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Original Research

Open-label, multicentre safety study of vemurafenib in 3219 patients with *BRAF*^{V600} mutation-positive metastatic melanoma: 2-year follow-up data and long-term responders' analysis

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Abstract ***Background:*** The orally available BRAF kinase inhibitor vemurafenib is an effective and tolerable treatment option for patients with metastatic melanoma harbouring *BRAF*^{V600} mutations. We assessed the safety of vemurafenib in a large population of patients with few alternative treatment options; we report updated 2-year safety.
Methods: This was an open-label, multicentre study of vemurafenib (960 mg bid) in patients with previously treated or untreated *BRAF* mutation-positive metastatic melanoma (cobas® 4800 BRAF V600 Mutation Test). The primary end-point was safety; efficacy end-points were secondary. An exploratory analysis was performed to assess safety outcomes in patients with long duration of response (DOR) (≥12 or ≥24 months).
Results: After a median follow-up of 32.2 months (95% CI, 31.1–33.2 months), 3079/3219 patients (96%) had discontinued treatment. Adverse events (AEs) were largely consistent with previous reports; the most common all-grade treatment-related AEs were arthralgia (37%), alopecia (25%) and hyperkeratosis (23%); the most common grade 3/4 treatment-related AEs were squamous cell carcinoma of the skin (8%) and keratoacanthoma (8%). In the exploratory analysis, patients with DOR ≥12 months (n = 287) or ≥24 months (n = 133) were more likely to experience grade 3/4 AEs than the overall population. No new specific safety signals were observed with longer vemurafenib exposure.
Conclusions: After 2 years' follow-up, safety was maintained in this large group of patients with *BRAF*^{V600} mutation-positive metastatic melanoma who are more representative of routine clinical practice than typical clinical trial populations. These data suggest that long-term vemurafenib treatment is effective and tolerable without the development of new safety signals.
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1. Introduction

Vemurafenib is a selective inhibitor of oncogenic BRAF kinase that has shown high response rates and improved progression-free survival (PFS) and overall survival (OS) compared with chemotherapy in patients with *BRAF*^{V600} mutation-positive melanoma [1,2]. A second selective BRAF inhibitor, dabrafenib, has also been shown to be active in this patient population [3]. More recently, phase III studies have demonstrated that combined MEK and BRAF inhibition improves clinical outcomes compared with BRAF inhibition alone [4–6], with the result that such combinations have become the standard of care for this population. As observed with monotherapy, patients on combination therapy with elevated lactate dehydrogenase (LDH) levels at baseline do not appear to benefit as much as those with normal levels [5,7,8]; nonetheless, combination therapy has been shown to be superior to monotherapy in patients with elevated LDH levels at baseline [5,8].

The open-label vemurafenib safety study was designed to establish the safety of vemurafenib in patients with metastatic melanoma and documented *BRAF*^{V600} mutations. A third interim analysis of this study (data cut-off 31st January 2013) reported that the most common all-grade adverse events (AEs) were rash, arthralgia, fatigue, photosensitivity reaction, alopecia and nausea; grade 3/4 AEs included cutaneous squamous cell carcinoma, rash, arthralgia, fatigue and liver function abnormalities [7].

The primary objectives of this fourth interim analysis were to evaluate the safety and tolerability of vemurafenib 2 years after the last patient was enrolled. The long duration of follow-up in this large study allowed us to perform an exploratory analysis of the safety of vemurafenib in patients who had a long duration of response (DOR; ≥12 months and ≥24 months).

2. Methods

2.1. Study design and patients

The design of this study, which was conducted in 44 countries across Europe, South America, Australia, North America, Africa and Asia, has been described

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