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To the editor:

Targeted therapies in 54 patients with Erdheim-Chester disease, including follow-up after interruption (the LOVE study)

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Erdheim-Chester disease (ECD) is a non-Langerhans cell histiocytosis that is characterized by the accumulation of foamy histiocytes in the retroperitoneum, long bones, and large vessel areas.[1] It may be a life-threatening condition, especially in cases of heart or central nervous system (CNS) involvement.[2,3] Almost 60% of ECD patients carry a *BRAF*^{V600E}-activating mutation of the RAS-RAF-MEK-extracellular signal-regulated kinase signaling pathway.[4-6]

In multisystemic, severe forms of this disease, targeted treatments with the BRAF inhibitors, vemurafenib and dabrafenib, have been efficiently used in *BRAF*-mutated patients.[7-9] In wild-type (WT) *BRAF* patients, cobimetinib, a MEK inhibitor, has also been used with success.[10] These treatments have shown good efficacy with a follow-up of ≤16 months.[8] Longer follow-up has not been reported. In particular, the outcomes after targeted treatment interruption have not yet been assessed. In this study, we report the results of targeted therapy with vemurafenib, dabrafenib, and/or cobimetinib for ECD patients who were seen at least once in our institution and were included in the French Histiocytosis Registry. We also report the outcomes after treatment interruption (the long-term outcomes after vemurafenib/BRAF inhibitors interruption in ECD [LOVE] study; www.clinicaltrials.gov #NCT 02089724).

Among the 165 ECD patients seen at least once in our institution between 1995 and 2016, 133 (81%) had a successful determination of their *BRAF* status. The methods for obtaining the *BRAF* status were described elsewhere.[4] Among them, 88 (66%) were found to carry a *BRAF*^{V600E} mutation. The other 45 patients were considered as WT *BRAF* patients. All patients were included in the French Histiocytosis Registry (approved by the Comité de Protection des Personnes Ile de France III [#2011-A00447-34]). Patients were included in the current report if they: (1) had a definite diagnosis of ECD based on consistent clinical and radiological features and a histological sample that was centrally reviewed, showing an infiltration by foamy histiocytes (immunohistochemistry; these histiocytes were CD68 positive and CD1a negative); (2) had a successful determination of their *BRAF* status; and (3) received a treatment with vemurafenib, dabrafenib, and/or cobimetinib, regardless of the duration of this treatment. All patients gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

The primary end point was the [^{18}F]fluorodeoxyglucose (^{18}F-FDG) positon emission tomography (PET)–computed tomography (CT) at 6 months (M6) after treatment initiation. The definitions of the metabolic terms have been extensively described elsewhere,[8] but, briefly, as assessed by the PET Response Criteria in Solid Tumors (PERCIST) criteria, patients were classified as complete metabolic responders (CMRs; complete resolution of pathologic ^{18}F-FDG uptake), partial metabolic responders (PMRs; reduction of ≥30% in activity of target lesions), stable metabolic disease (not CMR, PMR), or progressive metabolic disease (increase of a minimum of ≥30% in the activity of target lesions or presentation of a new lesion). In contrast to the PERCIST suggestions, the tumor standardized uptake value (SUV) maximum rather than peak SUV was measured. Target lesions were defined by the most active lesion on ^{18}F-FDG–PET/CT study before treatment, and for each patient, 1 or 2 secondary target lesions among the most active lesions were also studied.

The inclusion criteria for the LOVE study were (1) age ≥18 years, (2) clinical and radiological presentation concordant with ECD, (3) presence of histological proof of ECD, (4) treatment with vemurafenib or another BRAF inhibitor, and (5) agreement to participate. The exclusion criteria were pregnancy or patients who exceed the safe weight limit of the PET/CT bed (220 kg) or who could not fit through the PET/CT bore (diameter: 70 cm).

The primary end point was the modification of the SUV maximum between treatment initiation and M6 or at the time of the relapse for each lesion (see the definition of the PERCIST metabolic response above).

Table 1. Clinical characteristics of treated patients

	Vemurafenib* (n = 50) or dabrafenib (n = 1)	Cobimetinib (n = 15)
Sex	15 females and 36 males	3 females and 12 males
Age at diagnosis, median (range), y	57 (17-72)	56 (34-71)
BRAF^{V600E}	49 (96)	10† (67)
BRAF WT	2† (4)	5 (33)
Mixed histiocytosis (ECD + LCH)	15 (29)	5 (33)
CNS	26 (51)	9 (60)
Cerebellar	15 (29)	7 (47)
Lung	18 (35)	6 (40)
Vascular	39 (76)	12 (80)
Heart	38 (75)	10 (67)
Xanthelasma	19 (37)	3 (20)
Diabetes insipidus	23 (45)	5 (33)
Retroperitoneal fibrosis	33 (65)	11 (73)
Bones	44 (86)	13 (87)
Previous treatments		
Anakinra	6 (12)	2 (13)
Interferon-α	36 (71)	11 (73)
Deaths	5 (10)	0
Targeted treatments‡		
Vemurafenib/dabrafenib, n	51	12
Cobimetinib, n	12	15

Values are n (%) unless otherwise indicated.
LCH, Langerhans cell histiocytosis.
*Three patients received dabrafenib after vemurafenib due to side effects.
†Six patients received a BRAF inhibitor alone and then combination therapy, 3 patients received a BRAF inhibitor alone and then cobimetinib alone, 3 patients received combination therapy alone, and 3 patients received only cobimetinib.
‡Two patients had a MAP2K1 mutation.

The secondary outcome measures were the specific organ assessment (cardiac, retroperitoneal, and neurological) and the C-reactive protein value (milligram per liter) at M6 or at the time of the relapse.

When the patients relapsed, targeted therapy was resumed depending on the clinician's decision, and its efficacy was assessed by using the same criteria as above.

A total of 54 patients who received ≥1 dose of vemurafenib, dabrafenib, and/or cobimetinib were included in this cohort study. The clinical characteristics are presented in Table 1.

Fifty-one patients were treated with a BRAF inhibitor. Fifty patients were treated with vemurafenib. Among them, 3 successively received vemurafenib and then dabrafenib; in all cases, this was because of side effects with vemurafenib. One additional patient was treated with dabrafenib from the beginning.

Nine patients were treated with both a BRAF inhibitor and cobimetinib. Three patients were treated with combination therapy starting at the beginning of the treatment. For 6 patients, cobimetinib was added after an initial course of BRAF inhibitor alone because of persistent neurological disability (n = 4), persistent hypermetabolism in PET scanning (n = 1), and chronic myelomonocytic leukemia (n = 1). Three WT *BRAF* patients received cobimetinib alone. Three patients received cobimetinib alone after a BRAF inhibitor (2 WT patients who were treated with vemurafenib before obtaining a *BRAF* status and 1 V600E-mutated patient who experienced a drug reaction with eosinophilia and systemic symptoms [DRESS] with vemurafenib and then with dabrafenib).

Five patients died during follow-up. Four patients had been included in the LOVE study and are detailed below. One additional patient died of respiratory failure due to pulmonary involvement of ECD after a few days of vemurafenib treatment.

The BRAF inhibitor treatment efficacy was evaluated with a ^{18}F-FDG–PET scanner at M6 in 48 patients (this treatment was stopped in 3 patients before 3 months because of side effects). The response rate was 88%; 2 patients (who were *BRAF* WT) had progressive metabolic disease, 4 had stable metabolic disease, 35 had PMR, and 7 had CMR. Responses were sustained, and we did not observe any progression after metabolic remission (see below).

Among the 15 patients treated with cobimetinib, 3 patients prematurely stopped the treatment (before efficacy evaluation) for the following reasons: 1 for severe rhabdomyolysis (combination therapy), 1 for severe nausea and diarrhea (with cobimetinib alone), and 1 for a severe allergic reaction (cobimetinib alone). As a result, the MEK inhibitor treatment efficacy could be evaluated in 12 patients. Eight patients were treated with both cobimetinib and a BRAF inhibitor. At 6 months, 5 achieved PMR and 3 had CMR. Four patients were treated with cobimetinib alone; 2 had PMR and 2 had CMR. The median duration of treatment for patients on cobimetinib alone was 5.5 months (range: 0.1-14 months).

Disease regression (vascular, CNS, or retroperitoneal) was observed in all patients, and improvement in disease-related symptoms was also observed in all but 1 patient. With a median treatment duration of 12 months (range: 1-48 months), none of the metabolic responders had disease progression while receiving treatment.

The side effects that occurred during BRAF or MEK inhibitor therapy are presented in Table 2. The most frequent side effects when treated with BRAF inhibitors were skin complications, ranging from pilar keratosis and photosensitivity to spinocellular carcinoma and melanoma. The most frequent side effects of cobimetinib were nausea, acneiform rash, and rhabdomyolysis. Eleven patients discontinued treatment due to side effects; 8 were receiving vemurafenib, and 3 were receiving cobimetinib.

BRAF inhibitors were stopped in 20 patients after a median treatment time of 20 months (range: 1-31 months). The clinical characteristics of the patients are detailed in supplemental Table 1 (available on the *Blood* Web site). In 7 cases, the treatment was stopped because of side effects; 1 patient stopped because of disease progression, 1 patient stopped because of progression and side effects, and 11 patients stopped because they were in PMR or CMR after 9 to 31 months of treatment.

Table 2. Side effects of BRAF and MEK inhibitors

	Vemurafenib, n (%)	Cobimetinib, n (%)
Photosensibility, pilar keratosis	16 (32)	—
Acne rash	—	8 (53)
DRESS	2 (4)	—
DRESS-like*	1 (2)	—
Cutaneous allergy	1 (2)	1 (7)
Spinocellular carcinoma	4 (8)	—
Basocellular carcinoma	3 (6)	—
Melanoma	1 (5)	—
Actinic keratosis	2 (4)	—
Bowen disease	1 (2)	—
Multiple nevi	3 (6)	—
Eyelid keratoacanthoma	1 (2)	—
Nausea, vomiting	1 (2)	4 (27)
Arthralgia	7 (14)	—
Renal vasculitis	1 (2)	—
Tuberculosis	1 (2)	—
Deep vein thrombosis	1 (2)	—
Neutropenia	1 (2)	—
Scotoma and syncope	1 (2), combination therapy; ophthalmic examination was normal, and electrocardiogram and electrophysiological studies were also normal	
QT prolongation, torsade de pointes and cardiac arrest	1, treatment was resumed after ICD implantation (2)	—
Gastric cancer	1 (no RAF or RAS mutation) (2)	—
Cardiac failure	1 case, reversible when the dose was tapered (2)	—
Hypertriglyceridemia	1 (2)	—
Depressive episode	1 (2)	—
Rhabdomyolysis	—	4 (27)
Sarcoidosis-like disease	3 (6)	—

ICD, implantable cardioverter-defibrillator.
*Cholestasis and eosinophilia were reversible after treatment was stopped.

Relapses occurred in 15 cases (75%) with a median time to relapse of 6 months (supplemental Figure 1). The C-reactive protein levels and median SUV were significantly higher at the time of relapse ($P = .03$ and $< .0001$, respectively) (supplemental Figure 1).

Treatment with a BRAF inhibitor was resumed in 10 patients, resulting in improvement for all patients.

Four patients died during follow-up for the LOVE study; 1 had experienced severe side effects, and BRAF inhibitor treatment was not resumed (patient 7); 1 died of intracranial hemorrhage without an evident link to the disease (patient 1); 1 died of septic shock after immunosuppressive treatment of vemurafenib-induced vasculitis (patient 2); and 1 died of gastric carcinoma 4 months after vemurafenib was resumed (patient 9).

The results from this study show a high response rate of 88% in ECD and 91% in $BRAF^{V600E}$-mutated ECD. This was previously suggested in a basket study in which 18 Langerhans-cell histiocytosis or ECD patients were enrolled.[9] This study, as well as others from our group,[7,8] yielded preliminary results suggesting that BRAF inhibition in ECD has a clinically relevant benefit, although ECD is a rare orphan disease with no approved therapies for adults. An important point that we observed with a longer follow-up than previously reported is that no patients experienced disease progression during treatment. In addition to a metabolic response, we also observed tumor regression in all sites.

This study also found early signals of activity of the MEK inhibitor, cobimetinib, which was used in combination therapy with e BRAF inhibitor or as a unique therapy in WT *BRAF* patients or $BRAF^{V600E}$ patients who did not tolerate BRAF inhibitors. Although we could not draw firm conclusions in this study because of the small number of patients, metabolic responses and tumor regression were also observed under cobimetinib.

Adverse events were frequent in this study. These safety data were similar to those reported in previous studies of melanoma patients,[11,12] although the sample size did not allow for a definitive comparison.

Most patients relapsed after BRAF inhibitor interruption. All patients improved after the treatment was resumed. We could not identify predictive factors of relapse, which was probably due to the small sample size. However, promising tools were not used, such as circulating residual disease.[13,14]

This study is limited by the retrospective evaluation of the metabolic response. However, the radiologist was blinded to treatments. Another limitation is the absence of evaluation of the circulating residual disease (*BRAF* mutation detection in peripheral blood), because it has been done in several myeloproliferative disorders.

In conclusion, we report the results of targeted therapy in 54 ECD patients. We found that $BRAF^{V600E}$ is a targetable oncogene in ECD and that cobimetinib is a promising treatment independent of the molecular profiling of patients. Safety data should be kept in mind, and targeted treatments should be considered in the more severe patients.

The online version of this article contains a data supplement.

There is an Inside *Blood* Commentary on this article in this issue.

Contribution: F.C.A., J.-F.E., Z.A., J.D., and J.H. designed the study; F.C.A., J.-F.E., F. Charlotte, N.B., P.M., and J.H. collected the data; J.-F.E. and F. Charlotte centrally reviewed the histological samples; J.-F.E. determined the *BRAF* status; F.C.A. and F. Carrat conducted the statistical analysis; F.C.A., J.-F.E., F. Carrat, F. Charlotte, J.D., Z.A., P.M., A.I., S.B., K.H.-X., and J.H. analyzed and interpreted the data; P.M. centrally reviewed the PET-CT scans; F.C.A., J.-F.E., F. Carrat, Z.A., and J.H. wrote the manuscript; and all authors critically reviewed and approved the final version of the manuscript.

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To the editor:

Platelet soluble CD40-ligand level is associated with transfusion adverse reactions in a mixed threshold-and-hit model

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Platelets are the principal source of soluble CD40-ligand (sCD40L) found in blood.[1] This biological response modifier has been reported to be a candidate mediator for acute reactions after platelet transfusions.[2] Serious adverse reactions (SARs) associated with excessive levels of sCD40L are febrile nonhemolytic transfusion reactions, transfusion-related acute lung injury (TRALI), and allergic reactions,[2-4] although there is not a consensus on the role of sCD40L in TRALI.[5,6] An elevated level of sCD40L in SAR-causing transfusions was found to be 1 element of a broader spectrum of biological response modifiers.[7-9] sCD40L was modeled for likeliness to be predictive of SARs compared with other mediators:[10] in the presence of elevated levels of sCD40L, elevated levels of MIP1α were associated with febrile nonhemolytic transfusion reactions, whereas low levels were associated with allergic type reactions.[7] In SARs, exacerbated sCD40L was attributed to platelet secretion in bags.[9] Although there is extensive polymorphism in genes that control both sCD40L isotype and production in donors,[11,12] no such polymorphisms proved statistically associated with SARs.[12] We evaluated whether elevated levels of infused sCD40L associate with SARs by following a large series of platelet concentrate (PC) transfusions.[7,8,10] Most patients who developed SARs received a high amount of sCD40L, but many patients who also received high amounts of sCD40L did not develop a SAR. Thus, only a subgroup of recipients manifested inflammation.

Single-donor apheresis (SDA) PCs and pooled platelet concentrates (PPCs) were produced in 1 regional setting of the French Blood Establishment). All PCs were leukoreduced to $<10^6$/bag and suspended in 35% native plasma/65% nutritive solution.[7,8,10] PCs from female donors were tested for anti-HLA. Platelets became outdated 5 days (d5) after collection. The study included 9206 successive PCs (issued to patients in the 2 university hospitals), of which 2850 were sampled at the time of delivery to the patient, allowing case control for the day of processing. A total of 140 SARs (grades 2-3; accountability 2-3)[9] was reported, for which samples were shipped back to the Blood Bank. The processing procedure and the incident/accident declaration strictly conformed to the national protocols.[8] Platelets incriminated in a SAR were immediately shipped back the Blood Bank for investigation. All samples obtained from PCs not associated with SAR (referred to as "no.AR") were used as controls. All samples were prepared as reported,[7,8,10] stored at −80°C, assayed for sCD40L by Luminex (HCYTOMAG-60K-06, Merck Millipore, Molsheim, France), and analyzed using Bioplex Software (Biorad, Marnes-la-Coquette, France). Statistical analyses consisted in paired *t* and nonparametric Mann-Whitney *U* tests. Analysis of variance, followed by the Kruskal-Wallis test with Dunn posttest, were performed to compare sCD40L concentrations during storage (GraphPad, La Jolla, CA). "Pathogenic" thresholds were calculated by