ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Health-related quality of life after chemotherapy with or without rituximab in primary central nervous system lymphoma patients: results from a randomised phase III study

M. van der Meulen[1*†], K. Bakunina[2†], M. Nijland[3], M. C. Minnema[4], G. Cull[5,6], W. B. C. Stevens[7], J. W. Baars[8], K. D. Mason[9], A. Beeker[10], M. Beijert[11], M. J. B. Taphoorn[12,13], M. J. van den Bent[1], S. Issa[14], J. K. Doorduijn[15], J. E. C. Bromberg[1] & L. Dirven[12,13]

[1]Department of Neuro-Oncology, Erasmus MC Cancer Institute, Brain Tumor Center, University Medical Center, Rotterdam; [2]HOVON Data Center, Department of Hematology, Erasmus MC Cancer Institute, Rotterdam; [3]Department of Hematology, University Medical Center Groningen, Groningen; [4]Department of Hematology, University Medical Center Utrecht, Utrecht, The Netherlands; [5]Haematology Department, Sir Charles Gairdner Hospital and PathWest Laboratory Medicine, Nedlands; [6]University of Western Australia, Crawley, Australia; [7]Department of Hematology, Radboud University Medical Center, Nijmegen; [8]Department of Hemato-Oncology, Antoni van Leeuwenhoek Hospital/Dutch Cancer Institute, Amsterdam, The Netherlands; [9]Department of Hematology, Royal Melbourne Hospital, Melbourne, Australia; [10]Department of Hematology, Spaarne Gasthuis, Haarlem; [11]Department of Radiotherapy, University Medical Center Groningen, Groningen; [12]Department of Neurology, Leiden University Medical Center, Leiden; [13]Department of Neurology, Haaglanden Medical Center, The Hague, The Netherlands; [14]Department of Hematology, Middlemore Hospital, Auckland, New Zealand; [15]Department of Hematology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands

Available online XXX

Background: The impact of rituximab on health-related quality of life (HRQoL) in primary central nervous system lymphoma patients is not well known. We determined the impact of rituximab added to standard high-dose methotrexate-based treatment on HRQoL in patients in a large randomised trial.

Patients and methods: Patients from a large phase III trial (HOVON 105/ALLG NHL 24), randomly assigned to receive standard chemotherapy with or without rituximab and followed by 30 Gy whole brain radiotherapy (WBRT) in patients $\leq$60 years, completed the EORTC QLQ-C30 and QLQ-BN20 questionnaires before and during treatment, and up to 24 months of follow-up or progression. Differences between treatment arms over time in global health status, role functioning, social functioning, fatigue, and motor dysfunction were assessed. Differences $\geq$10 points were deemed clinically relevant. The effect of WBRT on HRQoL was analysed in irradiated patients.

Results: A total of 160/175 patients eligible for the HRQoL study completed at least one questionnaire and were included. Over time, scores improved statistically significantly and were clinically relevant in both arms. Between arms, there were no differences on any scale (range: -3.8 to $+4.0$). Scores on all scales were improved to a clinically relevant extent at 12 and 24 months compared with baseline in both arms, except for fatigue and motor dysfunction at 12 months (-7.4 and -8.8, respectively). In irradiated patients ($n = 59$), scores in all preselected scales, except motor dysfunction, remained stable up to 24 months compared with shortly after WBRT, overall mean difference ranging between 0.02 and 4.570.

Conclusion: Compared with baseline, treatment resulted in improved HRQoL scores. The addition of rituximab to standard chemotherapy did not impact HRQoL over time. WBRT did not result in deterioration of HRQoL in the first 2 years.

Key words: health-related quality of life, primary central nervous system lymphoma, radiation, rituximab

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is a rare non-Hodgkin's lymphoma confined to the brain, leptomeninges, spinal cord, and eyes. Over the last three decades, the incidence rate has increased, mainly amongst patients >60 years old, and prognosis has improved significantly.[1,2] This prolonged survival has largely been determined by improvements in treatment.[1,3]

In systemic diffuse large B-cell lymphoma patients, the addition of rituximab, a chimeric monoclonal antibody targeting the CD20 cell surface protein, to standard treatment has been shown to improve progression-free survival and overall survival.[4,5] Since most PCNSL are diffuse large B-cell lymphoma (DLBCL), it has been

*Correspondence to: Dr Matthijs van der Meulen, Department of Neuro-Oncology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Dr. Molewaterplein 40, 3015 GD, Rotterdam, The Netherlands. Tel: +31 (0)107040704

E-mail: m.vandermeulen.2@erasmusmc.nl (M. van der Meulen).

†Contributed equally.

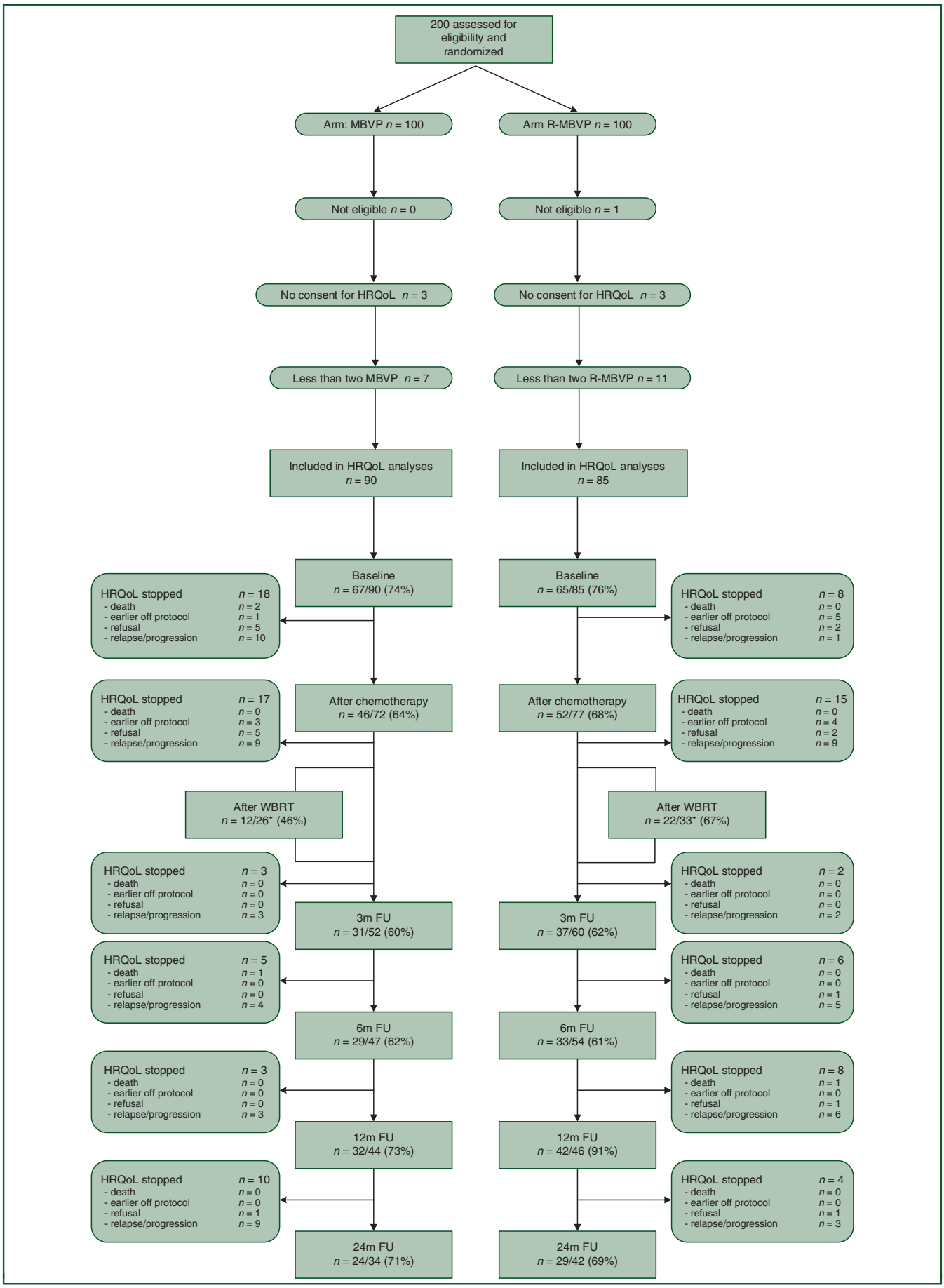
200 assessed for eligibility and randomized
Arm: MBVP n = 100
Arm R-MBVP n = 100
Not eligible n = 0
Not eligible n = 1
No consent for HRQoL n = 3
No consent for HRQoL n = 3
Less than two MBVP n = 7
Less than two R-MBVP n = 11
Included in HRQoL analyses n = 90
Included in HRQoL analyses n = 85
Baseline n = 67/90 (74%)
Baseline n = 65/85 (76%)
HRQoL stopped n = 18
- death n = 2
- earlier off protocol n = 1
- refusal n = 5
- relapse/progression n = 10
HRQoL stopped n = 8
- death n = 0
- earlier off protocol n = 5
- refusal n = 2
- relapse/progression n = 1
After chemotherapy n = 46/72 (64%)
After chemotherapy n = 52/77 (68%)
HRQoL stopped n = 17
- death n = 0
- earlier off protocol n = 3
- refusal n = 5
- relapse/progression n = 9
HRQoL stopped n = 15
- death n = 0
- earlier off protocol n = 4
- refusal n = 2
- relapse/progression n = 9
After WBRT n = 12/26* (46%)
After WBRT n = 22/33* (67%)
HRQoL stopped n = 3
- death n = 0
- earlier off protocol n = 0
- refusal n = 0
- relapse/progression n = 3
HRQoL stopped n = 2
- death n = 0
- earlier off protocol n = 0
- refusal n = 0
- relapse/progression n = 2
3m FU n = 31/52 (60%)
3m FU n = 37/60 (62%)
HRQoL stopped n = 5
- death n = 1
- earlier off protocol n = 0
- refusal n = 0
- relapse/progression n = 4
HRQoL stopped n = 6
- death n = 0
- earlier off protocol n = 0
- refusal n = 1
- relapse/progression n = 5
6m FU n = 29/47 (62%)
6m FU n = 33/54 (61%)
HRQoL stopped n = 3
- death n = 0
- earlier off protocol n = 0
- refusal n = 0
- relapse/progression n = 3
HRQoL stopped n = 8
- death n = 1
- earlier off protocol n = 0
- refusal n = 1
- relapse/progression n = 6
12m FU n = 32/44 (73%)
12m FU n = 42/46 (91%)
HRQoL stopped n = 10
- death n = 0
- earlier off protocol n = 0
- refusal n = 1
- relapse/progression n = 9
HRQoL stopped n = 4
- death n = 0
- earlier off protocol n = 0
- refusal n = 1
- relapse/progression n = 3
24m FU n = 24/34 (71%)
24m FU n = 29/42 (69%)

Table 1. Baseline sociodemographic and clinical characteristics of the patients included in the health-related quality of life analysis

Baseline characteristics	MBVP $N = 90$	R-MBVP $N = 85$
Sex, *n* (% male)	56 (62)	41 (48)
Age (years), median (IQR)	61 (55–66)	61 (55–67)
WHO performance score, *n* (%)		
WHO 0	19 (21)	23 (27)
WHO 1	46 (51)	42 (49)
WHO 2	15 (17)	12 (14)
WHO 3	10 (11)	8 (9)
Comorbidities active at baseline, *n* (% ≥2)	54 (60)	51 (60)
Solitary lesion, *n* (%)	46 (51)	44 (52)
Missing (NA)	10 (11)	4 (5)
Bilateral involvement, *n* (%)	33 (37)	33 (39)
Missing (NA)	10 (11)	4 (5)
Deep structures involved, *n* (%)	55 (61)	57 (67)
Study drug exposure		
HD cytarabine (Ara-C), *n* (%)	82 (91)	76 (89)
WBRT, *n* (%)	33 (37)	34 (40)
Radiation boost given, *n* (%)	15 (17)	23 (27)
Intrathecal treatment given, *n* (%)	8 (9)	8 (9)

MBVP, methotrexate, tenoposide, BCNU (carmustine), and prednisolone; R-MBVP, rituximab with methotrexate, tenoposide, BCNU (carmustine), and prednisolone; NA, not applicable in case of no brain lesion(s); IQR, interquartile range; HD, high-dose; WBRT, whole brain radiotherapy; WHO, World Health Organization.

hypothesised that the addition of rituximab to standard treatment with high-dose methotrexate (HD-MTX)-based chemotherapy could also improve survival in PCNSL patients. The HOVON 105/ALLG NHL 24, a large international multicenter phase III randomised, controlled trial (RCT), investigated the addition of rituximab to standard HD-MTX-based chemotherapy, followed by 30 Gy whole brain radiotherapy (WBRT) in patients aged ≤60 years. The primary end point, the 1-year event-free survival, was not improved by rituximab [HD-MTX, tenoposide, BCNU (carmustine), and prednisolone without (MBVP) versus with rituximab (R-MBVP): 49% versus 52%, $P = 0.99$].[6]

When introducing a new treatment, information on both survival and the patients' functioning and well-being should be taken into account. Combined, these outcomes determine the 'net clinical benefit' of a treatment strategy. By combining both sources of information, clinicians and patients are better able to make well-informed decisions concerning which treatment is most suitable for an individual patient.

In this study, we describe the health-related quality of life (HRQoL) trajectories in one of the largest RCTs in PCNSL patients and determined whether the addition of rituximab to standard therapy had an impact on HRQoL. Second, we aimed to determine the effect of a lower dose WBRT on HRQoL in this patient population.

METHODS

Study design and patient population

In the HOVON 105/ALLG NHL 24 study, 199 immunocompetent patients aged 18–70 years, with a newly diagnosed, CD20-positive B-cell PCNSL were included from Dutch, Australian, and New Zealand hospitals between 2010 and 2016.[6] Patients were randomised between two courses of HD-MTX, tenoposide, BCNU, and prednisolone without (MBVP) or with rituximab (R-MBVP). Irrespective of treatment arm, this induction regimen was followed by consolidative HD-cytarabine chemotherapy in responding patients, and in patients ≤60 years old, 30 Gy WBRT was subsequently added. An integrated boost to the tumor-bed of 10 Gy was given to patients who only achieved partial response.[7] (Immuno-)chemotherapy treatment duration was 2.5–3.5 months and WBRT was administered in 1 month. Further details on the study design and treatment have been published previously.[6] The study was approved by the ethics committees of all participating centres. All participants who signed informed consent for the RCT and for participating in the HRQoL study were eligible for inclusion in this analysis.

HRQoL

HRQoL was one of the prespecified secondary outcomes. HRQoL was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30),[8] and the brain cancer module (QLQ-BN20).[9,10] The QLQ-C30 comprises five functional scales (physical, role, emotional, social, and cognitive functioning), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status (GH)/QoL scale, and six single items assessing additional symptoms (dyspnea, sleep disturbance, appetite loss, constipation, and diarrhoea) and perceived financial difficulties. The QLQ-BN20 module includes 20 items, comprising four scales (visual disorders, motor dysfunction, communication deficit, and future uncertainty), and seven disease- or toxicity-related symptoms (headache, seizures, drowsiness, hair loss, itchy skin, weakness of the legs, and bladder control).

According to protocol, patients had to complete the questionnaires before starting chemotherapy, after completion of all chemotherapy, after completion of radiotherapy (if given), and 3, 6, 12, and 24 months after completion of protocol treatment. The assessment of HRQoL was stopped when a relapse or progression occurred, or when a patient wanted to withdraw from participation in either the RCT or HRQoL sub-study. Only questionnaires that were completed within a prespecified time window (see supplementary Methods, available at

Figure 1. Consolidated Standards of Reporting Trials diagram representing the compliance with HRQoL assessments during follow-up, separately for the two treatment arms.

FU, months of follow-up after end of treatment; HRQoL, health-related quality of life; MBVP, methotrexate, tenoposide, BCNU (carmustine), and prednisolone; R-MBVP, rituximab with methotrexate, tenoposide, BCNU (carmustine), and prednisolone; WBRT, whole brain radiotherapy.
*In those who had WBRT only.

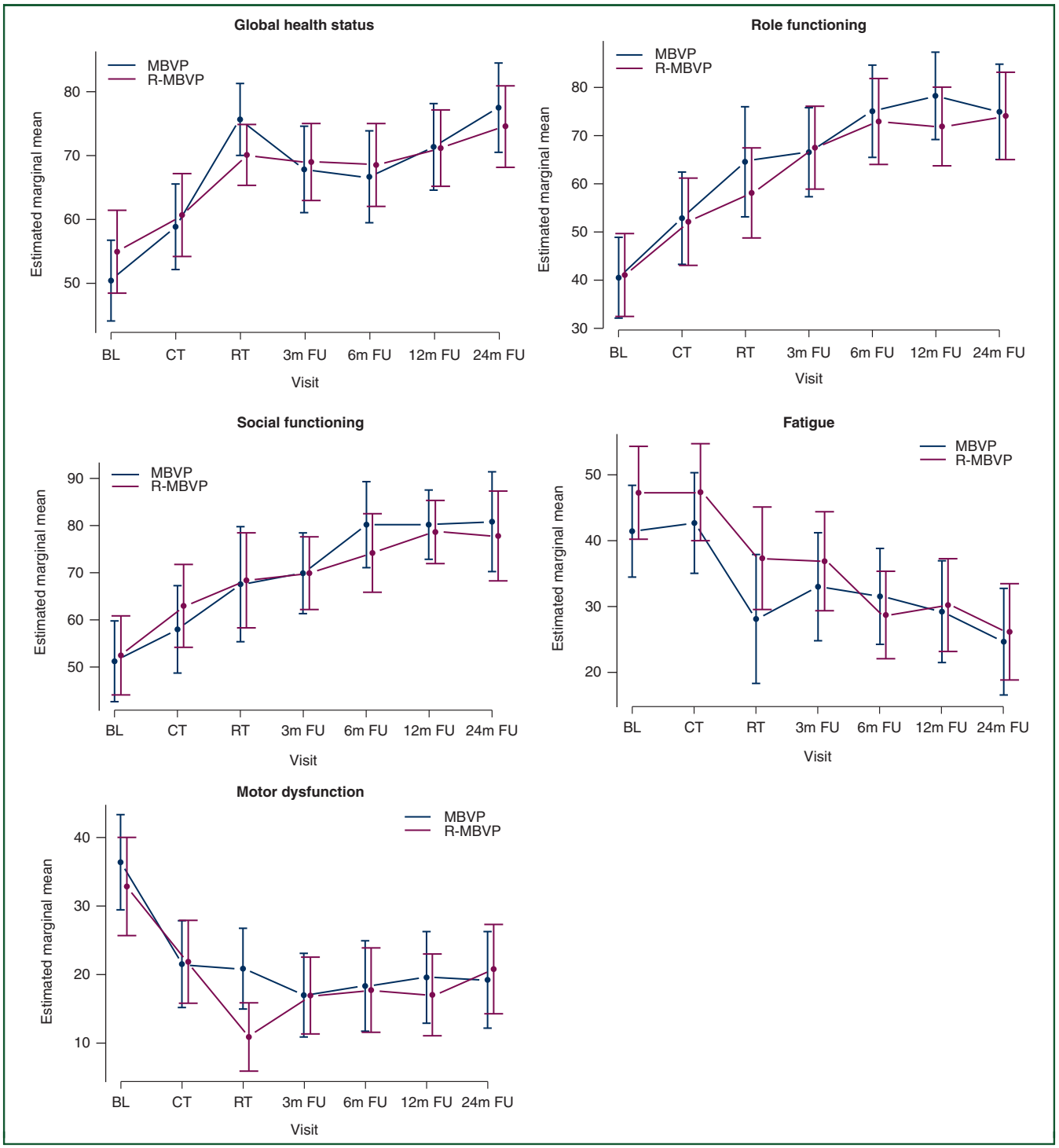

Figure 2. Health-related quality of life scores over time for the five primary scales [(i) global health status; (ii) role functioning; (iii) social functioning; (iv) fatigue; (v) motor dysfunction], separately for both treatment arms in the total study population, based on results of the linear mixed model analyses.
Estimated marginal means for each evaluation point by treatment arm, where the vertical bars represent 95% confidence interval of the group mean.
BL, baseline; CT, chemotherapy; FU, follow-up; MBVP, methotrexate, tenoposide, BCNU (carmustine), and prednisolone; R-MBVP, rituximab with methotrexate, tenoposide, BCNU (carmustine), and prednisolone; RT, radiotherapy.

Annals of Oncology online.) for each evaluation point were included in the statistical analysis.

Statistical analysis

Calculation of HRQoL scores. Following the EORTC procedures, raw item scores were converted to a linear scale ranging from 0 to 100.[11] A difference of $\geq$10 points on each HRQoL scale/item was defined as clinically relevant.[12] Based on clinical relevance for PCNSL patients, these five scales were selected for primary analysis: three functional scales [GH, role functioning (RF), and social functioning (SF), with higher scores representing better functioning], and two symptom scales [fatigue and motor dysfunction (MD), with

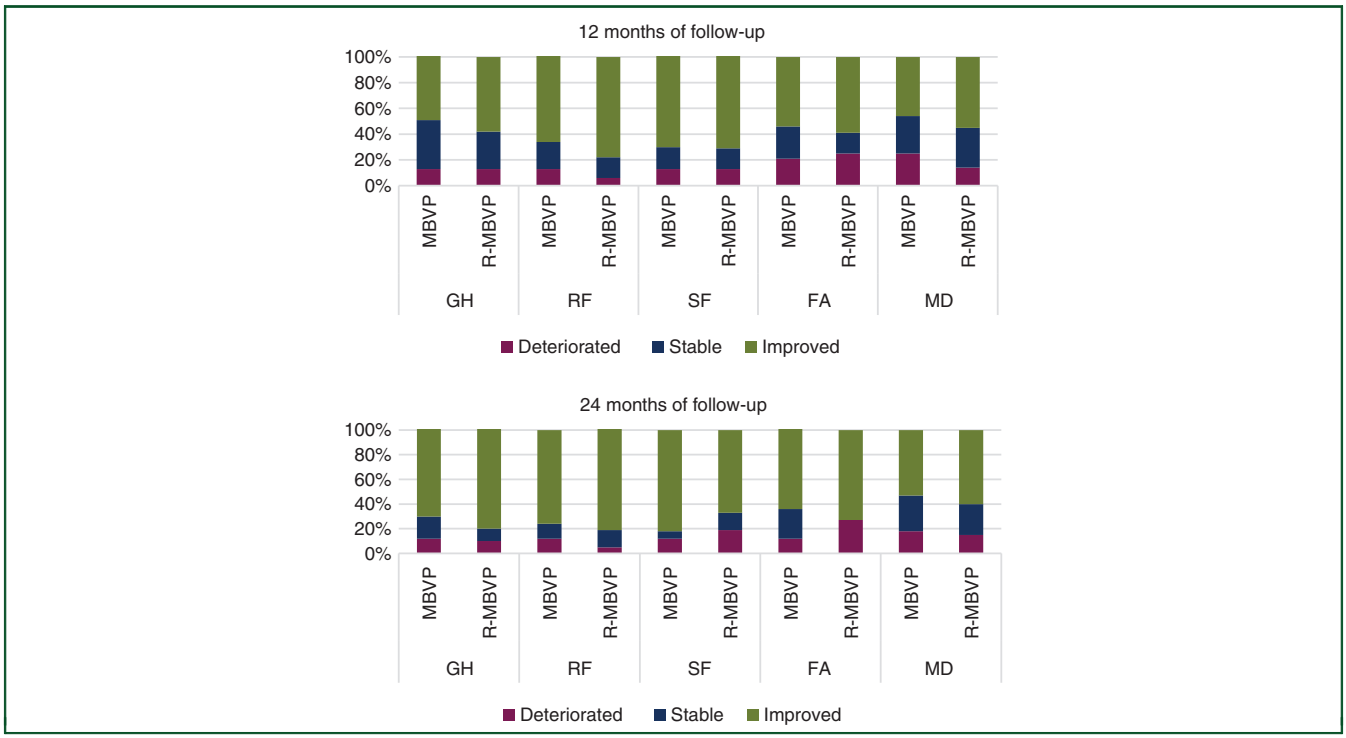

Figure 3. Individual changes in health-related quality of life from baseline to 12 months and 24 months of follow-up.
FA, fatigue; GH, global health status/quality of life; MBVP, methotrexate, tenoposide, BCNU (carmustine), and prednisolone; MD, motor dysfunction; R-MBVP, rituximab with methotrexate, tenoposide, BCNU (carmustine), and prednisolone; RF, role functioning; SF, social functioning.

high scores representing worse functioning]. Results of the primary analysis (i.e. scores over time assessed with linear mixed models in the five predetermined scales), were corrected for multiple testing. The remaining scales and items were analysed on an exploratory basis. All analyses were conducted with Stata, version 15, and a P value <0.05 was considered to be statistically significant.

Descriptive statistics. Patients eligible for the HOVON 105/ALLG NHL 24 study who received less than two courses of (R-)MBVP, or who did not give consent for the HRQoL sub-study, were excluded from the analysis. We carried out a non-response analysis to assess possible imbalances between those who gave consent for the HRQoL sub-study and those who did not with respect to sociodemographic and clinical characteristics.

Differences were tested using a chi-square test for categorical data and Mann—Whitney U or independent t-test for continuous data, depending on the distribution of the data. Normality was determined with the Kolmogorov—Smirnov test. In addition, for each time point, the compliance was evaluated, defined as the number of completed questionnaires divided by the number of questionnaires expected at that time point. We defined a completed questionnaire as a returned form from which at least a score of one of the predetermined primary scales could be derived.

HRQoL scores over time. At group level, mean changes from baseline were calculated and plotted for those patients who filled in the questionnaire at baseline and at least at one follow-up point. Differences between arms at 12 and 24 months of follow-up were assessed with an independent t-test. A linear mixed model, which allows inclusion of all patients, with fixed effects for treatment arm, time (i.e. evaluation moments) as a categorical covariate, and their interaction, was used to assess whether there is a difference in the HRQoL scores over time between the treatment arms. For each scale, the most suitable covariance structure was chosen to estimate the impact of the treatment on HRQoL over time.

At the individual patient level, changes in HRQoL between baseline and both 12 and 24 months of follow-up were calculated for those patients to whom the questionnaires at these time points were available. Patients were categorised as deteriorated, stable, or improved, based on a change of $\geq$10 points. Differences between treatment arms were assessed with the chi-square statistic.

Deterioration-free survival and time to deterioration. Deterioration-free survival was defined as a deterioration of $\geq$10 points on a scale/item compared with baseline without an improvement of $\geq$10 points at the subsequent HRQoL assessment, or progressive disease (PD) or death in the absence of definite deterioration before the next assessment. Time to deterioration was defined similarly as deterioration-free survival, only excluding PD as an event.[13] PD was defined according to the international PCNSL response criteria.[7] Magnetic resonance images were centrally reviewed; the centrally scored progression data were used for these analyses. Questionnaires filled in at the time of, or after centrally scored PD were excluded. Kaplan—Meier curves were generated for both deterioration-free

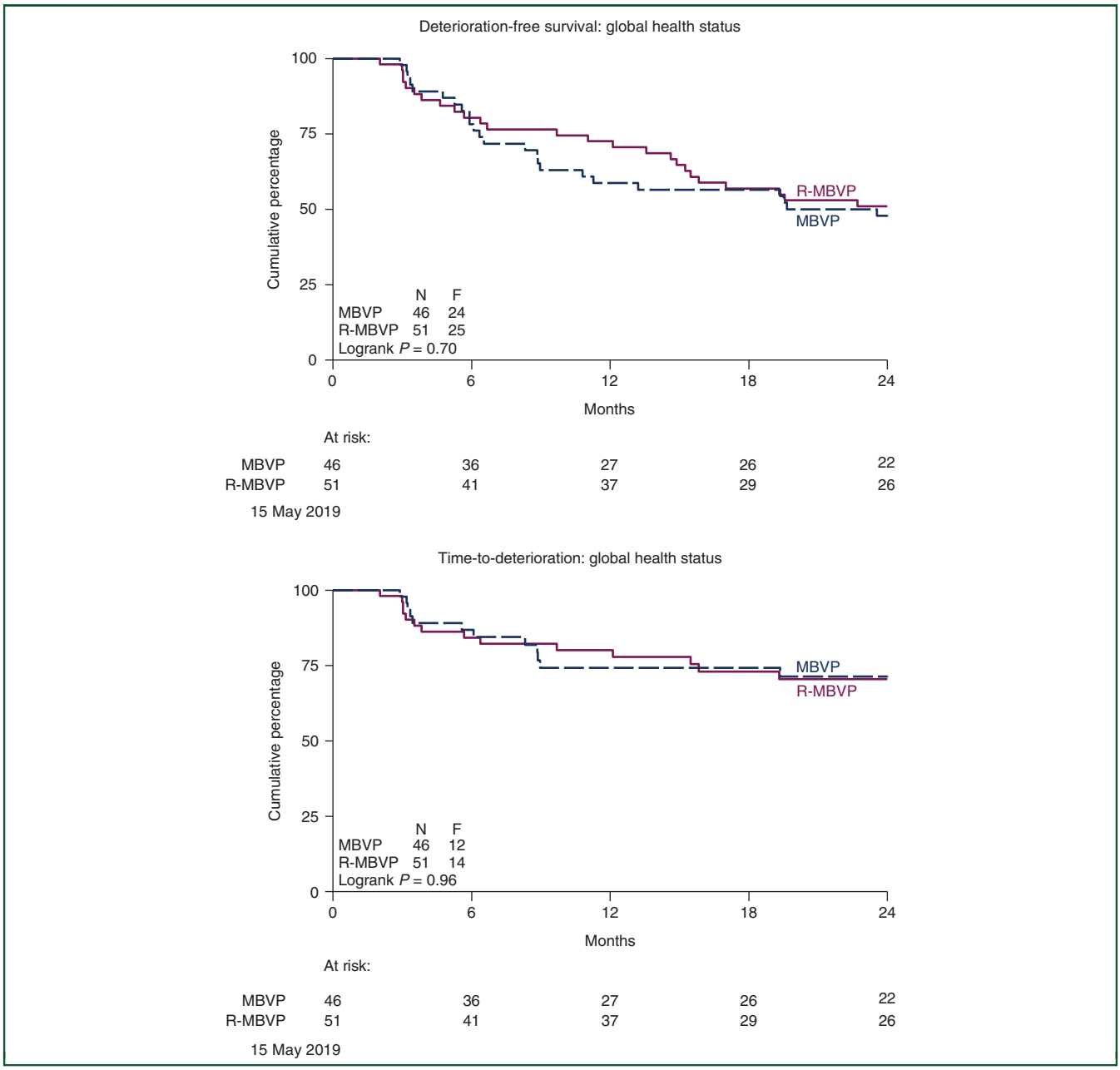

Figure 4. Deterioration-free survival and time to deterioration for Global health status (GH), separately for the treatment arms.
MBVP, methotrexate, tenoposide, BCNU (carmustine), and prednisolone; R-MBVP, rituximab with methotrexate, tenoposide, BCNU (carmustine), and prednisolone.

survival and time to deterioration, and 95% confidence intervals were calculated using the Greenwood formula.

Impact of WBRT. The impact of radiation on HRQoL was evaluated in a subgroup of those who received WBRT ($n = 59$). The mean changes from the 'after WBRT' time point onwards were calculated and linear mixed model analyses were carried out to analyse HRQoL scores over the post-WBRT period.

RESULTS

Patients

Of the 199 patients included in the HOVON 105/ALLG NHL 24 trial, 193 (97%) gave informed consent for HRQoL assessment. Eighteen patients were excluded because they did not complete two courses of (R-)MBVP, resulting in 175/199 (88%) eligible patients for the HRQoL analysis. Of these 175 patients included in the HRQoL analysis, 160 completed at least one questionnaire. Compliance of HRQoL evaluation was $\geq$60% at each time point, except 'after WBRT' in the MBVP arm (46%) (Figure 1).

In the population participating in the HRQoL analysis, patients in the treatment arms were well balanced with respect to clinical and sociodemographic features and study drug exposure. Those included in this HRQoL analysis had a median age of 61 years (interquartile range 55–66 years), and 74% had a WHO performance score $<$2, which is similar

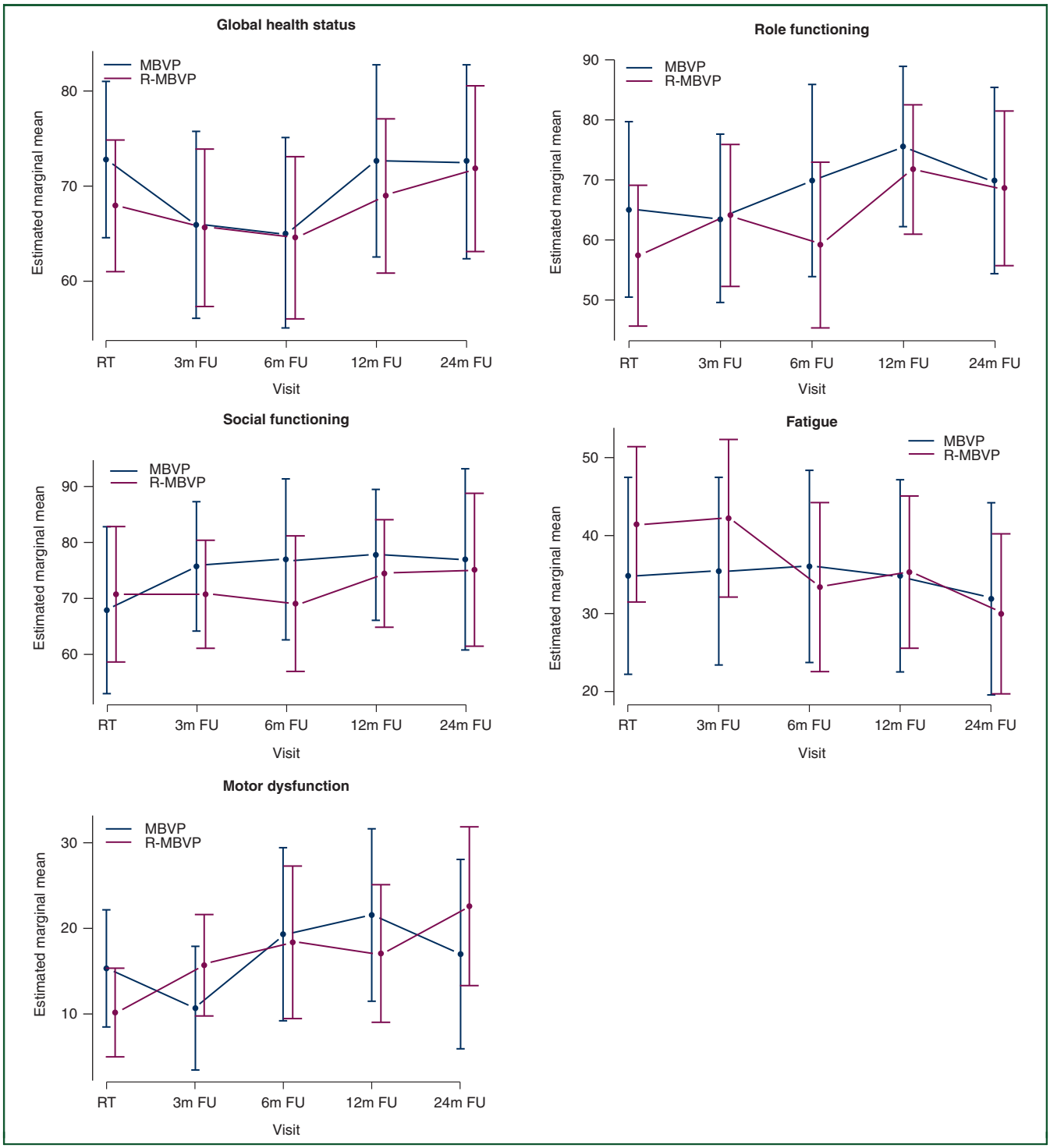

Figure 5. Health-related quality of life scores from post-whole brain radiotherapy up to 24 months follow-up for the preselected scales [(i) global health status; (ii) role functioning; (iii) social functioning; (iv) fatigue; (v) motor dysfunction], separately for the treatment arms, in the irradiated patients only ($n = 59$).
Estimated marginal means for each evaluation point by treatment arm, where the vertical bars represent 95% confidence interval of the group mean.
FU, follow-up; MBVP, methotrexate, tenoposide, BCNU (carmustine), and prednisolone; R-MBVP, rituximab with methotrexate, tenoposide, BCNU (carmustine), and prednisolone; RT, radiotherapy.

to the total trial population[6] (Table 1). The non-response analysis showed that there were no significant differences with respect to baseline characteristics between those who gave consent for the HRQoL sub-study and those who did not (supplementary Table S1, available at *Annals of Oncology* online.). Baseline HRQoL scores for all scales and items for both treatment arms are summarised in supplementary Table S2, available at *Annals of Oncology* online.

HRQoL scores over time

In all selected primary scales, the mean change from baseline, assessed in those who filled in the questionnaires

https://doi.org/10.1016/j.annonc.2020.04.014

at baseline and at least once thereafter, showed a statistically significant (all $P < 0.002$) and clinically relevant improvement in both arms after the end of treatment (i.e. 'after chemotherapy' or 'after WBRT'), when compared with baseline, except for fatigue. Fatigue improved more slowly; clinically relevant improvement was not reached before 3 months after treatment. The differences in scores between the arms at 12 and 24 months of follow-up were not statistically significant or clinically relevant for any of the scales. Only fatigue at 12 months after treatment was clinically relevant worse in the R-MBVP arm, but this was not statistically significant; R-MBVP versus MBVP: −18.1 versus −7.4 ($P = 0.677$). For most exploratory scales and items, similar patterns were observed. See supplementary Figure S1 and Table S3, available at *Annals of Oncology* online, for the graphs presenting the mean change from baseline over time for all scales/items and the actual mean difference at each time point, respectively.

In a next step, HRQoL scores over time were assessed with linear mixed models, allowing inclusion of all patients as these models impute data at all time points (Figure 2). These analyses showed that the mean HRQoL score improved significantly in all primary selected scales over time in both arms ($P < 0.001$), confirming the previous analyses. We did not find any statistically significant or clinically relevant differences over time between the treatment arms for any of the preselected scales: overall mean difference over time in MBVP versus R-MBVP: GH = −0.074 ($P = 0.981$), RF = 2.160 ($P = 0.635$), SF = 0.531 ($P = 0.902$), fatigue = −3.350 ($P = 0.378$), and MD = 2.139 points ($P = 0.511$). The results of the linear mixed models show that the largest improvements in scores were between baseline and 'end of treatment', thereafter, the scores gradually improved further, but to a lesser extent. GH remained stable from end of treatment until 24 months after treatment. Exploratory scales and items are shown in supplementary Figure S2, available at *Annals of Oncology* online.

Assessing the change from baseline scores at the individual level, in all patients who filled in the questionnaires at baseline and at least at one point thereafter, we observed in a large proportion of patients in both arms an improvement to a clinically relevant extent in HRQoL scores on all primary scales. At 12 months of follow-up, 46%−78% of the patients had improved scores compared with baseline, and these percentages were between 53% and 82% at 24 months of follow-up (Figure 3). There were no significant differences between the arms. See supplementary Table S4 available at *Annals of Oncology* online, for the exact number of patients who improved, remained stable, or deteriorated in both the preselected and exploratory HRQoL scales and items.

Deterioration-free survival and time to deterioration

The addition of rituximab to MBVP-chemotherapy did not result in a statistically significant longer deterioration-free survival or time to deterioration in any of the preselected scales. The median deterioration-free survival in RF was not reached. The median deterioration-free survival in MBVP versus R-MBVP was for GH: 19.6 versus not reached, SF: 19.6 versus 22.7, fatigue: 6.7 versus 6.7, and MD: 4.2 versus 3.8 months. For time to deterioration, the median was not reached in GH, RF, and SF. The median time to deterioration in MBVP versus R-MBVP in fatigue was 10.2 versus 7.5 and MD: 4.7 versus 3.8 months. See Figure 4 for the deterioration-free survival and time to deterioration for GH and supplementary Figure S3 and Table S5, available at *Annals of Oncology* online, for the remaining primary scales/items.

Impact of WBRT

Seventy patients received WBRT, of whom 59 participated in the HRQoL evaluation. The linear mixed model analysis (which allows inclusion of all 59 patients) showed no statistically significant change over time after WBRT up to 24 months, except for a deterioration in MD ($P = 0.048$). There were no significant differences between treatment arms: overall mean difference MBVP versus R-MBVP GH = 1.951 ($P = 0.694$), RF = 4.570 ($P = 0.542$), SF = 3.007 ($P = 0.677$), fatigue = −1.887 ($P = 0.776$), and MD = 0.020 ($P = 0.997$), see Figure 5.

The change in HRQoL from WBRT onwards was only determined in those patients who were irradiated and who filled in the questionnaires at the evaluation 'after WBRT' and at least at one of the follow-up evaluations ($n = 34$). This subpopulation was comparable to the total irradiated population (data not shown). We observed an improvement (>10 points) in RF in both arms ($P = 0.002$), from 62.1 after WBRT to 78.8 at 24 months follow-up in the R-MBVP arm, and from 65.3 to 77.5 in the MBVP arm. Scores in the other preselected scales remained stable in both treatment arms (see supplementary Figure S4, available at *Annals of Oncology* online, for the preselected scales).

DISCUSSION

In the HOVON 105/ALLG NHL 24 trial, the addition of rituximab to standard chemotherapy in adult PCNSL patients did not prolong event-free survival (EFS) or progression-free survival (PFS). In this HRQoL analysis in 160 patients (80% of total study population), we showed that the addition of rituximab did not improve or deteriorate the patients' functioning and well-being, either. We did, however, observe that antitumour treatment resulted in improvements in HRQoL, which were statistically significant and clinically relevant, but did not differ between patients treated with or without rituximab.

The largest improvements in HRQoL were observed directly after treatment (i.e. after induction chemotherapy with or without rituximab and after consolidation with WBRT, if given). Thereafter, HRQoL scores remained relatively stable or improved more slowly, but gradually over time. Other non-randomised studies investigating the effect of chemotherapy and/or chemotherapy with rituximab on HRQoL have described a similar pattern: an initial improvement after treatment, followed by stabilisation of

HRQoL scores for up to 3 years of follow-up.[14–16] Two small studies (in which 12/52 and 16/33 of the patients participated in the HRQoL sub-study) even showed an ongoing improvement in HRQoL scores (as measured with the Functional Assessment of Cancer Therapy-Brain; FACT-Br) up to 12[17] and 24 months of follow-up.[18] Clinical relevance of this change was, however, not defined. Nevertheless, this pattern suggests that HRQoL in PSCNL patients is mainly compromised by the lymphoma itself rather than by the treatment, and that treating the tumour improves patient-reported HRQoL.

Mean baseline HRQoL scores in our cohort are much lower (≥20 points) than in the general population,[19] and also lower (≥10 points) than in patients with brain metastases, low-grade glioma, and glioblastoma.[20–22] HRQoL scores in our population improved significantly over time, to levels of the general population for some scales, whereas scores in low- and high-grade glioma patients typically remain stable up to 24 months of follow-up.[21,22] The non-significant differences between treatment arms in deterioration-free survival and time to deterioration for any of the HRQoL scales suggest that treatment itself did not cause a major deterioration in HRQoL.

WBRT as consolidation treatment is under debate because of its presumed negative effect on neurocognitive functioning and subsequently on HRQoL.[23] Surprisingly, we found that the HRQoL scores of those patients receiving radiation remained stable for up to 2 years of follow-up after WBRT, suggesting that the WBRT dose (30 Gy) used in this study does not compromise HRQoL in patients up to 60 years old in the period covered by this analysis, despite the fact that 17% of the patients in the MBVP arm and 27% in the R-MBVP arm also received an integrated boost of 10 Gy to the tumour bed. A possible explanation for the stable HRQoL in our cohort after WBRT may be that the 24 month period in our study is too short to develop radiation-induced damage detectable with HRQoL instruments, or that the lower radiation dose is less detrimental. Our findings are supported by a study by Correa et al.[24] in which patients treated with R-MPV followed by low-dose WBRT (23.4 Gy) also remained stable in their HRQoL scores, even up to 5 years of follow-up. Only a small number of patients could be analysed in our subanalysis and results should therefore be interpreted with caution. In addition, patients who received WBRT could not be compared directly to those who did not receive WBRT because of the age difference between the irradiated and non-irradiated patients. Thus, although our results cannot be generalised and follow-up is still short, our results do challenge the negative role of a relatively low-dose WBRT in this younger subpopulation.

The strengths of our study are the size and standardised treatment of the population studied, the use of validated measures for brain cancer patients, and the fact that the majority of this trial population participated in the HRQoL sub-study. Although the compliance at most time points was relatively high (≥60%), which is sufficient for robust longitudinal analyses with linear mixed models, the results should be interpreted with some caution. This is emphasised by the fact that the actual number of patients who filled in the questionnaires was relatively low at 12 and 24 months of follow-up ($n = 74$ and $n = 53$, respectively) due to progression or death, and patients filling out the questionnaires might have a higher level of functioning and well-being than those not filling out the questionnaires. Also, HRQoL was not systematically assessed at the moment of and beyond progression, hampering information on the impact of progression on HRQoL in this patient population. Another limitation is possible selection bias, because we analysed (subgroups of) a trial population and results may therefore not be generalisable to all patients. However, most patients in the trial also participated in the HRQoL sub-study and only those who did not tolerate two complete courses of (R-)MBVP were excluded. Lastly, the impact of treatment on neurocognition is important in this patient population, and will be described in a separate publication.

In conclusion, HRQoL scores improved after treatment but were not impacted by the addition of rituximab to standard chemotherapy in adult PCNSL patients. Secondly, treatment with 30 Gy WBRT did not reduce HRQoL in the first 2 years after treatment in patients up to 60 years old.

FUNDING

This work was supported by Roche (no grant number), the Dutch Cancer Society [grant number 2009-4589], and Stichting STOPhersentumoren.nl (no grant number).

DISCLOSURE

The authors have declared no conflicts of interest.

REFERENCES

1. van der Meulen M, Dinmohamed AG, Visser O, et al. Improved survival in primary central nervous system lymphoma up to age 70 only: a population-based study on incidence, primary treatment and survival in the Netherlands, 1989-2015. *Leukemia*. 2017;31:1822–1825.
2. Villano JL, Koshy M, Shaikh H, et al. Age, gender, and racial differences in incidence and survival in primary CNS lymphoma. *Br J Cancer*. 2011;105:1414–1418.
3. Ferreri AJ, Reni M, Pasini F, et al. A multicenter study of treatment of primary CNS lymphoma. *Neurology*. 2002;58:1513–1520.
4. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med*. 2002;346:235–242.
5. Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). *Lancet Oncol*. 2008;9:105–116.
6. Bromberg JEC, Issa S, Bakunina K, et al. Rituximab in patients with primary CNS lymphoma (HOVON 105/ALLG NHL 24): a randomised, open-label, phase 3 intergroup study. *Lancet Oncol*. 2019;20:216–228.
7. Abrey LE, Batchelor TT, Ferreri AJ, et al. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. *J Clin Oncol*. 2005;23:5034–5043.
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;85:365–376.

9. Osoba D, Aaronson NK, Muller M, et al. The development and psychometric validation of a brain cancer quality-of-life questionnaire for use in combination with general cancer-specific questionnaires. *Qual Life Res*. 1996;5:139—150.
10. Taphoorn MJ, Claassens L, Aaronson NK, et al. An international validation study of the EORTC brain cancer module (EORTC QLQ-BN20) for assessing health-related quality of life and symptoms in brain cancer patients. *Eur J Cancer*. 2010;46:1033—1040.
11. Fayers PM, Aaronson NK, Bjordal K, et al. *The EORTC QLQ-c30 Scoring Manual*. Brussels, Belgium: European Organization for Research and Treatment of Cancer; 2001.
12. Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol*. 1998;16:139—144.
13. Taphoorn MJ, Henriksson R, Bottomley A, et al. Health-related quality of life in a randomized phase III study of bevacizumab, temozolomide, and radiotherapy in newly diagnosed glioblastoma. *J Clin Oncol*. 2015;33:2166—2175.
14. Omuro A, Chinot O, Taillandier L, et al. Methotrexate and temozolomide versus methotrexate, procarbazine, vincristine, and cytarabine for primary CNS lymphoma in an elderly population: an intergroup ANOCEF-GOELAMS randomised phase 2 trial. *Lancet Haematol*. 2015;2:e251—e259.
15. Fritsch K, Kasenda B, Schorb E, et al. High-dose methotrexate-based immuno-chemotherapy for elderly primary CNS lymphoma patients (PRIMAIN study). *Leukemia*. 2017;31:846—852.
16. Correa DD, Rocco-Donovan M, DeAngelis LM, et al. Prospective cognitive follow-up in primary CNS lymphoma patients treated with chemotherapy and reduced-dose radiotherapy. *J Neurooncol*. 2009;91:315—321.
17. Morris PG, Correa DD, Yahalom J, et al. Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: final results and long-term outcome. *J Clin Oncol*. 2013;31:3971—3979.
18. Omuro A, Correa DD, DeAngelis LM, et al. R-MPV followed by high-dose chemotherapy with TBC and autologous stem-cell transplant for newly diagnosed primary CNS lymphoma. *Blood*. 2015;125:1403—1410.
19. van de Poll-Franse LV, Mols F, Gundy CM, et al. Normative data for the EORTC QLQ-C30 and EORTC-sexuality items in the general Dutch population. *Eur J Cancer*. 2011;47:667—675.
20. Habets EJ, Dirven L, Wiggenraad RG, et al. Neurocognitive functioning and health-related quality of life in patients treated with stereotactic radiotherapy for brain metastases: a prospective study. *Neuro Oncol*. 2016;18:435—444.
21. Reijneveld JC, Taphoorn MJB, Coens C, et al. Health-related quality of life in patients with high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study. *Lancet Oncol*. 2016;17:1533—1542.
22. Taphoorn MJB, Dirven L, Kanner AA, et al. Influence of treatment with tumor-treating fields on health-related quality of life of patients with newly diagnosed glioblastoma: a secondary analysis of a randomized clinical trial. *JAMA Oncol*. 2018;4:495—504.
23. Doolittle ND, Korfel A, Lubow MA, et al. Long-term cognitive function, neuroimaging, and quality of life in primary CNS lymphoma. *Neurology*. 2013;81:84—92.
24. Correa DD, Braun E, Kryza-Lacombe M, et al. Longitudinal cognitive assessment in patients with primary CNS lymphoma treated with induction chemotherapy followed by reduced-dose whole-brain radiotherapy or autologous stem cell transplantation. *J Neurooncol*. 2019;144:553—562.