case report

Vemurafenib in Patients With Relapsed Refractory Multiple Myeloma Harboring *BRAF*^{V600} Mutations: A Cohort of the Histology-Independent VE-BASKET Study

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INTRODUCTION

Multiple myeloma (MM) is a genetically heterogeneous, complex disease that arises as a result of a variety of mutations in pathways deregulating the intrinsic biology of the plasma cell.[1] Although immunomodulatory drugs and proteasome inhibitors have improved outcomes in patients with MM,[2,3] patients with relapsed or refractory disease have a poor prognosis.[4] Despite the identification of many of the genetic events involved in the development of MM, no treatments specifically targeting genetic mutations have been developed to date. Aberrant signaling in the MAPK/ERK pathway plays an important role in the progression of disease in patients with MM,[5,6] with mutations in oncogenic drivers, including *BRAF*, *KRAS*, and *NRAS*, occurring in more than one half of patients.[1] In a recent whole-exome sequencing study, mutations in *KRAS*, *NRAS*, and *BRAF* were reported in 21%, 19%, and 7%, respectively, of patients with newly diagnosed myeloma.[7]

Vemurafenib is a selective inhibitor of the BRAF^{V600} kinase, with efficacy in patients with *BRAF*^{V600}-mutated metastatic melanoma,[8,9] non–small-cell lung cancer,[10] glioma,[11] Erdheim-Chester disease/Langerhans cell histiocytosis,[12] and papillary thyroid cancer.[13] Treatment with vemurafenib has also shown clinical activity in two patients with *BRAF*^{V600} mutation–positive myeloma after the failure of autologous stem-cell transplant and other therapies[14] and in a patient with relapsed refractory myeloma with plasmablastic differentiation.[15] The multicenter, single-arm Vemurafenib-Basket (VE-BASKET) study (ClinicalTrials.gov identifier NCT01524978) was designed to explore the efficacy and safety of vemurafenib in patients with *BRAF*^{V600} mutation–positive cancers other than melanoma and papillary thyroid cancer[16]; here we report the efficacy and safety findings in a cohort of patients with MM and describe two cases in detail.

CASE REPORT

Study Design

Patients were enrolled in six prespecified cohorts according to diagnosis (non–small-cell lung cancer, ovarian cancer, colorectal cancer, cholangiocarcinoma, breast cancer, and MM); patients with other solid tumors were enrolled in a seventh cohort, as described previously.[16] Patients received vemurafenib (960 mg orally twice daily). The study was designed by the steering committee in collaboration with the team from F. Hoffmann-La Roche and was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. Institutional review boards or human research ethics committees at each participating center approved the protocol. Additional study design details are described in the Data Supplement.

Patients

Patients in the MM cohort had to have previously treated, measurable, relapsed or refractory MM with confirmed *BRAF*^{V600} mutation.

Patients with *BRAF*^{V600} mutation–positive cancers were identified through mutation analysis assays according to the institutional standards of the participating centers. The presence of *BRAF*^{V600} mutations was confirmed retrospectively in a central laboratory using the Roche companion diagnostic cobas 4800 BRAF V600 Test or other standard methodology.

Assessments

The following assessments for MM were performed 8 weeks after the start of therapy and every 4 weeks thereafter: serum protein electrophoresis with quantitation of monoclonal protein level; urine protein electrophoresis using 24-hour urine protein electrophoresis; and serum levels of free light chains, lactate dehydrogenase, and β-2 microglobulin. Bone marrow analysis was performed only to confirm complete response (CR) after two consecutive immunofixation analyses were negative.

Efficacy was evaluated using International Myeloma Working Group Uniform Response Criteria.[17,18] Evaluations were performed at baseline, 8 weeks after the start of vemurafenib administration, every 4 weeks thereafter during treatment, and at the end of treatment. Responses were classed as CR, stringent CR, very good partial response (VGPR), partial response (PR), stable disease (SD), progressive disease, and clinical relapse. A response required confirmation at two consecutive assessments; response categories required no evidence of progressive lesions or new bone lesions if radiographic studies were performed. Responders were defined as those patients with PR or better (ie, CR, stringent CR, PR, or VGPR).

Statistical Analysis

The primary efficacy end point of VE-BASKET was the response rate at week 8. Secondary end points included best overall response rate, progression-free survival (PFS), and overall survival (OS). For the purposes of this analysis, two response assessments were required with no specified time between these assessments, although the protocol required that these two assessments be 4 weeks apart.

An adaptive Simon two-stage design was used to minimize the number of patients treated if vemurafenib was deemed ineffective for a specific tumor type. A 15% response rate at week 8 was considered a low response, 45% a high desirable response rate, and 35% a low desirable response rate. Assuming response rates as specified in the hypothesis testing, a power of 80% for a high desirable response and 70% for a low desirable response, and a two-sided α of 0.1, the number of patients required in each cohort was seven for stage 1, and 13 or 19 for stage 2, depending on the results in stage 1. However, if a clear clinical benefit was observed for patients in a cohort (eg, the majority of patients recorded SD at week 8 and no CR or PR was recorded), then enrollment in stage 2 might be allowed for the cohort after discussion with the sponsor and study steering committee. The data presented here are the results of the final analysis.

Seven patients entered stage 1 of the MM cohort of the VE-BASKET study, followed by enrollment of an additional two patients because clear clinical benefit was observed, even though the prespecified minimal response rate was not achieved. Nine patients therefore composed the intent-to-treat and safety populations (Data Supplement). Patient characteristics are summarized in Table 1. At the time of study closure, after a median follow-up of 13.4 months (range, 2.0 to 27.2 months), all patients had discontinued vemurafenib in this study as a result of the following: disease progression (n = 5), adverse event (n = 1), physician decision (n = 1), and rolling over into an extension study (n = 2; ClinicalTrials.gov identifier: NCT01739764). The median duration of treatment was 4.4 months (range, 1.9 to 24.4 months).

Efficacy

In this final analysis, performed after database lock, the best confirmed overall response rate was 33% (Data Supplement). Two patients treated at a single institution achieved PRs after extensive treatment with other therapies. The first patient presented in November 2007 with multiple lytic lesions, T3 cord compression, and mild anemia. The patient was diagnosed with immunoglobulin G kappa, International Staging System stage 3 MM. The patient received palliative radiotherapy and eight cycles of lenalidomide, bortezomib, and dexamethasone before undergoing high-dose melphalan therapy with autologous stem-cell transplantation in November 2008. On progression in July 2012, the patient began

Table 1. Baseline Characteristics of Patients With *BRAF*^{V600} Mutation–Positive Multiple Myeloma Treated With Vemurafenib

Characteristic	Patients With Multiple Myeloma (n = 9)
Sex	
Male	6 (66.7)
Female	3 (33.3)
Age, years, median (range)	63 (55-68)
ECOG performance status	
0	3 (33.3)
1	5 (55.6)
2	1 (11.1)
BRAF^{V600} mutation type*†	
V600E	8 (88.9)
V600K	1 (11.1)
Monoclonal protein	
IgA kappa	1 (11.1)
IgA lambda	1 (11.1)
IgG kappa	5 (55.6)
IgG lambda	2 (22.2)
Risk stratification	
High‡	2 (22.2)
Standard	7 (77.8)
Lines of prior systemic therapies	
2	4 (44.4)
≥ 3	5 (55.6)
Prior systemic therapies*	
Immunomodulators (lenalidomide, thalidomide, pomalidomide)	9 (100)
Corticosteroids (dexamethasone)	8 (88.9)
Alkylating agents (cyclophosphamide, melphalan, bendamustine)	8 (88.9)
Proteasome inhibitors (bortezomib, carfilzomib)	7 (77.8)
Cytotoxic agents (doxorubicin, idarubicin)	3 (33.3)
Platinum agent (cisplatin)	3 (33.3)
Topoisomerase inhibitors (etoposide)	3 (33.3)
Novel antineoplastic agents (ACY-1215, CC-223)	2 (22.2)

NOTE. Data are presented as No. (%) unless indicated otherwise.
Abbreviations: ECOG, Eastern Cooperative Oncology Group performance status; Ig, immunoglobulin.
*On the basis of a manual review of the data.
†Testing was by SNaPshot (n = 2), capillary electrophoresis single-strand conformation analysis (n = 2), direct (Sanger) sequencing (n = 1), Sequenom (n = 1), single-strand conformation analysis (n = 1), 3730 DNA analyzer (n = 1), and immunohistochemistry (n = 1).
‡Defined by the presence of t(4:14).

treatment with bortezomib and dexamethasone, followed in November 2012 by ricolinostat, lenalidomide, and dexamethasone. In November 2014, the patient, who had an isolated *BRAF*^{V600}mutation identified by SNaPshot,[19] relapsed and was entered into the VE-BASKET study, achieving a PR and continuing treatment with vemurafenib until January 2017 (treatment duration, 22.3 months). At the time of closure of the VE-BASKET study, the patient was still receiving treatment in the extension study.

The second patient was diagnosed with smoldering MM in May 2006 and progressed to stage II active MM in December 2009, at which time he was treated with lenalidomide, bortezomib, and dexamethasone. Stem cells were collected in April 2010, and the patient began receiving maintenance lenalidomide. On relapse in September

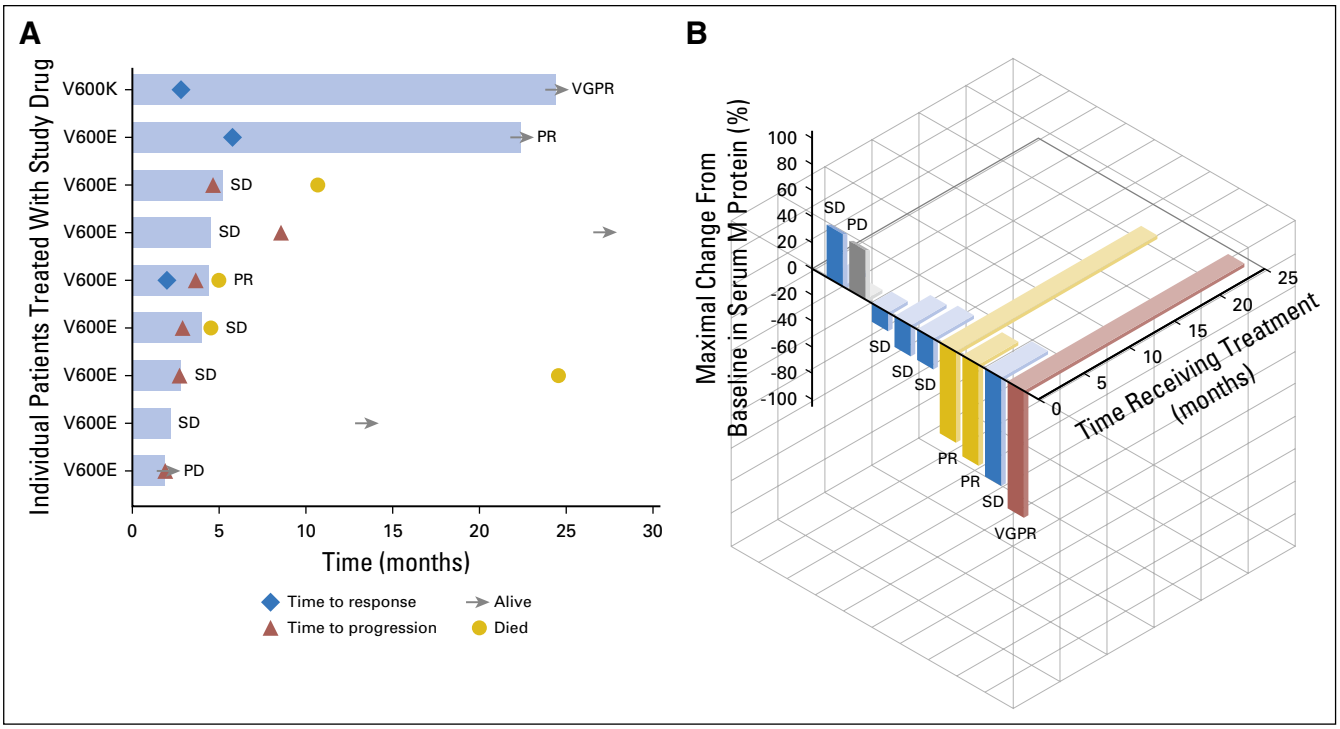

Fig 1. (A) Time to events according to best overall response in patients with *BRAF*^{V600} mutation–positive multiple myeloma treated with vemurafenib (n = 9). (B) Change from baseline in serum M protein according to best overall response in individual patients with *BRAF*^{V600} mutation–positive multiple myeloma treated with vemurafenib (n = 9). One patient with a substantial reduction in serum M protein level had an unconfirmed PR but was considered to have SD because the patient had PD at the subsequent assessment. M, monoclonal component; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

2011, the patient began treatment with cyclophosphamide, bortezomib, and dexamethasone before undergoing autologous stem-cell transplant in January 2012, followed by maintenance bortezomib. Subsequent relapses were treated with cyclophosphamide, lenalidomide, and dexamethasone (April 2013); carfilzomib, thalidomide, and dexamethasone (August 2013); pomalidomide, bortezomib, and dexamethasone (March 2014); and carfilzomib, pomalidomide, and dexamethasone (August 2014). The patient had a *BRAF*^{V600E} mutation identified by SNaPshot. He was enrolled in the VE-BASKET study in September 2014 and received five cycles of vemurafenib, initially reporting a PR, but then progressing rapidly. SNaPshot testing of bone marrow aspirate identified an additional *NRAS* mutation at the time of relapse that had not been seen at study entry and was reported after study closure; the original *BRAF*^{V600G} mutation was also present at this time.

One other patient, who had been treated previously with bortezomib and dexamethasone in the first line, the mammalian target of rapamycin inhibitor CC-223 on relapse, and lenalidomide in the third line, had a VGPR after treatment with vemurafenib. This patient had a *BRAF*^{V600K} mutation and was considered to have high-risk disease. The patient's treatment duration was 24.4 months in VE-BASKET, with an overall duration of response of 20.9 months. The patient was subsequently rolled over into the extension study.

Five additional patients had SD lasting ≥ 6 weeks (durations: 2.7, 2.9, 3.3 [censored], 4.6, and 8.5 months). One patient achieved an 83% reduction in serum monoclonal protein level and had a PR at one assessment but progressive disease at the next assessment, for a best overall response of SD. Time to event details and change from baseline in serum monoclonal protein for individual patients are shown in Figure 1.

At the time of study closure, disease progression was observed in six patients. Median investigator-assessed PFS was 4.63 months (95% CI, 2.89 months to not estimable); the 6-month PFS rate was 40% (95% CI, 6% to 74%), and the median time to progression was 4.63 months (95% CI, 2.89 months to not estimable). At the time of study closure, four patients had died. Median OS was 24.54 months (95% CI, 4.96 months to not estimable); the 6-month OS rate was 75% (95% CI, 45% to 100%). Kaplan-Meier plots of PFS and OS are shown in the Data Supplement.

Safety

The median vemurafenib dose intensity was 79% (range, 51% to 100%). All nine patients experienced at least one adverse event of any grade,

Table 2. Adverse Events Occurring in ≥ 20% of Patients With *BRAF*^{V600} Mutation–Positive Multiple Myeloma Treated With Vemurafenib (n = 9)

Event	Any Grade	Grade 3 or 4
Any	9 (100)	7 (77.8)
Alopecia	5 (55.6)	0 (0.0)
Melanocytic nevus	4 (44.4)	0 (0.0)
Anemia	3 (33.3)	2 (22.2)
Hypokalemia	3 (33.3)	0 (0.0)
Keratosis pilaris	3 (33.3)	1 (11.1)
Skin papilloma	3 (33.3)	0 (0.0)
Sunburn	3 (33.3)	0 (0.0)
Upper respiratory tract infection	3 (33.3)	0 (0.0)
Acne	2 (22.2)	0 (0.0)
Back pain	2 (22.2)	0 (0.0)
Blood alkaline phosphatase increase	2 (22.2)	1 (11.1)
Constipation	2 (22.2)	1 (11.1)
Diarrhea	2 (22.2)	0 (0.0)
Dysphonia	2 (22.2)	0 (0.0)
Fatigue*	2 (22.2)	1 (11.1)
Hyperkeratosis	2 (22.2)	0 (0.0)
Increased alanine aminotransferase	2 (22.2)	0 (0.0)
Keratosis follicular	2 (22.2)	1 (11.1)
Leukoplakia oral	2 (22.2)	0 (0.0)
Rash papular	2 (22.2)	0 (0.0)
Seborrheic keratosis	2 (22.2)	0 (0.0)
Skin lesion	2 (22.2)	1 (11.1)
Xerosis	2 (22.2)	0 (0.0)

NOTE. Data are presented as No. (%)
*Includes fatigue and asthenia.

eight patients had at least one treatment-related adverse event, and seven patients had a grade 3 or 4 adverse event. There were no fatal events. The most common adverse events were alopecia and melanocytic nevus (Table 2). Serious adverse events occurred in four patients. One patient had grade 2 hypercalcemia, which was judged unrelated to vemurafenib treatment and resolved without treatment interruption, and a grade 3 chest infection, also unrelated to treatment, during which treatment was interrupted temporarily. The second patient had grade 4 diabetes that was judged unrelated to the study drug but resulted in dose reduction and grade 3 cellulitis that was also unrelated to treatment but required treatment interruption. The third patient had grade 3 pneumonia that was judged unrelated to treatment and required no dose adjustment. The final patient had treatment-related grade 4 sepsis that resolved with dose reduction and treatment-related grade 3 skin lesion and grade 2 upper respiratory infection that were not considered serious but resulted in permanent discontinuation of treatment. No other adverse events led to treatment discontinuation. Seven patients had at least one adverse event leading to dose reduction or interruption (infections [n = 4], skin disorders [n = 2], anemia [n = 1], blood alkaline phosphatase increased [n = 1], keratosis follicular [n = 1], diabetes mellitus [n = 1], and acute kidney injury [n = 1]); one patient had a dose interruption for cataract surgery.

QT prolongation, squamous cell carcinoma of the skin, and keratoacanthoma were not observed. Three patients had liver function laboratory abnormalities; these were reported as alanine aminotransferase increased (n = 2), blood alkaline phosphatase increased (n = 2 [22%]), aspartate aminotransferase increased (n = 1), blood bilirubin increased (n = 1), and hyperbilirubinemia (n = 1).

DISCUSSION

Despite a better understanding of the genomic landscape in MM, clinical trials focusing on personalized mutation-specific approaches have been lacking to date. However, identification of the *BRAF*^{V600} mutation as a driver mutation in MM may lead to patients with this mutation benefitting from targeted treatment with BRAF^{V600} inhibitors.[1,7,20] In this study, we have shown that vemurafenib has promising efficacy in patients with *BRAF*^{V600} mutation–positive MM: two patients of nine had encouraging and long-lasting responses to treatment that were ongoing at the time of study closure, and an additional patient had a shorter response. These patients had been treated previously with bortezomib and lenalidomide, among other agents, suggesting that resistance mechanisms in those patients did not prevent response to vemurafenib.

In this study, not all patients with the *BRAF*^{V600} mutation responded to therapy, providing us with the opportunity to study mechanisms of resistance in this patient population in the future. Moreover, the *BRAF*^{V600} mutation may not be the driver mutation in patients who do not respond to treatment with vemurafenib. Development of resistance to treatments for MM is almost inevitable. Clonal evolution of MM cells and changes in the bone marrow environment have been implicated in resistance,[21] and alterations in the ERK pathway are present in almost one half of patients with MM. Interestingly, the patient in our study who relapsed after achieving a PR had acquired an *NRAS* mutation, suggesting an escape mechanism and possible resistance via this molecular pathway. Alternative mechanisms, including driver mutations within subclonal populations, may also account for differential responses. Understanding resistance mechanisms could lead to the development of new therapies acting on the RAS/RAF pathway, either alone or in combination, or to the use of MEK or pan-RAF inhibitors. This subject is being addressed in an ongoing clinical trial using a BRAF inhibitor and a MEK inhibitor (dabrafenib and trametinib, respectively; ClinicalTrials.gov identifier: NCT03091257).

The safety profile of vemurafenib in this patient cohort was broadly similar to that reported previously,[8,9] and no new safety signals were identified. Compared with other studies, arthralgia was less common and alopecia was more common in our patients. Cutaneous squamous cell carcinoma, which has been reported in vemurafenib-treated patients in earlier studies,[8,9] was not observed in our patients.

In conclusion, vemurafenib may be an appropriate and effective choice for patients with MM in whom a *BRAF*^{V600} mutation has been identified. Because the VE-BASKET study included few patients with MM, additional studies are required to establish the role of vemurafenib, whether as monotherapy or in combination with other agents, for early- or later-stage disease in the treatment of this poor-prognosis population. If a patient has mutation-positive disease, we propose that targeted treatment should be considered earlier rather than later.

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