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ORIGINAL RESEARCH

Long term activity of vemurafenib in cancers with *BRAF* mutations: the ACSE basket study for advanced cancers other than BRAF^{V600}-mutated melanoma

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Background: BRAF inhibitors are approved in *BRAF*^{V600}-mutated metastatic melanoma, non-small-cell lung cancer (NSCLC), Erdheim—Chester disease (ECD), and thyroid cancer. We report here the efficacy, safety, and long-term results of single-agent vemurafenib given in the AcSé vemurafenib basket study to patients with various BRAF-mutated advanced tumours other than *BRAF*^{V600}-mutated melanoma and NSCLC.

Patients and methods: Patients with advanced tumours other than *BRAF*^{V600E} melanoma and progressing after standard treatment were eligible for inclusion in nine cohorts (including a miscellaneous cohort) and received oral vemurafenib 960 mg two times daily. The primary endpoint was the objective response rate (ORR) estimated with a Bayesian design. The secondary outcomes were disease control rate, duration of response, progression-free survival (PFS), overall survival (OS), and vemurafenib safety.

Results: A total of 98 advanced patients with various solid or haematological cancers, 88 with *BRAF*^{V600} mutations and 10 with *BRAF*^{nonV600} mutations, were included. The median follow-up duration was 47.7 months. The Bayesian estimate of ORR was 89.7% in hairy cell leukaemias (HCLs), 33.3% in the glioblastomas cohort, 18.2% in cholangiocarcinomas, 80.0% in ECD, 50.0% in ovarian cancers, 50.0% in xanthoastrocytomas, 66.7% in gangliogliomas, and 60.0% in sarcomas. The median PFS of the whole series was 8.8 months. The 12-, 24-, and 36-month PFS rates were 42.2%, 23.8%, and 17.9%, respectively. Overall, 54 patients died with a median OS of 25.9 months, with a projected 4-year OS of 40%. Adverse events were similar to those previously reported with vemurafenib.

Conclusion: Responses and prolonged PFS were observed in many tumours with BRAF mutations, including HCL, ECD, ovarian carcinoma, gliomas, ganglioglioma, and sarcomas. Although not all cancer types responded, vemurafenib is an agnostic oncogene therapy of cancers.

Key words: vemurafenib, objective response rate, progression-free survival, overall survival, BRAF^{V600} mutations, efficacy, safety

INTRODUCTION

The activating mutations of *BRAF* are observed in different cancer types.[1-4] BRAF inhibitors (BRAFis; vemurafenib, dabrafenib, and encorafenib) as single agent, and in combination with MEK inhibitors (MEKis), were approved for BRAF^{V600}-mutated metastatic melanoma,[5-8] non-small-cell

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lung cancer (NSCLC),[9] Erdheim–Chester disease (ECD),[10,11] and thyroid cancer.[12,13] However, single-agent BRAFi has no or modest efficacy in other *BRAF*^{V600}-mutated cancers such as colorectal adenocarcinoma.[11,14] So far, the efficacy and long-term duration of efficacy of BRAFi in many rare cancers with *BRAF*^{V600} mutations are not well documented.

An early phase II basket study of vemurafenib in *BRAF*^{V600} mutation-positive non-melanoma cancers reported the activity of vemurafenib in NSCLC, ECD, and Langerhans cell histiocytosis; anaplastic xanthoastrocytoma; thyroid cancer; cholangiocarcinoma; and ovarian cancer.[14] In the MSK-IMPACT study,[15] 41/71 (53%) patients with melanoma and 75/211 (36%) patients with non-melanoma cancers showing *BRAF* mutations were treated with a BRAFi, with a similar clinical benefit rate observed in patients with nonmelanoma and melanoma (71%). A multicohort basket study of 172 patients with nonmelanoma solid tumours with *BRAF*^{V600} mutations treated with vemurafenib monotherapy reported an objective response rate (ORR) of 32.6%.[16] Responses were seen in 13 cancer types including histiocytic neoplasms, gliomas, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, and sarcoma.[16] Using dabrafenib and trametinib, the NCI-MATCH trial reported an ORR of 38% with a median duration of response of 25.1 months in a cohort of 29 patients with 16 different tumour types.[17] Similarly, a recently published multicohort basket study of patients with non-melanoma *BRAF*-mutated solid tumours tested the dabrafenib and trametinib combination in anaplastic thyroid carcinoma, biliary tract cancer, gastrointestinal stromal tumours, small intestine adenocarcinoma, low-and high-grade gliomas, hairy cell leukaemia (HCL), and myeloma. The primary endpoint, investigator-assessed overall response rate, ranged from 33% to 89% in seven of the eight cohorts.[18]

In 2013, the French National Cancer Institute (INCa) initiated the basket AcSé vemurafenib trial, which assessed the safety and efficacy of single-agent vemurafenib in 216 patients with non-melanoma with a *BRAF*-mutated tumour. The results of the 118 patients enrolled in the NSCLC cohorts (BRAF^{V600} and BRAF^{nonV600}) have already been published.[19] We herein report the efficacy, safety, and for the first time long-term follow-up results of the 98 patients included in the nine other cohorts of the AcSé vemurafenib trial.

METHODS

Study design and participants

AcSé vemurafenib (EudraCT N° 2014 – 001225-33) is a multicentric, open-label, nonrandomised, phase II trial conducted in 116 hospitals in France, sponsored by the academic research group (UNICANCER), and funded by the French National Cancer Institut (INCa) and the Fondation ARC. Patients aged ≥18 years, with Eastern Cooperative Oncology Group (ECOG) performance status ≤2, and life expectancy ≥3 months were eligible. Only patients with unresectable locally advanced or metastatic tumours, from 10 cohorts gathering a total of 19 cancer types, resistant to standard treatment, harbouring a *BRAF* mutation, and with measurable disease, were eligible. Patients also required adequate haematological, renal, and liver functions. Patients with *BRAF*^{V600}-mutated melanoma or colorectal cancers and those previously treated with a BRAFi and/or an MEKi were not eligible. Eligibility criteria are listed in Supplementary Appendix S1, available at https://doi.org/10.1016/j.esmoop.2023.102038.

Patients were enrolled in one of the following cohorts (n = 10; Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2023.102038): NSCLC (BRAF^{V600}/BRAF^{nonV600}), ovarian cancer (BRAF^{V600}), cholangiocarcinoma (BRAF^{V600}), thyroid cancer (BRAF^{V600}), prostate cancer (BRAF^{V600}), bladder cancer (BRAF^{V600}/BRAF^{nonV600}), sarcoma (including gastrointestinal stromal tumours BRAF^{V600}), multiple myeloma (BRAF^{V600}), HCL (BRAF^{V600}), or other cancers harbouring a BRAF mutation (BRAF^{V600}/BRAF^{nonV600}). In the later 'miscellaneous cohort', the BRAF^{V600} subgroup included glioblastomas, xanthoastrocytomas, gangliogliomas, nephroblastoma, gastrointestinal adenocarcinoma, lymphoma, prostate adenocarcinoma, whereas the BRAF^{nonV600} subgroup included lymphoma, melanoma, prostate adenocarcinoma, and undifferentiated carcinoma (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2023.102038). The first cohort (NSCLC) was already reported and will not be presented here.[19]

The trial was performed in accordance with the declaration of Helsinki and all applicable French and European laws. All patients provided written informed consent before participating in the trial.

Procedures

Patient's demographic and relevant medical history, as well as their disease characteristics and treatment data, were collected at baseline. Oral vemurafenib was given at a dose of 960 mg twice daily until progression, intolerance, or patient request. For reporting purposes, a 28-day treatment cycle was defined. Patients with HCL and chronic lymphocytic leukaemia were initially treated with two cycles of vemurafenib. If after two cycles a complete response (CR) had not been achieved, two additional cycles could be administered. All other patients were treated until disease progression, unacceptable toxicity, concomitant disease preventing treatment, or the patient's decision to stop treatment. To manage adverse events (AEs), the dose of vemurafenib could be reduced, but not <480 mg twice daily.

Study visits were planned 30 days after treatment discontinuation and then every 3 months for 2 years for patients with solid tumours and for 4 years for those with haematological malignancies.

Tumour response to vemurafenib was assessed every 8 weeks until disease progression or initiation of another treatment in the case of treatment discontinuation for reasons other than progression using the following: (i) RECIST version 1.1 for solid tumours,[20] (ii) International Myeloma Working Group (IMWG) response criteria for multiple myeloma,[21] (iii) International Workshop on Chronic

Lymphocytic Leukaemia (IWCLL) for chronic lymphocytic leukaemia,[22] and (iv) clinical and biological parameters for HCL.[23] Tumours were assessed by imaging, computed tomography and magnetic resonance imaging, and/or biological assessment depending on the tumour type and according to the current guidelines for each tumour. Other tumour assessments were at the discretion of the investigators.

Safety was assessed by clinical, biological, and cardiac assessments and graded using the Common Terminology for Adverse Events (CTCAE) version 4.0. AEs data were collected, at each visit, up until 30 days after the last intake of vemurafenib. Serious AEs data were collected throughout the study.

Outcomes

The primary endpoint was the ORR, defined as the proportion of patients with a CR or a partial response (PR) as best overall response during the study. Secondary efficacy outcomes were disease control rate (DCR), duration of response, progression-free survival (PFS), and overall survival (OS). Duration of response was defined as the time interval between the first documented disease response (either CR or PR) and disease progression or death of any cause, whichever occurred first. DCR was defined as the proportion of patients with a tumour response of CR, PR, or stable disease as best overall response during the study. PFS was the time interval between starting treatment and disease progression or death of any cause, whichever occurred first. OS was defined as the time interval between starting treatment and death from any cause.

Statistical analysis

AcSé Vemurafenib was designed as an adaptive trial using a Bayesian approach, allowing continuous monitoring of efficacy, and early stopping in case of futility.[24] Initially, a sample size of 30-50 patients was planned in each of the cohorts. The primary outcome (ORR) was sequentially analysed in each cohort. The first interim analysis was planned once the first 10 patients enrolled had 16 weeks of follow-up, and then when every subsequent 5 patients had 16 weeks of follow-up. Enrolment was not suspended between analyses unless the accrual rate was two or more patients/month for at least 3 months. Cohorts showing huge efficacy signals could include up to 100 patients.

The probability of success (objective response) was estimated using a beta-binomial model.[24] In the absence of a strong idea about the response rates to be observed, a non-informative prior [beta (1,1)] was used as the initial probability distribution of the ORR. After each interim analysis, the posterior distributions were updated based on the results obtained, and a futility rule recommended that enrolment of a cohort should be stopped in case of high probability ($\geq$80%) that the ORR was $\leq$10% in that cohort (the futility bound). If no early stopping occurred, study treatment would be considered worthy for further evaluation if there was a 90% probability that the estimated ORR was $\geq$30% (the efficacy bound). Enrolment was planned until stopped for futility or until the maximum planned number of patients had been reached. Bayesian estimation of the mean ORR was summarized, together with its 95% credibility interval (measure of Bayesian estimation precision). Efficacy analyses were performed in patients who received at least one cycle of treatment or who discontinued treatment during the first cycle due to disease progression or toxicity and without a major protocol deviation that would bias the analyses. Safety was assessed in all patients treated with vemurafenib.

Qualitative data are described using frequency and percentage. Quantitative data are described using number of observations, median with interquartile range (IQR), minimum and maximum. Bayesian estimation of the mean ORR was summarized, together with its 95% credibility interval. Posterior probabilities of success were calculated. Time-to-event endpoints were estimated by the Kaplan—Meier method and reported as medians with associated 95% confidence intervals (CIs). Safety was assessed using the frequency and percentage of AEs.

This trial is registered at EudraCT (2014-001225-33) and at ClinicalTrials.gov (NCT02304809).

Role of the funding source

The study was funded by the French National Cancer Institute (INCa), the Fondation ARC, and Unicancer, the French Federation of Comprehensive Cancer Centres. Vemurafenib was provided by Roche (Boulogne, France). Unicancer was the study sponsor responsible for designing the study, collecting, analysing, and interpreting the data. JYB, CC, and CG-R had access to all the data and made the final decision to submit this article for publication.

RESULTS

Patients and disease characteristics

Between 1 October 2014 and 15 October 2019, 216 patients were enrolled in the AcSé program. The 118 NSCLCs were already reported.[19] Here we report on the 88 patients with advanced cancer with $BRAF^{V600}$ mutations and on the 10 patients with $BRAF^{nonV600}$ mutations. Detailed patients' baseline characteristics are presented in Tables 1 and 2 and Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.102038. V600E mutation was the most common $BRAF^{V600}$ mutation (84/88, 95.5%). The most common cancer types were HCL ($n = 27$), glioblastoma ($n = 10$), cholangiocarcinoma ($n = 9$), ECD ($n = 8$), ovarian cancer ($n = 6$), thyroid cancer ($n = 6$), xanthoastrocytoma ($n = 5$), and melanoma with $BRAF^{nonV600}$ mutation ($n = 5$). The median age was 61.5 years (IQR 49.0-69.0 years); 49 patients (50.0%) were females. Overall, patients had received a median number of two prior lines of chemotherapy (IQR 2.0-4.0) in the metastatic setting.

Treatment administration and follow-up

All the 98 patients were followed up for a median duration of 47.7 months (IQR 34.9-54.6 months). A total of 97 patients were treated with vemurafenib with a median

Table 1. Patients' demographics and disease characteristics for cancers with $n \geq 5$

Patient characteristics	All patients ($n = 98$)	HCL ($BRAF^{V600}$) ($n = 27$)	Glioblastoma ($BRAF^{V600}$) ($n = 10$)	Cholangiocarcinoma ($BRAF^{V600}$) ($n = 9$)	ECD and histiocytosis ($BRAF^{V600}$) ($n = 8$)	Ovarian ($BRAF^{V600}$) ($n = 6$)	Thyroid ($BRAF^{V600}$) ($n = 6$)	Xanthoastrocytoma ($BRAF^{V600}$) ($n = 5$)	Melanoma ($BRAF^{nonV600}$) ($n = 5$)
Age (years)									
Median	61.5	67.0	41.5	71.0	54.5	55.5	69.0	27.0	64.0
Q1-Q3	49.0-69.0	59.0-70.0	34.0-60.0	68.0-76.0	51.0-61.0	47.0-59.0	68.0-78.0	23.0-27.0	61.0-68.0
Range	18.0-84.0	42.0-80.0	19.0-65.0	50.0-84.0	37.0-82.0	46.0-63.0	58.0-84.0	21.0-29.0	53.0-74.0
Age (years), *n* (%)									
≤60	47 (48.0)	7 (25.9)	8 (80.0)	2 (22.2)	6 (75.0)	5 (83.3)	1 (16.7)	5 (100.0)	1 (20.0)
>60	51 (52.0)	20 (74.1)	2 (20.0)	7 (77.8)	2 (25.0)	1 (16.7)	5 (83.3)	0(0.0)	4 (80.0)
Sex, *n* (%)									
Male	49 (50.0)	19 (70.4)	2 (20.0)	2 (22.2)	5 (62.5)	0 (0.0)	2 (33.3)	2 (40.0)	1 (20.0)
Female	49 (50.0)	8 (29.6)	8 (80.0)	7 (77.8)	3 (37.5)	6 (100.0)	4 (66.7)	3 (60.0)	4 (80.0)
WHO PS									
Missing, *n*	0	0	0	0	3	0	0	0	1
0, *n* (%)	2 (33.3)	18 (66.7)	2 (20.0)	2 (22.2)	2 (50.0)	2 (33.3)	2 (33.3)	1 (20.0)	0 (0.0)
1, *n* (%)	4 (66.7)	6 (22.2)	5 (50.0)	7 (77.8)	2 (50.0)	4 (66.7)	4 (66.7)	3 (60.0)	2 (50.0)
2, *n* (%)	0 (0.0)	3 (11.1)	3 (30.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	2 (50.0)
Number of previous lines of chemotherapy for metastatic disease									
Median	2.0	3.0	1.5	2.0	1.0	2.0	1.0	—	1.5
Q1-Q3	2.0-4.0	2.0-5.0	1.0-2.0	2.0-2.0	1.0-1.0	2.0-4.0	1.0-2.0	—	1.0-2.0
Range	1.0-6.0	2.0-9.0	1.0-2.0	1.0-6.0	1.0-1.0	1.0-6.0	1.0-2.0	—	1.0-2.0

ECD, Erdheim—Chester disease; HCL, hairy cell leukaemia; WHO PS, performance status according to the World Health Organization.

Table 2. Patients' demographics and disease characteristics for cancers with $n < 5$

Patient characteristics	Ganglioglioma ($BRAF^{V600}$) ($n = 4$)	Sarcoma ($BRAF^{V600}$) ($n = 3$)	Bladder ($BRAF^{V600}$) ($n = 2$)	Multiple myeloma ($BRAF^{V600}$) ($n = 2$)	Nephroblastoma ($BRAF^{V600}$) ($n = 2$)	Gastro intestinal adenocarcinoma ($BRAF^{V600}$) ($n = 2$)	Lymphoid hemopathy ($BRAF^{V600}$) ($n = 1$)	Prostate ($BRAF^{V600}$) ($n = 1$)	Lymphoid hemopathy ($BRAF^{nonV600}$) ($n = 1$)	Prostate ($BRAF^{nonV600}$) ($n = 1$)	Other pathologies ($BRAF^{nonV600}$) ($n = 3$)
Age (years)											
Median	32.0	45.0	64.0	53.0	40.0	64.0	69.0	70.0	68.0	68.0	70.0
Q1-Q3	25.5-39.0	18.0-62.0	57.0-71.0	48.0-58.0	28.0-52.0	57.0-71.0	69.0-69.0	70.0-70.0	68.0-68.0	68.0-68.0	69.0-73.0
Range	20.0-45.0	18.0-62.0	57.0-71.0	48.0-58.0	28.0-52.0	57.0-71.0	69.0-69.0	70.0-70.0	68.0-68.0	68.0-68.0	69.0-73.0
Age (years)											
≤60	4 (100.0)	2 (66.7)	1 (50.0)	2 (100.0)	2 (100.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>60	0 (0.0)	1 (33.3)	1 (50.0)	0 (0.0)	0 (0.0)	1 (50.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	3 (100.0)
Sex, *n* (%)											
Male	3 (75.00)	1 (33.3)	2 (100.0)	1 (50.0)	2 (100.0)	1 (50.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	2 (66.7)
Female	1 (25.0)	2 (66.7)	0 (0.0)	1 (50.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)
WHO PS											
Missing, *n*	0	0	0	0	0	0	0	0	0	0	0
0, *n* (%)	3 (75.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
1, *n* (%)	1 (25.0)	1 (33.3)	1 (50.0)	1 (50.0)	2 (100.0)	1 (100.0)	1 (100.0)	0 (0.0)	1 (100.0)	1 (100.0)	2 (66.7)
2, *n* (%)	0 (0.0)	1 (33.3)	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)
Number of previous lines of chemotherapy to treat metastasis											
Median	—		4.0	9.0	1.5	2.0	4.0	3.0	2.0	—	3.0
Q1-Q3	—		1.0-7.0	9.0-9.0	1.0-2.0	2.0-2.0	4.0-4.0	3.0-3.0	2.0-2.0	—	1.0-3.0
Range	—		1.0-7.0	9.0-9.0	1.0-2.0	2.0-2.0	4.0-4.0	3.0-3.0	2.0-2.0	—	1.0-3.0

WHO PS, performance status according to the World Health Organization.

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Table 3. ORR and DCR in the different cancer cohorts

Cancer types	Confirmed objective response[a], *n/N* (%)	Bayesian estimation of ORR % (95% credibility interval)	DCR[b], *n/N* (%)
All patients ($n = 97$)	**50/97 (51.5)**	52.0% (42.2% to 61.8%)	**78/97 (80.2)**
HCL ($BRAF^{V600}$) ($n = 27$)	25/2 (92.6)	89.7 (76.5-97.7)	25/25 (100.0)
Non-HCL patients ($n = 70$)	**25/69 (36.2)**	36.6 (25.9-48.1)	**53/70 (75.7)**
Glioblastoma ($BRAF^{V600}$) ($n = 10$)	3/10 (30.0)	33.3 (10.9-61.0)	4/9 (44.4)
Cholangiocarcinoma ($BRAF^{V600}$) ($n = 9$)	1/9 (11.1)	18.2 (2.5-44.5)	7/9 (77.8)
ECD and histiocytosis ($BRAF^{V600}$) ($n = 8$)	7/8 (87.5)	80.0 (51.8-97.2)	7/8 (87.5)
Ovarian ($BRAF^{V600}$) ($n = 6$)	3/6 (50.0)	50.0 (18.4-81.6)	3/5 (60.0)
Thyroid ($BRAF^{V600}$) ($n = 6$)	0/6 (0.0)	NE	4/6 (66.7)
Xanthoastrocytoma ($BRAF^{V600}$) ($n = 5$)	2/4 (50.0)	50.0 (14.7-85.3)	4/4 (100.0)
Ganglioglioma ($BRAF^{V600}$) ($n = 4$)	3/4 (75.0)	66.7 (28.4-94.7)	4/4 (100.0)
Sarcoma ($BRAF^{V600}$) ($n = 3$)	2/3 (66.7)	60.0 (19.4-93.2)	2/2 (100.0)
Bladder ($BRAF^{V600}$) ($n = 2$)	0/2 (0.0)	NE	1/2 (50.0)
Multiple myeloma ($BRAF^{V600}$) ($n = 2$)	1/2 (50.0)	50.0 (9.4-90.6)	1/1 (100.0)
Nephroblastoma ($BRAF^{V600}$) ($n = 2$)	0/2 (0.0)	NE	1/1 (100.0)
Gastrointestinal adenocarcinoma ($BRAF^{V600}$) ($n = 1$)	1/1 (100.0)	66.7 (15.8-98.7)	1/1 (100.0)
Lymphoid hemopathy ($BRAF^{V600}$) ($n = 1$)	0/1 (0.0)	NE	1/1 (100.0)
Prostate ($BRAF^{V600}$) ($n = 1$)	1/1 (100.0)	66.7 (15.8-98.7)	1/1 (100.0)
Melanoma ($BRAF^{nonV600}$) ($n = 5$)	1/5 (20.0)	28.6 (4.3-64.1)	3/4 (75.0)
Lymphoid hemopathy ($BRAF^{nonV600}$) ($n = 1$)	0/1 (0.0)	NE	0/1 (0.0)
Prostate ($BRAF^{nonV600}$) ($n = 1$)	0/1 (0.0)	NE	0/1 (0.0)
Other pathologies ($BRAF^{nonV600}$) ($n = 3$)	0/3 (0.0)	NE	0/3 (0.0)

One patient never received vemurafenib and was excluded from the efficacy analysis.
One patient each with $BRAF^{nonV600}$-mutated melanoma and xanthoastrocytoma were not evaluable for response and DCR.
ECD, Erdheim—Chester disease; DCR, disease control rate; HCL, hairy cell leukaemia; NE, not evaluable; ORR, objective response rate.
[a]The ORR was defined as the proportion of patients with a complete response or a partial response as best overall response during the study [RECIST for solid tumors, International Myeloma Working Group response criteria for myeloma, International Workshop on Chronic Lymphocytic Leukemia, clinical examination, blood tests (blood count), and bone marrow exam for HCL].
[b]DCR was defined as the proportion of patients with a complete response or a partial response or a stable disease as best overall response during the study.

duration of treatment of 3.0 months (IQR 1.8-7.8 months). One of the 98 patients (with gastrointestinal adenocarcinoma) did not receive treatment because of a deterioration of general condition. Vemurafenib treatment was modified (dose reductions and/or treatment delays) due to toxicity in 66 (68.0%) patients. It was discontinued in 45 (46.4%) patients due to disease progression and in 18 (18.6%) patients due to the occurrence of AEs. Six (6.2%) patients were still under treatment at the cut-off date.

Efficacy

The efficacy population included the 97 patients treated with vemurafenib. The ORR was 52.0% (95% credibility interval 42.2% to 61.8%) and the DCR was 80.2% for the whole cohort. The ORR is presented by cancer cohort in Table 3. The individual response of patients with $BRAF^{nonV600}$ mutations, along with the nature of the mutations, is presented in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.102038. Individual patients' response and duration of tumour control are detailed in Figures 1 and 2.

For the largest cohort, HCL, three interim analyses were carried out after inclusion of 10, 14, and 27 patients successively: the final mean Bayesian estimated success rate was 89.7% (95% credibility interval 76.5% to 97.7%). The posterior probability (estimated using the Bayesian approach) that the ORR was above the efficacy bound (30%) was 100.0% and the probability that the ORR was above 85% is 81.0% (Supplementary Appendix S1, available at https://doi.org/10.1016/j.esmoop.2023.102038). For the remaining cohorts, interim analyses were not carried out due to the insufficient sample size ($\leq$10 patients per cohort). In the overall population of patients with non-HCL,

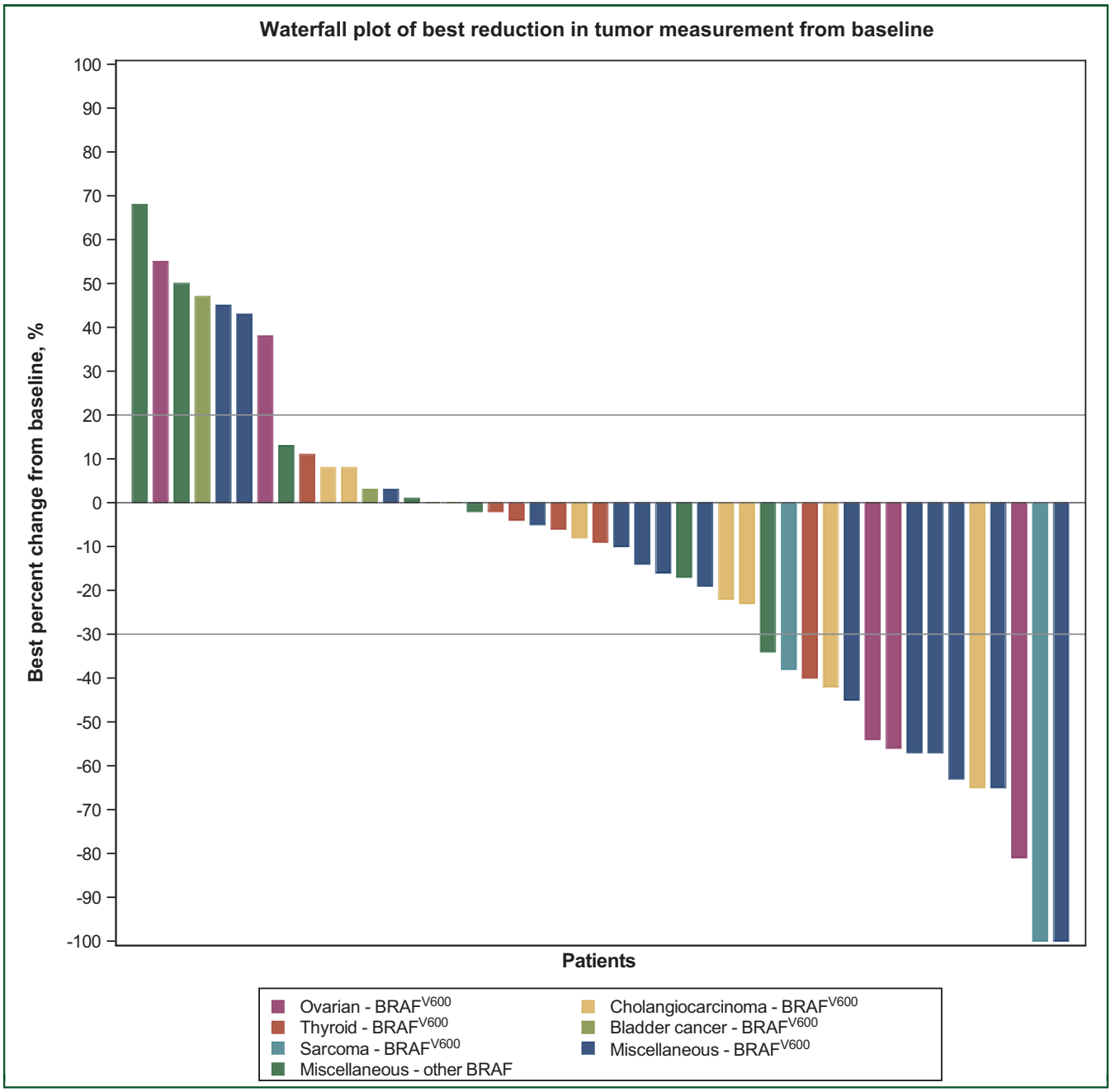

Figure 1. Best reduction in tumour measurement from baseline in solid tumours. The line at −30% represents the threshold for a partial response, according to RECIST version 1.1. The line at +20% demarcates disease progression. Bars show maximum reduction from baseline sum of diameters by the best confirmed response. Evaluable measurements for RECIST criteria were available for 45 patients.

the mean estimated Bayesian success rate was 36.6% (95% credibility interval 25.9-48.1). The mean Bayesian estimated success rate was 33.3% (95% credibility interval 10.9% to 61.0%) in the glioblastoma cohort, 18.2% (95% credibility interval 2.5% to 44.5%) in the cholangiocarcinoma cohort, 80.0% (95% credibility interval 51.8% to 97.2%) in the ECD cohort, 50.0% (95% credibility interval 18.4% to 81.6%) in the ovarian cancer cohort, 50.0% (95% credibility interval 14.7% to 85.3%) in the xanthoastrocytoma cohort, 66.7% (95% credibility interval 28.4% to 94.7%) in the ganglioglioma cohort, and 60.0% (95% credibility interval 19.4% to 93.2%) in the sarcoma cohort (Table 3).

The median PFS of the whole cohort was 8.8 months (95% CI 7.8-13.1). The 12-, 24-, and 36-months PFS were 42.2% (95% CI 33.3-53.4), 23.8% (95% CI 16.6-34.2), and 17.9% (95% CI 11.5-27.9), respectively (Figure 3A). Overall, 54 patients died with a median OS of 25.9 months (95% CI 15.1-not evaluable [NE]). The 2-year OS was 51.4% (95% CI 42.2-62.5; Figure 3B). The median PFS and OS of patients with solid tumours with *BRAF*^{V600} mutations were 7.6 and 15.6 months, respectively (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2023.102038).

In the HCL cohort, the median PFS was 17.5 months (95% CI 13.1-24.9; Figure 3C). There were 4 deaths in the 27

Figure 2. Vemurafenib treatment duration and activity. For hairy cell leukaemia (HCL), vemurafenib is prescribed for two cycles (first assessment) and possibly for two additional cycles if a complete response is not achieved at cycle 2. In total, treatment is stopped at day 112 (maximum) whatever the response. OR, objective response; PD, progressive disease.

patients, at 11.9, 22.4, 24.3, and 37.2 months with a 3-year OS of 87.5% (95% CI 75.2-100.0; Figure 3D). The median PFS was 2.0 months (95% CI 1.7-NE) in the glioblastoma cohort, 5.3 months (95% CI 3.6-NE) in the cholangiocarcinoma cohort, and 25.9 months (95% CI 13.7-NE) in the ECD and histiocytosis cohort (Figure 3C). The median OS was 9.0 months (95% CI 2.6-NE) in the glioblastoma cohort and 12.9 months (95% CI 8.3-NE) in the cholangiocarcinoma cohort (Figure 3D). Two deaths were reported in the ECD and histiocytosis cohort, at 15 and 36 months (Figure 3D).

Long-term survivors at >24 months were patients with HCL (22/27), ECD (7/8), ganglioglioma (4/4), xanthoastrocytoma (3/5), sarcoma (2/3), glioblastoma (2/10), ovarian cancer (2/6), cholangiocarcinoma (1/9), thyroid cancer (1/6), and melanoma with $BRAF^{nonV600}$ mutation (1/5; Figure 2). Of note, the subsequent treatments were not collected as part of the protocol.

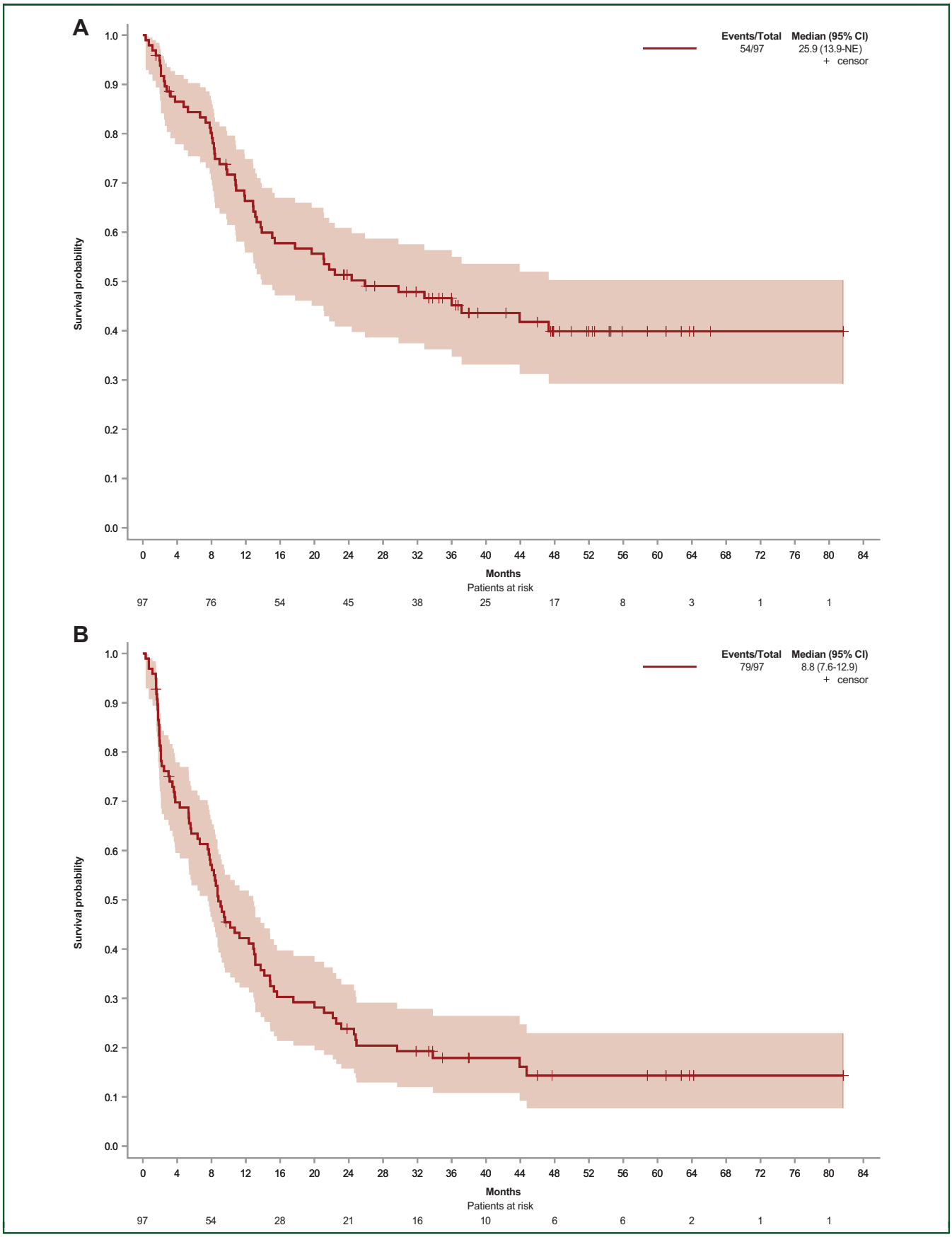

Figure 3. Overall survival and progression-free survival (PFS). (A and B) in the global cohort and (C and D) in hairy cell leukaemia, glioblastoma, cholangiocarcinoma, and Erdheim–Chester disease, and histiocytosis cohorts.
CI, confidence interval; ECD, Erdheim–Chester disease; NE, not evaluable.

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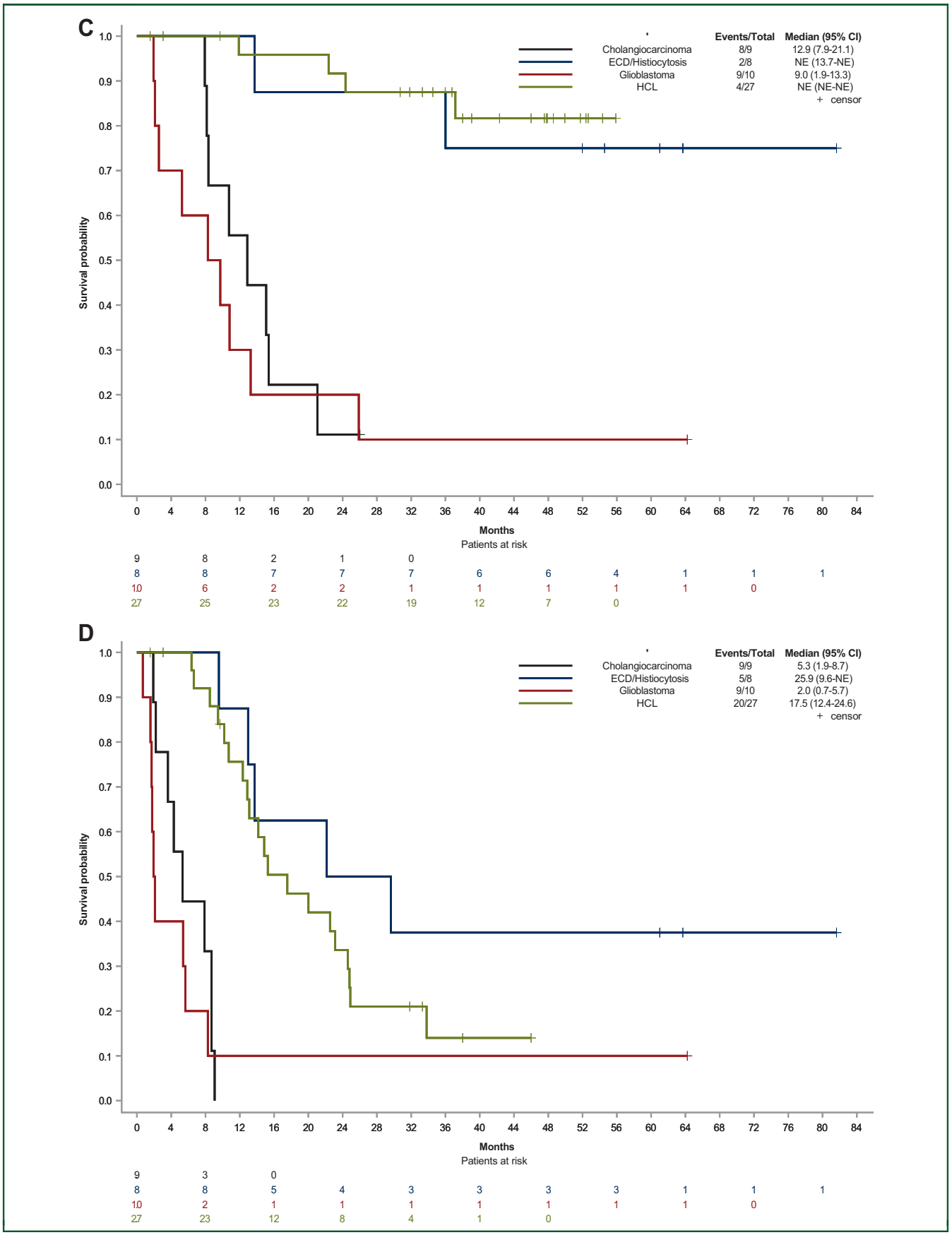

Figure 3. Continued.

Safety

The most common AEs that were reported in at least 20 patients are presented in Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2023.102038, by grade of severity according to CTCAE version 4.0. Among the 97 patients included in the safety analysis, 93 (95.9%) had at least one treatment-related AE. The most frequently reported AEs were fatigue (64.9%), photosensitivity reaction (42.3%), acneiform dermatitis (42.3%), keratosis pilaris (41.2%), pruritus (37.1%), decreased appetite (29.9%), nausea (29.9%), lymphopenia (29.9%), and alopecia (29.9%). In the global cohort, 49 (50.5%) patients had at least one treatment-related grade $\geq$3 AE. The most frequently reported were lymphopenia (9 patients, 9.3%), neutropenia (6 patients, 6.2%), leukopenia (5 patients, 5.2%), fatigue (5 patients, 5.2%), and dermatitis (5 patients, 5.2%). Serious treatment-related AEs were reported in 30 patients (30.9%). None of the patients had a grade 5 AE.

Transient treatment interruption occurred in 65 (67%) patients, because of toxicity in 57 (58.8%) patients and/or because of intercurrent disease or other in 29 (29.9%) patients. Finally, 18 patients (18.6%) permanently discontinued study treatment due to toxicity. Similarly, dose reductions were applied in 43 (44.3%) patients, because of toxicity in 26 (26.8%), intercurrent disease in 5 (5.2%), and/or other causes in 26 (26.8%) patients. Doses were reduced to 720 mg two times daily for 43 (44.3%) patients, then to 480 mg two times daily for (34.7%) patients

DISCUSSION

In this article, we report on the long-term efficacy of single-agent vemurafenib in a group of nonmelanoma tumours harbouring *BRAF* mutations in a basket trial, identifying histotypes where prolonged efficacy is observed. The efficacy of vemurafenib was confirmed in a variety of cancer types with $BRAF^{V600}$ mutations, including HCL (ORR 89.7%), glioblastoma (ORR 33.3%), ECD (ORR 80%), xanthoastrocytoma (ORR 50%), ovarian cancer (ORR 50%), gangliglioma (ORR 66.7%), sarcoma (ORR 60%), and multiple myeloma (ORR 50%). Durable responses were seen across the global cohort with a median PFS of 8 months, a median OS of 25 months, and prolonged (>3 years) PFS and survival were observed in ovarian carcinoma, sarcoma, gangliogliomas, thyroid carcinoma, and HCL. The ORRs observed in these cohorts are comparable to those reported in previous basket studies also testing vemurafenib single-agent[14-16] or a combination of dabrafenib and trametinib.[17,18] Overall, via indirect comparison, the combination of BRAFi and MEKi provides numerically higher responses rates as compared with single-agent vemurafenib, as observed in randomized clinical trials in advanced melanoma.[14-18,25]

The present study provides information on the long-term activity of vemurafenib, which was given until progression in the present AcSé study. The median PFS was 8.8 months and median OS was 25.9 months for the 97 patients included with solid and haematological malignancies. Long-term survivors beyond 24 months were mostly patients with HCL (n = 22), ECD (n = 7), gangliglioma (n = 4), and xanthoastrocytoma (n = 3), as well as those with ovarian carcinoma, sarcomas, and glioblastoma. The patient with sarcoma with the longest PFS stopped vemurafenib at his request and continues to be in CR 3 years after interruption.

These findings confirm the prolonged efficacy of single-agent vemurafenib in the treatment of refractory or relapsed HCL,[26,27] in ECD,[14,16] multiple myeloma,[27-29] ovarian cancer,[14,16] and xanthoastrocytoma.[14] Prolonged vemurafenib efficacy is also observed in very rare $BRAF^{V600}$-mutated cancer types, such as gangliglioma and sarcomas. Vemurafenib single agent is thus active in advanced cancers beyond its currently approved indications and can be considered as an agnostic therapy as suggested also recently for the dabrafenib and trametinib combination in the same patient population.[9,10,12,13,18,24] As such, the presence of BRAF mutation should be tested broadly, as part of gene panels, in patients with cancers who have exhausted standard therapeutic options, when access to BRAFi is possible for patients with such mutations.

In patients with thyroid cancer (ORR 12.5%), cholangiocarcinoma (ORR 18.2%), and bladder cancer (ORR 25%), single-agent vemurafenib had an antitumor activity often numerically inferior to that reported in trials exploring a combination of BRAFi with MEKi.[5-8,18] Similar findings concerning the combination activity were also observed for NSCLC and melanoma.[5-8,30] At the launch of the AcSé program, reports showing the significant activity of the combination were not available yet. The results in the present series support the use of a combination of BRAFi and MEKi in these indications. Very rare molecular subgroups of cancers with $BRAF^{V600}$ mutations such as nephroblastoma, or lymphoma, or prostate cancer had no or short duration of response to vemurafenib, but the very small, often one, number of patients treated precludes any definitive conclusions on these subtypes. One of the two patients with a melanoma with nonV600 BRAF mutation (mutation Thr599dup) responded to vemurafenib, which was consistent with recent reports.[31] International registries collecting these ultrarare entities are needed to better characterized the natural history and outcome of these tumours.

Vemurafenib safety was similar to previous reports. No grade 5 AEs were reported, and vemurafenib was only discontinued due to toxicity in 18 patients (18.6%). The most common AEs in this study were fatigue and skin-related toxic effects that are usually manageable. The safety profile of vemurafenib in our study was similar to those reported previously,[14,32] and in the series of patients with NSCLC treated within the same trial.[5-8,14,32] Indirect comparison with published series again indicated that BRAFi monotherapy may be less well tolerated than the combination of BRAFi and MEKi.[5-8]

This study has several limitations. First, only a small number of patients are present in most cohorts. When only one or two patients are treated without response for a given histotype, vemurafenib efficacy cannot be excluded and require additional data. The study tested single-agent BRAFi while the combination with an MEKi could have

improved the tolerability and efficacy profiles. The optimal duration of vemurafenib therapy was also not tested in this study. However, the AcSé Vemu study confirms the clinical activity of vemurafenib in patients with rare molecular types of common histotypes bearing *BRAF* mutations; it identifies novel cancer types where prolonged activity was observed, and shows long-term survival in a fraction of patients with no progressions reported after 4 years.

In conclusion, this study confirms and identifies the activity of single-agent BRAFi in a broad variety of histotypes, with prolonged PFS observed in cancers where BRAFi activity was seldom reported such as paraganglioma and sarcomas. Very prolonged duration of efficacy was observed in a variety of cancer types, within and outside its approved indications. This study provides further evidence[18] that BRAFi is an agnostic targeted oncogene therapy, as also reported with a combination of BRAFis and MEKis.

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DATA SHARING

Unicancer will share deidentified individual data that underlie the results reported in this article under the following conditions: the data shared will be limited to that required for independent mandated verification of the published results, the reviewer will need authorisation from Unicancer for personal access, and data will only be transferred after signing of a data access agreement. A decision concerning the sharing of other study documents, including protocol and statistical analysis plan, will be examined upon request. Unicancer will consider access to study data upon written detailed request, from 6 months to 5 years after the publication of this article.

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