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Original Research

Effect of concomitant dosing with acid-reducing agents and vemurafenib dose on survival in patients with $BRAF^{V600}$ mutation–positive metastatic melanoma treated with vemurafenib ± cobimetinib

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KEYWORDS
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Abstract ***Background:*** We conducted a retrospective analysis to evaluate the impact of concomitant acid-reducing agents (ARAs) and vemurafenib dose on the efficacy of vemurafenib in patients with $BRAF^{V600}$ mutation–positive unresectable or metastatic melanoma treated with vemurafenib or cobimetinib plus vemurafenib.
Methods: Data were pooled for patients treated with vemurafenib or cobimetinib plus vemurafenib in the BRIM-2, BRIM-3, BRIM-7, and coBRIM studies. The primary end-points were progression-free survival and overall survival across patient subgroups defined by vemurafenib dose (full vs reduced) and concomitant ARA use (yes vs no). Objective response rate (ORR) was also analysed. Steady-state vemurafenib concentrations were evaluated according to vemurafenib dosing and concomitant ARA use across treatment cohorts in a subset of patients from BRIM-7 and coBRIM with available concentration data.

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Results: Efficacy analyses included 920 patients: 641 in the vemurafenib cohort and 279 in the cobimetinib plus vemurafenib cohort. Overall, no significant differences in survival outcomes were observed across subgroups according to vemurafenib dose and ARA use, with or without adjustment for known prognostic covariates, in both treatment cohorts. ORR was also similar across subgroups in both treatment cohorts. Steady-state vemurafenib concentrations were analysed in 389 patients (193 in the vemurafenib cohort and 196 in the cobimetinib plus vemurafenib cohort) and were generally similar across vemurafenib dose subgroups, regardless of ARA use in both treatment cohorts.

Conclusions: Results of this retrospective pooled analysis suggest that ARAs can be used concomitantly with vemurafenib, alone or in combination with cobimetinib, without compromising the efficacy of vemurafenib.

1. Introduction

Vemurafenib is a BRAF kinase inhibitor (BRAFi) indicated for the treatment of adult patients with $BRAF^{V600}$ mutation–positive unresectable or metastatic melanoma. Vemurafenib was approved as monotherapy in >100 countries worldwide based on the results of the phase 3 BRIM-3 study, in which vemurafenib significantly improved progression-free survival (PFS) and overall survival (OS) compared with dacarbazine [1,2]. Vemurafenib is also approved in the United States and the European Union for use in combination with cobimetinib, a MEK inhibitor (MEKi), for the treatment of adult patients with $BRAF^{V600}$ mutation–positive unresectable or metastatic melanoma, based on the results of the phase 3 coBRIM study, in which cobimetinib combined with vemurafenib improved PFS and OS compared with placebo plus vemurafenib [3,4]. The coBRIM study, along with other phase 3 randomised trials, established combined BRAFi and MEKi therapy as a standard of care for this population.

Concomitant use of acid-reducing agents (ARAs) is common in patients with cancer, with an estimated prevalence of 14%–29% in patients with melanoma [5]. Increasing gastric pH with ARAs has the potential to reduce absorption of orally administered cancer therapeutics, particularly those that display pH-dependent solubility, which may result in underexposure to and impaired efficacy of these drugs [5]. A number of orally administered, targeted anticancer therapies have demonstrated reduced exposure [6–8] and lower efficacy [9] with concomitant administration of ARAs. Drugs with low aqueous solubility (Biopharmaceutics Classification System [BCS] class II or IV) appear to be the most susceptible to drug–drug interactions with ARAs [10]. Vemurafenib is a BCS class IV drug with low aqueous solubility and low intestinal permeability, although solubility is relatively independent of pH [11].

A recent retrospective chart review involving 112 patients with $BRAF^{V600}$ mutation–positive melanoma suggested that patients who are able to tolerate full-dose vemurafenib are underexposed to the drug and that concomitant use of ARAs in patients who are able to tolerate full-dose vemurafenib is associated with an increased risk of progression, presumably because of increased underexposure to vemurafenib [12]. Therefore, we conducted a retrospective analysis in a larger data set of patients with $BRAF^{V600}$ mutation–positive unresectable or metastatic melanoma treated with vemurafenib or cobimetinib combined with vemurafenib to clarify the impact of concomitant use of ARAs on vemurafenib efficacy when used as monotherapy or in combination with cobimetinib.

2. Methods

2.1. Study design and patients

Data were pooled for patients treated with vemurafenib or cobimetinib plus vemurafenib in the BRIM-2 [13], BRIM-3 [1,2], BRIM-7 [14], and coBRIM [3,4] studies. Detailed methods for each study were previously reported. Briefly, BRIM-2 was an open-label, multicenter phase 2 trial of oral vemurafenib 960 mg twice daily. BRIM-3 was an open-label, multicenter, randomised phase 3 trial of oral vemurafenib 960 mg twice daily compared with intravenous dacarbazine 1000 mg/m^2 every 3 weeks. BRIM-7 was an open-label, multicenter phase 1b dose-escalation study of oral cobimetinib plus oral vemurafenib at various doses. coBRIM was a randomised, double-blind phase 3 study of the combination of oral cobimetinib 60 mg once daily for 21 days followed by a 7-day break (ie, a 21/7 schedule) plus oral vemurafenib 960 mg twice daily compared with placebo plus vemurafenib. Key eligibility criteria were similar across trials; eligible patients were aged ≥18 years with unresectable stage IIIC or IV melanoma harbouring a $BRAF^{V600}$ mutation, Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and adequate organ function. BRIM-3 and coBRIM

Table 1
Baseline characteristics.

Characteristic	Vemurafenib cohort					Cobimetinib + vemurafenib cohort				
	Overall (n = 641)	Full-dose vemurafenib + no ARA use (n = 246)	Full-dose vemurafenib + ARA use (n = 87)	Reduced-dose vemurafenib + no ARA use (n = 203)	Reduced-dose vemurafenib + ARA use (n = 105)	Overall (n = 279)	Full-dose vemurafenib + no ARA use (n = 119)	Full-dose vemurafenib + ARA use (n = 47)	Reduced-dose vemurafenib + no ARA use (n = 59)	Reduced-dose vemurafenib + ARA use (n = 54)
Age, n (%)	(n = 641)	(n = 246)	(n = 87)	(n = 203)	(n = 105)	(n = 279)	(n = 119)	(n = 47)	(n = 59)	(n = 54)
<65 years	482 (75.2)	193 (78.5)	64 (73.6)	154 (75.9)	71 (67.6)	212 (76.0)	96 (80.7)	35 (74.5)	44 (74.6)	37 (68.5)
≥65 years	159 (24.8)	53 (21.5)	23 (26.4)	49 (24.1)	34 (32.4)	67 (24.0)	23 (19.3)	12 (25.5)	15 (25.4)	17 (31.5)
Sex, n (%)	(n = 641)	(n = 246)	(n = 87)	(n = 203)	(n = 105)	(n = 279)	(n = 119)	(n = 47)	(n = 59)	(n = 54)
Female	267 (41.7)	89 (36.2)	32 (36.8)	96 (47.3)	50 (47.6)	114 (40.9)	43 (36.1)	15 (31.9)	28 (47.5)	28 (51.9)
Male	374 (58.3)	157 (63.8)	55 (63.2)	107 (52.7)	55 (52.4)	165 (59.1)	76 (63.9)	32 (68.1)	31 (52.5)	26 (48.1)
Race, n (%)	(n = 641)	(n = 246)	(n = 87)	(n = 203)	(n = 105)	(n = 279)	(n = 119)	(n = 47)	(n = 59)	(n = 54)
White	622 (97.0)	236 (95.9)	86 (98.9)	198 (97.5)	102 (97.1)	264 (94.6)	113 (95.0)	43 (91.5)	55 (93.2)	53 (98.1)
Non-white	19 (3.0)	10 (4.1)	1 (1.1)	5 (2.5)	3 (2.9)	15 (5.4)	6 (5.0)	4 (8.5)	4 (6.8)	1 (1.9)
Region, n (%)	(n = 641)	(n = 246)	(n = 87)	(n = 203)	(n = 105)	(n = 279)	(n = 119)	(n = 47)	(n = 59)	(n = 54)
North America	197 (30.7)	52 (21.1)	20 (23.0)	82 (40.4)	43 (41.0)	72 (25.8)	11 (9.2)	5 (10.6)	27 (45.8)	29 (53.7)
Europe	351 (54.8)	160 (65.0)	56 (64.4)	89 (43.8)	46 (43.8)	164 (58.8)	87 (73.1)	40 (85.1)	21 (35.6)	16 (29.6)
Australia/NZ/ others	93 (14.5)	34 (13.8)	11 (12.6)	32 (15.8)	16 (15.2)	43 (15.4)	21 (17.6)	2 (4.3)	11 (18.6)	9 (16.7)
Disease stage, n (%)	(n = 641)	(n = 246)	(n = 87)	(n = 203)	(n = 105)	(n = 279)	(n = 119)	(n = 47)	(n = 59)	(n = 54)
Unresectable IIIC/ M1a/M1b	241 (37.6)	93 (37.8)	26 (29.9)	81 (39.3)	41 (39.0)	109 (39.1)	42 (35.3)	14 (29.8)	29 (49.2)	24 (44.4)
M1c	400 (62.4)	153 (62.2)	61 (70.1)	122 (60.1)	64 (61.0)	170 (60.9)	77 (64.7)	33 (70.2)	30 (50.8)	30 (55.6)
ECOG PS, n (%)	(n = 640)	(n = 246)	(n = 87)	(n = 203)	(n = 104)	(n = 276)	(n = 118)	(n = 47)	(n = 59)	(n = 52)
0	413 (64.5)	171 (69.5)	50 (57.5)	130 (64.0)	62 (59.6)	202 (73.2)	93 (78.8)	35 (74.5)	41 (69.5)	33 (63.5)
1	227 (35.5)	75 (30.5)	37 (42.5)	73 (36.0)	42 (40.4)	73 (26.4)	25 (21.2)	12 (25.5)	18 (30.5)	18 (34.6)
2	0	0	0	0	0	1 (0.4)	0	0	0	1 (1.9)
LDH level, n (%)	(n = 604)	(n = 232)	(n = 80)	(n = 195)	(n = 97)	(n = 255)	(n = 109)	(n = 39)	(n = 53)	(n = 54)
Normal	350 (57.9)	136 (58.6)	40 (50.0)	119 (61.0)	55 (56.7)	140 (54.9)	55 (50.5)	24 (61.5)	32 (60.4)	29 (53.7)
Elevated ≤2 × ULN	165 (27.3)	65 (28.0)	23 (28.8)	55 (28.2)	22 (22.7)	82 (32.2)	32 (29.4)	10 (25.6)	19 (35.8)	21 (38.9)
Elevated >2 × ULN	89 (14.7)	31 (13.4)	17 (21.3)	21 (10.8)	20 (20.6)	33 (12.9)	22 (20.2)	5 (12.8)	2 (3.8)	4 (7.4)
Liver metastasis, n (%)	(n = 637)	(n = 244)	(n = 86)	(n = 202)	(n = 105)	(n = 279)	(n = 119)	(n = 47)	(n = 59)	(n = 54)
Yes	200 (31.4)	78 (32.0)	32 (37.2)	57 (28.2)	33 (31.4)	89 (31.9)	43 (36.1)	18 (38.3)	15 (25.4)	13 (24.1)
No	437 (68.6)	166 (68.0)	54 (62.8)	145 (71.8)	72 (68.6)	190 (68.1)	76 (63.9)	29 (61.7)	44 (74.6)	41 (75.9)
SLD, mm	(n = 631)	(n = 242)	(n = 86)	(n = 199)	(n = 104)	(n = 279)	(n = 119)	(n = 47)	(n = 59)	(n = 54)
Median (range)	67.0 (9 −1310)	64.0 (10−1310)	85.0 (9−335)	65.0 (10−489)	63.2 (10−280)	63.0 (10 −398)	63.0 (10−398)	59.0 (10−354)	63.0 (10−225)	73.0 (11−243)

ARA, acid-reducing agent; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; NZ, New Zealand; SLD, sum of longest diameter; ULN, upper limit of normal.

Table 2
Efficacy outcomes according to vemurafenib dose and ARA use.

Outcomes	Vemurafenib cohort				Cobimetinib + vemurafenib cohort			
	Full-dose vemurafenib + no ARA use (n = 246)	Full-dose vemurafenib + ARA use (n = 87)	Reduced-dose vemurafenib + no ARA use (n = 203)	Reduced-dose vemurafenib + ARA use (n = 105)	Full-dose vemurafenib + no ARA use (n = 119)	Full-dose vemurafenib + ARA use (n = 47)	Reduced-dose vemurafenib + no ARA use (n = 59)	Reduced-dose vemurafenib + ARA use (n = 54)
PFS								
n (events)	212	72	180	91	90	32	36	42
Median, months (95% CI)	5.13 (4.63–5.78)	4.93 (2.93–6.90)	5.19 (4.83–6.28)	5.03 (3.85–6.28)	12.48 (9.23–14.52)	8.64 (6.60–14.62)	16.69 (8.28–32.59)	9.49 (8.15–17.38)
Hazard ratio (95% CI)[a]	1.0 (Reference)	0.98 (0.74–1.30)	1.08 (0.87–1.34)	1.21 (0.92–1.59)	1.0 (Reference)	1.21 (0.78–1.88)	0.84 (0.53–1.32)	1.18 (0.76–1.83)
P value[a]	NA	0.8930	0.4763	0.1677	NA	0.4050	0.4487	0.4565
OS								
n (events)	175	61	140	75	72	22	29	31
Median, months (95% CI)	14.56 (12.52–17.32)	10.64 (8.87–15.54)	16.33 (13.01–19.39)	12.68 (9.20–17.28)	20.57 (17.25–29.11)	NE (16.49–NE)	32.59 (21.29–NE)	25.99 (19.78–31.61)
Hazard ratio (95% CI)[a]	1.0 (Reference)	1.06 (0.78–1.44)	1.01 (0.80–1.29)	1.27 (0.95–1.69)	1.0 (Reference)	0.80 (0.47–1.36)	0.86 (0.52–1.44)	1.10 (0.66–1.83)
P value[a]	NA	0.6972	0.9138	0.1082	NA	0.4045	0.5751	0.7155
ORR								
ORR, % (95% CI)	63.0 (56.6–69.1)	55.2 (44.1–65.9)	60.1 (53.0–66.9)	55.2 (45.2–65.0)	79.8 (71.5–86.6)	80.9 (66.7–90.9)	81.4 (69.1–90.3)	81.5 (68.6–90.8)
Odds ratio (95% CI)[b]	1.0 (Reference)	0.71 (0.41–1.21)	0.77 (0.50–1.17)	0.63 (0.38–1.07)	1.0 (Reference)	0.98 (0.36–2.64)	0.71 (0.27–1.88)	0.76 (0.27–2.13)
P value[b]	–	0.2085	0.2229	0.0853	–	0.9633	0.4944	0.6064

ARA, acid-reducing agent; CI, confidence interval; NA, not applicable; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

[a] Cox proportional hazards regression model adjusting for age, sex, race, geographic region, Eastern Cooperative Oncology Group performance status, lactate dehydrogenase level, disease stage, liver metastases and sum of longest diameter of target lesion.

[b] Logistic regression model adjusting for age, sex, race, geographic region, Eastern Cooperative Oncology Group performance status, lactate dehydrogenase level, disease stage, liver metastases, and sum of longest diameter of target lesion.

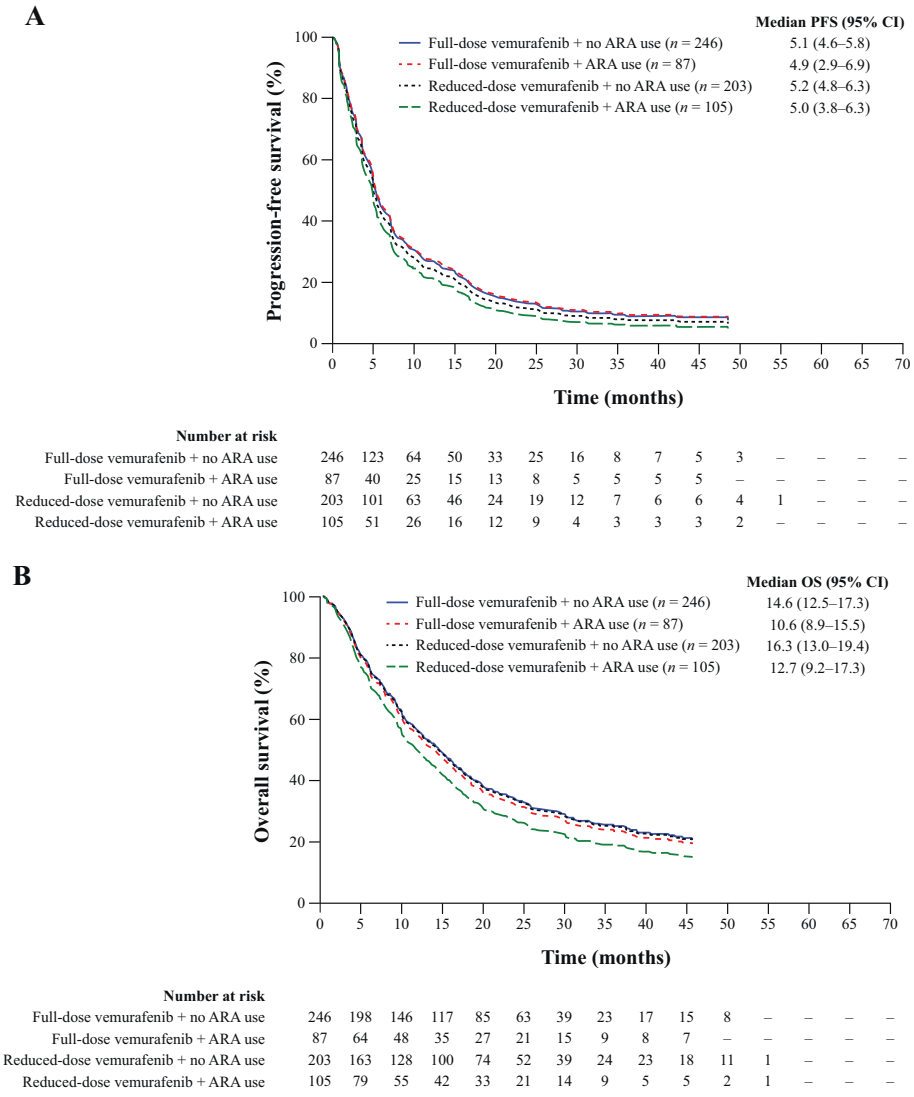

Fig. 1. Kaplan–Meier curves for (A) PFS and (B) OS according to vemurafenib dose and ARA use in the vemurafenib cohort ($n = 641$), adjusted for baseline covariates. ARA, acid-reducing agent; CI, confidence interval; OS, overall survival; PFS, progression-free survival.

enrolled previously untreated patients only, whereas BRIM-2 enrolled patients who had received prior systemic treatment for advanced disease, and BRIM-7 enrolled both previously treated and untreated patients. All analysed patients received vemurafenib 960 mg orally twice daily with or without cobimetinib 60 mg orally daily on a 21/7 schedule.

Each trial was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical and Laboratory Practice and with the approval of appropriate ethics committees. All participants provided written informed consent.

2.2. Efficacy analyses

The primary end-points for this analysis were PFS and OS, estimated using the Kaplan–Meier method. PFS was defined as the time from randomisation/treatment start date + 60 days to the first occurrence of disease progression or death from any cause. OS was defined as the time from randomisation/treatment start date + 60 days to death from any cause. The objective response rate (ORR), defined as complete or partial response based on Response Evaluation Criteria in Solid Tumours, was evaluated as a secondary end-point. Within each treatment cohort (vemurafenib monotherapy and cobimetinib plus vemurafenib), outcomes were evaluated across patient subgroups defined by vemurafenib dosing (full vs reduced dose) and concomitant ARA use (yes vs no) within the first 60 days after treatment initiation.

Four subgroups were defined: (1) full-dose vemurafenib + no ARA use, (2) full-dose vemurafenib + ARA use, (3) reduced-dose vemurafenib + no ARA use and (4) reduced-dose vemurafenib + ARA use. Full-dose vemurafenib was defined as no dose reduction of vemurafenib within 60 days after treatment initiation; reduced-dose

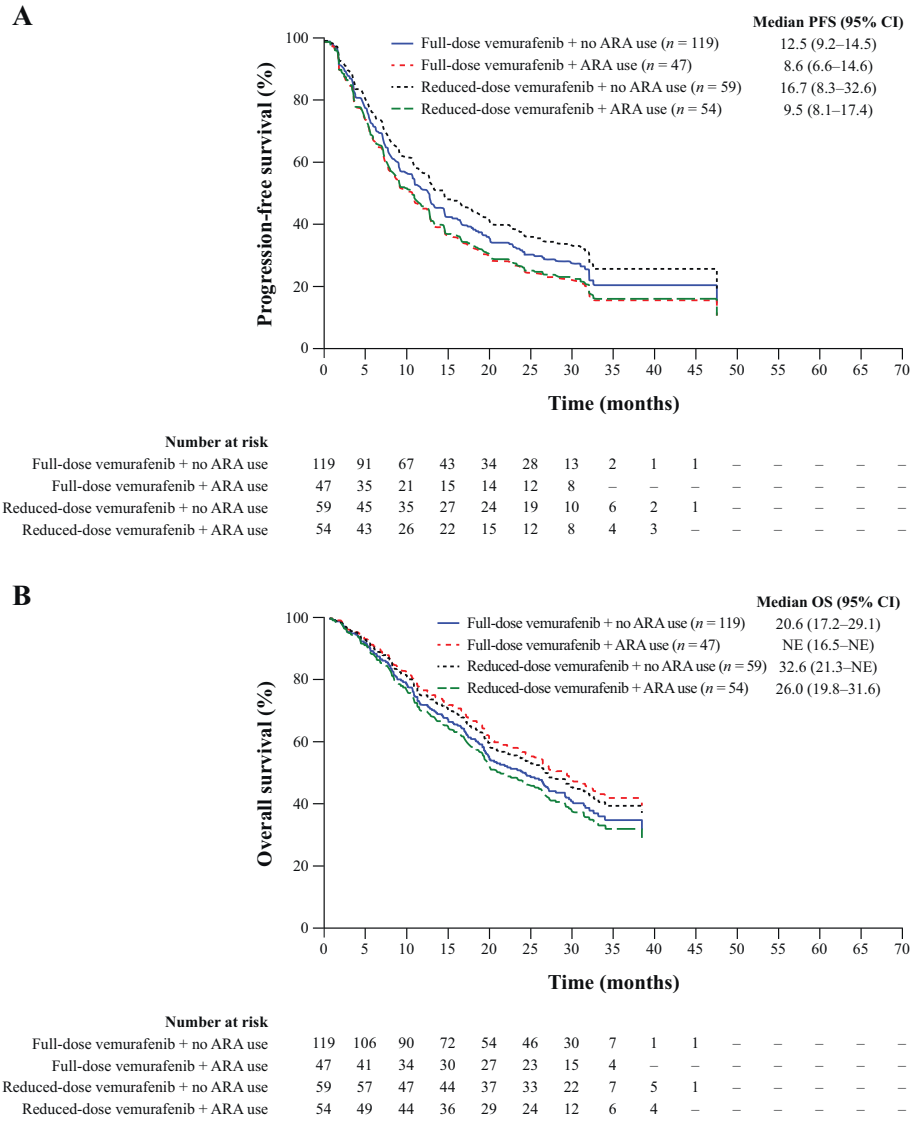

Fig. 2. Kaplan–Meier curves for (A) PFS and (B) OS according to vemurafenib dose and ARA use in the cobimetinib plus vemurafenib cohort (n = 279), adjusted for baseline covariates. ARA, acid-reducing agent; CI, confidence interval; OS, overall survival; PFS, progression-free survival; NE, not estimable.

vemurafenib was defined as reduction of vemurafenib dose to less than 960 mg twice daily (e.g. 720 mg or 480 mg twice daily) within 60 days after treatment initiation. ARA use was defined as concomitant use of any ARA (antacids/antacids not elsewhere classifiable, histamine H2-receptor antagonists and proton pump inhibitors) within 60 days after treatment initiation; no ARA use was defined as no use of any ARA within 60 days after treatment initiation.

Survival analyses used Cox proportional hazards regression models adjusted for patient demographics (age, sex, race and geographic region), ECOG performance status, baseline lactate dehydrogenase (LDH) level, disease stage, liver metastases and sum of longest diameters (SLDs) of target lesion. ORR analyses used logistic regression models, adjusted for the same covariates.

Analyses were conducted using data cut-off dates of 1 February 2012 for BRIM-2, 8 July 2015 for BRIM-3, 25 April 2016 for BRIM-7 and 20 June 2016 for coBRIM. All eligible patients, as defined for each protocol, who had been followed up for ≥60 days from the randomisation/treatment start date were included in the analysis.

2.3. Pharmacokinetic analyses

Vemurafenib concentrations were determined in plasma samples using validated liquid chromatography with tandem mass spectrometric detection methods by an independent laboratory (Covance, Madison, WI, USA). Within each treatment cohort (vemurafenib monotherapy and cobimetinib plus vemurafenib), steady-state concentrations (C_{ss}) of vemurafenib were evaluated on

Table 3
Efficacy outcomes according to ARA use.

All patients	Pooled cohorts		Vemurafenib cohort		Cobimetinib + vemurafenib cohort	
	No ARA use (n = 627)	ARA use (n = 293)	No ARA use (n = 449)	ARA use (n = 192)	No ARA use (n = 178)	ARA use (n = 101)
PFS						
n (events)	518	237	392	163	126	74
Median, months (95% CI)	6.31 (5.49–7.23)	6.60 (5.42–7.29)	5.19 (4.90–5.69)	5.00 (3.88–5.85)	12.75 (10.71–15.54)	9.20 (7.72–14.62)
Hazard ratio (95% CI)[a]	1.0 (Reference)	1.07 (0.91–1.26)	1.0 (Reference)	1.05 (0.87–1.28)	1.0 (Reference)	1.27 (0.93–1.73)
P value[a]	NA	0.4112	NA	0.5970	NA	0.1370
OS						
n (events)	416	189	315	136	101	53
Median, months (95% CI)	17.41 (16.10–19.25)	15.54 (13.47–19.98)	15.44 (13.04–17.41)	11.47 (9.89–14.75)	24.97 (19.35–31.41)	27.01 (20.01-NE)
Hazard ratio (95% CI)[a]	1.0 (Reference)	1.10 (0.91–1.31)	1.0 (Reference)	1.16 (0.94–1.43)	1.0 (Reference)	1.00 (0.70–1.44)
P value[a]	–	0.3250	–	0.1686	–	0.9856
ORR						
ORR, % (95% CI)	67.0 (63.2–70.7)	64.2 (58.4–69.7)	61.7 (57.0–66.2)	55.2 (47.9–62.4)	80.3 (73.7–85.9)	81.2 (72.2–88.3)
Odds ratio (95% CI)[b]	1.0 (Reference)	0.88 (0.64–1.21)	1.0 (Reference)	0.75 (0.52–1.10)	1.0 (Reference)	0.97 (0.48–1.96)
P value[b]	–	0.4358	–	0.1408	–	0.9397
Full-dose vemurafenib	No ARA use (n = 365)	ARA use (n = 134)	No ARA use (n = 246)	ARA use (n = 87)	No ARA use (n = 119)	ARA use (n = 47)
PFS						
n (events)	302	104	212	72	90	32
Median, months (95% CI)	6.51 (5.42–7.43)	6.44 (4.96–7.52)	5.13 (4.63–5.78)	4.93 (2.93–6.90)	12.48 (9.23–14.52)	8.64 (6.60–14.62)
Hazard ratio (95% CI)[a]	1.0 (Reference)	1.04 (0.82–1.33)	1.0 (Reference)	0.94 (0.70–1.26)	1.0 (Reference)	1.19 (0.76–1.87)
P value[a]	NA	0.7280	NA	0.6926	NA	0.4556
OS						
n (events)	247	83	175	61	72	22
Median, months (95% CI)	16.92 (14.56–18.76)	15.01 (10.64–24.38)	14.56 (12.52–17.32)	10.64 (8.87–15.54)	20.57 (17.25–29.11)	NE (16.49-NE)
Hazard ratio (95% CI)[a]	1.0 (Reference)	0.99 (0.75–1.29)	1.0 (Reference)	1.05 (0.77–1.44)	1.0 (Reference)	0.76 (0.44–1.33)
P value[a]	NA	0.9229	NA	0.7471	NA	0.3396
ORR						
ORR, % (95% CI)	68.5 (63.5–73.2)	64.2 (55.4–72.3)	63.0 (56.6–69.1)	55.2 (44.1–65.9)	79.8 (71.5–86.6)	80.9 (66.7–90.9)
Odds ratio (95% CI)[b]	1.0 (Reference)	0.77 (0.48–1.21)	1.0 (Reference)	0.69 (0.40–1.20)	1.0 (Reference)	0.84 (0.31–2.32)
P value[b]	NA	0.2554	NA	0.1890	NA	0.7410
Reduced-dose vemurafenib	No ARA use (n = 262)	ARA use (n = 159)	No ARA use (n = 203)	ARA use (n = 105)	No ARA use (n = 59)	ARA use (n = 54)
PFS						
n (events)	216	133	180	91	36	42
Median, months (95% CI)	6.21 (5.19–7.79)	7.00 (5.36–7.72)	5.19 (4.83–6.28)	5.03 (3.85–6.28)	16.69 (8.28–32.59)	9.49 (8.15–17.38)
Hazard ratio (95% CI)[a]	1.0 (Reference)	1.04 (0.83–1.31)	1.0 (Reference)	1.20 (0.91–1.57)	1.0 (Reference)	1.27 (0.78–2.07)
P value[a]	NA	0.7257	NA	0.1984	NA	0.3413

(*continued on next page*)

Table 3 (*continued*)

All patients	Pooled cohorts		Vemurafenib cohort		Cobimetinib + vemurafenib cohort	
	No ARA use (n = 627)	ARA use (n = 293)	No ARA use (n = 449)	ARA use (n = 192)	No ARA use (n = 178)	ARA use (n = 101)
OS						
n (events)	169	106	140	75	29	31
Median, months (95% CI)	18.63 (16.33–21.39)	17.28 (13.44–20.57)	16.33 (13.01–19.39)	12.68 (9.20–17.28)	32.59 (21.29–NE)	25.99 (19.78–31.61)
Hazard ratio (95% CI)[a]	1.0 (Reference)	1.17 (0.91–1.51)	1.0 (Reference)	1.31 (0.98–1.77)	1.0 (Reference)	1.14 (0.67–1.96)
P value[a]	NA	0.2319	NA	0.0725	NA	0.6239
ORR						
ORR, % (95% CI)	64.9 (58.8–70.7)	64.2 (56.2–71.6)	60.1 (53.0–66.9)	55.2 (45.2–65.0)	81.4 (69.1–90.3)	81.5 (68.6–90.8)
Odds ratio (95% CI)[b]	1.0 (Reference)	1.07 (0.68–1.68)	1.0 (Reference)	0.82 (0.48–1.40)	1.0 (Reference)	0.97 (0.33–2.88)
P value[b]	NA	0.7847	NA	0.4744	NA	0.9559

ARA, acid-reducing agent; CI, confidence interval; NA, not applicable; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

[a] Cox proportional hazards regression model adjusting for age, sex, race, geographic region, Eastern Cooperative Oncology Group performance status, lactate dehydrogenase level, disease stage, liver metastases and sum of longest diameters of target lesion.

[b] Logistic regression model adjusting for age, sex, race, geographic region, Eastern Cooperative Oncology Group performance status, lactate dehydrogenase level, disease stage, liver metastases and sum of longest diameter of target lesion.

Table 4
Vemurafenib concentrations on cycle 2, day 15, according to vemurafenib dose and ARA use.

Vemurafenib concentration, μg/mL	Vemurafenib cohort				Cobimetinib + vemurafenib cohort			
	Full-dose vemurafenib + no ARA use (n = 114)	Full-dose vemurafenib + ARA use (n = 30)	Reduced-dose vemurafenib + no ARA use (n = 33)	Reduced-dose vemurafenib + ARA use (n = 16)	Full-dose vemurafenib + no ARA use (n = 119)	Full-dose vemurafenib + ARA use (n = 33)	Reduced-dose vemurafenib + no ARA use (n = 29)	Reduced-dose vemurafenib + ARA use (n = 15)
Mean (SD)	57.8 (22.8)	61.3 (20.4)	45.0 (24.5)	64.3 (30.7)	48.5 (18.7)	47.9 (22.0)	41.8 (19.1)	37.2 (18.4)
Geometric mean (% CV)	51.0 (73.7)	58.1 (34.3)	25.5 (453.4)	54.8 (78.8)	43.3 (66.7)	41.4 (70.8)	28.6 (296.9)	25.5 (271.2)

ARA, acid-reducing agent; CV, coefficient of variation; SD, standard deviation.

cycle 2, day 15, using data from BRIM-7 and coBRIM across patient subgroups defined by vemurafenib dosing (full vs reduced dose) and concomitant ARA use (yes vs no) between cycle 1, day 1, and cycle 2, day 15. Full-dose vemurafenib was defined as no dose reduction or interruption of vemurafenib between cycle 1, day 1, and cycle 2, day 15; reduced-dose vemurafenib was defined as dose reduction of vemurafenib to less than 960 mg twice daily or dose interruption between cycle 1, day 1, and cycle 2, day 15. ARA use was defined as concomitant use of ARA at the time of initiation of study treatment through cycle 2, day 15, or initiation of ARA between cycle 1, day 1, and cycle 1, day 21; patients who discontinued ARA between cycle 1, day 1, and cycle 2, day 15, or initiated ARA use between cycle 1, day 22, and cycle 2, day 15, were excluded from the analysis. Sensitivity analysis was performed using vemurafenib concentrations at cycle 1, day 15.

3. Results

3.1. Patients

A total of 920 patients were included in the analysis: 641 in the vemurafenib cohort and 279 in the cobimetinib plus vemurafenib cohort. Of the 920 patients, 293 (31.8%) had concomitant use of any ARA within 60 days after vemurafenib treatment initiation, predominantly proton pump inhibitors (≥85% of patients with ARA use across cohorts; Supplementary Table S1). Small differences in the distribution of known prognostic factors (i.e. disease stage, LDH level, ECOG performance status and SLD) were noted across dose and ARA subgroups at baseline (Table 1).

3.2. Impact of vemurafenib dose and ARA use on efficacy outcomes

Overall, survival outcomes were similar across dose and ARA use subgroups; no significant differences in survival outcomes were observed across subgroups, with or without adjustment for known prognostic covariates (Table 2). In the vemurafenib cohort, adjusted hazard ratios for PFS were 0.98 (95% confidence interval [CI], 0.74–1.30; $P = 0.8930$) for full-dose vemurafenib + ARA use, 1.08 (95% CI, 0.87–1.34; $P = 0.4763$) for reduced-dose vemurafenib + no ARA use and 1.21 (95% CI, 0.92–1.59; $P = 0.1677$) for reduced-dose vemurafenib + ARA use, compared with full-dose vemurafenib + no ARA use (reference) (Table 2; Fig. 1). These findings were confirmed in the cobimetinib plus vemurafenib cohort, with adjusted hazard ratios for PFS of 1.21 (95% CI, 0.78–1.88; $P = 0.4050$) for full-dose vemurafenib + ARA use, 0.84 (95% CI, 0.53–1.32; $P = 0.4487$) for reduced-dose vemurafenib + no ARA use and 1.18 (95% CI, 0.76–1.83; $P = 0.4565$) for reduced-dose vemurafenib + ARA use, compared with full-dose vemurafenib + no ARA use (reference) (Table 2; Fig. 2). Results of OS analyses were similar and consistent with the results from PFS analyses (Table 2; Figs. 1 and 2). Unadjusted Kaplan–Meier curves for PFS and OS according to vemurafenib dose and ARA use in the vemurafenib cohort and the cobimetinib plus vemurafenib cohort are shown in Supplementary Fig. S1 and Supplementary Fig. S2, respectively. Comparable results were also observed when evaluating PFS and OS according to ARA use within vemurafenib dose cohorts (Table 3).

ORR was similar across dose and ARA use subgroups (Table 2). In the vemurafenib cohort, adjusted odds ratios for ORR were 0.71 (95% CI, 0.41–1.21; $P = 0.2085$) for full-dose vemurafenib + ARA use, 0.77 (95% CI, 0.50–1.17; $P = 0.2229$) for reduced-dose vemurafenib + no ARA use and 0.63 (95% CI, 0.38–1.07; $P = 0.0853$) for reduced-dose vemurafenib + ARA use, compared with full-dose vemurafenib + no ARA use (reference) (Table 2). In the cobimetinib plus vemurafenib cohort, adjusted odds ratios for ORR were 0.98 (95% CI, 0.36–2.64; $P = 0.9633$) for full-dose vemurafenib + ARA use, 0.71 (95% CI, 0.27–1.88; $P = 0.4944$) for reduced-dose vemurafenib + no ARA use, and 0.76 (95% CI, 0.27–2.13; $P = 0.6064$) for reduced-dose vemurafenib + ARA use compared with full-dose vemurafenib + no ARA use (reference) (Table 2). Comparable results were observed when evaluating ORR according to ARA use within vemurafenib dose cohorts (Table 3).

3.3. Impact of vemurafenib dose and concomitant ARA use on vemurafenib concentrations

A total of 389 patients were included in the analysis of vemurafenib concentrations on cycle 2, day 15 (193 in the vemurafenib cohort and 196 in the cobimetinib plus vemurafenib cohort). Of the 389 patients, 94 (24.2%) had concomitant use of any ARA between cycle 1, day 1, and cycle 2, day 15, most commonly proton pump inhibitors (≥80% of patients with ARA use across cohorts; Supplementary Table S2). ARA use did not influence systemic exposure to vemurafenib as measured by vemurafenib C_{ss}. Vemurafenib concentrations at cycle 2, day 15, were generally similar within dosing subgroups, regardless of ARA use in both the vemurafenib and cobimetinib plus vemurafenib cohorts (Table 4). Results were similar in sensitivity analyses using vemurafenib concentrations on cycle 1, day 15.

4. Discussion

In this large data set of patients with $BRAF^{V600}$ mutation–positive unresectable or metastatic melanoma

treated with vemurafenib or cobimetinib combined with vemurafenib, efficacy as assessed by tumour response and survival outcomes was not significantly affected by concomitant use of ARAs. In contrast with the findings of Knapen *et al.* [12], we found that PFS and OS outcomes were similar, regardless of vemurafenib dose or concomitant ARA use. Additionally, we found that ORR was similar across subgroups, providing further support of comparable clinical activity, regardless of the need for vemurafenib dose reduction or concomitant ARA use.

While many protein kinase inhibitors demonstrate pH-dependent solubility, vemurafenib demonstrates low solubility across all pH ranges [11]. Therefore, increasing gastric pH with ARAs would not necessarily be expected to affect the absorption of vemurafenib, although no formal pharmacokinetic studies have been conducted to evaluate potential drug–drug interactions between ARAs and vemurafenib. Our findings are consistent with these observations; ARA use did not influence systemic exposure based on analysis of steady-state vemurafenib concentrations, and no evidence of underexposure was observed in patients receiving concomitant ARAs. Observed steady-state concentrations are consistent with prior population pharmacokinetic modelling for vemurafenib [15].

Knapen *et al.* postulated that patients who are able to tolerate full-dose vemurafenib are underexposed to the drug and that vemurafenib efficacy may, therefore, be impaired in these patients [12]. Although substantial intrapatient and interpatient variability in vemurafenib exposure has been observed, population pharmacokinetic analyses have shown no relationship between exposure and survival outcomes, while clinically meaningful tumour response was regularly seen at vemurafenib C_{ss} ~25 μg/mL and above [15]. Consistent with these findings, our analysis demonstrated similar tumour response and survival outcomes between patients treated with full-dose versus reduced-dose vemurafenib in both the vemurafenib and the cobimetinib plus vemurafenib cohorts. Pharmacokinetic analyses revealed that vemurafenib C_{ss} remained in the range of concentrations associated with clinical activity in population pharmacokinetic analysis. Importantly, there was no evidence of underexposure to vemurafenib in patients receiving full-dose vemurafenib in either the vemurafenib cohort or in the cobimetinib plus vemurafenib cohort.

Strengths of our analysis include the large patient cohort (920 patients, compared with 112 patients in the analysis by Knapen *et al.*), prospective collection of data using a standardised schedule and method and availability of a large cohort of patients ($n = 389$) with serial plasma vemurafenib concentrations for pharmacokinetic analyses. However, our analysis is also subject to some limitations. As this was a retrospective exploratory analysis, treatment cohorts were not randomised; as a result, there were some differences in the distribution of demographics and baseline characteristics in our analysis. However, these differences were small and affected different characteristics between the vemurafenib and cobimetinib plus vemurafenib cohorts. Results of survival analyses were consistent between the vemurafenib and cobimetinib plus vemurafenib cohorts, suggesting that these small differences did not substantially affect the results of the analyses.

In conclusion, results of this retrospective pooled analysis suggest that ARAs can be used concomitantly with vemurafenib, alone or in combination with cobimetinib, without compromising the efficacy of vemurafenib.

Conflict of interest statement

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Appendix A. Supplementary data

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