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Regulatory Issues: FDA

FDA Approval Summary: Vemurafenib for the Treatment of Patients with Erdheim-Chester Disease with the *BRAF*V600 Mutation

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Non-Langerhans cell histocytosis • Vemurafenib • Zelboraf • Histiocytosis • *BRAF*V600 mutations

Abstract

On November 6, 2017, the U.S. Food and Drug Administration (FDA) granted regular approval to vemurafenib for the treatment of adult patients with Erdheim-Chester disease (ECD) with *BRAF*V600 mutation. ECD is a type of histiocytosis, a rare disorder characterized by an abnormal accumulation and behavior of cells of the mononuclear phagocytic system, which includes antigen-processing cells, dendritic cells, monocytes, or macrophages. Recently published data confirm a frequency of 54% of *BRAF*V600E mutations in patients with ECD.

Approval was based on a cohort of 22 patients who received 960 mg of vemurafenib twice daily within the VE Basket Trial (MO28072), a single-arm, multicenter, multiple cohort study. Patients in the ECD cohort had histologically confirmed ECD with *BRAF*V600 mutations that were refractory to standard therapy. The ECD cohort achieved an overall response rate of 54.5% (95% confidence interval: 32.2–75.6), with a complete response rate of 4.5%. With a median duration of follow-up of 26.6 months, the median duration of response has not been reached. The most frequently reported adverse reactions (>50%) in the ECD cohort were arthralgia, rash maculo-papular, alopecia, fatigue, electrocardiogram QT interval prolonged, and skin papilloma. The median treatment duration for ECD patients in this study was 14.2 months. This article describes the FDA review of the vemurafenib efficacy supplement for patients with ECD with *BRAF*V600 mutations. ***The Oncologist*** 2018;23:1520–1524

Implications for Practice: Vemurafenib, an oral monotherapy targeting a mutation in BRAF, is the first U.S. Food and Drug Administration approval for the treatment of Erdheim-Chester disease (ECD). ECD is an extremely rare hematopoietic neoplasm that represents clonal proliferation of myeloid progenitor cells. ECD may involve bone and one or more organ systems, primarily affecting adults in their 5th and 7th decades of life, with a slight male predominance. This approval provides an effective and reasonably safe therapy for patients with a serious and life-threatening condition for which no approved therapy exists.

Introduction

Erdheim-Chester disease (ECD) is a slow-growing blood cancer that originates in the bone marrow. ECD causes an increased production of histiocytes, a type of white blood cell. Excess histiocytes can result in tumors infiltrating many organs and tissues throughout the body, including the heart, lungs, brain, and others. ECD is estimated to affect 600–700 patients worldwide. Approximately 54% of patients with ECD have the *BRAF*V600 mutation [1].

This rare, non-Langerhans histiocytosis was described by Jakob Erdheim and William Chester in 1930 [2]. Tissue biopsy, preferably of an osteosclerotic bone lesion, is needed to confirm the diagnosis with CD68+/CD1a-/S-100-/Langerin- foamy histocytes. This differentiates ECD from Langerhans cell histiocytosis (LCH), in which the Langerhans cells are positive for CD1a, S-100 protein, and Langerin. The disease primarily affects the bone but can impact any organ system. Approximately 20% of patients present with symptoms, most commonly bone pain, neurological and constitutional symptoms, and diabetes insipidus [3–5].

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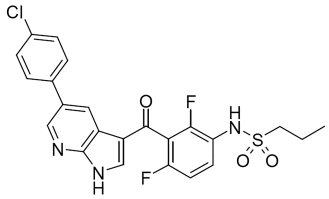
Laboratory workup, including complete blood count and chemistries, are usually nondescript for this diagnosis unless urine electrolytes highlight evidence of diabetes insipidus. There is no universally accepted staging, prognostic, or scoring system for ECD. Staging evaluations include magnetic resonance imaging (MRI) of the brain, computed tomography (CT) scan or MRI of the heart and aorta, CT scan of the chest, abdomen, and pelvis, and $_{18}$F-fluoro-2-glucose-positron emission tomography/computed tomography (FDG-PET/CT), echocardiogram (if heart involvement is suspected), and MRI of the spine (if spine involvement is suspected). The most specific imaging findings would be symmetrical diaphyseal and metaphyseal osteosclerosis of long bone on plain radiographs, increased radiotracer uptake in the proximal and distal ends of tibia and proximal ends of femurs by bone scan or FDG-PET/CT, respectively, and infiltration of perinephric fat and circumferential soft-tissue sheathing of the aorta on CT. It has been suggested that FDG-PET/CT along with C-reactive protein elevation may predict disease activity. Therefore, the diagnosis of ECD relies heavily on the established radiological and histological criteria, because the clinical picture is variable [5].

Although previously reported in only 600–700 patients, the diagnosis of ECD has dramatically increased in the last 10 years due to increasing recognition of the disease. ECD primarily affects adults between their 5th and 7th decades of life, with a slight male predominance noted. The etiology of the disease is unknown, and there is no evidence that ECD is an inheritable genetic disorder. ECD, and the related histiocytic disorder Langerhans cell histiocytosis, are hematopoietic neoplasms that represent clonal proliferation of myeloid progenitor cells. This was demonstrated by finding the *BRAF*V600E mutation in subsets of dendritic cells, mature monocytes, committed myeloid progenitors, and CD34+ cells of affected ECD and LCH patients. Somatic mutations in components of the mitogen-activated protein kinase (MAPK) signaling pathway are present in most patients with ECD. *BRAF*V600E mutations have been found in approximately half of ECD cases, and the mutation of this serine-threonine kinase enhances cell proliferation and survival by activating the RAS-RAF-MEK-MAPK signaling pathway [6]. ECD can involve bone, central nervous system, the retroperitoneum, skin, lungs, heart, and endocrine glands. Patients with ECD can be heavily symptomatic and debilitated, but the symptoms are varied between patients due to the heterogeneity of organ involvement between patients. The 1-year and 5-year survival rates for patients with ECD have been reported at 96% and 68%, respectively [7,8].

Vemurafenib is a kinase inhibitor that works by blocking enzymes in a cell growth-promoting pathway. The U.S. Food and Drug Administration (FDA) first approved vemurafenib in 2011 for the treatment of patients with unresectable or metastatic melanoma with *BRAF*V600E mutation as detected by an FDA-approved test. Vemurafenib is not recommended for use in patients with wild-type melanoma [9]. Vemurafenib was first approved in 2011 for the treatment of patients with unresectable or metastatic melanoma with *BRAF*V600E mutation as detected by a U.S. Food and Drug Administration (FDA)-approved test (Table 1). Vemurafenib is not recommended for use in patients with wild-type melanoma [9].

Table 1. Background information: vemurafenib

Structure	
Mechanism of action	Inhibition of some mutated forms of BRAF serine-threonine kinase, including *BRAF*V600E. Also inhibits other kinases in vitro such as CRAF, ARAF, wild-type BRAF, SRMS, ACK1, MAP4K5, and FGR at similar concentrations. Some mutations in the BRAF gene including V600E result in constitutively activated BRAF proteins, which can cause cell proliferation in the absence of growth factors that would normally be required for proliferation.
Pharmacokinetics	The observed and population PK data following a dose of vemurafenib 960 mg orally twice daily appear similar in patients with different diseases, including metastatic melanoma, NSCLC, and ECD.
Prior approvals	2011, for the treatment of patients with unresectable or metastatic melanoma with *BRAF*V600E mutation as detected by an FDA-approved test.

Abbreviations: ECD, Erdheim-Chester disease; FDA, U.S. Food and Drug Administration; NSCLC, non-small cell lung cancer; PK, pharmacokinetic.

The FDA granted orphan drug designation to vemurafenib for the treatment of ECD in August 2016. Breakthrough therapy designation was granted to vemurafenib for the treatment of patients with ECD with *BRAF*V600 mutation in April 2017.

At the time of this review, there were no FDA-approved products for the treatment of ECD. The treatment of ECD has included off-label use of pegylated and nonpegylated interferons (IFN-α), anakinra, cladribine, imatinib, infliximab, tocilizumab, and a combination of sirolimus and prednisone. In 2013, a report [7] was published describing rapid clinical and tumor responses for three patients with *BRAF*V600E mutation ECD who received vemurafenib. The current approval was granted on November 6, 2017, 1 month prior to the goal date. Herein, we describe the FDA review of the evidence submitted for this application and the clinical implications for the rare ECD population.

Clinical Trial Design

M028072 (ClinicalTrials.gov identifier NCT01524978) was an open-label, multicenter, multicohort, multinational, nonrandomized basket trial exploring the efficacy and safety of vemurafenib monotherapy in a diverse population of patients with cancers known to harbor *BRAF*V600 mutations (excluding melanoma and papillary thyroid cancer). Cohort 7A included 22 patients with ECD in addition to 4 patients with LCH. Eligible patients were adults with histologically confirmed cancers (excluding melanoma and papillary

thyroid cancer) who harbored *BRAF*V600 mutation refractory to standard therapy or for which standard or curative therapy did not exist, and who had measurable disease per RECIST 1.1. Patients were selected for enrollment based upon *BRAF*V600 mutation analysis assays as routinely performed at each participating site according to local procedure. However, sites could submit a tumor sample for retrospective confirmation of the BRAF mutation using the Roche CDx cobas 4800 *BRAF*V600 test or other standard methodology by a central laboratory.

Patients must have had adequate hematologic function (defined as absolute neutrophil count $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L). Patients with concurrent ECD and LCH, as well as patients with ECD and/or LCH and active or untreated central nervous system involvement, were eligible.

Patients received vemurafenib 960 mg orally twice daily with or without food until the development of progressive disease, unacceptable toxicity, withdrawal of consent, protocol violation endangering the patient's safety, death, reasons deemed critical by the treating physician, or study termination. Patients with ECD could discontinue vemurafenib treatment after 1 year, if the Investigator considered it to be in the best interests of the patient. Patients were eligible to resume treatment if they became symptomatic or if they had radiographic evidence of progressive disease.

Prior to the closure of the trial, patients who had completed the protocol-mandated minimum 12-month safety follow-up and who continued to benefit from vemurafenib therapy were offered the opportunity to receive continued vemurafenib treatment via enrollment in the GO28399 extension trial. Patients in Study GO28399 trial were followed for survival for a minimum period of 12 months after the last patient has been enrolled or until all patients had died, withdrawn consent, or were lost to follow-up, whichever occurred first.

The primary endpoint of the final analysis for Cohort 7a (patients with ECD) was the overall response rate (ORR), which was defined as the proportion of patients who had a complete response (CR) or partial response (PR) confirmed on two occasions at least 4 weeks apart, as assessed by the Investigator using RECIST 1.1. Secondary endpoints included progression-free survival (PFS) and time to tumor progression, best overall response, clinical benefit rate, time to response, duration of response (DoR), and overall survival (OS).

Efficacy assessments included baseline tumor assessment by CT/MRI of the chest, abdomen, and pelvis as well as clinically relevant tumor assessment to define baseline extent of disease (i.e., brain MRI, cardiac MRI/echocardiogram, bone scan, ^{18}F-FDG-PET). Tumor assessments were conducted every 8 weeks after the start of vemurafenib. There were no formal statistical hypotheses for this cohort.

Pharmacokinetic (PK) samples were collected before the dose on multiple occasions, including Cycle 1 Day 15 (C1D15), C2D1, C3D1, and C4D1 in a single patient with ECD. PK data were available for 21 additional patients enrolled in the basket trial. A population analysis was completed.

Table 2. Efficacy results for vemurafenib in *BRAF*V600-mutation positive Erdheim-Chester disease

Efficacy results	ECD patients (n = 22)
Median duration of follow-up, months (Min, Max)	26.64 (3.0, 44.3)
ORR by Investigator (95% CI)	>12 (54.5%) (32.21–75.61)
Complete response	1 (4.5%)
Partial response	11 (50.0%)
Stable disease	9 (40.9%)
Progressive disease	0
Not measurable	1 (4.5%)

Abbreviations: CI, confidence interval; ECD, Erdheim-Chester disease; Max, maximum; Min, minimum; ORR, overall response rate.

Results

Trial M028072 (VE Basket) initiated on April 11, 2012, and completed on October 27, 2016. The data cutoff for the application submission was January 12, 2017. The trial enrolled 208 patients into seven different cohorts. Twenty-two patients with ECD with *BRAF*V600 mutation enrolled in Cohort 7a. Enrolled ECD patients had a median age of 58.5 years (34–77 years), had a slight male predominance (55%), and were predominantly white (96%). Eastern Cooperative Oncology Group (ECOG) scores at baseline were mostly 1 (54%), with 23% of patients having a score of 2, 18% having a score of zero, and 5% "not applicable." Fifteen patients (68%) had at least one prior systemic therapy for ECD. At the time of data cutoff, all patients were no longer receiving study treatment and had discontinued from the study.

Efficacy

The overall response rate (ORR) was 54.5% (95% confidence interval: 32.2–75.6). One patient had a CR, and eleven had PRs (Table 2). The remaining nine patients had stable disease, and one patient's outcome was not measurable. The median DoR was not estimable with a median duration of follow-up of 26.6 months (3–44.3 months). The median time to response was 11 months (3.7–14.6 months). The median time to treatment discontinuation was 14.2 months (1.6–44.2 months). The median PFS and OS were not estimable.

Efficacy narratives, abstracted from medical records, for all ECD patients were reviewed. The narratives provided statements describing changes in disease symptomatology, physical function, and quality of life while receiving vemurafenib. Fifteeen were documented by the clinician to have had an improvement in disease-related symptoms or physical function after starting treatment with vemurafenib. Examples include improvements in symptoms (i.e., dysarthria, ataxia, headache, visual disturbances, fatigue, bone pain, lymphedema, pain, skin lesions, night sweats, urinary frequency, arthralgias, dyspnea) and physical function (i.e., resumption of activities of daily living, wheelchair-bound patient ambulating independently, returning to work, navigating stairs without assistance, and ECOG 2 to 0). The efficacy narratives provided supportive evidence that patients with ECD treated with vemurafenib experienced an improvement in the way they felt and functioned.

Safety

The safety review of vemurafenib in patients with ECD was based on 22 patients with *BRAF*V600-mutation ECD (enrolled in trial MO28072 and including longer-term data from 8 patients who rolled over to the extension study [GO28399]). Due to the small sample size and rarity of the condition, supportive safety data from 3,378 non-ECD patients who had been treated at the same vemurafenib dose and schedule (including non-ECD patients from trial MO28072 and patients with metastatic melanoma from trial MO25515) were also included.

The study population was monitored for deaths, serious adverse events, adverse events (graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0), and laboratory test abnormalities. Scheduled clinical visits including safety assessments occurred at baseline; on Cycle 1 Days 1, 15, 29; at the start of every subsequent 28-day cycle; and 1 month after the final dose.

The most commonly reported adverse reactions (incidence >50%) in 22 patients with *BRAF*V600 mutation-positive ECD treated with vemurafenib were arthralgia, rash maculo-papular, alopecia, fatigue, electrocardiogram QT interval prolonged, and skin papilloma. The most common (≥10%) grade 3–4 adverse reactions were squamous cell carcinoma of the skin, hypertension, rash maculo-papular, and arthralgia. Nonfatal serious adverse events occurred in 73% of patients with ECD. There were no fatal adverse events (grade 5) reported among the ECD patients within 100 days of the final dose.

All patients with ECD had at least one dose reduction (DR) from the starting dose of 960 mg orally twice daily and one dose interruption (DI) due to an adverse reaction. The most frequent adverse reaction leading to DR or DI were maculopapular rash, fatigue, arthralgia, palmar-plantar erythrodysaesthesia, and increased lipase. The duration of DI ranged from 1 to 29 days. The dose was reduced to 720 mg orally twice daily in 8 patients, and ultimately to 480 mg orally twice daily in 14 patients. The median duration of treatment was longer following dose reduction to 480 mg (236 days; 21–924 days) compared with 720 mg (77 days; 4–1,325 days). The efficacy was maintained in these patients based on the ORR. These events were similar to those leading to dose modifications in previous trials in non-small cell lung cancer and metastatic melanoma; however, more patients with ECD needed DR and DI due to adverse reactions. Due to DR and DI in the ECD population, the relative dose intensity in these patients was lower (62%) than that in the non-ECD patients from Trial MO28072 (80%) and that in the patients with metastatic melanoma from Trial MO25515 (90%).

Discussion

It was agreed in advance of the application submission that the FDA would not require a companion diagnostic for vemurafenib for the *BRAF*V600-mutation assay with this application.

The efficacy of vemurafenib was based on response rate as assessed by the Investigator using RECIST 1.1 response criteria. In addition to the overall response rate among the patients with ECD, supportive evidence of symptomatic and physical function improvement was reported in 68% of the 22 patients after starting treatment with vemurafenib. These results were derived from "efficacy narratives" created from excerpts from the patient medical records. The documented evidence of clinician-reported functional and symptomatic improvement while on vemurafenib does represent a favorable benefit to risk ratio to support regular approval of vemurafenib for patients with ECD. The functional and disease symptom improvements are very likely to be due to vemurafenib treatment, and not a function of disease waxing and waning. Many of these symptomatic responses were rapid and not always identified concurrent with radiographic (RECIST) responses.

This is a common problem in obtaining drug approvals for rare diseases. Typically, the natural history of the disease is not clear, often due to heterogeneity. Clinical outcome measures for rare diseases have never or rarely been described or tested, and longitudinal follow-up may be limited. Finally, the predictive biomarker measurements based on patient response, patient selection, or assessing activity may not be precise or reproducible. Hence, the need for developing a comprehensive natural history program involving the affected patients early in the developmental drug program is crucial. Meanwhile, precision medicine cancer trials such as "basket" trials with biomarker-defined targets across histologic diagnoses should be considered (e.g., the trial used here). In exploring outcome measures when the treatment effect is unknown, it may be important to consider randomization in efficiently finding if there is a treatment effect. In this basket trial, the dose was reduced to 720 mg or 480 mg orally twice daily for all patients with ECD from the starting dose of 960 mg twice daily and one dose-interruption due to an adverse reaction; however, the efficacy was maintained in these patients based on the ORR, and no differences in the minimum trough concentrations were observed regardless of disease type across clinical trials.

Given the rarity of ECD and the lack of available therapies, the FDA agreed to accept data from a small cohort of a basket trial for review. The rarity of this condition as well as the lack of an established standard therapy would have also prevented the conduct of a randomized clinical trial.

Conclusion

Prior to the approval of vemurafenib, there were no FDA approvals for the treatment of patients with ECD. When treated with single-agent vemurafenib, patients with *BRAF*V600 mutation ECD experienced an ORR of 54.5% as assessed by the investigator. An exploratory evaluation of efficacy narratives identified supportive evidence that patients also reported to the treating clinician, improvements in disease-related symptoms and physical function. The efficacy and safety results from trial MO28072 demonstrated an acceptable benefit-risk (see Table 3) profile for vemurafenib for the treatment of adult patients with *BRAF*V600 mutation-positive ECD. Evidence of a 54.5% ORR along with supportive evidence of clinician-reported improvements in disease-related symptoms and physical function permitted the FDA to grant regular approval for the proposed indication.

Table 3. U.S. Food and Drug Administration benefit-risk assessment

Dimension	Evidence and uncertainties	Conclusions and reasons
Analysis of condition	• Heterogeneous clinical course; prognosis depends upon extent and distribution of disease. Bone pain is most common presenting symptom. Disease may involve skeletal, cardiovascular, CNS, ocular, urologic, pulmonary, and retroperitoneal areas. • 1-year and 5-year survival rates for patients with Erdheim-Chester disease are estimated at 96% and 68%, respectively. • Deaths occur due to cardiovascular, pulmonary, or CNS involvement. • Unmet medical need for all patients with ECD.	ECD is a symptomatic, debilitating, and life-threatening disease.
Current treatment options	• No approved therapies for treatment of ECD.	No available therapies; no standard treatments.
Benefit	Trial MO28072: • ORR of 54.5%; median DoR was not estimable at the time of data cutoff. • Clinician-reported improvements in disease-related symptoms and physical function were documented in efficacy narratives for 68% of patients.	Vemurafenib resulted in a high overall response rate and clinician reports of improvements in disease-related symptoms and physical function in a single-arm trial.
Risk	• Rate of permanent discontinuation of vemurafenib due to adverse events was 59%. Events leading to permanent discontinuation included arthralgia, increased ALT, diarrhea, fatigue, posterior reversible encephalopathy syndrome, pancreatitis, small bowel obstruction, splenic infarction, and vomiting. • Most common adverse reactions (≥50% of patients): arthralgia, maculopapular rash, alopecia, fatigue, ECG QT prolonged, skin papilloma, hyperkeratosis, and diarrhea. • Safety profile of vemurafenib is well characterized in patients with other advanced malignancies.	Safety profile observed with vemurafenib is acceptable given life-threatening illness and compares favorably with other therapies used off-label for this condition.
Risk management	• Risk of developing new primary malignancies, hypersensitivity reactions, dermatologic reactions, QT prolongation, hepatotoxicity, uveitis, renal failure, and Dupuytren's Contracture are adequately described in the prescribing information.	No significant safety concerns identified during sNDA review requiring risk management beyond labeling.

Abbreviations: ALT, alanine aminotransferase; CNS, central nervous system; DoR, duration of response; ECD, Erdheim-Chester disease; ECG, electrocardiogram; ORR, overall response rate; QT, electrocardiogram QT corrected interval prolonged; sNDA, supplemental new drug application.

Author Contributions

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Data analysis and interpretation: Patricia A. Oneal, Virginia Kwitkowski, Lola Luo, Yuan Li Shen, Sriram Subramaniam, Stacy Shord
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Final approval of manuscript: Patricia A. Oneal, Virginia Kwitkowski, Lola Luo, Yuan Li Shen, Sriram Subramaniam, Stacy Shord, Kirsten B. Goldberg, Amy E. McKee, Edvardas Kaminskas, Ann Farrell, Richard Pazdur

Disclosures

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