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ORIGINAL ARTICLE

Vemurafenib in non-small-cell lung cancer patients with $BRAF^{V600}$ and $BRAF^{nonV600}$ mutations

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Available online 6 January 2020

Background: *BRAF* mutations occurring in 1%—5% of patients with non-small-cell lung cancer (NSCLC) are therapeutic targets for these cancers but the impact of the exact mutation on clinical activity is unclear. The French National Cancer Institute (INCA) launched the AcSé vemurafenib trial to assess the efficacy and safety of vemurafenib in cancers with various *BRAF* mutations. We herein report the results of the NSCLC cohort.

Patients and methods: Tumour samples were screened for *BRAF* mutations in INCA-certified molecular genetic centres. Patients with *BRAF*-mutated tumours progressing after ≥1 line of treatment were proposed vemurafenib 960 mg twice daily. Between October 2014 and July 2018, 118 patients were enrolled in the NSCLC cohort. The primary outcome was the objective response rate (ORR) assessed every 8 weeks (RECIST v1.1). A sequential Bayesian approach was planned with an inefficacy bound of 10% for ORR. If no early stopping occurred, the treatment was of interest if the estimated ORR was ≥30% with a 90% probability. Secondary outcomes were tolerance, response duration, progression-free survival (PFS), and overall survival (OS).

Results: Of the 118 patients enrolled, 101 presented with a $BRAF^{V600}$ mutation and 17 with $BRAF^{nonV600}$ mutations; the median follow-up was 23.9 months. In the $BRAF^{nonV600}$ cohort, no objective response was observed and this cohort was stopped. In the $BRAF^{V600}$ cohort, 43/96 patients had objective responses. The mean Bayesian estimated success rate was 44.9% [95% confidence intervals (CI) 35.2%—54.8%]. The ORR had a 99.9% probability of being ≥30%. Median response duration was 6.4 months, median PFS was 5.2 months (95% CI 3.8—6.8), and OS was 10 months (95% CI 6.8—15.7). The vemurafenib safety profile was consistent with previous publications.

Conclusion: Routine biomarker screening of NSCLC should include $BRAF^{V600}$ mutations. Vemurafenib monotherapy is effective for treating patients with $BRAF^{V600}$-mutated NSCLC but not those with $BRAF^{nonV600}$ mutations.

Trial registration: ClinicalTrials.gov identifier: NCT02304809.

Key words: lung cancer, *BRAF*, vemurafenib, basket trial, biomarker, personalised therapy

INTRODUCTION

BRAF mutations occur in 1%—5% of non-small-cell lung cancer (NSCLC) patients.[1—3] About half of these occur by transversion of thymidine to adenosine at nucleotide *T1799A* on exon 15 thus effectively substituting valine with glutamate at codon 600 (*V600E*).[1] *G469A* and *D594G BRAF* mutations are also frequently observed.[1] *BRAF* mutations

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are distinguished by kinase activity and their signalling via the mitogen-activated protein kinase (MAPK) pathway.[4] *BRAF*^{V600} mutations, class I, signal as monomers with or without activated RAS. *BRAF*^{nonV600} mutations are classified as either class II that signal as dimers when RAS is activated or class III with impaired kinase activity but increased MAPK pathway signalling. This recent classification may help predict tumour response to targeted therapies.[4]

Few studies have assessed BRAF inhibitors, such as vemurafenib and dabrafenib since *BRAF* mutations are rare. A multiple non-melanoma basket trial reported a response rate of 42% in the 19 NSCLC patients with *BRAF*^{V600}-mutated tumours treated with vemurafenib.[5] Dabrafenib was assessed in pretreated metastatic NSCLC patients in two phase II non-randomized trials.[6,7] Dabrafenib monotherapy gave an overall response rate of 33%.[6] Dabrafenib combined with trametinib, a MEK inhibitor, gave an overall response rate of 63%.[7] The ESMO guidelines recommend dabrafenib combined with trametinib for BRAF-inhibitor naive patients with *BRAF*^{V600}-mutated NSCLC (stage IV).[8]

In 2013, the French National Cancer Institute (INCa) initiated the ongoing AcSé program. AcSé aims to identify and treat patients with cancers harbouring mutations for which a potential targeted therapy exists but is not yet approved.[9] A national screening program identified patients with *BRAF*-mutated tumours. Eligible patients were enrolled in disease cohorts of the basket phase II, open-label, AcSé trial. We herein report the results for the NSCLC cohorts of patients with *BRAF*^{V600}- and *BRAF*^{nonV600}-mutated tumours treated with vemurafenib.

PATIENTS AND METHODS

Patients with histologically confirmed advanced NSCLC, *BRAF* mutations, measurable lesion, and ECOG performance status $\leq$2 were enrolled in either the *BRAF*^{V600} mutation or the *BRAF*^{nonV600} mutation cohorts of the AcSé vemurafenib trial. Patients received oral vemurafenib (960 mg twice daily) until disease progression, unacceptable toxicity, or if in the interest of the patient. The primary objective was to evaluate the efficacy of vemurafenib in each cohort, using the confirmed objective response rate (ORR) as the primary endpoint. The tumour response was assessed every 8 weeks from baseline by CT scan using RECIST v1.1. The secondary efficacy outcomes included the duration of response, progression-free survival (PFS), and overall survival (OS). Safety was assessed by clinical, biological, and cardiac evaluations. The study included a dermatological follow-up to detect skin-related adverse events (AEs). AEs were graded by the common terminology criteria for adverse events (CTC-AE) v4.0.

Statistical design and analyses

AcSé vemurafenib used a sequential Bayesian approach with continuous monitoring of the main efficacy outcome. The trial initially planned to enrol between 30 and 50 patients in each cohort. The analysis of the primary outcome (ORR) was carried out after 16 weeks of follow-up for the first 10 patients and then after every five additional patients had completed follow-up. In each cohort, enrolment was to be stopped if there was a $\geq$80% probability that the ORR was $\leq$10%, the inefficacy boundary. If no early stopping occurred, vemurafenib would be considered promising if there was a $\geq$90% probability that the estimated ORR was $\geq$30%, the efficacy boundary. If efficacy was shown in a cohort, recruitment could continue up to 100 patients. Efficacy was analysed in patients treated with at least one cycle of vemurafenib or who discontinued treatment during the first cycle for disease progression or toxicity. PFS, duration of response, and OS were analysed using the Kaplan—Meier method. Survival estimates are provided with their associated 95% confidence intervals (CI). Safety was assessed in patients treated with vemurafenib. Further details concerning the study design and statistical methods can be found in the protocol (supplementary material, available at *Annals of Oncology* online).

RESULTS

Patient and disease characteristics

Between October 2014 and July 2018, we enrolled 194 patients in the AcSé program. All patients files were analysed by J. Mazieres for IFCT (French Intergroup of Thoracic Cancer) and JY Blay (for UNICANCER) before enrollment. Of the 118 patients in the NSCLC cohorts, 101 patients were in the *BRAF*^{V600} cohort and 17 were in the *BRAF*^{nonV600} mutation cohort. The *BRAF*^{V600} mutations observed were *V600E* (97 patients, 96%), *V600K* (2, 2%), *V600D* (1, 1%), and *V600M* (1, 1%). The *BRAF*^{nonV600} mutations observed were *G469A* (3 patients, 18%), *G466V* (3, 18%), *N581S* (3, 18%), *K601E* (3, 18%), *K601N* (2, 12%), *G466A* (1, 6%), *G469V* (1, 6%), and *G596R* (1, 6%), see flow chart (supplementary Figure S1, available at *Annals of Oncology* online). The median age was 68.0 years in the *BRAF*^{V600} mutation cohort and 65.0 years in the *BRAF*^{nonV600} mutation cohort. There were 51 males (51%) and 58 smokers (69%) in the *V600* cohort versus 10 males (59%) and 12 smokers (86%) in the *nonV600* cohort. All but two patients had adenocarcinoma. In the NSCLC cohorts, 27 patients (22.9%) had brain metastasis at baseline: 22 (22%) in the *V600* mutation cohort and 5 (29%) in the *nonV600* mutation cohort. Baseline characteristics are presented in Table 1.

Treatment administration and follow-up

Overall, 115 NSCLC patients were treated with vemurafenib: 100 with *BRAF*^{V600} mutations and 15 with *BRAF*^{nonV600} mutations. The median duration of treatment was 3.3 months (range 0.03—27.4) in the *V600* cohort and 1.5 months (range 0.2—2.1) in the *nonV600* cohort. Treatment was modified (dose reductions and/or treatment delays) due to toxicity in 60 patients (60%) with *V600* mutations and 12 patients (80%) with *nonV600* mutations. In the *V600* cohort, 56 patients (56%) discontinued vemurafenib due to disease progression and 24 (24%) due to toxicity. Similarly, in the *nonV600* cohort, 10 patients (67%) discontinued vemurafenib due to disease progression and 3 (20%) due to toxicity.

Table 1. Demographics and disease characteristics

Characteristics	*BRAF*^{V600} (*N* = 101)	*BRAF*^{nonV600} (*N* = 17)
Age (years) [extreme]	68.0 [41.0; 85.0]	65.0 [34.0; 83.0]
Sex		
Male	51 (50.5%)	10 (58.8%)
Female	50 (49.5%)	7 (41.2%)
Tobacco		
smokers + ex-smokers	58 (69.0%)	12 (85.7%)
WHO PS[a]		
0	27 (27.0%)	4 (27.0%)
1	54 (54.0%)	7 (46.0%)
2	19 (19.0%)	4 (27.0%)
No. of previous lines of chemotherapy		
1	50 (49.5%)	3 (17.6%)
2	24 (23.8%)	8 (47.2%)
3 or more	6 (6.0%)	3 (17.6%)
Received any chemotherapy	80 (79.3%)	14 (82.4%)
Histology subtypes		
Adenocarcinoma	99 (98.0%)	17 (100%)
Undifferentiated carcinoma	2 (2.0%)	

WHO PS, Performance status according to World Health Organization.
[a] *V600*: 1 missing data; *nonV600*: 2 missing data.

Efficacy

After a median follow-up of 23.9 months (95% CI 19.8—25.0), we assessed the efficacy in 115 patients: 100 in the *V600* cohort and 15 in the *nonV600* cohort. In the *BRAF*^{V600} cohort, 4 patients discontinued vemurafenib before a study tumour assessment and were not analysed for efficacy. Of the 96 patients analysed, 43 (44.8%) had objective responses (Figure 1). The mean Bayesian estimated success rate was 44.9% (95% credibility interval 35.2%—54.8%). There was a 99.9% probability that the ORR was above the efficacy bound (30%). The median response duration was 6.4 months (95% CI 5.1—7.3), the median PFS was 5.2 months (95% CI 3.8—6.8), and the median OS was 10 months (95% CI 6.8—15.7) (Figure 2D). In the patients with *V600* non E mutations, PFS was 3.8 months (*V600-D*), 5.9 months (*V600-M*), 2.1 and 6.8 months (two patients with *V600-K*), respectively. In the *BRAF*^{nonV600} cohort, no tumour response was observed. The mean Bayesian estimated success rate was 5.9% (95% credibility interval 0.2%—20.6%) (Figure 2A). The stopping criterion was met after enrolling 15 patients, with an 81.5% probability that the ORR would be below the futility boundary (10%). Therefore, in November 2017 we stopped enrolment in this cohort. The median PFS was 1.8 months (95% CI 1.4—2.1) and median the OS was 5.2 months (95% CI 2.8—18.7).

The median PFS was 1.9 months (95% CI 1.5—3.9) in the 26 patients (22.6%) with brain metastasis and 5.4 months (95% CI 3.8—7.2) in the 89 patients (77.4%) without brain

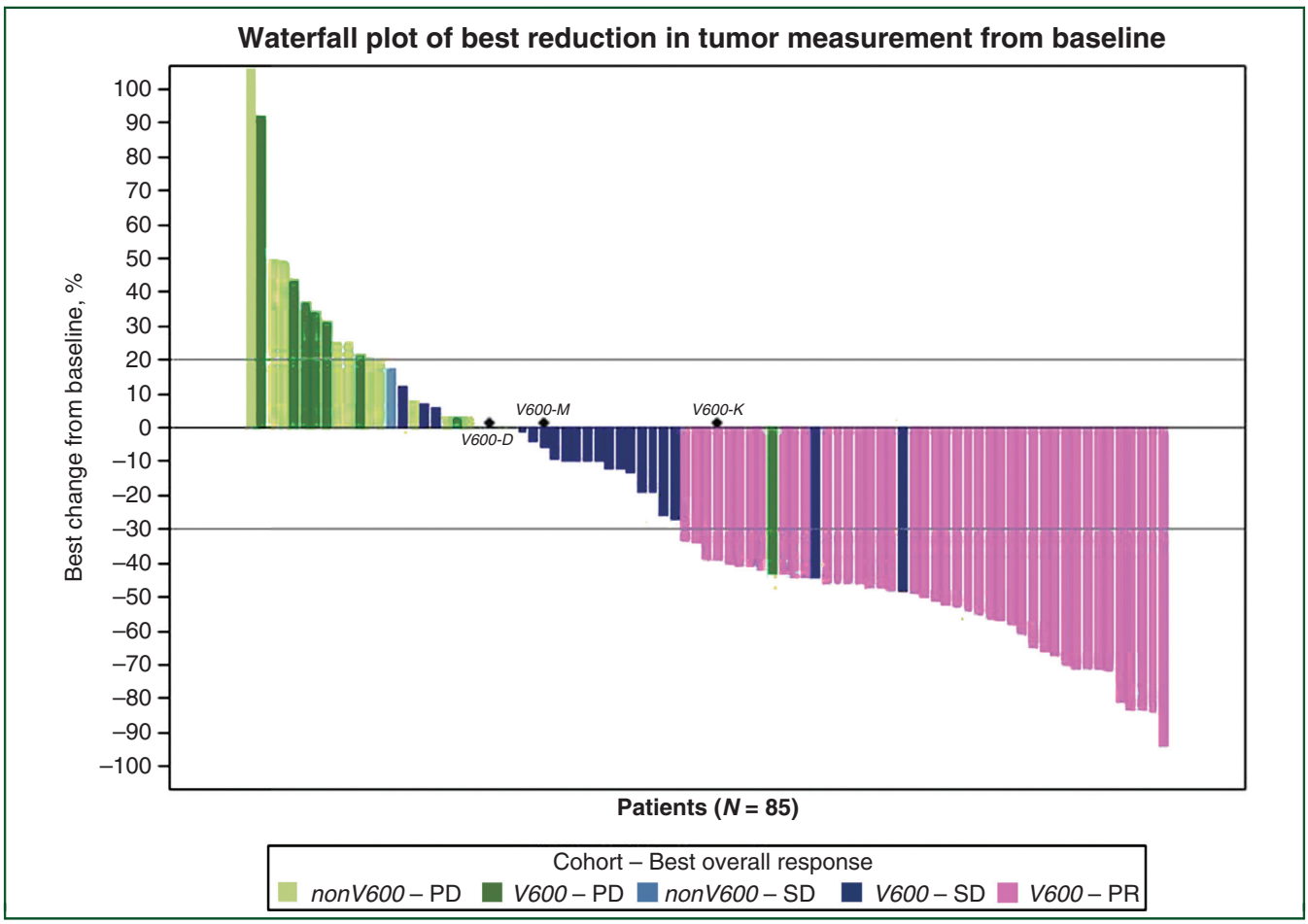

Figure 1. Best response in the *BRAF*^{V600} cohort and *BRAF*^{nonV600} cohort.

https://doi.org/10.1016/j.annonc.2019.10.022

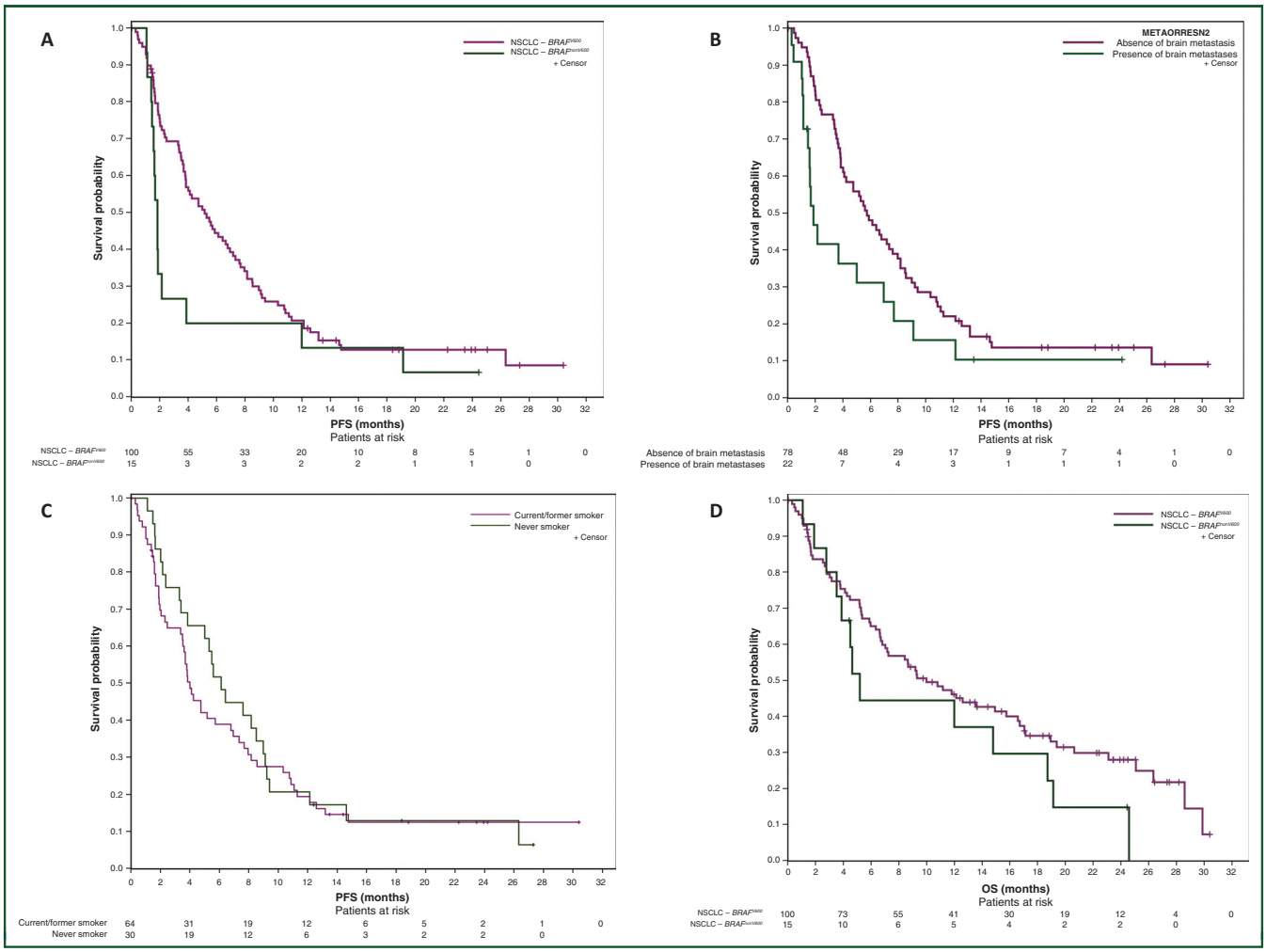

Figure 2. **Progression-free survival (PFS) (A–C) and overall survival (D).**

metastasis (Figure 2B). No significant difference in PFS was observed between smokers and non-smokers (Figure 2C).

Safety

In the *BRAF*^{V600} cohort, the most frequently reported treatment-related AEs of any grade were asthenia (56%), decreased appetite (46%), acneiform dermatitis (37%), and nausea and diarrhoea (35%) (Figure 3). Grade $\geq$3 treatment-related AEs were asthenia (10 patients, 10%), cutaneous epidermoid carcinoma (8, 8%), dermatitis (6, 6%), and increased gamma glutamyl transpeptidase (GGT) levels (6, 6%). In the *BRAF*^{nonV600} mutation cohort, the most frequently reported grade $\geq$3 treatment-related AEs were asthenia (4 patients, 27%), general physical health deterioration (2, 13%), and pruritus (2, 13%). Three patients died from grade 5 toxicities; the causes of death were dehydration, pneumonia, and neutropenic sepsis. Treatment was discontinued due to toxicity for 27 patients: 24 in the *V600* cohort and 3 in the *nonV600* cohort. The following toxicities resulted in treatment discontinuation: cutaneous toxicity ($n = 8$), infections ($n = 5$), and hepatitis ($n = 4$) (supplementary Figure S2, available at *Annals of Oncology* online). Serious AEs were reported in 36 patients (36%) in the *BRAF*^{V600} mutations cohort and 4 (27%) in the *BRAF*^{nonV600}.

DISCUSSION

Our study demonstrates the activity of vemurafenib single agent in *BRAF*^{V600} mutated patients and not in other *BRAF* mutations. Heavily pretreated patients with ECOG performance status $\leq$2 and those with brain metastasis were eligible. In the *BRAF*^{V600} cohort, we obtained an ORR of 44.9%, a median PFS of 5.2 months, and a median OS of 10 months. This is evidence that vemurafenib single agent is an active drug in this population. In contrast, patients in the *BRAF*^{nonV600} mutated NSCLC cohort did not benefit from vemurafenib.

Our results in the *BRAF*^{V600} NSCLC cohort are in line with those published in this setting and better than those reported in the second line, regardless of the treatment given.[10] In this population, the reported median second-line PFS was 3.1 months compared with 5.2 months in our cohort.[10] A small retrospective cohort of 35 patients treated with vemurafenib yielded a response rate of 53% and a PFS of 5.0 months.[11] Also, a basket trial assessing vemurafenib in patients with non-melanoma cancers with *BRAF*^{V600} mutations[5] reported

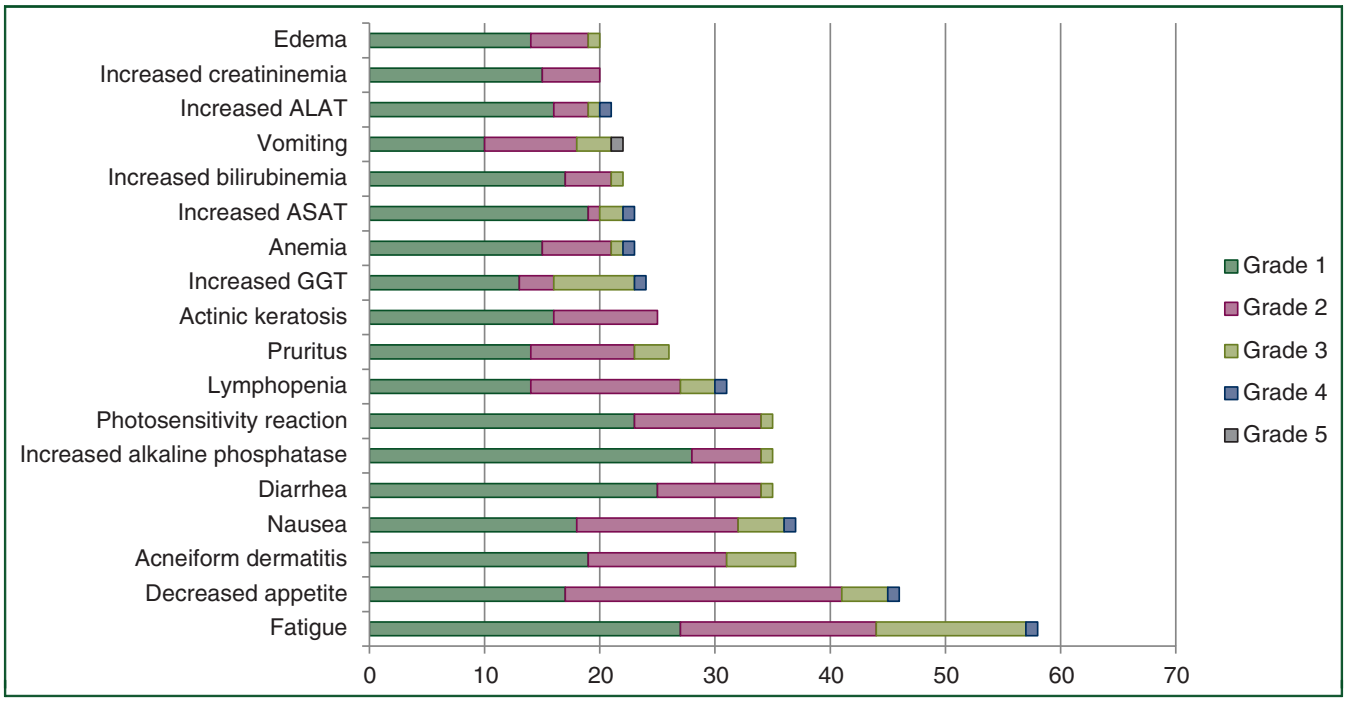

Figure 3. Safety profile.
Adverse events in at least 20 patients Two grade 5 toxicities (one pneumonia and one neutropenic sepsis) do not appear on the graph because pneumonia and neutropenic sepsis occurred in less than 20 patients. ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; GGT, gamma glutamyl transpeptidase.

an ORR of 42% and a PFS of 7.3 months.[5] A phase II study assessed dabrafenib, a BRAF inhibitor, in 78 metastatic NSCLC patients previously treated: the ORR was 33% and the PFS was 5.5 months.[6] More recently, dabrafenib, a BRAF inhibitor, combined with trametinib, a MEK inhibitor, was assessed in 57 patients, with $BRAF^{V600E}$-mutant metastatic NSCLC, previously treated; the ORR was 66.7% and the PFS was 10.2 months, as assessed by the investigators.[7] Following these results, the dabrafenib—trametinib combination was approved for treating metastatic NSCLC patients with $BRAF^{V600}$ mutations with *V600E* mutations in the US. Despite the absence of data from a randomized clinical trial, the ESMO guidelines recommend the BRAF inhibitor dabrafenib, combined with trametinib, in $BRAF^{V600}$-mutated NSCLC patients with an estimated Magnitude of Clinical Benefit Score of 2.[8] Our results confirm that vemurafenib is an alternative when the dabrafenib—trametinib combination is contraindicated and in countries, such as France, where the combination is not reimbursed.

BRAF inhibitors are competing with immunotherapies to treat *BRAF*-mutated NSCLC patients.[12] Unfortunately, the *BRAF*-mutated subgroup of patients was not assessed in pivotal immunotherapy trials. Recently, a retrospective cohort reported that 25% of patients with $BRAF^{V600E}$-mutated tumours and 60% with $BRAF^{nonV600}$ mutated tumours had high PD-L1 expression levels (tumour proportion score $\geq$50%).[13] In addition, the median tumour mutational burden was higher in $BRAF^{nonV600}$E mutants compared with $BRAF^{V600E}$ mutants.[14] In the ImmunoTarget *BRAF*-mutant cohort ($n = 43$), the response rate was 24% and the median PFS was 3.1 months.[15] Nevertheless, we should consider BRAF inhibitors and immunotherapy as sequential options. The combination of immunotherapy and BRAF inhibitors could also be of interest but requires a careful evaluation of its toxicity in dedicated trials.

The safety profile of vemurafenib monotherapy was consistent with previous reports. In our study, three patients had grade 5 AEs and 27 discontinued treatment due to toxicity. The toxicity reported is comparable with that observed with dabrafenib. In the 84 metastatic NSCLC patients with $BRAF^{V600E}$ mutation treated with dabrafenib, four patients (5%) reported grade 4 AEs and one patient (1%) reported a grade 5 AE.[6] Five patients (6%) had AEs that led to dabrafenib discontinuation. Moreover, 36/84 patients (43%) and 15/84 (18%) had AEs that led to dose interruptions and reductions, respectively. In our study, vemurafenib was considered tolerable and manageable with dose adaptations.

Our results are the first to show that vemurafenib is not effective in NSCLC patients with $BRAF^{nonV600}$-mutated tumours. The reason for this lack of activity is unknown. Perhaps these mutations play only a minor role in oncogenesis, or perhaps, vemurafenib has a limited inhibitory effect with these mutations. Preclinical data suggest that the NSCLC tumours of some $BRAF^{nonV600}$ mutants may be sensitive to dabrafenib combined with trametinib, but less sensitive with dabrafenib alone.[16] A review of patients with class II mutant *BRAF* tumours treated with MAPK inhibitors revealed that single-agent MEK inhibitors gave higher reported response rates than single-agent BRAF inhibitors.[17] Research needs to focus on therapies, including combination therapies, specifically target $BRAF^{nonV600}$ mutations and/or downstream pathways in this population.

https://doi.org/10.1016/j.annonc.2019.10.022

In conclusion, the results obtained in the NSCLC cohort of the AcSé study demonstrate that vemurafenib monotherapy is effective for *BRAF*^{V600}-mutated NSCLC but not for *BRAF*^{nonV600}-mutated NSCLC. Vemurafenib is a treatment option for *BRAF*^{V600}-mutated NSCLC patients when the dabrafenib—trametinib combination is not feasible or not reimbursed.

ACKNOWLEDGEMENTS

The authors thank patients and families, the AcSé Vemurafenib investigators teams, and Trevor Stanbury PhD (Unicancer) for providing medical writing support.

FUNDING

This work was financially supported by INCa, the ARC Foundation, Unicancer's partner for personalized medicine research. JYB is supported by the following grants: NetSarc (INCA & DGOS) and RREPS (INCA & DGOS), RESOS (INCA & DGOS) and LYRICAN (INCA-DGOS-INSERM 12563), Association DAM's, Eurosarc (FP7-278742), la Fondation ARC, Infosarcome, InterSARC (INCA), LabEx DEvweCAN (ANR-10-LABX-0061), PIA Institut Convergence Francois Rabelais PLAsCAN, Ligue de L'Ain contre le Cancer, La Ligue contre le Cancer, EURACAN (EC 739521) funded this study. This work was institutionally supported by Roche.

DISCLOSURE

JM reports research grants from Roche, Astra-Zeneca, and BMS and honoraria from Roche, Astra-Zeneca, Boehringer, BMS, MSD, Pharmamar, Pfizer, and Takeda. FB reports personal financial interests: Astra-Zeneca, Bristol-Myers Squibb, Boehringer—Ingelheim, Eli Lilly Oncology, F. Hoffmann—La Roche Ltd, Novartis, Merck, MSD, Pierre Fabre, Pfizer, and Takeda; institutional financial interests: Abbvie, ACEA, Amgen, Astra-Zeneca, Bayer, Bristol-Myers Squibb, Boehringer—Ingelheim, Eisai, Eli Lilly Oncology, F. Hoffmann—La Roche Ltd, Genentech, Ipsen, Ignyta, Innate Pharma, Loxo, Novartis, Medimmune, Merck, MSD, Pierre Fabre, Pfizer, Sanofi-Aventis, and Takeda. PJS reports research support and honoraria from Abbvie, Amgen, Astra-Zeneca, BMS, Boehringer—Ingelheim, Chugai, Merck, Merimack, MSD, Novartis, Pfizer, and Roche. JC reports a research grant from Astra-Zeneca and Novartis. Honoraria form Astra-Zeneca, Boehringer, BMS, Lilly, MSD, Novartis, Pfizer, Roche, and Takeda.

DM-S reports personal fees from Roche during the conduct of the study and personal fees from Pfizer, Astra-Zeneca, Novartis, Abbvie, Takeda, and Boehringer outside the submitted work. GRF reports honoraria from Roche, Astra-Zeneca, Boehringer, BMS, MSD, and General Electric. JYB reports research support, honoraria, and research grants from Roche, Novartis, and GSK. The other authors have declared no conflicts of interest.

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