Original Research

Health-related quality of life in patients with fully resected $BRAF^{V600}$ mutation−positive melanoma receiving adjuvant vemurafenib

Dirk Schadendorf [a,b,*], Anna Maria Di Giacomo [c], Lev Demidov [d], Barbara Merelli [e], Igor Bondarenko [f], Paolo A. Ascierto [g], Christopher Herbert [h], Andrzej Mackiewicz [i], Piotr Rutkowski [j], Alexander Guminski [k], Grant R. Goodman [l], Brian Simmons [l], Chenglin Ye [l], Agnes Hong [l], Karl Lewis [m], the BRIM8 Investigators

[a] *Department of Dermatology, University Hospital Essen, Hufelandstr. 55, 45122, Essen, Germany*
[b] *The German Cancer Consortium, Heidelberg, Germany*
[c] *Division of Medical Oncology and Immunotherapy, Center for Immuno-Oncology, University Hospital of Siena, Banchi di Sotto, 55, 53100, Siena, SI, Italy*
[d] *N. N. Blokhin Russian Cancer Research Center, Ministry of Health, Russian Academy of Medical Sciences, Kashirskoye Shosse 24, 115478, Moscow, Russian Federation*
[e] *Department of Oncology and Haematology, Papa Giovanni XXIII Cancer Center Hospital, Centro Ospedaliero, 24129, Bergamo, BG, Italy*
[f] *Dnipropetrovsk State Medical Academy, Volodymyra Vernadskoho St, 9, Dnipropetrovsk, 49044, Ukraine*
[g] *Melanoma Unit, Cancer Immunotherapy and Development Therapeutics, Istituto Nazionale Tumori, IRCCS Fondazione Pascale, Via Mariano Semmola, 53, 80131, Napoli, NA, Italy*
[h] *Bristol Haematology and Oncology Centre, Horfield Rd, Avon, Bristol, BS2 8ED, United Kingdom*
[i] *Department of Cancer Immunology, Poznan University for Medical Sciences, Med-POLONIA, Collegium Maius, Fredry 10, 61-701, Poznań, Poland*
[j] *Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Institute − Oncology Center, Wawelska 15 B, 00-001, Warsaw, Poland*
[k] *Melanoma Translational Research Group, Melanoma Institute Australia, 40 Rocklands Rd, Wollstonecraft NSW, 2065, New South Wales, Australia*
[l] *Genentech, Inc., 410 Allerton Ave, South San Francisco, CA, 94080, USA*
[m] *University of Colorado Comprehensive Cancer Center, 1665 Aurora Court Anschutz Cancer Pavilion, Aurora, CO 80045, USA*

* *Corresponding author*: Department of Dermatology, University Hospital Essen, Hufelandstr. 55, 45122, Essen, Germany. Fax: +49 201 723-5935.
 E-mail address: dirk.schadendorf@uk-essen.de (D. Schadendorf).

Abstract   *Aim of study:* The aim of the study was to assess the impact of treatment with adjuvant vemurafenib monotherapy on health-related quality of life (HRQOL) in patients with resected stage IIC−IIIC melanoma.

Methods: The phase 3 BRIM8 study (NCT01667419) randomised patients with $BRAF^{V600}$ mutation−positive resected stage IIC−IIIC melanoma to 960 mg of vemurafenib twice daily or matching placebo for 52 weeks (13 × 28-day cycles). Patients completed the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) version 3 at baseline, cycle 1 (days 1, 15 and 22), cycle 2 (days 1 and 15), day 1 of every subsequent 4-week cycle, the end-of-treatment visit and each visit during the follow-up period.

Results: Completion rates for the EORTC QLQ-C30 questionnaire were high (>80%). There was a mean decline in the global health status (GHS)/quality of life (QOL) score of 17.4 (±22.9) and 17.3 (±24.1) points at days 15 and 22 of cycle 1, respectively, among vemurafenib-treated patients who recovered to approximately 10 points below baseline for the remainder of the treatment period. A similar trend was observed in all functional scales except for cognitive function (<10-point change from baseline at all visits) and in the symptom scores for appetite loss, fatigue and pain. As observed for the GHS/QOL score, all scores rapidly returned to baseline after completion of planned vemurafenib treatment or treatment discontinuation.

Conclusions: The schedule of HRQOL assessments allowed for an accurate and complete evaluation of the impact of acute treatment-related symptoms. Vemurafenib-treated patients experience clinically meaningful moderate worsening in some treatment- or disease-related symptoms and GHS/QOL that resolve over time.

1. Introduction

Surgical resection of the primary tumour and/or affected lymph nodes is the standard of care for patients with stage II/III melanoma [1]. However, even if the primary tumour is completely surgically resected, the risk of disease recurrence and death in this patient population remains high [2−4], prompting the evaluation of several systemic adjuvant options to mitigate this risk. A key consideration in the benefit:risk evaluation of systemic adjuvant interventions in this patient population is the impact of treatment-emergent adverse events (AEs) on health-related quality of life (HRQOL), especially as these patients have minimal disease burden and symptoms after their surgical resection.

Several recent phase 3 studies have reported on the benefit of systemic adjuvant options in patients with resected stage II−IV disease [5−7]. The BRIM8 study (ClinicalTrials.gov, NCT01667419) explored the efficacy and safety of adjuvant vemurafenib monotherapy in patients with resected stage IIC−IIIC melanoma [7]. In the prespecified exploratory pooled intention-to treat analysis of both cohorts of BRIM8, vemurafenib reduced the risk of disease-free survival and distant metastasis-free survival events versus placebo (hazard ratio [HR]: 0.65; 95% confidence interval [CI]: 0.50−0.85; and HR: 0.70; 95% CI: 0.52−0.96, respectively). In this report, we present a longitudinal analysis of patient-reported HRQOL scores from the BRIM8 study and compare the change in HRQOL scores from baseline between those who received adjuvant treatment with 960 mg of vemurafenib twice daily versus placebo.

2. Methods

2.1. Study design

BRIM8 was a previously described phase 3, international, double-blind, randomised, placebo-controlled study [7]. The study enrolled adult patients (aged ≥18 years) with histologically confirmed cutaneous melanoma (pathological stage IIC or stage III per the American Joint Committee on Cancer Staging Criteria, version 7) [2], completely resected and confirmed to be $BRAF^{V600+}$ by the cobas® BRAF V600 Mutation Test (Roche Diagnostics, Indianapolis, IN, USA). Additional eligibility criteria included an Eastern Cooperative Oncology Group performance status of 0 or 1; adequate haematological, liver and renal function and complete recovery from any major surgery or any prior traumatic injury.

Patients with stage IIC−IIIB disease were enrolled in cohort 1, and patients with stage IIIC disease were enrolled in cohort 2. Patients were randomised 1:1 to receive oral vemurafenib (960 mg twice daily for 52 weeks in thirteen 28-day cycles) or matching placebo

unless their disease recurred, they experienced unacceptable toxicity or they withdrew consent.

The study conduct conformed with the International Conference on Harmonisation E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research was conducted, whichever afforded greater protection to the patient. Patients provided written informed consent before the conduct of any study procedures.

2.2. Patient-reported assessments of HRQOL, functioning and symptoms

Disease- and treatment-related symptoms, functioning and HRQOL were evaluated using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) version 3 [8]. In this questionnaire, functional domains and symptom-related items are measured over the previous week on a 4-point scale, ranging from 'not at all' to 'very much'. The two items that make up the global health status (GHS)/quality of life (QOL) score are also measured over the previous week but use a 7-point scale, ranging from 'very poor' to 'excellent'. For GHS and functioning scales, an increase in scores indicates improvement, whereas a decrease in scores indicates improvement for symptom scales or items.

To characterise the impact of symptomatic AEs on patients' HRQOL, it was important to capture patients' assessments more frequently in the first few treatment cycles when the likelihood of experiencing AEs was high. Therefore, the EORTC QLQ-C30 was administered at baseline, cycle 1 (days 1, 15 and 22 ± 3 days), cycle 2 (days 1 and 15, each ± 3 days), day 1 (±3 days) of every subsequent 4-week cycle, the end-of-treatment (EOT) visit and each scheduled and unscheduled visit during the follow-up period, including the early termination visit. In post-treatment follow-up, the EORTC QLQ-C30 questionnaire was completed every 13 ± 2 weeks from the last dose of the study drug until recurrence of melanoma, occurrence of a new primary melanoma or 5 years after day 1 of cycle 1, whichever occurred first. Patients who discontinued treatment early for any reason other than death underwent an EOT visit and post-treatment follow-up.

Initially, the data for each cohort were analysed separately. The analyses suggested that the observed differences between vemurafenib monotherapy and placebo were similar in nature and magnitude between cohorts 1 and 2, so the patient-reported outcome (PRO) data for both cohorts were pooled for this report. A change of ≥10 points from baseline in any scale (GHS, functioning or symptoms) was considered clinically meaningful [9].

2.3. Statistical analysis

Patients with an EORTC QLQ-C30 assessment at baseline and at least one post-baseline assessment were defined as the PRO-evaluable population and were included in the analysis. Mean change from baseline scores for each EORTC QLQ-C30 scale was analysed at each time point by treatment arm and reported descriptively. There were no imputation considerations for missing scores. Additional exploratory analyses included (1) a descriptive summary of the proportion of patients who reported a score on GHS, fatigue, appetite loss, pain and cognitive function using the categories poor (0−24), poor to moderate (25−49), moderate to high (50−74) and high (75−100) by treatment arm; (2) a heat map to illustrate magnitude of mean change in the GHS score from baseline by treatment arm; (3) development of a multiple logistic regression model to predict a clinically meaningful decrease (≥10 points) from baseline in the GHS score at the EOT visit accounting for disease stage, age, gender, disease recurrence or occurrence of a new primary melanoma and (4) development of an analysis of covariance (ANCOVA) model adjusting for the baseline GHS score to assess the effect of treatment and disease recurrence or an occurrence of a new primary melanoma on GHS change from the baseline score in each treatment cohort. All descriptive analyses were conducted using data at each assessment time point, including EOT (for any cause).

3. Results

In the BRIM8 study, 498 patients with fully resected melanoma were randomised 1:1 to treatment with either adjuvant vemurafenib or matching placebo for 1 year; this included 184 patients in cohort 2 (stage IIIC at diagnosis) and 314 patients in cohort 1 (stage IIC−IIIB at diagnosis). All except four patients in cohort 1 (3 in the vemurafenib group and 1 in the placebo group) received their allocated treatment. The median dose intensity in the vemurafenib group was 82.1% versus 99.0% in the placebo group, and the median treatment duration was 364 days in both treatment groups.

The pooled PRO-evaluable subpopulation comprised 461 patients: 285 patients from cohort 1 and 176 patients from cohort 2. Baseline characteristics of the PRO-evaluable population were similar to those of the overall study population (Table S1). Completion rates for the EORTC QLQ-C30 questionnaire were high (>80%) in the pooled cohorts at baseline, during study treatment and at the 13-week post-treatment assessment. Baseline scores were indicative of minimal disease burden; high scores were observed in the functional domains (range: 83−93) and low scores in the symptom domains (2−19), respectively, and they were comparable between the treatment arm and placebo arm (Table S1).

Shortly after initiation of adjuvant treatment, there was a mean decline in the GHS score of 17.4 (±22.9) and 17.3 (±24.1) points at days 15 and 22 of cycle 1, respectively, among vemurafenib-treated patients (Fig. 1); the GHS score recovered to approximately 10 points below baseline for the remainder of the treatment period. After cycle 1, ≥84% of the patients who received vemurafenib reported moderate or high HRQOL (GHS scores in the range of 50—74 and 75—100, respectively) at each time point after cycle 1 (Fig. 2A). In the placebo arm, ≥89% of the patients reported moderate to high HRQOL while under study (Fig. 2B). After completion of planned vemurafenib treatment or treatment discontinuation, the GHS scores returned to baseline values at week 13 of post-treatment evaluation.

This clinically meaningful worsening in patient-reported GHS/QOL score status (≥10-point difference) was also reflected in all functional scales except for cognitive function (Fig. S1) and in the symptom scores for appetite loss, fatigue and pain (Fig. S2). The deterioration of physical function scores was transient, recovering to <10-point difference by cycle 2. As observed for GHS, all scores rapidly returned to baseline after completion of planned vemurafenib treatment or treatment discontinuation.

A mixed-effect model that evaluated covariates associated with the observed differences in the GHS/QOL score between arms showed that treatment, time on study, treatment-by-time interaction and the baseline GHS score were statistically significant factors ($P < 0.0001$ for all) in each treatment cohort. However, disease stage and region of enrolment/treatment were not significantly associated with the observed HRQOL differences in cohort 1, and region of enrolment/treatment was not significantly associated with the observed HRQOL differences in cohort 2.

A multiple logistic regression model used to evaluate disease and demographic parameters showed that the disease stage at diagnosis, age, sex and disease recurrence were not associated with a clinically meaningful decline in the GHS score (≥10 points) in the pooled cohort of patients (Table 1). These results were consistent with an ANCOVA analysis, which showed that although disease progression had a negative effect on the GHS score assessed at the EOT visit that was statistically significant in both treatment arms, the decline did not approach the clinically meaningful threshold of 10 points (Fig. S3). This analysis also showed that among patients who did not experience disease progression, vemurafenib treatment was strongly associated with worsening in the GHS score, but again, the reduction (−3.91 points from baseline) did not reach the clinically meaningful 10-point threshold. Overall, the majority of patients in the vemurafenib arm who experienced an initial worsening in HRQOL change from baseline reported improvement in scores over time (Fig. S3).

4. Discussion

The PRO data from the BRIM8 study provide complementary information to traditional safety and efficacy assessments of the effects of adjuvant treatment in patients with resected melanoma. In the initial two cycles of treatment, PRO assessments were conducted multiple times (days 1, 15 and 22 for cycle 1 and days 1 and 15 for cycle 2) to capture the effects of treatment at initiation as it is well known that patients treated with BRAF inhibitors, with or without MEK inhibitors, experience AEs characterised by early onset [10]. For the remainder of the study, PROs were assessed at the beginning of each treatment cycle.
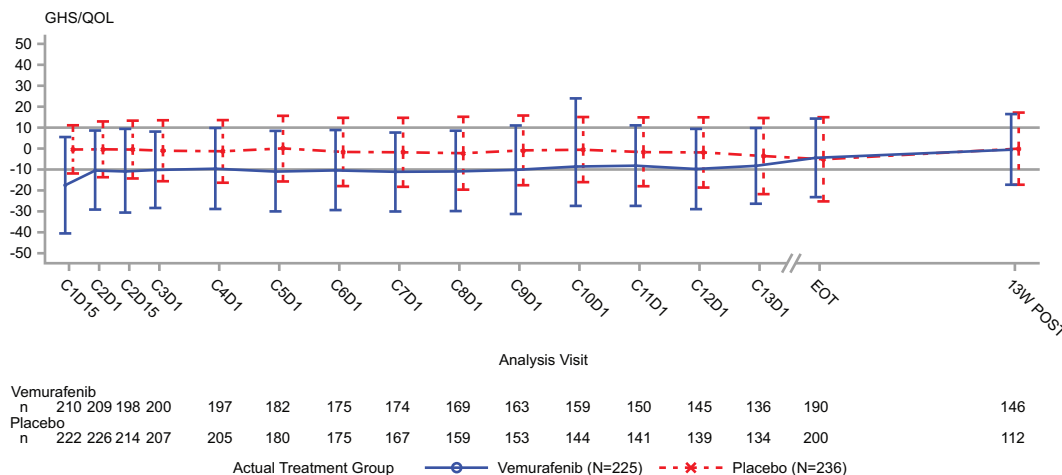

Fig. 1. Mean change from the baseline GHS score in patients receiving vemurafenib or placebo. A negative change in the GHS score indicates deterioration in QOL. The EOT visit includes patients who completed the planned treatment and those who discontinued treatment at any time before cycle 13 as a result of either unacceptable toxicity or disease recurrence. EOT, end-of-treatment; GHS, global health status; QOL, quality of life; SD, standard deviation.
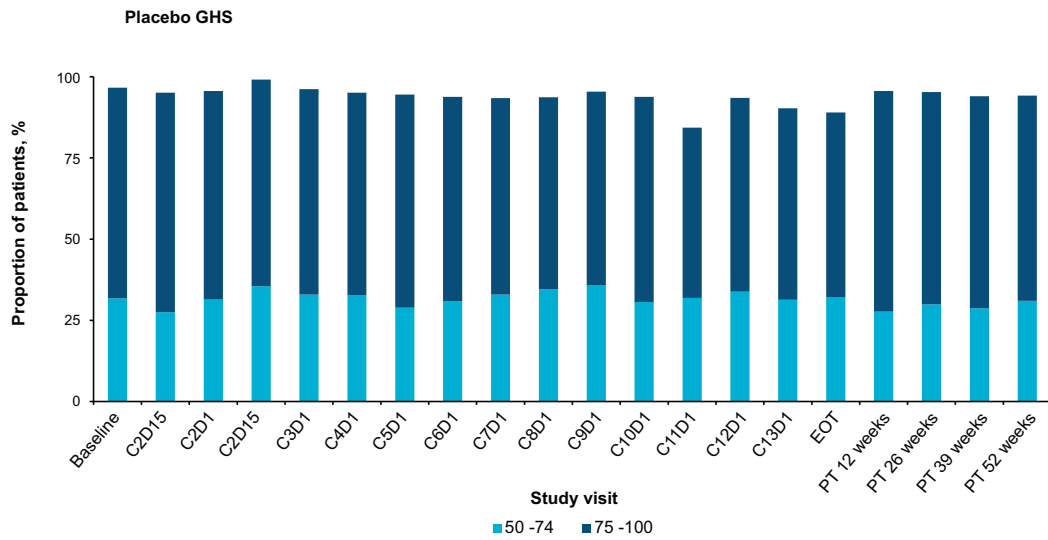
A
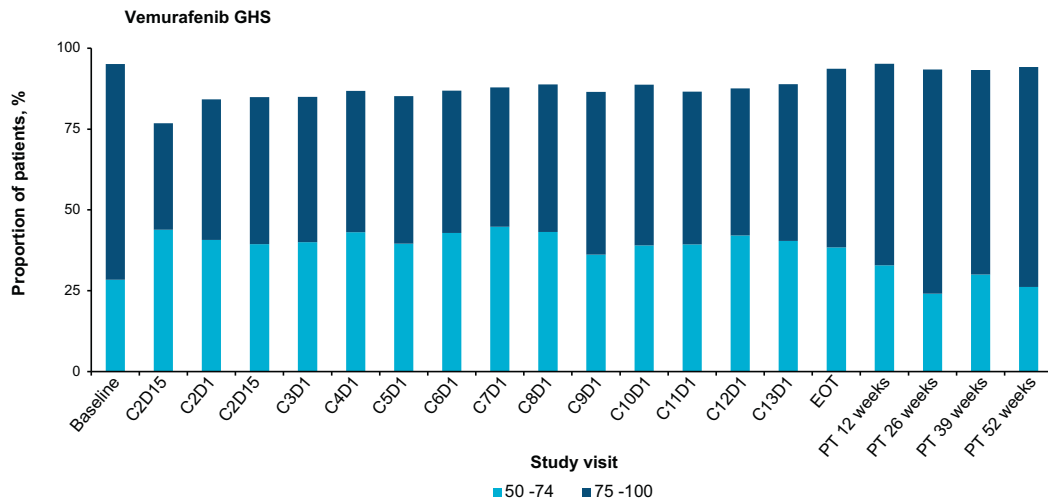
B

Fig. 2. Proportion of patients with reported moderate or high health-related quality of life (GHS score in the range of 50–74 and 75–100, respectively) at each study visit who received either (A) adjuvant vemurafenib or (B) placebo. EOT, end-of-treatment; GHS, global health status; PT, post-treatment.

Table 1
Multiple logistic regression model for predicting clinically meaningful decrease (>10 points) from baseline in the GHS/HRQOL score at the end-of-treatment visit.

Variable	Odds ratio (95% CI)	P value
Disease stage (IIC vs IIIC)	0.523 (0.162–1.688)	0.2784
Disease stage (IIIA vs IIIC)	0.826 (0.417–1.635)	0.5838
Disease stage (IIIB vs IIIC)	1.074 (0.651–1.772)	0.7801
Age	1.014 (0.997–1.032)	0.1161
Gender (female vs male)	0.857 (0.546–1.346)	0.5034
Disease recurrence or an occurrence of a new primary melanoma (yes vs no)	1.192 (0.751–1.892)	0.4570

CI, confidence interval; GHS, global health status; HRQOL, health-related quality of life.

The timing of the questionnaire administration relative to the dosing schedule is a key consideration. Most questionnaires, including the EORTC QLQ-C30, are based on patients' reports of their experience over the last 7 days. Thus, infrequent assessments or assessments that occur 1 week or later after the last dose of the drug may not capture the patient's perspective of the impact of selected acute treatment-related symptoms [8].

In other recent studies of adjuvant treatment, assessments of HRQOL and functional and symptom domains were not performed as frequently as in the BRIM8 study. Furthermore, the timing of the treatment and administration of the PRO questionnaire were such that the impact of acute treatment-related symptoms

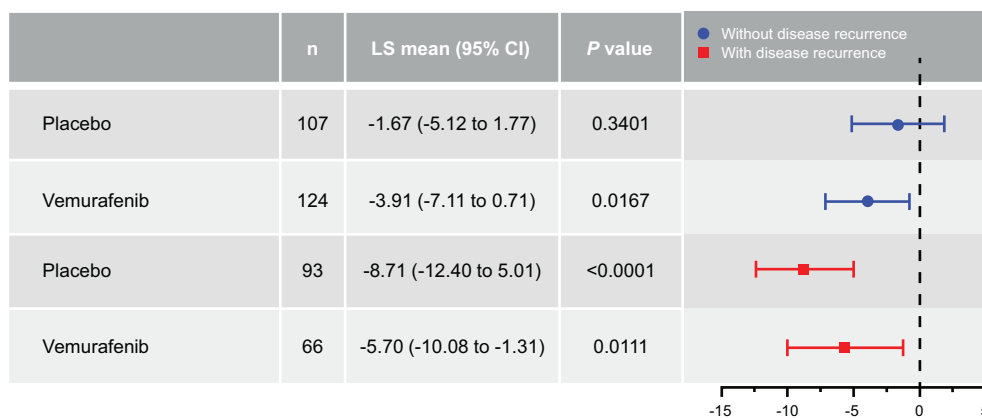|	n	LS mean (95% CI)	P value	
				● Without disease recurrence / ■ With disease recurrence
Placebo	107	-1.67 (-5.12 to 1.77)	0.3401	
Vemurafenib	124	-3.91 (-7.11 to 0.71)	0.0167	
Placebo	93	-8.71 (-12.40 to 5.01)	<0.0001	
Vemurafenib	66	-5.70 (-10.08 to -1.31)	0.0111	

Fig. 3. Impact of disease recurrence or occurrence of a new primary melanoma on global health status change from the baseline score at the end of treatment. CI, confidence interval; LS, least squares.

may have been underestimated. For example, in the phase 3 CheckMate 238 study, adjuvant nivolumab was administered every 2 weeks, and adjuvant ipilimumab was administered every 3 weeks for four doses and then every 12 weeks, whereas the HRQOL questionnaire was administered at baseline and at weeks 5, 7, 11, 17, 25, 37 and 49 [6]. Therefore, the timing of administration of the HRQOL questionnaire may not have been optimal to discern acute treatment effects.

Similarly, in the placebo-controlled EORTC 18071 study evaluating adjuvant ipilimumab, ipilimumab was administered every 3 weeks for four doses and then every 12 weeks, whereas the HRQOL questionnaire was administered at baseline and at weeks 4, 7, 10 and 24 and then every 12 weeks up to 2 years [11,12]. The week 4 and week 7 assessments could be completed 1 week earlier or later; the week 10 assessment could be completed 1 week earlier or 3 weeks later and the week 24, 36, 48, 60, 72, 84, 96 and 108 assessments could be completed 3 weeks earlier or 5 weeks later. A high proportion of patients in the ipilimumab arm discontinued adjuvant treatment with ipilimumab as a result of toxicity (52%), and as per protocol, administration of the EORTC QLQ-C30 continued regardless of disease recurrence and treatment discontinuation [11,12]. However, in the published report, it is not clear whether the HRQOL data from patients who discontinued ipilimumab treatment were excluded from the aggregate summary [11]. While patients enrolled in the BRIM8 study were also administered the HRQOL questionnaire after recurrence and treatment discontinuation, these data were separated and included in the EOT and post-treatment follow-up. Most recently, HRQOL data from the COMBI-AD study were reported [13]. Unlike other reports, this study reported QOL based on the EQ-5D-3L, which 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 in which patients rate

their current health state. PRO assessments were performed at baseline and every 3 months during treatment; thus, any acute effects of therapy would not have been captured. This study also assessed the impact of class-specific AEs on QOL. However, as acknowledged by the authors, patients included in the analysis could have experienced the AE at any point during the treatment period. Therefore, patients who were not experiencing the specific AE at a specific QOL assessment contributed to the aggregate analysis, confounding the interpretation of these results.

The baseline HRQOL data from BRIM8 confirm the minimal disease burden in this patient population, as evidenced by low symptom scores and high GHS scores. The observed changes in EORTC QLQ-C30 scores in the vemurafenib arm are consistent with previous experience that vemurafenib-treated patients experience early-onset AEs that result in a moderately clinically meaningful worsening in some treatment- or disease-related symptoms and HRQOL that resolve over time. This is evident from the data showing the change from baseline over the study duration for individual patients and also from the aggregate data, indicating that a majority of patients maintained a moderate to high HRQOL and low treatment burden after cycle 1 and throughout the study (Fig. 2, Fig. S3). It is also clear that disease progression in this patient population is significantly associated with deterioration in QOL (Fig. 3); therefore, prevention/delay of recurrence is a relevant clinical goal.

5. Conclusions

Taken together, the schedule of HRQOL assessments and the methods of analysis used in the BRIM8 study allowed for more complete and accurate evaluation of the impact of acute treatment-related symptoms. This study illustrates the importance of the timing of administration of the QOL questionnaire and may be considered an appropriate model for these types of

analyses in the adjuvant setting in melanoma. Overall, the study data confirm that vemurafenib monotherapy is adequately tolerated in this patient population.

Funding

Conflict of interest statement

D.S. reports personal fees and non-financial support from Roche/Genentech; personal fees, non-financial support and other from Novartis; personal fees, non-financial support and other from Bristol-Myers Squibb; personal fees from Merck Sharp & Dohme; personal fees and non-financial support from Merck Serono; personal fees and non-financial support from Amgen; personal fees from Immunocore; personal fees from Incyte, 4SC, Pierre Fabre, Mologen, Sanofi/Regeneron and Roche; non-financial support from Merck and personal fees from Sysmex, the Grünenthal Group, Agenus, Array BioPharma, AstraZeneca, LEO Pharma, Pfizer, Philogen and Regeneron, outside the submitted work. A.M.D.G. reports non-financial support from Roche, during the conduct of the study, and personal fees from Bristol-Myers Squibb, Incyte and feesPierre Fabre, outside the submitted work. L.D. reports grants and personal fees from Roche, during the conduct of the study; grants and personal fees from Amgen, Novartis, MSD, BMS and BIOCAD and non-financial support from Merck, outside the submitted work. B.M. reports no conflict of interest. I.B. reports no conflict of interest. P.A.A. reports grants and personal fees from BMS and Roche-Genentech; personal fees and other from MSD, grants and personal fees from Array and personal fees from Novartis, Merck Serono, Pierre Fabre, Incyte, Genmab, NewLink Genetics, MedImmune, AstraZeneca, Syndax, Sun Pharma, Sanofi, Idera, Ultimovacs, Sandoz, Immunocore and 4SC, outside the submitted work. C.H. reports no conflict of interest. A.M. reports no conflict of interest. P.R. reports personal fees from Novartis, MSD, BMS, Roche, Amgen, Eli Lilly, Pfizer, Blueprint Medicines and Pierre Fabre, outside the submitted work. A.G. reports personal fees from Regeneron; other from Sun Pharma, Merck KgA and BMS; personal fees from Pfizer, Merck MSD and Roche, outside the submitted work. G.R.G. and C.Y. report that they are employees of and hold stock in Roche/Genentech. B.S. reports employment with Roche/Genentech. A.H. reports former employment with Roche/Genentech. K.L. reports research grants and fees from Roche during the conduct of this study.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.09.019.

References

[1] Coit DG, Thompson JA, Algazi A, et al. Melanoma, version 2.2016, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw 2016;14:450–73.

[2] Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 2009;27:6199–206.

[3] Balch CM, Gershenwald JE, Soong SJ, et al. Multivariate analysis of prognostic factors among 2,313 patients with stage III melanoma: comparison of nodal micrometastases versus macrometastases. J Clin Oncol 2010;28:2452–9.

[4] Sivendran S, Chang R, Pham L, et al. Dissection of immune gene networks in primary melanoma tumors critical for antitumor surveillance of patients with stage II-III resectable disease. J Investig Dermatol 2014;134:2202–11.

[5] Long GV, Hauschild A, Santinami M, et al. Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. N Engl J Med 2017;377:1813–23.

[6] Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med 2017;377:1824–35.

[7] Maio M, Lewis K, Demidov L, et al. Adjuvant vemurafenib in resected, BRAF(V600) mutation-positive melanoma (BRIM8): a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. Lancet Oncol 2018;19:510–20.

[8] Aaronson NK, Ahmedzai S, Bergman B, et al. The European organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.

[9] Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998;16:139–44.

[10] Daud A, Tsai K. Management of treatment-related adverse events with agents targeting the MAPK pathway in patients with metastatic melanoma. Oncologist 2017;22:823–33.

[11] Coens C, Suciu S, Chiarion-Sileni V, et al. Health-related quality of life with adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): secondary outcomes of a multinational, randomised, double-blind, phase 3 trial. Lancet Oncol 2017;18:393–403.

[12] Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. Lancet Oncol 2015;16:522–30.

[13] Schadendorf D, Hauschild A, Santinami M, et al. 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. Lancet Oncol 2019;20:701–10.