Patient-reported outcomes in patients with resected, high-risk melanoma with *BRAF*^{V600E} or *BRAF*^{V600K} mutations treated with adjuvant dabrafenib plus trametinib (COMBI-AD): a randomised, placebo-controlled, phase 3 trial

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Summary

Background In the phase 3 COMBI-AD study, patients with resected, stage III melanoma with *BRAF*^{V600E} or *BRAF*^{V600K} mutations received adjuvant dabrafenib plus trametinib or placebo. The primary analysis showed that dabrafenib plus trametinib significantly improved relapse-free survival at 3 years. These results led to US Food and Drug Administration approval of dabrafenib plus trametinib as adjuvant treatment for patients with resected stage III melanoma with *BRAF*^{V600E} or *BRAF*^{V600K} mutations. Here, we report the patient-reported outcomes from COMBI-AD.

Methods COMBI-AD was a randomised, double-blind, placebo-controlled, phase 3 study done at 169 sites in 25 countries. Study participants were aged 18 years or older and had complete resection of stage IIIA (lymph node metastases >1 mm), IIIB, or IIIC cutaneous melanoma as per American Joint Committee on Cancer 7th edition criteria, with *BRAF*^{V600E} or *BRAF*^{V600K} mutations, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were randomly assigned (1:1) via an interactive voice response system, stratified by mutation type and disease stage, to receive oral dabrafenib (150 mg twice daily) plus oral trametinib (2 mg once daily) or matching placebos for 12 months. Patients, physicians, and the investigators who analysed the data were masked to treatment allocation. The primary endpoint was relapse-free survival, reported elsewhere. Health-related quality of life, reported here, was a prespecified exploratory endpoint, and was assessed with the European Quality of Life 5-Dimensions 3-Levels (EQ-5D-3L) questionnaire in the intention-to-treat population. We used a mixed-model repeated-measures analysis to assess differences in health-related quality of life between groups. This study is registered with ClinicalTrials.gov, number NCT01682083. The trial is ongoing, but is no longer recruiting participants.

Findings Between Jan 31, 2013, and Dec 11, 2014, 870 patients were enrolled and randomly assigned to receive dabrafenib plus trametinib (n=438) or matching placebos (n=432). Data were collected until the data cutoff for analyses of the primary endpoint (June 30, 2017). The median follow-up was 34 months (IQR 28–39) in the dabrafenib plus trametinib group and 33 months (20·5–39) in the placebo group. During the 12-month treatment phase, there were no significant or clinically meaningful changes from baseline between groups in EQ-5D-3L visual analogue scale (EQ-VAS) or utility scores. During treatment, there were no clinically meaningful differences in VAS scores or utility scores in the dabrafenib plus trametinib group between patients who did and did not experience the most common adverse events. During long-term follow-up (range 15–48 months), VAS and utility scores were similar between groups and did not differ from baseline scores. At recurrence, there were significant decreases in VAS scores in both the dabrafenib plus trametinib group (mean change –6·02, SD 20·57; p=0·0032) and the placebo group (–6·84, 20·86; p<0·0001); the mean change in utility score also differed significantly at recurrence for both groups (dabrafenib plus trametinib –0·0626, 0·1911, p<0·0001; placebo –0·0748, 0·2182, p<0·0001).

Interpretation These findings show that dabrafenib plus trametinib did not affect patient-reported outcome scores during or after adjuvant treatment, and suggest that preventing or delaying relapse with adjuvant therapy could be beneficial in this setting.

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Introduction

The incidence of cutaneous melanoma has continued to increase in recent years.[1] In the metastatic setting, the introduction of targeted therapies (BRAF and MEK inhibitors) and immune checkpoint inhibitors has led to rapid improvement in patient outcomes.[2] Adjuvant therapies for patients with stage III melanoma, who have a high risk of disease recurrence after resection,[3–5] have

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for clinical studies published up to Aug 21, 2018, using the terms "BRAF," "melanoma," and "adjuvant," and identified four articles, of which two were analyses from prospective phase 3 trials of BRAF or MEK inhibitor regimens in patients with resected *BRAF*^{V600}-mutant melanoma. The first of these articles described the primary analysis results from the BRIM8 trial of adjuvant vemurafenib in patients with resected *BRAF*^{V600}-mutant melanoma; no quality-of-life data were reported. The second article was the primary analysis of the COMBI-AD trial.

Added value of this study

We report the health-related quality-of-life outcomes, an exploratory endpoint, from the phase 3 COMBI-AD trial investigating adjuvant dabrafenib plus trametinib versus placebo in patients with resected *BRAF*^{V600}-mutant stage III melanoma. Patient-reported outcomes suggest no change in health-related quality of life in patients treated with adjuvant dabrafenib plus trametinib either during the 12-month treatment phase or during long-term follow-up. To our knowledge, our findings represent the first report of health-related quality of life in patients receiving BRAF or MEK inhibitors as adjuvant therapy for resected melanoma.

Implications of all the available evidence

Our findings provide evidence that adjuvant dabrafenib plus trametinib did not have any substantial effect on patient health-related quality of life. Furthermore, there was a substantial decrease in health-related quality of life after disease recurrence, highlighting the benefit to patients of remaining relapse-free and supporting the use of dabrafenib plus trametinib on the basis of a significant improvement in relapse-free survival in the primary analysis.

been shown to improve relapse-free survival in patients with resected melanoma treated with immune checkpoint inhibitors (ipilimumab,[6] nivolumab,[7] and pembrolizumab[8]) or the targeted combination of BRAF and MEK inhibitors, dabrafenib and trametinib.[9]

In the COMBI-AD trial, patients with stage III cutaneous melanoma harbouring a *BRAF*^{V600E} or *BRAF*^{V600K} mutation who had undergone complete resection were randomly assigned to receive either combination therapy with dabrafenib plus trametinib or two matched placebos.[9] With a median follow-up of 34 months (IQR 28–39) in the dabrafenib plus trametinib arm and 33 months (20·5–39) in the placebo arm, the estimated 3-year relapse-free survival was 58% (95% CI 54–64) for the combination therapy versus 39% (35–44) with placebo (hazard ratio 0·47, 95% CI 0·39–0·58; p<0·001).

The safety profile of dabrafenib plus trametinib in COMBI-AD was similar to that observed in phase 3 trials investigating the combination in patients with advanced melanoma,[10–15] with the most common adverse events of any grade being pyrexia (273 [63%] of 435), fatigue (204 [47%]), and nausea (172 [40%]).[9] However, the proportion of patients discontinuing treatment because of adverse events was higher in the combination therapy arm of the COMBI-AD trial (114 [26%] of 435) when indirectly compared with the combination therapy groups in phase 3 trials in the metastatic setting (14–16%).[12,15]

In the adjuvant setting, it is important to understand patient-reported outcomes during therapy, because some patients might have long-term benefit after surgery, without further intervention. Assessment of patient-reported outcomes with the European Quality of Life 5-Dimensions 3-Levels (EQ-5D-3L) questionnaire was a prespecified exploratory endpoint of the COMBI-AD trial. Here, we report the EQ-5D-3L results during the 12-month adjuvant treatment period, as well as analysis of adverse events that might influence patient-reported outcomes. We also investigated the EQ-5D-3L results during long-term follow-up, and the effect of recurrence on these results.

Methods

Study design and participants

COMBI-AD is a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial done at 169 sites in 25 countries (appendix pp 5–7). Details about patients and methods have been published previously.[9] Briefly, study participants were aged 18 years or older who had complete resection of stage IIIA (lymph node metastases >1 mm), IIIB, or IIIC cutaneous melanoma per American Joint Committee on Cancer (AJCC) 7th edition criteria[16] with *BRAF*^{V600E} or *BRAF*^{V600K} mutation. *BRAF* mutation testing in primary tumour or lymph node tissue was done in central laboratories with the bioMérieux *BRAF* THxID assay (Marcy-l'Etoile, France). Patients were required to have had complete lymphadenectomy and have no clinical or radiographic evidence of residual nodal disease up to 12 weeks before randomisation, have recovered from surgery, and have an Eastern Cooperative Oncology Group performance status of 0 or 1. Full inclusion and exclusion criteria are included in the appendix (p 3).

This study was done in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by the institutional review board at each participating centre. All patients provided written, informed consent.

Randomisation and masking

Patients were randomly assigned (1:1) to receive dabrafenib plus trametinib or two matched placebos. The investigator or designee contacted an interactive voice response system to register, randomly assign, and stratify patients by mutation type (*BRAF*^{V600E} or *BRAF*^{V600K}) and

AJCC 7th edition disease stage (IIIA, IIIB, or IIIC). Patients, physicians, and the investigators who analysed data were masked to treatment allocation. Matching placebo capsules and tablets were used to ensure masking.

Procedures

Patients received either oral dabrafenib (150 mg twice daily plus oral trametinib 2 mg once daily) or two matched placebos for 12 months or until disease recurrence, unacceptable toxicity, withdrawal of consent, or death. Patients were followed up for disease recurrence until the first recurrence event was observed, and then followed up for survival. The disease assessment schedule and procedure have been described previously and are outlined in the appendix (pp 3, 4).[9]

We assessed patient-reported outcomes in the COMBI-AD trial using the EQ-5D-3L questionnaire. The EQ-5D-3L consists of a descriptive assessment of health status spanning five functional dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) and a vertical visual analogue scale (VAS) in which patients rate their current health state, from 100 (best imaginable health state) to 0 (worst imaginable health state).[17] The EQ-5D-3L utility score is derived from answers to the descriptive assessment across all five dimensions. Answers range from 1 to 3, based on whether patients perceive no problem (1), some problems (2), or substantial problems (3). These answers are then converted to a 0 to 1 utility score based on societal preferences (appendix p 4). A change (from baseline or before and after recurrence) or difference between comparator groups of 7 points (0–100 scale) on the VAS or 0·08 points (0–1 scale) in utility score is considered clinically important. Patient-reported outcome assessments were done at baseline and every 3 months during treatment. If a patient discontinued treatment before 12 months, an assessment was done at discontinuation. During follow-up, patients without disease recurrence were assessed every 3 months for the first 24 months, and every 6 months thereafter until study completion, withdrawal, or death. It was prespecified that patients with recurrence remained in the study for assessment. After disease recurrence, patients completed the EQ-5D-3L every 3 months for the first 24 months and then every 6 months thereafter until study completion, withdrawal, or death.

Analyses of adverse events and laboratory values have been described previously.[9] Briefly, adverse events and laboratory values were assessed at screening, at the time of randomisation, at least once per month for 12 months, and then at each visit for assessment of disease recurrence after 12 months. Adverse events were graded by the investigator according to Common Terminology Criteria for Adverse Events (version 4.0). Pyrexia was characterised further, by incidence, time to onset, time to resolution, and management strategies.

Outcomes

The primary endpoint was relapse-free survival. Secondary endpoints included overall survival, distant metastasis-free survival, freedom from relapse, and safety. Here, we report health-related quality of life, assessed with the EQ-5D-3L, which was a prespecified exploratory endpoint.

Statistical analysis

We included EQ-5D-3L data from the intention-to-treat population that were collected until the data cutoff for analyses of the primary endpoint (June 30, 2017). Because health-related quality of life was an exploratory outcome, the analyses presented here are not powered for statistical comparison. Safety analyses included all patients who had received at least one dose of trial drug. Baseline scores were reported with standard descriptive statistics. We summarised changes in scores from baseline at each assessment for the VAS and all five EQ-5D-3L dimensions. We did ANCOVA to assess differences between groups in utility and VAS scores, adjusted for baseline score with mixed-model repeated measures, and with time, treatment, baseline score by time interaction, and treatment by time interaction as fixed effects. We used an unstructured covariance matrix for the change from baseline utility and VAS scores. We generated p values for comparison of mean scores between pre-recurrence and post-recurrence assessments using a two-tailed, paired *t* test with a 5% level of significance. We also used this approach for the comparison of post-recurrence assessments with baseline scores and assessment of anxiety or depression subscale scores before and after recurrence. Clinical significance indicates that the difference in score meets an established

	Dabrafenib plus trametinib group (n=438)		Placebo group (n=432)	
	Patients completing assessment	Available patients completing assessment	Patients completing assessment	Available patients completing assessment
Baseline	430 (98%)	430/438 (98%)	422 (98%)	422/432 (98%)
Month 3	383 (87%)	383/406 (94%)	366 (85%)	366/383 (96%)
Month 6	363 (83%)	363/391 (93%)	299 (69%)	299/320 (93%)
Month 9	343 (78%)	343/380 (90%)	254 (59%)	254/268 (95%)
Month 12	338 (77%)	338/365 (93%)	237 (55%)	237/245 (97%)
Month 15	318 (73%)	318/350 (91%)	208 (48%)	208/219 (95%)
Month 18	304 (69%)	304/328 (93%)	198 (46%)	198/202 (98%)
Month 21	273 (62%)	273/300 (91%)	176 (41%)	176/188 (94%)
Month 24	254 (58%)	254/283 (90%)	172 (40%)	172/183 (94%)
Month 30	233 (53%)	233/260 (90%)	166 (38%)	166/174 (95%)
Month 36	186 (42%)	186/202 (92%)	132 (31%)	132/146 (90%)
Month 42	104 (24%)	104/120 (87%)	84 (19%)	84/92 (91%)
Month 48	43 (10%)	43/55 (78%)	31 (7%)	31/33 (94%)

Data are n (%) or n/N (%).

Table: **Proportion of patients completing the EQ-5D-3L questionnaire at assessment timepoints**

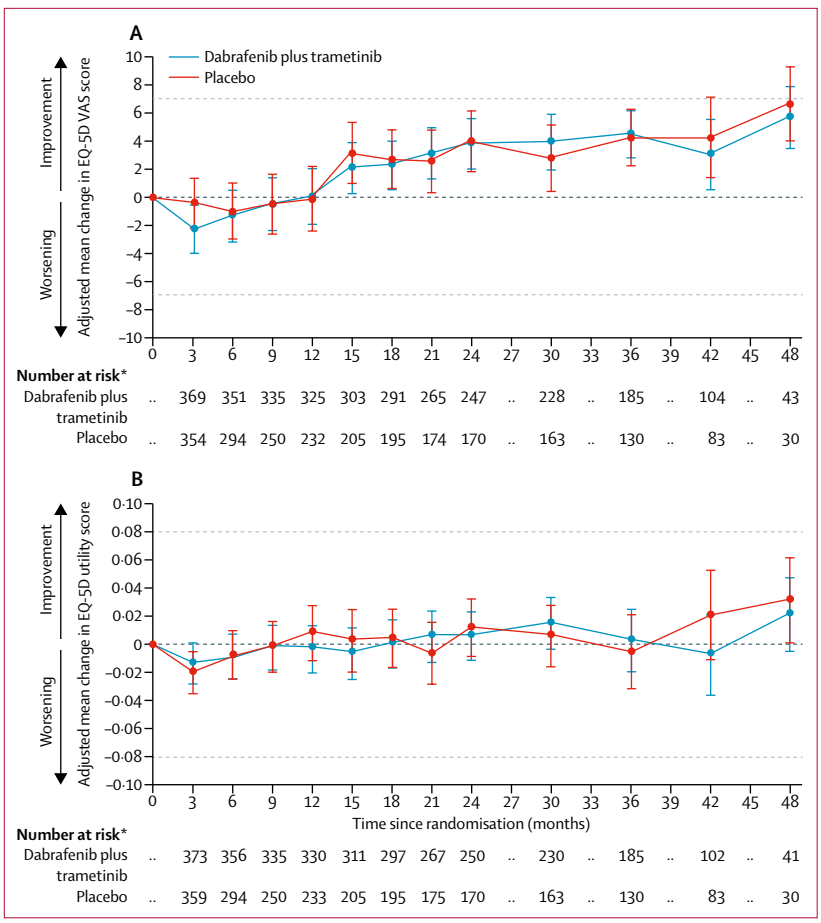


Figure 1: **Change from baseline in EQ-5D-3L VAS and utility scores**
Adjusted mean change (95% CI) from baseline in European Quality of Life 5-Dimensions 3-Levels visual analogue scale (EQ-5D-3L VAS; A) and utility (B) scores during the 12-month treatment phase and long-term follow-up (15–48 months). Dashed lines represent the threshold for clinically meaningful change from baseline. An improved score is indicated by a positive value; a worsened score is indicated by a negative value. *Number of patients with all available covariates at each timepoint.

threshold (seven points for VAS and 0·08 for the utility score) that has previously been shown to be the minimal change that is perceived by the patient as being beneficial or detrimental, or would result in a change in treatment. To assess whether adverse events experienced during treatment affected patient perception of health status, we assessed utility and VAS scores in patients who did and did not have specific adverse events (pyrexia, nausea, headache, chills, diarrhoea, vomiting, arthralgia, and rash) during treatment in the dabrafenib plus trametinib group in a post-hoc analysis. We used SAS (version 9.3) for all the analyses presented in the manuscript. This trial is registered with ClinicalTrials.gov, number NCT01682083.

Role of the funding source

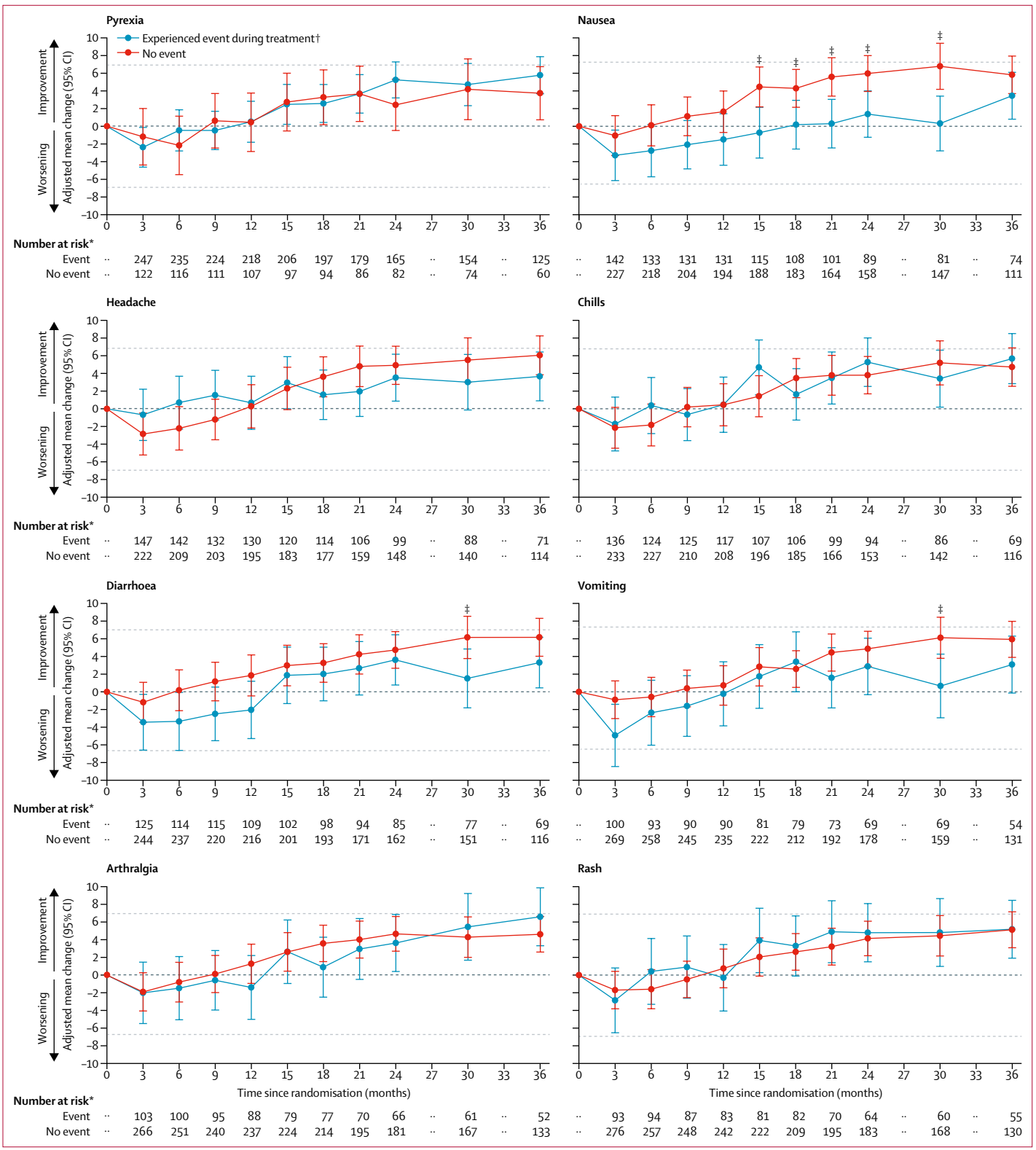
The study was designed by the authors in conjunction with representatives of the sponsor. Data were collected and analysed by the sponsor and analysed in collaboration with the authors. The sponsor was involved in the writing of the report and data interpretation. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Results

Between Jan 31, 2013, and Dec 11, 2014, 870 patients were enrolled and randomly assigned to receive dabrafenib plus trametinib (n=438) or two matching placebos (n=432) for 12 months. Baseline characteristics and disease history were reported previously, and were well balanced between groups.[9] The median follow-up was 34 months (IQR 28–39) in the dabrafenib plus trametinib group and 33 months (20·5–39) in the placebo group. All patients were included in the assessment of patient-reported outcomes, and the number of patients available for health-related quality-of-life assessment throughout the study is presented in the appendix (p 15). The proportion of patients completing the EQ-5D-3L questionnaire, in both groups, was more than 95% at baseline, more than 90% at 36 months, and more than 75% at 48 months (table). The number of patients available for assessment of patient-reported outcomes decreased over time in both groups.

At baseline, mean EQ-5D-3L VAS and utility scores were similar between groups (mean EQ-5D-3L VAS 79·0 [SD 21·9] for dabrafenib plus trametinib group *vs* 80·4 [19·1] for placebo group; mean utility score 0·8577 [0·1763] *vs* 0·8676 [0·1707]; appendix pp 8–9). During the treatment phase, adjusted mean VAS scores remained similar to those at baseline, with no clinically meaningful changes between treatment groups (figure 1A; appendix p 10). The maximum observed difference in adjusted mean VAS scores between treatment groups occurred at the 3-month assessment (–1·86, 95% CI –4·34 to 0·61), with lower scores in the dabrafenib plus trametinib group. Adjusted mean EQ-5D-3L utility scores were similar between treatment groups, with no clinically meaningful changes from baseline observed in either group (figure 1B; appendix p 11). A similar proportion of patients in each group reported some or extreme problems across all five dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) at baseline (appendix p 16). At 12 months, a higher proportion of patients in the dabrafenib plus trametinib group than in the placebo group reported

Figure 2: **Effect of adverse events on EQ-5D-3L VAS scores**
Adjusted mean change (95% CI) in European Quality of Life 5-Dimensions 3-Levels visual analogue scale (EQ-5D-3L VAS) score from baseline in patients in the dabrafenib plus trametinib arm based on adverse events experienced during treatment. Dashed lines represent the threshold for clinically meaningful change from baseline. An improved score is indicated by a positive value; a worsened score is indicated by a negative value. *Number of patients with all available covariates at each timepoint. †Includes any patient who experienced the respective adverse event at any point during the 12-month treatment phase. ‡Descriptive p value is below the threshold (p=0·05) between arms.


Pyrexia
Experienced event during treatment†
No event
Improvement
Worsening
Adjusted mean change (95% CI)
Nausea
Headache
Chills
Diarrhoea
Vomiting
Arthralgia
Rash
Time since randomisation (months)
Number at risk*
Event 247 235 224 218 206 197 179 165 154 125
No event 122 116 111 107 97 94 86 82 74 60
Event 142 133 131 131 115 108 101 89 81 74
No event 227 218 204 194 188 183 164 158 147 111
Event 147 142 132 130 120 114 106 99 88 71
No event 222 209 203 195 183 177 159 148 140 114
Event 136 124 125 117 107 106 99 94 86 69
No event 233 227 210 208 196 185 166 153 142 116
Event 125 114 115 109 102 98 94 85 77 69
No event 244 237 220 216 201 193 171 162 151 116
Event 100 93 90 90 81 79 73 69 69 54
No event 269 258 245 235 222 212 192 178 159 131
Event 103 100 95 88 79 77 70 66 61 52
No event 266 251 240 237 224 214 195 181 167 133
Event 93 94 87 83 81 82 70 64 60 55
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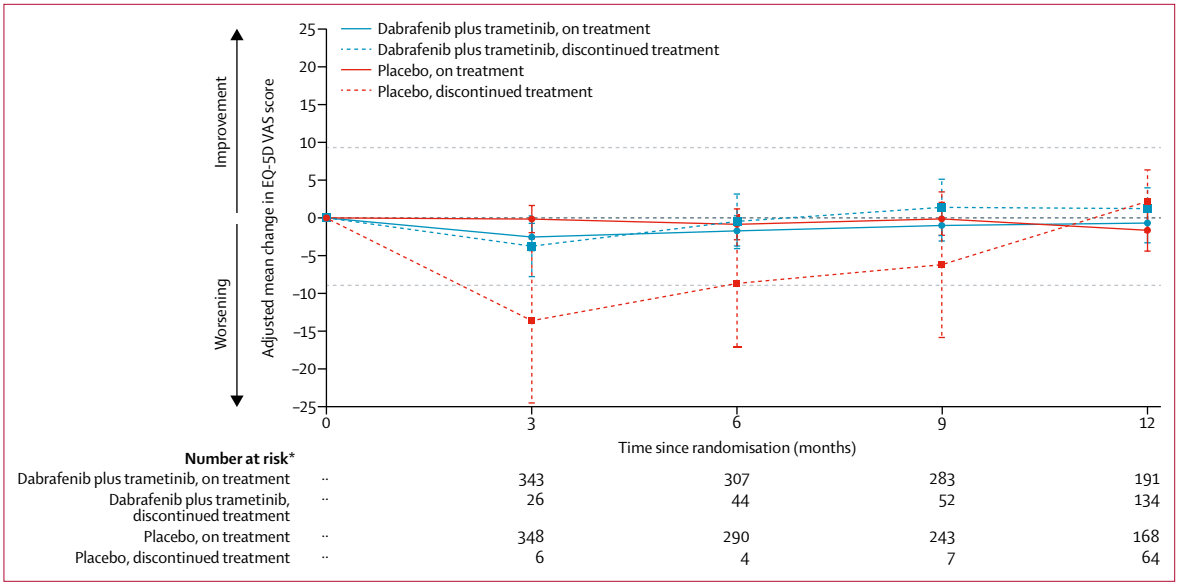

Figure 3: **Change from baseline in EQ-5D-3L VAS score based on early treatment discontinuation**
Adjusted mean change from baseline (95% CI) in European Quality of Life 5-Dimensions 3-Levels visual analogue scale (EQ-5D-3L VAS) score in patients who discontinued or were on treatment at corresponding timepoints. Dashed lines represent the threshold for clinically meaningful change from baseline. An improved score is indicated by a positive value; a worsened score is indicated by a negative value. *Number of patients with all available covariates at each timepoint.

problems in mobility (55 [15%] of 365 *vs* 19 [8%] of 245) and usual activities (68 [19%] *vs* 32 [13%]), while a higher proportion of patients in the placebo group reported problems in the anxiety or depression dimension than in the dabrafenib plus trametinib group (65 [27%] *vs* 81 [22%]; appendix p 16).

After the 12-month treatment period, we continued the assessments to assess EQ-5D-3L scores during long-term follow-up. From 15 to 48 months, adjusted mean VAS scores remained similar between groups (figure 1; appendix p 10). At 48 months, adjusted mean change in VAS score was 5·79 (95% CI 2·21) in the dabrafenib plus trametinib group and 6·77 (2·65) in the placebo group. Adjusted mean utility scores remained similar to baseline in both arms, with no differences noted between treatment groups (figure 1; appendix p 11). 130 patients received dabrafenib, trametinib, or the combination as post-therapy treatment (44 patients in the dabrafenib plus trametinib group, 86 patients in the placebo group). 114 (88%) of 130 patients started post-therapy treatment after 18 months, and compliance with patient-reported outcome assessments in these patients was low (appendix p 13).

In a post-hoc analysis of the most common adverse events, there were no clinically meaningful changes in EQ-5D-3L scores between patients who did and did not experience the event in the dabrafenib plus trametinib group (figure 2). There were no clinically meaningful differences in utility score (figure 2). These data represent all patients who experienced the respective adverse event at any point during the 12-month treatment phase and not necessarily at the time of quality-of-life assessment; thus, they should be interpreted cautiously. There was no clinically meaningful difference in VAS scores between patients who did and did not experience any of the most common adverse events during any point in the treatment phase, and VAS scores improved over time in patients who experienced each of the most common adverse events. Patients who had gastrointestinal adverse events (ie, nausea, vomiting, diarrhoea) were the only group to report any significant difference in EQ-5D-3L scores, but these differences occurred after the end of treatment. Notably, there were no clinically meaningful differences between patients in the dabrafenib plus trametinib group who experienced and did not experience pyrexia during the 12-month treatment phase (figure 2). Because pyrexia was the most frequent adverse event,[9] we further characterised the timing and management of events to provide additional context to these results. Most patients had the first occurrence of pyrexia within the first 6 months of treatment (median time to onset in patients receiving the combination 23 days [IQR 11–63 days]; appendix pp 12, 17), with pyrexia events lasting a median of 3 days (IQR 2–7) in both groups (appendix p 12). Pyrexia recurrence was common, since 209 (72%) of 292 patients who experienced pyrexia had two or more episodes in the dabrafenib plus trametinib group. However, 289 (99%) of 292 patients who experienced pyrexia had resolution of symptoms and most were managed with interruption of dabrafenib (202 [69%]) or trametinib (121 [41%]).

We further assessed the effect of early treatment discontinuation on patient perception of health status in post-hoc analyses. We did a subgroup analysis based on whether patients were on treatment or had discontinued treatment at the 3-month, 6-month, 9-month, and

12-month assessments. In the placebo group, VAS scores were lower in patients who discontinued treatment early than in those who remained on treatment at the 3-month, 6-month, and 9-month assessments (figure 3). However, very few patients had discontinued treatment at these timepoints, which limited comparison between groups. Assessment of VAS scores in patients in the dabrafenib plus trametinib group who remained on treatment compared with those who discontinued treatment showed similar adjusted mean changes from baseline throughout the four assessment periods (figure 3).

To investigate whether disease recurrence had an effect on patient perception of health status, we did a post-hoc analysis to compare mean EQ-5D-3L VAS and utility scores at the visit before diagnosis of recurrence and at the visit after diagnosis of recurrence. After recurrence, mean VAS scores significantly decreased in both the dabrafenib plus trametinib and placebo group (mean change –6·02, SD 20·57; p=0·0032) and placebo group (–6·84, 20·86; p<0·0001; figure 4A). Similar results were observed for utility scores, with a significant decrease in both groups after recurrence (mean change –0·0626, SD 0·1911, p<0·0001 in the dabrafenib plus trametinib group and mean change –0·0748, 0·2182, p<0·0001 in the placebo group; figure 4B). There were similar findings when we compared post-recurrence assessments with baseline scores (appendix p 14).

To assess the psychological effect of disease recurrence, we assessed the effect of recurrence on patient perception of anxiety or depression on the EQ-5D-3L with a post-hoc analysis (appendix p 18). After recurrence, anxiety and depression scores worsened in both treatment groups, compared with the pre-recurrence assessment (mean change 0·11; p=0·028 for the dabrafenib plus trametinib group; 0·13; p<0·0001 for the placebo group).

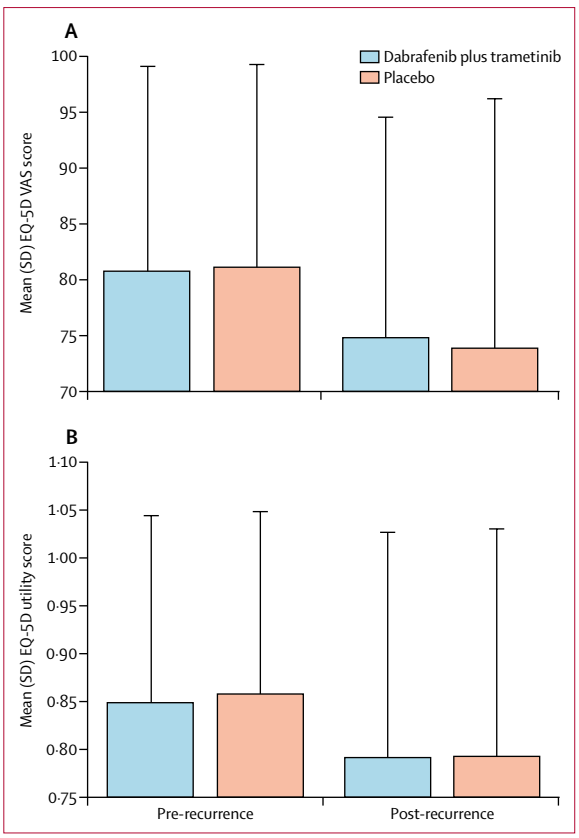

Figure 4: **Effect of recurrence on EQ-5D-3L VAS and utility scores**
Mean (SD) European Quality of Life 5-Dimensions 3-Levels visual analogue scale (EQ-5D-3L VAS) scores (A) and utility scores (B) at assessments before and after recurrence.

Discussion

The results from this prespecified patient-reported outcome analysis suggest that treatment with dabrafenib plus trametinib had no substantial effect on patients' perception of their health status, as measured by EQ-5D-3L VAS and utility scores, either during the 12-month treatment period or in long-term follow-up.

During the treatment phase, there was an initial decrease in VAS scores in patients in the dabrafenib plus trametinib group at 3 months, but this did not differ, statistically or clinically, from VAS scores at baseline or in the placebo group. Subsequently, VAS scores then returned to baseline levels by month 12. This result might be attributable to some patients initially experiencing adverse events that affected patient-reported health status and the subsequent improvement in management of adverse events over time. There were no clinically meaningful changes from baseline VAS scores at the time of discontinuation in patients who discontinued treatment early in the dabrafenib plus trametinib group.

There are some limitations to these analyses. In the assessment of the effect of adverse events on EQ-5D-3L scores, patients were divided according to whether they had the adverse event at any time during the treatment phase; thus, patients might not have been experiencing an adverse event at the time of the assessments and this could lead to recall bias. Additionally, selection bias might have influenced these findings, because patients with the most detriment to health might have withdrawn early from the study and therefore might not be captured in later assessments. The EQ-5D-3L also has some inherent limitations as an assessment tool, including limited assessment of social and psychosocial function, insensitivity to mild health changes compared with disease-specific assessments, and the potential for ceiling effects. The EQ-5D-3L was an exploratory endpoint of the trial and was not adequately powered for statistical assessment of the effect of treatment on EQ-5D-3L scores.

Recently, several trials have investigated drugs as adjuvant treatment in patients with resected melanoma, including the immune checkpoint inhibitors ipilimumab, nivolumab, and pembrolizumab. The EORTC 18071 trial[6] showed significant improvement in relapse-free survival

and overall survival with ipilimumab as adjuvant therapy in patients with resected stage III melanoma. The CheckMate-238 trial[7] showed a significant improvement in relapse-free survival benefit with nivolumab compared with ipilimumab. More recently, results from the KEYNOTE-054 trial[8] showed a significant improvement in relapse-free survival in patients treated with adjuvant pembrolizumab. There were some design differences between adjuvant trials.[6–9] In the EORTC 18071 trial, ipilimumab was given at 10 mg/kg every 3 weeks for four doses and then every 3 months for up to 3 years, whereas in the COMBI-AD, CheckMate-238, and KEYNOTE-054 trials, treatment could be continued for a maximum of 1 year. Additionally, the COMBI-AD, EORTC 1807, and KEYNOTE-054 trials enrolled patients with resected stage IIIA/B/C disease as per AJCC 7th edition criteria; however, the CheckMate-238 trial enrolled patients with resected stage IIIB/C or IV melanoma.

Both the EORTC 18071 and CheckMate-238 trials assessed patient-reported outcomes. There was no significant deterioration in global health status as assessed by the EORTC Quality of Life Questionnaire-C30 (QLQ-C30) in the EORTC 18071 trial after induction of treatment, despite substantial toxicity in the ipilimumab group (254 [54%] of 471 patients had grade 3–4 adverse events; 245 (52%) patients discontinued because of adverse events).[18] The toxicity in the ipilimumab group was reflected by significantly worse symptom scores for diarrhoea, insomnia, and fatigue with ipilimumab than for placebo. In the CheckMate-238 trial, there were no significant or clinically meaningful changes from baseline in either treatment group (nivolumab or ipilimumab) for EORTC QLQ-C30 global health status or EQ-5D-3L VAS or utility scores.[7] It should be noted that the follow-up in CheckMate-238 (median 19·5 months) was considerably shorter than that in the COMBI-AD trial (median 2·8 years).[7,9] The shorter follow-up period in the CheckMate-238 trial might limit the ability to interpret factors affecting patient-reported outcomes after treatment discontinuation.

Patient-reported outcomes during treatment with dabrafenib plus trametinib have been previously reported in the COMBI-d and COMBI-v trials of patients with *BRAF*^{V600}-mutant unresectable or metastatic melanoma.[19,20] In this population, treatment with dabrafenib plus trametinib led to improvement from baseline in health-related quality of life outcomes, which was significantly better than with vemurafenib monotherapy (COMBI-v) or dabrafenib monotherapy (COMBI-d). In this trial, there were no clinically meaningful changes relative to baseline in either treatment group for EQ-5D-3L VAS or utility scores, and no significant or clinically meaningful differences were reported between the combination therapy and placebo groups. These findings could be due to the relatively high baseline EQ-5D-3L scores reported in patients with resected disease in this study (EQ-5D-3L utility score 0·8577 [SD 0·176], EQ-5D-3L VAS score 79·0 [21·88] in the combination group) when indirectly compared with those in patients with unresectable or metastatic disease, who might have higher symptom burden, treated with the combination (EQ-5D-3L utility score 0·751, EQ-5D-3L VAS score 68·3 in the COMBI-v combination group).[20] For reference, in the UK, the mean EQ-5D-3L utility score was 0·849 and the mean VAS score was 82·0, with index population data from people aged 45–54 years.[21] Although reference data are widely variable, patients with resected melanoma in the COMBI-AD trial might have a perception of health status that is closer to the general population at baseline, compared with those previously assessed in the metastatic setting, providing less opportunity for improvement in patient-reported health status.

Patients in both treatment groups reported a significant deterioration in EQ-5D-3L VAS scores after disease recurrence. These findings are consistent with those from patients with metastatic melanoma, in whom disease progression is associated with deterioration in patient-reported outcomes, regardless of treatment received.[19,20,22] Findings from an observational study in patients with stage IIIB/C melanoma showed that distant recurrence was associated with a greater decrease in health-related quality of life compared with locoregional recurrence.[23] Notably, results from a population-based analysis showed that disease recurrence or progression was associated with lower scores across functional domains on the EORTC-QLQ-C30, with the greatest decrease in emotional, role, and social functioning domains.[24] On the basis of the substantial effect of relapse on EQ-5D-3L scores, it is likely that the reduced risk of relapse in the dabrafenib plus trametinib group contributed to maintenance of patient-reported health status, despite an increase in toxicity.

Pyrexia was the most common adverse event in the COMBI-AD trial,[9] but nearly all patients who had pyrexia (99%) recovered, with a median time to resolution of 3 days; most were managed through dose interruption of dabrafenib, trametinib, or both. Further characterisation showed that most patients experienced the first episode of pyrexia early during the course of treatment (median time to onset of first occurrence 23 days). This finding is consistent with reports in a pooled analysis of trials investigating dabrafenib plus trametinib in patients with unresectable or metastatic melanoma, which showed that the incidence of nearly all adverse events, including pyrexia, decreased substantially with increased time on treatment.[25] Assessment of adjusted mean change from baseline in VAS and utility scores showed no clinically meaningful decrease in EQ-5D-3L scores in patients who experienced pyrexia compared with those who did not. However, interpretation of the effect of pyrexia on patient-reported health status is difficult because, despite the high incidence of pyrexia in the trial, a much smaller proportion of patients would probably have an ongoing episode of pyrexia at the time

of any individual assessment. Furthermore, the results could be confounded by the nature of a placebo-controlled trial, whereby patients can interpret the emergence of adverse events as being associated with active therapy and the potential for treatment benefit. Although pyrexia was well managed in this trial, additional management strategies based on clinical practice could help to minimise the effect of pyrexia and associated discontinuations.[9,26] Unlike pyrexia, some gastrointestinal adverse events were associated with a decrease in VAS scores during the 12-month treatment, which could play a part in overall wellbeing for these patients, but none of these decreases were clinically meaningful.

By contrast with adverse events in the dabrafenib plus trametinib group, most treatment-related adverse events in patients receiving nivolumab in the CheckMate-238 trial[7] had a longer median time to onset (median across categories 3·3–14·2 weeks), took longer to resolve (range of median times to resolution across categories 0·1–48·1 weeks), and many had not resolved by the data cutoff. However, with the shorter follow-up time in CheckMate-238, it is unknown whether persistent adverse events after the treatment period could affect long-term patient-reported outcomes.

In the absence of disease-related symptoms in the adjuvant setting, the results from these analyses suggest that dabrafenib plus trametinib did not negatively affect EQ-5D-3L scores during treatment or in long-term follow-up, similar to observations from patients with breast cancer receiving adjuvant therapy.[27] Furthermore, EQ-5D-3L scores decreased in both groups upon disease recurrence, suggesting the value to patients of remaining recurrence free. When combined with previous results that showed a significant improvement in relapse-free survival in patients who received dabrafenib plus trametinib, the lack of a decrement in EQ-5D-3L scores in the COMBI-AD trial suggests a favourable risk-benefit profile for adjuvant dabrafenib plus trametinib.

Contributors

RK was a member of the Trial Steering Group. CR, BM, RK, RD, JMK, and GVL designed the study. VC-S and RP were involved in patient recruitment and treatment. AHau, MS, VA, MM, VC-S, JL, MN, AHay, CR, LM, RP, BM, RD, JMK, JS, and GVL collected the data. DS and MM reviewed the data. AHau, VA, CR, LM, KD, SM, BM, RD, JS, and JMK analysed the data. DS, AHau, VA, VC-S, JL, AHay, CR, LM, RP, SM, BM, RK, RD, JMK, JS, and GVL interpreted the data. DS, AHau, VA, VC-S, JL, AHay, RP, SM, RD, JMK, KD, JS, and GVL wrote the manuscript. KD drafted and reviewed the manuscript. CD, CR, RP, BM, RK, KD, JS, and JMK reviewed the manuscript. MS and JMK revised the manuscript. JL, AHay, and TL did a final review of the manuscript. DS and MM approved the manuscript.

Declaration of interests

DS reports personal fees from Amgen, Boehringer Ingelheim, Leo Pharma, Roche, Merck Sharp & Dohme (MSD), Novartis, Incyte, Regeneron, 4SC, AstraZeneca, Bristol-Myers Squibb, Pierre Fabre, Merck-EMD, Pfizer, Philogen, and Array; and patients' fees from Roche, Merck/MSD, Novartis, Regeneron, Bristol-Myers Squibb, Merck-EMD, and Philogen. AHau reports personal fees for consultancy from Novartis; clinical trial support grants from Amgen, Bristol-Myers Squibb, Merck Serono, MSD, Philogen, Pierre Fabre, Provectus, Regeneron, and Roche to his institution; personal fees for speaker's honoraria from Amgen, Bristol-Myers Squibb, Merck Serono, MSD, Pierre Fabre, Provectus, and Roche; and personal fees for consultancy from Amgen, Bristol-Myers Squibb, Merck Serono, MSD, Philogen, Pierre Fabre, Provectus, Regeneron, Roche, and OncoSec. VA reports honoraria from Bristol-Myers Squibb, MSD, Novartis, Pierre Fabre, and Merck Serono; consultancy or advisory role for Bristol-Myers Squibb, MSD, Novartis, Pierre Fabre, and Merck Serono; speakers' bureau for Bristol-Myers Squibb, MSD, Novartis, and Roche; and travel, accommodations, expenses for Bristol-Myers Squibb. MM reports grants for advisory board and speech from Bristol-Myers Squibb, MSD, Novartis, and Roche. VC-S reports consultancy in advisory boards for Novartis, MSD, Merck Serono, Pierre Fabre, and Bristol-Myers Squibb; and personal fees for medical congress expense from Bristol-Myers Squibb. JL reports consultancy for Eisai, GlaxoSmithKline, Kymab, Roche/Genentech, Secarna, Pierre Fabre, and EUSA Pharma; and research and consultancy for Bristol-Myers Squibb, MSD, Pfizer, and Novartis. MN reports honorarium paid to hospital, no personal fees, from Novartis Norwegian advisory board, Incyte Nordic advisory board, Novartis lecture, and Bristol-Myers Squibb lecture. CD reports consultancy or advisory role for Bristol-Myers Squibb, MSD, Novartis, and Roche. AHay reports personal fees for advisory board participation and honoraria from Novartis and Merck. CR reports personal fees for consultant advisory board from Bristol-Myers Squibb, Pierre Fabre, Novartis, Amgen, Merck, and Roche. LM reports travel for medical congress from Novartis. TL reports clinical trial grant and personal fees from Roche and personal fees from Bristol-Myers Squibb, MSD, and Novartis. RP reports clinical trial costs to institution from GlaxoSmithKline and Novartis; and personal fees for chairing a speaker meeting from Novartis. KD and RKo report employment by Novartis. SM reports employment by Novartis and stock ownership in Novartis. BM reports employment by Novartis and stock ownership in Novartis, GlaxoSmithKline, Incyte, and AstraZeneca. RKe reports conference reporting from Bristol-Myers Squibb and Amgen; advisory board for Teva; and institutional reimbursement for advisory boards from Novartis and GlaxoSmithKline. RD reports intermittent, project focused consulting or advisory relationships with Novartis, Merck Sharp & Dohme, Bristol-Myers Squibb, Roche, Amgen, Takeda, Pierre Fabre, and Sun Pharma. JMK reports personal fees from Bristol-Myers Squibb, Merck, Novartis, Roche, Genentech, EMD Serono, and Array BioPharma; and grants from Merck and Prometheus. GVL reports consultancy or advisory role for Bristol-Myers Squibb, Roche/Genentech, Amgen, Merck, Novartis, Array BioPharma, Pierre Fabre, Incyte, and Oncosec, and honoraria from Bristol-Myers Squibb, Merck, Roche, Novartis, and Incyte. MS and JS declare no competing interests.

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