Health-related quality-of-life results from the randomised phase II TAVAREC trial on temozolomide with or without bevacizumab in 1p/19q intact first-recurrence World Health Organization grade 2 and 3 glioma (European Organization for Research and Treatment of Cancer 26091)

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Jaap C Reijneveld, Abigirl Machingura, Corneel Coens, Martin J.B. Taphoorn, Walter Taal, et al.. Health-related quality-of-life results from the randomised phase II TAVAREC trial on temozolomide with or without bevacizumab in 1p/19q intact first-recurrence World Health Organization grade 2 and 3 glioma (European Organization for Research and Treatment of Cancer 26091). European Journal of Cancer, 2023, 190, pp.112946. 10.1016/j.ejca.2023.112946 . hal-04251278

HAL Id: hal-04251278

https://hal.sorbonne-universite.fr/hal-04251278

Submitted on 20 Oct 2023

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European Journal of Cancer 190 (2023) 112946

Available online at www.sciencedirect.com

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Clinical Trial

Health-related quality-of-life results from the randomised phase II TAVAREC trial on temozolomide with or without bevacizumab in 1p/19q intact first-recurrence World Health Organization grade 2 and 3 glioma (European Organization for Research and Treatment of Cancer 26091)

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Received 11 April 2023; Received in revised form 9 June 2023; Accepted 12 June 2023
Available online 19 June 2023

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https://doi.org/10.1016/j.ejca.2023.112946
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KEYWORDS
Health-related quality of life;
Glioma;
Bevacizumab;
Temozolomide;
EORTC;
RCTs

Abstract ***Background:*** In an international randomised controlled phase II study of temozolomide (TMZ) versus TMZ in combination with bevacizumab (BEV) in locally diagnosed non-1p/19q co-deleted World Health Organization grade 2 or 3 gliomas with a first and contrast-enhancing recurrence after initial radiotherapy, and overall survival at 12 months was not significantly different (61% in the TMZ arm and 55% in the TMZ + BEV arm).
Objectives: Health-related quality of life (HRQoL) was a key secondary end-point in this trial, and the main objective of this study was to determine the impact of the addition of BEV to TMZ on HRQoL.
Methods: HRQoL was assessed using the European Organization for Research and Treatment of Cancer QLQ-C30 (version 3) and QLQ-BN20 at baseline, and then every 12 weeks until disease progression. The pre-selected primary HRQoL end-point was the QLQ-C30 global health scale, with self-perceived cognitive functioning and pain selected as secondary HRQoL issues. Analysis was undertaken using linear mixed modelling and complemented with sensitivity analyses using summary statistics. A difference was considered clinically relevant with ≥10 points difference on a 100-point scale.
Results: Baseline compliance was high at 94% and remained above 60% until 72 weeks, limiting the analysis to 60 weeks. Compliance was similar in both arms. We found no statistically significant or clinically significant differences between the primary HRQoL end-point in both treatment arms ($p = 0.2642$). The sensitivity analyses confirmed this finding. The overall test for post-baseline differences between the two treatment arms also showed no statistically or clinically significant differences regarding the selected secondary end-point scales.
Interpretation: The addition of BEV to TMZ in this patient group neither improves nor negatively impacts HRQoL.
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1. Introduction

In the prospective randomised phase II, European Organization for Research and Treatment of Cancer (EORTC) 26091 trial, the use of bevacizumab (BEV) in recurrent World Health Organization (WHO) grade 2 and grade 3 glioma was evaluated. In view of the occurrence of pseudo-responses in BEV-treated glioblastoma questioning the usefulness of progression-free survival (PFS), overall survival at 12 months (OS12) was selected as the primary end-point. The trial showed that the addition of BEV to temozolomide (TMZ) did not improve OS12, nor PFS or OS (see [1]).

In particular for cancer patients who cannot be cured of their disease but may have a slow-growing tumour (e.g. lower-grade glioma), health-related quality of life (HRQoL) is the most relevant end-point [2]. HRQoL is a multidimensional concept that incorporates physical, social and psychological aspects and has become a major secondary end-point, and sometimes even a primary end-point in cancer clinical trials [3]. Previous studies showed that the HRQoL of lower-grade glioma patients is already compromised at the time of diagnosis [4,5] and might further deteriorate during the disease course [6–9]. If TMZ alone and combined with BEV has a different impact on HRQoL; for example, through the corticosteroid-sparing effect of the addition of BEV, this might influence clinical decision-making in patients with recurring WHO grade 2 and 3 1p/19q non-codeleted gliomas requiring treatment.

This article reports a head-to-head comparison of TMZ alone versus TMZ in combination with BEV regarding the impact on HRQoL, which was a secondary end-point in the EORTC 26091 study [1].

2. Methods

2.1. Study design

The EORTC 26091 TAVAREC was a prospective randomised phase II difference study conducted by 32 institutions over eight countries. This study was designed as a two-arm open-label randomised study to assess the survival benefit of BEV in combination with TMZ against TMZ alone. Eligible patients were randomised and stratified by a minimisation procedure to ensure overall balance. Stratification factors were institution, histology, WHO performance status (0, 1 versus 2) and prior treatment (radiotherapy alone, TMZ or procarbazine, CCNU (lomustine), and vincristine (PCV) alone, versus combined chemo-irradiation with TMZ). Patients were electronically randomised through the EORTC web-based ORTA system. The study sample size was 144 patients (72 in each treatment arm), which was based on the primary end-point (overall survival rate at month 12). More details about the study design are presented in van den Bent et al. [1].

2.2. Participants

The EORTC 26091 study enrolled patients aged 18 years presenting a locally histopathologically diagnosed grade 2 or 3 glioma at first diagnosis (without 1p/19q co-deletion at first recurrence after radiotherapy with or without chemotherapy) according to the WHO 2007 glioma classification. Patients were eligible when relapse was more than 3 months after the end of radiotherapy. High-dose radiotherapy (> 65 Gy) was an exclusion criterion unless the recurrence was histologically proven. PCV or TMZ was the only inclusion criterion for prior chemotherapy, and patients needed to be more than 6 months off chemotherapy before progression. Prior treatment with anti-angiogenic treatments was an exclusion criterion. Surgery at the time of the recurrence was an inclusion criterion, in which case residual and measurable disease after surgery were not required, but histology must have confirmed recurrent tumour, irrespective of tumour grade.

Non-operated patients needed to have an enhancing recurrence with bidimensionally measurable disease (minimal square diameters enhancing lesion 10 mm) on magnetic resonance (MR) scan, with stable or decreasing dosage of steroids for 7 days prior to the baseline MR scan. Patients needed to have adequate haematological, renal and hepatic function, and no other diseases interfering with follow-up, including other malignancies, except for any previous malignancy which was treated with curative intent more than 5 years prior to randomisation, and except for adequately controlled limited basal cell carcinoma of the skin, squamous carcinoma of the skin or carcinoma *in situ* of the cervix. Other exclusion criteria included the presence of cardiovascular disorders, significant vascular disease within 6 months prior to randomisation, history of hypertensive crisis or hypertensive encephalopathy, inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 m Hg); any thrombotic or haemorrhagic event, a history of active gastroduodenal ulcer(s) or a history of abdominal fistula as well as non-gastrointestinal fistula, gastrointestinal perforation or intra-abdominal abscess within the 6 months prior to inclusion. More details about the inclusion criteria are presented in van den Bent et al. [1].

2.3. Randomisation and masking

Patients were randomised to (1) TMZ 200 mg/m^2 on days 1–5 every 4 weeks for a maximum of 12 cycles, with patients having received prior chemotherapy starting at 150 mg/m^2 with dose escalation to 200 mg/m^2 in case of no or minimal toxicity; or to (2) the same TMZ treatment regimen combined with 10 mg/kg BEV intravenously every 2 weeks until progression. Treatment was discontinued at progression, unacceptable toxicity or patient refusal. Dose reductions were made as described elsewhere [10]. One treatment cycle was defined as a period of 4 weeks.

2.4. Follow-up

The baseline evaluation included a standardised MR protocol, HRQoL assessment, cognitive testing, full clinical and neurological evaluation, electrocardiogram, as well as complete blood count, blood chemistry and urinalysis. Every 12 weeks, neurological evaluation, MR scanning, HRQoL evaluation and cognitive testing were performed. Response assessment was done according to the RANO criteria [11]. In case of equivocal progressive disease (PD; target or non-target), treatment could continue until the next assessment, but if PD was confirmed at the next follow-up, the earlier date was used as the date of progression. All decisions on the assessment and interpretation of disease status were done locally, with preplanned central review afterwards. More details about the study assessments are presented in van den Bent et al. [1].

2.5. Outcomes

The primary outcome was OS12, which was reported elsewhere [1]. Secondary end-points included PFS, OS, toxicity, cognitive functioning (mini-mental state examination for all and cognitive test battery for selected centres) and HRQoL, which is reported here.

2.6. HRQoL assessment

We selected two of the most commonly used HRQoL tools in brain cancer clinical trials (EORTC QLQ-C30, version 3, and the EORTC Brain Cancer Module QLQ-BN20) to assess the QoL. These are well-established tools and have been validated and translated into all the required languages for our trial [3,12–14]. Both tools have robust psychometric properties that result from rigorous testing and refinement through their use in several international clinical cancer trials [5]. The items from both measures were scaled and scored according to the scoring manual methodology whereby responses are aggregated and transformed into a linear scale that ranged from 0 to 100, in which a higher score represents a higher level of functioning (function scales) or a higher level of symptoms (symptom scales). If at least half of the items in the scale were completed, the scale score was calculated with only those items for which values existed [15]. The results are presented in accordance with the guidelines for reporting HRQoL [16–18].

The EORTC QLQ-C30 (version 3.0) includes 30 items, which are transformed into 15 scales according to a standardised scoring procedure. The QLQ-C30 includes five function scales (physical, role, emotional, cognitive and social), eight symptom scales (fatigue,

pain, nausea or vomiting, dyspnoea, insomnia, appetite loss, constipation and diarrhoea), a scale to assess financial difficulties and one global health status/quality-of-life scale (GHQ). The EORTC QLQ-BN20, which is designed for use in patients undergoing chemotherapy or radiotherapy, includes 20 items assessing visual disorders, motor dysfunction, communication deficit, future uncertainty, as well as other specific symptoms, such as headaches, seizures or drowsiness. GHQ, pain and cognitive functioning were preselected for the study as the main HRQoL end-points of interest based on previous studies and expert opinion. All other scales and items were analysed on an exploratory basis.

Administration of paper HRQoL questionnaires took place at the hospital when patients came for a scheduled visit according to the EORTC guidelines for assessing QoL in EORTC clinical trials and followed the clinical assessment schedule of the trial. Baseline HRQoL assessments were performed within 6 weeks before the start of treatment. Follow-up assessments were performed every 12 weeks until disease progression, with no time constraint. Due to concerns regarding feasibility, HRQoL data collection stopped in the case of progression, as well as death, loss-to-follow-up or if the patient refused further participation. For this analysis, forms received after progression were excluded from the analysis set. Time windows for eligible follow-up assessment were set at 6 weeks before and 4 weeks after the scheduled follow-up assessment. Forms completed outside eligible time windows or duplicates within a window were removed from the analysis. HRQoL was a mandatory aspect of this clinical trial protocol to ensure optimal compliance, and guidelines for administering questionnaires were provided, ensuring standardisation by all personnel [18].

2.7. Statistical analysis

HRQoL was a secondary study end-point. To reduce multiplicity, we preselected three key HRQoL scales for the primary analysis, specifically the global health/QoL status (GH/Q), cognitive functioning and pain. The standard deviation of the selected HRQoL scales is approximately 20 points [19], so that with a two-sided alpha set at 5% a minimum of 128 patients (64 per treatment arm) is sufficient to achieve a power of 80% to detect a difference of 10 points (effect size of 0.5). Bonferroni approach ($p < 0.00625 = 0.05/8$) was used for treatment comparisons. The remaining HRQoL variables and any other TAVAREC trial: EORTC 26091 comparisons (e.g. per time point) were examined at 5% significance on an exploratory basis only. According to the work by Osoba et al. [20] and King [21], changes in scores of 5–10 represent a small difference and 10–20 represent a moderate difference, with 10 points being considered as the threshold for clinically relevant changes. A change was therefore considered clinically relevant when > 10 points. The use of the 10-point threshold itself might be nuanced as work by Maringwa et al. found different thresholds for various QLQ-C30 scales depending on improvement or deterioration over time [22], but the current trial was not statistically powered for attributing statistical significance to smaller differences. Analyses were done on the intention-to-treat (ITT) population, that is, all randomised patients according to their allocated treatment. A linear mixed-effects model was constructed with treatment, a time effect and time–treatment interactions as fixed effects and a patient-specific random effect to account for the longitudinal nature of the data.

Sensitivity analyses were conducted to assess the robustness of the results. The main findings were replicated on the per-protocol population (all eligible patients who started their allocated treatment). The change from baseline to the average, minimum, maximum and last available HRQoL assessment was calculated per patient as well as whether each patient experienced a 10-point or more deterioration from baseline at any follow-up visit and compared between the two treatment arms using non-parametric rank tests for patients with both baseline and at least one follow-up HRQoL assessment. The primary analysis was replicated with missing HRQoL data imputed with values predicted from a linear regression model that included the following factors: treatment arm, assessment time, WHO performance status, age, gender, molecular testing, type of histology and MRI contrast enhancement. SAS version 9.3 was used for all analyses.

2.8. Organisation of the trial

The trial was developed by the principal investigator (MvdB) in collaboration with the leading investigators at that time for neuroimaging (MS), molecular analysis (PF), neurocognitive functioning (MK) and HRQoL (MT), as well as the EORTC Headquarters (VG, CC and AB). All data have been reviewed by EORTC collaborators, where appropriate. Statistical analyses were performed by CC and AM. The trial sponsor was the EORTC. The trial was supported by an unrestricted educational grant and free BEV supply by Hoffmann La Roche. The drug manufacturer was not involved in trial design or analysis. The study was registered at EudraCT# 2009-017422-39 and ClinicalTrials.gov NCT01164189. The protocol was approved by the ethics committees and competent authorities of all participating centres and countries. All patients gave written informed consent for trial participation, pathology review and molecular testing.

2.9. Role of the funding source

The trial was supported by an unrestricted educational grant and free supply of BEV by Roche. The drug manufacturer was not involved in trial design, data collection or analysis, interpretation of the data, nor in

the writing of this report. JCR, CC, AB, MT and MvdB had full access to all of the data and the final responsibility to submit for publication.

3. Results

3.1. Recruitment and participant flow

Between 8 February 2011 and 31 July 2015, 155 patients were randomised; the final database lock was on 10 January 2017. The median age was 43 years, 101 (65%) of 131 tested tumours showed an *IDHmt* and 27% of patients had received prior chemotherapy. Patient characteristics were well balanced between treatment arms (see Table 1). At review, 12 patients (8 in the combination arm) were considered to not fully meet the entry criteria [inadequate baseline MR imaging (7); hypertension (1); no target lesion (3) and second recurrence (1)]. Four patients never started treatment (two of whom were also ineligible). The median number of TMZ cycles in the TMZ monotherapy arm was 7 and in the combination arm 8. The median number of BEV cycles (4 weeks) in the combination arm was 8. In the TMZ arm, 46 (60%) of patients discontinued TMZ because of progression, 20 (26%) because of the completion of 12 cycles and 6 (8%) for toxicity. In the TMZ + BEV arm, 42 (54%) of patients discontinued TMZ because of progression, 14 (18%) because of the completion of 12 cycles and 10 (13%) for toxicity. BEV was discontinued in 49 (63%) patients for progression, in 12 (15%) for toxicity, in 10 for other reasons; treatment was ongoing in five patients at the time of database lock (for further details, see van den Bent et al. [1]).

Table 1
Patient characteristics

	TMZ (N = 77)	TMZ + BEV (N = 78)	Total
	N (%)	N (%)	N (%)
Sex: male	45 (58.4)	57 (73.1)	102 (65.8)
Median age at randomisation (years)	43.1	44.6	43.3
Prior chemotherapy given			
No	56 (72.7)	57 (73.1)	113 (72.9)
TMZ (concomitant and/or adjuvant = one line)	21 (27.3)	16 (20.5)	37 (23.9)
PCV	0 (0.0)	5 (6.4)	5 (3.2)
WHO grade at first (local) diagnosis			
II	40 (51.9)	43 (55.1)	83 (53.5)
III	36 (46.8)	34 (43.6)	70 (45.2)
Missing	1 (1.3)	1 (1.3)	(1.3)
WHO performance status			
0	34 (44.2)	31 (39.7)	65 (41.9)
1	35 (45.5)	38 (48.7)	73 (47.1)
2	8 (10.4)	9 (11.5)	17 (11.0)
Prior irradiation given			
No	2 (2.6)	5 (6.4)	7 (4.5)
Yes	75 (97.4)	73 (93.6)	148 (95.5)
Surgery at the time of progression			
Yes	22 (28.6)	24 (30.8)	46 (29.7)
Corticosteroids intake			
Yes	27 (35.1)	22 (28.2)	49 (31.6)
Time since the last radiotherapy (months)			
Median	29.3	28.1	28.7
Range	3.6–177.1	4.2–239.6	3.6–239.6
MGMT			
Unmethylated	12 (15.6)	22 (28.2)	34 (21.9)
Methylated	51 (66.2)	40 (51.3)	91 (58.7)
Not determinable	14 (18.2)	16 (20.5)	30 (19.4)
IDH			
Wildtype	14 (18.2)	16 (20.5)	30 (19.4)
Mutated	53 (68.8)	48 (61.5)	101 (65.2)
Undetermined	10 (13.0)	14 (17.9)	24 (15.5)

BEV, bevacizumab; TMZ, temozolomide; WHO, World Health Organization; PCV, procarbazine, CCNU (lomustine), and vincristine; MGMT, O(6)-Methylguanine-DNA-methyltransferase; IDH, isocitrate dehydrogenases 1.

3.2. HRQoL compliance and baseline scores

The overall HRQoL compliance rates in the ITT population (n = 155) are shown in Table 2. The initial compliance for filling out HRQoL questionnaires was very good, with 145/155 (93.5%) of the patients completing the questionnaires at baseline. However, we restricted the analysis to the first 60 weeks as average compliance rates decreased over time to 65% at that time. Beyond 60 weeks, the available data were both too sparse to draw reliable results and low compliance was likely causing selection bias. The cut-off at 60 weeks was chosen to maintain statistical integrity of the results. The main documented reason for missing data was administrative failure (i.e. not related to the patient's health or refusal), accounting for 38% (46/121) of all reported reasons. Fig. 1 shows the CONSORT diagram of this study. Compliance did not systematically differ between treatment arms. The baseline scores were similar between the two treatment arms. For the three key scales, the GH/Q baseline scores were comparable to normative values from a healthy population, cognitive functioning scores were notably worse and pain scores tended to be better than normative values (Table 3).

3.3. HRQoL primary analysis

The overall test for post-baseline differences between the two treatment arms resulting from the longitudinal mixed-effects analysis was not statistically significant for all the primary scales of interest (GH/Q: $p = 0.26$; cognitive functioning: $p = 0.13$; pain: $p = 0.24$). Differences in the GH/Q scale between the two treatment arms assessed at each time point were less than 10 points and not statistically significant (Fig. 2). For cognitive functioning, differences between the two treatment arms

Table 2
HRQoL compliance rates

	HRQoL compliance	
	TMZ (n = 77)	TMZ + BEV (n = 78)
Baseline	72/77 (93.5)	73/78 (93.6)
Week 12	56/66 (84.8)	65/71 (91.5)
Week 24	43/47 (91.5)	42/53 (79.2)
Week 36	30/33 (90.9)	26/33 (78.8)
Week 48	19/25 (76.0)	21/26 (80.8)
Week 60	12/21 (57.1)	14/19 (73.7)
Week 72	7/15 (46.7)	5/13 (38.5)
Week 84	4/13 (30.8)	4/10 (40.0)
Week 96	3/11 (27.3)	2/9 (22.2)
Week 108	2/7 (28.6)	3/5 (60.0)
Week 120	1/5 (20.0)	2/4 (50.0)
Week 132	0/3 (0.0)	1/4 (25.0)
Week 144	0/2 (0.0)	3/3 (100.0)
Week 156	0/2 (0.0)	3.3 (100.0)
Week 168	–	2/3 (66.7)
Week 180	–	1/3 (33.3)
Week 192	–	1/3 (33.3)
Week 204	–	1/3 (33.3)
Week 216	–	1/2 (50.0)
Week 228	–	1/1 (100.0)
Week 240	–	1/1 (100.0)

BEV, bevacizumab; HRQoL, health-related quality of life; TMZ, temozolomide.

assessed at each time point were not statistically significant (Fig. 3). For pain, differences between the two treatment arms assessed at each time point were also not statistically significant (Fig. 4). In both arms, the mean GH/Q, cognitive functioning and pain scores tended to be stable over time. Among the other scales, social functioning [$p = 0.0254$; week 36 difference 17.6 (confidence interval, CI, 6.4, 28.8), week 48 difference 11.7 (CI −0.1, 23.6)], physical functioning [$p = 0.0388$, week 36 difference 11.1 (CI 1.9, 20.2)] and itchy skin [$p = 0.0364$, week 60 difference −9.7 (CI −26, 6.7)] were significantly in favour of the TMZ arm, while motor dysfunction [$p = 0.0285$, week 12 difference −10.6 (CI −19.3, 1.8), week 36 difference −11.2 (CI −21.3, −1.1)] scores were better in the TMZ + BEV arm.

3.4. Sensitivity analyses

Non-compliance was found to be related to the institution, with higher compliance both in centres with the most and the fewest recruited patients. In general, there was no systematic trend that HRQoL is decreasing if the patient drops out of the HRQoL assessment schedule. The only notable exception is at 24 weeks, where patients dropping out at that time had significant (and relevant) lower scores.

The primary analysis on GH/Q was replicated in the per-protocol population ($N = 141$; 423 HRQoL forms) which generally resulted in larger observed treatment differences. Clinically relevant differences (> 10 points) in favour of the TMZ arm were observed for the GHQ scale at weeks 36 and 60; for pain at week 60 and for cognitive functioning at weeks 36, 48 and 60. Imputation confirmed the primary result of no statistically significant differences (data not shown). Since the original study reported higher toxicity levels in the combination arm [grade 3/4 adverse events reported in 23% (17/75) and 58% (44/76) of patients in the TMZ alone arm and combination arm, respectively], an investigation into the relationship between toxicity and HRQoL compliance was undertaken. Table 4 shows the compliance according to toxicity severity with no major differences observed until week 60, suggesting no compliance bias due to toxicity.

4. Discussion

Our study showed no significant difference in HRQoL between the two treatment modalities, at least during the first 60 weeks of follow-up. The addition of BEV to TMZ failed to be associated with improved HRQoL and self-reported symptoms. Our study shows that the self-perceived cognitive functioning of this patient group already is compromised at the time of treatment initiation compared to healthy individuals [23]. This observation is in agreement with prior reports and large cross-sectional studies, though a detailed comparison is hampered by the use of different HRQoL measurement tools in these studies.

To our knowledge, this is the first randomised controlled trial assessing the impact on HRQoL of the addition of BEV to TMZ in recurrent lower-grade glioma. Given the underlying mechanism of BEV, a recombinant, humanised, monoclonal antibody against vascular endothelial growth factor rapidly and effectively closing the blood–brain barrier and thereby reducing peritumoral oedema, one might have expected beneficial effects on neurological functioning and HRQoL, including self-perceived cognitive functioning. If this would be the case, addition of BEV would be clinically meaningful as it would result in the preservation of HRQoL in this patient group with a rather limited survival. Previous studies assessing the impact of the addition of BEV to standard treatment (including TMZ) in newly diagnosed glioblastoma patients, however, also showed no [24,25] or even a negative impact on HRQoL during the progression-free period [22], whereas the addition of BEV to lomustine chemotherapy in recurrent glioblastoma did not improve HRQoL either [26,27]. Therefore, our results also do not support the addition of BEV to TMZ chemotherapy in patients with recurrent low-grade gliomas.

The incidence of treatment-related adverse events of grade 3 or higher was greater in the combination group than in the TMZ group [1]. However, these effects were not reflected in the HRQoL scales. Exploratory analyses showed that adverse events are consistently reported by the patients in their corresponding QLQ-C30 scale. These reduced scores in the QLQ-C30 scales are not

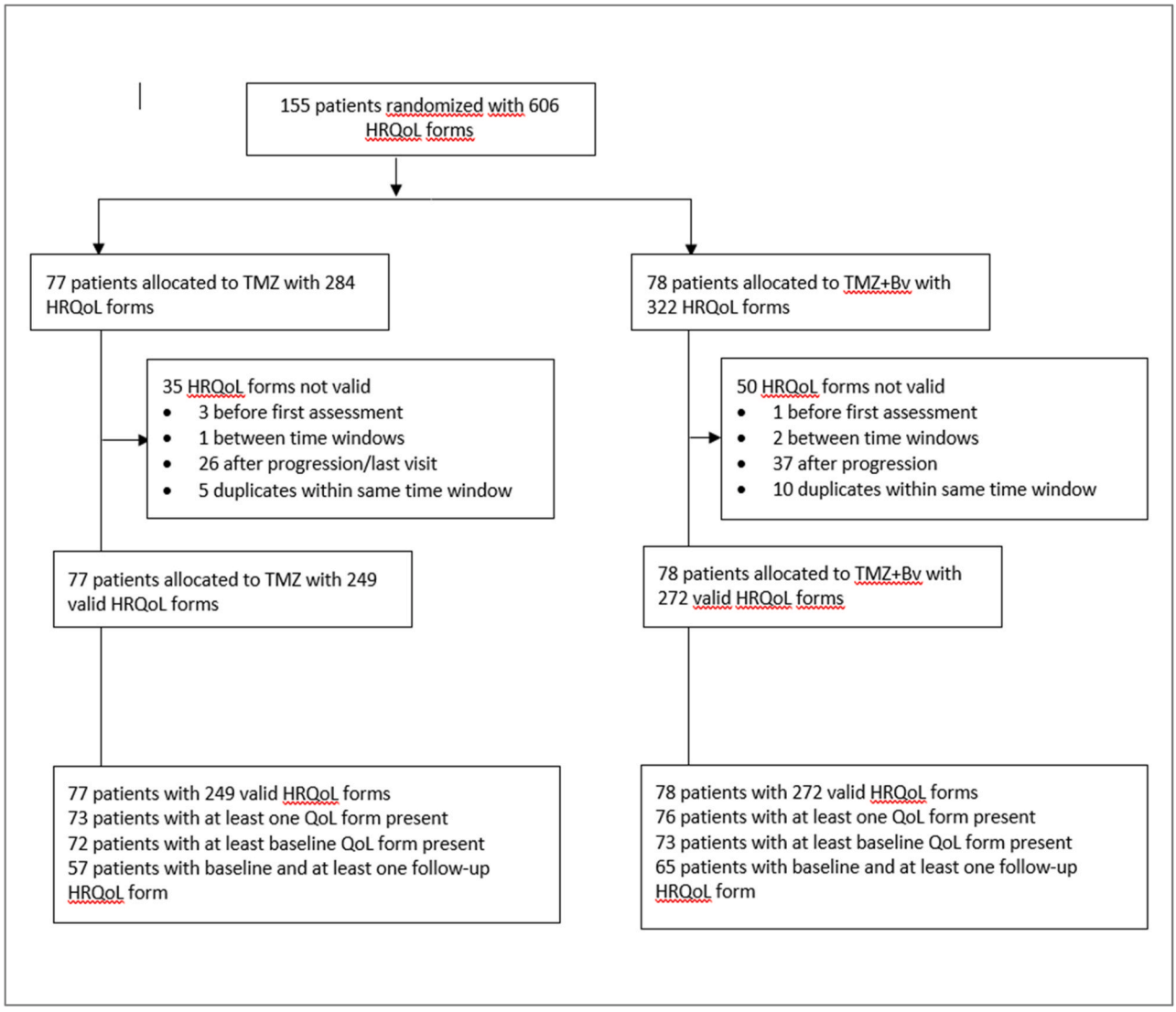


Fig. 1. CONSORT flowchart. Trial profile showing HRQoL compliance**.** HRQoL forms were considered valid if they were collected within the pre-specified time windows in relation to the target assessment time. Forms were considered invalid if any of the following were true: (1) all questions on the form were blank; (2) the completion date was unknown or it could not be assigned to a single assessment time point; (3) the completion date fell outside the time windows or (4) multiple forms were received during the same time window. In the case of multiple forms for the same time point, the form closest to the intended assessment time was kept. In the case of equidistance, the earlier form was kept. BV, bevacizumab; HRQoL, health-related quality of life; TMZ, temozolomide.

substantial enough to result in relevant changes on the population level or for the overall GHQ scale. Adverse events not being reflected in the patient-reported outcomes can be a result of the masking of the treatment, whereby patients have treatment side-effects as indicators of drug activity or due to successful AE management (e.g. medication for pain). In a post hoc comparison of baseline scores to normative data obtained from a healthy population sample, the GHQ and cognitive functioning scores obtained in this study are

Table 3
HRQoL mean scores versus normative data

	Mean scores (standard deviations)		
	Healthy population normative values	TMZ (n = 77) baseline scores	TMZ + BEV (n = 78) baseline scores
Global health/QL	66.1 (21.7)	65.20 (26.19)	63.89 (21.26)
Cognitive functioning	84.8 (21.3)	69.29 (27.31)	71.30 (24.58)
Pain	23.5 (27.1)	16.90 (25.56)	17.35 (25.53)

BEV, bevacizumab; HRQoL, health-related quality of life; QL, quality of life; TMZ, temozolomide.

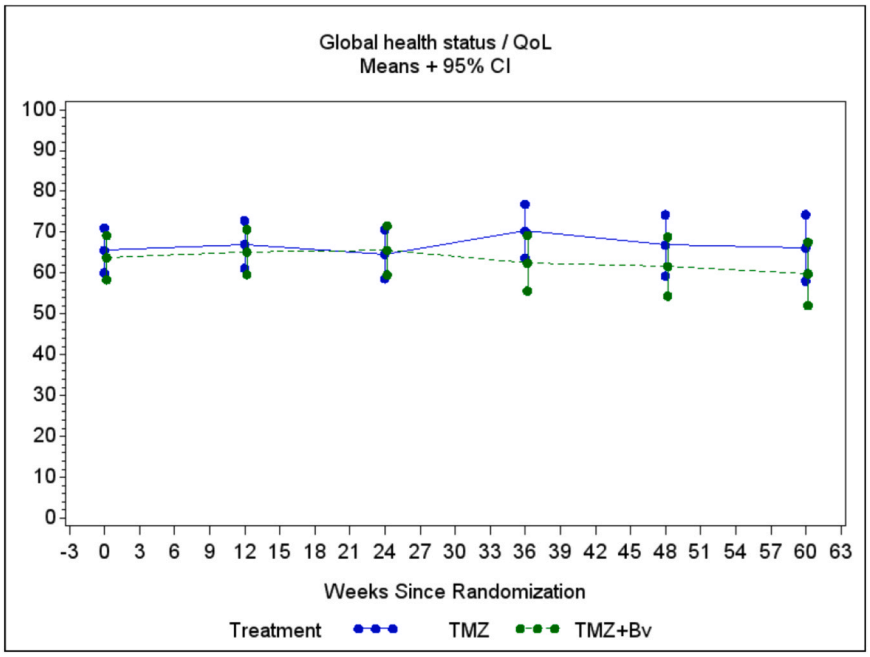


Fig. 2. Global health status mean scores. Bv, bevacizumab; CI, confidence interval; QoL, quality of life; TMZ, temozolomide.

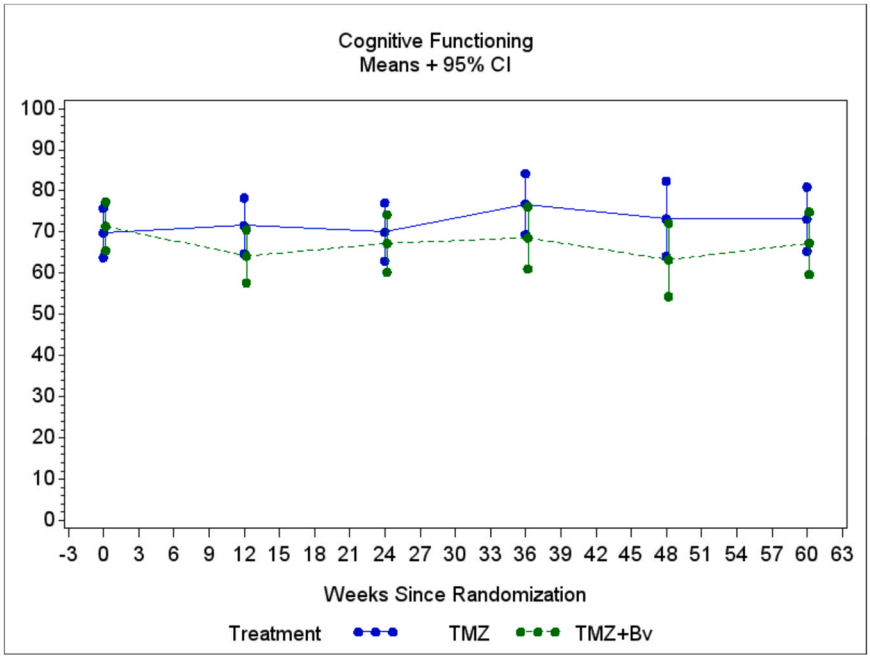


Fig. 3. Cognitive functioning mean scores. Bv, bevacizumab; CI, confidence interval; TMZ, temozolomide.

significantly lower for both groups (GHQ: 65.2 in the TMZ group, 63.9 in the combination group versus 66.1; cognitive functioning: 69.2 in the TMZ group, 71.3 in the combination group versus 84.8) (Table 3). Pain scores are significantly lower for both groups (16.9 in the TMZ group, 17.3 in the combination group versus 23.5) (Table 3). This could be explained by the selection criteria for the clinical trial, which required patients to be more than 6 months off chemotherapy before progression to be included in the study.

The major strengths of this study are the randomised nature of the trial and the large sample size ($n = 155$), consisting of a homogeneous group of patients with first recurrences of histologically verified diffuse lower-grade glioma with similar performance levels and pre-specified criteria for the start of treatment. Furthermore, the high baseline compliance, the prospective study design with pre-specified time points for HRQoL measurements and key scales for the primary analysis, and the application of the EORTC QLQC-30 and BN20, which are

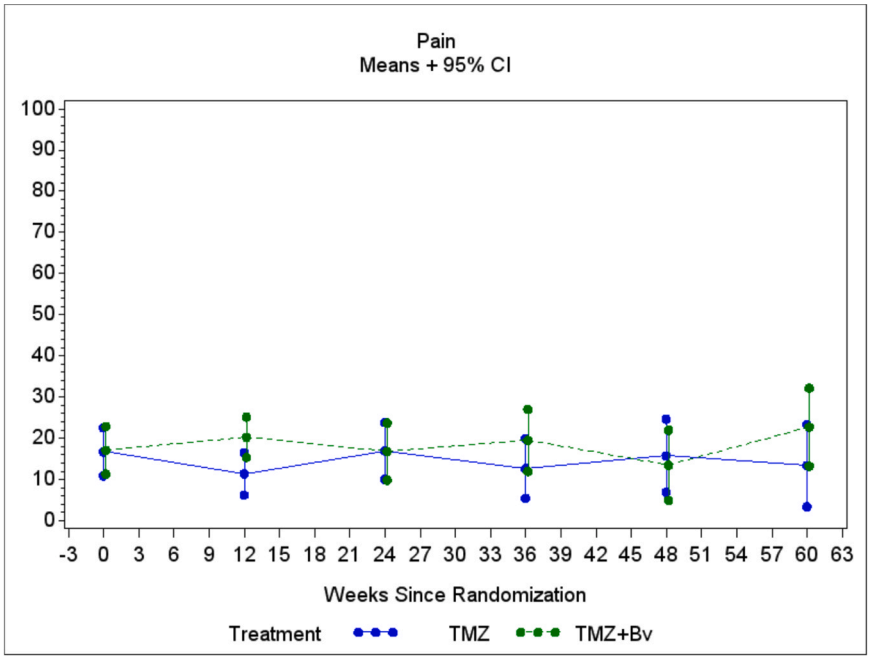


Fig. 4. Pain mean scores. Bv, bevacizumab; CI, confidence interval; TMZ, temozolomide.

Table 4
Compliance rates by toxicity

	Compliance by toxicity	
	Grade 1/2	Grade 3/4
# of patients/HRQoL forms	89/282	62/232
Baseline	82 (94.3)	58 (95.1)
Week 12	66 (86.8)	53 (89.8)
Week 24	48 (84.2)	37 (86.0)
Week 36	37 (86.0)	19 (82.6)
Week 48	25 (75.8)	15 (83.3)
Week 60	13 (54.2)	13 (81.3)
Week 72	4 (26.7)	8 (61.5)
Week 84	2 (15.4)	6 (60.0)

Maximum common toxicity criteria (CTC) grade for any adverse event.
HRQoL, health-related quality of life.

extensively validated tools for measurement of HRQoL in (brain) cancer patients with robust validity and reliability, are the strong points.

However, our study has some limitations, common to HRQoL studies in general, the most important being missing data. [2] Compliance rates dropped significantly during follow-up, limiting the primary analysis to the first 60 weeks as beyond that time point the available data are both too sparse to draw reliable results and low compliance is likely causing selection bias [2]. The data obtained after week 60 were unfortunately considered to be too sparse to yield reliable results. Therefore, the deliberate decision was made to truncate at week 60 rather than present potentially misleading data. Sensitivity analysis suggested no impact of toxicity on patients' compliance, with even higher compliance reported at later time points among patients with grade 3/4 toxicities, likely due to these patients being under more intensive follow-up. Frequent reasons for missing data in brain tumour trials are administrative failure, patient refusal and poor health status of the patient, [2] and this was also the case in our study. Compliance was not systematically different between treatment arms but differed per institution. It should, however, be noted that there were a large number of institutions involved in this trial ($n = 32$) with many contributing only a few patients. Furthermore, as is the case in many cancer trials [2], the patients of our trial might not be fully representative of the patient population in general as patients with lower performance scores or cognitive deficits preventing them from providing informed consent were excluded. Lastly, a frequent observation throughout the study results was that statistically significant results were not clinically relevant as the magnitude of the treatment difference did not exceed the pre-set threshold of 10 points [28].

Funding

This study was supported by an unrestricted educational grant and free supply of BEV by Roche.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank all patients and their relatives for their willingness to participate in this clinical trial. We thank the European Organisation for Research and Treatment of Cancer (EORTC) Cancer Research Fund and EORTC staff for their invaluable assistance and support of this trial (Roxana Albu, Pieter Jespers, Jelena Laverty, Sylvie Ledroit, Sara Meloen, Jean-Paul Nzanzu, Christine Olungu, Nabila Sebti, Thibault Smets, Zineb Wadid and Lorraine Wheeler). We also thank all trial staff at the participating sites and the staff at Roche involved in this study.

Appendix

Tables A1 and A2.

Secondary scales

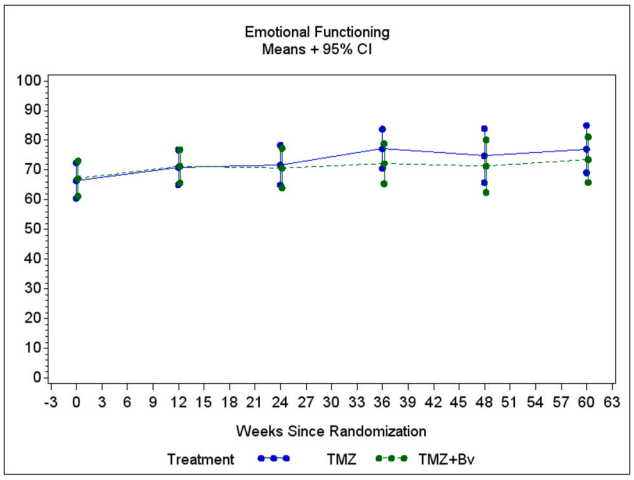


Table A1
Reasons for non-compliance per treatment arm

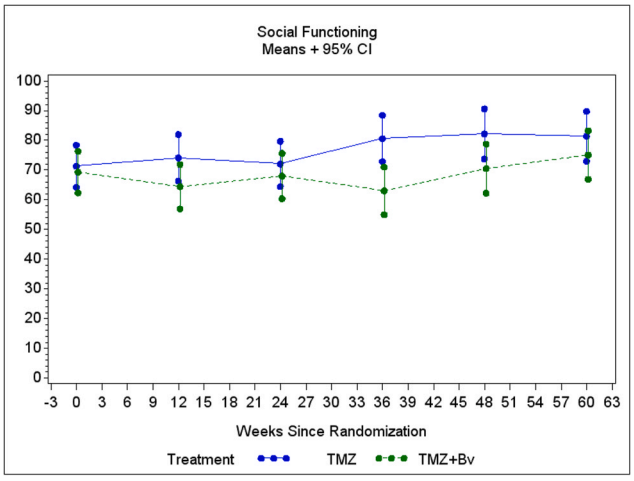
	Treatment		Total ($N = 121$)
	TMZ ($N = 44$) *N* (%)	TMZ + BEV ($N = 77$) *N* (%)	*N* (%)
Specify the main reason for not completing QoL form			
Patient too ill	1 (2.3)	11 (14.3)	12 (9.9)
Clinician or nurse felt the patient is too ill	2 (4.5)	3 (3.9)	5 (4.1)
Patient felt inconvenienced, takes too much time	2 (4.5)	16 (20.8)	18 (14.9)
Patient didn't understand the language/illiterate	0 (0.0)	4 (5.2)	4 (3.3)
Administrative failure to distribute	16 (36.4)	30 (39.0)	46 (38.0)
Other	23 (52.3)	13 (16.9)	36 (29.8)

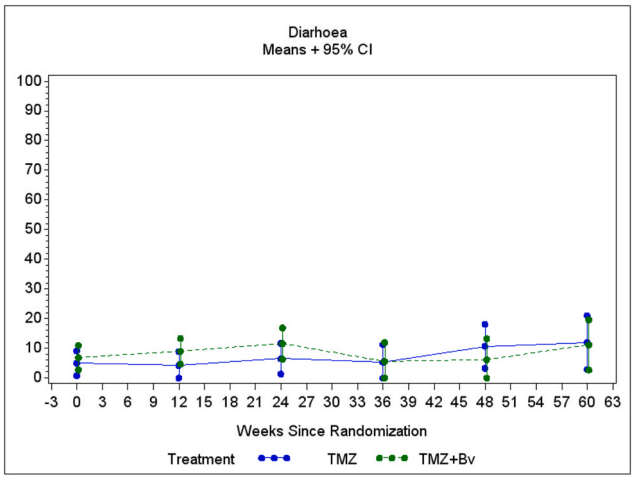
BEV, bevacizumab; QoL, quality of life; TMZ, temozolomide.

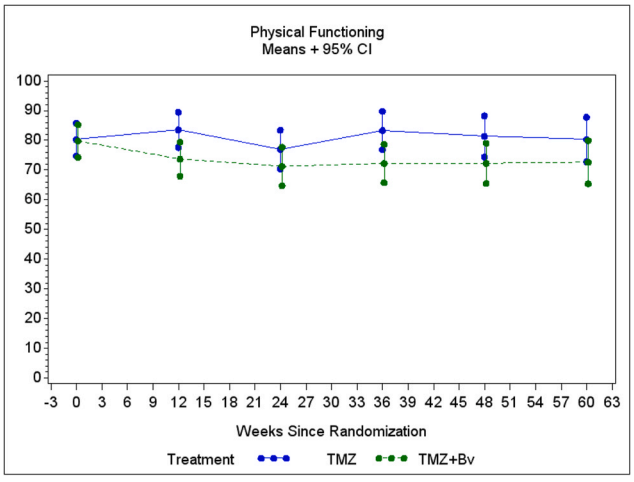
Table A2
Reasons for non-compliance per assessment time

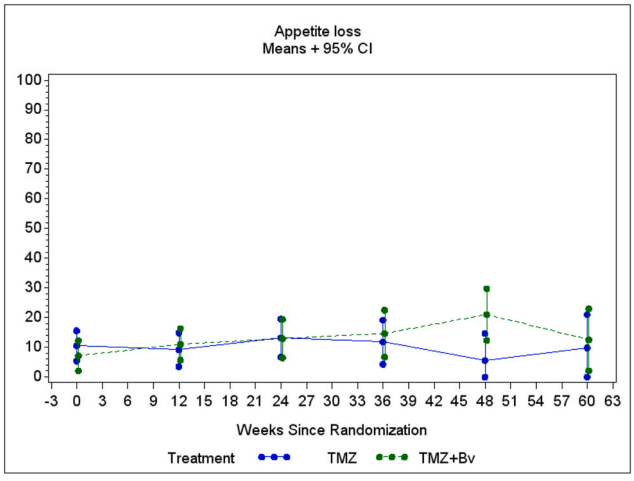
	QoL completion time				Total ($N = 121$)
	Baseline ($N = 5$) N (%)	During year 1 ($N = 79$) N (%)	During year 2 ($N = 30$) N (%)	After year 2 ($N = 7$) N (%)	N (%)
Specify the main reason for not completing QoL form					
Patient too ill	1 (20.0)	10 (12.7)	1 (3.3)	0 (0.0)	12 (9.9)
Clinician or nurse felt the patient is too ill	0 (0.0)	4 (5.1)	1 (3.3)	0 (0.0)	5 (4.1)
Patient felt inconvenienced, takes too much time	0 (0.0)	7 (8.9)	7 (23.3)	4 (57.1)	18 (14.9)
Patient didn't understand the language/illiterate	1 (20.0)	3 (3.8)	0 (0.0)	0 (0.0)	4 (3.3)
Administrative failure to distribute	0 (0.0)	31 (39.2)	13 (43.3)	2 (28.6)	46 (38.0)
Other	3 (60.0)	24 (30.4)	8 (26.7)	1 (14.3)	36 (29.8)

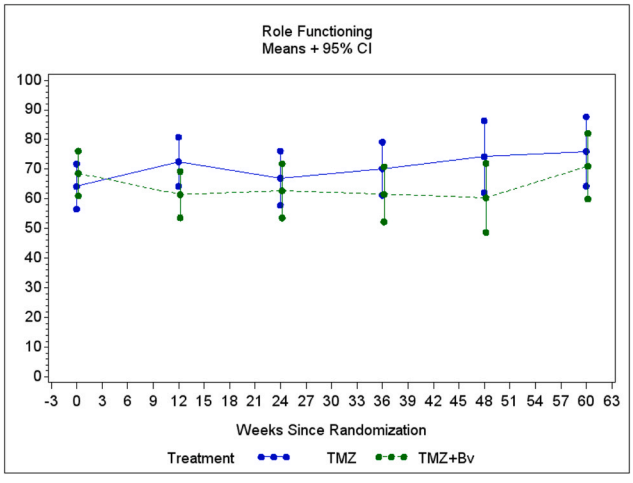
QoL, quality of life.

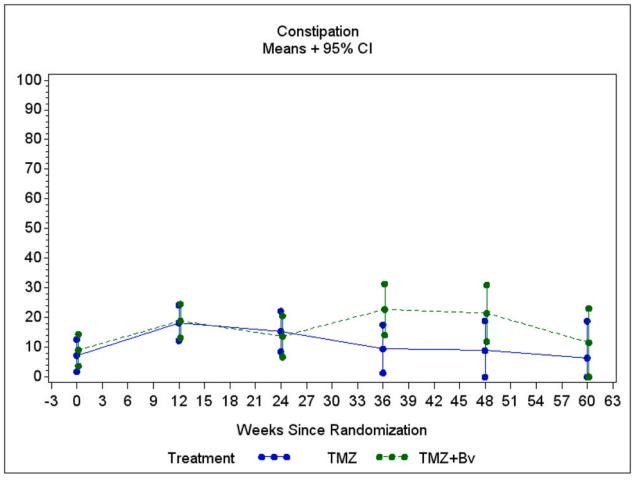

Social Functioning
Means + 95% CI
Weeks Since Randomization
Treatment TMZ TMZ+Bv

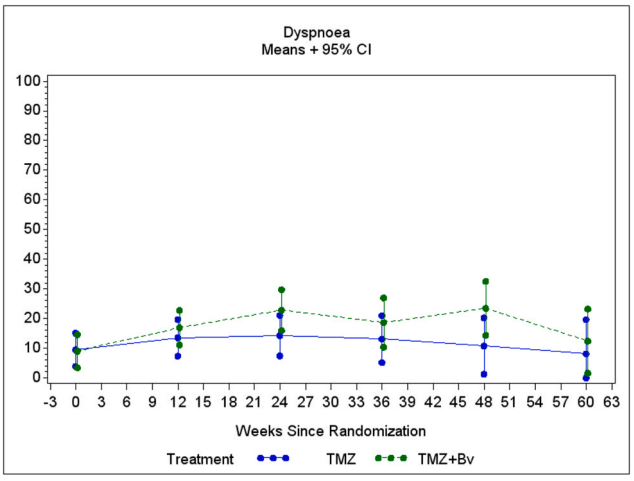

Diarhoea
Means + 95% CI
Weeks Since Randomization
Treatment TMZ TMZ+Bv

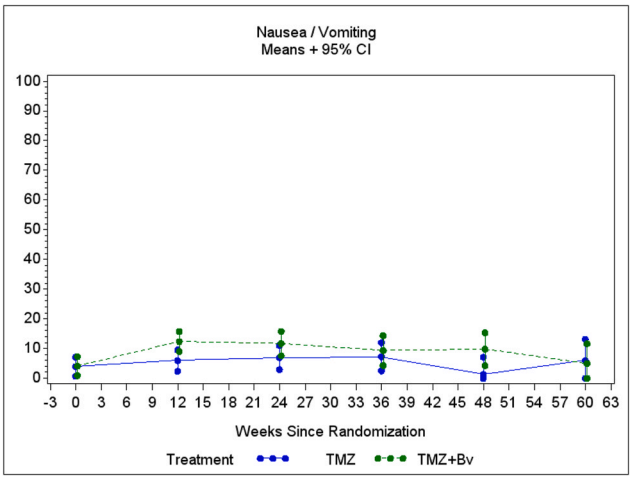

Physical Functioning
Means + 95% CI
Weeks Since Randomization
Treatment TMZ TMZ+Bv

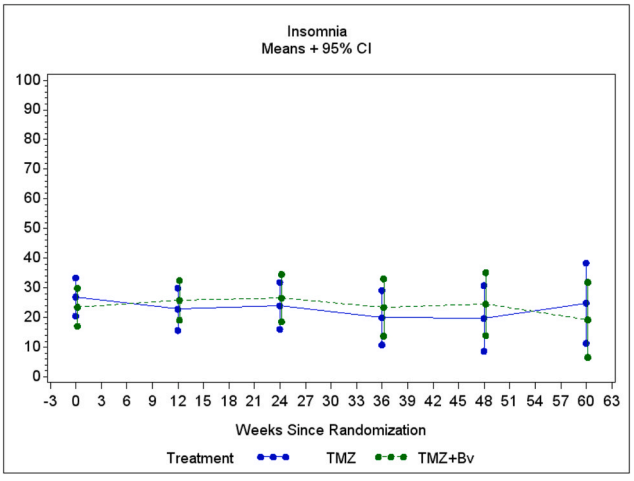

Appetite loss
Means + 95% CI
Weeks Since Randomization
Treatment TMZ TMZ+Bv

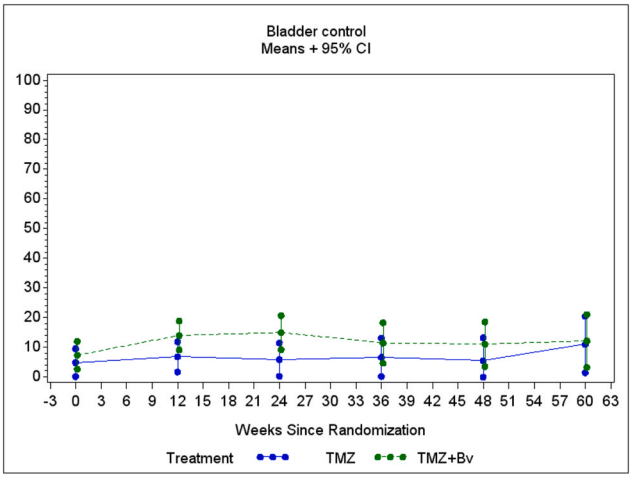

Role Functioning
Means + 95% CI
Weeks Since Randomization
Treatment TMZ TMZ+Bv

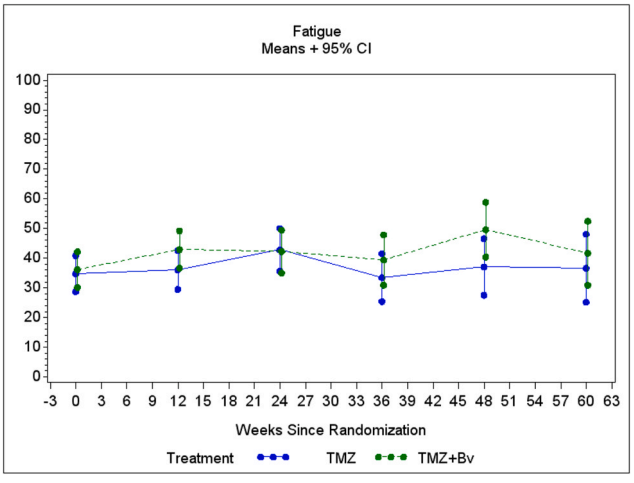

Constipation
Means + 95% CI
Weeks Since Randomization
Treatment TMZ TMZ+Bv

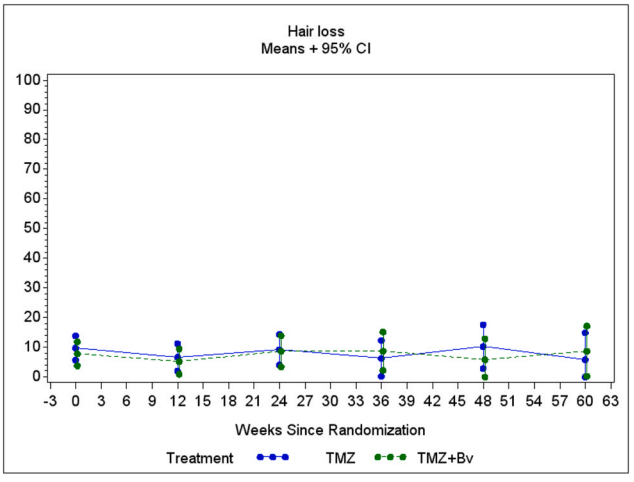

Dyspnoea
Means + 95% CI
Weeks Since Randomization
Treatment TMZ TMZ+Bv

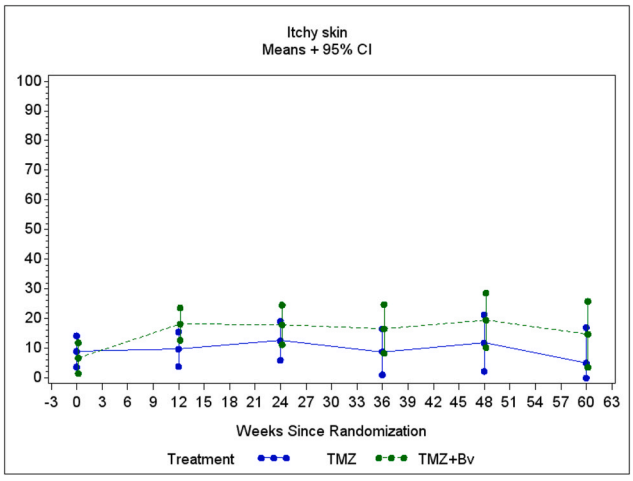

Nausea / Vomiting
Means + 95% CI
Weeks Since Randomization
Treatment TMZ TMZ+Bv

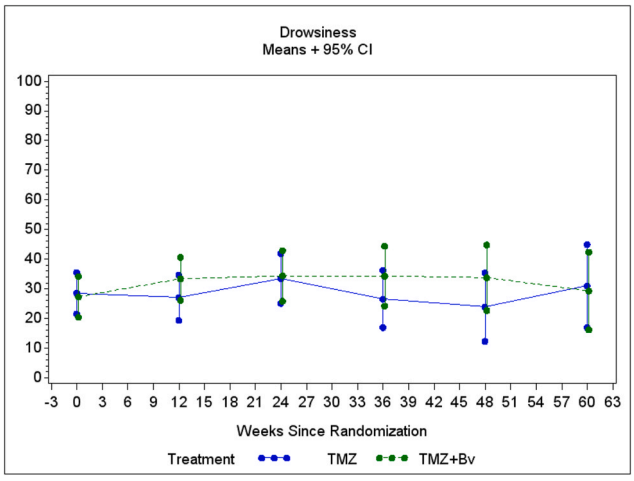

Insomnia
Means + 95% CI
Weeks Since Randomization
Treatment TMZ TMZ+Bv

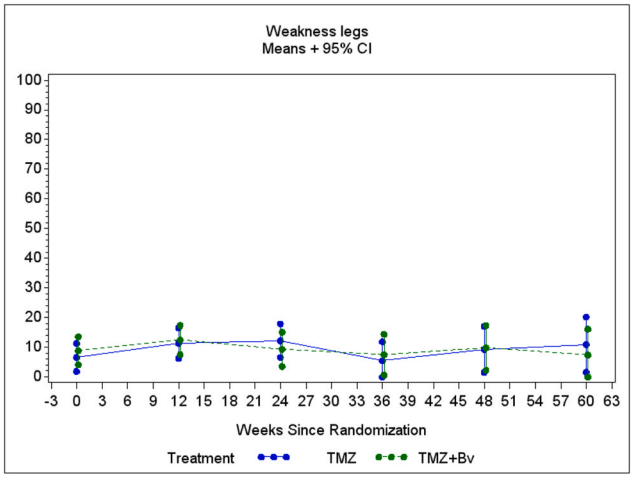

Bladder control
Means + 95% CI
Weeks Since Randomization
Treatment TMZ TMZ+Bv


Fatigue
Means + 95% CI
Weeks Since Randomization
Treatment TMZ TMZ+Bv


Hair loss
Means + 95% CI
Weeks Since Randomization
Treatment TMZ TMZ+Bv


Itchy skin
Means + 95% CI
100 90 80 70 60 50 40 30 20 10 0
-3 0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54 57 60 63
Weeks Since Randomization
Treatment TMZ TMZ+Bv


Drowsiness
Means + 95% CI
100 90 80 70 60 50 40 30 20 10 0
-3 0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54 57 60 63
Weeks Since Randomization
Treatment TMZ TMZ+Bv


Weakness legs
Means + 95% CI
100 90 80 70 60 50 40 30 20 10 0
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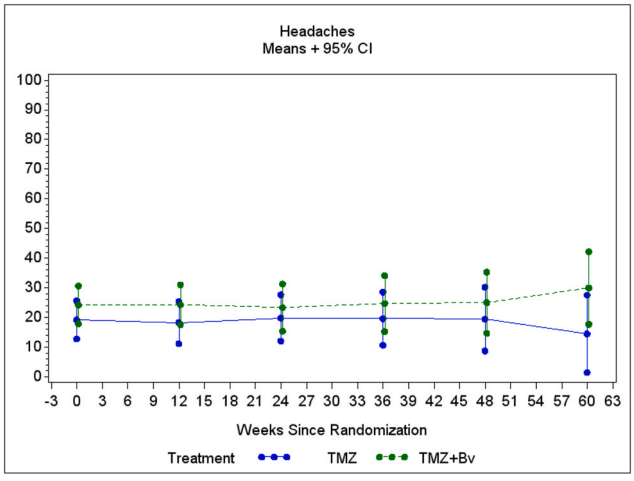
Weeks Since Randomization
Treatment TMZ TMZ+Bv


Headaches
Means + 95% CI
100 90 80 70 60 50 40 30 20 10 0
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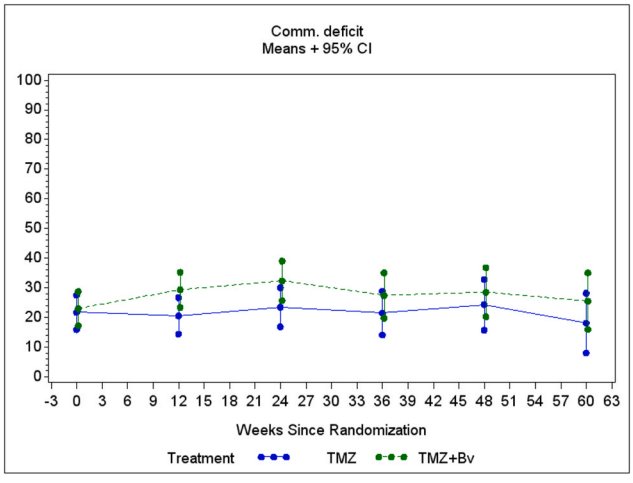
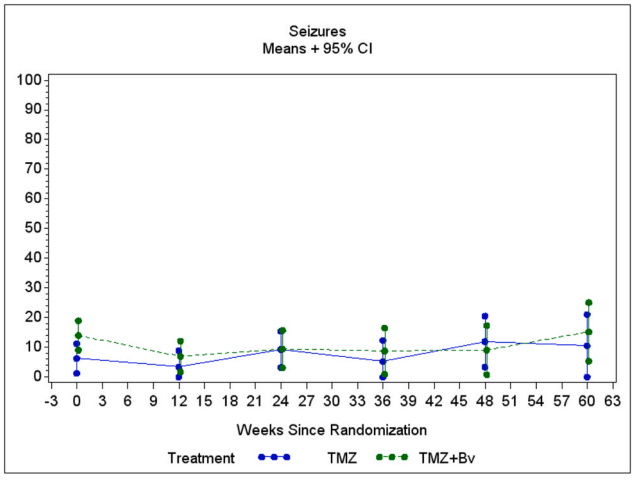
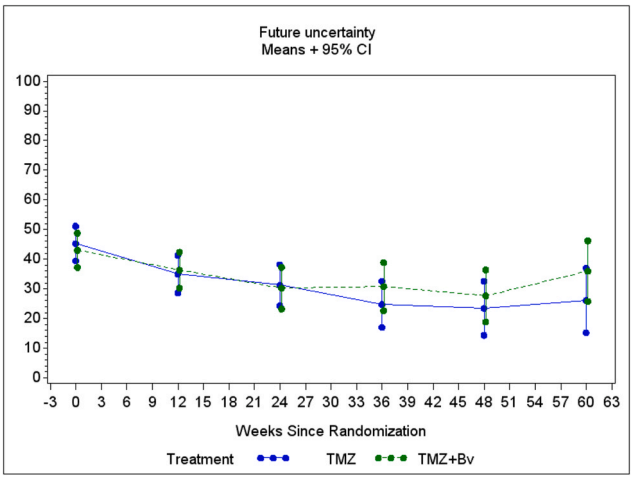
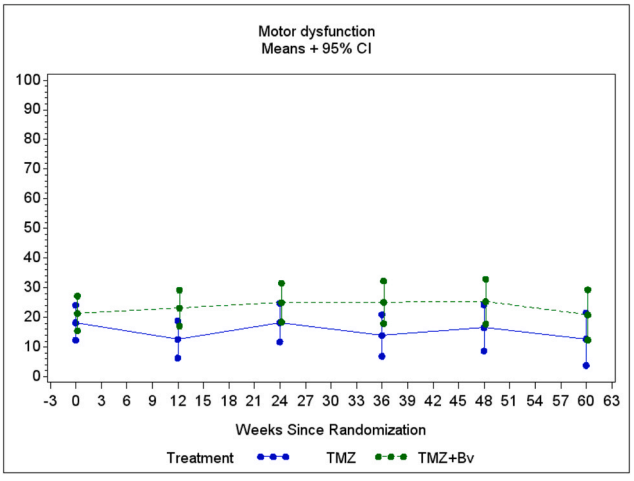
Weeks Since Randomization
Treatment TMZ TMZ+Bv


Comm. deficit
Means + 95% CI
100 90 80 70 60 50 40 30 20 10 0
-3 0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54 57 60 63
Weeks Since Randomization
Treatment TMZ TMZ+Bv


Seizures
Means + 95% CI
100 90 80 70 60 50 40 30 20 10 0
-3 0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54 57 60 63
Weeks Since Randomization
Treatment TMZ TMZ+Bv





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