Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial

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Summary

Background Previously, a study of ours showed that the combination of dabrafenib and trametinib improves progression-free survival compared with dabrafenib and placebo in patients with BRAF Val600Lys/Glu mutation-positive metastatic melanoma. The study was continued to assess the secondary endpoint of overall survival, which we report in this Article.

Methods We did this double-blind phase 3 study at 113 sites in 14 countries. We enrolled previously untreated patients with BRAF Val600Glu or Val600Lys mutation-positive unresectable stage IIIC or stage IV melanoma. Participants were computer-randomised (1:1) to receive a combination of dabrafenib (150 mg orally twice daily) and trametinib (2 mg orally once daily), or dabrafenib and placebo. The primary endpoint was progression-free survival and overall survival was a secondary endpoint. This study is registered with ClinicalTrials.gov, number NCT01584648.

Findings Between May 4, 2012, and Nov 30, 2012, we screened 947 patients for eligibility, of whom 423 were randomly assigned to receive dabrafenib and trametinib (n=211) or dabrafenib only (n=212). The final data cutoff was Jan 12, 2015, at which time 222 patients had died. Median overall survival was 25·1 months (95% CI 19·2–not reached) in the dabrafenib and trametinib group versus 18·7 months (15·2–23·7) in the dabrafenib only group (hazard ratio [HR] 0·71, 95% CI 0·55–0·92; p=0·0107). Overall survival was 74% at 1 year and 51% at 2 years in the dabrafenib and trametinib group versus 68% and 42%, respectively, in the dabrafenib only group. Based on 301 events, median progression-free survival was 11·0 months (95% CI 8·0–13·9) in the dabrafenib and trametinib group and 8·8 months (5·9–9·3) in the dabrafenib only group (HR 0·67, 95% CI 0·53–0·84; p=0·0004; unadjusted for multiple testing). Treatment-related adverse events occurred in 181 (87%) of 209 patients in the dabrafenib and trametinib group and 189 (90%) of 211 patients in the dabrafenib only group; the most common was pyrexia (108 patients, 52%) in the dabrafenib and trametinib group, and hyperkeratosis (70 patients, 33%) in the dabrafenib only group. Grade 3 or 4 adverse events occurred in 67 (32%) patients in the dabrafenib and trametinib group and 66 (31%) patients in the dabrafenib only group.

Interpretation The improvement in overall survival establishes the combination of dabrafenib and trametinib as the standard targeted treatment for BRAF Val600 mutation-positive melanoma. Studies assessing dabrafenib and trametinib in combination with immunotherapies are ongoing.

Funding GlaxoSmithKline.

Introduction

Dabrafenib, an oral BRAF inhibitor, combined with trametinib, an oral MEK inhibitor, improved progression-free survival compared with dabrafenib monotherapy in patients with BRAF Val600Lys/Glu mutation-positive stage IIIC unresectable melanoma or stage IV melanoma in a randomised phase 2 study[1] and in the primary analysis of this phase 3 study (COMBI-d).[2] In the primary analysis of COMBI-d, with a median follow-up of 9 months (range 0–16), median progression-free survival was 9·3 months for the combination and 8·8 months for dabrafenib monotherapy, with a hazard ratio (HR) of 0·75 (95% CI 0·57–0·99; p=0·0348). The combination also improved progression-free survival and overall survival compared with single agent vemurafenib, another oral BRAF inhibitor, in a second phase 3 study (COMBI-v).[3] In that study, median overall survival was not reached for the combination and was 17·2 months for vemurafenib, with an HR of 0·69 (95% CI 0·53–0·89; p=0·0049). In all three studies, adverse events related to paradoxical activation of the MAPK pathway were reduced with the combination compared with BRAF inhibitor monotherapy, however, pyrexia was more common and more severe.

We report the final overall survival analysis for the randomised, double-blind phase 3 study of dabrafenib combined with trametinib compared with dabrafenib

Research in context

Evidence before this study

We searched PubMed up to March 8, 2015, for phase 1–3 clinical trials with the terms "combination", "BRAF", "MEK", and "melanoma". We identified 154 articles; of which, five were phase 1, 2, or 3 clinical trials of combined BRAF and MEK inhibitors. We searched the American Society for Clinical Oncology conference abstracts and identified three additional abstracts of clinical trials of combined BRAF and MEK inhibition that had not been published in full. BRAF and MEK inhibition decreased the number of hyperkeratotic skin toxic effects caused by paradoxical activation of the MAPK pathway, and delayed the onset of resistance compared with single-drug BRAF inhibition in preclinical studies of Val600Glu BRAF mutant models. This finding led to a phase 1/2 study of combined dabrafenib and trametinib in patients with Val600 BRAF mutation-positive metastatic melanoma. The phase 1 part of the study showed more responses, longer progression-free survival, and fewer cases of cutaneous squamous-cell carcinoma compared with historic controls treated with a single BRAF inhibitor. In the randomised phase 2 part of the study, the combination resulted in more responses (76% *vs* 54%, p=0·0264) and longer progression-free survival (9·4 months *vs* 5·8 months, HR 0·39, p<0·0001) than did monotherapy, with decreased oncogenic toxic effects (cutaneous squamous cell carcinoma and hyperkeratosis). Similarly, results of early-phase studies of other BRAF inhibitor and MEK inhibitor combinations showed more responses, a longer progression-free survival, and reduced incidence of cutaneous squamous-cell carcinoma, strongly supporting the rationale for a phase 3 trial of combined dabrafenib and trametinib versus BRAF inhibitor monotherapy.

Added value of this study

We report the final overall survival analysis of a double-blind, placebo-controlled, phase 3, randomised trial of the combination of dabrafenib and trametinib versus dabrafenib monotherapy. This study is also the most mature survival analysis for any phase 3 trial assessing the superiority of combined BRAF and MEK inhibition versus BRAF inhibition alone; thus we report the first median overall survival for any of the BRAF and MEK combinations from a phase 3 study (25·1 months). It adds weight to the open-label phase 3 trial of the same combination versus vemurafenib (the first BRAF inhibitor shown to improve overall survival compared with chemotherapy), which also resulted in improved overall survival (HR 0·69, p=0·0049) in favour of the combination.

Implications of all the available evidence

Our findings confirm the superiority of dabrafenib and trametinib in terms of the number of responses, duration of response, progression-free survival, and overall survival compared with the internationally approved BRAF inhibitors dabrafenib and vemurafenib. The combination reduced oncogenic adverse events caused by MAPK pathway reactivation. These data support the use of combined dabrafenib and trametinib as the standard targeted treatment for patients with Val600 BRAF mutation-positive metastatic melanoma.

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combined with placebo in previously untreated patients with BRAF Val600Glu/Lys mutation-positive metastatic melanoma, and provide the latest findings for progression-free survival, response rate, duration of response, and safety.

Methods

Study design and patients

We did this double-blind, randomised, phase 3 study at 113 sites in 14 countries. Eligible patients were at least 18 years old and had histologically confirmed, unresectable stage IIIC or stage IV metastatic melanoma with BRAF Val600Glu or Val600Lys mutations, as determined by PCR (ThxID BRAF Assay, bioMérieux) done at a central reference laboratory. Patients were ineligible if they had previous systemic treatment for advanced or metastatic cancer. Patients with brain metastases that had been definitively treated and stable for at least 12 weeks were eligible. The complete eligibility criteria are available in the study protocol (appendix).

The protocol was approved by the independent review board at each participating institution (appendix). All patients provided written informed consent.

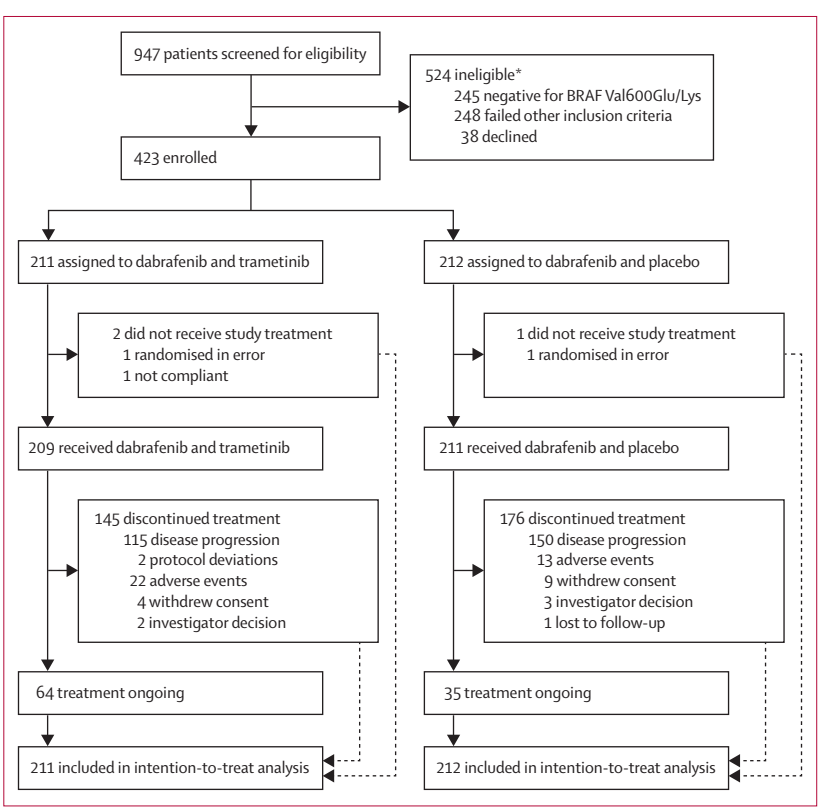

Figure 1: **Trial profile**
*Some patients were ineligible for more than one reason.

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See Online for appendix

*Employees of GlaxoSmithKline during the study

	Dabrafenib and trametinib (n=211)	Dabrafenib and placebo (n=212)
Median age (range, years)	55·0 (22–89)	56·5 (22–86)
Male patients	111 (53%)	114 (54%)
Previous immunotherapy	57 (27%)	61 (29%)
ECOG performance score		
0	155 (73%)	150 (71%)
1	55 (26%)	61 (29%)
BRAF mutation*		
Val600Glu	179 (85%)	181 (85%)
Val600Lys	32 (15%)	30 (14%)
Stage at screening		
IVM1c	142 (67%)	138 (65%)
IIIc, IVM1a, or IVM1b	69 (33%)	73 (34%)
M stage at screening		
M0	5 (2%)	10 (5%)
M1a	19 (9%)	31 (15%)
M1b	45 (21%)	32 (15%)
M1c	142 (67%)	138 (65%)
Baseline lactate dehydrogenase		
>Upper limit of normal	77 (36%)	71 (33%)
≤Upper limit of normal	133 (63%)	140 (66%)
Visceral disease†		
Yes	165 (78%)	145 (68%)
No	46 (22%)	66 (31%)
Number of disease sites‡		
<3	109 (52%)	119 (56%)
≥3	101 (48%)	92 (43%)

In the dabrafenib and trametinib group, one patient was randomised in error, and no baseline data were recorded for this patient in four categories (previous immunotherapy, ECOG performance score, lactate dehyrdrogenase, and number of disease sites). In the dabrafenib only group, one patient was randomised in error, and no baseline data were recorded for this patient. ECOG=Eastern Cooperative Oncology Group. *One patient had both BRAF Val600Glu and BRAF Val600Lys mutations and is included in the Val600Lys group here. †Defined as the soft internal organs including the lungs, heart, and organs of the digestive, excretory, reproductive, and circulatory systems but excluding lymph nodes. ‡Number of body sites of disease based on unique RECIST target and non-target lesions identified by the investigator, not the number of metastases.

***Table 1*: Baseline characteristics**

Randomisation and masking

We randomly assigned patients (1:1) to receive either a combination of dabrafenib and trametinib or a combination of dabrafenib and placebo (figure 1). Patients were stratified according to baseline lactate dehydrogenase concentration and *BRAF* genotype. A centrally located, computerised, interactive, voice-activated response system controlled the random assignment. Investigators, site staff, and patients were unaware of assignment throughout the study, and masking was maintained by using tablets and bottles of active drug and placebo that were identical in appearance. At the time of the primary analysis, only the sponsor and those assessing the data were made aware of treatment group assignments.

Procedures

Patients were administered either oral dabrafenib (150 mg twice daily) and oral trametinib (2 mg once daily), or oral dabrafenib (150 mg twice daily) and placebo. We assessed tumour response with Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1).[4] Patients who were eligible for continued study treatment beyond progression (appendix) continued all assessments according to the protocol. All responses were confirmed.

Patients underwent baseline assessment of demographics, medical history, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, electrocardiogram, and echocardiogram, ophthalmological assessment, blood laboratory analysis, physical examination with dermatological assessment, and pelvic and rectal examinations. A tumour assessment was done at baseline by CT scan or MRI) scan of the chest, abdomen, and pelvis, and skin lesions were photographed. Disease was assessed every 8 weeks to 56 weeks, and every 12 weeks thereafter until disease progression, death, or withdrawal from the study. Physical examinations with dermatologic assessment, assessment of ECOG performance status, vital signs, chemistry, and haematology tests were repeated every 4 weeks. Electrocardiogram and echocardiogram assessments were repeated at 4 weeks and every 12 weeks thereafter. An ophthalmological assessment was repeated at 4 weeks and as symptomatically warranted.

Patients were followed up for survival and start of new cancer treatment every 12 weeks until death, withdrawal of consent, or loss to follow-up.

Outcomes

The primary endpoint was investigator-assessed progression-free survival, defined as the time from randomisation until progression or death of any cause. Overall survival was a key secondary endpoint, defined as the time from randomisation to death of any cause. The other secondary endpoints were investigator-determined proportion of patients who achieved responses, defined as the proportion of patients with measurable disease at baseline who had a confirmed RECIST response; duration of response, defined as time from first RECIST response to progression; safety; and pharmacokinetics (published previously[2]).

Adverse events were graded by the site investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0)[5] throughout the study until 30 days after the discontinuation of study treatment.

Statistical analysis

The results of the primary analysis have been reported.[2] The study was continued after the primary analysis without crossover to preserve the integrity of the secondary endpoint of overall survival. The study site

staff, investigators, and patients remained unaware of the study treatment assignment. We used stratified log-rank tests to test for treatment differences in progression-free survival and overall survival; we used χ^2 tests to test for treatment differences in overall response.

At the primary analysis for progression-free survival, the study design required that progression-free survival was statistically significant before doing an interim analysis of overall survival. In addition, because we did not anticipate that the overall survival data would be mature enough to statistically differentiate between treatments at the time of the primary analysis, a conservative α was set to preserve the majority of α spending at the final analysis. At the primary analysis, progression-free survival was significant at a level of 0·05 but overall survival was not significant at the pre-specified level of 0·00028.[2]

We did the final overall survival analysis when 70% (220 events) of the intention-to-treat population, based on the original target enrolment (340 patients) had died or been lost to follow-up (anticipating a 5% loss to follow-up). When the study was designed, we estimated that 220 events would provide roughly 80% power to detect an HR of 0·675. We used a Lan and DeMets α spending function,[6] with O'Brien & Fleming-like boundaries for efficacy,[7] to control the type 1 error rate for overall survival, with a global α of 5%. We used EAST 5.4 software to calculate the appropriate bounds on the basis of interim analysis after 95 deaths and a final analysis after 220 events. The threshold for significance was a two-sided p value of less than 0·0496. We did the analyses with SAS (version 9.3).

An independent data monitoring committee periodically assessed safety until the primary endpoint had been reached. This study is registered with ClinicalTrials.gov, number NCT01584648.

Role of the funding source

The study was designed by the authors and the funder. Data were collected by the study site staff and monitored by the funder. The funder was also involved in data analysis, data interpretation, and writing the report. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

From May 4, 2012, to Nov 30, 2012, we screened 947 patients. The most common reason for screening failure was absence of a *BRAF* mutation. 423 were randomly assigned to receive a combination of dabrafenib and trametinib (211 patients), or dabrafenib and placebo (212 patients; figure 1). The treatment groups were well balanced for age, sex, ECOG performance status, lactate dehydrogenase, and M stage (table 1). As of the Jan 12, 2015 final data cutoff, 64 (30%) of 211 patients in the dabrafenib and trametinib group were on their originally assigned treatment compared with 35 (17%) of 212 in the dabrafenib only group (figure 1). Median time on-study was 20 months (range 0–30) for the dabrafenib and trametinib group and 16 months (range 0–32 months) for the dabrafenib only group.

	Dabrafenib and trametinib (n=211)	Dabrafenib and placebo (n=212)	Comparison	p value
Overall survival				
Died	99 (47%)	123 (58%)		
Median (95% CI, months)	25·1 (19·2–NR)	18·7 (15·2–23·7)	0·71 (0·55–0·92)*	0·0107
1-year overall survival estimate (95% CI)	74% (67–79)	68% (61–74)		
2-year overall survival estimate (95% CI)	51% (44–58)	42% (35–49)		
Progression-free survival†				
Events	139 (66%)	162 (76%)		
Median (95% CI, months)	11·0 (8·0–13·9)	8·8 (5·9–9·3)	0·67 (0·53–0·84)*	0·0004
Best response†‡				
CR	33 (16%)	28 (13%)		
PR	111 (53%)	84 (40%)		
Stable disease	50 (24%)	66 (31%)		
Progressive disease	13 (6%)	19 (9%)		
Not evaluable	3 (1%)	13 (6%)		
Overall responses†‡				
CR + PR (95% CI)	144 (69%; 62–75)	112 (53%; 46–60)	15% (6–25)§	0·0014
Duration of response†‖				
Progressed or died	86 (60%)	79 (70%)		
Median (95% CI, months)	12·9 (9·4–19·5)	10·6 (9·1–13·8)		

CR=complete response. HR=hazard ratio. NR=not reached. ORR=overall response rate. PR=partial response. *HR (95% CI); a Pike estimator; both the HR and the p value from a log-rank test stratified for baseline lactate dehydrogenase and BRAF mutation status. †Events were investigator assessed. ‡Best response includes only patients who had measurable disease at baseline (210 in each group); p values from a χ^2 test. §Difference. ‖Includes all responding patients (144 in the dabrafenib and trametinib group, 113 in the dabrafenib only group).

Table 2: **Outcomes**

At data cutoff, 99 (47%) of 211 patients in the dabrafenib and trametinib group had died versus 123 (58%) of 212 in the dabrafenib only group, with an HR of 0·71 (95% CI 0·55–0·92; p=0·0107; table 2). Median overall survival was 25·1 months (95% CI 19·2–not reached) for the dabrafenib and trametinib group and 18·7 months (15·2–23·7) for the dabrafenib only group (figure 2A, table 2). 1-year survival and 2-year survival were both greater in the dabrafenib and trametinib group than in the dabrafenib only group (table 2). Overall survival was greatest in the dabrafenib and trametinib group for all subgroups analysed (figure 2B).

At data cutoff, 139 (66%) of 211 patients had progressed or died in the dabrafenib and trametinib group versus 162 (76%) of 212 in the dabrafenib only group (HR 0·67, 95% CI 0·53–0·84, p=0·0004; table 2). Median progression-free survival was longer in the dabrafenib and trametinib group than in the dabrafenib only group (11·0 *vs* 8·8; figure 3A, table 2), and progression-free survival was longest in the dabrafenib and trametinib group for all prespecified subgroups (figure 3B).

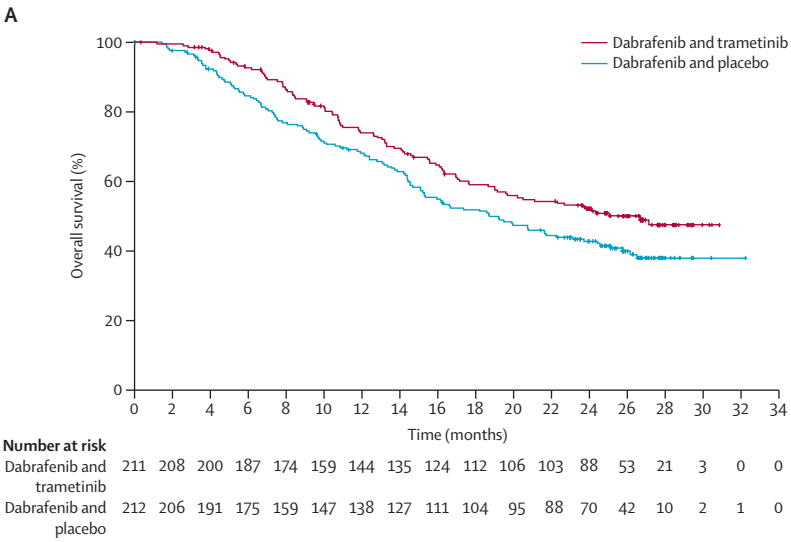

Figure 2: **Overall survival**
In the intention-to-treat population (A) and in pre-specified subgroups (B). LDH=lactate dehydrogenase. ULN=upper limit of normal. ECOG PS=Eastern Cooperative Oncology Group Performance Status.

More confirmed, investigator-assessed responses occurred in the dabrafenib and trametinib group than in the dabrafenib only group (p=0·0014; table 2). More patients had a complete response in the dabrafenib and trametinib group compared with the dabrafenib only group and the median duration of response was longer (table 2).

A similar number of patients continued their assigned study treatment after progression (appendix p 1). 70 patients (33%) in the dabrafenib and trametinib group received cancer treatment after cessation of study treatment compared with 108 (51%) in the dabrafenib only group (appendix p 1). The most common follow-up treatment in both groups was ipilimumab. Anti-PD1 treatment was rare: six (3%) of 211 patients in the dabrafenib and trametinib group versus 14 (7%) of 212 patients in the dabrafenib only group (appendix p 1).

Adverse events related to study treatment occurred in 181 (87%) of 209 patients who received study treatment in the dabrafenib and trametinib group versus 189 (90%) of 211 in the dabrafenib only group. The most common treatment-related adverse events were pyrexia, chills, fatigue, rash, and nausea in the dabrafenib and trametinib group, and hyperkeratosis, fatigue, hand-foot syndrome, alopecia, pyrexia, and arthralgia in the dabrafenib only group (table 3). Fewer patients in the dabrafenib and trametinib group had cutaneous squamous-cell carcinoma, hyperkeratoses, skin papillomas, alopecia, and hand-foot syndrome than did patients in the dabrafenib only group. Conversely, pyrexia was more common in the dabrafenib and trametinib group (table 2). 24 (11%) of 209 patients in the dabrafenib and trametinib group versus 14 (7%) of 211 in the dabrafenib only group permanently discontinued treatment because of adverse events, most often because of pyrexia (five patients [2%] *vs* two [1%]) and ejection fraction decrease (three [1%] *vs* three [1%]).

Grade 3 and 4 treatment-related adverse events occurred in similar proportions in each treatment group (table 3). Five deaths caused by adverse events occurred in the dabrafenib and trametinib group and were not considered related to study treatment: three from cerebral haemorrhage (two of the three patients had brain metastases at death, one of whom was taking an anticoagulant drug), one from pneumonia, and one from drowning. One death related to adverse events occurred in the dabrafenib only group, caused by bile duct adenocarcinoma. New primary malignant cutaneous melanoma was reported in less than 1% of patients in the trametinib and dabrafenib group compared with 2% in the dabrafenib only group. Non-cutaneous treatment-emergent cancers were reported for two patients (1%) in the trametinib and dabrafenib group compared with four (2%) in the dabrafenib only group.

Discussion

In this study, we showed that first-line treatment with a combination of dabrafenib and trametinib significantly improved overall survival and reduced the risk of death by 29% in patients with BRAF Val600Glu/Lys positive metastatic melanoma compared with dabrafenib alone. This survival benefit occurred despite more patients in the dabrafenib only group having subsequent cancer treatments after progression and cessation of study treatment, including treatments that prolong survival in patients with metastatic melanoma (ipilimumab[8] and anti-PD1 treatment[9]).

These results are consistent with COMBI-v, a phase 3 open-label trial[3] of dabrafenib and trametinib combination versus vemurafenib monotherapy, which showed a 31% reduction in the risk of death with the combination.[3] The two studies had similar 1-year survival rates for the dabrafenib and trametinib combination: 74% in our study and 72% in COMBI-v. Our study had longer follow-up than other phase 3 studies of BRAF and MEK inhibitor combinations,[3,10] and was sufficient to show a median overall survival of more than 2 years for the dabrafenib and trametinib combination. This result is also consistent with a randomised phase 2 study.[11,12]

The updated progression-free survival analysis was based on 17 months of additional follow-up compared with the primary analysis.[2] Median progression-free survival for the dabrafenib and trametinib group was longer than that reported in the primary analysis (9·3 months) and similar to that of COMBI-v (11·4 months).[3] Median progression-free survival for the dabrafenib only group was unchanged from the primary analysis, and is the longest median reported for dabrafenib monotherapy. A phase 3 study[10] of vemurafenib combined with cobimetinib—another MEK inhibitor—showed improved progression-free survival compared with vemurafenib monotherapy (median 9·9 *vs* 6·2 months, HR 0·51, p<0·001).

Progression-free survival and overall survival were longer with combination treatment than for dabrafenib only for every subgroup analysed. Furthermore, our results compare favourably with those from trials of single-drug immunotherapies. Ipilimumab given to patients with metastatic melanoma[8] resulted in responses in 11% of patients, 1-year survival of 46%, and 2-year survival of 24%, which are much lower than the results in the dabrafenib and trametinib group in this study (69%, 74%, and 51%, respectively). In a large phase 1 study[13] of pembrolizumab, 40% of ipilimumab-naive patients had a response, and 1-year survival was 74%. In the phase 3 trial,[14] a third of patients had a response and 1-year survival was 74%. Similarly, in a phase 3 study of nivolumab for first-line treatment of patients with *BRAF* wildtype melanoma,[9] 40% of patients had a response and 1-year survival was 73%. These 1-year landmark survival estimates are similar to those reported for dabrafenib and trametinib, and a comparison with the longer survival outcomes will be important as more mature data emerge.

Combined dabrafenib and trametinib was well tolerated, and no new or unexpected adverse events were reported. Pyrexia was still the most common adverse event related to the combination of dabrafenib and trametinib, and was recurrent (three or more episodes) in 53% of patients who had pyrexia on the combination; however, it is manageable.[15] Toxic effects related to paradoxical activation of the MAPK pathway[16] were less common in the dabrafenib and trametinib group than in the dabrafenib only group, including hyperkeratosis, cutaneous squamous cell carcinoma, new primary melanomas, and non-cutaneous treatment-emergent cancers. Five deaths occurred in the combination group (three caused by haemorrhage), none of which were deemed to be treatment-related, compared with one treatment-related death in the dabrafenib only group. Continued vigilance is needed to ascertain whether a subset of patients—eg, those with brain metastases or taking anti-coagulant drugs—have an increased risk of a fatal event in addition to their background risk.

Our findings support the choice of combined dabrafenib and trametinib as the standard targeted

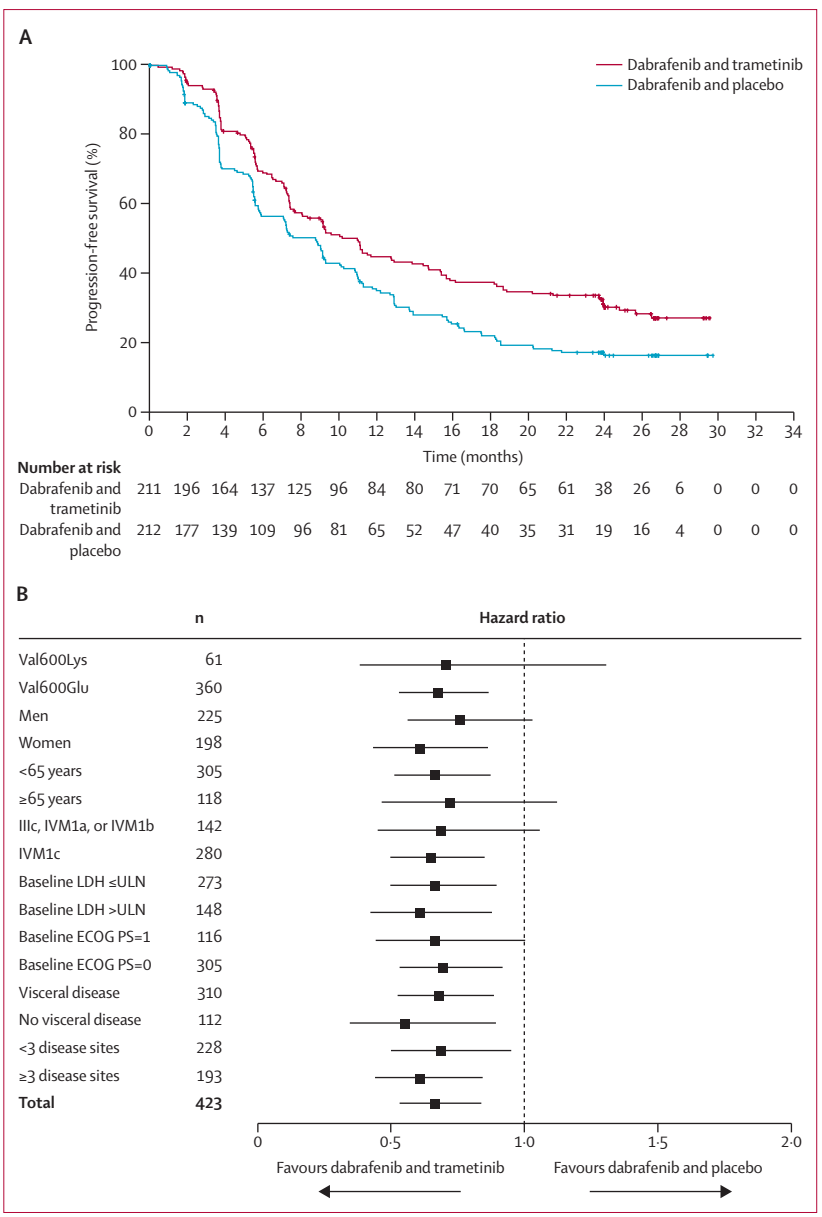

***Figure 3*: Progression-free survival**
In the intention-to-treat population (A) and in pre-specified subgroups (B). LDH=lactate dehydrogenase. ULN=upper limit of normal. ECOG PS=Eastern Cooperative Oncology Group Performance Status.

	Dabrafenib and trametinib (n=209)			Dabrafenib and placebo (n=211)		
	Any grade	Grade 2	Grade 3	Any grade	Grade 2	Grade 3
Events occurring in ≥10% of patients						
Any	181 (87%)	67 (32%)	66 (32%)	189 (90%)	69 (33%)	63 (30%)
Pyrexia*	108 (52%)	47 (22%)	15 (7%)	52 (25%)	21 (10%)	4 (2%)
Chills	58 (28%)	13 (6%)	0	29 (14%)	5 (2%)	1 (<1%)
Fatigue	56 (27%)	20 (10%)	4 (2%)	59 (28%)	21 (10%)	2 (<1%)
Rash	50 (24%)	7 (3%)	0	42 (20%)	5 (2%)	1 (<1%)
Nausea	41 (20%)	8 (4%%)	0	31 (15%)	3 (1%)	1 (<1%)
Headache	39 (19%)	6 (3%)	0	35 (17%)	11 (5%)	0
Diarrhoea	38 (18%)	6 (3%)	1 (<1%)	19 (9%)	3 (1%)	2 (1%)
Arthralgia	34 (16%)	6 (3%)	1 (<1%)	49 (23%)	17 (8%)	0
Vomiting	30 (14%)	5 (2%)	1 (<1%)	20 (9%)	1 (<1%)	1 (<1%)
Aspartate aminotransferase increased	22 (11%)	4 (2%)	6 (3%)	6 (3%)	1 (<1%)	1 (<1%)
Oedema peripheral	22 (11%)	3 (1%)	2 (1%)	4 (2%)	0	0
Alanine aminotransferase increased	20 (10%)	6 (3%)	4 (2%)	7 (3%)	2 (1%)	0
Dry skin	19 (9%)	0	0	29 (14%)	3 (1%)	0
Pruritus	15 (7%)	3 (1%)	0	23 (11%)	3 (1%)	0
Hyperkeratosis	13 (6%)	0	0	70 (33%)	13 (6%)	1 (<1%)
Hand-foot syndrome†	13 (6%)	3 (1%)	1 (<1%)	57 (27%)	17 (8%)	1 (<1%)
Alopecia	10 (5%)	0	0	55 (26%)	5 (2%)	0
Skin papilloma	3 (1%)	0	0	39 (18%)	6 (3%)	0
Adverse events of interest occurring in <10% of patients						
Dermatitis acneiform	17 (8%)	4 (2%)	0	7 (3%)	3 (1%)	0
Bleeding events‡	13 (6%)	0	1 (<1%)	9 (4%)	2 (1%)	1 (<1%)
Ejection fraction decreased	9 (4%)	6 (3%)	3 (1%)	7 (3%)	3 (1%)	4 (2%)
cuSCC§	6 (3%)	0	6 (3%)	20 (9%)	0	20 (9%)
Vision blurred	4 (2%)	1 (<1%)	0	4 (2%)	0	0
Non-cutaneous malignancies¶	2 (1%)	1 (<1%)	1 (<1%)	4 (2%)	0	4 (2%)
Chorioretinopathy	1 (<1%)	0	0	1 (<1%)	1 (<1%)	0
New primary melanoma	1 (<1%)	0	1 (<1%)	4 (2%)	2 (1%)	1 (<1%)

cuSCC=cutaneous squamous-cell carcinoma. One grade 4 event occurred in the dabrafenib and trametinib group (pancytopenia), and three occurred in the dabrafenib and placebo group (thrombocytopenia, febrile neutropenia, hypokalaemia). No grade 5 events occurred in the dabrafenib and trametinib group, and one occurred in the dabrafenib and placebo group (bile duct adenocarcinoma deemed related to study-treatment by investigator). *Body temperature ≥38·5°C. †Includes palmar-plantar erythrodysaesthesia and palmoplantar keratoderma. ‡Includes epistaxis, decreased haemoglobin, purpura, gingival bleeding, decreased haematocrit, decreased international normalised ratio, muscle haemorrhage, decreased red blood cell count, contusion, peritoneal haemorrhage, subarachnoid haemorrhage, and vaginal haemorrhage. §Includes keratoacanthoma and Bowen's disease. ¶One papillary thyroid and one prostate cancer occurred in the dabrafenib and trametinib group; neither were tested for *RAS* mutation status. One bile duct adenocarcinoma (*KRAS* mutation positive), one breast cancer (*RAS* mutation negative), one invasive ductal carcinoma (not tested for *RAS* mutation), and one transitional cell carcinoma (not tested for *RAS* mutation) occurred in the dabrafenib and placebo group.

***Table* 3: Treatment-related adverse events**

treatment, rather than single drug BRAF inhibition, for the patients with BRAF Val600 mutation-positive metastatic melanoma.

Contributors

GVL, DS, PN, CR, AR, DJDeM, JGI, JJL, and KF contributed to the study design. GVL, DS, HG, EL, FdB, JL, CG, TJ, AH, J-JG, VC-S, CL, MMa, MMi, IB, JBAGH, JH, JU, VF, NK, PM, VP, DS, PN, CR, and AA recruited patients and collected data. GVL, HG, FdB, JL, CG, TJ, AH, J-JG, VC-S, CL, MMa, MMi, JU, PM, VP, DS, PN, CR, AR, DJDeM, SS, JJL, FJ, BM, and KF analysed and interpreted data. All authors wrote and approved the report.

Declaration of interests

GVL has received honoraria for consultancy from Bristol-Myers Squibb, Merck, Provectus, Roche, and GlaxoSmithKline and has received personal fees for consultancy from Amgen and Novartis. HG has received research grants and personal fees from GlaxoSmithKline, Bristol-Myers Squibb, Roche, and Novartis, and has received personal fees from MSD and Amgen. EL has received research grants from GlaxoSmithKline, MedImmune, and Roche. JL is supported by the NIHR Royal Marsden Hospital/Institute of Cancer Research Biomedical Research Centre for Cancer. CG has received research grants and personal fees for advisory boards, lectures, consulting, and travel expenses from Roche; has received research grants and personal fees for advisory boards and lecture honoraria from Bristol-Myers Squibb and Roche; has received personal fees for advisory board participation from Amgen and Novartis; and has received personal fees and lecture honorarium from MSD. TJ has received a congress invitation and offered meeting support to GlaxoSmithKline. AH has received honoraria and research grants, and acted as a consultant for Amgen, Bristol-Myers Squibb, Celgene, Eisai, GlaxoSmithKline, MedImmune, MelaSciences, Merck Serono, MSD/Merck, Novartis, Oncosec, and Roche. J-JG has received research grants to his institution and personal fees for advisory boards and lectures from Roche, and has received personal fees for advisory boards and lectures from

GlaxoSmithKline, Bristol-Myers Squibb, Merck, Novartis, and Amgen. VC-S has participated in congresses and advisory boards for GlaxoSmithKline, Roche, Merck, Bristol-Myers Squibb, and Amgen. CL has received personal fees for advisory boards from GlaxoSmithKline, Roche, Bristol-Myers Squibb, MSD, and Novartis. MMa has received personal fees from GlaxoSmithKline, Roche, and Bristol-Myers Squibb, and has received non-financial support from GlaxoSmithKline. AA has received a research grant and personal fees from Roche, and has received personal fees from GlaxoSmithKline and Bristol-Myers Squibb. JBAGH has received a research grant for an investigator-initiated study from GlaxoSmithKline. JH's institution has received a research grant for costs for participation in this trial from GlaxoSmithKline; JH has received personal fees for advisory boards from Roche, Bristol-Myers Squibb, and Merck/MSD. JU has received personal fees for advisory boards from Roche and GlaxoSmithKline. PM has received personal fees, non-financial support, and other support for board membership and lectures, including participation in speakers' bureaus, from GlaxoSmithKline, MSD, Roche, Bristol-Myers Squibb, and Novartis. DS has received personal fees for advisory boards and speaker's bureaus, and study support from Roche, Novartis, GlaxoSmithKline, Bristol-Myers Squibb, and Merck, and has received personal fees for advisory boards and speaker's bureaus from Boehringer Ingelheim and LeoPharma. PN has received personal fees and non-financial support from GlaxoSmithKline. CR has received personal fees for advisory boards from Bristol-Myers Squibb, GlaxoSmithKline, Novartis, Amgen, Merck, and Roche. AR owns stock in Kite/Pharma, and has received honoraria for consultancy from Amgen, Compugen, Flexus, Fabre, GlaxoSmithKline, Genentech, Novartis, and Merck. DJDeM is an employee of GlaxoSmithKline; has a patent issued for "pharmaceutical composition containing trametinib" (Licensee: GlaxoSmithKline) and patent pending for "combinations of trametinib + gemcitabine" (Licensee: GlaxoSmithKline), and owns stock in GlaxoSmithKline. JGI, SS, and JJL are employees of and own stock in GlaxoSmithKline. FJ was an employee of GlaxoSmithKline at the time of study. BM is an employee of GlaxoSmithKline, and holds stock in GlaxoSmithKline, AstraZeneca, and Incyte. KF has acted as a consultant for GlaxoSmithKline, Novartis, and Roche. DS, FdeB, MMi, IB, VF, NK, and VP declare no competing interests.

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