The outcomes of Polish patients with advanced BRAF-positive melanoma treated with vemurafenib in a safety clinical trial

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Aim of the study: The BRAF inhibitor vemurafenib has improved progression-free survival and overall survival in patients with BRAFV600-mutation-positive metastatic melanoma. Here we present the results of an open-label safety study with vemurafenib in patients with metastatic melanoma enrolled in Polish oncological centres.

Material and methods: Patients with untreated or previously treated Stage IIIC/IV BRAFV600 mutation-positive melanoma were treated with oral vemurafenib in an initial dose of 960 mg twice daily. Assessments for safety and efficacy were made every 28 days. For the survival analysis the Kaplan-Meier estimator was used with the log-rank tests for bivariate comparisons.

Results: In total, 75 Polish patients were enrolled in the safety study across four centres. At data cut-off, 28 patients died (37%), mainly (26) due to disease progression; 33 (44%) patients continued vemurafenib after disease progression. The objective response rate was 46%, including two patients with a complete response and 29 with a partial response. Median progression-free survival was 7.4 months. The one-year overall survival rate was 61.9% (median overall survival was not reached). Seventy-three (97.3%) patients reported adverse events (AEs), and grade 3–5 toxicity was reported in 49.4% (37) patients. The most common AEs were: skin lesions (including rash and photosensitivity), arthralgia, and fatigue.

Conclusions: The overall safety profile and response rate of vemurafenib were comparable to those reported in previous studies of this drug. Our study confirmed the value of well-established prognostic features for overall survival, such as initial LDH (lactate dehydrogenase) level and AJCC staging.

Key words: melanoma, metastatic, vemurafenib, BRAF inhibition.

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Introduction

BRAF inhibitors are a currently the standard of care in the treatment of patients with advanced melanomas harbouring the BRAF V600 mutation. Vemurafenib was the first molecular targeting agent acting on the mutated BRAF kinase, which demonstrated improvement of overall survival (OS) in a phase III randomised trial. In the study comparing vemurafenib and dacarbazine in untreated stage IV and unresectable stage IIIC patients with BRAF-mutated melanomas, vemurafenib demonstrated rapid objective responses in approximately 50% of cases, but control of the tumour growth was observed in up to 90% of cases [1]. Progression-free survival (PFS) was 6.9 months in the vemurafenib arm versus 1.6 months in the dacarbazine arm, and median OS was 13.6 months [1, 2]. The results of this study led to worldwide approval of vemurafenib for the therapy of advanced BRAF-mutated disease. Recently in a large safety study with more than 3000 patients, the safety profile and efficacy of vemurafenib were confirmed in real-world clinical practice [3]. As the general results of this open-label, multicentre study have been already published, we report here the detailed outcomes of patient cohorts treated in Polish centres only.

Material and methods

In this open-label study (MO25515, NCT01307397) 75 patients from four Polish oncological centres were included to assess the safety and efficacy of vemurafenib in advanced (unresectable stage IIIC or stage IV) melanoma harbouring BRAF V600 mutation confirmed with the cobas 4800 BRAF V600 Mutation Test (Roche Molecular Systems, Branchburg, NJ, USA). The eligible patients were treated with oral vemurafenib in an initial dose of 960 mg twice daily until disease progression (treatment after progression was allowed after a joint decision by the investigator and the sponsor), unacceptable toxicity, consent withdrawal, or death [3]. The rules for dose modifications and interruptions were described previously [3]. The patient

characteristics are presented in Table 1. Thirty-six (48%) patients underwent prior systemic therapy (including 6 patients after ipilimumab failure). None of the patients was previously treated with BRAF or MEK inhibitor. Seven patients (9.3%) had brain metastases (stable, asymptomatic after previous local therapy) at the time of therapy start. The primary end-point of the trial was safety. Patients were assessed every 28 days. The secondary variables comprised objective response (evaluated by investigators using Response Evaluation Criteria in Solid Tumours RECIST version 1.1), progression-free survival (PFS, calculated from the date of start of vemurafenib therapy to date of progression or death), and overall survival (OS, calculated from the date of start of vemurafenib therapy to the date of death, living patients were censored). For survival analysis the Kaplan-Meier estimator was used with the log-rank tests for bivariate comparisons. Statistical analyses were done with SAS (version 9.2) software.

Table 1. Patients' characteristics (n = 75)

Subgroup	*N* (%)
Gender	
Male	39 (52.0)
Female	36 (48.0)
Age (median, years) 53	
Age < 65 years	65 (86.7)
Age ≥ 65 years	10 (13.3)
ECOG 0–1 at baseline ECOG ≥ 2 at baseline	72 (96.0) 3 (4.0)
Normal LDH at baseline/screening	43 (57.3)
Elevated LDH at baseline/screening	32 (42.7)
Patients with brain metastases at baseline	7 (9.3)
Patients without brain metastases at baseline	68 (90.7)
Prior Ipilimumab	6 (8.0)
No prior Ipilimumab	69 (92.0)

Results

All 75 of the enrolled patients started therapy with vemurafenib from October 2011 to June 2012. We present interim analysis prepared on 28 July 2014 with a cut-off date on 31 Jan 2013. Forty-two (56%) discontinued therapy, with 33 due to progressive disease, one due to adverse events, and three due to death.

The best confirmed responses were as follows: two patients (3%) had complete response, 29 (43%) partial response, 30 (45%) stable disease, and six (8%) had disease progression. Median duration of response was 7.4 months (95% CI: 5.7–9.2). Only eight patients received further systemic therapy (chemotherapy only) after discontinuation of vemurafenib.

Median PFS time was 7.4 months (95% CI: 5.5–9.2), and one-year PFS rate was 26.5% (95% CI: 15.3–37.8). Progression-free survival significantly correlated with initial lactate dehydrogenase level (median PFS in the LDH normal subgroup was 10.9 months [95% CI: 7.5–] vs. 3.8 months [95% CI: 3.6–7.2] in the LDH elevated subgroup) (Fig. 1), and the presence of brain metastases at baseline (median PFS was 3.7 months [95% CI: 3.6–9.3] in the brain metastases subgroup vs. 7.5 months [95% CI: 5.6–10.3] in patients without brain metastases). For M1 stage subgroups median PFS times were as follows: 7.4 months (95% CI: 1.4–) in the M1a subgroup, 10.9 months (6.9–) in the M1b subgroup, and 7.4 (95% CI: 4.6–8.3) in the M1c subgroup.

Median OS was not reached; the one-year OS rate was 61.9% (95% CI: 50.1–73.6). OS significantly correlated with initial lactate dehydrogenase level (the one-year OS rate was 85.1% [74.0–96.1] in the subgroup with normal LDH and 31.4% [95% CI: 14.0–48.9] in the subgroup with elevated LDH [Fig. 2]), and M1 stage (one-year OS rate was 77.8% [95% CI: 50.6–104.9] in the M1a subgroup, 75.0% [95% CI:

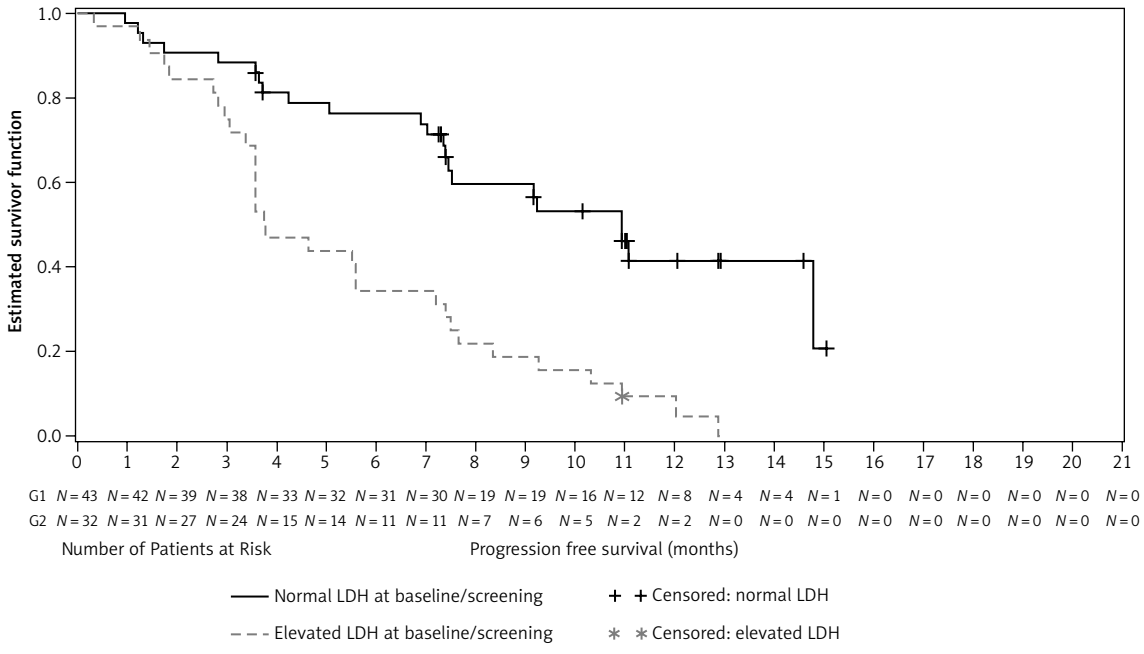

Fig. 1. PFS depending on LDH level at the treatment start

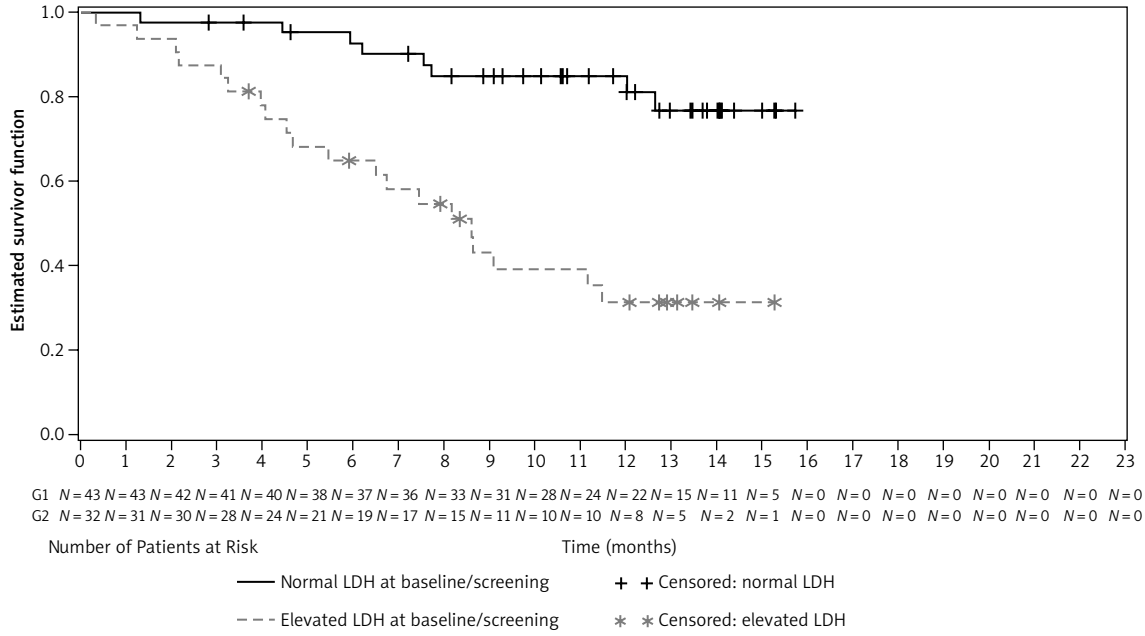

Fig. 2. OS depending on LDH level at the treatment start

Table 2. Adverse events grades 3 and 4 by system organ class and preferred term

Adverse event	Grade 3 (*N* = 75) *n* (%)	Grade 4 (*N* = 75) *n* (%)
Number of patients with at least one AE	35 (46.7)	0
Neoplasms benign, malignant and unspecified	18 (24.0)	0
keratoacanthoma	5 (6.7)	0
papilloma	2 (2.7)	0
squamous cell carcinoma of skin	3 (4.0)	0
malignant melanoma	2 (2.7)	0
melanocytic naevus	2 (2.7)	0
skin papilloma	2 (2.7)	0
basal cell carcinoma	1 (1.3)	0
fibrous histiocytoma	1 (1.3)	0
seborrhoeic keratosis	1 (1.3)	0
Skin and subcutaneous tissue disorders	10 (13.3)	0
acanthosis	5 (6.7)	0
rash	5 (6.7)	0
hyperkeratosis	1 (1.3)	0
Investigations	6 (8.0)	0
alanine aminotransferase increased	2 (2.7)	0
aspartate aminotransferase increased	2 (2.7)	0
blood alkaline phosphatase increased	2 (2.7)	0
electrocardiogram qt prolonged	1 (1.3)	0
hyponatraemia	3 (4.0)	0
Blood and lymphatic system disorders	4 (5.3)	0
anaemia	3 (4.0)	0
neutropaenia	1 (1.3)	0
Cardiac disorders	4 (5.3)	0
angina unstable	1 (1.3)	0
myocardial infarction	1 (1.3)	0
hypertension	3 (4.0)	0
Fatigue	1 (1.3)	0
Arthralgia	1 (1.3)	0
Convulsion	1 (1.3)	0
Urinary tract obstruction	1 (1.3)	0

45–105] in the M1b subgroup, and 57% [95% CI: 42.9–71.0] in the M1c subgroup). The presence of asymptomatic brain metastases, stable after previous therapy at baseline, had no significant impact on OS.

At the time of data cut-off 28 patients died (37%), mainly (26) due to disease progression. Thirty-three (44%) patients continued vemurafenib after disease progression.

Due to adverse events (AEs) 44 patients (57%) needed at least one dose modification (reduction or interruption), and 28 patients (37%) needed dose reduction. 97.3% (73) of patients had at least one AE, and grade 3–5 toxicity was reported in 49.4% (37) patients. The most common AEs were as previously reported: skin lesions (including rash and photosensitivity), arthralgia, and fatigue. Table 2 summarises AEs occurring in at least 10% of patients, and Table 3 shows AEs at grade 3–4. Eight patients (10.7%) developed cutaneous squamous cell carcinoma (cuSCC), and two – new primary melanomas.

Discussion

The constitutive hyperactivation of the RAS/RAF/MEK/ERK pathway (also termed the Mitogen Activated Protein Kinase – MAPK pathway) has been identified in the majority of melanomas as the critical player in the regulation of cell proliferation, invasion, and survival [1, 2, 4]. In 50–70% of cases this genetic background is achieved via oncogenic mutation of the *BRAF* gene, mainly V600E point mutation. Vemurafenib is the first BRAF inhibitor class agent approved worldwide for therapy of advanced *BRAF*-mutated melanoma, and has demonstrated improvement in OS and PFS as compared to dacarbazine. Thereafter, BRAF inhibitors (vemurafenib and dabrafenib) have become the worldwide standard of care for the majority of BRAF-mutant metastatic melanomas (especially established in patients with high tumour burden or progression after immunotherapy). The data presented in our analysis confirm other long-term follow-up studies demonstrating

median PFS more than six months, and approximately one fourth of patients were still alive after a longer period of time [2, 5]. However, the future of monotherapy with BRAF inhibitors is limited due to the relatively short duration of response in the majority of patients. The addition of a MEK inhibitor to a BRAF inhibitor enhances inhibition of tumour growth and delays acquired resistance [6]. The results from recently published three phase III studies provide convincing evidence that combination therapy with either vemurafenib and cobimetinib or dabrafenib and trametinib will become a new standard treatment for advanced BRAF-mutant melanoma. These randomised trials report median progression-free survival ranging from 9.3 to 11.4 months in combination-therapy groups. In addition, higher response rates (64–68%) have been achieved with no additional overall toxicity [7–9].

Nevertheless, the current study demonstrates on a national level the efficacy of vemurafenib monotherapy in a group of patients with advanced melanoma with eligibility criteria similar to routine practice and requirements for reimbursement of vemurafenib therapy in Poland. The overall survival data from this study are very encouraging, especially taking into account that almost 50% of the patients were treated with previous systemic therapy. Moreover, our study confirmed the value of well-established prognostic features for overall survival such as initial LDH level and AJCC staging [10, 11]. The presence of stable brain metastases had no impact on overall survival in our patients, which confirms the activity of vemurafenib for controlling brain lesions and implies that the mechanism of disease progression is equally related to the lesions outside the central nervous system [12]. The fact that vemurafenib was continued in 44% of patients after objective disease progression may also have a positive impact on survival [13].

The safety profile observed was consistent with that reported in previous studies, with cutaneous manifestations, arthralgia, and fatigue as the most common AEs. The number of patients with grade 3 or 4 treatment-related adverse events was up to 50%, but only two patients discontinued therapy due to unacceptable toxicity. Photosensitivity (related probably to the chemical structure of the vemurafenib molecule, not to BRAF inhibition *per se*) is commonly reported during vemurafenib therapy, whereas pyrexia (characteristic for dabrafenib) was rarely noted. cuSCC occurred in approximately 11% of patients, and their pathogenesis can be related to paradoxical activation of the MAPK pathway in BRAF wild-type cells during selective BRAF V600 mutant kinase inhibitor therapy. Keratoproliferative lesions often require additional surgery, and their frequency implies careful skin examinations every four weeks during vemurafenib therapy.

To summarise, our analysis confirms the efficacy of vemurafenib in a large group of Polish patients treated within the frames of a treatment-use clinical trial. The adverse events were manageable, and the number of cuSCCs was even lower than in phase II–III clinical trials [4, 14]. The understanding of the mechanisms of resistance to BRAF inhibitors monotherapy and development of combination strategy for overcoming early disease progression is the most important issue for the immediate future in the therapy of advanced melanoma.

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The authors declare no conflict of interest.

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