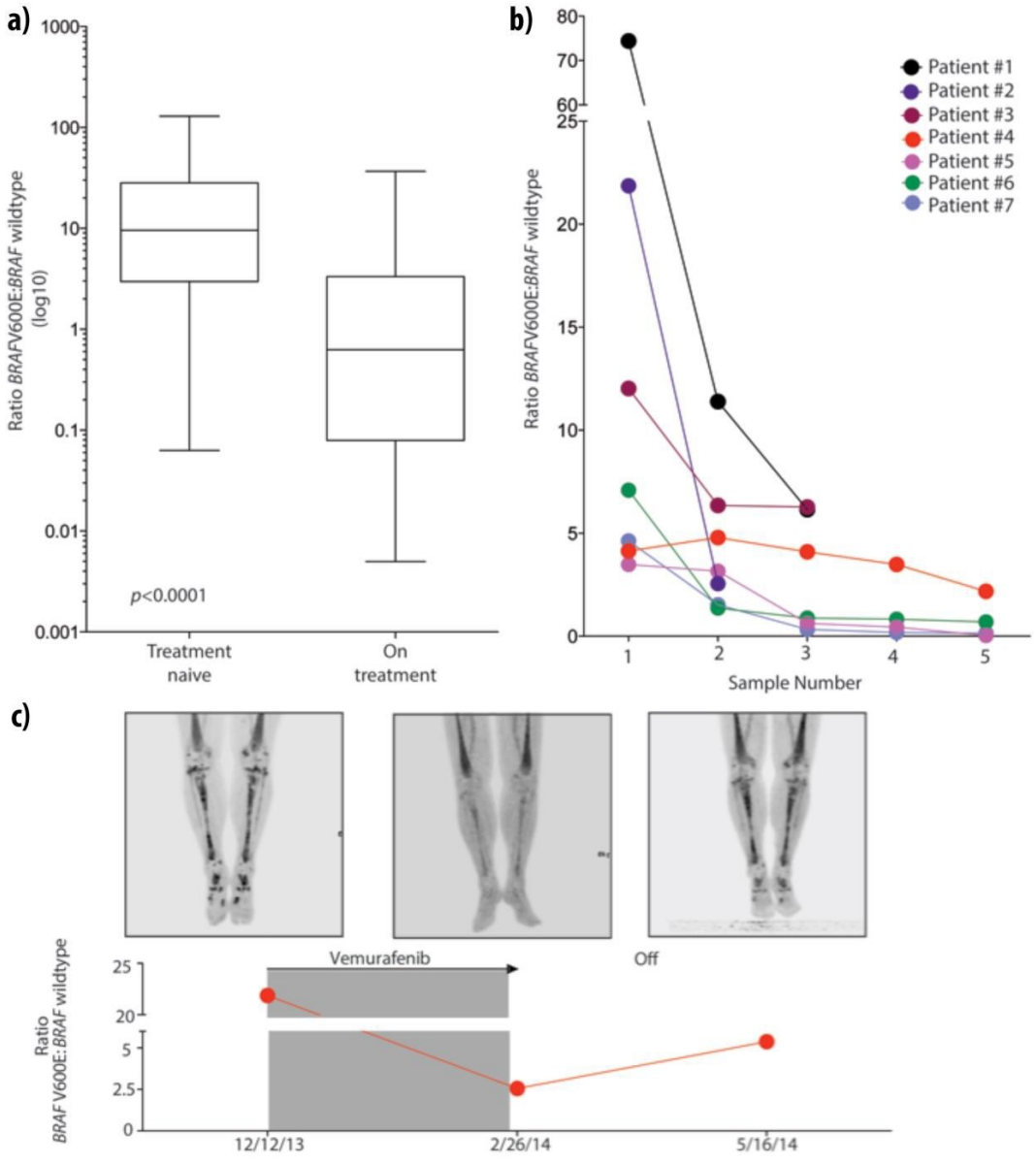


Figure 5: Paired Tumor Biopsies in Langerhans Cell Histiocytosis Before and During Vemurafenib Therapy. (a) H&E shows intense fibrotic reaction replacing area previously infiltrated by histiocytes. (b) VE1 immunohistochemistry (IHC) staining that selectively binds to *BRAF*^{V600E} mutant protein, shows complete absence of staining in the on-treatment tissue consistent with a complete pathologic response. Of note, the patient had continued measurable target lesion on corresponding imaging.

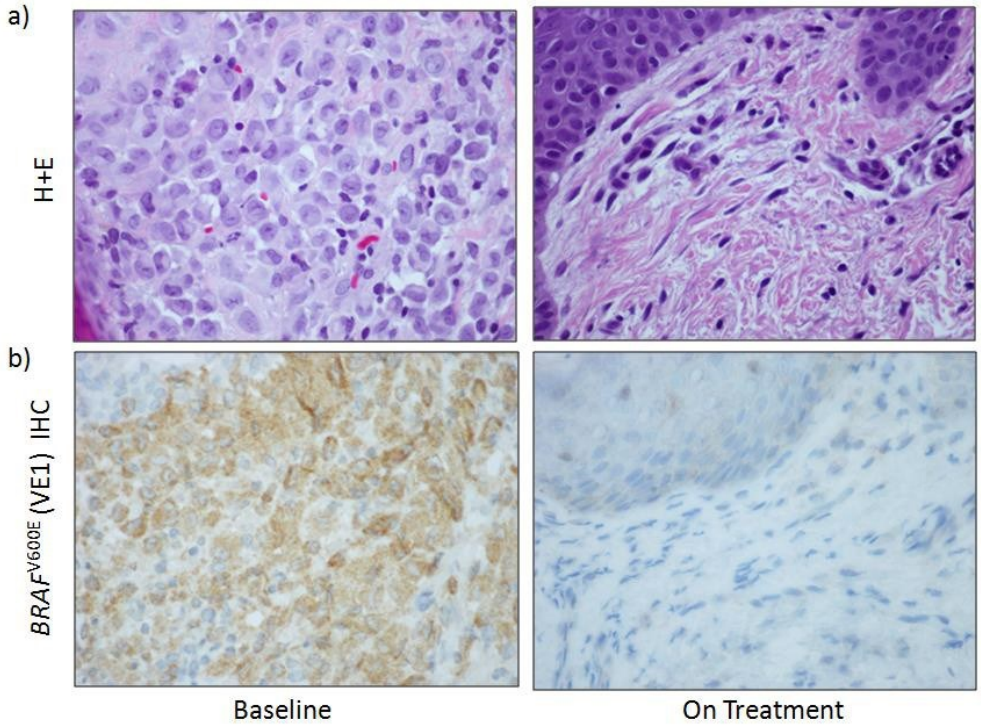


Figure 6: Dynamic monitoring of disease response using cell-free DNA (cfDNA) analyses in patients with systemic histiocytic disorders. Brain MRI and FDG-PET scan images from a *BRAF*V600E-mutant Erdheim-Chester Disease (ECD) patient pre-Vemurafenib (top left) versus following 8 weeks of Vemurafenib (top right). Green arrows indicate histiocyte lesions present pretreatment with Vemurafenib. Biweekly urinary cfDNA measurement of *BRAF*V600E allele burden in the same patient.

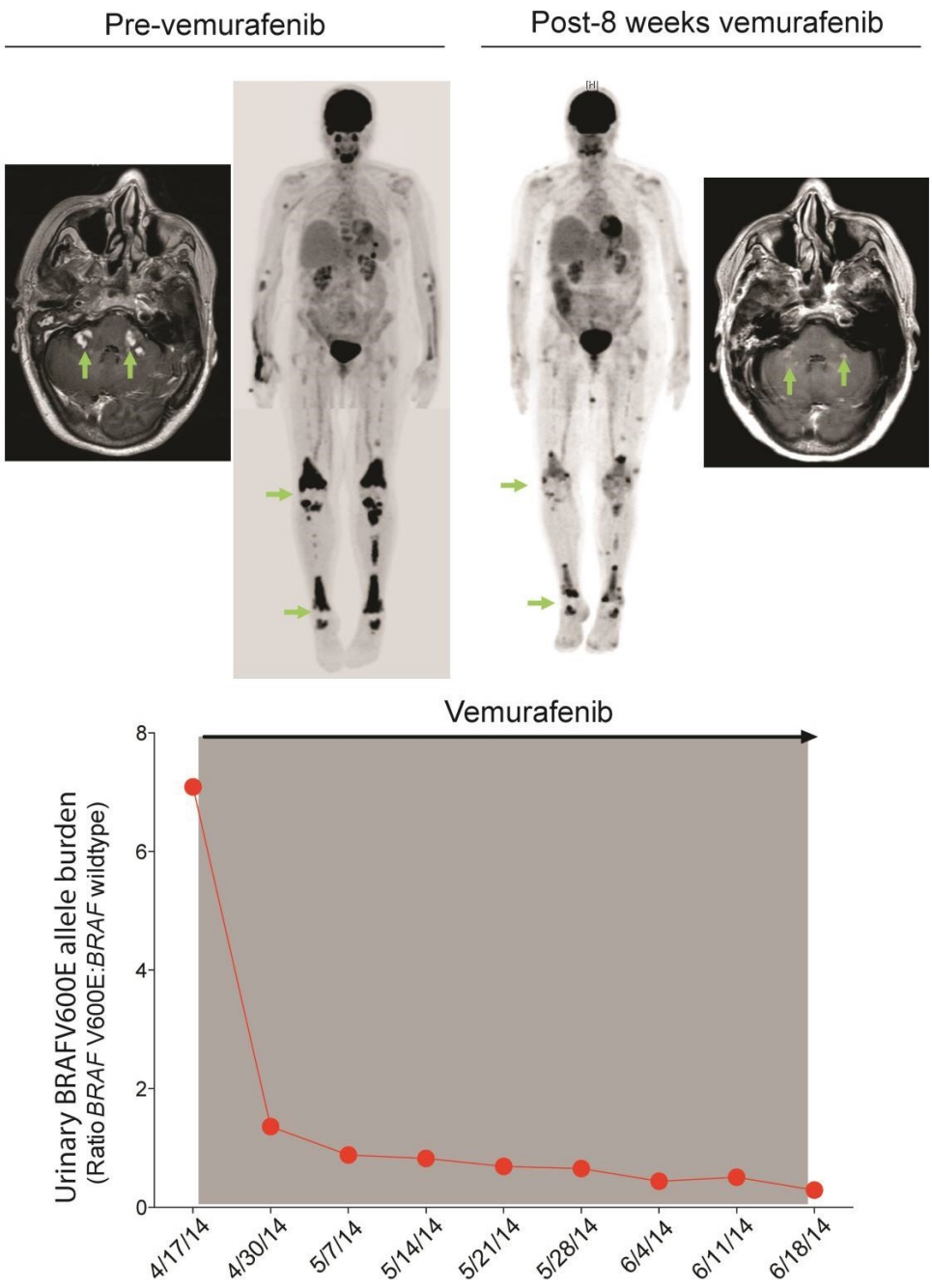


Figure 7: Discrepancy between PET Response Criteria and RECIST. Brain MRI and FDG-PET scan images from a *BRAF*V600E-mutant Erdheim-Chester Disease (ECD) patient pre-Vemurafenib (top and bottom left) versus following 8 weeks of Vemurafenib (top and bottom right). Yellow arrow indicate hypothalamic tumor with complete metabolic response, while red arrows indicate partial response.

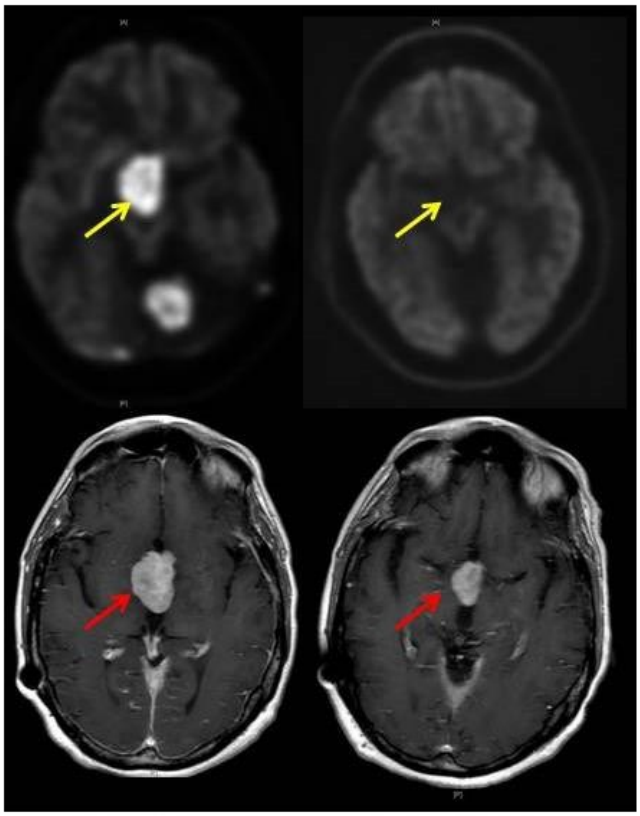


Figure 8: Results of combined whole exome sequencing (WES) and mRNA sequencing (RNA-seq) analysis of prospectively acquired systemic histiocytic disorder tissue biopsies. Each patient is displayed in one column with genetic alterations displayed in each row.

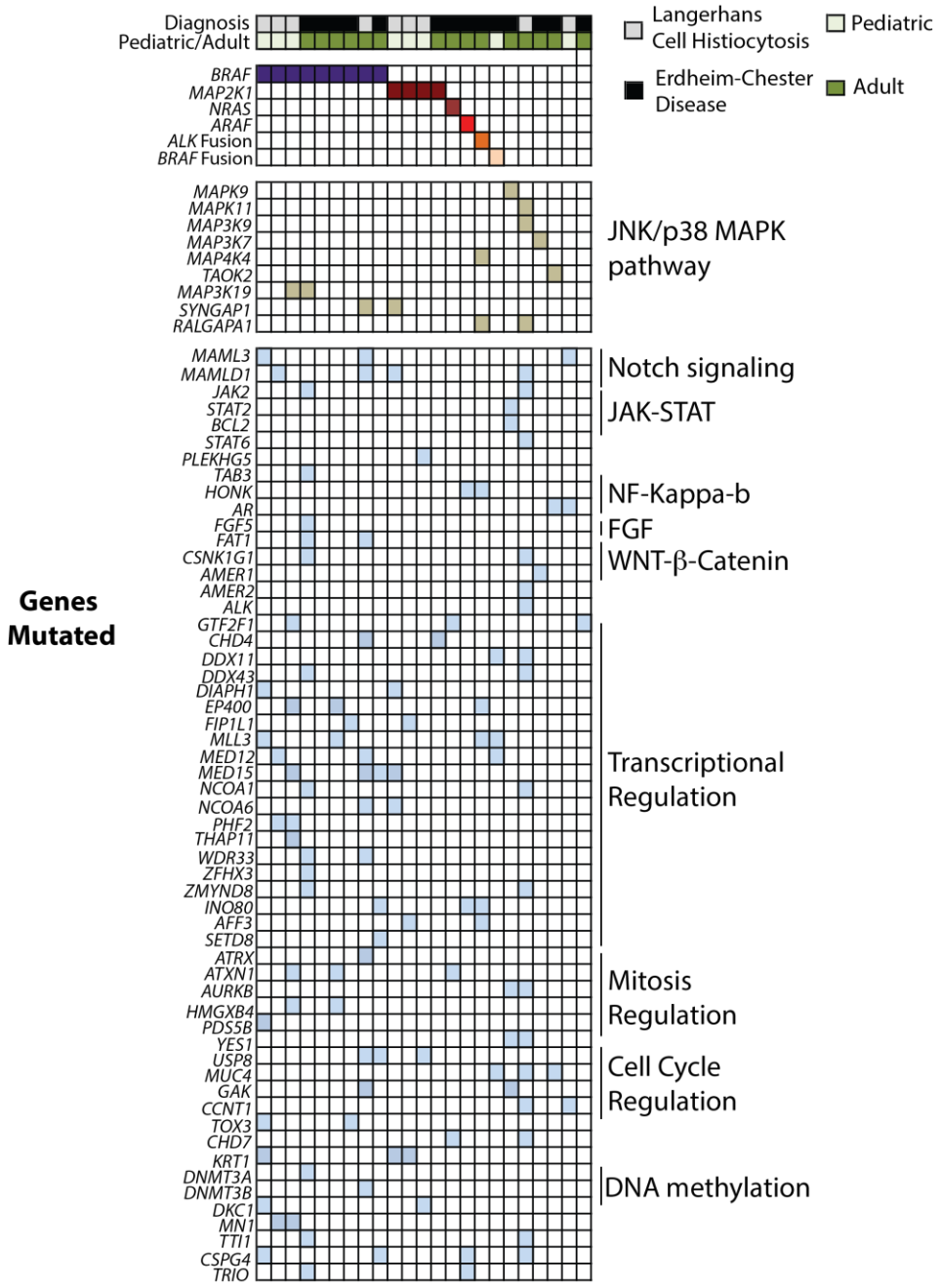


Figure 9: *ARAF*^{S214}-mutant Erdheim Chester Disease (ECD). (A) FDG-PET scan image showing characteristic femoral and tibial lesions of ECD. (B) Screen shot from the Integrated Genomics Viewer revealing the *ARAF*^{S214A} mutation in histiocyte DNA but not in paired peripheral blood DNA. (C) Photos of tissue biopsy hematoxylin-eosin stain (top) revealing characteristic foamy macrophages of ECD and pERK stain (bottom) in the same cells.

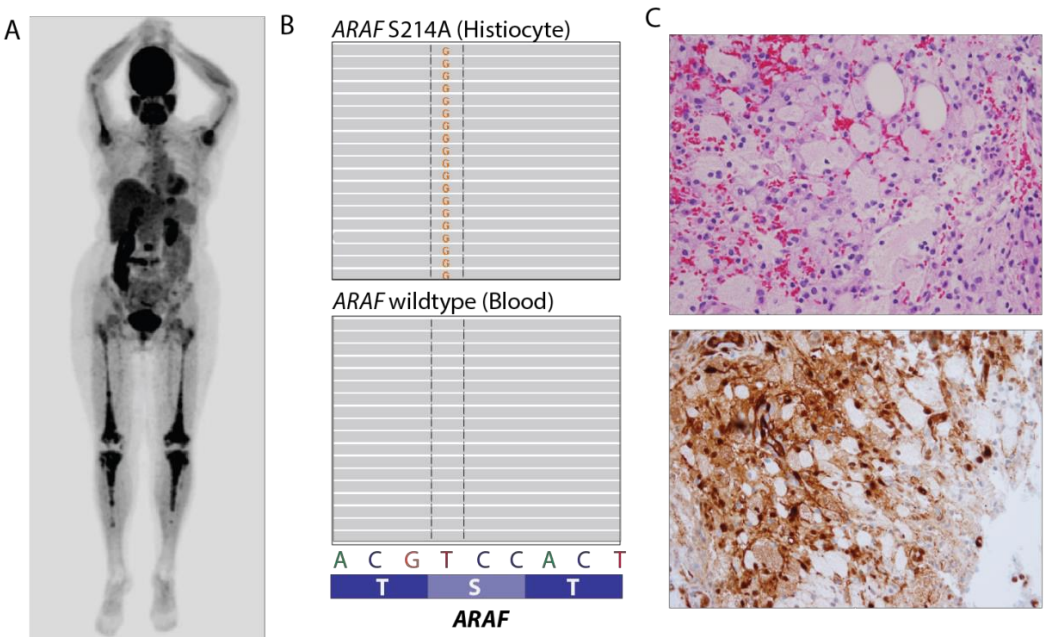


Figure 10: Recurrent *NRAS*, *KRAS*, and *MAP2K1* mutations in *BRAF*^{V600}-wildtype non-Langerhans Cell Histiocytoses. (A) Results of Sanger sequencing of a set of archival FFPE-derived DNA samples from patients known to have *BRAF*^{V600}-wildtype disease. Each patient is represented in one column with the genetic alteration listed in rows. (B) Gene diagram of the *MAP2K1* mutations identified in this study.

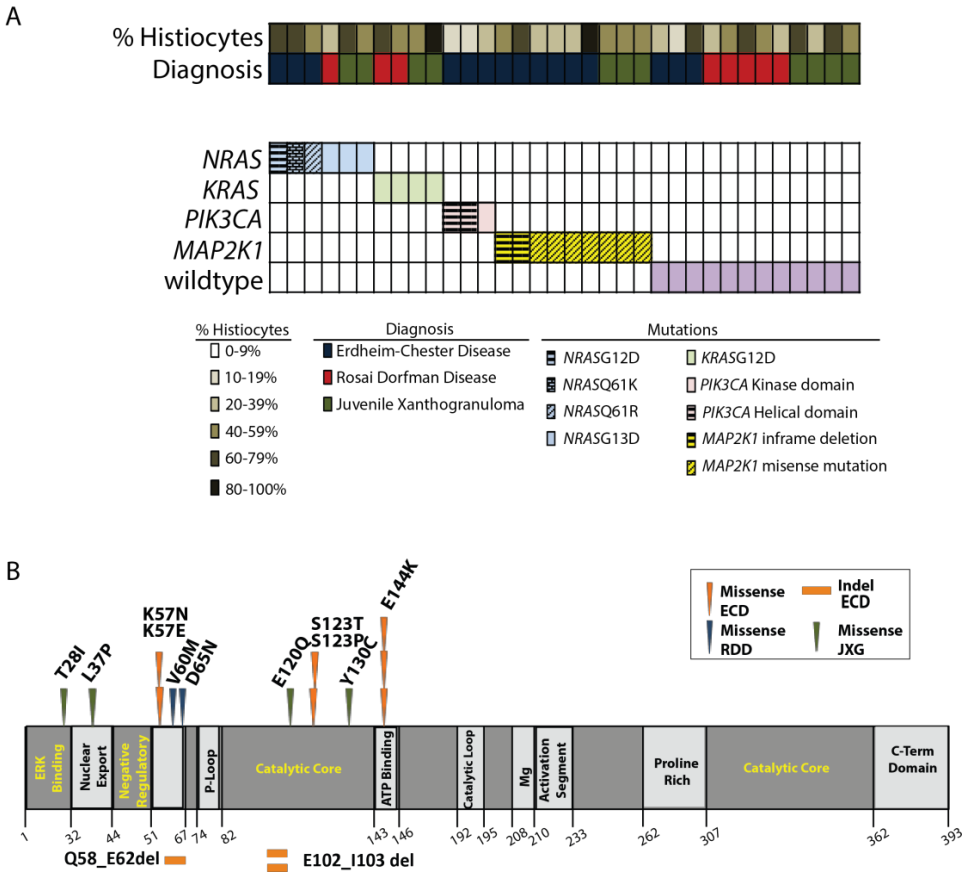


Figure 11: Diverse kinase fusions in *BRAF*V600-wildtype ECD patients. (A) Novel *BRAF* fusion (*RNF11-BRAF*; top) identified in histiocyte brain biopsy from a pediatric non-Langerhans patient. (B) A *KIF5B-ALK* fusion with novel breakpoints (bottom) identified in the histocyte skin lesions from a 25-year old ECD patient. In each case, Sanger sequencing confirmation of cDNA obtained from RNA used for RNA-seq is shown.

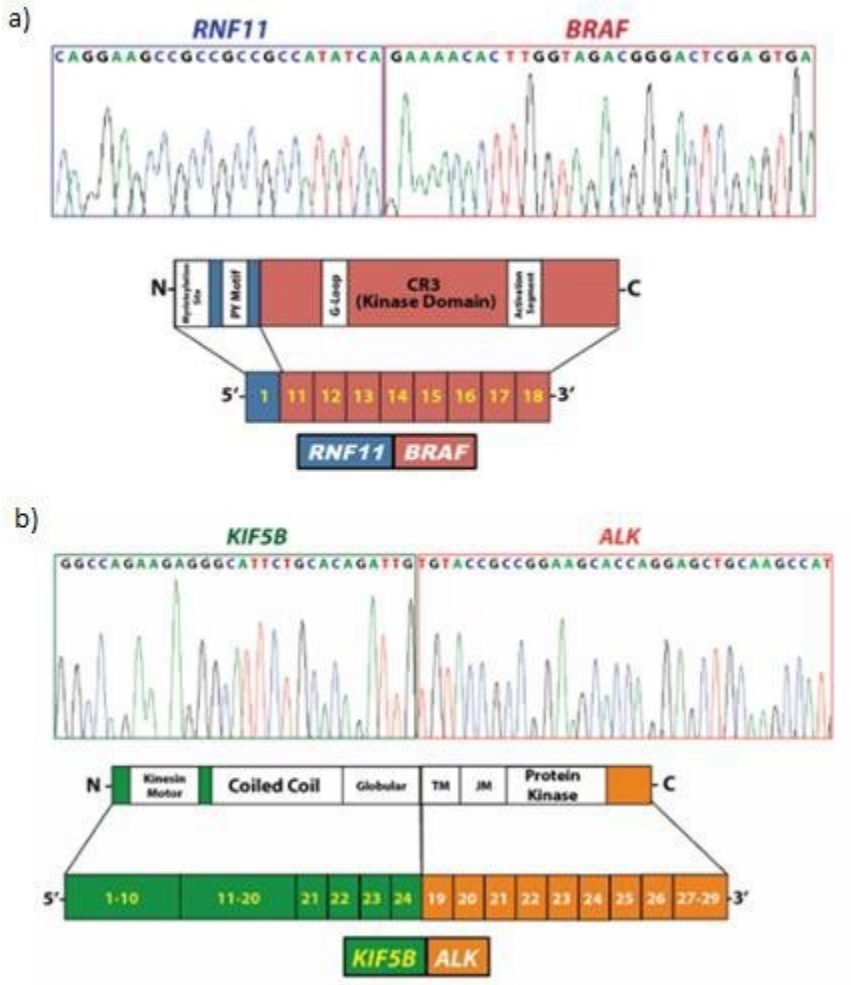
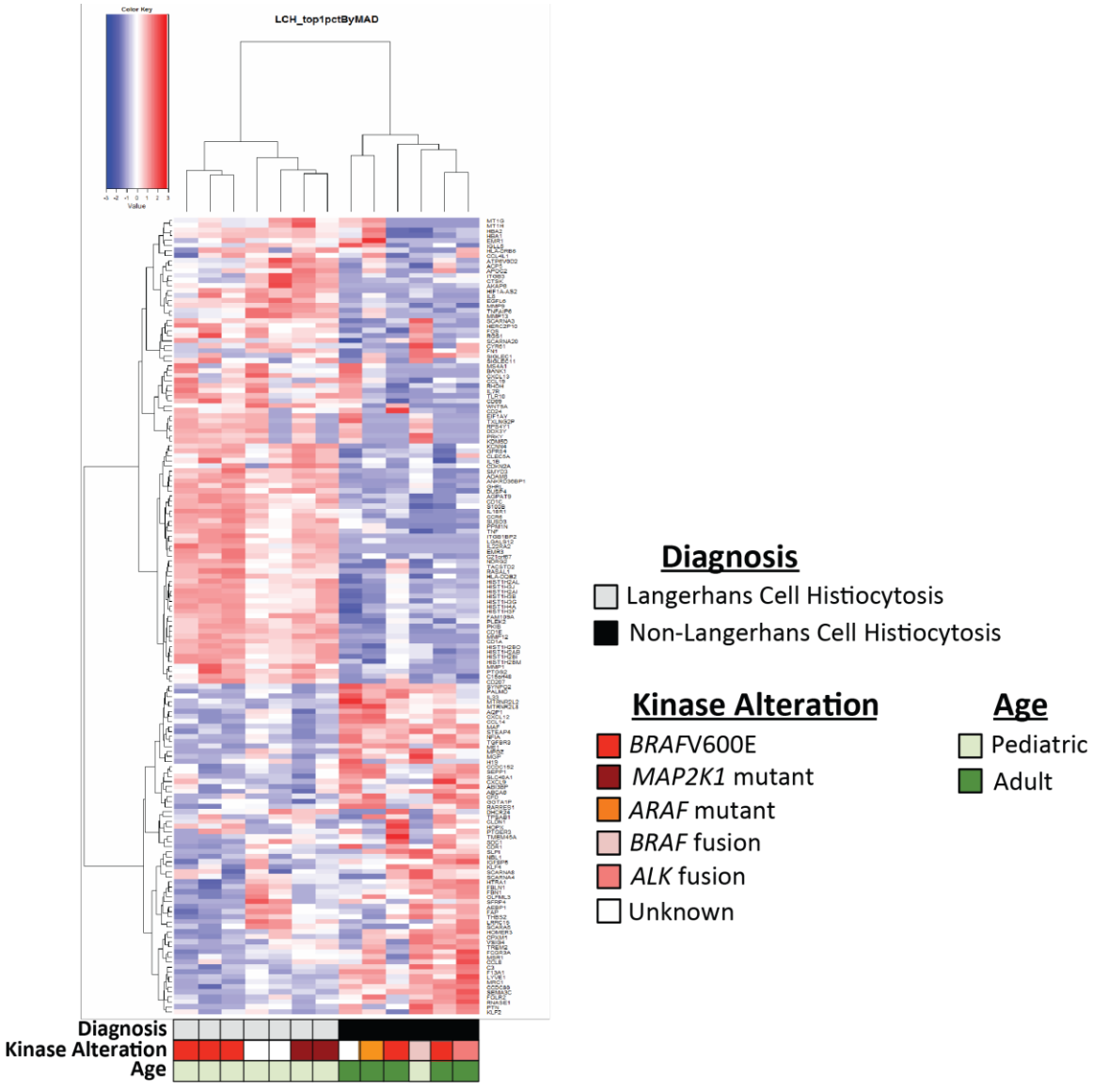


Figure 12: Unsupervised clustering of the top 1% most up-/down-regulated genes in histocytic disorder tissue biopsies by RNA-seq. As shown, patient samples clustered first by type of histiocytic disorder, then by activating kinase mutation. Patients whose tumor had no identifiable kinase alteration had similar transcriptional profiles as those with known MAP kinase pathway gain-of-function alterations.

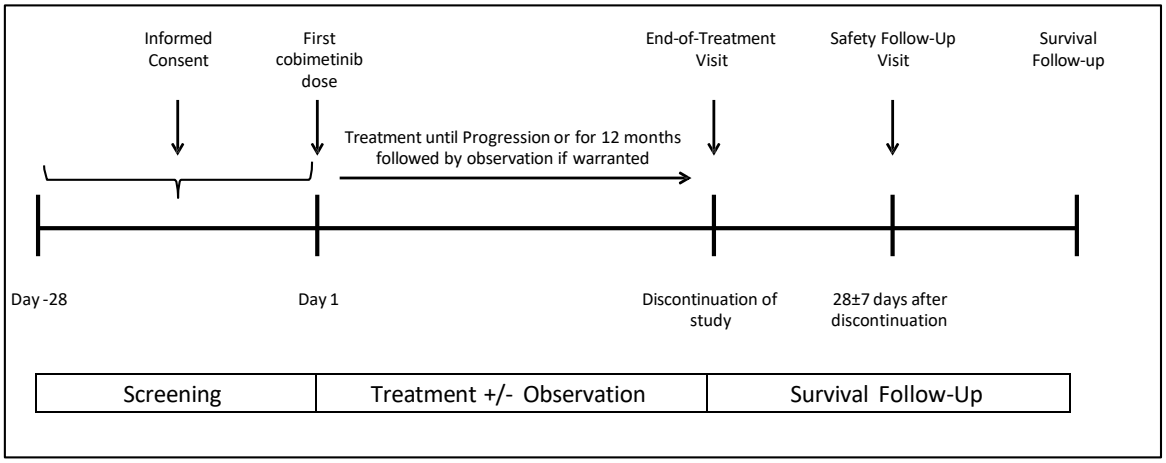


4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is an open-label, single-center, phase II study exploring the efficacy and safety of single-agent Cobimetinib in patients with histiocytic disorders whose tumors are 1) $BRAF^{V600}$ wildtype or 2) $BRAF^{V600E}$ mutant and are intolerant to, or unable to access, BRAF inhibitors. MSKCC and the Mayo Clinic are major referral centers for adults with ECD and other histiocytosis, and patients will be enrolled from both existing cohorts or from new patients establishing care. We anticipate an accrual rate of one patient every 4-6 weeks. Currently, *BRAF*V600 mutational status is typically not known for patients newly seeking evaluation and treatment, and for these patients genomic analysis is performed on outside or in-house biopsy material by way of IMPACT testing under IRB # 12-245 at MSK or with other next generation sequencing methods at Mayo. Pre-treatment biopsy will be performed for $BRAF^{V600}$ wildtype patients, either as a clinically necessary test or as a research test, for the purpose of delineating the underlying MAPK alteration in each patient's tumor. This biopsy requirement can be waived if, in the opinion of investigator, the biopsy poses an unacceptable risk to the patient. The trial will consist of a Screening Period (Day -28 to -1), a Treatment Period/Optional Monitoring Period, an End-of-Treatment Visit occurring when study medication is discontinued for any reason, a Safety-Follow-Up visit occurring 28 (±7 days) after the last dose of study medication and a Survival Follow-Up period lasting a minimum of 12 months after the last patient has been enrolled or until all patients have died, withdrawn consent or are lost to follow-up (whichever comes first) to monitor survival status. Day 1 of the study (baseline) will be defined as the first day patient receives study medication. Day 1 will take place within 28 days of consent. One cycle of therapy will be defined as 28 days of treatment. Patients will be asked to attend clinic visits at regular intervals during the study for safety and efficacy assessments.

Patients will maintain a log documenting all doses of the study drug and this will also be recorded in the study database.



Treatment will continue until the development of progressive disease (as per Investigator assessment), unacceptable toxicity, withdrawal of consent, protocol violation endangering the patient's safety, death, reasons deemed critical by the treating physician, or study termination. Patients who develop disease progression but, in the opinion of the investigator, would still benefit from continuing study treatment may continue treatment on the study in consultation with the Principal Investigator.

4.3 Intervention

Patients in this study will receive single-agent Cobimetinib 60mg oral daily for days 1-21 of each 28 day cycle. The rationale for single agent therapy, as described above, is the evidence for robust and sustained response to BRAF inhibitor monotherapy in histiocytic disorders harboring the $BRAF^{V600E}$ mutation.

5.1 THERAPEUTIC/DIAGNOSTIC AGENTS

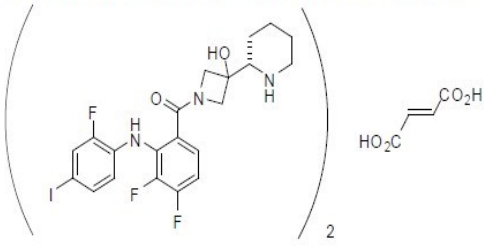
5.1 Physical and Chemical Properties of Cobimetinib

The physical and chemical properties of Cobimetinib are shown in the table 1 (below).

Cobimetinib Drug Product is supplied as a 20-mg film coated, immediate-release tablet. Drug concentrations and strengths of tablet drug products are expressed as the free-base equivalents. The tablet formulation consists of the Cobimetinib drug product and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate (non-bovine), and Opadry White film coat. All excipients used in the tablet formulation are compendial (USP/NF and/or EP) grade with the exception of the film coating. The tablet coating consists of polyvinyl alcohol-part hydrolyzed, titanium dioxide, polyethylene glycol 3350, and talc. The ingredients in the film coating are compendial.

Cobimetinib tablets should not be stored above 25 °C. Information on the shelf life of the capsules and tablets are provided on the trial material labels.

Table 1: Properties of Cobimetinib

Product/Code number	Cobimetinib/GDC-0973/XL518/RO5514041
Chemical name	(*S*)-[3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl] [3 hydroxy-3-(piperidin-2-yl)azetidin-1-yl]methanone hemifumarate
Chemical structure	
Molecular formula	$C_{46}H_{46}F_6I_2N_6O_8$
Molecular weight	1178.69 g/mol as hemifumarate salt 531.31 g/mol as free base
Description	Cobimetinib API is a hemifumarate salt, appearing as a white to off-white solid.
Physicochemical properties	Melting point 240°C Hygroscopicity: not hygroscopic Partition coefficient: log p = 3.81 pKa: 8.85 measured
Solubility	Cobimetinib exhibits a pH dependent solubility (37°C): 25.97 mg/mL in pH 1.0 (50 mM USP buffer), 2.71 mg/mL in pH 2.0,1.55 mg/mL in pH 3.0, 1.34 mg/mL in pH 4.0, 0.79mg/mL in phosphate buffer (pH = 6.5), 0.75 mg/mL in phosphate buffer (pH = 6.8), and 0.55 mg/mL in 50 mM USP buffer (pH = 7.5). At 37°C, the solubility of cobimetinib is 0.744 mg/mL in water, 0.89 mg/mL in FaSSIF, and 0.72 mg/mL in FeSSIF. Solubility of cobimetinib in solvents at 25°C is 0.35 mg/mL in acetone, 2.23 mg/mL in acetonitrile, and 0.79 mg/mL in ethanol.
Stability	Solid-state stability studies showed that cobimetinib is stable against light and heat. In solution, cobimetinib is stable under acidic condition and slightly sensitive to oxidative and basic conditions.
Storage	Stability studies indicate that cobimetinib API is stable in the recommended storage configuration up to 30°C.

API = active pharmaceutical ingredient.

5.2 Dosage of Cobimetinib

Cobimetinib (GDC-0973, XL518) is a potent and highly selective inhibitor of MEK1 and MEK2, central components of the RAS/RAF pathway.

The dose for Cobimetinib is 60mg daily for 21 days on, then 7 days off, in a 28 day treatment cycle. The 20 mg Cobimetinib drug product is a film-coated, immediate release tablet. The white tablet is round with the engraving “ROCHE” on one side. Cobimetinib will be packaged in blister packs. Cobimetinib should not be stored above 25°C (77°F).

Study MEK4592g was a multicenter, Phase I, non-randomized, open-label, dose-escalation study of Cobimetinib in patients with solid tumors investigating several doses and schedules. The primary objectives of this study were to evaluate the safety, tolerability, and MTD of Cobimetinib administered orally as repeated doses in patients with solid tumors. In Stage I, 36 patients with advanced solid malignancies were enrolled in successive cohorts and received Cobimetinib on a 21-day on, 7-day off (21/7) dosing

schedule at the following dose levels: 0.05 mg/kg, 0.10 mg/kg, and 0.20 mg/kg in liquid dosage formulation and 10 mg, 20 mg, 40 mg, 60 mg, and 80 mg in capsule formulation (Cohorts 1−8, respectively). The maximal administered dose (MAD) during Stage I was 80 mg; the MTD is 60 mg when Cobimetinib is administered on a 21/7 dosing schedule. In Stage IA, 20 patients were treated with Cobimetinib on a 14-day on, 14-day off (14/14) dosing schedule in successive cohorts at the following dose levels: 60 mg, 80 mg, 100 mg, and 125 mg in capsule formulation (Cohorts 1A − 4A, respectively). The MAD of Stage IA was 125 mg; and the MTD is 100 mg when Cobimetinib is administered on a 14/14 dosing schedule. Stages II and IIA are expansion stages that further evaluate the safety, potential efficacy, and pharmacodynamic effects of Cobimetinib at the MTDs determined in Stage I and Stage IA in patients with RAS- or RAF-mutant tumors. In Stage II, 20 patients were enrolled and received 60 mg Cobimetinib on a 21/7 dosing schedule. In Stage IIA, 21 patients were enrolled and received 100 mg Cobimetinib on a 14/14 dosing schedule.

5.3 Clinical Pharmacokinetics of Cobimetinib

Cobimetinib pharmacokinetics (PK) has been characterized in cancer patients following oral administration after single and multiple dosing in the Phase Ia dose-escalation study (MEK4592g). Cobimetinib has a moderate rate of absorption (median t_{max} of 1 to 3 hours). Exposure increased with increasing doses and was dose-proportional from 0.05 mg/kg (approximately 3.5 mg for a 70 kg adult) to 80 mg (clinically relevant dose range). The Cobimetinib mean terminal half-life following single-agent administration was 48.8 hours (range: 23.1 to 80.0 hours). Plasma samples were also analyzed for EXEL-0382, a metabolite of Cobimetinib. Since the metabolite concentrations were less than 10% of the parent drug and showed no dose proportional increase in exposure, further analysis of the metabolite was not conducted in subsequent studies. Overall, Cobimetinib demonstrates dose proportional and time independent PK with a moderate rate of absorption and a mean half-life of 48.8 hours. In vitro studies showed that Cobimetinib is a time-dependent inhibitor of CYP3A and a competitive inhibitor of CYP2D6. In vitro studies also show that Cobimetinib is a substrate of CYP3A and UGT2B7. However, an in-human dose-escalation study suggests that Cobimetinib is not an inducer or inhibitor of CYP2D6 or CYP3A.

Cobimetinib showed high variability in PK parameters during the dose-escalation phase of the study, MEK4592g.

Cobimetinib had a median T_{max} of 2-6 hours similar, to the T_{max} observed in study MEK4592g, the single agent Cobimetinib study in cancer patients. On the 14-day-on/ 14-day-off schedule, plasma concentration data were collected during the dosing holiday to allow estimation of half-life. For the 21/7 schedule, data were not collected to allow estimation of t1/2. The half-life in study NO25395 ranged from 32.9-96 hours and was similar to the half-life (range, 23-80 hours) in study MEK4592g. The apparent clearance in this study was also consistent with the apparent clearance in MEK4592g (geometric mean, 12.5 L/h).

5.4 Pharmacokinetic Drug Interactions of Cobimetinib

- In vitro CYP inhibition studies suggest that Cobimetinib has a moderate potential to interact with drugs that are substrates for CYP2D6 or CYP3A and that cobimetinib may be an inducer of CYP3A. However, an in-human dose-escalation study suggests that Cobimetinib is not an inducer or inhibitor of CYP2D6 or CYP3A. Mediciations that are substrates of these enzymes may be given with Cobimetinib.
- Cobimetinib is a substrate of CYP3A and thus has the potential to interact with inducers or inhibitors of CYP3A. Co-administration of cobimetinib with drugs that are moderate to strong inhibitors or inducers of CYP3A should be avoided.
- Cobimetinib appears to be a substrate but not an inhibitor of P-glycoprotein. Clinically relevant DDI with p-glycoprotein inhibitors or inducers is unlikely.
-Cobimetinib is not a substrate of breast cancer resistant protein (BCRP) but is a weak to moderate inhibitor of BCRP (IC50 3.34-40μM). Clinically relevant DDI with BCRP inhibition is unlikely.
- Cobimetinib is not a substrate of the liver uptake transporters OATP1B1, OATP1B3, and OCT1, however, it weakly inhibits these transporters at IC50's of 118, 85, and 49 μM, respectively. The clinical relevance of these findings has not been investigated, however, as these IC50's are high, at relevant clinical concentrations, transporter drug interactions would not be expected with Cobimetinib. Cobimetinib is not an inhibitor of the renal uptake transporters OAT1, OAT3 and OCT2.

Below is a table of medications that are moderate to strong CYP3A inducers or inhibitors:

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Table 2: Strong and moderate CYP3A inducers and inhibitors.

Inhibitors[a]	Inducers[b]
Strong • Atazanavir • Clarithromycin • Conivaptan • Delavirdine • Grapefruit juice • Indinavir • Itraconazole • Ketoconazole • Nefazodone • Nelfinavir • Posaconazole • Ritonavir • Saquinavir • Voriconazole	Strong • Aprepitant • Carbamazepine • Dabrafenib (unknown) • Dexamethasone (unknown) • Eslicarbazepine (unknown) • Felbamate (unknown) • Fosphenytoin • Nevirapine (unknown) • Oxcarbazepine (unknown) • Pioglitazone (unknown) • Phenytoin • Phenobarbital • Primidone • Rifabutin • Rifampin • Topiramate (unknown) • Vemurafenib (unknown) • St. John's Wort
Moderate • Amiodarone • Aprepitant • Cimetidine • Clotrimazole • Cyclosporine • Diltiazem • Erythromycin • Fluconazole • Fosaprepitant • Imatinib • Tetracycline • Verapamil	Moderate • Efavirenz • Modafinil (unknown)

[a]Serum concentrations of cobimetinib may be increased when administered with these drugs.
[b]Serum concentrations of cobimetinib may be decreased when administered with these drugs.

5.5 Toxicology of Cobimetinib

The Cobimetinib nonclinical toxicology program was designed to evaluate the safety profile of Cobimetinib, to establish a safe clinical starting dose for Phase I trials, and to support continued daily administration of Cobimetinib in the clinic. The nonclinical toxicity assessment of Cobimetinib included GLP-compliant single-dose and repeat-dose studies in rats and dogs, in vitro bacterial and mammalian genotoxicity bioassays, and CV, respiratory, and neurobehavioral safety pharmacology studies. Additional non-GLP, dose-range-finding studies were also conducted in rats and dogs to select doses for the pivotal studies.

Key findings in the 4- and 13-week repeat-dose toxicity studies in rats and dogs were generally similar to those identified at higher dose levels and exposures in single-dose and pilot toxicity studies. After 4 weeks of dosing in rats, multi-organ degenerative effects were present in the bone marrow, thymus, and adrenal gland at a tolerated dose level (3 mg/kg/day), and in liver, spleen, lymph node, kidney, skin, heart, ovary, and vagina at 10

mg/kg/day, which was not tolerated. All changes, except lymphoid depletion in the rat lymph node, were reversible upon discontinuation of Cobimetinib administration. No Cobimetinib-related effects were noted up to 3 mg/kg/day in the 13-week rat toxicity study. In contrast, dogs tolerated higher systemic exposures (AUC) compared to rats, with GI degeneration as a prominent finding in dogs. Evidence of GI effects and moribundity were present after single-dose (≥30 mg/kg) or repeat-dose (≥3 mg/kg/day in the 7-day pilot toxicity study) administration. Associated clinical signs included fecal changes and decreased food consumption and body weight. No effects were noted up to 1 mg/kg/day in the 4-week study in dogs. After 13 weeks of dosing in dogs, dose-related chronic active inflammation and degeneration of the esophagus associated with varying degrees of gastroenteropathy resulted in increased moribundity at ≥1 mg/kg/day. Additionally, at 3 mg/kg/day, bone marrow degeneration affected the erythroid lineage and resulted in decreased circulating red cell mass. Significant findings identified in repeat-dose studies up to 13 weeks are summarized below. All changes, aside from lymphoid depletion in the lymph node, were reversible upon discontinuation of Cobimetinib administration. Corresponding events in clinical trials are monitorable, manageable, and are expected to be reversible.

1. Hematopoietic/lymphopoietic systems: Degenerative effects (increased apoptosis/necrosis) in the bone marrow and lymphoid tissues (thymus and lymph node) and decreased circulating red cell mass were present in rats and dogs. Decreased platelets were also noted in rats.

2. Adrenal gland: Degeneration of the adrenal cortex was present at tolerated and non-tolerated dose levels in rats. Lesions were characterized in more severe cases by cell loss, sinusoidal dilatation, and hemorrhage and at lower severity by individual cell shrinkage, apoptosis, or necrosis.

3. Liver: Centrilobular and random hepatocyte necrosis and periportal hepatocyte hypertrophy were present in moribund rats. Some animals with increased serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and/or □-glutamyltransferase did survive until the final necropsy, and had random hepatocyte necrosis and periportal hepatocyte hypertrophy.

4. Kidney: In rats, increased blood urea nitrogen (BUN) was associated with renal findings that included cortical tubule dilatation in the distal convoluted tubule with flattened epithelium in moribund females and one male and one female at the scheduled necropsy. Renal papillary necrosis was noted in one moribund male. In dogs, increased BUN, creatinine, and inorganic phosphorus were noted 3 days after single-dose administration at non-tolerated dose levels.

5. Reproductive tissues: Degenerative changes observed in reproductive tissues included increased apoptosis/necrosis of corpora lutea and seminal vesicle, epididymal and vaginal epithelial cells in rats, and epididymal epithelial cells in dogs.

6. GI system: Epithelial degeneration and chronic inflammation of the esophageal mucosa with associated emesis and fecal changes (mucoid, discolored, nonformed, liquid) were observed in dogs. Epithelial degeneration/necrosis was also present in stomach, colon, cecum, and rectum in rats.

7. Skin: Papillary necrosis and acanthosis, ulcerations, erosions, surface exudates, and epidermal necrosis were observed in skin/subcutis in rats. In juvenile rats dosed for 4

weeks beginning on postnatal Day 10, key findings and tolerability were similar to or less severe than those found in adolescent-adult rats at similar exposures. Exposures were higher on Study Day 1 than Day 28 in both male and female rats, potentially because of lower cytochrome P450 levels in young animals; however, Day 28 exposures were consistent with exposures in the general toxicity studies. The administration of 3 mg/kg/day Cobimetinib to juvenile rats resulted in two unscheduled deaths (1 male and 1 female) on postnatal Day 17. No gross or microscopic lesions were detected in these animals, and the cause of death is undetermined. Among animals surviving to the end of the 28-day treatment period, Cobimetinib administration resulted in decreased thymic weights, potentially related to the microscopic finding of increased single-cell necrosis (apoptosis) in thymic lymphocytes, and a decreased circulating lymphocyte count at 3 mg/kg/day; decreased liver weights correlating with decreased hepatocellular glycogen content; and decreased spleen and thyroid/parathyroid weights, which had no microscopic correlates. Additional minor findings with no associated histological correlates included increased serum phosphorus at 0.3-3 mg/kg/day Cobimetinib, increased serum total bilirubin and circulating red cell mass, and decreased serum triglyceride concentrations at 1 and 3 mg/kg/day.

Reproductive and Developmental Toxicity: In a dedicated embryo-fetal toxicity study in rats, Cobimetinib treatment resulted in mortality (1 of 10 dams), reductions in maternal body weight and maternal food consumption in the remaining dams, embryo-fetal toxicity (resorptions and reductions in fetal weight), and teratogenicity (malformations of the great vessels and skull) at the highest dose level tested (10 mg/kg/day, AUC of 6020 ng/mL/hr). The increase in resorptions occurred principally in 2 litters from dams that had marked effects on body weight gain; thus, the embryolethality may be secondary to maternal toxicity. In contrast, the malformations occurred in litters from dams without marked body weight effects and thus reflect a direct effect on the fetus. Embryolethality is also observed in mice deficient in *mek1* due to reduced vascularization in the labyrinthine region of the placenta; thus, inhibition of MEK by Cobimetinib in humans is a potential risk for the developing fetus. Cobimetinib also caused degenerative changes in the ovary, epididymis, seminal vesicle, and vagina at non-tolerated doses in general toxicity studies in rats and/or dogs and thus may affect fertility. Cobimetinib is currently being studied in a patient population for whom prior and concurrent therapies include chemotherapeutic agents that are known to pose reproductive risks; thus, patients should avoid pregnancy. Cobimetinib was not phototoxic or genotoxic in vitro or in vivo and has low potential for CV, neurobehavioral, or respiratory effects in patients based on in vitro and in vivo safety pharmacology studies.No carcinogenicity evaluations have been conducted.

Toxicities of Cobimetinib in humans from Phase I studies are summarized in Section 11.0.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

1. Histologically confirmed histiocytic disorder or histologic findings compatible with a histiocytic disorder in the context of confirmatory radiologic findings confirmed by the enrolling institution.
2. One of the following:

i. Documentation of BRAF V600E mutation and inability to access of BRAF inhibitor or prior treatment with a BRAF inhibitor discontinued due intolerable side effects or toxicity prior to progression, -OR-

ii. Documentation of wild-type BRAF V600 mutational status.

Patients with BRAF-mutated ECD/LCH who have had disease progression on BRAF inhibitor therapy would be eligible but would require tissue biopsy (or available tissue) for genotyping before participating.

3. Measurable disease according to PET Response Criteria, confirmed by an MSK investigator radiologist, with the exception of patients with cutaneous disease that can be measured and followed by RECIST criteria.
4. Histiocytic disorder must be (a) multi-system disease or (b) disease that is recurrent or refractory to standard therapies, or (c) single-system disease with that is unlikely to benefit from conventional and less toxic therapies, based on the best available evidence (for example, CNS or cardiac infiltration, retroperitoneal fibrosis, prior chemotherapy, or other medical history or co-morbidities, etc)
5. Life expectancy $>$ 12 weeks
6. Age ≥ 16 years
7. ECOG performance status ≤ 3 (May be converted from Karnofsky Performance Status)
8. Adequate bone marrow function as indicated by the following: ANC $>$ 1000/μL Platelets $\geq$ 50,000/μL Hemoglobin ≥ 8.5 g/dL. Patients with cytopenias below these thresholds deemed to be the result of disease will be considered eligible.
9. Adequate renal function, as indicated by:
    a. creatinine $\leq 1.5 \times$ the upper limit of normal (ULN) -OR-
    b. Estimated creatinine clearance of > 50 ml/min

    As for #9, patients with renal dysfunction deemed to be the result of disease will be considered eligible.
10. Adequate liver function, as defined by bilirubin $\leq 1.5\times$ ULN AND AST/ALT $< 3 \times$ ULN
11. Ability to swallow pills
12. Negative serum pregnancy test within 7 days prior to commencement of dosing in premenopausal women. Women of non-childbearing potential may be included without serum pregnancy test if they are either surgically sterile or have been postmenopausal for ≥ 1 year.
13. Fertile men and women must use an effective method of contraception during treatment and for at least 6 months after completion of treatment as directed by their physician. Effective methods of contraception are defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and

correctly (for example implants, injectables, combined oral contraception or intra-uterine devices). At the discretion of the Investigator, acceptable methods of contraception may include total abstinence in cases where the lifestyle of the patient ensures compliance. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

14. Patients must be willing to consent for protocol #12-245 for IMPACT testing (for MSK patients ONLY).

6.3 Subject Exclusion Criteria

1. Prior treatment with a MEK inhibitor
2. Active infection requiring intravenous antibiotics
3. Pregnant, lactating or breast feeding women
4. Prior radiation therapy within the last 14 days
5. Unwillingness or inability to comply with study and follow-up procedures.
6. Any foods/supplements that are strong inhibitors or inducers of CYP3A are prohibited at least 7 days prior to initiation of and during study treatment
7. History of or evidence of retinal pathology on ophthalmologic examination that is considered a risk factor for neurosensory retinal detachment, RVO, or neovascular macular degeneration
8. The risk factors for RVO are listed below. Exclusion should be considered by clinical discretion if they have the following conditions:
   a. Uncontrolled glaucoma with intra-ocular pressures > 21mmHg
   b. Serum cholesterol ≥ Grade 2
   c. Hypertriglyceridemia ≥ Grade 2
   d. Hyperglycemia ≥ Grade 2
9. History of clinically significant cardiac dysfunction, unless deemed to be the direct result of disease, including the following:
   a. Current unstable angina
   b. Symptomatic congestive heart failure of NYHA class 2 or higher
   c. Uncontrolled hypertension > Grade 2 (patients with a history hypertension controlled with anti-hypertensives to ≤ Grade 2 are eligible).
   d. Left ventricular ejection fraction (LVEF) below institutional lower limit of normal or below 50%
   e. Uncontrolled arrhythmias

f. Myocardial infarction, severe/unstable angina, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack within the previous 6 months

7.0 RECRUITMENT PLAN

Patients for this study will be recruited by physicians from the Departments of Neurology and Medicine at MSKCC as well as from an external participating institution. There have been approximately ~100 adult patients with Erdheim-Chester disease, 75 adult patients with Langerhans cell histiocytosis, and 40 adult patients with other histiocytoses evaluated at MSKCC in the past five years, and referrals are escalating as our institution emerges as a referral center for these diseases. A significant number of patients present for diagnostic evaluation and such patients will be approached to participate. Moreover, the external participating site (Mayo clinic) has a comparably large cohort of histiocytosis patients.

55 patients with a confirmed histiocytic disorder (confirmed by examination of biopsy material in the setting of appropriate clinical and radiologic findings) will be enrolled in this study. Patients will be considered evaluable upon completion of their first response assessment. If any patients are unevaluable for any reason prior to the first response assessment, this patients slot will be opened to another patient. All adult patients ≥16 years are eligible for participation regardless of sex or race. Every effort will be made to encourage eligible women and minorities to enroll in this study. Prior to study entry, the staff will explain to each potential subject the research objectives, risks and benefits of study participation, alternative treatments available, and the subjects' rights and responsibilities. If the patient agrees to participate in the study, informed consent will be obtained by a consenting individual on the study. All patients must sign written informed consent prior to being registered on this protocol.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship with for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC or the external participating institution in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff with destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the

treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in the screening log of patients approached (if applicable).

8.1 PRETREATMENT EVALUATION

8.1 **Screening Period**:

The following assessments should be performed within 28 days before the first administration of study medication on Day 1 of the first cycle, unless they have already been conducted during this time period as part of the patient's routine clinical care:

- Signed written informed consent
- Medical history (including demographics)
- Physical examination, including the evaluation of the head, eyes, ears, nose, and throat (HEENT); cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and a neurological systems examination; height and weight (height will only be measured during screening)
- Vital signs (blood pressure, heart rate, temperature, respiratory rate)
- ECOG Performance Status (May be converted from Karnofsky Performance Status)
- Hematology, including hemoglobin, hematocrit, platelet count, white blood cell count (WBC) and absolute neutrophil count (ANC)
- Biochemistry (including creatinine phosphokinase (CPK), glucose, amylase, lipase, glucose, blood urea nitrogen ([BUN]], creatinine or creatinine clearance, sodium, potassium, calcium, magnesium, bicarbonate ([if routinely performed on venous blood samples]), total bilirubin with fractionation into direct and indirect (if total bilirubin elevated during the study), alkaline phosphatase, AST ([SGOT]], ALT [(SGPT)], triglycerides, and cholesterol panel.
- Serum inflammatory markers (ESR and C-reactive protein) on Day 1, Day 29, and every 28 days thereafter until study drug discontinuation.
- Serum pregnancy test within 7 days prior to commencement of dosing for women of child-bearing potential. Women surgically sterile or postmenopausal for ≥ 1 year are not to be considered for a pregnancy test.
- Whole-body ^{18}FDG-PET/CT including the distal extremities. A window of 56 days is allowable for inclusion as the natural history of this disease has shown these scans change very slowly in these diseases.
- MRI of the brain if clinically indicated.
- Concomitant medications
- AEs (including SAEs) related to study-mandated procedures from time ICF is signed

- Quantitative LVEF evaluation by transthoracic echocardiogram or multiple gated ejection acquisition scan (MUGA).
- Dermatologic evaluation.
- Ophthalmologic evaluation performed and interpreted by a qualified ophthalmologist, including visual acuity testing, intraocular pressure measurements by tonometry, slit-lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography; if not available, may be substituted with time-domain OCT.

8.2 **Pretreatment Biopsy:**

All patients must have a tissue biopsy genotyped at MSKCC by IMPACT or an outside platform, such that testing has successfully identified the tumor's MAPK pathway (or other) driver alteration, and therefore patients must be willing to consent to IMPACT testing via MSKCC protocol 12-245 or using the Make-an-IMPACT initiative. If sequencing was completed and a driver mutation has been identified this will not be required. However, IMPACT testing does not need to have resulted by the time of treatment on study. This is because the sensitivity of the various underlying mutations to MEK inhibition is not known and this information will be necessary in light of the presence or absence of favorable clinical/radiographic response to therapy. Prior biopsy at MSKCC or elsewhere is acceptable even if before the screening period if genotyping has been successful. Patients without a known alteration at the time of study enrollment, and without existing archival tissue for genotyping, will undergo biopsy.

Biopsy will either be done as part of standard clinical care if indicate, or alternatively as a research-non-billable (RNB) procedure if it not required as a standard of care procedure. Biopsy of multiple target lesions (obtaining cores from abdominal soft tissue as well as from an osseous, cutaneous, or other soft tissue lesion) may be performed as standard clinical evaluation for these disorders in order to maximize the yield of lesional tissue.

At the discretion of the Principal Investigator, a patient can be enrolled in the study if biopsy is not possible for reasons of safety or unacceptable risk to the patient (for example, for intracranial or cardiac lesions), or pressing need to treat the patient.

9.0 TREATMENT/INTERVENTION PLAN

Cobimetinib will be administered at a dose of 60mg daily for 21 days on, then 7 days off, in a 28 day treatment cycle. Patients will have the option to discontinue treatment after 12 cycles and will be monitored for disease relapse for an additional 12 months. In the event that disease relapse occurs within the 12 month monitoring period, patients will restart treatment and continue on study. Upon restarting, the assessment schedule will restart at rechallenge-cycle 1 (R-C1) and all assessments will occur at the frequency and intervals described below. Cycle 1 Day 15 visits will not be required for patients that restart treatment after relapse. Participants will re-sign consent upon rechallenging.

Cobimetinib should be taken once daily at approximately the same time each day. Cobimetinib can be taken with or without a meal. Cobimetinib tablets should never be chewed, cut, or crushed. At least 7 days off Cobimetinib is required prior to starting a new treatment cycle, however at the discretion of the treating investigator treatment may be held longer for the management of adverse events, comorbidities, or other situations where clinically indicated.

10.1 EVALUATION DURING TREATMENT/INTERVENTION

10.1 Treatment Period

Visits during the treatment period are to be completed on Day 1, Day 15 (this visit can be by telephone), Day 29, and every 28 days thereafter. For patients treated on the study for six months, at the discretion of the Principal Investigator, visits can be spaced out to every 56 days (every 2 cycles instead of every cycle). In such instance, labs and other protocol assessments will not be required at these timepoints unless clinically indicated, or otherwise stated. A window of ±7 days is allowed for each visit from Cycle 2 onwards (28-day cycle). A window of ±3 days is allowed for the Cycle 1, Day 15 visit. When using a window, not all assessments need to be completed on the same day (i.e.: blood work can be done in advance of the MD visit as long as within window). If screening exams are completed within 14 days of Cycle 1, Day 1, these will not be repeated unless clinically indicated or otherwise stated (i.e.: blood work will be repeated after 7 days). Should treatment be withheld for any reason, any evaluations done prior to the **intended time-point** are acceptable and will not be repeated unless clinical necessary (ie. opthalmologic visit that occurs the day before a treatment hold is decided and the cycle calendar is pushed back - unless the patient clinically requires a repeat visit).

The following assessments should be performed during the **Active** Treatment Period:

- Physical examination (as described previously) on Day 1, Day 15 (not needed if this is visit is by telephone), Day 29 and every 28 days thereafter until study drug discontinuation.
- Vital signs (as described previously) on Day 1, Day 15 (not needed if this is visit is by telephone), Day 29 and every 28 days for the first 6 cycles and then every 8 weeks until study drug discontinuation.
- ECOG performance status on Day 1, Day 15, Day 29 and every 28 days for the first 6 cycles and then every 8 weeks thereafter until study drug discontinuation (May be converted from Karnofsky Performance Status).
- Hematology (as described previously) on Day 1, Day 15, Day 29 and every 28 days thereafter until study drug discontinuation. Hematology assessments do not need to be repeated on Day 1 if performed within 7 days prior to the first Cobimetinib administration.
- Biochemistry (as described previously*) on Day 1, Day 15, Day 29 and every 28 days thereafter until study drug discontinuation. Biochemistry assessments do not need to be repeated on Day 1 if performed within 7 days prior to the first Cobimetinib administration.

-Triglycerides and cholesterol panel are required only for screening and will not be collected per protocol during followup visits.

- Serum inflammatory markers (ESR and C-reactive protein) on Day 1, Day 29, and every 28 days thereafter until study drug discontinuation. Serum inflammatory markers do not need to be repeated on Day 1 if performed within 7 days prior to the first Cobimetinib administration.
- Complete ophthalmologic evaluation (detailed above) to be performed on Day 1 (± 2 weeks) of cycles 2, 5, 9, 13, 17, 21, 27, 33, 39, and so on as clinically needed. In the absence of any visual disturbances during the first year of treatment, the PI may remove the requirement of these assessments for further cycles unless new symptoms arise. These assessments will occur more frequently if clinically indicated. *For patients that discontinue treatment and enter the 12 month monitoring period, this assessment will occur at cycle 13 and subsequently during the period of treatment interruption only as clinically indicated. Should a patient relapse during the monitoring period, the clock will restart and the assessment schedule will occur again at the rechallenge-cycles 2, 5, and only as clinically needed thereafter.
- Dermatologic evaluation (detailed above) to be performed on Day 1 (± 2 weeks) of cycles 2, 5, 9, 13, 17, 21, 27, 33, 39, and so on as clinically needed. If a participant has no skin toxicities during the first year of treatment these visits are not mandatory and can be scheduled as needed. These assessments will occur more frequently if clinically indicated. *For patients that discontinue treatment and enter the 12 month monitoring period, this assessment will occur at cycle 13 and subsequently during the period of treatment interruption only as clinically indicated. Should a patient relapse during the monitoring period, the clock will restart and the assessment schedule will occur again at the rechallenge-cycles 2, 5, and only as clinically needed thereafter.
- Quantitative LVEF measurement (as above) to be performed on Day 1 (± 2 weeks) of cycles 2, 5, 9, 13, 17, 21, 27, 33, 39, and so on as clinically needed. The modality of assessment will be consistent for individual patients. In the absence of any cardiac disturbances during the first year of treatment, the PI may remove the requirement of these assessments for further cycles unless new symptoms arise. These assessments will occur more frequently if clinically indicated. *For patients that discontinue treatment and enter the 12 month monitoring period, this assessment will occur at cycle 13 and subsequently only as clinically indicated. Should a patient relapse during the monitoring period, the clock will restart and the assessment schedule will occur again at the rechallenge-cycles 2, 5, and only as clinically needed thereafter.
- Research bloods (two Streck tubes and three sodium heparin tubes) for cell-free DNA extraction and cytokine analysis on Day 1, Day 29, and every cycle with an in-person visit thereafter until study drug discontinuation. See Appendix G and I. Patients who must have their blood drawn outside of MSK for logistical or financial reasons are not required to have research bloods drawn. These are non-mandatory and will be collected at the investigators discretion without deviations for missed research blood draws.
- Research urine for exploratory cell-free DNA analysis throughout the course of treatment. See appendix K, M and N for details. As of January, 2018, urine collections are not required moving forward. These are non-mandatory and will be collected at the investigators discretion.

- Quality of life (QOL) and patient-reported outcome (PRO) assessments(Appendix J and L). For patients that have already begun treatment, it is allowable to collect C1D1 assessments within 28 days of starting treatment. These are non-mandatory and will be collected at the investigator's discretion.
- The following tumor assessments are to be performed;
  - Whole-body or brain FDG-PET/CT, and anatomic imaging (e.g. MRI brain or CT chest/abdomen pelvis) as clinically indicated every 8 weeks after starting study drug. The same imaging technique (CT or MRI) should be used for each patient throughout the study. FDG-PET/CT will not be required for follow-up for patients without FDG-avid disease (those with cutaneous disease only) unless clinically indicated. A window of ± 2 weeks is allowable for all scans.
  - If, after 12 cycles of treatment, imaging studies demonstrate sustained response in the opinion of the principal investigator, tumor assessments can be performed up to every 16 weeks.
  - If, after 24 cycles of treatment, imaging studies demonstrate sustained response in the opinion of the principal investigator, tumor assessments can be performed up to every 1 year.
- Cobimetinib dispensation on Day 1 and every 28 days thereafter until study drug discontinuation*.
  - If participants are using a window or are not coming for a clinical visit given the cycle, Cobimetinib may be mailed to them in concordance with Federal, State and International Regulations. Compliance will be monitored by study staff.
  - If participants are being seen every other month, a two month supply will be supplied or mailed at the clinicians discretion.
- Cobimetinib accountability (Appendix A) every 28 days after starting Cobimetinib until study drug discontinuation.
- Review of the Cobimetinib Pill Diary (Appendix B) every 28 days after starting Cobimetinib until study drug discontinuation.
- Concomitant medications throughout the Treatment Period.
- AEs (including SAEs) throughout the Treatment Period.

10.1.1 Treatment Monitoring and Rechallenge

Patients whose disease relapses in the monitoring phase and who restart Cobimetinib will enter a modified follow-up schedule as monitoring for toxicity with restarting the drug at a previously tolerated drug does not to be as stringent as when starting the drug de novo. For purpose of clarity, cycles during rechallenge will be called R-C1D1, R-C2D1, etc. A visit (telephone or in-person) on R-C1D15 is not needed as it is for C1D15. The patient will return for labs and MD visit on R-C2D1, R-C3D1, and then resume visits every other cycle as they were immediately prior to entering monitoring. Echocardiogram, ophthalmologist, and dermatology will be required for the R-C2D1 and R-C5D1 visits and then only as clinically indicated thereafter as described below.

10.2 End-of-Treatment Visit

The End-of-Treatment Visit will occur when the patient discontinues Cobimetinib for any reason, unless the patient withdraws consent or is lost to follow up. The following assessments will be conducted at the End-of-Treatment visit:

- Physical examination (as described previously)
- Vital signs (as described previously)
- Quantitative LVEF assessment (as above). Does not need to be performed if an evaluation was done within the last 12 weeks and there are no clinical significant findings and/or changes from baseline. As stated above, the modality of assessment will be the consistent for individual patients.
- ECOG Performance Status
- Hematology (as described previously)
- Biochemistry (as described previously)
- Serum inflammatory markers (as described previously)
- Tumor assessments (as described previously) if not done within the last 8 weeks or whatever scan interval had been adopted for the patient.
- Dermatology evaluation by a dermatologist if not done within the previous 12 weeks, unless these evaluations had been stopped per investigator discretion.
- Drug accountability
- Review of the Pill Diary
- Concomitant medications
- AEs (including SAEs)

10.3 Safety Follow-Up Assessment

The safety follow-up visit will occur approximately 28 days (-/+ 7 days) after discontinuation of Cobimetinib. The following assessments will be conducted as the Safety Follow-Up Visit: A telephone assessment for AEs is sufficient if the patient cannot return in person for logistic or health reasons.

- Physical examination (as described previously; in-person only)
- Vital signs (as described previously; in-person only)
- ECOG Performance Status; in-person only
- Hematology (as described previously; in-person only)
- Biochemistry (as described previously; in-person only)
- AEs (including SAEs)

10.4 Survival Follow-Up Period

The following assessment will be conducted during the Survival Follow-Up Period:

- Optional post-progression research tumor biopsy for repeat sequencing to determine mechanism(s) of acquired resistance. Only patients achieving a partial or complete response by the PRC will be candidates for this biopsy.

- Survival status every 3 months after the last dose until death or for a minimum of 12 months after the last patient has been enrolled or until all patients have died, withdrawn consent or are lost to follow-up (whichever occurs first).

Table 4: Schedule of Assessments

	Screening Period	Treatment Period[2]								Monitoring Period[23]	EOT Visit[3]	Safety Follow-Up Visit[4]	Survival FU[5]
Cycle		1	1	2	3	4	5	6	7 onwards			Post Treat. disc.	Every 3 months
Day	-28 to -1	1	15	29	57	85	113	141	Every 28 days		(+/-7) days	28 (+/-7) days	
Informed consent	X												
Documentation of histiocytic diagnosis[1]	X												
Tissue pre-treatment biopsy[6]	X												
Medical history	X												
Physical examination[7]	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[8]	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology[9,10]	X	X	X	X	X	X	X	X	X	X	X		
Biochemistry[11]	X	X	X	X	X	X	X	X	X	X	X		
Serum inflammatory markers (ESR and C-reactive protein)	X	X[2]		X	X	X	X	X	X	X	X		
Serum pregnancy test[12]	X												
Transthoracic echo or MUGA[13]	X			X			X[13]			X[13]	X[13]		
Dermatologic evaluation[14]	X			X			X[14]			X[14]	X[14]		
Ophthalmologic evaluation[15]	X			X			X[15]			X[15]			
Concomitant medications[16]	X	X	X	X	X	X	X	X	X	X	X	X	
Tumor assessments[17]	X				X		X[18]			X[18]	X[18]		
Additional tumor assessments/ Research Bloods[19] /Research Urine[21]	X			X	X	X	X	X	X	X			
Quality of Life and Patient-Reported Outcome Measures[22]		X				X			X	X			
Adverse events	X		X	X	X	X	X	X	X	X	X	X	
Drug dispensation		X		X	X	X	X	X	X				
Drug accountability				X	X	X	X	X	X		X		
Follow-up for disease progression													X
Optional Post-Progression Tumor Biopsy												X	
Survival status													X

1. Confirmation of the diagnosis of a histiocytosis will performed as the first step before the remaining screening procedures. This will be done by review of clinical data, radiologic data, and of biopsy/resection material.
2. Visits during the Treatment Period are to be completed on Day 1, Day 15 (can be telephone), Day 29 and every 28 days thereafter until study drug discontinuation. A window of 3 days (-3 days to + 3 days) is allowed prior to or after the scheduled Day 15 visit. A window of 7 days prior to the scheduled visit date and seven days after the scheduled visit date (–7 days / + 7 days) is allowed for each visit from Cycle 2 onwards. *Patients that stop treatment and enter the monitoring period will be monitored every 8 weeks with a window of seven days (–7 days / + 7 days).
3. The End of Treatment Visit will be performed within 7 days from when the patient discontinues Cobimetinib regardless of when it occurs.
4. The Safety Follow-Up Visit will be performed after 28 (±7) days from discontinuation of Cobimetinib.
5. The Survival Follow-Up period will last for a minimum of 12 months after the last patient has been enrolled or until all patients have died, withdrawn consent or are lost to follow-up (whichever occurs first).
6. Prior biopsy with adequate available material will be acceptable.
7. Includes the evaluation of the head, eyes, ears, nose, and throat (HEENT); cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal and neurological systems examination; and height (cm) and weight (kg). Height will only be measured during screening.
8. Includes blood pressure, heart rate, temperature and respiratory rate.
9. Includes hemoglobin, hematocrit, platelet count, white blood cell count (WBC) and absolute neutrophil count (ANC)
10. Hematology and biochemistry assessments do not need to be repeated on Day 1 if performed within 7 days of first Cobimetinib administration. NB: if it is necessary to repeat these blood tests, the results must be known before the patient receives first dose of Cobimetinib to ensure that the inclusion and exclusion criteria related to these tests are met.
11. Includes creatinine phosphokinase (CPK), amylase, lipase, glucose, blood urea nitrogen [BUN], creatinine or creatinine clearance, sodium, potassium, calcium, magnesium, bicarbonate ([if routinely performed on venous blood samples],), total bilirubin with fractionation into direct and indirect (if total bilirubin elevated during the study), alkaline phosphatase, AST ([SGOT]], ALT ([SGPT]]. ** Triglycerides and cholesterol panel are required only for screening and will not be collected per protocol during followup visits.
12. Serum pregnancy test to be performed within 7 days prior to first Cobimetinib administration for women with childbearing potential.
13. Performed on Day 1 (± 2 weeks) of cycles 2, 5, 9, 13, 17, 21, 27, 33, 39, and so on, or more frequently as clinically needed. May be repeated more frequently if in the evaluation of diminished left ventricular ejection fraction. In the absence of any cardiac disturbances during the first year of treatment, the PI may remove the requirement of these assessments for further cycles unless new symptoms arise. After treatment interruption for reduction in LVEF, all patients restarting treatment with a dose reduction of Cobimetinib should have LVEF measurements taken at approximately 2 weeks, 4 weeks, 10 weeks and 16 weeks, and then as clinically indicated until treatment discontinuation. If there are any significant findings and/or changes from baseline, quantitative LVEF will be performed at EOT visit, only if the most recent assessment is greater than 12 weeks prior. *For patients that discontinue treatment and enter the 12 month monitoring period, this assessment will occur at cycle 13 and as clinically indicated. As described above, should a patient relapse during the monitoring period, the clock will restart and the assessment schedule will occur again at cycles R-C2, R-C5, and only as clinically needed thereafter.

14. Performed by a dermatologist on Day 1 (± 2 weeks) of cycles 2, 5, 9, 13, 17, 21, 27, 33, 39, and so on, or more frequently as clinically needed. If no skin toxicities are seen, this evaluation is not mandatory and can be scheduled as needed. Dermatologist evaluation required at EOT only if the most recent evaluation is greater than 12 weeks prior. *For patients that discontinue treatment and enter the 12 month monitoring period, this assessment will occur at cycle 13 and as clinically indicated. As described above, should a patient relapse during the monitoring period, the clock will restart and the assessment schedule will occur again at cycles RC2, RC5, and only as clinically needed thereafter.
15. Can be done more frequently for the evaluation of retinopathy. Ophthalmologic evaluation (detailed above) to be performed on Day 1 (± 2 weeks) of cycles 2, 5, 9, 13, 17, 21, 27, 33, 39, and so on, or more frequently as clinically needed. In the absence of any visual disturbances during the first year of treatment, the PI may remove the requirement of these assessments for further cycles unless new symptoms arise. *For patients that discontinue treatment and enter the 12 month monitoring period, this assessment will occur at cycle 13 and as clinically indicated. As described above, should a patient relapse during the monitoring period, the clock will restart and the assessment schedule will occur again at cycles RC2, RC5, and only as clinically needed thereafter.
16. All concomitant medications during the study started within 14 days prior to the screening visit and up to the end of study visit must be recorded.
17. Will include whole-body FDG-PET and/or CT chest/abdomen/pelvis, as well as organ specific imaging as clinically indicated for the participant's disease (e.g.: MRI brain, MRI orbit, MRI heart). A window of 56 days is allowable for screening FDG-PET. Followup whole-body FDG-PET/CT will not be repeated for the patients without FDG-avid disease (those with cutaneous disease only) unless clinically indicated.
18. Tumor assessments will be performed every 8 weeks for the first 12 cycles of treatment. After 12 cycles of treatment, if imaging demonstrates sustained stability in the opinion of the principal investigator, tumor assessments can be performed every 8-16 weeks rather than strictly every 8 weeks. After 24 cycles of treatment, if imaging demonstrates sustained stability in the opinion of the principal investigator, tumor assessments can be performed ever 1 year. Tumor assessments will be performed at EOT visit if the most recent assessments were obtained greater than 8 weeks prior. For patients that are in the 12 month monitoring period, tumor assessments will be performed at 8-16 weeks at the discretion of the principal investigator.
19. Will include collection of two (Streck) tubes of blood for exploratory analysis such as detection and quantification of plasma cell-free DNA. This will also include the collection of three sodium heparin tubes for collection of peripheral blood mononuclear cells and cytokines. This will depend on the RAF/RAS/MAP2K mutational status of the patient. Consent for this will be acquired by way of protocol MSK IRB # 12-245. See Appendix C. These are non-mandatory and will be collected at the investigators discretion.
20. Serum inflammatory markers do not need to be repeated on Day 1 if performed within 7 days prior to the first Cobimetinib administration.
21. Will include serial urine collections to allow for the option of non-invasive monitoring of mutational allele burden in urine cell-free DNA. These assessments are optional and at the discretion of the principal investigator. See appendix K and M for details. As of January, 2018, urine collections are not required moving forward.
22. Will include brief patient-oriented assessments performed at multiple time points (baseline, C4D1, C7D1, etc., all with ±14-day windows) completed on paper or via an online platform (REDCap). This portion is not mandatory, however patients will be encouraged to complete these assessments. For patients that have already begun treatment, it is allowable to collect C1D1 assessments within 28 days of starting treatment. See Appendix J and L for assessments and descriptions. Participants in the monitoring period will complete these assessments prior to entering the monitoring period, as well as at the time of disease re-activation, should this occur

during the monitoring period. These are non-mandatory and will be collected at the investigators discretion.

23. Patients will discontinue treatment after 12 cycles and enter a 12 month monitoring period. Patients on monitoring will be evaluated every odd cycle for 12 cycles. In the event of disease relapse (progressive metabolic disease as described below), patients will be allowed to restart treatment at the discretion of the principal investigator per the assessment schedule already described.

11.0 TOXICITIES/SIDE EFFECTS

11.1 Adverse Events and Laboratory Abnormalities

11.1.1 Clinical Adverse Events

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

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with LCH/ECD that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

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?”

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations. The adverse event log will take precedence over visit notes with respect to grading/relationship to study medication/etc.

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.

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

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").

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.

Pregnancy
If a female subject becomes pregnant while receiving the study drug or within 28 days after the last dose of study drug, a report should be completed and expeditiously submitted to Genentech, Inc. Patients will be informed to follow up with investigators to report the outcome of the pregnancy should this occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported to the investigator, who will report this information to Genentech, Inc. No further follow up will be required from research staff at Memorial Sloan Kettering Cancer Center.

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 {study drug} 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, patients will be directed to inform the investigator immediately, who will then report the information to the drug company. No further follow up will occur from the research staff.

Reconciliation

The Sponsor agrees to conduct reconciliation for the product. Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange quarterly (line listings of cases received by the other party.

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

11.1.2 Intensity

Intensity of all adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events, Version 4.0 (CTCAE, v4.0) on a five-point scale (Grade 1 to 5) and reported in detail on the eCRF.

Adverse events not listed on the CTCAE v4.0 should be graded as described below.

Table 5: Adverse Event Grading (Severity) Scale

CTC Grade	Equivalent to:	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the patient
Grade 3	Severe	Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the subject at direct risk.
Grade 4	Life threatening/ disabling	An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival.
Grade 5	Death	AE resulting in death

11.1.3 Drug – Adverse Event relationship

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

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

Yes
There is a plausible temporal relationship between the onset of the AE and administration of Cobimetinib, 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 Cobimetinib and/or the AE abates or resolves upon discontinuation of the Cobimetinib or dose reduction and, if applicable, reappears upon re-challenge.

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

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B).

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

11.1.4 Serious Adverse Events (Immediately Reportable to Genentech: See Section 17.2)

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

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

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

****The term sudden death should be used only when the cause is of a cardiac origin as per standard definition. The terms death and sudden death are clearly distinct and must not be used interchangeably**.

The study will comply with all local regulatory requirements and adhere to the full requirements of the **ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting.**

After informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in).

11.1.5 Progression of Disease

Progression of Disease is not reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST criteria, or other criteria as determined by protocol. This includes also deaths solely due to underlying malignancy. An SAE with outcome death solely due to progression of the underlying malignancy does not need to be reported as an SAE. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as a serious adverse event. Clinical symptoms of progression may be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

Symptomatic deterioration may indicate progressive disease (PD), however radiological confirmation of PD is strongly recommended. In this situation, progression is evident in the subject's clinical symptoms, but is not supported by the tumor measurements. Or, the disease progression is so evident that the Investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.

If there is any uncertainty about an adverse event being due only to the disease under study, it should be reported as an AE or SAE.

11.1.6 Treatment and Follow-up of AEs

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 (± 7) 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.

Related AEs: Follow until one of the following occurs:

- Resolved or improved to baseline
- Relationship is reassessed as unrelated
- Death
- Start of new anti-cancer regimen
- Investigator confirms that no further improvement can be expected
- Clinical or safety data will no longer be collected, or final database closure

Unrelated severe or life threatening AEs: Follow until one of the following occurs:

- Resolved or improved to baseline
- Severity improved to Grade 2
- Death

- Start of new anti-cancer regimen
- Investigator confirms that no further improvement can be expected
- Clinical or safety data will no longer be collected, or final database closure

Unrelated Grade 1 or Grade 2 AEs: Follow until **28 days from the last dose of study drug.**
The final outcome of each adverse event must be recorded on the database.

11.1.7 Laboratory Test Abnormalities

Local laboratories will be used for all laboratory tests. Laboratory test results will be recorded on the laboratory results form of the database.

Any laboratory result abnormality fulfilling the criteria for a serious adverse event (SAE) should be reported as such, in addition to being recorded as an AE in the database.

Any treatment-emergent abnormal laboratory result that is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the adverse event page in the database.

11.1.8 Follow-up of Abnormal Laboratory Test Values

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the database.

11.2 Toxicities from Cobimetinib by Organ System

11.2.1 Skin Toxicity

In the Phase I single-agent study (MEK4592g), reported rash events included rash (49.6% all grades, 4.3% Grade ≥ 3 events) and maculo-papular rash (1.7% all grades, 0.9% Grade ≥ 3 events).

The appearance of rash and other dermatologic events should be closely monitored. Patients who develop mild-to-moderate skin toxicity may be treated with concomitant medications (e.g., topical agents or oral antibiotics) at the discretion of the investigator. Skin toxicity should be managed according to institutional guidelines.

No evidence of phototoxicity was observed with Cobimetinib as a single agent. Photosensitivity events in Cobimetinib-treated patients should be managed according to institutional guidelines, and patients are to receive maximal supportive care including treatment with topical medications as clinically indicated. Any modification of study treatment for photosensitivity events should follow the guidelines in the present study protocol.

11.2.2 Gastrointestinal Toxicity

11.2.2.1 Nausea and Vomiting

Nausea and vomiting were reported in the Phase I clinical trial with Cobimetinib at the single-agent MTD of 60 mg on a 21/7 dosing schedule.

11.2.2.2 Diarrhea

In the Phase I single-agent study (MEK4592g), diarrhea of any grade was reported in 67.0% of patients, 6.1% of patients experienced Grade 3 diarrhea, and no Grade 4 or 5 events were reported as of the data cutoff date. Serious events of diarrhea were reported in 1.7% of patients. In the majority of cases, diarrhea was effectively managed with antidiarrheal agents and supportive care.

Diarrhea should be managed according to institutional guidelines. Patients are to receive maximal supportive care. Patients should be monitored for symptoms of clinically significant volume depletion/dehydration and decreased oral intake.

11.2.2.3 Other Gastrointestinal Events

Other gastrointestinal (GI) events reported have included events of GI inflammation (reported as mucosal inflammation, mucositis, mucosal inflammation, stomatitis, colitis, and GI ulceration), GI obstruction, and/or GI perforation.

Gastrointestinal toxicities will be managed according to institutional guidelines, with the exception of fluconazole for stomatitis, which will be replaced with a non-interacting agent. During the study, patients are to receive maximal supportive care as clinically indicated.

11.2.3 Ocular Toxicities

Serous retinopathy (fluid accumulation within the layers of the retina) has been observed with MEK inhibitors, including Cobimetinib. The majority of events in Cobimetinib-treated patients were reported as chorioretinopathy or retinal detachment. . In MEK4592g, with ocular examinations prescribed for patients reporting visual disturbances, 2.6% of patients experienced serous retinopathy events, all of which were Grade 1 or 2.

Patients with neurosensory detachment of the retinal typically present with visual disturbances such as blurred vision, seeing spots, and photophobia; however, some patients have been asymptomatic. Most of these cases have been reversible and most patients were able to continue treatment at the same or reduced dose.

To address the potential ocular toxicity, patients with a history of RVO or glaucoma, visible retinal pathology, intraocular pressure > 21 mmHg, and predisposing factors to RVO (e.g., uncontrolled hypertension, diabetes, or hyperlipidemia, coagulopathy) will be excluded. Patients will be asked about any vision changes at each symptom directed physical examination. All new patients will have complete ophthalmologic examinations performed and interpreted by a qualified ophthalmologist, including visual acuity testing, intraocular pressure measurements by tonometry, slit lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography. These complete ophthalmologic examinations will be performed at baseline, and subsequently as clinically indicated, if patients note any visual disturbances. For patients reporting new or worsening

visual disturbances, an ophthalmologic examination is recommended. If serous retinopathy is diagnosed, Cobimetinib treatment should be withheld until visual symptoms improve to Grade 1. Serous retinopathy can be managed with treatment interruption, dose reduction or with treatment discontinuation.

11.2.4 Liver Laboratory Abnormalities

In MEK4592g, there were no reported AEs or SAEs for clinically significant Grade 4 elevations in liver laboratory tests, and no patient experienced findings suggestive of drug-induced liver injury or liver failure. Patients must have adequate liver function, as manifested by measurements of total bilirubin, alkaline phosphatase, and hepatic transaminases, to be eligible for this study. Patients with diseases that affect liver function, such as viral hepatitis, should be excluded. Hepatic parameters should be assessed prior to each cycle of the study regimen. Dose modification parameters are detailed below in 11.3.8.

11.2.5 Hypersensitivity

Cobimetinib is contraindicated in patients with known hypersensitivity to Cobimetinib or any of the excipient. There have been few reports of hypersensitivity and/or anaphylaxis in clinical trials with patients who have been exposed to Cobimetinib monotherapy. These have appeared to be isolated reports, and in some cases occurred in patients with histories of drug allergies. In reported cases occurring in patients exposed to Cobimetinib, signs and symptoms of hypersensitivity or anaphylaxis improved or resolved after treatment with steroids and/or other medications as clinically indicated.

Investigators should promptly evaluate and treat patients who are suspected of experiencing a hypersensitivity reaction. Suspected hypersensitivity events in Cobimetinib-treated patients should be managed according to institutional guidelines, and patients are to receive maximal supportive care as well as diagnostic workups as clinically indicated.

11.2.6 Cardiac Effects

In MEK4692g, there were no events in this risk category reported. There was a single case of symptomatic Grade 3 dilated cardiomyopathy has been reported in the Phase Ib trial (NO25395) involving Cobimetinib in combination with Vemurafenib. No Grade 4 of 5 events of reduction in LVEF have been reported in single-agent Cobimetinib clinical studies as of the data cutoff dates for the current investigational brochure. Decrease in left ventricular ejection fraction (LVEF) from baseline has been reported in patients receiving MEK inhibitors other than Cobimetinib.

LVEF will be evaluated before initiation of treatment to establish baseline values,then (at a minimum) after the first month of treatment and at least every 3 months or as clinically indicated until treatment discontinuation. Patients with baseline LVEF lower than 50% will be excluded unless diminished systolic function is considered referable to the patient's histiocytosis, in which case the patient can be studied at the discretion of the Principal Investigator. Decrease in LVEF from baseline can be managed using treatment interruption, dose reduction or with treatment discontinuation. After treatment interruption

for reduction in LVEF, all patients restarting treatment with a dose reduction of Cobimetinib should have LVEF measurements taken at approximately 2 weeks, 4 weeks, 10 weeks and 16 weeks, and then as clinically indicated until treatment discontinuation. Precise timing of LVEF surveillance can be determined by the clinician investigator.

11.2.7 CPK Elevation

Elevations in CPK have been observed in patients receiving Cobimetinib monotherapy. These events were not associated with rhabdomyolysis or myocardial injury. One event of rhabdomyolysis was reported in the Phase III Study GO28141 (cobimetinib + vemurafenib), and rhabdomyolysis has been reported in postmarketing experience. In Study GO28141, CPK elevations was reported as an AE more frequently in patients treated with cobimetinib + vemurafenib (32.4% all grades, 11.3% Grade ≥ 3 events) than with placebo + vemurafenib (8.1% all grades, 0% Grade ≥ 3 events).

Events of CPK elevation in Cobimetinib-treated patients should be monitored and managed according to institutional guidelines, and patients are to receive maximal supportive care as well as diagnostic workups as clinically indicated.

11.2.8 Special Patient Populations

In a dedicated embryo-fetal toxicity study, Cobimetinib produced fetal toxicity (resorptions and reductions in fetal weight), and teratogenicity (malformations of the great vessels and skull) at similar systemic exposures to those observed in patients administered the 60-mg dose. In combination with embryolethality observed in mice deficient in mek1 due to reduced vascularization in the labyrinthine region of the placenta (Giroux et al. 1999), inhibition of MEK by Cobimetinib in humans is a potential risk for the developing fetus. Therefore, Cobimetinib should not be administered to pregnant women, and women of childbearing potential should use effective birth control. Female patients of childbearing potential may be included in initial trials, provided they have a negative pregnancy test and agree to use effective contraception while in the study.

It is not known whether Cobimetinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse drug reactions in nursing infants, Cobimetinib should not be administered to nursing mothers.

11.3 Dose Modification Guidelines:

Dose modifications, interruptions, and delays of Cobimetinib study treatment should be made on the basis of the guidelines provided below. The dose modification guidelines are not intended to replace clinical judgment or dictate care of individual patients. Should patients experience intolerable toxicities that do not meet the grading requirements below, clinical decision making will be at the discretion of the PI or investigator on whether or not to dose reduce (i.e. intolerable grade 2 rash, etc.). These reasons will be clearly documented in the medical visit notes and deviations need not be filed. Should a patient be dose reduced and the reason for the reduction resolves, rechallenging with the previous dose level is allowable if there is a clinical reason to do so and at the discretion of the Principal Investigator.

Table 6: Recommended Dose Levels for Dose Reductions

Dose Reduction	Cobimetinib
Starting Dose	60mg daily, 21 days on, 7 days off
Dose Level -1	40 mg daily, 21 days on, 7 days off
Dose Level -2	20 mg daily, 21 days on, 7 days off
Dose Level -3	Discontinue Therapy

11.3.1 Rash (≥Grade 3)

The appearance of rash is characterized as acneiform or non-acneiform. No change in Cobimetinib dosing will be implemented for Grade ≤2 rash unless deemed intolerable by the investigator. Patients will receive maximal supportive care per institutional guidelines

Acneiform Rash:

Hold Cobimetinib dosing until Grade ≤ 2. Reduce Cobimetinib by 1 dose level. If after restarting at a reduced dose and the patient experiences skin toxicity Grade ≥ 3, further reduce Cobimetinib by another dose level. Permanently discontinue Cobimetinib if, after restarting after a second dose reduction, the patient experiences skin toxicity Grade ≥ 3. Permanently discontinue Cobimetinib if rash Grade ≥ 3 persists for > 28 days despite adequate supportive care.

- Non-acneiform or maculopapular rash: Cobimetinib dosing may continue.

11.3.2 Photosensitivity (≥Grade 3)

Patients should be advised to avoid sun exposure, wear protective clothing and use a broad-spectrum UVA/UVB sunscreen and lip balm (SPF≥30) when outdoors.

Grade ≤ 2 photosensitivity should be managed with supportive care, and treatment of Cobimetinib may be continued. If Grade 2 photosensitivity does not resolve to Grade ≤ 1 after 7 days or if photosensitivity worsens to Grade ≥ 3 despite best supportive care, then cobimetinib treatment must be interrupted until the photosensitivity resolves to a Grade ≤ 1.

If resolution to Grade ≤ 1 occurs within 28 days, treatment may be re-initiated without change in Cobimetinib dose. If the photosensitivity does not resolve to Grade ≤ 1 by 28 days, then the therapy Cobimetinib should be discontinued.

If the photosensitivity recurs to Grade ≥ 3 with Cobimetinib, re-initiation despite prophylactic measures and dose reduction, then the study drug should be held until the photosensitivity resolves to Grade ≤ 1 or less.

11.3.3 Visual Symptoms (Grade ≥ 2, Per NCI CTCAE V 4.0)

Interrupt Cobimetinib.

Consult ophthalmology and undergo complete ophthalmologic examination, which includes visual acuity testing, intraocular pressure measurements by tonometry, slit-lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography.

If RVO is diagnosed, Cobimetinib dosing should be permanently discontinued and RVO treated per institutional guidelines.

If neurosensory retinal detachment is diagnosed, Cobimetinib dosing should be interrupted until symptoms improve to Grade 1. Cobimetinib should be dose reduced by 1 dose level. If visual symptoms of Grade ≥ 2 recur despite dose reduction, Cobimetinib should be permanently discontinued.

If RVO and neurosensory retinal detachment are not identified:

- If visual symptoms have not resolved to Grade 1 within 28 days, then discontinue Cobimetinib permanently.
- If visual symptoms have resolved to Grade 1 within 28 days, resume use of Cobimetinib at current dose.
- If visual symptoms of Grade ≥ 2 recur, Cobimetinib should be dose reduced by 1 level. If visual symptoms of Grade ≥ 2 recur despite dose reduction, Cobimetinib should be permanently discontinued.

11.3.4 Diarrhea (≥Grade 3)

No change in Cobimetinib dosing will be implemented for Grade ≤ 2 diarrhea unless deemed intolerable by the investigator; patients should receive maximal supportive care.

If Grade ≥ 3 diarrhea occurs despite adequate supportive care, then the drug should be held until the diarrhea has improved to Grade ≤ 1. If this occurs within 28 days, Cobimetinib may be restarted reduced by 1 dose level.

If the diarrhea is not completely resolved by 28 days, then Cobimetinib should be discontinued.

If the diarrhea recurs at Grade ≥ 3 despite supportive care and dose reductions of 2 dose levels in both drugs (i.e. to 20 mg once daily), then the drug should be permanently discontinued.

11.3.5 Creatine Phosphokinase Elevations (Grade ≥ 3)

Rule out cardiac cause and rhabdomyolysis as clinically indicated, per institutional standards. Consider permanent discontinuation of Cobimetinib if there is evidence of clinically significant cardiac injury or rhabdomyolysis.

Assess patient for any history of strenuous physical activity, blunt trauma, or recent intramuscular injections as these can be an alternative explanation for elevated CPK.

For Grade 3 CPK elevations that are asymptomatic and deemed not clinically significant, continue Cobimetinib at current dose and schedule. Recheck CPK every 1-2 weeks. If CPK remains Grade 3 or decreases, continue Cobimetinib at current dose and schedule.

For Grade 4 CPK elevations that are asymptomatic and deemed not clinically significant, hold Cobimetinib and recheck CPK within 3 days. When CPK is Grade ≤ 3, Cobimetinib may be resumed with a dose reduction by 1 dose level on the same schedule (e.g., 60 mg to 40 mg). If Grade 4 CPK elevation recurs after 1 dose reduction, Cobimetinib may be reduced by another dose level (e.g., 40 mg to 20 mg).

Permanently discontinue Cobimetinib if Grade 4 CPK elevation recurs after 2 dose reductions of Cobimetinib.

11.3.6 Reduction in Left Ventricular Ejection Fraction

- All patients who require dose reduction of Cobimetinib should have LVEF measurements at approximately 2 weeks, 4 weeks, then every 6 weeks for 12 weeks, and then as clinically indicated until treatment discontinuation. Precise timing of LVEF surveillance can be determined by the clinician investigator.

  For a symptomatic decrease in LVEF or symptomatic heart failure:

  - A cardiology consultation is strongly recommended. Hold Cobimetinib. Strong consideration should be given to permanently discontinuing Cobimetinib if it is attributed to have caused the cardiac symptoms.
  - If cardiac symptoms resolve completely within 28 days and LVEF returns to LLN, reduce Cobimetinib by 1 dose level. The patient should have LVEF measurements at 2 weeks, 4 weeks, then every 6 weeks for 12 weeks, and then as clinically indicated until treatment discontinuation.
  - If cardiac symptoms resolve within 28 days but LVEF remains below the LLN, see the tables and diagram below.

Table 7: NCI CTCAE v 4.0 for Decreased LVEF:

Grade	Description
1	
2	Resting EF 50%−40%; 10%−19% drop from baseline
3	Resting EF 39%−20%; > 20% drop from baseline
4	Resting EF <20%

The table below contains dose modification guidelines for Cobimetinib in patients with LVEF dysfunction. These parameters will, by definition, not be applicable, to patients who start therapy with LVEF<50% per PI discretion. The PI will use these as guidance for such patients for dose modification.

Table 8: Recommended Dose Modifications for Cobimetinib in patients with left ventricular ejection fraction (LVEF) decrease from baseline

Patient	LVEF value	Recommended Cobimetinib dose modification	LVEF value following treatment break	Recommended Cobimetinib daily dose
Asymptomatic	≥ 50% (or 40 – 49% and <10% absolute decrease from baseline)	Continue at current dose	N/A	N/A
	< 40% (or 40 – 49% and ≥ 10% absolute decrease from baseline)	Interrupt treatment for 2 weeks	<10% absolute decrease from baseline	1st occurrence: 40mg
				2nd occurrence: 20mg
				3rd occurrence: permanent discontinuation
			< 40% (or ≥ 10% absolute decrease from baseline)	Permanent discontinuation
Symptomatic	N/A	Interrupt treatment for 4 weeks	Asymptomatic and <10% absolute decrease from baseline	1st occurrence: 40mg
				2nd occurrence: 20mg
				3rd occurrence: permanent discontinuation
			Asymptomatic and < 40% (or ≥ 10% absolute decrease from baseline)	Permanent discontinuation

			Symptomatic regardless of LVEF	Permanent discontinuation

11.3.7 Other Grade 3 or 4 Non-Hematologic Adverse Events Related to Study Drugs (Except for GGT or CPK Elevation)

Interrupt dosing of Cobimetinib.

If the AE resolves to Grade ≤ 1 within 28 days, then restart dosing of Cobimetinib. Cobimetinib should be decreased by 1 dose level.

If the AE does not resolve to Grade ≤ 1 by 28 days, discontinue study treatment.

If a Grade 4 AE recurs (a second time), then Cobimetinib should be discontinued.

11.3.8 Liver Function Tests

If Grade 3 and below, continue current dose of Cobimetinib

If Grade 4, see Section 11.3.7 above

No dose modification is required for isolated GGT elevation in the absence of clinically significant above baseline grade in AST, ALT, ALP, and bilirubin.

11.4 Stopping Rule for Participant Safety

A stopping rule will be incorporated into this study in order to address safety. For purposes of evaluating whether the study should be stopped for safety, toxicities will be examined after 9 patients (half of the expected patients) are enrolled and have completed 2 cycles of treatment and at the end of the study.

The rates of SAE, therapy completion rate, and protocol completion will be reported at this time.

Safety will be measured by the frequency of grade 3 or 4 treatment-related clinically significant toxicities (NCI Common Terminology Criteria for Adverse Events version 3.0), aside from Grade 3 or 4 hematologic or laboratory abnormalities and aside from Grade 3 or 4 rash that resolves within 21 days (as this is an expected toxicity of this particular drug class), unless they are deemed unexpected or clinically significant.

We assume that a 15% rate of clinically significant treatment-related adverse event, such as persistent or unexpected renal injury or pulmonary toxicity, or clinically significant laboratory abnormality, is an acceptable toxicity rate, and we assume that a 35% rate is unacceptable. Therefore, the trial will be terminated if 4 or more out of the 9 patients experience a grade 3/4 protocol-related adverse event (with the exception of rash, as above) that is probably or definitely attributable to the study drug within 2 cycles of treatment. At the end of the study, we will declare the regimen unsafe if >=5/18 experience DLTs within 2 cycles. This stopping rule has a 13% chance of declaring the drug unsafe if the true rate is 15% while it has a 66% chance of declaring the drug unsafe if the true rate is 35% or higher [Ivanova A, Qaqish BF

and Schell MJ. (2005). Continuous Toxicity Monitoring in Phase II Trials in Oncology. Biometrics 61, 540-545].

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Primary Objective: Metabolic Response by ^{18}F-FDG-PET Response Criteria (PRC):

Target lesions will be assessed by PRC as outlined below. The primary efficacy variable will be best overall response rate according to PET Response Criteria (PRC).

Response assessments will be performed at MSK by the investigator radiologists. However, treating investigators at participating sites are expectred to review scans with collaborating clinical radiologists and decide about continuing protocol therapy based on local scan interpretation and the patient's clinical status. Treatment need not be held for purpose of response assessment performed at MSK

Histiocytic infiltrations in ECD/LCH are typically multifocal and can involve osseous, soft tissue, and CNS structures. Because lesions are heterogeneously composed of histiocytes, inflammatory stroma, and mixed fibrosis, favorable treatment response may not be reflected in measurement of tumoral size alone. Rather, serial metabolic assessment with ^{18}-F-FDG PET has been found to be the most reliable imaging marker of treatment response for these disorders.(12, 13) PERCIST criteria(10) was proposed as a system of evaluating response to treatment based on FDG-PET metabolism. These criteria are problematic in the assessment of ECD/LCH for several reasons:

(1) The FDG-avidity metric of PERCIST, the SULpeak, suffers from poor reproducibility in lesions with lower levels of avidity, as is the case in ECD/LCH
(2) PERCIST uses a single most avid lesion, and ECD/LCH are nearly universally multifocal in nature, and therefore serial assessment of a single lesion is likely inadequate for these diseases.
(3) the SULpeak is not widely measured, rendering this a difficult assessment to extent to the general clinical setting.

We therefore implemented PET response criteria (PRC) in the VE-BASKET trial (#12-131) that are similar to PERCIST but with modifications. These criteria have been published in their implementation in other cancers as well. Below summarizes the published description of PRC assessment (14):

Up to 5 lesions are selected, no more than two per organ system. SUVs are normalized for body weight. FDG avidity of each lesion is calculated at $SUV_{max\ lesion}$ - $SUV_{max\ liver\ background}$ = $SUV_{corrected\ for\ background}$ or simply "SUV." For brain lesions, a brain background is used in lieu of a liver background. Values less than zero are treated as 0. This allows the FDG avidity of a lesion to be considered as the excess avidity above background.

Complete metabolic response is defined as all lesions decreased to at or below $SUV_{max\ liver\ background}$ (or brain for brain lesions). Partial metabolic response and progressive metabolic

disease require 50% changes in sum of SUVs in order to increase specificity of calling changes in disease status.

Response is determined as shown in the **Table 9** below:

Table 9: **PET Response Criteria Definitions**

RESPONSE CATEGORY	**CRITERIAbased on SUV from up to 5 target lesions**
Complete Metabolic Response	Normalization of all lesions' (target and non-target) SUV to background SUVliver (or SUVbrain for brain lesions only)
Partial Metabolic Response	≥50% decrease from baseline in sum of SUV of all target lesions relative to SUVliver (or SUVbrain for brain lesions only)
Progressive Metabolic Disease	≥50% increase from nadir in sum of SUV of all target lesions relative to SUVliver (or SUVbrain for brain lesions only) with a minimal absolute increase of 3 units of SUV per target lesion (e.g. SUV 3 to SUV 6.)
	New evaluable lesions deemed to represent unequivocal disease progression
Stable Metabolic Disease	Does not meet other criteria

12.3 Safety outcomes:

The following will be the primary safety outcomes:

- Incidence, nature, and severity of AEs and SAEs, graded according to NCI CTCAE v 4.0
- Adverse events of special interest (AESI) including rash grade 3 and above, photosensitivity grade 3 and above, retinal venous occlusion, serous retinopathy, decrease in LVEF grade 2 and above, cases of elevated ALT and/or AST in combination with either elevated bilirubin or clinical jaundice suggestive of drug-induced liver injury, Grade >= 3 CPK or rhabdomyolysis, Grade ≥ 3 hemorrhage event or any grade cerebral hemorrhage and pneumonitis.

The following will be the secondary safety outcomes: Changes in vital signs and clinical lab results in the course of the study.

12.4 Responses in the context of **Exploratory Objectives/Correlative Studies (Appendix C)**: We would like to determine (i) whether there is a association between MAP kinase pathway mutations and response to single-agent MEK inhibition with Cobimetinib (binary outcome CR/PR versus SD/PD) and (ii) whether any mutations (either in MAP kinase signaling pathway or outside of it) may modify response to MEK inhibition. In order to address this question we propose the following:

1. We will perform pretreatment biopsies for collection of fresh frozen material for tumor genotyping when a patient's underlying driver mutation is not known and there is insufficient adequate archival material for genotyping as outlined above. In addition, peripheral blood will be collected on all patients to extract peripheral blood mononuclear DNA as a source of paired somatic normal DNA. Laboratory procedures will be performed by the Abdel-Wahab Laboratory

2. We will perform targeted sequencing of the tumor biopsy material using a next-generation sequencing panel of 410 genes available at MSKCC, for MSK patients (the IMPACT assay). Laboratory procedures will be performed by the Abdel-Wahab Laboratory or the clinical environment. This will provide pretreatment genotyping for mutations in *BRAF, NRAS, KRAS,* and *MAP2K1* as well as mutational data on genes known to be involved in cancer and co-occurring with the MAP kinase pathway mutations. This assay can be performed on paraffin-embedded archival tissue or fresh biopsies. Whole exome sequencing and/or RNA Sequencing will be performed for patient samples where we fresh biopsies have been acquired to compliment the targeted sequencing by identifying mutations and/or gene fusions which would not be detected from the targeted sequencing approach. Next generation sequencing will performed at the Mayo clinic per their standard clinical testing, or at MSK by way of make-an-IMPACT.

3. We will ultimately attempt to associate clinical response to mutational genotype in order to determine if mutation in any particular MAP kinase member is correlated to response to Cobimetinib. Fisher's exact test will be used to assess the association of response with the presence or absence of an identified mutation. Given the number of patients being enrolled, this will be a primarily descriptive and exploratory aim. However, since it is currently not known how *BRAF*V600*, NRAS, KRAS,* or *MAP2K1* mutant disease responds to MEK inhibition, this effort may be critical in the design of future trials.

   In addition to correlating mutations to patient response, we will utilize mutational data from tumor tissue to provide a marker to track disease response in plasma cell-free DNA during therapy. We have successfully performed cell-free DNA analysis for *BRAF*V600E mutations to monitor response to Vemurafenib in LCH/ECD(15) as well as for *NRAS*12D mutations(16). We would hope to track *BRAF*V600, *NRAS, KRAS,* and *MAP2K1* mutations similarly throughout therapy with Cobimetinib to monitor

response to therapy dynamically in this study. If technically possible, custom mutation-specific PCR assays will be developed to follow quantitative allele burden for each patient before and during treatment. Relative decrease in allele burden has been shown in our prior work to reflect and even precede radiographic response.

4. The rationale and justification for this is identical to objective 3 above. We will collect urine for measurement of mutation-specific allele-burden as measured by cell-free DNA analysis. This is an exploratory but entirely non-invasive correlative analysis that allows for exploring mutational burden at a variety of timepoints during treatment.

5. This small trial in a rare disease is not powered to detect significant changes in patient-reported outcomes (PRO) or quality of life (QOL) assessments. Nonetheless the histiocytic disorders are intensely symptomatic diseases and it is appropriate to make a sincere effort to document this dimension of treatment and treatment response. We have assembled a brief and histiocytosis-specific PRO/QOL assessment set based on IRB-approved focus groups in this specific patient population. These surveys will be entirely optional to patients although their avid participation in focus groups suggests that these issues are of pressing and relevant concern to them. See appendix J and L for assessments.

13.0 CRITERIA FOR REMOVAL FROM STUDY

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

Progressive disease

Unacceptable toxicity

Patient election to discontinue therapy (for any reason)

Physician's judgment

Patients have the right to withdraw from the study at any time for any reason. Patients who discontinue the study will be asked to return to the clinic for an End of Treatment visit and a Safety Follow-Up Visit 28 (± 7) days after the last dose of Cobimetinib. As stated above, this will be not be required if the patient cannot return for logistic or heath reasons and a phone assessment for AEs can be performed.

If lost to follow-up, the Investigators will make all possible efforts to contact the patient or a responsible relative by telephone followed by registered mail to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study.

When applicable, patients should be informed of circumstances under which their participation may be terminated by the Investigator without the patient's consent. The

Investigator may withdraw patients from the study in the event of intercurrent illness, adverse events, treatment failure after a prescribed procedure, lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits), cure or any reason where it is felt by the Investigator that it is in the best interest of the patient to be terminated from the study. Any administrative or other reasons for withdrawal must be documented and explained to the patient.

If the reason for removal of a patient from the study is an AE, the principal specific event will be recorded on the eCRF. The patient should be followed until the AE has resolved. Should a patient decide to withdraw, all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible.

14.1 BIOSTATISTICS

The primary objective of this study is to assess the activity of Cobimetinib in patients with ECD and LCH. The primary endpoint is best overall response (BOR) by PET Response Criterial (PRC), with a dichotomous BOR of CR or PR versus neither of those. Assuming we use this binary endpoint of response, defined as best overall response of CR or PR versus not using the PET Response Criteria (PRC), a sample size of 18 patients provides 90% power to test the hypothesis that the response rate is promising (defined as 35% or higher) against a non-promising rate of 10% or lower. The lack of any approved therapies or prospective studies in this disease utilizing strict response criteria makes establishing a historical response rate difficult. However, anecdotal experience with use of a variety of off-label agents suggest that in this patient population these therapies typically have an ORR < 10%. Therefore, using an exact, one-sample test for binomial proportion, with Type I error=10%, Type II error=10% and the above rates provides a sample size of 18 patients. At the end of the study, if at least 4/18 responses are observed then this will be considered a positive study (i.e. conclude that RR is >10%). If a patient with cutaneous disease who does not have PRC-evaluable disease is enrolled, then the study will continue to enroll 18 patients evaluable for the primary endpoint.

Given the high observed RR as of review of efficacy data on 11/14/2017 (RR=14/16) the study was amended for expansion to enroll 12 additional patients to the planned sample size of 18, for a total of 30 patients. This analysis has not yet taken place, and, given further review of efficacy data and the favorable response rate (21/26 as of 3/20/2019) the study will be expanded to enroll 25 additional patients to the amended sample size of 30, for a total of 55 patients. We will continue to enroll patients until we obtain 55 evaluable patients for efficacy by PET criteria and analyze the data at that time. No changes in eligibility criteria or response assessment will be made as part of this amendment. The table below shows the half width of the 95% confidence interval around the RR given hypothetical rates and a sample of 55 patients assuming binomial proportions. The reason the sample size is increased to 55 is to increase the precision around the estimate of RR and to decrease the variance. No changes will be done in the safety monitoring rule described in section 11.4.

Observed RR	Half width of confidence interval
0.5	0.13
0.7	0.12
0.8	0.11
0.87	0.09

In addition to the planned analyses above, data will be cleaned and analyzed in response to regulatory requests by the FDA should such a request be issued.

Definition of Best Overall Response: the best (confirmed) overall response (BOR) is defined as the best response recorded from the first day of study treatment until disease progression/recurrence or death. To be assigned a status of PR or CR (i.e., a responder), changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met, i.e., patients need to have two consecutive assessments of PR or CR to be a responder. Patients without a post-baseline tumor assessment will be considered to be non-responders.

Inclusion of $BRAF^{v600}$-mutated patients in the primary endpoint:

In practice, we anticipate that the vast majority *BRAF*^{V600}-mutated patients will not be enrolled to this study as the publication of deep and durable Vemurafenib activity in this population (Haroche JCO 2015, Hyman NEJM 2015; Diamond JAMA Oncology 2018)) and FDA approval of this drug for BRAF-mutated ECD. Only patients intolerant to BRAFi or the very small remaining minority who cannot access them for financial reasons would be enrolled to this study. For these reasons, we believe that *BRAF*^{V600}-mutated patients should be included in the primary endpoint with the other participants.

Patients with *BRAF*^{V600}-mutated disease that has developed resistance to RAF inhibitors may constitute a unique population and although eligible, these patients would not contribute to the 18 patients evaluated for the primary endpoint. That said, after almost 3 years of following Vemurafenib treated patients, none have developed acquired resistance and therefore there are currently no patients who would qualify for enrollment on this basis.

Secondary Objectives:

- Best Overall response rate according to RECIST v1.1 (for the subset of patients with RECIST-measurable disease)
- duration of PET response (DOR)
- time to progression (by PRC)
- clinical benefit rate (CR, PR, and stable disease)
- PFS
- overall survival (OS)

With the exception of the first secondary objective, which is BOR by RECIST for patients with RECIST-measurable diseases, "response" in the secondary objectives refers to response by PRC.

Best overall response rate according to RECIST v1.1 (for the subset of patients with RECIST-measurable disease) will be calculated where a responder is defined as best overall response of CR or PR using RECIST criteria. The rate will be calculated assuming binomial proportion.

Duration of response: Duration of Response will be defined in the subject of patient with a confirmed partial of complete metabolic response as defined by the PRC. In these patients, duration of response will be defined beginning with the date of response and ending with the data of progression, beginning of an alternative anti-cancer therapy, or death. Patients who do not meet any of these criteria will be censored at the time of study closure."

Patients who withdraw from the study, in the absence of progressive disease by scans, and continue MEK inhibitor therapy off-trial will not be considered to have had a progression event and will be censored.

PFS is defined as the time from the first day of study treatment, until the first documented progression of disease or death from any cause, whichever occurs first. Patients with no PFS events will be censored at the time of the last follow up date. Patients who discontinued cobimetinib (in the absence of progression) to receive an off-label MEK inhibitor will be censored for duration of response and progression-free survival at the final follow-up date. Patients with no tumor assessment after the baseline visit will be censored at the time of the first day of study treatment plus 1 day.

Overall survival (time to death) is defined as time between the first day of study treatment and date of death of any cause. Patients for whom no death is captured on the clinical database are censored at the most recent date they were known to be alive.

Time to progression is defined as time from the first day of study treatment to the first occurrence of progressive disease (by PRC). Patients who have not progressed at the time of study completion (including patients who have died before progressive disease) or who are lost to follow-up are censored at the date of the last tumor assessment.

Clinical benefit rate includes patients whose best response was:

- PR or
- CR or
- Stable disease (SD) that have lasted at least 24 weeks.

Clinical benefit will be calculated assuming binomial proportion.

Exploratory objectives:

1. With regards to urine and blood cell-free DNA analysis, this is nascent technology and there are no established parameters for defining response vis a vis proportional reduction in mutational allele burden. Based on pilot data, we preliminarily stipulate that 50% reduction in allele burden with constitute a favorable response, but this will be considered in light of radiographic response.

   Safety will be defined descriptively using CTCAE v 4.0.

2. Baseline QOL and PRO scores will be non-statistically compared to those reflecting three and then six months of treatment. The number and proportion of patients with symptom reduction (improvement in pain, for example) or improved QOL will be summarized.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 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 or not 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).

15.3 Randomization

N/A

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA 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 the institutional secure database, CRDB. Source documents must be available to support the computerized patient record.

Accrual rates and accuracy of evaluations will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion.

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of the registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations 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 once per year, more frequently if indicated.

16.3 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 September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: *http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1*. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at:

https://one.mskcc.org/sites/pub/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are 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 Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) Will be addressed and the monitoring procedures will be established at the time of protocol activation. A description of the institutional Data and Safety Monitoring (DSM) Plans and how it impacts on this trial is required. The NCI/NIH requirements for Data and Safety Monitoring should include: 1) how trials are monitored, including frequency and data elements to be reviewed; 2) plans for assuring compliance regarding adverse event reporting; 3) plans for assuring appropriate action if a monitored trial results in a temporary or permanent suspension; 4) plans for assuring data accuracy and protocol compliance; and 5) a description of the process and means to avert potential conflicts of interest.

If the trial sponsor has an independent data and safety monitoring process (e.g., independent Data and safety Monitoring Board (DSMB) who works for the pharmaceutical

sponsor) then the procedures by which the independent DSMB functions should be clearly described.

17.1 PROTECTION OF HUMAN SUBJECTS

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).

17.2 Privacy

MSK'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 other qualified researchers.

17.3 Serious Adverse Event (SAE) 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 participant 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

17.2.1 Reporting of Serious Adverse Events to Genentech (MSK ONLY)

The MSK investigators must report all related SAEs to Genentech, Inc. within 1 business day of the Awareness Date in accordance with CFR 312.32 (IND Safety Reports). The completed Medwatch SAE report should be faxed immediately upon completion to Genentech Drug Safety at using the Genentech Safety Reporting Fax Cover Sheet (Appendix F):

(650) 225 4682

OR

(650) 225 4630

- Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.
- Serious AE reports and AEs of Special Interest (regardless of causality) will be transmitted to Genentech within fifteen (15) days of the Awareness Date.

For non-serious events, the study site will forward a copy of the Final Study Report to Roche upon completion of the Study.

In addition to SAEs, pregnancy reports and AESIs, the following Special Situations Reports should be collected and transmitted to Roche even in the absence of an Adverse Event within thirty (30) calendar days:

- Data related to product usage during pregnancy or breastfeeding
- Data related to overdose, abuse, misuse, inadvertent/erroneous administration, medication error or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol
- Lack of therapeutic efficacy

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

Refer to Appendix I Multicenter Addendum for SAE Reporting Guidelines for the participating external sites.

MedWatch 3500A SAE Reporting Guidelines

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

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

Follow-up Information

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

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

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

MedWatch 3500A SAE reporting (Mandatory Reporting) form is available at http://www.fda.gov/medwatch/getforms.html

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: vemurafenib-gsur@gene.com

Additional Reporting Requirements for IND Holders (if applicable). 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 Cobimetinib. An unexpected adverse event is one that is not already described in the Cobimetinib 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 Cobimetinib. An unexpected adverse event is one that is not already described in the Cobimetinib 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 SAE reporting form, but alternative formats are acceptable (e.g., summary letter).

FDA fax number for IND Safety Reports:

Fax: 1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-4630
See appendix D for Genetech's safety reporting fax cover sheet.

And sent to the Site IRB as per section 17.2.

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

Copies to Genentech:
All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. Copies of such reports should be faxed to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-4630

17.2.1 Ethics and good clinical practice

The study will be conducted in accordance with the ICH-GCP and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and the Investigator's Brochure.

Institutional Review Board

The protocol, Investigator's Brochure, Informed Consent Form, advertisements (if applicable), written information given to the patients (including dairy cards), safety updates, progress reports, and any revisions to these documents will be provided to the MSKCC IRB by the Principal Investigator. Any amendment must be approved after review by the IRB.

17.2.2 Investigational Product Complaints

A product complaint is 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.

For all Investigator Initiated Studies (interventional and non-interventional):

Product Complaints with an AE (adverse event) should be reported via email/fax to:

Usds_aereporting-d@gene.com OR 650-238-6067

Product Complaints without an AE (adverse event) should be reported via email to:

For Interventional Investigator Initiated Studies:

kaiseraugst.global_impcomplaint_management@roche.com

All complaints must be filed within 1 business day for pre-approved products and 15 calendar days for approved products. Complaints can be reported using a Medwatch, CIOMS or any Genentech-approved reporting form (same as SAEs, AESI etc.).

18.1 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

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20.1 APPENDICES

A. Pill Diary
B. Research Blood/Exploratory Analysis Manual
C. Genentech Safety Reporting Fax Cover Sheet
D. CYP3A Fact Card
E. PET Assessment Form
F. Quality of Life (QOL) and Patient-Reported Outcome (PRO) Assessments – Assessment Plan
G. Quality of Life (QOL) Measures and Patient-Reported Outcomes (PROs) - Patient Surveys
H. Opthalmology Assessment Response Form
I. Multicenter Addendum
J. Multicenter External Site SAE Report Form