Randomized phase III study of whole-brain radiotherapy for primary CNS lymphoma

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ABSTRACT

Objective: This is the final report of a phase III randomized study to evaluate whole-brain radiotherapy (WBRT) in primary therapy of primary CNS lymphoma (PCNSL) after a median follow-up of 81.2 months.

Methods: Patients with newly diagnosed PCNSL were randomized to high-dose methotrexate (HDMTX)–based chemotherapy alone or followed by WBRT. We hypothesized that the omission of WBRT would not compromise overall survival (OS; primary endpoint), using a noninferiority design with a margin of 0.9.

Results: In the per-protocol population (n = 320), WBRT nonsignificantly prolonged progression-free survival (PFS) (median 18.2 vs 11.9 months, hazard ratio [HR] 0.83 [95% confidence interval (CI) 0.65–1.06], $p = 0.14$) and significantly PFS from last HDMTX (25.5 vs 12.0 months, HR 0.65 [95% CI 0.5–0.83], $p = 0.001$), but without OS prolongation (35.6 vs 37.1 months, HR 1.03 [95% CI 0.79–1.35], $p = 0.82$). In the intent-to-treat population (n = 410), there was a prolongation by WBRT of both PFS (15.4 vs 9.9 months, HR 0.79 [95% CI 0.64–0.98], $p = 0.034$) and PFS from last HDMTX (19.4 vs 11.9 months, HR 0.72 [95% CI 0.58–0.89], $p = 0.003$), but not of OS (32.4 vs 36.1 months, HR 0.98 [95% CI 0.79–1.26], $p = 0.98$).

Conclusion: Although the statistical proof of noninferiority regarding OS was not given, our results suggest no worsening of OS without WBRT in primary therapy of PCNSL.

Classification of evidence: This study provides Class II evidence that in PCNSL HDMTX-based chemotherapy followed by WBRT does not significantly increase survival compared to chemotherapy alone. The study lacked the precision to exclude an important survival benefit or harm from WBRT. *Neurology*® 2015;84:1242–1248

GLOSSARY

CHT = chemotherapy; **CI** = confidence interval; **CR** = complete response; **G-PCNSL-SG** = German PCNSL Study Group; **HD-Ara-C** = high-dose cytarabine; **HDMTX** = high-dose methotrexate; **HR** = hazard ratio; **ITT** = intent-to-treat; **KPS** = Karnofsky Performance Score; **OS** = overall survival; **PCNSL** = primary CNS lymphoma; **PFS** = progression-free survival; **PP** = per protocol; **PR** = partial remission; **WBRT** = whole-brain radiotherapy.

Standards of care have not been well-defined for primary CNS lymphoma (PCNSL). High-dose methotrexate (HDMTX) is the only undisputed standard of care, whereas the addition of whole-brain radiotherapy (WBRT) has been increasingly questioned because of the high frequency of late neurotoxicity after combined modality treatment. In 1999, the German PCNSL Study Group (G-PCNSL-SG) had designed a prospective, randomized trial to test the hypothesis that primary HDMTX-based chemotherapy (CHT) alone was not inferior to primary CHT followed by WBRT for immunocompetent patients with newly diagnosed PCNSL. The 2010 report of overall survival (OS; the primary endpoint) at a median

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Supplemental data at Neurology.org

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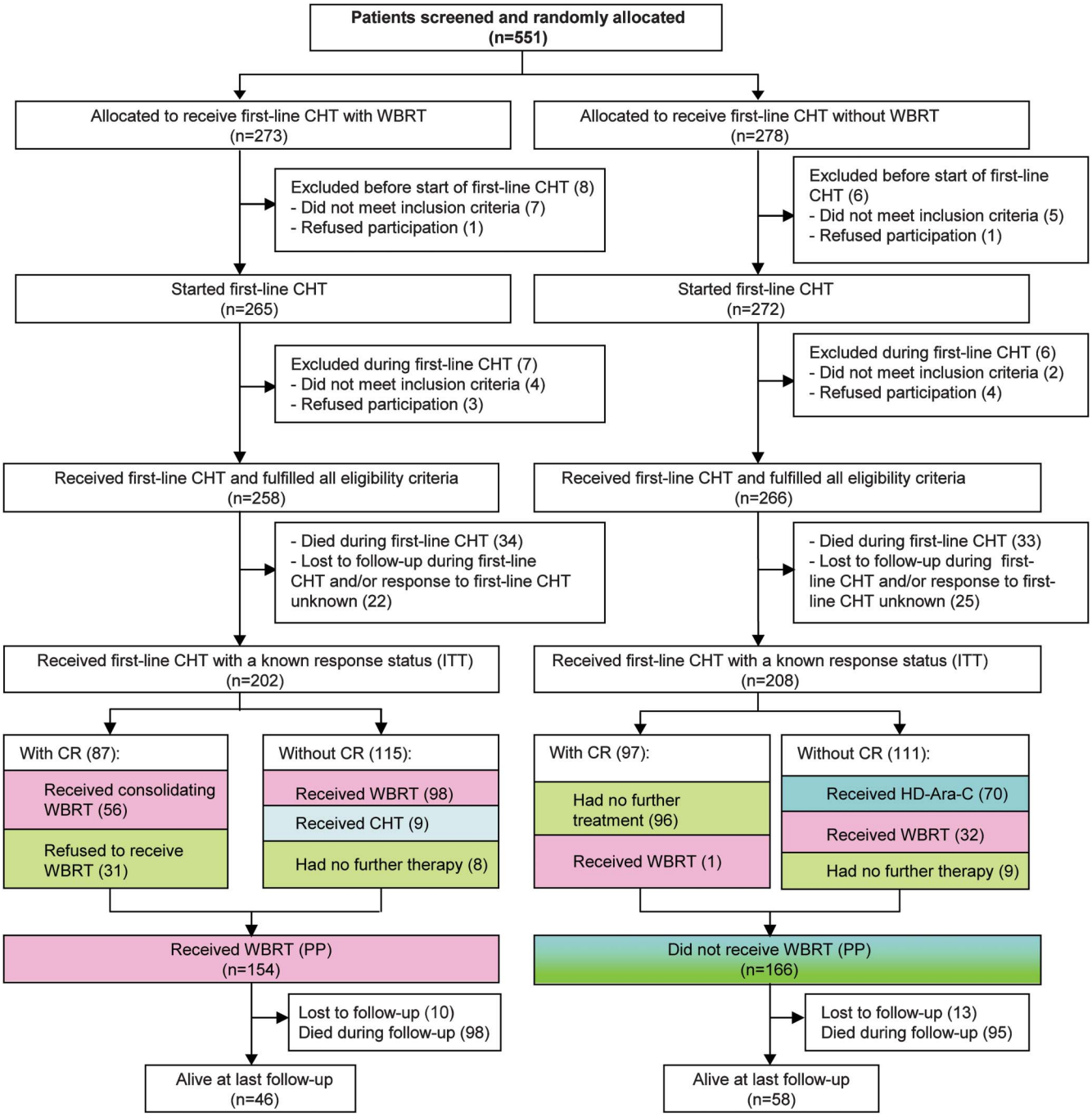
follow-up of 31.8 months had resulted in the conclusion that WBRT can be omitted from first-line treatment of PCNSL without compromising OS although noninferiority had not been formally proven.[1] Here, we present updated and final data including a new as-treated analysis after a median follow-up of 81.2 months.

Figure 1 Trial profile (CONSORT flow diagram)



As compared to reference 1 (Thiel et al.): Study arm whole-brain radiotherapy (WBRT): 2 additional patients were excluded during high-dose methotrexate (HDMTX)–based chemotherapy (CHT) (one with spinal lymphoma, classified as "did not meet inclusion criteria," and one who refused CHT continuation in 2-week intervals, classified as "refused participation"). For one patient, the documentation of sixth HDMTX course and complete response (CR) achievement was obtained, and he was reclassified as "intent-to-treat (ITT), with CR, no further treatment." One patient was reclassified by the treating physician as having CR and moved from "ITT, without CR, had no further therapy" to "ITT, CR, refused to receive WBRT." Study arm no WBRT: One patient was wrongly classified as "lost to follow-up during first-line CHT," although he died within 4 weeks after last HDMTX, and is now classified as "died during first-line CHT." In 2 patients, documentation of second-line therapy with high-dose cytarabine (HD-Ara-C) was obtained, and they were moved from "did not receive HD-Ara-C" to "received HD-Ara-C." In one patient, remission status (stable disease) was changed after review of all scans to CR by the treating physician, and he was moved from "ITT, without CR, received WBRT" to "ITT, with CR, received WBRT." PP = per protocol.

Table 1 Baseline characteristics of patients in the intent-to-treat population

	WBRT (n = 202)	No WBRT (n = 208)	p
Age, y, median (SD)	62 (10.8)	61 (11.6)	0.112
Sex, n (%)			0.84
Female	87 (43)	87 (42)	
Male	115 (57)	121 (58)	
KPS, %, median (SD)	80 (18.5)	75 (18.5)	0.955
KPS, n (%)			0.803
70–100	114 (56)	113 (54)	
<70	56 (28)	57 (27)	
Missing	32 (16)	38 (18)	
MSKCC score, n (%)			0.711
1	38 (19)	42 (20)	
2	91 (45)	82 (39)	
3	46 (23)	54 (26)	
Missing	27 (13)	30 (14)	
Serum LDH, n (%)			0.208
Elevated	46 (23)	35 (17)	
Normal	81 (40)	81 (39)	
Missing	75 (37)	92 (44)	
Number (%) of lesions			0.958
0–1	101 (50)	107 (51)	
≥2	64 (32)	64 (31)	
Missing	37 (18)	37 (18)	

Abbreviations: KPS = Karnofsky Performance Score; LDH = lactate dehydrogenase; MSKCC = Memorial Sloan Kettering Cancer Center; WBRT = whole-brain radiotherapy.

METHODS

Standard protocol approvals, registrations, and patient consents. The study was approved by the local Human Investigations Committee, and informed consent was obtained from each participant. The study is registered with ClinicalTrials.gov, number NCT00153530.

Study design, selection of participants, and interventions. The G-PCNSL-SG-1 included immunocompetent patients with newly diagnosed PCNSL.[1] Patients were enrolled by treating institution and randomized in a 1:1 ratio to receive first-line CHT based on HDMTX with or without subsequent WBRT. The allocation sequence was generated by block randomization (block size of 6) in the biostatistics center (Department of Biostatistics and Clinical Epidemiology, Charité Berlin, Germany) by use of a self-written computer program. Patients were stratified by age (<60 vs ≥60 years; based on literature on PCNSL available until 1999) and institution (Berlin vs Tübingen vs all other sites). After HDMTX-based primary CHT, patients were to receive HDMTX from 1999 to 2007 and HDMTX plus ifosfamide thereafter. Patients achieving complete response (CR) received consolidating WBRT or no further treatment, whereas patients without CR received WBRT or second-line CHT with high-dose cytarabine (HD-Ara-C).

All data were collected in the biostatistics center at Charité Berlin.

Primary research question. The primary research question was as follows: Does the omission of WBRT with 45 Gy in 1.5 Gy fractions compromise OS in immunocompetent patients with newly diagnosed PCNSL?

Study endpoints and statistical analysis. The goal of the trial was to demonstrate that the omission of WBRT from first-line treatment does not compromise OS as the primary endpoint using a noninferiority design with a margin of 0.9. Omission of WBRT was defined as noninferior to WBRT if the lower 95% confidence interval (CI) of the hazard ratio (HR) of WBRT vs no WBRT was not below 0.9. The study was designed to have 60% power to prove noninferiority of omission of WBRT with a HR of 1.2 for WBRT vs no WBRT. The sample size needed to detect this noninferiority margin was 151 patients per group.

OS was measured from the time of randomization until death; progression-free survival (PFS) was measured until progression or death. Further, to better assess the role of therapy administered after HDMTX-based CHT (HD-Ara-C or WBRT), an additional PFS calculation was performed from the time of last HDMTX-based CHT to progression or death per response group (CR vs partial remission [PR], stable disease, and progressive disease pooled), herein referred to as PFS from last HDMTX. Additionally, we analyzed the intent-to-treat (ITT) population by the treatment that was actually given (as-treated), e.g., patients randomized to WBRT who did not receive WBRT (and received second-line CHT instead or no further therapy) were analyzed as no WBRT and patients randomized to no WBRT who received WBRT were analyzed as WBRT. As a consequence, patients with CR after HDMTX-based CHT were divided into 2 groups: WBRT and no WBRT (no further therapy), whereas non-CR patients were divided in 3 groups: WBRT, CHT, and no therapy (patients who were left with PR, stable disease, or progressive disease after HDMTX-based CHT without any further therapy). The comparison of potential baseline confounding variables between treatment groups was performed using χ^2 and Mann-Whitney *U* tests. Multivariate analysis was performed by using the Cox proportional hazard model. All hazard ratios refer to the comparison of WBRT vs no WBRT; i.e., HRs lower than 1 are in favor of WBRT. Further details on statistical methods used to compare groups for primary and secondary outcomes have been reported.[1]

RESULTS

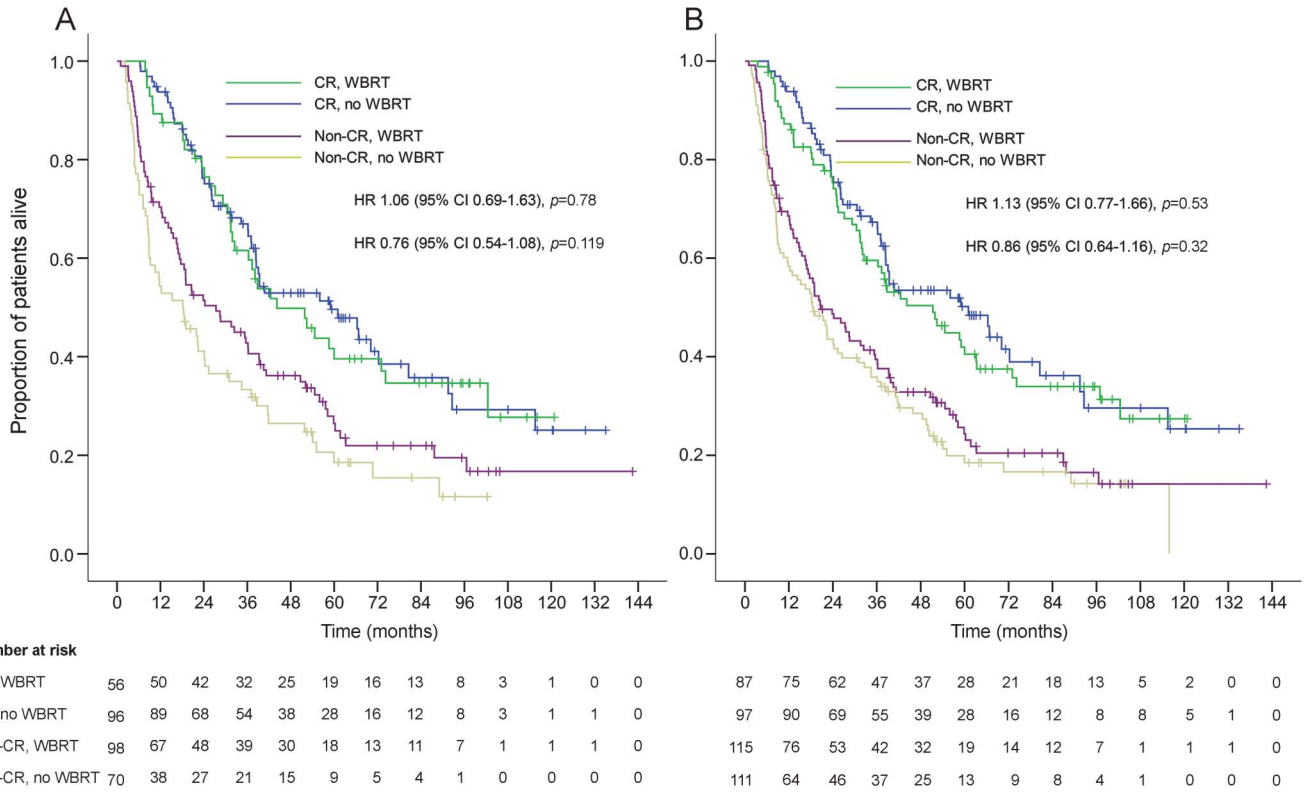
From 1999 to 2009, 551 patients (median age 63 years) were enrolled; of those, 524 fulfilled the eligibility criteria and started HDMTX-based primary CHT (primary eligibility population), 410 entered the post-HDMTX phase with a known response status (ITT population), and 320 were treated as randomized (per-protocol [PP] population)[1] (figure 1). The termination of recruitment has been described.[1]

The baseline variables were balanced between both randomization arms (table 1).

The median follow-up was 81.2 months. In the PP population, there was a nonsignificant PFS prolongation with WBRT (median 18.2 vs 11.9 months, HR 0.83 [95% CI 0.65–1.06], $p = 0.14$), and a significant prolongation of PFS from last HDMTX (25.5 vs 12.0 months, HR 0.65 [95% CI 0.5–0.83], $p = 0.001$). In contrast, early WBRT did not prolong OS (35.6 vs 37.1 months, HR 1.03 [95% CI 0.79–1.35], $p = 0.82$).

When CR and non-CR patients were considered separately, any potential positive impact of WBRT

Figure 2 Overall survival according to remission status (CR vs non-CR) after high-dose methotrexate-based chemotherapy



(A) Per-protocol population. (B) Intent-to-treat population. CI = confidence interval; CR = complete response; HR = hazard ratio; WBRT = whole-brain radiotherapy.

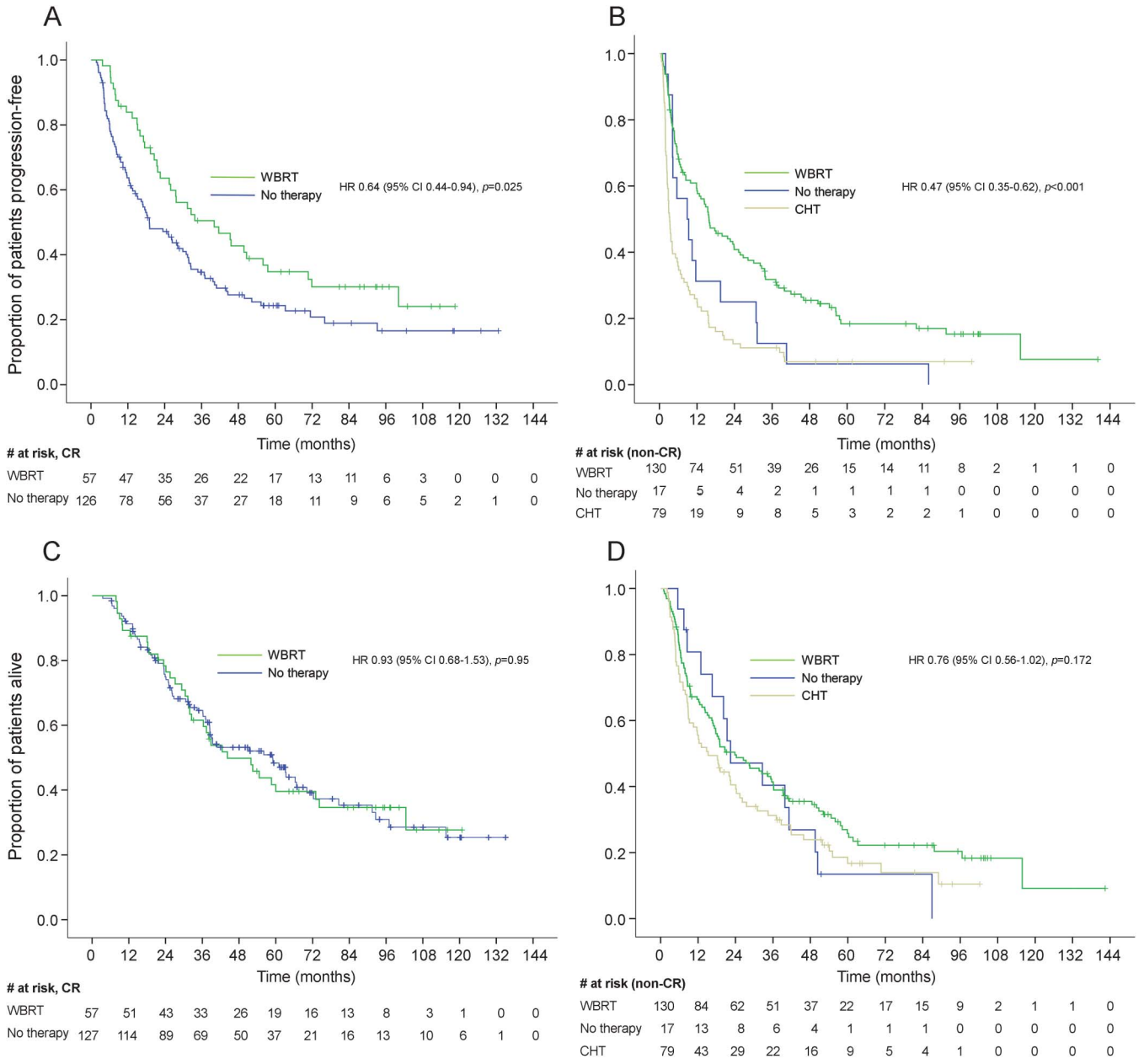
was more prominent in non-CR patients. In CR patients, a nonsignificant prolongation of PFS and PFS from last HDMTX were found with WBRT (42.5 vs 22.3 months, HR 0.69 [95% CI 0.46–1.03], $p = 0.065$; and 40.1 vs 19.1 months, HR 0.68 [95% CI 0.46–1.01], $p = 0.057$, respectively). There was no difference in OS (44.2 vs 59.0 months, HR 1.06 [95% CI 0.69–1.63], $p = 0.78$). In non-CR patients, both PFS and PFS from last HDMTX were prolonged with WBRT (5.0 vs 2.9 months, HR 0.6 [95% CI 0.43–0.83], $p = 0.002$; and 16.1 vs 2.9 months, HR 0.41 [95% CI 0.29–0.57], $p < 0.001$, respectively), whereas no difference in OS was found (27.4 vs 18.2 months, HR 0.76 [95% CI 0.54–1.08], $p = 0.119$) (figure 2A).

The results in the ITT population were similar to those in the PP population with prolongation by WBRT of both PFS (15.4 vs 9.9 months, HR 0.79 [95% CI 0.64–0.98], $p = 0.034$) and PFS from last HDMTX (19.4 vs 11.9 months, HR 0.72 [95% CI 0.58–0.89], $p = 0.003$), but not of OS (32.4 vs 36.1 months, HR 0.98 [95% CI 0.79–1.26], $p = 0.98$). In CR patients, no differences in PFS, PFS from last HDMTX, and OS were found (29.9 vs 25.7 months, HR 0.85 [95% CI 0.6–1.2], $p = 0.35$; 27.8 vs 23.4 months, HR 0.84 [95% CI 0.6–1.19], $p = 0.33$; and 51.3 vs 61.0 months, HR 1.13 [95% CI 0.77–1.66], $p = 0.53$, respectively). In non-CR patients, there was a prolongation of both PFS (4.7 vs 2.9 months, HR 0.67 [95% CI 0.51–0.89], $p = 0.004$) and PFS from last HDMTX (15.5 vs 5.7 months, HR 0.58 [95% CI 0.44–0.77], $p < 0.001$) with WBRT, but no difference in OS (20.7 vs 18.6 months, HR 0.86 [95% CI 0.64–1.16], $p = 0.32$) (figure 2B).

Multivariate analysis revealed lower Karnofsky Performance Score (KPS) as a risk factor for PFS in both the PP and the ITT population. For PFS from last HDMTX, besides lower KPS, not having received WBRT was a risk factor. For OS, higher age and lower KPS were risk factors in the PP and the ITT population, whereas male sex was a risk factor only in the PP, but not in the ITT population (table e-1 on the *Neurology*® Web site at Neurology.org).

Results of the as-treated analysis supported the observations made in the PP and ITT populations (figure 3). In CR patients, PFS from last HDMTX was 33.8 months with WBRT and 19.0 months without (HR 0.64 [95% CI 0.44–0.94], $p = 0.025$) and OS 51.9 vs 59.0 months (HR 0.93 [95% CI 0.68–1.53], $p = 0.95$). In non-CR patients, PFS from last HDMTX was 15.9 months with WBRT, 3.2 months with CHT, and 8.9 months without further therapy (HR 0.47 [95% CI 0.35–0.62], $p < 0.001$); OS was 23.8, 14.8, and 27.5 months, respectively (HR 0.76 [95% CI 0.56–1.02], $p = 0.172$).

Figure 3 PFS from last high-dose methotrexate-based chemotherapy and overall survival analyzed as-treated in the ITT population



(A) Progression-free survival (PFS) from last high-dose methotrexate (HDMTX)–based chemotherapy (CHT) in patients with complete response (CR). (B) PFS from last HDMTX-based CHT in patients without CR. (C) Overall survival (OS) in patients with CR. (D) OS in patients without CR. The good outcome of the non-CR patients without further treatment can be explained by the fact that 6 of them probably did in fact have CR after HDMTX-based CHT. They were documented as having CR upon follow-up without further therapy. Moreover, one additional patient received whole-brain radiotherapy (WBRT) without progression 6 months after HDMTX-based CHT. CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat.

DISCUSSION This is the largest ever and the only published randomized phase III study on this rare disease addressing one of the most important questions in the management of PCNSL: that of the role of WBRT as consolidation after HDMTX-based CHT. The results reported in the first publication were confirmed with a higher events number and much longer follow-up, which fortifies the conclusions. Moreover, an as-treated analysis is presented confirming the results of the ITT analysis of randomized study arms, which further supports the validity of the results. Finally, an analysis of PFS from the last HDMTX-based CHT is included, which sheds new light on the possible role of WBRT in maintaining disease control.

Long-term results of the G-PCNSL-SG-1 trial suggest that there is no significant difference in OS when WBRT is omitted from the first-line treatment of PCNSL. Yet the primary hypothesis of noninferiority according to the study protocol that asked for a lower confidence limit of 0.9 was not proven. There

was, however, a significant PFS prolongation with WBRT both in the PP and ITT population (in the PP population of PFS from last HDMTX only), which was most prominent in non-CR patients.

G-PCNSL-SG-1 may thus define a role of WBRT for disease control in PCNSL. WBRT was more effective than HD-Ara-C in patients with disease less sensitive or insensitive to HDMTX. This did not translate into a significant OS benefit, with only a trend towards longer OS in non-CR patients, probably because of the effectiveness of other salvage treatments. However, the study was not powered to detect differences in CR and non-CR patients evaluated separately. Compromised PFS, but not OS, by deferring WBRT has also been observed in 2 recent retrospective analyses.[2,3]

The execution of the trial was difficult with a relatively high mortality during HDMTX-based chemotherapy (13%), in part explained by a relatively high percentage of patients >70 years (relative mortality: 24%) and with a KPS ≤40% (relative mortality: 15%). Moreover, there were frequent protocol violations, and approximately 10% of patients were lost to follow-up. Further limitations were no central review for response determination, change of chemotherapy regimen from HDMTX to HDMTX plus ifosfamide, and lack of standardized neurocognitive testing.

Late neurotoxicity is the principal reason to withhold WBRT from initial therapy of PCNSL. In the G-PCNSL-SG-1 trial, clinical and radiologic signs of late neurotoxicity were found more frequently in patients after WBRT.[1] This is in accordance with the results of a retrospective analysis that identified WBRT as the only factor significantly associated with late neurotoxicity.[4] Moreover, in 2 recent analyses using detailed neuropsychologic testing, more cognitive dysfunction was observed with HDMTX-based CHT plus WBRT than with CHT alone.[5,6] Although elderly patients are considered at particular risk,[7] clinically manifest late neurotoxicity was also found in >20% of younger patients after combined CHT/WBRT[8,9] and even in 63% of patients when extensive neuropsychological assessment was used.[10] Whether reduced-dose WBRT is safe or necessary for improved outcome or both[11] requires a randomized trial such as RTOG 1114 (NCT 01399372).

Based on our results, WBRT can be postponed until relapse in patients with CR to HDMTX-based CHT in younger patients. Conversely, in patients aged 60 years or older who are at increased risk of both late neurotoxicity and relapse,[12] alternative strategies of CR consolidation must be explored. Since PCNSL exhibit multiple genetic properties of ABC-type diffuse large B-cell lymphomas,[13,14] antagonists of the B-cell receptor and downstream mediators including SYK, protein kinase C-β, PI-3 kinase-δ, and MALT1 (ibrutinib, fostamatinib, idelalisib, BKM120, GA101) or drugs addressing IRF4/MUM1 (lenalidomide, pomalidomide) are possible candidates. Another interesting path forward could be addressing the immunosuppressive microenvironment in PCNSL by PD1/PD-L1 axis inhibitors.[15]

AUTHOR CONTRIBUTIONS

A. Korfel designed and wrote the study protocol, contributed patients to the trial, and wrote and approved the report. E. Thiel designed and wrote the study protocol, contributed patients to the trial, and approved the report. P. Martus performed the statistical analyses and wrote and approved the report. R. Möhle contributed patients to the trial and approved the report. F. Griesinger contributed patients to the trial and approved the report. M. Rauch contributed patients to the trial and approved the report. A. Röth contributed patients to the trial and approved the report. B. Hertenstein contributed patients to the trial and approved the report. T. Fischer contributed patients to the trial and approved the report. T. Hundsberger contributed patients to the trial and approved the report. H.-G. Mergenthaler contributed patients to the trial and approved the report. C. Junghanß contributed patients to the trial and approved the report. T. Birnbaum contributed patients to the trial and approved the report. L. Fischer contributed patients to the trial and approved the report. K. Jahnke contributed patients to the trial and approved the report. U. Herrlinger designed and wrote the study protocol, contributed patients to the trial, and approved the report. P. Roth contributed patients to the trial and approved the report. M. Bamberg designed and wrote the study protocol, was responsible for central review of radiation oncology, and approved the report. T. Pietsch was responsible for central review of neuropathology and approved the report. M. Weller designed and wrote the study protocol, contributed patients to the trial, and wrote and approved the report.

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