disclosure

The authors have declared no conflicts of interest.

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Patient perception of the benefit of a BRAF inhibitor in metastatic melanoma: quality-of-life analyses of the BREAK-3 study comparing dabrafenib with dacarbazine

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Background: In a randomized phase III study (BREAK-3), dabrafenib showed prolonged progression-free survival (PFS) (median 5.1 versus 2.7 months; hazard ratio = 0.30; 95% confidence interval 0.18–0.53; $P < 0.0001$) compared with dacarbazine (DTIC) in patients with *BRAF* V600E metastatic melanoma. Assessing how these results are transformed into a real health benefit for patients is crucial.

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Methods: The EORTC QLQ-C30 questionnaire assessed quality of life (QoL) at baseline and follow-up visits.
Results: For DTIC, all functional dimensions except role dimension worsened from baseline at follow-up. For dabrafenib, all functionality dimensions remained stable relative to baseline or improved at week 6; mean change in seven symptom dimensions improved from baseline, with appetite loss, insomnia, nausea and vomiting, and pain showing the greatest improvement. In the DTIC arm, symptom dimensions were unchanged or worsened from baseline for all symptoms except pain (week 6), with the greatest exacerbations observed for fatigue and nausea and vomiting. Mixed-model-repeated measures analyses showed significant ($P < 0.05$) and/or clinically meaningful improvements from baseline in favor of dabrafenib for emotional and social functioning, nausea and vomiting, appetite loss, diarrhea, fatigue, dyspnea, and insomnia at weeks 6 and/or 12. After crossing over to dabrafenib upon progression ($n = 35$), improvements in all QoL dimensions were evident after receiving dabrafenib for 6 ($n = 31$) to 12 ($n = 25$) weeks.
Conclusions: This first reported QoL analysis for a BRAF inhibitor in metastatic melanoma demonstrates that the high tumor response rates and PFS superiority of dabrafenib over DTIC is not only a theoretical advantage, but also transforms in a rapid functional and symptomatic benefit for the patient.
Clinical Trials.gov identifier: NCT01227889.
Key words: melanoma, quality of life, dabrafenib, chemotherapy, BRAF

introduction

Cutaneous melanoma is the most aggressive form of skin cancer, with ~200 000 new cases and ~46 000 deaths estimated globally in 2008 [1]. In 2008, the direct cost of care for malignant melanoma was evaluated at $1.63 billion, representing a 2.8-fold increase since 1997 [2], which underlines the importance of assessing the real benefit of new therapeutic strategies from the patient and societal perspectives.

The RAF/MEK/ERK pathway is an important mediator of tumor cell proliferation in malignant melanoma. Approximately 40%–50% of cutaneous melanomas carry mutations in the *BRAF* gene [3, 4]. Eighty percent to 90% of *BRAF*-mutated melanomas have a V600E mutation, and 10%–20% have a V600K mutation. In the primary analysis of a phase III trial (BRF113683; BREAK-3), dabrafenib showed a 70% decrease in the risk of progression or death compared with dacarbazine (DTIC) in *BRAF*-mutated melanoma [progression-free survival (PFS), 5.1 versus 2.7 months; hazard ratio (HR) 0.30; 95% confidence interval (CI) 0.18–0.51; $P < 0.0001$; data as of 19 December 2011] [5]. Dabrafenib also induced an objective response in 53% of investigator-assessed patients. Treatment-related adverse events (>Common Terminology Criteria for Adverse Events grade 2) occurred in 53% of dabrafenib-treated patients and 44% of DTIC-treated patients. In an updated analysis (data as of 25 June 2012), median PFS was 6.9 months for dabrafenib versus 2.7 months for DTIC (HR 0.37; 95% CI 0.23–0.57; $P < 0.0001$) [6].

BRAF inhibitors (dabrafenib, vemurafenib), which show high tumor response rates, delayed progression and/or prolonged survival [5, 7] in patients with metastatic melanoma, and also caused adverse events that may interfere with patient quality of life (QoL), such as arthralgia, rash, photosensitivity, squamous cell carcinomas, and keratoacanthomas. Assessing whether these dual contrary effects are actually providing a real benefit from the patient perspective is crucial. QoL questionnaires/instruments are arguably the best way to measure this, since they capture deleterious effects (e.g. pain, fatigue, emotional distress) [8] of the metastatic disease itself and favorable and unfavorable effects of the therapy in a single holistic assessment from the patient perspective.

To support the BREAK-3 clinical trial objective to compare the change in QoL relative to baseline in *BRAF* V600E mutation-positive advanced and metastatic melanoma patients using the EORTC-QLQ-C30, these analyses evaluate and compare the impact of treatment with dabrafenib versus DTIC using data from 25 June 2012, at which point patients had median follow-up of 10.5 months.

methods

study design and treatment regimen

BREAK-3 (NCT01227889) is a two-arm, open-label, randomized, multicenter phase III study comparing dabrafenib with DTIC in patients with histologically confirmed advanced (unresectable stage III) or metastatic (stage IV) *BRAF* V600E mutation-positive melanoma. Details are reported elsewhere [5]. Briefly, patients were required to be treatment naive for metastatic disease, except for interleukin-2 treatment, surgery, or radiotherapy. Eligible patients were randomized 3:1 to receive either oral dabrafenib 150 mg twice daily or intravenous DTIC 1000 mg/m^2 every 3 weeks (supplementary Figure S1, available at *Annals of Oncology* online). Patients continued on treatment until disease progression, death, study treatment discontinuation, or withdrawal. Patients randomized to DTIC treatment were allowed to receive dabrafenib after initial progression was confirmed by independent review (IR). The primary end point was PFS as assessed by the investigator. Secondary end points included PFS assessed by IR, overall survival, objective response rate, PFS after crossover, duration of response, QoL, and safety and tolerability. Between 23 December 2010, and 1 September 2011, 250 patients were randomly assigned to receive dabrafenib (187 patients) or DTIC (63 patients). The protocol was approved by the independent review board at each participating institution. Signed and written informed consent was obtained from each participant before enrollment.

QoL assessments

QoL was evaluated using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) [9, 10]. Although several melanoma instruments are in development by groups dedicated to chronic disease and cancer, there are no widely used,

uniformly accepted, and fully validated disease specific instruments at this time to evaluate patient-reported outcomes. The EORTC QLQ-C30 was used in this study because it assesses multiple domains of general health, function, and symptoms. The psychometric properties of this instrument in populations with chronic disease and cancer are well published. The EORTC QLQ-C30 is a two-page, self-reporting, 30-item generic instrument for use in cancer patients across tumor types that includes 1 scale of overall health/global QoL, 9 symptom scales or single items (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) and 5 functional scales (physical, role, emotional, cognitive, and social functioning). The concept of 'role functioning' refers to the capacity of an individual to perform activities related to his/her social responsibility, 'social functioning' refers to the his/her ability of the individual to interact in the society, 'emotional functioning' to expression, and regulation of emotions, and 'cognitive functioning' to perception, thinking, and reasoning'. For functional and symptom scales or single items, patients assessed how true each of the statements has been for them during the reference period on a 4-point scale: 1 = not at all, 2 = a little, 3 = quite a bit, and 4 = very much. In contrast, 'global health dimension' status was assessed using a 7-item Likert scale ranging from 'poor' to 'excellent'. The scoring method of this questionnaire consists of a calculation of a raw score for all scales and single items, followed by a linear transformation to standardize the raw score so that the possible scores range from 0 to 100. For global health dimension and the functional scales, a higher score reflects better global health or functioning. Conversely, for symptom scales or single items, higher scores indicate greater symptom severity. The EORTC QLQ-C30 (the original English version as well as the translations into various languages) has been shown to have good reliability, validity, and responsiveness in different cancer populations [10–14]. Minimum clinically important differences (MCIDs) for the EORTC QLQ-C30 have been previously established and categorized as 'small' if mean change in scores = 5–10 points higher or lower, 'moderate' if = 10–20 points, and 'large' if >20 points [15]. QoL assessments were carried out at baseline (before any study drug was administered), at week 6, week 12, and week 15 during treatment, upon progression, and 4 weeks after progression was first determined. For patients receiving DTIC who crossed over to receive dabrafenib upon progression, the QoL assessment at the progression visit was the baseline for the crossover analyses. Patients then followed a similar QoL assessment schedule as in the randomized phase, i.e. week 6, week 12, etc.

statistical analysis

BREAK-3 was not powered to find a prespecified difference between the two treatment arms for any symptom or functional dimension of QoL. QoL data from the intent-to-treat population collected through 25 June 2012, were used. Analyses were carried out for the randomized phase of the study and also for the group of patients who crossed over to receive dabrafenib after IR-confirmed progression on DTIC. Baseline scores were reported with standard descriptive statistics. Changes in scores at each assessment relative to baseline scores were summarized for global health dimension and each functional and symptom scale or single item. Additionally, for the randomized phase, analysis of covariance adjusted for baseline score using mixed-model-repeated measures with time, treatment, and treatment-by-time interaction as fixed effects was carried out to assess for any differences between arms for global health and all functional and symptom dimension scores. Time was treated as the repeated variable within patient. Unstructured covariance matrices were used for these analyses. Visits with at least 80% of the required assessments were included in the analyses. There were no a priori hypotheses and no adjustments for multiple testing; all results should be considered exploratory.

results

randomized phase

baseline characteristics and QoL completion rates. Treatment groups were well balanced for age, sex, and disease status [5]. At least 90% of patients on each arm completed baseline QoL assessments. The majority of patients (81%) on the dabrafenib arm either completed all required QoL assessments or missed <3 postbaseline assessments; the corresponding percentage was 63% for the DTIC arm (Table 1). Visit times week 6 and week 12, which had at least 80% of required assessments, were included in the mixed-model analyses. At baseline, patients reported comparable levels of functional and symptom-related QoL between arms, with no differences exceeding 5 points (Table 2). Baseline scores from this trial were comparable with EORTC QLQ-C30 reference values data from an international sample of patients with stage III/IV malignant melanoma [16].

impact on functional and global health dimensions. When assessed for changes from baseline, mean functional dimension scores for patients receiving dabrafenib were stable or improved at week 6 (an average of 0.1–7 points higher across the domains) and worsened slightly at week 12 for only three dimensions ('physical', 'role', and 'cognitive functioning': an average of 1–3 points lower than baseline; Figure 1A). Considerable improvements in mean emotional functioning scores were observed at weeks 6 (7 points, small MCID) and 12 (9 points, small MCID). In contrast, in patients receiving DTIC, mean scores worsened from baseline for all functional dimensions at week 6 (an average of 1–6 points lower, small MCIDs for 'physical functioning' and cognitive functioning) and week 12 (an average of 2–8 points lower, small MCIDs for physical functioning and cognitive functioning, except for 'role functioning', which was 3 points higher), suggesting deterioration of functionality on average from treatment initiation that tended to worsen with time. The mean global health dimension scores showed quantitative improvement, with a greater increase in the dabrafenib arm at weeks 6 and 12 compared with the DTIC arm (2- to 3-point change for dabrafenib versus 0.5–1 points for DTIC; Figure 1A).

Table 1. Summary of completion of EORTC QLQ C-30 questionnaires in the randomized phase

QoL assessments category	Dabrafenib, *n* (%) (*N* = 187)	DTIC, *n* (%) (*N* = 63)
All required assessments	57 (30)	7 (11)
No baseline assessment	16 (9)	6 (10)
No postbaseline assessments	8 (4)	10 (16)
One or two missing postbaseline assessments	96 (51)	33 (52)
Three or more missing postbaseline assessments	10 (5)	7 (11)

Values may not add to 100% due to rounding.

Table 2. Summary of EORTC QLQ-C30 functional and symptom dimensions of QoL at baseline (ITT population)—randomized phase

Functionality or symptom scale score	Dabrafenib ($N = 187$)					Dacarbazine ($N = 63$)				
	n	Mean	SD	Min	Max	*n*	Mean	SD	Min	Max
Physical functioning (5 items)	180	83.59	19.71	13.33	100.00	60	86.22	18.93	26.67	100.00
Role functioning (2 items)	180	75.09	30.23	0.00	100.00	59	77.12	30.62	0.00	100.00
Emotional functioning (4 items)	180	72.64	22.39	0.00	100.00	60	71.94	20.58	8.33	100.00
Cognitive functioning (2 items)	180	87.69	17.82	0.00	100.00	59	88.98	15.97	16.67	100.00
Social functioning (2 items)	179	75.98	28.44	0.00	100.00	59	75.42	25.77	0.00	100.00
Global health status/QoL (2 items)	181	67.13	22.66	0.00	100.00	60	67.64	20.42	16.67	100.00
Fatigue (3 items)	178	27.34	26.17	0.00	100.00	60	25.19	24.45	0.00	100.00
Nausea and vomiting (2 items)	179	7.17	16.66	0.00	100.00	60	10.83	20.31	0.00	83.33
Pain (2 items)	181	26.52	30.83	0.00	100.00	60	22.22	26.87	0.00	100.00
Dyspnea (1 item)	182	13.55	22.15	0.00	100.00	60	10.56	21.69	0.00	100.00
Insomnia (1 item)	182	28.57	29.14	0.00	100.00	60	24.44	31.21	0.00	100.00
Appetite loss (1 item)	182	15.39	27.05	0.00	100.00	60	15.56	25.65	0.00	100.00
Constipation (1 item)	178	8.80	21.05	0.00	100.00	60	8.89	22.01	0.00	100.00
Diarrhea (1 item)	178	5.43	12.34	0.00	33.33	60	8.33	16.95	0.00	66.67

SD, standard deviation.

Statistical differences for functional dimensions and global health between arms were assessed using mixed-model repeated measure analysis (Table 3). When not adjusted for multiple testing, there were statistically significant and clinically meaningful improvements from baseline in favor of dabrafenib observed for 'emotional functioning' at weeks 6 and 12. A small but clinically meaningful improvement in 'social functioning' at week 12 was also observed. All other differences were not statistically or clinically significant; all except role functioning (difference of 1–2 points) favored dabrafenib.

At progression, mean functional dimension scores worsened in both arms relative to baseline but to a lesser degree in dabrafenib-treated patients compared with DTIC-treated patients; the largest changes (15 and 19 points lower than baseline, moderate MCIDs) were observed for social functioning and role functioning, respectively, on the DTIC arm (Figure 1B).

impact on symptoms. Mean symptom scale scores for patients receiving dabrafenib remained stable or decreased (i.e. initial symptoms stabilized or improved) compared with baseline for all symptoms except fatigue (slightly worse by 1–2 points at weeks 6 and 12, respectively, compared with a 7-point worsening in the DTIC arm at these assessments; Figure 2A). Appetite loss, insomnia, nausea and vomiting, and pain showed the most mean improvement with dabrafenib. Conversely, with DTIC, mean scores increased (symptoms worsened) at weeks 6 and 12 compared with baseline for almost all symptoms (except pain at week 6 with a 1-point improvement), with the most worsening observed for fatigue, nausea and vomiting, appetite loss, and dyspnea.

Statistical differences for symptom dimensions between arms were also assessed using mixed-model-repeated measures analysis (Table 4). At week 12, mean nausea and vomiting and appetite loss scores significantly improved from baseline by 13 and 11 points, respectively, in favor of dabrafenib (moderate clinically meaningful improvements). A statistically significant, 6-point mean improvement in diarrhea scores at both weeks 6 and 12 was observed in favor of dabrafenib (small clinically meaningful improvements). Similar differences were also observed in favor of dabrafenib for fatigue (week 12) and for dyspnea, appetite loss, and insomnia (week 6).

At the time of progression, mean symptom dimension scores tended to worsen in both arms relative to baseline but to a lesser degree in patients receiving dabrafenib compared with DTIC-treated patients; largest mean changes (12 and 21 points higher than baseline, i.e. moderate and large MCIDs) were observed for dyspnea and fatigue, respectively, for the DTIC arm (Figure 2B).

crossover phase. Patients randomized to DTIC who crossed over to the dabrafenib arm upon progression ($N = 35$) experienced large changes (improvement in functionality and symptoms) in mean scores relative to their baseline (progression visit) scores for 'overall global health' dimension and all functional and symptom scales. Four- to 10-point changes in mean scores were observed in patients receiving dabrafenib at 6 weeks ($N = 31$) and 5- to 11-point changes at 12 weeks ($N = 25$) across global health and functional domains (small to moderate MCIDs). Four- to 16-point changes in mean scores at crossover week 6 after progression and 1- to 13-point changes in mean scores at crossover week 12 were observed across the various symptoms (small to moderate MCIDs; data not shown). The largest improvements in mean scores were observed for functional dimensions (role functioning: 10 and 10 points; social functioning: 9 and 11 points; physical functioning: 7 and 11 points) and symptom dimensions (fatigue: 11 and 12 points; nausea and vomiting: 16 and 13 points; appetite loss: 11 and 13 points; diarrhea: 10 and 9 points) at crossover weeks 6 and 12, respectively.

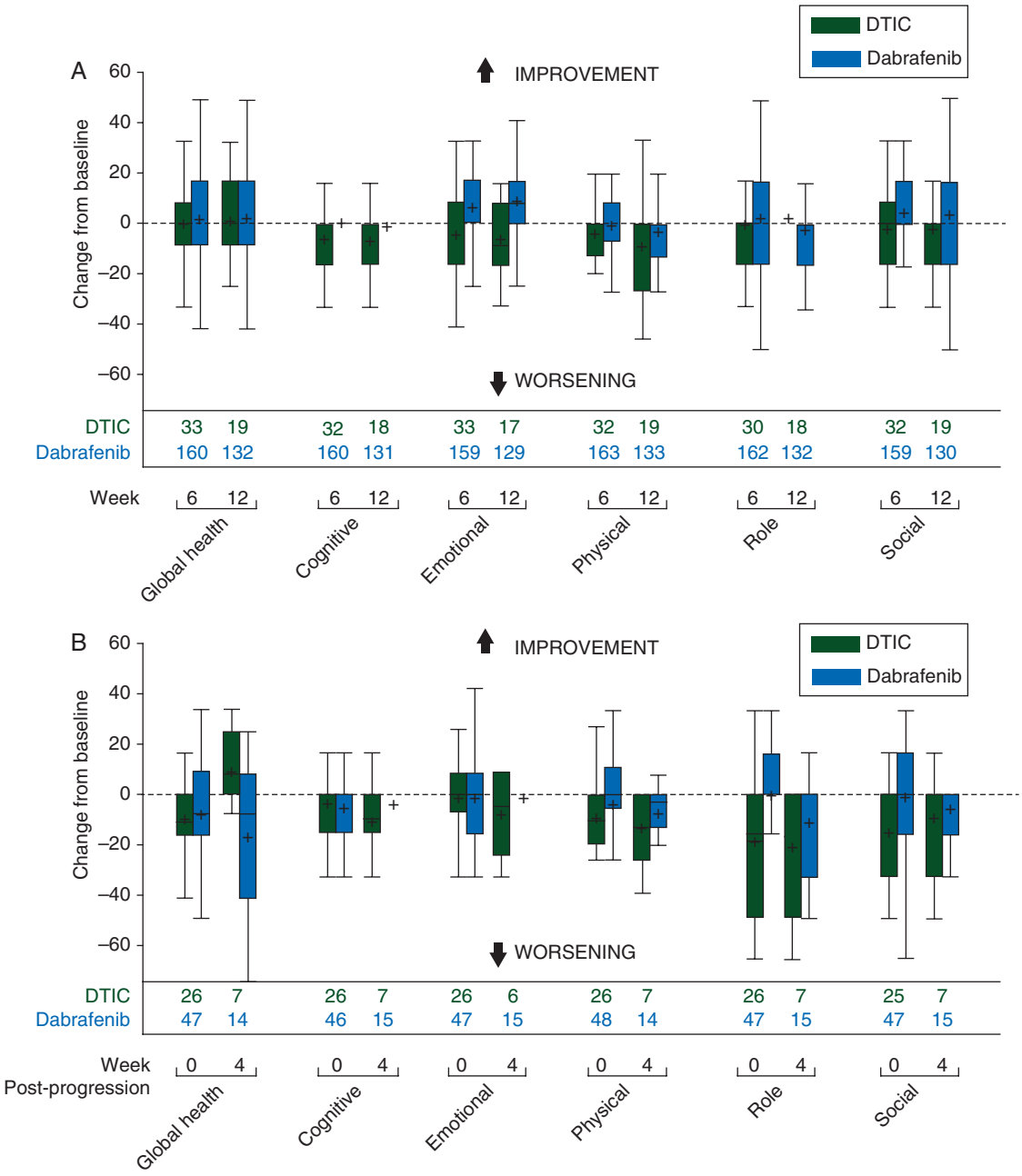

Figure 1. (A) Change from baseline to weeks 6 and 12 for EORTC QLQ-C30 global health dimension and functional status scores (randomized phase). (B) Change from baseline at progression for EORTC QLQ-C30 for the functional status domains and the global health dimension (randomized phase).

discussion

QoL results from the BREAK-3 study are the first evidence that improvement in PFS observed in *BRAF* V600E mutation-positive metastatic melanoma patients treated with BRAF inhibitors results in meaningful, measurable health advantages for the patient. Results can be considered as exploratory since there were no a priori hypotheses and no adjustments were made for multiple testing.

When assessed using change in QoL scores relative to baseline, patients receiving dabrafenib had consistently greater mean benefits on functional and symptom dimensions compared with DTIC-treated patients. Patients receiving dabrafenib improved on average within 6–12 weeks in functional dimensions and in several symptom scales, compatible with the rapid response observed with BRAF inhibitors. Conversely, patients receiving DTIC experienced worsening in the same dimensions.

The QoL end point for BREAK-3 was not powered to find a prespecified difference between treatment arms. Therefore, a clinical interpretation of the changes in QoL scores, defined as MCIDs, may be a better measure to compare the impact of the two treatments than multiple statistic tests assessing a large number of dimensions changes. Clinically, meaningful changes

Table 3. Summary of mixed-model-repeated measures analysis for change from baseline in functional dimension and global health scores in randomized phase

Domain	Change from baseline to	Treatment group	Number available for QoL	Adjusted mean	SE	Difference (dabrafenib versus DTIC)[a]	95% CI for treatment difference
Cognitive functioning	Week 6	Dabrafenib	160	−0.28	1.058	4.858	−0.285 to 10.001
		DTIC	32	−5.14	2.380		
	Week 12	Dabrafenib	131	−0.97	1.217	3.033	−3.705 to 9.771
		DTIC	18	−4.00	3.187		
Emotional functioning	Week 6	Dabrafenib	159	6.54	1.370	7.546[†]	1.021 to 14.072
		DTIC	33	−1.01	3.011		
	Week 12	Dabrafenib	129	8.32	1.436	8.649[†]	0.579 to 16.719
		DTIC	17	−0.33	3.827		
Physical functioning	Week 6	Dabrafenib	163	−0.58	1.115	4.335	−1.064 to 9.733
		DTIC	32	−4.91	2.497		
	Week 12	Dabrafenib	133	−2.41	1.356	3.338	−3.841 to 10.516
		DTIC	19	−5.75	3.376		
Role functioning	Week 6	Dabrafenib	162	−0.60	1.740	−0.819	−9.403 to 7.765
		DTIC	30	0.22	3.985		
	Week 12	Dabrafenib	132	−0.65	1.810	−2.356	−12.290 to 7.573
		DTIC	18	1.70	4.693		
Social functioning	Week 6	Dabrafenib	159	3.36	1.609	4.302	−3.468 to 12.072
		DTIC	32	−0.94	3.594		
	Week 12	Dabrafenib	130	3.58	1.812	6.573	−3.090 to 16.237
		DTIC	19	−3.00	4.547		
Global health	Week 6	Dabrafenib	160	2.00	1.234	0.698	−5.206 to 6.601
		DTIC	33	1.30	2.725		
	Week 12	Dabrafenib	132	2.47	1.441	1.920	−5.997 to 9.838
		DTIC	19	0.55	3.740		

Overall *N*: Dabrafenib = 187; DTIC = 63.

[a]A positive difference indicates improvement in favor of dabrafenib.

[†]$P < 0.05$.

were observed at weeks 6 and 12 for two of five functional and six of eight symptom dimensions. Although the remaining dimensions (except role functioning and pain) did not meet the MCIDs, the mean scores favored dabrafenib.

As the patients enrolled in this study exhibited very good physical status (>65% patients had Eastern Cooperative Oncology Group performance status 0 at enrollment) and were relatively younger (median age of 50–53 years across the arms) than the average metastatic melanoma patient, even an ideal drug cannot be expected to improve QoL functional dimensions [5]. Hence, compared with a treatment with lower efficacy, this new drug can only be expected to provide better preservation or slower degradation of these dimensions with time. In this regard, the comparison between mean scores at start of treatment and time of progression showed not only better preservation of QoL up to disease progression with dabrafenib than with DTIC, but also a longer preservation, since progression time was later in dabrafenib arm (PFS, 6.9 versus 2.7 months).

Previous research has shown that about one-third of patients with metastatic melanoma have reported clinically significant levels of 'psychological distress', with the highest levels observed around the time of diagnosis and immediately after treatment [17, 18]. The mean emotional perception of the clinical benefit induced by dabrafenib between baseline and 6 or 12 weeks was particularly strong and rapid in these patients. It suggests a sharp contrast between the stress of being diagnosed with advanced metastatic melanoma and the rapid perception of benefit with dabrafenib. Meanwhile, the corresponding scores for patients receiving DTIC showed a worsening relative to baseline, resulting in statistically and clinically important and meaningful differences between the two arms at weeks 6 and 12.

To confirm the ability of BRAF inhibitors to rapidly improve QoL in patients with advanced melanoma, we focused on the QoL in patients randomized to DTIC treatment who subsequently crossed over to dabrafenib upon progression. There was a meaningful improvement in most QoL dimensions as measured by changes in mean scores. This change probably illustrates the contrast between the severe alteration of QoL at the time of progression under DTIC and the intense and rapid benefits after the introduction of dabrafenib.

The goal of an active treatment in cancer is to improve quantity and quality of survival [19]. In a recent paper, Booth et al. [20] raised the question of what PFS means for the patient, or in other words, whether PFS is really a marker for improved QoL or symptom benefit. They underlined how QoL improvement is crucial in making an increase in PFS a real benefit for the patient.

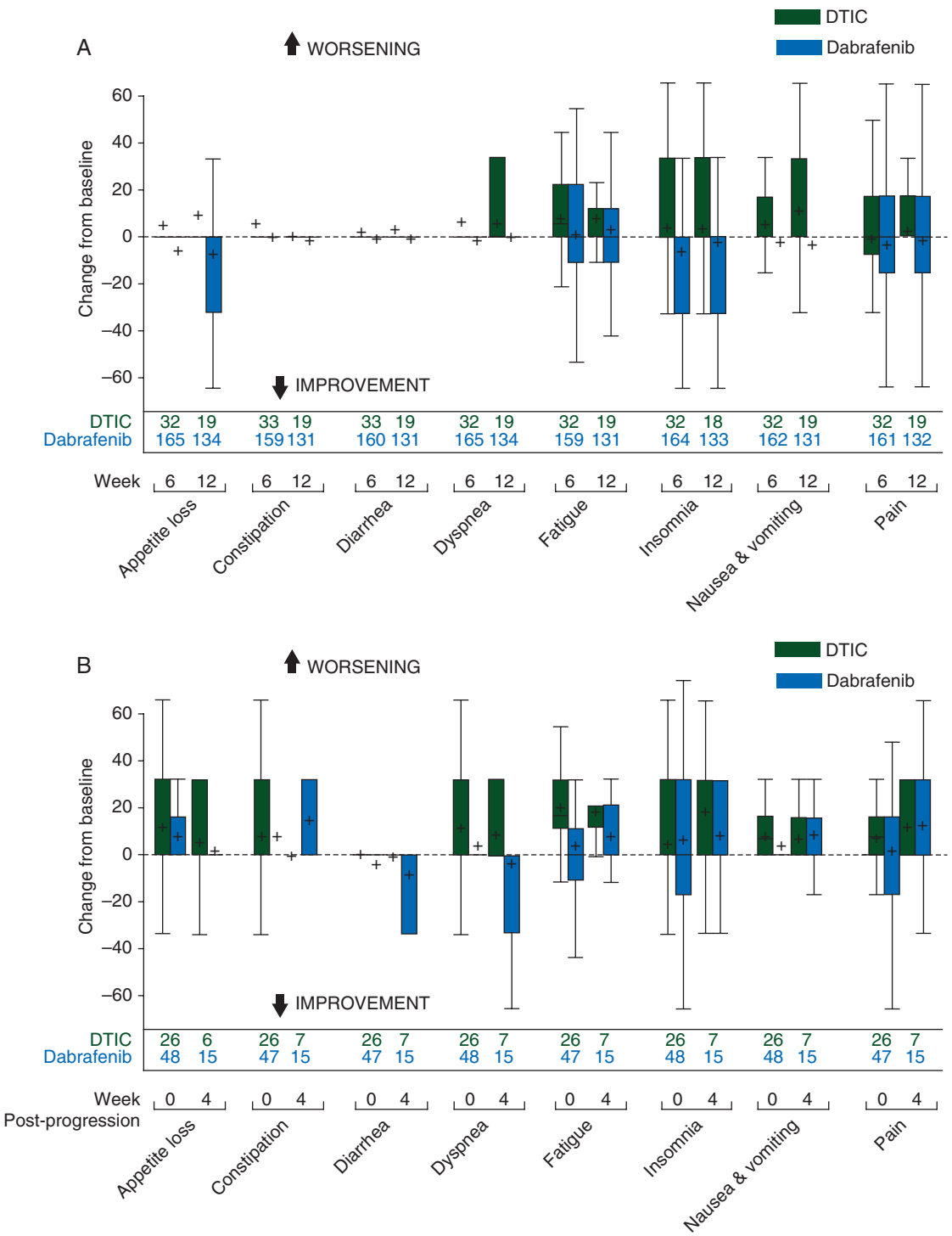

Figure 2. (A) Change from baseline to weeks 6 and 12 for EORTC QLQ-C30 symptom scores (randomized phase). (B) Change from baseline at progression for EORTC QLQ-C30 symptom scores (randomized phase).

They propose that health decisions should use measures that are actually important (benefit in QoL and symptoms) rather than merely easily measurable and analyzed (e.g. PFS) but not necessarily meaningful. While QoL is more difficult to measure than PFS or overall survival, it is arguably more relevant as a marker of health benefit. Our data with dabrafenib show that PFS improvement equates with a real QoL advantage for the patient.

No QoL results have been reported to date with a BRAF inhibitor, and none are available with vemurafenib. A few other phase III trials compared other treatments with the DTIC reference in terms of QoL. Another targeted therapy, trametinib, showed some benefit [21]. Temozolomide was associated with some functional improvements and decreased symptoms [22]; fotemustine was responsible for a general degradation of QoL dimensions [23], and a

Table 4. Summary of mixed-model-repeated measure analysis for change from baseline in symptom dimension scores in randomized phase

Domain	Change from baseline to	Treatment group	No. available for QoL	Adjusted mean	SE	Difference (dabrafenib versus DTIC)[a]	95% CI for treatment difference
Fatigue	Week 6	Dabrafenib	159	2.17	1.521	−3.805	−11.150 to 3.538
		DTIC	32	5.97	3.395		
	Week 12	Dabrafenib	131	1.05	1.782	−6.956	−16.480 to 2.564
		DTIC	19	8.01	4.482		
Nausea and vomiting	Week 6	Dabrafenib	162	−2.59	1.036	−4.705	−9.731 to 0.321
		DTIC	32	2.11	2.328		
	Week 12	Dabrafenib	131	−4.28	0.802	−12.834†	−17.250 to −8.421
		DTIC	19	8.55	2.086		
Pain	Week 6	Dabrafenib	161	−2.05	1.778	1.108	−7.432 to 9.647
		DTIC	32	−3.16	3.944		
	Week 12	Dabrafenib	132	−3.59	1.777	0.460	−9.098 to 10.019
		DTIC	19	−4.05	4.504		
Dyspnea	Week 6	Dabrafenib	165	−0.59	1.372	−5.402	−12.100 to 1.293
		DTIC	32	4.81	3.101		
	Week 12	Dabrafenib	134	0.12	1.616	−4.683	−13.490 to 4.119
		DTIC	19	4.80	4.157		
Insomnia	Week 6	Dabrafenib	164	−5.55	1.853	−5.889	−14.920 to 3.146
		DTIC	32	0.34	4.185		
	Week 12	Dabrafenib	133	−3.73	2.233	−3.654	−15.970 to 8.661
		TIC	18	−0.07	5.823		
Appetite loss	Week 6	Dabrafenib	165	−5.94	1.438	−6.295	−13.330 to 0.743
		DTIC	32	0.35	3.264		
	Week 12	Dabrafenib	134	−8.41	1.413	−10.792†	−18.430 to −3.155
		DTIC	19	2.38	3.600		
Constipation	Week 6	Dabrafenib	159	0.17	1.331	−4.098	−10.430 to 2.234
		DTIC	33	4.27	2.921		
	Week 12	Dabrafenib	131	−2.59	1.069	−1.609	−7.478 to 4.259
		DTIC	19	−0.98	2.773		
Diarrhea	Week 6	Dabrafenib	160	−1.49	1.131	−5.809†	−11.200 to −0.420
		DTIC	33	4.32	2.482		
	Week 12	Dabrafenib	131	−2.00	1.096	−6.041†	−12.010 to −0.072
		DTIC	19	4.04	2.815		

Overall *N*: Dabrafenib = 187; DTIC = 63.

[a]A negative difference indicates improvement in favor of dabrafenib.

†$P < 0.05$.

combination of DTIC plus ipilimumab induced no or moderate changes for all QoL domains and a decline in the global health status dimension score [24]. In patients with advanced melanoma randomized to receive ipilimumab plus glycoprotein 100 (gp100) or gp100 alone or ipilimumab alone [25], there was functional impairment and exacerbation of symptoms in the three groups. Although comparisons across these heterogeneous studies are difficult, the data with the BRAF inhibitor dabrafenib clearly demonstrate an unusually rapid and important benefit from the patient point of view.

The benefit of dabrafenib compared with DTIC may be underestimated in our study. First, more patients receiving DTIC did not complete post-treatment questionnaires than those receiving dabrafenib. It is well established that the better the response in a patient and the less the treatment toxicity, the more likely the patient is to complete all follow-up assessments [26]. Second, as in any trial assessing QoL, a 'response shift' should be considered in the interpretation of results. For instance patients with initial rapid benefit at Week 6 may recalibrate their QoL expectations at week 12 to a higher level compared with their initial expectations. They may then underscore the QoL benefit at week 12, which may lead to underestimating the superiority of dabrafenib over DTIC at week 12.

This paper presents the first reported QoL analysis of a BRAF inhibitor in metastatic melanoma. Results, although exploratory, demonstrate that high tumor response rates and PFS advantage obtained with dabrafenib compared with DTIC translate into rapid functional and symptomatic benefits, which are crucial to patients. Given the increasing possibility of several targeted therapies for the treatment of metastatic melanoma in the future, selecting treatments that provide real health benefits will require continual QoL assessment.

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disclosure

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