Cobimetinib combined with vemurafenib in advanced BRAFV600-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial

Summary

background

The combination of cobimetinib with vemurafenib improves progression-free survival compared with placebo and vemurafenib in previously untreated patients with BRAFV600-mutant advanced melanoma, as previously reported in the coBRIM study. In this Article, we report updated efficacy results, including overall survival and safety after longer follow-up, and selected biomarker correlative studies.

Methods

In this double-blind, randomised, placebo-controlled, multicentre study, adult patients (aged ≥18 years) with histologically confirmed BRAFV600 mutation-positive unresectable stage IIIC or stage IV melanoma were randomly assigned (1:1) using an interactive response system to receive cobimetinib (60 mg once daily for 21 days followed by a 7-day rest period in each 28-day cycle) or placebo, in combination with oral vemurafenib (960 mg twice daily). Progression-free and overall survival were primary and secondary endpoints, respectively; all analyses were done on the intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT01689519, and is ongoing but no longer recruiting participants.

Findings

Between Jan 8, 2013, and Jan 31, 2014, 495 eligible adult patients were enrolled and randomly assigned to the cobimetinib plus vemurafenib group (n=247) or placebo plus vemurafenib group (n=248). At a median follow-up of 14·2 months (IQR 8·5–17·3), the updated investigator-assessed median progression-free survival was 12·3 months (95% CI 9·5–13·4) for cobimetinib and vemurafenib versus 7·2 months (5·6–7·5) for placebo and vemurafenib (HR 0·58 [95% CI 0·46–0·72], p<0·0001). The final analysis for overall survival occurred when 255 (52%) patients had died (Aug 28, 2015). Median overall survival was 22·3 months (95% CI 20·3–not estimable) for cobimetinib and vemurafenib versus 17·4 months (95% CI 15·0–19·8) for placebo and vemurafenib (HR 0·70, 95% CI 0·55–0·90; p=0·005). The safety profile for cobimetinib and vemurafenib was tolerable and manageable, and no new safety signals were observed with longer follow-up. The most common grade 3–4 adverse events occurring at a higher frequency in patients in the cobimetinib and vemurafenib group compared with the vemurafenib group were γ-glutamyl transferase increase (36 [15%] in the cobimetinib and vemurafenib group vs 25 [10%] in the placebo and vemurafenib group), blood creatine phosphokinase increase (30 [12%] vs one [<1%]), and alanine transaminase increase (28 [11%] vs 15 [6%]). Serious adverse events occurred in 92 patients (37%) in the cobimetinib and vemurafenib group and 69 patients (28%) in the vemurafenib group. Pyrexia (six patients [2%]) and dehydration (five patients [2%]) were the most common serious adverse events reported in the cobimetinib and vemurafenib group. A total of 259 patients have died: 117 (47%) in the cobimetinib and vemurafenib group and 142 (58%) in the vemurafenib group. The primary cause of death was disease progression in most patients: 109 (93%) of 117 in the cobimetinib and vemurafenib group and 133 (94%) of 142 in the vemurafenib group.

Interpretation

These data confirm the clinical benefit of cobimetinib combined with vemurafenib and support the use of the combination as a standard first-line approach to improve survival in patients with advanced BRAFV600-mutant melanoma.

Funding

F Hoffmann-La Roche–Genentech.

Introduction

Around 40% of cutaneous melanomas harbour mutations in the BRAF gene, resulting in constitutive activation of the mitogen-activated protein kinase (MAPK) pathway. 1 ; 2 The treatment of advanced BRAF-mutant melanoma has been revolutionised by the introduction of new therapeutic agents such as the BRAF inhibitors vemurafenib or dabrafenib. These drugs have improved outcomes for patients with advanced BRAFV600-mutant melanoma, with high proportions of patients achieving a tumour response and improved progression-free and overall survival compared with cytotoxic chemotherapy. 3; 4; 5 ; 6 Acquired resistance to BRAF inhibitor monotherapy is the most common cause of treatment failure, limiting median progression-free survival duration to around 6 months. 3 ; 4 Although a diverse range of resistance mechanisms has been suggested, most mechanisms of resistance involve reactivation of the MAPK pathway mediated through MEK. 7; 8; 9; 10 ; 11

Research in context

Evidence before this study

We searched PubMed up until Sept 30, 2015, with the terms “clinical trials”, “advanced melanoma”, “BRAF inhibitor”, and “MEK inhibitor”. We also searched conference abstracts from the American Society of Clinical Oncology and the European Society of Medical Oncology with the same terms. The results showed that, in addition to the combination of vemurafenib and cobimetinib, BRAF and MEK inhibitor combinations of dabrafenib and trametinib, LGX818 and MEK162 (encorafenib and binimetinib), have been or are being assessed in patients with advanced BRAFV600-mutant melanoma. Data from two phase 3 studies have shown a benefit for the trametinib and dabrafenib combination, whereas other combinations resulted in promising activity in early-phase trials.

Added value of this study

We report the protocol-specified overall survival analysis of a double-blind, multicentre, placebo-controlled phase 3 study assessing the efficacy and safety of cobimetinib and vemurafenib compared with placebo and vemurafenib in previously untreated patients with BRAFV600 mutation-positive unresectable stage IIIC or IV melanoma. Effectiveness of the combination of cobimetinib and vemurafenib was superior to that of vemurafenib plus placebo for all efficacy endpoints and across a wide range of patient baseline characteristics, including in patients with normal baseline lactate dehydrogenase concentrations. To our knowledge, this is the first phase 3 comparative trial to do biomarker analyses to study the effect of baseline values of Ki67, pERK, and pS6 on median overall survival in both treatment groups.

Implications of all the available evidence

These data confirm the clear and definitive clinical benefit of the addition of cobimetinib to vemurafenib in patients with advanced BRAFV600-mutant melanoma and support the use of the combination as a standard targeted therapy for first-line treatment in this population.

Combined BRAF and MEK inhibition enables greater inhibition of the MAPK pathway, and combination therapy with cobimetinib (a MEK inhibitor) and vemurafenib (a BRAF inhibitor) has resulted in clinical benefit.12 ; 13 The randomised, double-blind, phase 3 coBRIM study13 compared the combination of cobimetinib and vemurafenib versus placebo and vemurafenib in previously untreated patients with advanced melanoma harbouring BRAFV600 mutations. In the primary analysis, with a median follow-up of 7·3 months (range 0·5–16·5), cobimetinib and vemurafenib significantly improved progression-free survival compared with vemurafenib alone (median 9·9 months [95% CI 9·0–not estimable] vs 6·2 months [5·6–7·4], hazard ratio [HR] 0·51 [0·39–0·68]; p<0·0001). Improvement in progression-free survival was recorded in every clinical subgroup assessed, including patients with disease characteristics recognised as poor prognostic factors: notably, increased lactate dehydrogenase (LDH) concentrations 14 and stage M1c disease. 14 ; 15 The proportion of patients achieving an objective response was also significantly greater in the combination therapy group compared with the vemurafenib plus placebo group (68% with cobimetinib and vemurafenib vs 45% with vemurafenib plus placebo; p<0·0001). 13 Another BRAF inhibitor and MEK inhibitor combination—dabrafenib and trametinib—has resulted in efficacy similar to that of the combination of cobimetinib and vemurafenib with respect to several efficacy measures, including proportion of patients achieving an overall response, progression-free survival, and overall survival, compared with either dabrafenib 16 ; 17 or vemurafenib18 as monotherapy in phase 3 trials in advanced melanoma.

In this Article, we report the results of an updated progression-free survival analysis and the final overall survival analysis for the coBRIM trial. Additionally, we report the results of exploratory analyses correlating molecular markers of MAPK and PI3K pathway activation in pre-treatment tumour samples with overall survival.

Methods

Study design and participants

coBRIM is an ongoing double-blind, multicentre, placebo-controlled, phase 3 study assessing the efficacy and safety of the combination of cobimetinib and vemurafenib, compared with placebo and vemurafenib, in previously untreated patients with BRAFV600 mutation-positive unresectable stage IIIC or stage IV melanoma. The study is being done at 135 clinical sites in 19 countries: the USA, Australia, New Zealand, Israel, Canada, and 14 countries in Europe (including Russia). The complete methods of the study have previously been published and the protocol is available online.13

Eligible patients were aged 18 years and older with histologically confirmed unresectable stage IIIC or stage IV melanoma harbouring a BRAFV600 mutation detected with the use of a real-time PCR assay (cobas 4800 BRAFV600 Mutation Test [Roche Molecular Systems, Branchburg, NJ, USA]); measurable disease according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.119 assessed by computed tomography; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and adequate haematological, hepatic, renal, and cardiac function. Life expectancy of eligible patients was at least 12 weeks. The cobas 4800 BRAFV600 Mutation Test has been approved by the US Food and Drug Administration (FDA) and the results were confirmed by subsequent deep sequencing. Patients with previously treated brain metastases were eligible if they had a history of stable disease for at least 3 weeks.

This trial is being done according to the provisions of the Declaration of Helsinki and its amendments and relevant Good Clinical Practice guidelines after approval by the local institutional review board, independent ethics committee, or research ethics board of all participating study sites. All study participants provided written informed consent. An independent data and safety monitoring committee did regular reviews and evaluations of safety data.

Randomisation and masking

Enrolled patients were randomly assigned 1:1 using a stratified permuted block randomisation scheme via an interactive response system (Perceptive Informatics [now Parexel International], Deerfield, IL, USA). Patients were stratified according to the American Joint Committee on Cancer stage (unresectable stage IIIc, M1a, and M1b vs stage M1c) and by geographical region (North America vs Europe vs Australia/New Zealand/other). The investigators, patients, and sponsor were masked to treatment assignment.

Procedures

Patients received either oral cobimetinib (60 mg once daily for 21 days followed by a 7-day rest period in each 28-day cycle) or placebo, in combination with oral vemurafenib (960 mg twice daily). Treatment continued until withdrawal of consent, the occurrence of unacceptable adverse events, or disease progression. Continuation of study treatment after disease progression or crossover to the alternate treatment was not allowed. Modification of the cobimetinib or vemurafenib dose was allowed for management of adverse events, with guidelines for events of prespecified type and grade (see protocol). Up to two dose-level reductions were allowed: for vemurafenib, reduction to 720 mg twice daily or to 480 mg twice daily; for cobimetinib, reduction to 40 mg once daily or to 20 mg once daily. Dose reduction of each study drug was independent of the other study drug. Dose re-escalation was not allowed.

Tumour assessments were done with CT scans at baseline and every 8 weeks thereafter. Haematology, chemistry, and liver laboratory tests were done at baseline, on days 1 and 15 of cycles 1–6, then on day 1 of subsequent cycles. Patient-reported quality of life outcomes were measured at baseline, days 1 and 15 of cycles 1 and 2, and day 1 of every other cycle thereafter (28-day cycles) until patient withdrawal or end of study. An independent data and safety monitoring committee regularly reviewed and evaluated the safety data.

Baseline expression of proteins Ki67 (#790-4286, Ventana Medical Systems Inc, Tucson, AZ, USA), pERK T202/Y204 (#4370, Cell Signaling Technology Inc, Danvers, MA, USA), and pS6 S235/236 (#4858, Cell Signaling Technology Inc) was assessed at a central laboratory (Histogenex, Antwerp, Belgium) with immunohistochemistry. Ki67 expression was quantified as the percentage of tumour nuclei that were positive for Ki67. For assessment of pERK and pS6, staining intensity (on a scale from 0–3) and staining percentage were quantified in the cytoplasmic compartment, and a histoscore (H-score, on a scale from 0–300) was calculated.20 Other biomarker expression levels were assessed on-treatment or at progression only for patients who consented to undergo optional biopsy at these prespecified timepoints.

Outcomes

The primary endpoint was progression-free survival as assessed by the investigator, according to RECIST version 1.1.15 Progression-free survival was defined as the time between the date of

randomisation and the date of the first documented event of disease progression or death, whichever occurred first. Secondary endpoints were overall survival, confirmed objective response (defined as a complete or partial response) according to RECIST version 1.1, response duration, progression-free survival assessed by an independent review facility, health-related quality of life as assessed by the European Organisation for Research and Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30),21 and safety. Prespecified biomarker analyses were exploratory.

Statistical analysis

The primary analysis of progression-free survival has previously been reported.13 We estimated that 206 progression events would provide at least 95% power to detect a hazard ratio for death or progression of 0·55, with a two-sided α of 0·05 (an increase in median progression-free survival from 6 months for placebo and vemurafenib to 11 months for cobimetinib and vemurafenib). The prespecified number of progression events (n=206) was reached in May, 2014, and results of the primary analysis for progression-free survival were reported after a median follow-up of 7·3 months (range 0·5–16·5).13 In this Article, we present the results of an updated progression-free survival analysis with a longer follow-up (median follow-up 14·2 months [IQR 8·5–17·3]) with the data cutoff date of Jan 16, 2015, which was around 1 year after the final patient was enrolled into the study.

For the overall survival analysis, we estimated that 250 survival events would provide 80% power to detect a hazard ratio for death of 0·70 (improvement in median overall survival from 15 months in the placebo and vemurafenib group to 21·4 months in the cobimetinib and vemurafenib group) with a two-sided α of 0·05. The type I error rate for the overall survival analysis was controlled at the 0·05 level by use of the Lan-DeMets implementation of the O'Brien-Fleming use function. We did the interim analysis for overall survival at the time of the primary analysis of progression-free survival, and the estimate of overall survival was not significant.13 85 patients had died at the time of the interim overall survival analysis: 34 in the cobimetinib and vemurafenib group and 51 in the placebo and vemurafenib group. The threshold for significance for the final overall survival analysis was a two-sided p value of less than 0·0499. The required number of deaths for the final overall survival analysis (n=250) was reached in August, 2015, and the data cutoff date for the final overall survival analysis was Aug 28, 2015, at which time 255 deaths had occurred.

We did all efficacy analyses in the intention-to-treat population. We used the Kaplan-Meier method to estimate rates of progression-free survival and overall survival; a stratified log-rank test for treatment comparisons; an unstratified log-rank test for the subgroup analyses; and a Cox model to estimate the hazard ratio and corresponding 95% CI. We did non-stratified analyses for progression-free survival and overall survival as sensitivity analyses. We assessed the proportional hazards assumption graphically by assessing the cumulative hazard function. The updated proportion of patients who achieved an overall response, and 95% CIs are reported for both treatment groups. We also used the Kaplan-Meier method to calculate medians and IQRs for duration of response. SAS version 9.2 was used for all analyses.

Quality of life data were evaluable through to cycle 8 day 1, after which there were less than 25% of patients with baseline quality of life scores who remained enrolled in the vemurafenib group, which was too few patients to allow meaningful conclusions to be drawn. We assessed change from baseline in each domain score for each timepoint by treatment group using descriptive statistics. A change of score from baseline of greater than or equal to ten points was judged to be clinically meaningful, and formal statistical comparisons were not done. We did safety analyses on the safety population, which consisted of all patients who received at least one dose of study treatment.

The effect of Ki67, pERK, and p56 biomarker expression on overall survival was analysed as a continuous variable and by comparing patients with expression above and below the median protein expression using Cox proportional hazards modelling.

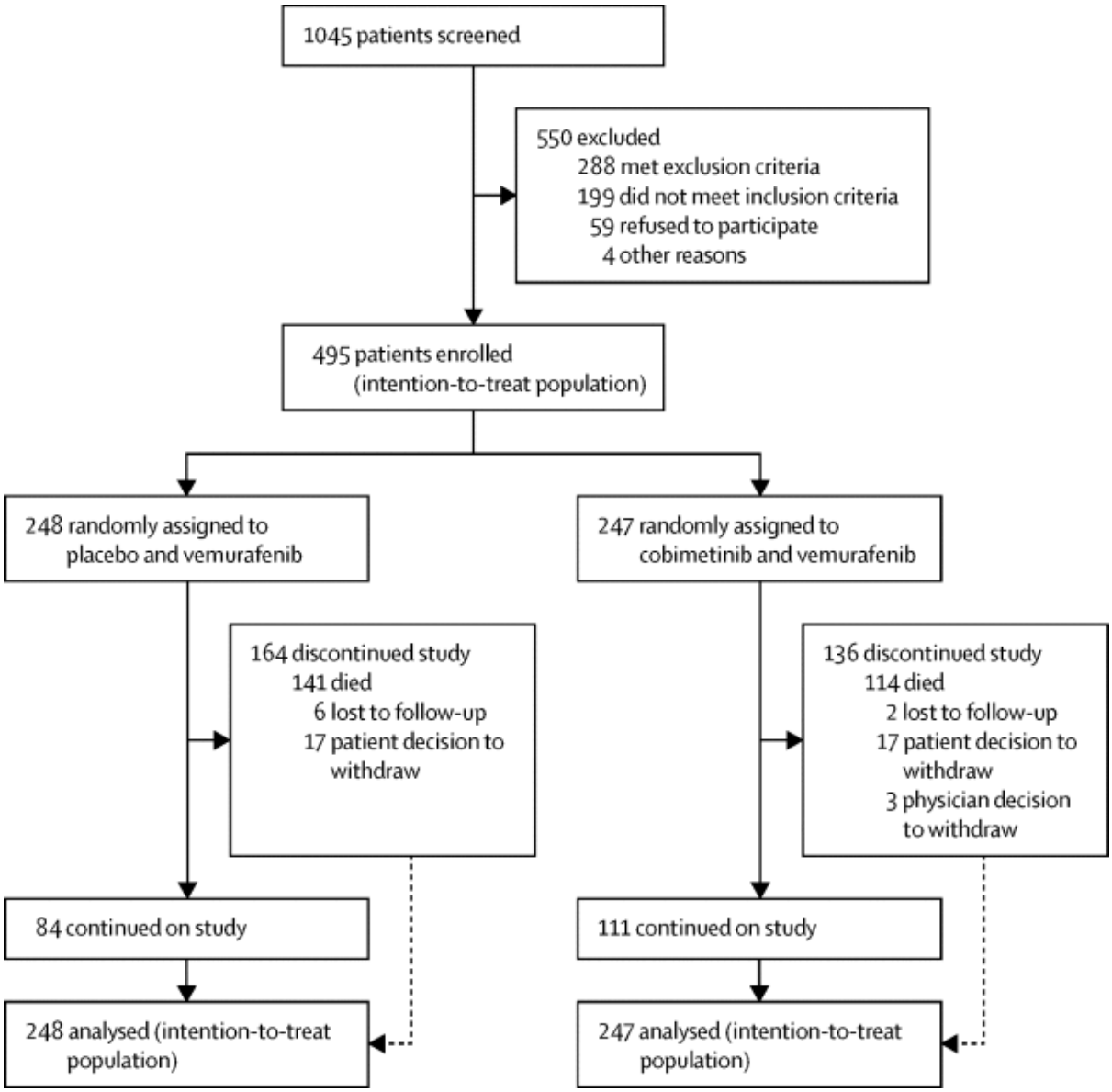
This study is registered with ClinicalTrials.gov, number NCT01689519. The study is closed to further enrolment, and patients already in the study will continue to be followed for long-term outcomes.

Role of the funding source

F Hoffmann-La Roche–Genentech funded, administered, and sponsored the study, which was designed by the academic authors in conjunction with Roche representatives. Data were collected by Roche and analysed in collaboration with the authors. The authors vouch for the accuracy and completeness of the data; YY, IC, JJH, MW, DOK, and IR had full access to all the raw data. JL, GAM, PAA, YY, IC, MW, DOK, and IR prepared the first draft of the report, and all authors contributed to subsequent drafts and made the decision to submit the report for publication. Editorial support was provided by ApotheCom (San Francisco, CA, USA), and was funded by F Hoffmann-La Roche–Genentech. The corresponding author had full access to all the data and had final responsibility to submit for publication.

Results

Between Jan 8, 2013, and Jan 31, 2014, 1045 patients were screened, and 495 eligible patients with BRAFV600-mutant metastatic melanoma were randomly assigned to receive cobimetinib and vemurafenib (n=247) or placebo and vemurafenib (n=248; figure 1). The most common cause of screening failure was a negative test result for the BRAFV600 mutation. Baseline patient characteristics were generally well balanced between the two study groups (table 1).13 Of those patients in the cobimetinib and vemurafenib group who remained on treatment at 1 year, the mean of the cumulative doses of cobimetinib and vemurafenib delivered was 87·2% (SD 18·4) and 84·6% (19·8) of the starting doses, respectively, and for those patients who remained on treatment at 2 years, the average of the cumulative doses delivered was 88·2% (SD 16·2) and 84·7% (19·7).



Trial profileData cutoff Aug 28, 2015. Adapted with permission from Larkin and ...

Figure 1.

Trial profile

Data cutoff Aug 28, 2015. Adapted with permission from Larkin and colleagues,13 with permission from the Massachusetts Medical Society.

Table 1.
Baseline characteristics

	Placebo and vemurafenib (n=248)	Cobimetinib and vemurafenib (n=247)
Age, years	55 (25–85)	56 (23–88)
Sex		
Men	140 (56%)	146 (59%)
Women	108 (44%)	101 (41%)
Race		
White	235 (95%)	227 (92%)
Other	13 (5%)	20 (8%)
Geographical region		
Australia/New Zealand/other	38 (15%)	40 (16%)
Europe	184 (74%)	182 (74%)
North America	26 (10%)	25 (10%)
ECOG performance status*		
0	164/244 (67%)	184/243 (76%)
1	80/243 (33%)	58/243 (24%)
Metastatic status†		
Unresectable stage IIIC	13 (5%)	21 (9%)
M1a	40 (16%)	40 (16%)
M1b	42 (17%)	40 (16%)
M1c	153 (62%)	146 (59%)
Raised lactate dehydrogenase concentration‡	104/242 (43%)	112/242 (46%)
History of brain metastases	2 (<1%)	1 (<1%)
BRAF mutation subtype§		
V600E	174 (70%)	170 (69%)
V600K	32 (13%)	24 (10%)
Not done¶	42 (17%)	53 (22%)

Data are median (range) or n (%). ECOG=Eastern Cooperative Oncology Group.

*
One patient randomly assigned to the vemurafenib and cobimetinib group had performance status 2 at baseline (this was discovered after randomisation before the first dose was received).

†
The criteria of the American Joint Committee on Cancer for distant metastasis are as follows: M0=no detectable evidence of distant metastases; M1a=metastases to skin, subcutaneous tissue, or distant lymph nodes; M1b=metastases to lung; and M1c=metastases to all other visceral sites or distant metastases to any site combined with an increased serum lactate dehydrogenase concentration.

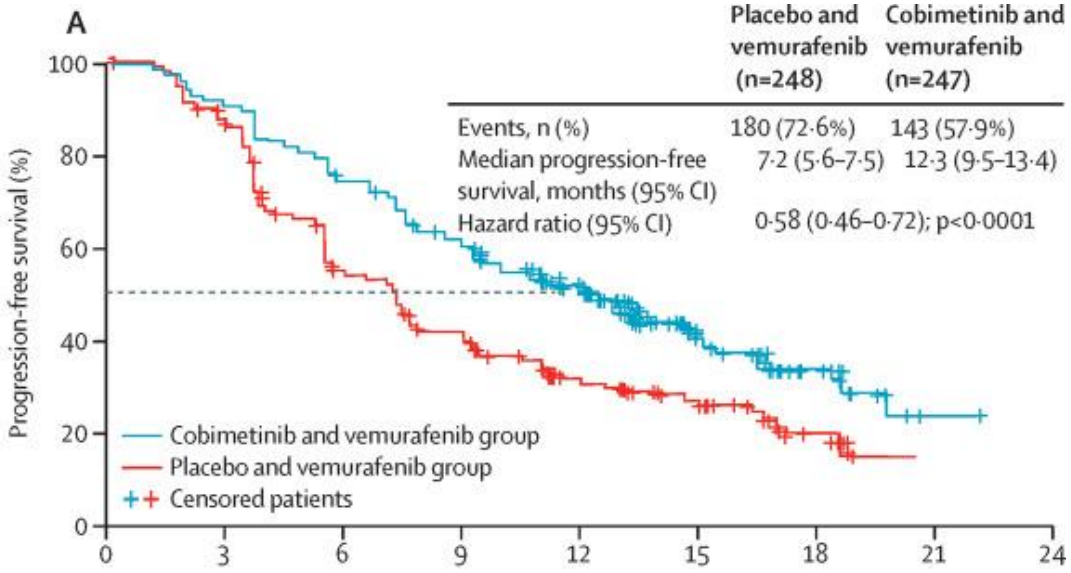
‡§

After randomisation, we further characterised tumour DNA to identify specific V600 mutations using next-generation sequencing.

¶
"Not done" refers to cases in which either no tumour sample was provided for mutation subtyping or sequencing could not be done on the tissue provided.

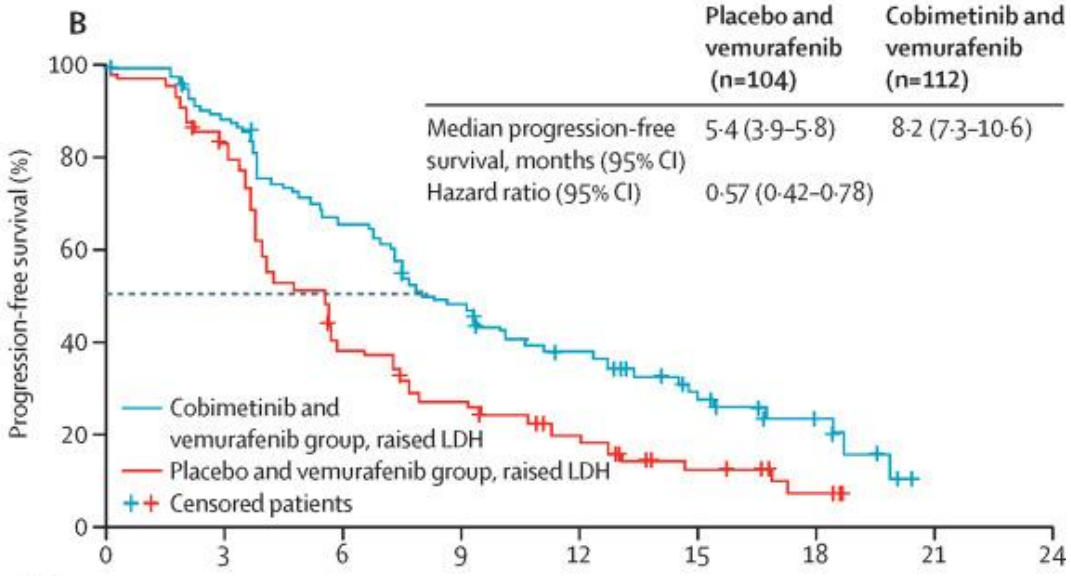
An updated analysis of progression-free survival and response data (data cutoff on Jan 16, 2015) was done after a median follow-up of 14·2 months (IQR 8·5–17·3). The analysis of the cumulative hazard function showed that the proportional hazards assumption was not violated. The median duration of cobimetinib treatment for patients in the cobimetinib and vemurafenib group was 9·0 months (95% CI 8·1–10·2) and median duration of vemurafenib treatment for patients in this group was 9·2 months (8·4–11·0). The median duration of vemurafenib treatment for patients in the vemurafenib and placebo group was 5·8 months (95% CI 5·5–7·4).

Median investigator-assessed progression-free survival was significantly longer in patients treated with cobimetinib and vemurafenib than in those treated with vemurafenib and placebo (stratified analysis; figure 2A). Figure 3 shows the hazard ratios (HRs) for progression-free survival in different patient subgroups (unstratified analysis). Survival curves for patients with lactate dehydrogenase concentrations of the upper limit of normal or higher are shown in figure 2B, and those with lactate dehydrogenase concentrations below the upper limit of normal are in figure 2C.



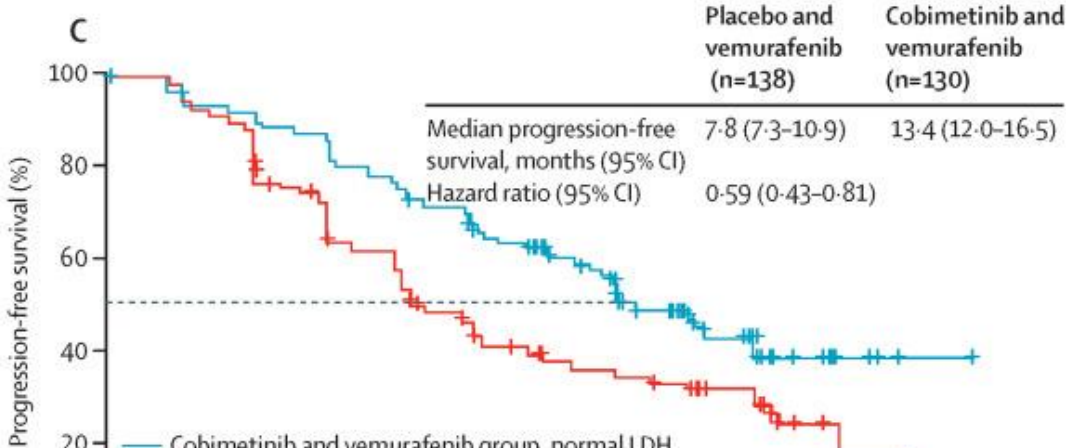
	Placebo and vemurafenib (n=248)	Cobimetinib and vemurafenib (n=247)
Events, n (%)	180 (72·6%)	143 (57·9%)
Median progression-free survival, months (95% CI)	7·2 (5·6–7·5)	12·3 (9·5–13·4)
Hazard ratio (95% CI)	0·58 (0·46–0·72); p<0·0001	

Number at risk									
Cobimetinib and vemurafenib group	247	215	174	142	104	46	19	1	..
Placebo and vemurafenib group	248	205	120	87	54	30	13	0	..



	Placebo and vemurafenib (n=104)	Cobimetinib and vemurafenib (n=112)
Median progression-free survival, months (95% CI)	5·4 (3·9–5·8)	8·2 (7·3–10·6)
Hazard ratio (95% CI)	0·57 (0·42–0·78)	

Number at risk									
Cobimetinib and vemurafenib group, raised LDH	112	96	70	50	35	16	8	..	..
Placebo and vemurafenib group, raised LDH	104	81	37	26	15	8	3	..	..



	Placebo and vemurafenib (n=138)	Cobimetinib and vemurafenib (n=130)
Median progression-free survival, months (95% CI)	7·8 (7·3–10·9)	13·4 (12·0–16·5)
Hazard ratio (95% CI)	0·59 (0·43–0·81)	

Progression-free survival(A) Kaplan-Meier curve of progression-free survival in ...
Figure 2.
Progression-free survival
(A) Kaplan-Meier curve of progression-free survival in all patients. (B) Progression-free survival in patients with raised (greater than institutional upper limit of normal) baseline LDH levels and (C) normal LDH levels. Unstratified analysis. HR=hazard ratio. LDH=lactate dehydrogenase.

	Placebo and vemurafenib (n=248)		Cobimetinib and vemurafenib (n=247)		Hazard ratio (95% CI)
	Events (n)/ total (N)	Median progression-free survival, months (95% CI)	Events (n)/ total (N)	Median progression-free survival, months (95% CI)	
Disease stage IIIC/M1a/M1b, or M1c					
M1c	128/153	5·5 (3·9–5·8)	94/146	9·5 (7·9–12·9)	0·52 (0·40–0·68)
Unresectable stage IIIC/M1a/M1b	52/95	11·0 (7·8–15·0)	49/101	13·4 (11·2–NE)	0·73 (0·49–1·08)
Age group (years)					
<65	128/179	7·2 (5·7–7·6)	107/183	12·6 (9·3–14·7)	0·61 (0·47–0·79)
≥65	52/69	5·6 (3·9–9·4)	36/64	11·2 (8·6–16·5)	0·52 (0·34–0·80)
Sex					
Women	72/108	7·5 (5·7–9·2)	52/101	12·9 (10·0–18·4)	0·57 (0·40–0·82)
Men	108/140	5·7 (5·5–7·4)	91/146	11·1 (9·0–13·0)	0·58 (0·44–0·77)
Geographical region					
Australia/New Zealand/Israel	26/38	7·4 (3·7–12·0)	20/40	13·3 (10·0–18·7)	0·57 (0·32–1·03)
Europe	138/184	6·0 (5·6–7·5)	107/182	11·2 (9·2–14·8)	0·58 (0·45–0·75)
North America	16/26	7·5 (6·0–11·0)	16/25	11·2 (5·5–14·9)	0·57 (0·28–1·17)
ECOG performance status					
0	110/164	7·6 (7·0–9·3)	100/184	12·9 (9·7–15·0)	0·65 (0·49–0·85)
1	66/80	5·5 (4·1–6·0)	41/58	10·0 (7·8–12·6)	0·53 (0·35–0·78)
Lactate dehydrogenase concentration					
Raised	85/104	5·4 (3·9–5·8)	78/112	8·2 (7·3–10·6)	0·57 (0·42–0·78)
Normal	90/138	7·8 (7·3–10·9)	65/130	13·4 (12·0–16·5)	0·59 (0·43–0·81)
Previous adjuvant therapy					
Yes	16/24	7·2 (4·8–16·7)	12/24	16·5 (8·2–NE)	0·60 (0·28–1·27)
No	164/224	7·2 (5·6–7·6)	131/223	11·2 (9·3–13·4)	0·59 (0·47–0·74)
***BRAF*^{V600} mutation status**					
V600E	126/174	7·2 (5·6–7·7)	102/170	10·6 (9·0–13·0)	0·64 (0·49–0·83)
V600K	24/32	6·0 (3·8–9·5)	14/24	12·4 (9·0–NE)	0·52 (0·27–1·02)
Overall*	**180/248**	**7·2 (5·6–7·5)**	**143/247**	**12·3 (9·5–13·4)**	**0·59 (0·47–0·73)**

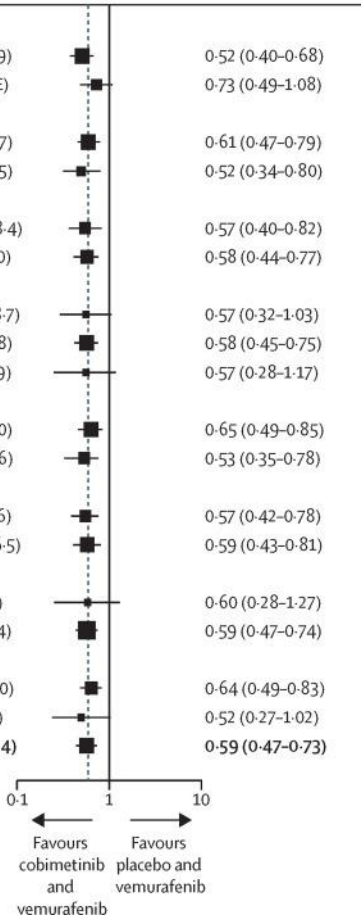


Figure 3.
Progression-free survival
Prespecified subgroup analysis. Data cutoff Jan 16, 2015. NE=not estimable. ECOG=Eastern Cooperative Oncology Group. LDH=lactate dehydrogenase. *Unstratified analysis.

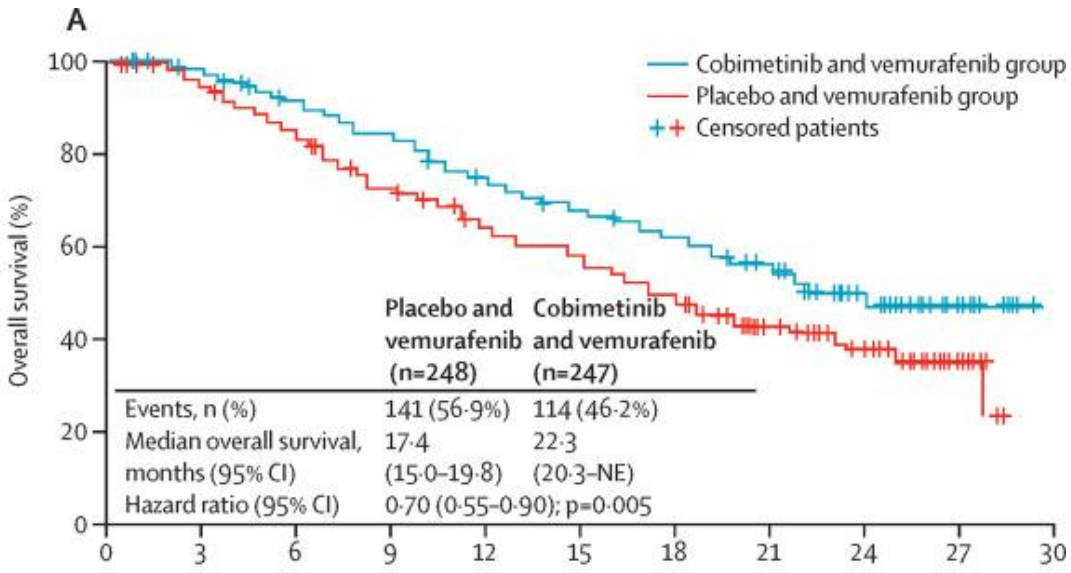
At the data cutoff date of Jan 16, 2015, 172 (70%) of 247 patients in the cobimetinib and vemurafenib group had an objective response, compared with 124 (50%) of 248 in the vemurafenib group (appendix p 32, table 2). Most responses were seen by the time of the first tumour assessment at 8 weeks.13 Median duration of response was 13·0 months (95% CI 11·1–16·6) in the cobimetinib and vemurafenib group and 9·2 months (95% CI 7·5–12·8) in the vemurafenib plus placebo group. 84 (49%) of 172 patients in the cobimetinib plus vemurafenib group who had achieved a response progressed versus 73 (59%) of 124 patients in the vemurafenib plus placebo group. The median duration of response for patients who had achieved a complete response was 18·1 months (95% CI 14·8–not estimable) in the cobimetinib and vemurafenib group and 16·9 months (16·9–not estimable) in the placebo plus vemurafenib group.

Table 2.
Best response

	Placebo and vemurafenib (n=248)	**Cobimetinib and vemurafenib (n=247)**
Complete response, n (%)	26 (10%)	39 (16%)
Partial response, n (%)	98 (40%)	133 (54%)
Stable disease, n (%)	92 (37%)	44 (18%)
Progressive disease, n (%)	25 (10%)	19 (8%)
Not done*	6 (2%)	12 (5%)
Complete or partial response, n (%; 95% CI)	124 (50%; 43·6–56·4)	172 (70%; 63·5–75·3)
p value	Reference	<0·0001

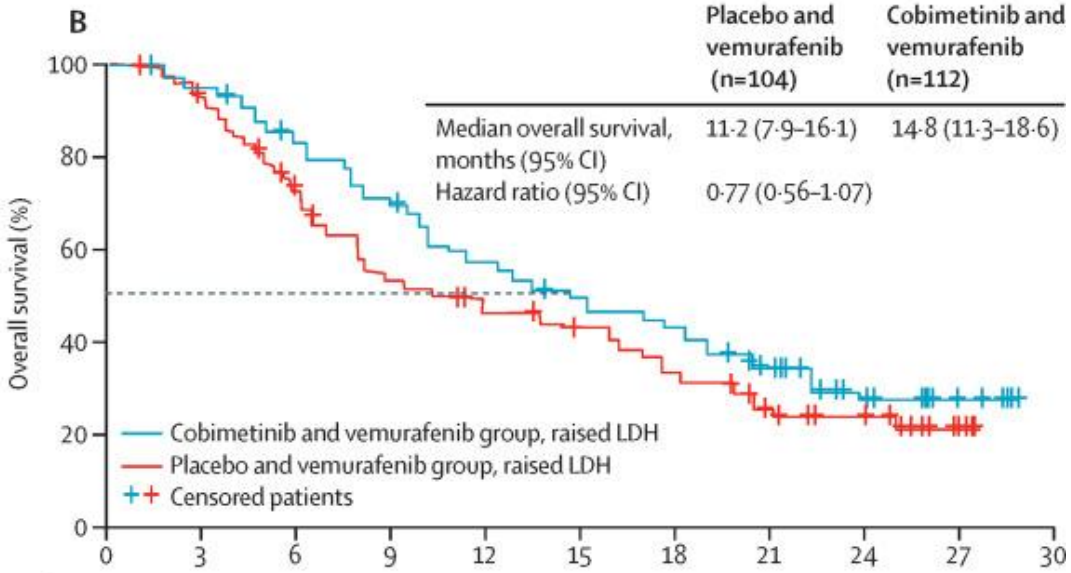
*
Responses could not be assessed for patients who withdrew consent, were withdrawn by the site investigator, died, or started new anticancer therapy before the first tumour assessment.

At the time of the protocol-specified final overall survival analysis (data cutoff Aug 28, 2015), median follow-up was 18·5 months (IQR 8·5–23·5). The combination of cobimetinib with vemurafenib significantly prolonged overall survival (stratified analysis; figure 4). The median overall survival for patients treated with cobimetinib and vemurafenib was 22·3 months (95% CI 20·3–not estimable) compared with 17·4 months (95% CI 15·0–19·8) for patients treated with vemurafenib (HR 0·70 [95% CI 0·55–0·90], p=0·005; figure 4A). 1-year overall survival was 74·5% (95% CI 68·9–80·2) in the cobimetinib and vemurafenib group and 63·8% (57·6–70·0) in the vemurafenib group; 2-year overall survival was 48·3% (41·4–55·2) and 38·0% (31·3–44·7), respectively. The HRs for overall survival in subgroups (unstratified analysis) are presented in figure 5. Survival curves for patients with lactate dehydrogenase concentrations at the upper limit of normal or higher are shown in figure 4B and those with lactate dehydrogenase concentrations below the upper limit of normal are in figure 4C.



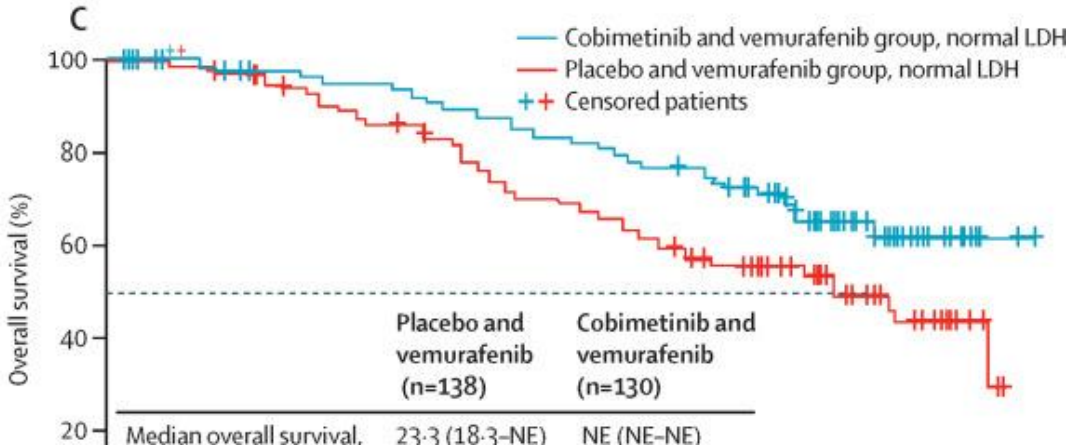
	Placebo and vemurafenib (n=248)	Cobimetinib and vemurafenib (n=247)
Events, n (%)	141 (56·9%)	114 (46·2%)
Median overall survival, months (95% CI)	17·4 (15·0–19·8)	22·3 (20·3–NE)
Hazard ratio (95% CI)	0·70 (0·55–0·90); p=0·005	

Number at risk											
Cobimetinib and vemurafenib group	247	232	210	192	169	152	139	107	48	14	..
Placebo and vemurafenib group	248	230	194	165	142	126	106	71	41	11	..



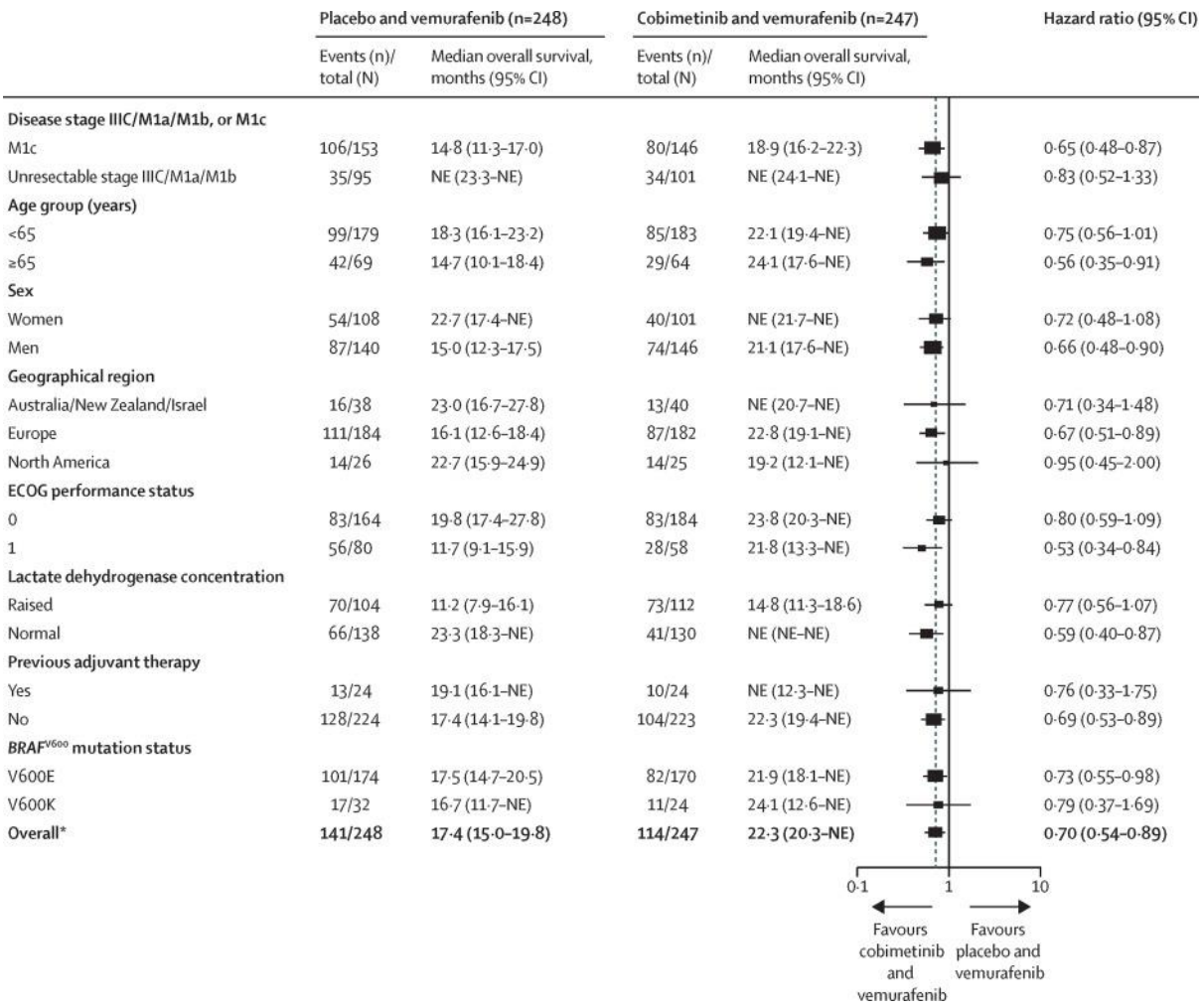
	Placebo and vemurafenib (n=104)	Cobimetinib and vemurafenib (n=112)
Median overall survival, months (95% CI)	11·2 (7·9–16·1)	14·8 (11·3–18·6)
Hazard ratio (95% CI)	0·77 (0·56–1·07)	

Number at risk											
Cobimetinib and vemurafenib group, raised LDH	112	105	89	75	61	51	45	29	14	6	..
Placebo and vemurafenib group, raised LDH	104	92	68	49	41	37	29	17	11	3	..



	Placebo and vemurafenib (n=138)	Cobimetinib and vemurafenib (n=130)
Median overall survival,	23·3 (18·3–NE)	NE (NE–NE)

Overall survival(A) Kaplan-Meier curve of overall survival in all patients. (B) ...
Figure 4.
Overall survival
(A) Kaplan-Meier curve of overall survival in all patients. (B) Overall survival in patients with raised (greater than institutional upper limit of normal) baseline LDH levels and (C) normal LDH levels. Data cutoff Aug 28, 2015. HR=hazard ratio. LDH=lactate dehydrogenase. NE=not estimable.



	Placebo and vemurafenib (n=248)		Cobimetinib and vemurafenib (n=247)		Hazard ratio (95% CI)
	Events (n)/ total (N)	Median overall survival, months (95% CI)	Events (n)/ total (N)	Median overall survival, months (95% CI)	
Disease stage IIIC/M1a/M1b, or M1c					
M1c	106/153	14·8 (11·3–17·0)	80/146	18·9 (16·2–22·3)	0·65 (0·48–0·87)
Unresectable stage IIIC/M1a/M1b	35/95	NE (23·3–NE)	34/101	NE (24·1–NE)	0·83 (0·52–1·33)
Age group (years)					
<65	99/179	18·3 (16·1–23·2)	85/183	22·1 (19·4–NE)	0·75 (0·56–1·01)
≥65	42/69	14·7 (10·1–18·4)	29/64	24·1 (17·6–NE)	0·56 (0·35–0·91)
Sex					
Women	54/108	22·7 (17·4–NE)	40/101	NE (21·7–NE)	0·72 (0·48–1·08)
Men	87/140	15·0 (12·3–17·5)	74/146	21·1 (17·6–NE)	0·66 (0·48–0·90)
Geographical region					
Australia/New Zealand/Israel	16/38	23·0 (16·7–27·8)	13/40	NE (20·7–NE)	0·71 (0·34–1·48)
Europe	111/184	16·1 (12·6–18·4)	87/182	22·8 (19·1–NE)	0·67 (0·51–0·89)
North America	14/26	22·7 (15·9–24·9)	14/25	19·2 (12·1–NE)	0·95 (0·45–2·00)
ECOG performance status					
0	83/164	19·8 (17·4–27·8)	83/184	23·8 (20·3–NE)	0·80 (0·59–1·09)
1	56/80	11·7 (9·1–15·9)	28/58	21·8 (13·3–NE)	0·53 (0·34–0·84)
Lactate dehydrogenase concentration					
Raised	70/104	11·2 (7·9–16·1)	73/112	14·8 (11·3–18·6)	0·77 (0·56–1·07)
Normal	66/138	23·3 (18·3–NE)	41/130	NE (NE–NE)	0·59 (0·40–0·87)
Previous adjuvant therapy					
Yes	13/24	19·1 (16·1–NE)	10/24	NE (12·3–NE)	0·76 (0·33–1·75)
No	128/224	17·4 (14·1–19·8)	104/223	22·3 (19·4–NE)	0·69 (0·53–0·89)
***BRAF*^{V600} mutation status**					
V600E	101/174	17·5 (14·7–20·5)	82/170	21·9 (18·1–NE)	0·73 (0·55–0·98)
V600K	17/32	16·7 (11·7–NE)	11/24	24·1 (12·6–NE)	0·79 (0·37–1·69)
Overall*	**141/248**	**17·4 (15·0–19·8)**	**114/247**	**22·3 (20·3–NE)**	**0·70 (0·54–0·89)**

Figure 5.
Overall survival
Prespecified subgroup analysis. Data cutoff Aug 28, 2015. NE=not estimable. ECOG=Eastern Cooperative Oncology Group. *Unstratified analysis.

Patients were followed up for subsequent anticancer therapy after progression (table 3). A similar proportion of patients received follow-up systemic therapy in each group; of those patients who received subsequent therapy, the most common type in both groups was immunotherapy (table 3). In most cases, the immunotherapeutic agent was ipilimumab (table 3).

Table 3.
Follow-up anticancer treatments[§] in the intention-to-treat population (data cutoff Sept 30, 2015)

	Placebo and vemurafenib (n=213)	Cobimetinib and vemurafenib (n=183)
Patients with at least one treatment	125 (59%)	105 (57%)
Any chemotherapy	37 (17%)	30 (16%)
Any targeted therapy	36 (17%)	32 (18%)
BRAF inhibitor monotherapy	24 (11%)	19 (10%)
Combination of a BRAF and a MEK inhibitor[*]	12 (6%)	15 (8%)
MEK inhibitor monotherapy	1 (1%)	2 (1%)
Any immunotherapy	89 (42%)	67 (37%)
Ipilimumab monotherapy	80 (38%)	53 (29%)
Anti-PD-1/anti-PD-L1 monotherapy	35 (16%)	28 (15%)
Combination of ipilimumab and an anti-PD-1/PD-L1[*]	4 (2%)	4 (2%)
Other[†]	1 (1%)	0
Other treatment, including multiple lines[‡]	0	2 (1%)

Data are n (%). PD-1=programmed death cell receptor 1. PD-L1=programmed death cell ligand 1.

*
Combination must have been administered in the same line of therapy.

†
Other immunotherapy agents included granulocyte colony-stimulating factor and adoptive immunotherapy.

‡
Other types of therapy included corticosteroids and an unknown investigational product.

§
Multiple uses of a type of therapy for an individual patient were only counted once in the frequency for that type of treatment; patients might have received multiple lines of treatment.

Baseline expression levels of Ki67, pERK, and pS6 and their correlation with overall survival were assessed. Tissue availability was low in some cases; for 290, 319, and 325 patients, samples were evaluable for Ki67, pERK, and pS6, respectively (table 4, appendix p 33). In the vemurafenib plus placebo group, patients with high Ki67 expression (defined as being greater than the median) had shorter overall survival than patients who had low Ki67 expression (HR 1·45 [95% CI 0·94–2·25]). However, in the cobimetinib and vemurafenib group, there was no difference in overall survival for patients with high Ki67 compared with that in patients with low Ki67 (table 4). No association between protein expression (assessed by H-score) of pERK or pS6 and overall survival was noted in either treatment group (table 4). Additionally, the effect of the baseline expression of each marker on overall survival was assessed as a continuous variable, and the findings were consistent with the binomial analysis (appendix p 3). No interactions between treatment and biomarker subgroups were recorded; however, these analyses were limited by the small size of the biomarker subpopulations. A full analysis of all biomarkers assessed will form the basis of a secondary report.

Table 4.

Overall survival by baseline biomarker status* (data cutoff Aug 28, 2015)

	Placebo and vemurafenib (n=248)		Cobimetinib and vemurafenib (n=247)	
Ki67				
>20%	66/140 (47%)	14·9 (9·5–19·1)	79/150 (53%)	21·6 (17·0–NE)
≤20%	74/140 (53%)	19·8 (13·3–NE)	71/150 (47%)	21·5 (18·1–NE)
HR of high *vs* low	NA	1·45 (0·94–2·25)	NA	0·95 (0·60–1·49)
pERK				
H-score >40	78/154 (51%)	14·9 (11·9–22·7)	81/165 (49%)	NE (18·3–NE)
H-score ≤40	76/154 (49%)	17·1 (12·6–24·9)	84/165 (51%)	21·1 (15·3–NE)
HR of high *vs* low H-score	NA	1·09 (0·72–1·66)	NA	0·75 (0·48–1·17)
pS6				
H-score >71	82/158 (52%)	19·1 (12·6–24·9)	80/167 (48%)	19·2 (16·2–NE)
H-score ≤71	76/158 (48%)	15·4 (11·9–20·5)	87/167 (52%)	24·1 (18·3–NE)
HR of high *vs* low H-score	NA	0·80 (0·53–1·21)	NA	1·14 (0·74–1·76)

Data are n/N (%), median overall survival in months (95% CI) or HR (95% CI). NE=not estimable. HR=hazard ratio. NA=not applicable.

*
Biomarker status is based on population median.

A total of 211 (85%) of 247 patients in the cobimetinib and vemurafenib group and 209 (85%) of 248 in the vemurafenib group were eligible for quality of life analysis. Patients in the cobimetinib and vemurafenib group had similar quality of life compared with patients in the vemurafenib arm throughout the evaluable period (cycles 1–8; figure 6).

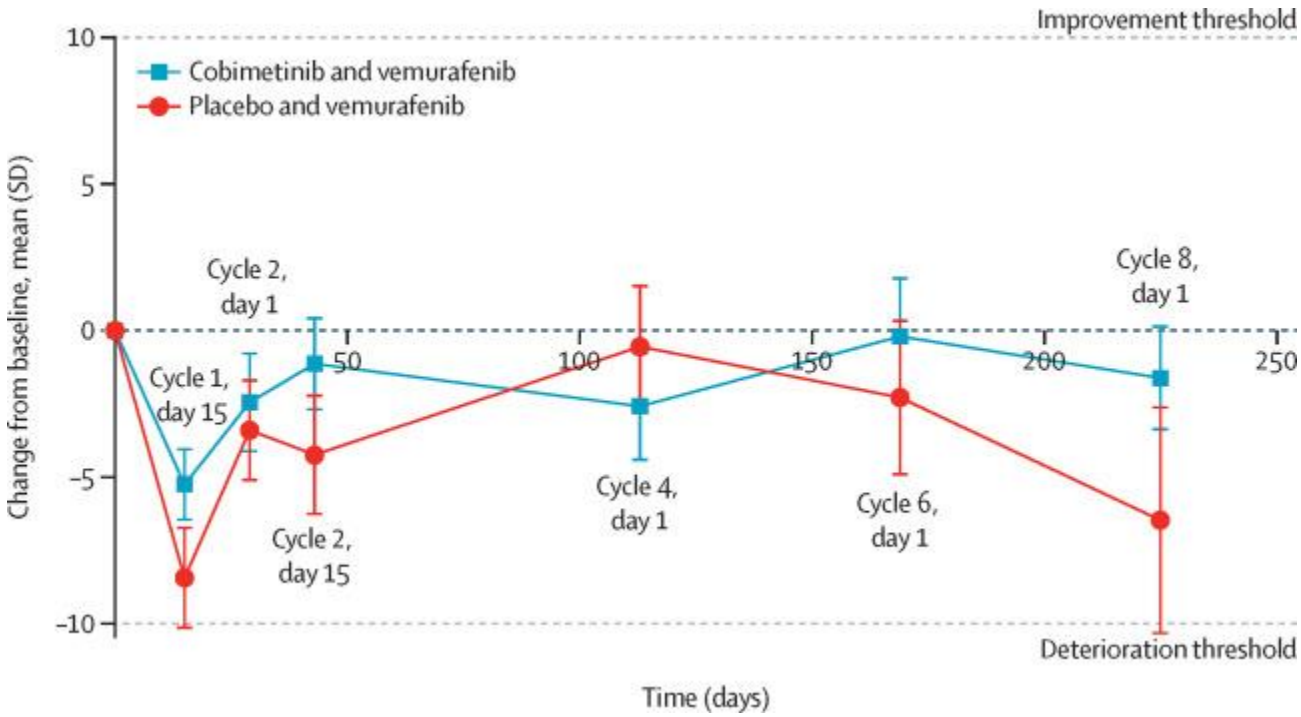


Figure 6.
EORTC QLQ-C30 global health status
The dashed horizontal lines represent clinically meaningful change (≥10 point change from baseline) for improvement or deterioration in global health status. Error bars are standard errors of the mean. EORTC=European Organization for the Research and Treatment of Cancer.

Updated safety data (data cutoff Sept 30, 2015) were consistent with those reported previously.13 At the time of the safety data cutoff, median follow-up was 18·5 months (IQR 8·5–23·5) for patients in the cobimetinib and vemurafenib group, median duration of cobimetinib treatment was 9·0 months (range 0·1–30·1), and median duration of vemurafenib treatment was 9·2 months (range 0·3–30·3); for patients in the placebo and vemurafenib group, median duration of vemurafenib treatment was 5·8 months (range 0·2–29·3). For the patients in the cobimetinib and vemurafenib group who remained on treatment at 1 year, the mean dose of cobimetinib was 52 mg (SD 11) per day and the mean dose of vemurafenib was 1624 mg (381) per day; for those who remained on treatment at 2 years, the mean doses were 53 mg (SD 10) per day and 1627 mg (378) per day, respectively.

Almost all patients in both groups had at least one adverse event, irrespective of association with treatment (table 5, appendix pp 4–27). Serious adverse events occurred in 92 patients (37%) in the cobimetinib and vemurafenib group and 69 patients (28%) in the vemurafenib group. Pyrexia (six patients [2%]) and dehydration (five patients [2%]) were the most common serious adverse events reported in the cobimetinib and vemurafenib group. All adverse events recorded in the study are reported in the appendix (pp 4–27).

Table 5.
Summary of adverse events in the safety population[‡] (data cutoff Sept 30, 2015)

	Placebo and vemurafenib (n=246)		Cobimetinib and vemurafenib (n=247)	
	All grades	Grade ≥3	All grades	Grade ≥3
Most common adverse events (occurring in ≥20% of patients in either group)				
Rash[*]	166 (68%)	40 (16%)	179 (73%)	42 (17%)
Arthralgia	103 (42%)	12 (5%)	94 (38%)	6 (3%)
Diarrhoea	82 (33%)	2 (1%)	150 (61%)	16 (7%)
Fatigue	82 (33%)	7 (3%)	91 (37%)	11 (5%)
Alopecia	75 (31%)	1 (<1%)	41 (17%)	1 (<1%)
Hyperkeratosis	67 (27%)	6 (3%)	25 (10%)	1 (<1%)
Nausea	64 (26%)	2 (1%)	105 (43%)	3 (1%)
Pyrexia	59 (24%)	0	71 (29%)	3 (1%)
Decreased appetite	50 (20%)	1 (<1%)	50 (20%)	0
Photosensitivity reaction	48 (20%)	0	84 (34%)	8 (3%)
Alanine aminotransferase concentration increase	44 (18%)	15 (6%)	65 (26%)	28 (11%)
γ-glutamyltransferase concentration increase	44 (18%)	25 (10%)	54 (22%)	36 (15%)
Vomiting	34 (14%)	2 (1%)	63 (26%)	4 (2%)
Aspartate aminotransferase concentration increase	31 (13%)	5 (2%)	60 (24%)	22 (9%)
Serous retinopathy[†]	9 (4%)	0	67 (27%)	7 (3%)
Blood creatine phosphokinase level increase	7 (3%)	1 (<1%)	87 (35%)	30 (12%)
Other selected adverse events (selected based upon known association with BRAF or MEK inhibition)				
Cutaneous squamous cell carcinoma	31 (13%)	31 (13%)	10 (4%)	9 (4%)
Keratoacanthoma	23 (9%)	21 (9%)	4 (2%)	3 (1%)
Decreased ejection fraction	13 (5%)	3 (1%)	29 (12%)	5 (2%)
QT prolongation	13 (5%)	3 (1%)	11 (5%)	3 (1%)

Data are n (%). All adverse events are preferred terms. All events are presented irrespective of association with study drug.

*
Combined terms: includes (in decreasing order of reported incidence) the preferred terms rash, rash maculopapular, erythema, dermatitis acneiform, folliculitis, rash macular, rash papular, rash erythematous, acne, dermatitis, rash pruritic, furuncle, rash generalised, dermatitis allergic, rash follicular, rash pustular, dermatitis exfoliative, generalised erythema, rash morbilliform, and drug eruption.

†
Combined terms include (in decreasing order of reported incidence) the preferred terms chorioretinopathy, retinal detachment, detachment of retinal pigment epithelium, macular oedema, macular fibrosis, retinal disorder, retinopathy, subretinal fluid, and detachment of macular retinal pigment epithelium.

‡
At the time of the primary analysis,[13] eight patients randomly assigned to the placebo and vemurafenib group were believed to have received cobimetinib owing to site medication dispensing error and, therefore, were included in the cobimetinib and vemurafenib group.

However, it was later established that seven of these eight patients did not in fact receive cobimetinib. These seven patients were reassigned to the placebo and vemurafenib group. Hence, for the safety population at the time of this update, relative to the original report of this study,[13] the safety denominators for the two groups have changed from 254 to 247 for the cobimetinib and vemurafenib group and from 239 to 246 for the placebo and vemurafenib group.

Adverse events judged to be related to study treatment were reported in 241 (98%) of 247 patients in the cobimetinib and vemurafenib group, with 147 (60%) of 247 patients experiencing a grade 3 or worse treatment-related event. In the vemurafenib group, 233 (95%) of 246 patients had treatment-related adverse events, with 128 (52%) experiencing a grade 3 or worse treatment-related event.

Regarding known vemurafenib-related adverse events, the frequency of cutaneous squamous cell carcinoma, keratoacanthoma, or Bowen's disease was lower in patients in the cobimetinib and vemurafenib group, occurring in 15 (6%) of 247 patients in this group compared with 48 (20%) of 246 patients treated with vemurafenib. This finding is consistent with abrogation of paradoxical activation of the MAPK pathway. Similar to the primary analysis,13 photosensitivity was more common in the cobimetinib and vemurafenib group, occurring in 84 (34%) of 247 patients compared with 48 (20%) of 246 patients in the vemurafenib group. Most events in both groups were grade 1 or 2 and were managed conservatively with topical medications; few patients required dose modifications.

MEK inhibitor-specific adverse events in the cobimetinib and vemurafenib group included serous retinopathy, decreased left ventricular ejection fraction, and increased creatine phosphokinase level.

Serous retinopathy of any grade occurred in 67 (27%) of 247 patients in the cobimetinib and vemurafenib group compared with nine (4%) of 246 patients in the vemurafenib group. Most of these events (60 [90%] of 67) were grade 1–2 (whereas seven events were grade 3 or worse), and the majority of patients maintained good visual acuity with conservative management (simple observation including counselling to the patient with monitoring under the care of an ophthalmologist and, where considered indicated by the ophthalmologist, interruption and/or dose reduction of one or both drugs). Seven patients in the cobimetinib and vemurafenib group had grade 3 or worse serous retinopathy events, and five of these had resolved or were resolving by the time of the data cutoff.

Decreased left ventricular ejection fraction grade 2 or worse occurred in 28 (11%) of 247 patients in the cobimetinib and vemurafenib group versus 12 (5%) of 246 patients in the vemurafenib group (appendix p 9). Most of these events were grade 2, with grade 3 events reported in five (2%) of 247 patients in the cobimetinib and vemurafenib group and three (1%) of 246 patients in the vemurafenib plus placebo group. This adverse event was managed effectively according to study protocol with a dose reduction of cobimetinib, and no grade 4 event or death from this adverse event occurred.

Elevated creatine phosphokinase level of grade 3 or worse occurred in 30 (12%) of 247 patients in the cobimetinib and vemurafenib group versus one (<1%) of 246 in the vemurafenib plus placebo group, respectively (see appendix p 9). Most cases were asymptomatic and managed conservatively with observation.

The treatment regimen was discontinued in 52 (11%) of 493 patients overall because of treatment-related adverse events, including 35 (14%) of 247 patients in the cobimetinib and vemurafenib group and 17 (7%) of 246 in the vemurafenib group. The most common reason for discontinuation of the regimen in the cobimetinib and vemurafenib group was aspartate aminotransferase increase (five

patients [2%]) and in the vemurafenib plus placebo group was γ-glutamyltransferase level increase and fatigue (each in two patients [<1%]).

In the cobimetinib and vemurafenib group, 87 (35%) patients had a dose reduction of vemurafenib as a result of adverse events, and 75 patients (30%) had a dose reduction of cobimetinib. In the placebo and vemurafenib group, 72 (29%) of 246 patients had a dose reduction of vemurafenib and 27 (11%) had a dose reduction of placebo.

Eight (2%) of 493 patients died during the study: five (2%) of 247 in the cobimetinib and vemurafenib group due to pneumonia, Clostridium difficile colitis, coma, cardiac arrest, and death (unspecified) and three (1%) of 246 in the vemurafenib group due to cardiac failure, atelectasis, and death (unspecified).

Discussion

This updated analysis of the coBRIM study, including more than a minimum of 1 year of follow-up, demonstrates a statistically significant and clinically meaningful improvement in median overall survival, progression-free survival, and the overall response in patients treated with the combination of cobimetinib and vemurafenib versus patients treated with vemurafenib plus placebo. Moreover, the estimated landmark 2-year overall survival shows sustained benefit of the combination of cobimetinib and vemurafenib versus vemurafenib plus placebo. The proportion of patients who achieved an overall response at the updated analysis were similar to those at the primary analysis; however, the proportions of patients achieving a complete response were higher at the updated analysis than at the primary analysis (in the cobimetinib and vemurafenib group, an increase from 25 [10%] of 247 at the primary analysis to 39 [16%] of 247 in the updated analysis, and in the vemurafenib group an increase to 26 [11%] of 248 from 11 [4%] of 248), indicating that some patients had an improved response with continued treatment. The safety profile remained consistent with that at the time of the primary analysis13 and quality of life was maintained.

The HRs for overall survival favoured the cobimetinib and vemurafenib group compared with vemurafenib in most prespecified patient subgroups assessed, including those with key prognostic clinical characteristics (ECOG performance status ≥1 vs 0, raised lactate dehydrogenase concentration, and advanced stage of disease). Of the MEK inhibitor–BRAF inhibitor phase 3 combination studies done so far, coBRIM enrolled the highest proportion of patients with raised baseline lactate dehydrogenase concentrations, who represent a distinct population with poorer prognosis 3; 4; 5; 6; 16; 17; 22; 23; 24 ; 25 than those with normal lactate dehydrogenase levels. As expected, patients with raised lactate dehydrogenase concentrations had shorter median survival than those with normal lactate dehydrogenase concentrations in both the cobimetinib and vemurafenib and the vemurafenib groups. Patients with normal lactate dehydrogenase concentrations, who are often considered for therapeutic options other than BRAF or MEK-targeted therapies, might benefit from long-term disease control with the combination of cobimetinib and vemurafenib. The treatment effect was similar in patients irrespective of the BRAF mutation of their tumour (BRAFV600E or BRAFV600K), which is consistent with previous reports concerning vemurafenib monotherapy.5

These data are in line with a recent long-term follow-up (median 21 months) of BRAF inhibitor-naive patients receiving cobimetinib and vemurafenib enrolled in the BRIM-7 phase 1 study12 which reported 87·3% (95% CI 76·7–94·4) of patients achieving an overall response, median progression-free survival of 13·8 months (95% CI 10·1–20·6), and median overall survival of 28·5 months (23·3–34·6) with 2-year overall survival of 61% (95% CI 47·8–74·4).26

Global health status score seemed to decrease at treatment cycle 8 for patients in the vemurafenib plus placebo group. The cycle 8 visit is the closest measure of quality of life to the timepoint at which median progression-free survival for patients enrolled in the vemurafenib group is reached (7·2 months), and thus this decrease in global health status score probably represents a decrease in quality of life that corresponds to disease progression.

Cobimetinib and vemurafenib were well tolerated and continued to show an acceptable and manageable safety profile compared with vemurafenib plus placebo; no new safety concerns were identified with longer follow-up. Compared with the primary analysis,13 the incidence of rash in the cobimetinib and vemurafenib group was nearly identical (101 [41%] of 247 vs 99 [39%] of 254) and was slightly higher in the vemurafenib plus placebo group (94 [38%] of 246 vs 85 [36%] of 239). Most adverse events were grade 1 or 2 and were effectively managed with supportive therapy and dose modifications. No specific adverse events necessitated withdrawal of the study regimen in more than 2% of patients. We have previously shown that most cobimetinib and vemurafenib-related adverse events occur early in the course of treatment (within the first 28 days for grade 3 or worse adverse events) and are mild or moderate, monitorable, and manageable by dose modification and supportive care. 27 Although tolerability of the phase 3 dose (and subsequent commercial dose) was determined based on the phase 1–2 BRIM-7 study,12 the regimen remained tolerable in the phase 3 study.

As expected, known MEK inhibitor-related adverse events, including serous retinopathy, decreased left ventricular ejection fraction, and increased creatine phosphokinase concentration, were more common in the cobimetinib and vemurafenib group compared with the vemurafenib plus placebo group but were generally mild or moderate and manageable. Most serous retinopathy events were grade 1–2 in severity, and most patients maintained good visual acuity with observation. Similarly, most decreased left ventricular ejection fraction events were grade 2, with no grade 4 events or deaths, and this event was effectively managed by adherence to protocol guidelines. Increased creatine phosphokinase level was typically asymptomatic and managed by observation.

Although photosensitivity, a known vemurafenib-related adverse event, also occurred more commonly in the cobimetinib and vemurafenib group, most events were grade 1 and 2 and no grade 4 events or deaths due to photosensitivity occurred. Proactive patient education, training of clinical staff, and ongoing management of expected adverse events is important to reduce the effect of photosensitivity.

The coBRIM study also assessed several molecular markers (Ki67, pERK, and pS6) in the baseline tumour samples for effect on survival and for interaction with the treatment groups. These markers were analysed to assess the potential effect of proliferative state (Ki67), MAPK activation (pERK), and pS6 (PI3K–MAPK downstream effector) on survival outcomes. High Ki67 expression at baseline was associated with a shorter median overall survival in the vemurafenib group but did not affect overall survival in the combination cobimetinib and vemurafenib group. This finding might be a result of baseline Ki67 level being indicative of activity of the BRAF–MEK–ERK pathway and the ability of vemurafenib combined with cobimetinib to more effectively inhibit the pathway than vemurafenib alone.28 Despite substantial variety in the staining score between individual patients, no associations were recorded between pERK and pS6 H-score and clinical outcome, which might be indicative of technical limitations of use of immunohistochemical analyses to quantify the output of these molecular pathways or of other factors that over-ride these signals. Although these are retrospective exploratory analyses that require validation, the results suggest that survival outcomes of combined BRAF and MEK inhibition might not be affected by the status of tumour cell signalling at baseline.

Comparison of the updated coBRIM data with the other phase 3 combination MEK inhibitor and BRAF inhibitor studies16; 17 ; 18 is not feasible because of study differences such as baseline patient population characteristics, crossover of patients from the placebo group to the combination group with disease progression (which was not allowed in coBRIM), and availability of ongoing treatment beyond progression with study drugs in case of limited progression of disease (also not permitted in coBRIM). Nevertheless, the overall efficacy data of the combination of cobimetinib and vemurafenib was similar to that of two randomised phase 3 trials; these studies compared the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib with dabrafenib (COMBI-d)16 ; 17 and dabrafenib and trametinib with vemurafenib (COMBI-v).18 However, this observation can only be confirmed with a head-to-head clinical study of the combinations, which would address the potential confounding factors described previously.

In conclusion, patients treated with the combination of cobimetinib and vemurafenib achieved a higher objective response, longer progression-free survival, and longer overall survival compared with patients treated with vemurafenib alone. HRs favoured most prespecified clinical and molecular subgroups assessed, and there were no differences in quality of life scores between the two groups. Safety was consistent with that previously reported.12; 13 ; 26 The combination of cobimetinib and vemurafenib was recently approved by the US Food and Drug Administration29 ; 30 and the European Medicines Agency31 ; 32 for the treatment of advanced BRAFV600-mutant melanoma and represents a new standard of treatment for patients with this disease.

Contributors

PAA participated in study design, patient enrolment, data collection, data analysis, data interpretation, and writing of the report. GAM participated in writing the report, study design, data collection, and data analysis. BD participated in study design, patient enrolment, data collection, and data analysis. VA participated in data collection and interpretation, and drafting and revision of the report. GL participated in data collection. AMDG participated in data collection, analysis, interpretation, and revision of the report. MM participated in patient enrolment, data collection and interpretation, and writing and revision of the report. LD participated in patient enrolment, data collection and data interpretation, and writing and revision of the report. DS participated in patient enrolment, data collection and interpretation, and writing and revision of the report. LT was a local principal investigator in the study, enrolled and followed up patients, collected data, reviewed the report, and provided scientific input. LdlC-M enrolled patients, collected data, and revised the manuscript. CD participated in patient enrolment, data collection and interpretation, and writing and revision of the report. CG participated in patient enrolment, data collection and interpretation, and writing and revision of the report. YY participated in data collection, data analysis, data interpretation, and writing of the report. MW contributed to data collection, data analysis, data interpretation, and writing of the report. IC participated in study design, data analysis, data interpretation, and writing of the report. JJH contributed to data analysis and interpretation. DOK participated in data collection, data interpretation, and writing of the report. IR provided active participation in data collection and interpretation, and writing and editing of the report. AR participated in patient enrolment, data collection and interpretation, and writing and revision of the report. JL participated in study design, data collection, data analysis, data interpretation, drafting and revision of the report, and final approval.

Declaration of interests

PAA has received grants and personal fees from Bristol-Myers Squibb, Roche-Genentech, and Ventana, and personal fees from Merck Sharp & Dohme, Novartis, and Amgen, outside the submitted work. GAM has received grants from Pfizer, Celgene, and Ventana, and consultant fees

from Provectus, outside the submitted work. BD has received grants and personal fees from Roche, grants from GlaxoSmithKline, and personal fees from Bristol-Myers Squibb, outside the submitted work. VA has received advisory board, travel support, and speaker fees from Merck Sharp & Dohme and Bristol-Myers Squibb, and travel support and speakers fees from Novartis, outside the submitted work. MM has received personal fees from Roche, GlaxoSmithKline, Bristol-Myers Squibb, and Merck Sharp & Dohme during the conduct of the study. LD has received personal fees from Roche, grants, personal fees, and other from Bristol-Myers Squibb, personal fees from Novartis, and personal fees from Merck Sharp & Dohme, outside the submitted work. LdlC-M has received grants from Roche Farma, outside the submitted work. CG has received grants and personal fees from Roche, during the conduct of the study; grants and personal fees from Bristol-Myers Squibb, grants and personal fees from GSK, grants and personal fees from Novartis, personal fees from Amgen, and personal fees from Merck Sharp & Dohme, outside the submitted work. YY is an employee of Genentech and has stock ownership in Roche/Genentech. MW reports that he is an employee and has stock ownership in Roche and stock ownership in ARIAD pharmaceuticals. IC, DOK, and IR are employees of Genentech and have stock ownership in Roche/Genentech. JJH is an employee of Genentech and owns Genentech stock. AR has received consultant fees or honoraria from Amgen, Merck, Pfizer, and Roche, and owns stock in Kite Pharma. GL, AMDG, DS, LT, CD, and JL declare no competing interests.

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