VOLUME 31 · NUMBER 3 · JANUARY 20 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Adjuvant Procarbazine, Lomustine, and Vincristine Chemotherapy in Newly Diagnosed Anaplastic Oligodendroglioma: Long-Term Follow-Up of EORTC Brain Tumor Group Study 26951

Martin J. van den Bent, Alba A. Brandes, Martin J.B. Taphoorn, Johan M. Kros, Mathilde C.M. Kouwenhoven, Jean-Yves Delattre, Hans J.J.A. Bernsen, Marc Frenay, Cees C. Tijssen, Wolfgang Grisold, László Sipos, Roelien H. Enting, Pim J. French, Winand N.M. Dinjens, Charles J. Vecht, Anouk Allgeier, Denis Lacombe, Thierry Gorlia, and Khê Hoang-Xuan

See accompanying editorial on page 299 and article on page 337

Martin J. van den Bent, Johan M. Kros, Mathilde C.M. Kouwenhoven, Roelien H. Enting, Pim J. French, and Winand N.M. Dinjens, Erasmus MC–Daniel den Hoed Cancer Center, Rotterdam; Martin J.B. Taphoorn and Charles J. Vecht, Medical Center Haaglanden, The Hague; Martin J.B. Taphoorn, Vrije Universiteit Medisch Centrum, Amsterdam; Hans J.J.A. Bernsen, Canisius Wilhelmina Ziekenhuis, Nijmegen; Cees C. Tijssen, St Elisabeth Hospital, Tilburg; Roelien H. Enting, University Medical Center Groningen, Groningen, the Netherlands; Alba A. Brandes, Azienda Unità Sanitaria Locale di Bologna, Bologna, Italy; Jean-Yves Delattre and Khê Hoang-Xuan, Groupe Hospitalier, Pitié-Salpêtrière, Paris; Marc Frenay, Centre Antoine Lacassagne, Nice, France; Wolfgang Grisold, Kaiser Franz Josef Hospital, Vienna, Austria; László Sipos, Institute of Neurosurgery, Budapest, Hungary; and Anouk Allgeier, Denis Lacombe, and Thierry Gorlia, European Organisation for Research and Treatment of Cancer Headquarters, Brussels, Belgium.

Published online ahead of print at www.jco.org on October 15, 2012.

Written on behalf of the European Organisation for Research and Treatment of Cancer Brain Tumor Group.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical trial information: NCT00002840.

Corresponding author: Martin J. van den Bent, MD, Neuro-Oncology Unit, Erasmus MC–Daniel den Hoed Cancer Center, PO Box 5201, 3008AE Rotterdam, the Netherlands; e-mail: m.vandenbent@erasmusmc.nl.

0732-183X/13/3103-344/$20.00

DOI: 10.1200/JCO.2012.43.2229

ABSTRACT

Purpose
Anaplastic oligodendroglioma are chemotherapy-sensitive tumors. We now present the long-term follow-up findings of a randomized phase III study on the addition of six cycles of procarbazine, lomustine, and vincristine (PCV) chemotherapy to radiotherapy (RT).

Patients and Methods
Adult patients with newly diagnosed anaplastic oligodendroglial tumors were randomly assigned to either 59.4 Gy of RT or the same RT followed by six cycles of adjuvant PCV. An exploratory analysis of the correlation between 1p/19q status and survival was part of the study. Retrospectively, the methylation status of the methyl-guanine methyl transferase gene promoter and the mutational status of the isocitrate dehydrogenase (*IDH*) gene were determined. The primary end points were overall survival (OS) and progression-free survival based on intent-to-treat analysis.

Results
A total of 368 patients were enrolled. With a median follow-up of 140 months, OS in the RT/PCV arm was significantly longer (42.3 *v* 30.6 months in the RT arm, hazard ratio [HR], 0.75; 95% CI, 0.60 to 0.95). In the 80 patients with a 1p/19q codeletion, OS was increased, with a trend toward more benefit from adjuvant PCV (OS not reached in the RT/PCV group *v* 112 months in the RT group; HR, 0.56; 95% CI, 0.31 to 1.03). *IDH* mutational status was also of prognostic significance.

Conclusion
The addition of six cycles of PCV after 59.4 Gy of RT increases both OS and PFS in anaplastic oligodendroglial tumors. 1p/19q-codeleted tumors derive more benefit from adjuvant PCV compared with non–1p/19q-deleted tumors.

J Clin Oncol 31:344-350. © 2012 by American Society of Clinical Oncology

INTRODUCTION

Uncontrolled trials have shown that recurrent anaplastic oligodendroglioma (AOD) and anaplastic oligoastrocytoma (AOA) are chemotherapy-sensitive tumors, with 60% to 70% of patients responding to chemotherapy with procarbazine, lomustine, and vincristine (PCV).[1,2] This raised the question whether adjuvant PCV chemotherapy given at the time of diagnosis as opposed to chemotherapy at the time of recurrence would improve overall outcome. To answer this question, the European Organisation for Research and Treatment (EORTC) Brain Tumor Group initiated in 1995 a prospective randomized phase III trial (EORTC study 26951) to determine whether adjuvant PCV given after 59.4 Gy of radiotherapy (RT) in fractions of 1.8 Gy would improve survival. This multicenter trial accrued 368 patients between August 13, 1996, and March 3, 2002, and was reported in 2006 when 217 (59%) of the randomly assigned patients had died.[3] The results at that time showed an increase in progression-free survival (PFS) in adjuvant PCV-treated patients, but no statistically significant increase in overall survival (OS). A similar North American study (Radiation Therapy Oncology

Group [RTOG] study 9402) conducted at the same time but in which PCV chemotherapy was given with an intensified PCV regimen before 59.4 Gy of RT showed similar results.[4]

During the accrual phase of these trials, retrospective studies had shown that, in particular, oligodendroglial tumors in which both the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) are deleted (1p/19q codeletion) are responsive to PCV chemotherapy, with 90% to 100% of the codeleted cases responding.[5,6] Therefore, the trial was amended during the accrual phase to make 1p/19q status part of the study analysis. Both the European and the North American study noted at that time a significant prognostic effect of the presence of the 1p/19q codeletion, but no predictive effect on the outcome to PCV chemotherapy. However, in 2006, median survival had been reached in neither study in the patients with 1p/19q-codeletion tumors. We now present long-term follow-up data of this study. The present report includes an update on the prognostic impact of methyl-guanine methyl transferase (*MGMT*) gene promoter methylation and of isocitrate dehydrogenase (*IDH*) gene mutations on outcome, which analyses were conducted and reported after the first publication (post hoc) of the clinical study results.[7,8]

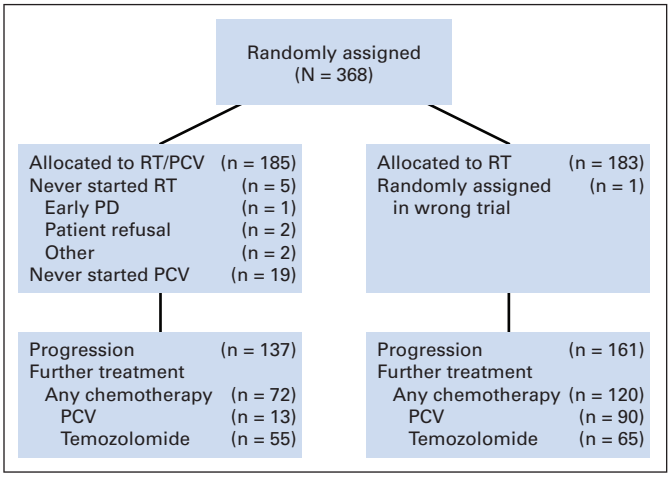

Fig 1. CONSORT diagram. PCV, procarbazine, lomustine, and vincristine; PD, progressive disease; RT, radiotherapy.

PATIENTS AND METHODS

Eligibility criteria have been described before (see also Appendix, online only).[3] Patients were eligible for this study if they had been diagnosed by the local pathologist with an AOD or with a mixed AOA with at least 25% oligodendroglial elements according to the WHO 1993 classification for brain tumors,[9] with at least three of five anaplastic characteristics (high cellularity, mitosis, nuclear abnormalities, endothelial proliferation, or necrosis).

Molecular Assessments

Deletion of 1p and 19q were primarily assessed with fluorescence in situ hybridization with locus-specific probes for the region 1p36.6 (D1S32) and 19q (BAC 426G3); a few available snap-frozen samples were assessed with array comparative genomic hybridization, as described elsewhere.[3,10,11] O6-methylguanine-methyltransferase (*MGMT*) promoter methylation was assessed using a semiquantitative methylation-specific multiplex ligation-dependent probe amplification as described elsewhere.[7] The presence of isocitrate dehydrogenase (*IDH*)-1 and -2 mutations were assessed by bidirectional cycle sequencing of polymerase chain reaction–amplified fragments as described previously.[8] Only one tumor with an *IDH2* mutation was identified; this case is considered together with the *IDH1* mutations.

Treatment

Treatment details have been provided previously.[3] Radiotherapy was given to a dose of 59.4 Gy in fractions of 1.8 Gy. PCV chemotherapy consisted of six cycles of standard PCV chemotherapy given in 6 week, and was started within 4 weeks after the end of RT. Treatment at the time of progression was left to the discretion of the local investigators, but the protocol strongly advised the treating physicians to consider (PCV) chemotherapy, especially for patients in the RT-only arm.

Follow-Up

At baseline and at every 3 months until progression, patients were followed up with a neurologic examination including Eastern Cooperative Oncology Group (ECOG) performance status, mini-mental status examination, quality-of-life questionnaire, and magnetic resonance imaging or computed tomography scans (the same imaging modality was to be used throughout the entire study). Details have been provided previously.[3] Thereafter patients were to be followed up every 3 months for survival. Progression was defined according to Macdonald's criteria.[12]

Statistical Design and Randomization

Details have been described before; see also the Appendix (online only). Primary end points of the study were OS and PFS in the intent-to-treat population. Of note, in amendment 3 (May 2001), 1p/19q testing and a preplanned exploratory correlative analysis of 1p/19q status with OS and PFS were incorporated in the study design. All survival analyses were done according to the Kaplan and Meier method with two-sided log-rank statistics with .05 level of significance and were performed using SAS version 9.2 (SAS Institute, Cary, NC). Log-rank test for interaction was used to compare treatment effect in different molecular subsets.

RESULTS

Between August 13, 1995, and March 3, 2002, 368 patients were randomly assigned: 183 were assigned to receive initial RT alone and 185 to RT followed by adjuvant PCV. The clinical characteristics of patients in the two groups were well balanced (Appendix Table A1, online only). The details of treatment delivery, tolerance, and toxicity have been published previously.[3] At the time of this report (February 20, 2012), 298 patients (81.0%) had been diagnosed with disease progression, and 281 patients (76.4%) were reported dead. Central pathology review confirmed the presence of an oligodendroglial tumor in 257 patients (AOD, 175; mixed AOA, 82). Tissue was available for 1p/19q analysis in 316 patients, for *MGMT* promoter methylation analysis in 183 patients, and for *IDH* mutational status assessment in 179 patients. Figure 1 shows the updated CONSORT diagram, with the details of treatment at the time of progression.

Survival

Ten years after the conclusion of enrollment and with a median follow-up of 140 months, OS was significantly better in the RT/PCV arm (median OS, 42.3 *v* 30.6 months after RT alone, hazard ratio [HR], 0.75; 95% CI, 0.60 to 0.95; Fig 2A, Table 1). Similarly, PFS was significantly better after RT/PCV (median PFS, 24.3 months after RT/PCV *v* 13.2 months with RT only; HR, 0.66; 95% CI, 0.52 to 0.83; Fig 2B). In a risk-adjusted analysis entering age (≤ 40 *v* > 40 years), surgery (biopsy *v* resection), WHO performance status (0, 1 *v* 2), and previous surgery for low-grade glioma (yes *v* no), the assigned treatment remained an independent factor for OS (HR, 0.76; 95% CI, 0.60 to 0.97).

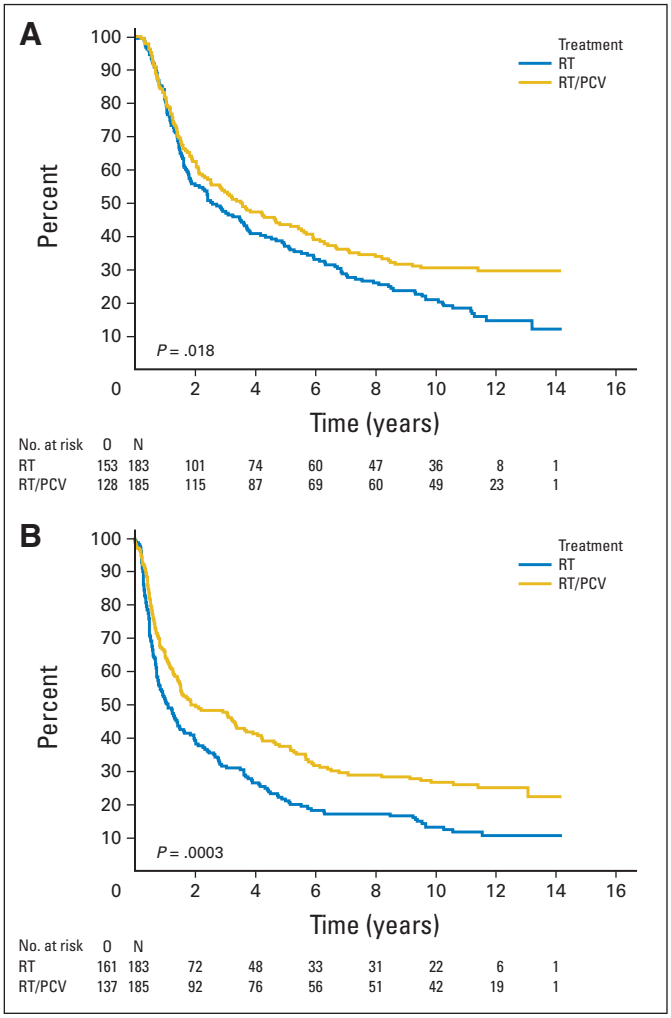

Fig 2. (A) Overall survival and (B) progression-free survival in both treatment arms in the intent-to-treat population. N, total number of events; O, observed events; PCV, procarbazine, lomustine, and vincristine; RT, radiotherapy.

Subgroup Analysis by 1p/19q Status and Pathology Review

The HR reduction of the addition of PCV seemed more pronounced in the patients with 1p/19q-codeleted tumors (Table 1). In 80 (25%) of the 316 cases with tissue available for 1p/19q assessment, codeletion of 1p/19q was found. In these patients with codeleted tumors, OS was not reached in the RT/PCV group versus 112 months in the RT group (HR, 0.56; 95% CI, 0.31 to 1.03; Fig 3A). In the patients with noncodeleted tumors, the risk reduction was less: OS of 25 versus 21 months (HR, 0.83; 95% CI, 0.62 to 1.10; Fig 3B). The magnitude of the treatment effect was not significantly different between the two subgroups defined by 1p/19q status as estimated by the Peto's log-rank ($P = .25$), which is not unexpected in view of the number of patients with codeleted tumors.[13] PFS increase was also larger in the codeleted group. In the codeleted group, PFS was 157 months after RT/PCV and 50 months after RT only (HR, 0.42; 95% CI, 0.24 to 0.74; Fig 4A). In the patients with noncodeleted tumors, PFS was 15 months in the RT/PCV group and 9 months in the RT only group (HR, 0.73; 95% CI, 0.56 to 0.97; Fig 4B). In the subgroup with confirmed anaplastic oligodendroglial histology (n = 257) at central review, a similar HR reduction for OS was observed after RT/PCV (HR, 0.73; 95% CI, 0.55 to 0.96) compared with the intent-to-treat population.

Other Molecular Factors and Outcome

Patients tested for 1p/19q status, *IDH* status, and *MGMT* promoter methylation status had similar clinical characteristics and outcome compared with the patients who were not tested, except for a slight increase in resection in the patients tested for *IDH* and 1p/19q (91% *v* 81%, and 87% *v* 77%, respectively, other data not shown). Appendix Table A2 (online only) summarizes the median OS and PFS according to 1p/19q, *IDH*, and *MGMT* status. Both PFS and OS were significantly better in the patients with codeleted tumors compared with the patients with noncodeleted tumors (PFS, 76 *v* 11 months; HR, 0.39; 95% CI, 0.28 to 0.53; OS, 123 *v* 23 months; HR, 0.36; 95% CI, 0.26 to 0.50). Similarly, OS and PFS were better in patients with *MGMT* promoter methylated and in *IDH*-mutated tumors. Table 1 summarizes the median and 5-year OS in the various subgroups in relation to assigned treatment. Patients with *MGMT* promoter methylation, *IDH*-mutated tumors, or confirmed anaplastic oligodendroglial histology seemed to derive more benefit from the addition of PCV. Tests for interaction of these characteristics with assigned treatment remained insignificant.

Both *MGMT* promoter methylation and *IDH* mutational status could be determined in 158 patients and were correlated (correlation coefficient, 0.51; only two patients with a mutated *IDH*-1 showed an unmethylated *MGMT*; all other *IDH*-mutated patients [n = 69] showed *MGMT* promoter methylation). The OS was similar in patients without *MGMT* promoter methylation compared with patients with *MGMT* promoter methylation but no *IDH* mutation (HR, 0.88; 95% CI, 0.57 to 1.36). In 150 cases, data on both 1p/19q, *MGMT*, and *IDH* results were available. In a multivariate prognostic model with these three factors, *IDH* and 1p/19q were independently significant but not *MGMT*, with a similar OS HR reduction for *IDH*-mutated (0.356) and 1p/19q-codeleted (0.424) tumors.

DISCUSSION

The present long-term survival analysis of EORTC study 26951 is the first trial of grade 3 glioma to show a clinically relevant and significant increase in OS in the intent-to-treat population with the addition of adjuvant chemotherapy to radiotherapy. The 2006 analysis of this study already showed an increased PFS after adjuvant PCV chemotherapy. We assumed that the absence of a significant OS benefit despite the PFS increase after adjuvant PCV was the result of crossover chemotherapy treatment at the time of progression, with 75% of RT-only patients receiving chemotherapy at that time. With a median follow-up duration of 140 months, the increase in PFS is now reflected in a 12-month increase in OS. This increase in OS was achieved despite the fact that most patients randomly assigned to the RT/PCV arm did not complete the full series of six adjuvant cycles of PCV. As described previously, the median number of PCV cycles was three, with 30% of patients completing the intended six cycles.[3] Most patients that discontinued PCV prematurely did so for (usually asymptomatic) hematologic toxicity or for tumor progression. A quality-of-life analysis that was part of this study has shown that patients in the RT/PCV arm complained more frequently of nausea/vomiting, loss of appetite, and

Table 1. Median and 5-Year Overall Survival and Progression-Free Survival According to Assigned Treatment in the Various Subgroups

Population and Treatment	No. of Patients	Overall Survival							Progression-Free Survival					
		Events	Hazard Ratio	95% CI	Median (months)	95% CI	5 Year (%)	95% CI	Events	Hazard Ratio	95% CI	Median (months)	95% CI	5 Year (%)	95% CI
Intent-to-treat population															
RT	183	153	1		30.6	21.5 to 44.5	37.0	30.0 to 44.0	161	1		13.2	9.2 to 17.9	22	16.0 to 27.9
RT/PCV	185	128	0.75	0.60 to 0.95	42.3	28.7 to 62.0	43.4	36.2 to 50.5	137	0.66	0.52 to 0.83	24.3	17.4 to 40.7	37.5	30.5 to 44.4
1p/19q status															
Deleted															
RT	37	26	1		111.8	75.7 to 134.3	73.0	55.6 to 84.4	30	1		49.9	27.8 to 101.8	46.0	29.6 to 60.9
RT/PCV	43	18	0.56	0.31 to 1.03	NR		76.2	60.3 to 86.4	20	0.42	0.24 to 0.74	156.8	68.1 to NR	71.4	55.2 to 82.7
Nondeleted															
RT	122	107	1		21.1	17.6 to 28.7	25.1	17.7 to 33.0	110	1		8.7	7.1 to 11.7	13.5	8.1 to 20.3
RT/PCV	114	90	0.83	0.62 to 1.10	25.0	18.0 to 36.8	31.6	23.3 to 40.2	96	0.73	0.56 to 0.97	14.8	9.9 to 21.1	25.4	17.8 to 33.7
IDH status															
Mutated															
RT	36	26	1		64.8	36.9 to 111.8	52.8	35.5 to 67.4	29	1		36.0	17.2 to 58.6	33.3	18.8 to 48.6
RT/PCV	45	21	0.53	0.30 to 0.95	NR		68.2	52.3 to 79.8	26	0.49	0.29 to 0.84	71.2	47.1 to NR	59.1	43.2 to 71.9
Wild type															
RT	50	48	1		14.7	11.9 to 19.1	16.0	7.5 to 27.4	49	1		6.8	5.4 to 8.6	4.0	0.74 to 12.1
RT/PCV	47	42	0.78	0.52 to 1.18	19.0	14.6 to 30.2	21.3	11.0 to 33.8	42	0.56	0.37 to 0.86	10.0	7.8 to 18.2	17.0	8.0 to 29.0
MGMT promoter															
Methylated															
RT	62	48	1		43.3	21.9 to 66.2	41.9	29.6 to 53.8	54	1		15.2	8.7 to 34.5	21.0	11.9 to 31.8
RT/PCV	74	45	0.65	0.43 to 0.98	70.9	42.0 to 136.8	54.8	42.7 to 65.4	50	0.52	0.35 to 0.76	55.6	20.4 to 73.6	48.0	36.2 to 58.8
Unmethylated															
RT	24	22	1		15.6	11.4 to 19.1	8.3	1.4 to 23.3	23	1		7.1	4.4 to 8.7	4.2	0.3 to 17.6
RT/PCV	23	20	0.81	0.44 to 1.49	16.3	9.1 to 30.3	17.4	5.4 to 35.0	20	0.63	0.34 to 1.16	9.8	4.6 to 15.4	17.4	5.4 to 35.0
Confirmed anaplastic oligodendroglial histology															
RT	126	109	1		28.7	19.3 to 41.7	33.0	25.0 to 41.3	115	1		10.4	8.4 to 16.9	17.9	11.8 to 25.1
RT/PCV	131	92	0.73	0.55 to 0.96	35.0	24.2 to 56.2	41.5	33.0 to 49.8	100	0.62	0.47 to 0.81	19.1	15.2 to 40.0	35.4	27.3 to 43.6

Abbreviations: NR, not reached; PCV, procarbazine, lomustine, and vincristine; RT, radiotherapy.

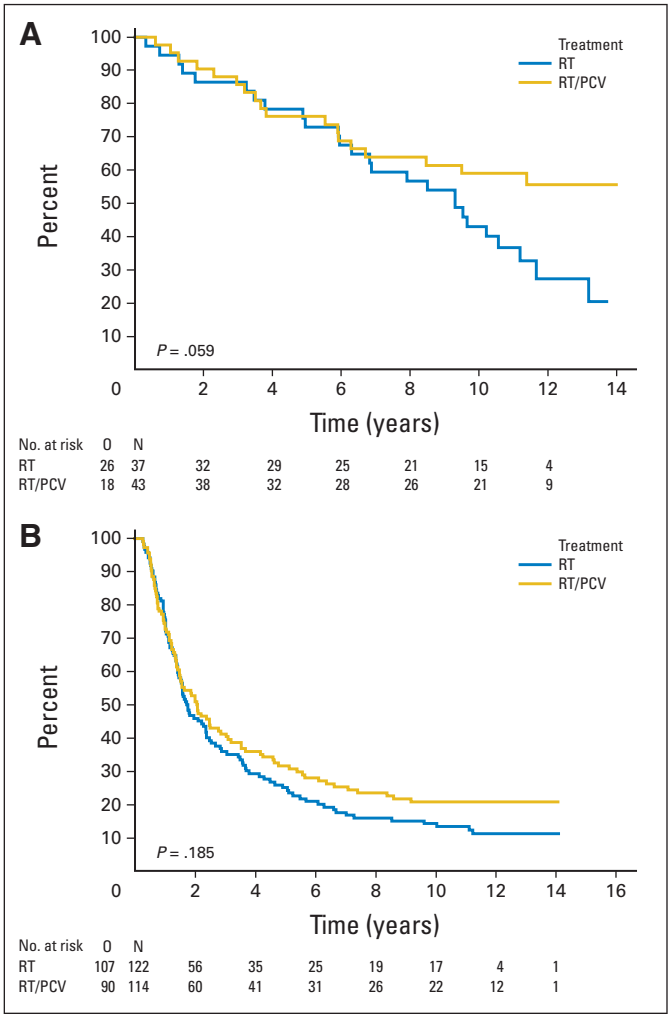

Fig 3. Overall survival in both treatment arms for (A) the patients with 1p/19q-codeleted tumors (n = 80) and (B) the patients with non–1p/19q-codeleted tumors (n = 236). N, total number of events; O, observed events; PCV, procarbazine, lomustine, and vincristine; RT, radiotherapy.

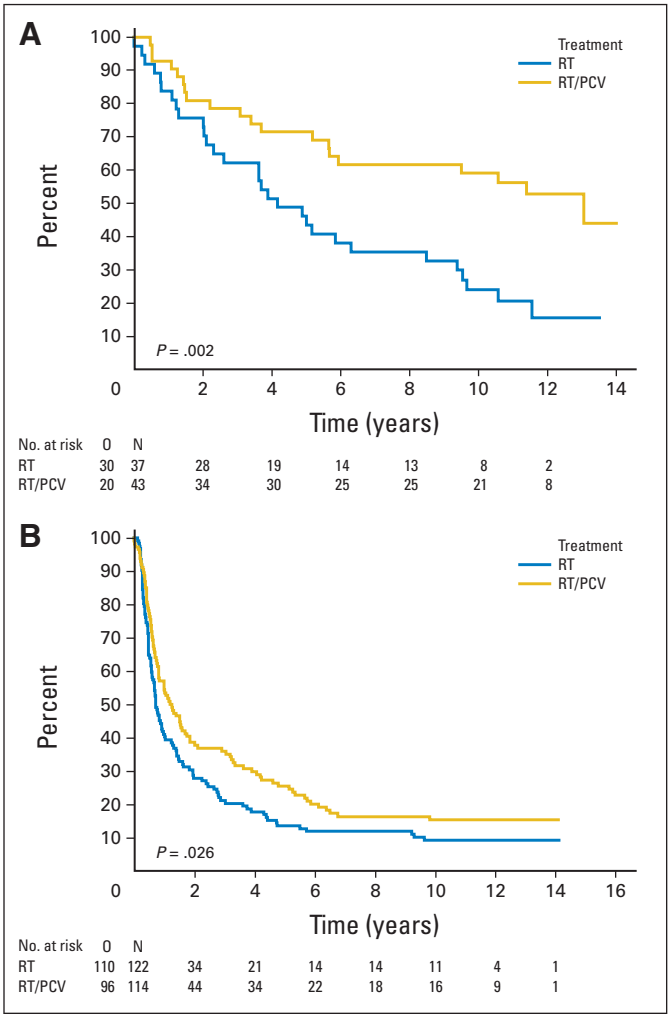

Fig 4. Progression-free survival in both treatment arms for (A) patients with 1p/19q-codeleted tumors (n = 80) and (B) patients with non–1p/19q-codeleted tumors (n = 236). N, total number of events; O, observed events; PCV, procarbazine, lomustine, and vincristine; RT, radiotherapy.

drowsiness during and shortly after PCV chemotherapy.[14] There were, however, no long-term effects of PCV chemotherapy on quality of life identified.

As opposed to the similar North American RTOG 9402 study on neoadjuvant intensified PCV in anaplastic oligodendroglial tumors, patients were entered based on the local histologic diagnosis with central pathology review after inclusion. The central pathology review confirmed the anaplastic oligodendroglial histology in almost 70% of patients. This rate of interobserver variation is typical for studies in grade 2 and 3 glioma.[15-17] The morphologic criteria for oligodendroglioma have been subject to trends over time, with recently a shift toward a more strict use of the criteria to diagnose oligodendroglial tumors.[18,19] Obviously, inclusion based on locally diagnosed oligodendroglial tumors results in a more heterogeneous patient study population. Although that is a caveat for the interpretation of this study, it does reflect the day-to-day clinical situation more accurately as patients are treated based on a local diagnosis.[20] Still, the HR reduction after adjuvant PCV in the central pathology review–confirmed AOD tumors was similar to HR reduction in the intent-to-treat population (0.73 *v* 0.75).

Although a trend (HR, 0.83; $P = .185$ in the 236 patients with noncodeleted tumors) toward improved OS after RT/PCV is present in the patients with noncodeleted tumors, our study shows a larger risk reduction (HR, 0.56; upper limit of the 95% CI of 1.03; $P = .0594$) in the 80 patients with 1p/19q-codeleted tumors. This is consistent with the major increase in PFS after adjuvant PCV in patients with 1p/19q-codeleted tumors: from 50 months with RT only to 156 months with RT/PCV. Of note, in most studies, the response duration of 1p/19q-codeleted AOD tumors relapsing after RT and treated with PCV chemotherapy varies between 12 and 24 months.[5,21,22] The present trial demonstrates, therefore, that the addition of PCV chemotherapy to RT as opposed to PCV at the time of progression results in a major improvement of outcome in 1p/19q-codeleted tumors. Further support for the major increase in OS after adjuvant PCV is derived from the RTOG study 9402, which observed in 120 patients with 1p/19q-codeleted tumors a similar risk reduction with the addition of PCV to RT (OS, 14.7 years after RT/PCV *v* 7.3 years after RT only; HR for 1p/19q codeleted, 0.59; HR after PCV/RT for the entire study population, 0.79).[22a]

After the conclusion of enrollment for this study, two other markers were identified that affect outcome in diffuse glioma: *MGMT* promoter methylation and *IDH* mutations.[23-26] In the present study, all three markers (1p/19q codeletion, *MGMT* promoter methylation, and *IDH* mutation) were correlated with and highly prognostic for patient survival. A clinically relevant question is which biomarker(s) have the strongest prognostic value for benefit of adjuvant PCV chemotherapy. In multivariate analysis of the present study, only 1p/19q and *IDH* status were of independent prognostic significance, but in the non–1p/19q-codeleted tumors, no clear statistically significant increase in OS was observed. Recent studies suggest that *IDH* mutations are causal for the glioma CpG island hypermethylated phenotype, and *MGMT* promoter methylation is part of this CpG island hypermethylated phenotype profile.[27-29] Moreover, in vitro studies indicate that the *IDH*-mutation induced metabolic alterations (in particular, increased production of 2-hydroxy-glutarate) may ultimately result in this hypermethylated state.[30-32] Most likely, *MGMT* promoter methylation in grade 3 *IDH*-mutated tumors is a result of genome-wide methylation, and the prognostic impact in univariate analysis of *MGMT* promoter methylation in grade 3 diffuse glioma is merely reflecting the improved outcome of *IDH*-mutated tumors. From the present study, no definitive conclusions can be drawn regarding the predictive value of *MGMT* promoter methylation alone or of *IDH* mutations in the absence of 1p/19q codeletion. Despite trends that are observed, the numbers of these patients are small, the *MGMT* and *IDH* analyses are post hoc, and all tests for interaction remained negative.

How should 1p/19q-codeleted tumors now be treated? Taken together, the EORTC and the RTOG studies show that for 1p/19q-codeleted oligodendroglial tumors, the combination of RT and PCV should be the standard of care. The similar risk reduction in the adjuvant standard-dose EORTC study and in the neoadjuvant intensified PCV RTOG study suggests that it is neither the timing (immediately before or after RT) nor the dose-intensity of the PCV schedule that matters. An obvious question is whether combined chemoirradiation with temozolomide or RT followed by temozolomide can be considered equivalent to RT/PCV. A formal head-to-head comparison of PCV versus temozolomide has never been conducted, although with limited follow-up (with only 43% of patients having reached the primary end point, time to treatment failure) and not powered for comparison between temozolomide and PCV, the German NOA 4 trial on grade 3 gliomas did not reveal differences between these regimens.[33,34] Assuming that combined chemo-irradiation with temozolomide provides equivalent results compared with RT/PCV remains therefore a leap of faith. Another question is whether RT can be safely postponed in patients with 1p/19q-codeleted tumors. Delayed effects of RT on cognition have been documented, and in many centers, temozolomide chemotherapy only has become the standard approach for 1p/19q-deleted oligodendroglioma while withholding RT until progression.[35,36] The ongoing CODEL (Codeleted Tumors) study on anaplastic 1p/19q-codeleted oligodendroglioma assesses the efficacy of RT with temozolomide as compared with RT alone and is based on the 2006 report of this study and of RTOG 9402. In the third exploratory arm (with a cognitive end point), patients are treated with temozolomide alone. This trial was put on hold once the first long-term results of RTOG 9402 became available; this decision is supported by results of the present study. It is currently under consideration to amend the RT-alone arm into RT plus PCV and to continue the other two arms (RT/temozolomide chemoirradiation and temozolomide alone). This design would address the above questions. Still, the NOA4 study on grade 3 glioma observed similar results after RT and after chemotherapy at the time of the first report.[33] Thus the possibility exists that similar to RT first and chemotherapy at progression, sequential treatment with chemotherapy first and RT at progression will also adversely affect OS in comparison with initial treatment with RT/PCV.

The other question is how patients with noncodeleted grade 3 glioma should be treated. Many of those patients will not have oligodendroglial morphology and were not eligible for the present trial. In patients without 1p/19q codeletion who were enrolled onto the trial, no statistically significant OS benefit of adjuvant PCV was identified. Post hoc analysis also suggests a benefit for *IDH*-mutated tumors, but many of these were also 1p/19q codeleted, and the limited sample size does not allow further meaningful analysis of this subgroup. The currently ongoing CATNON (Concurrent and Adjuvant Temozolomide Chemotherapy in Non-1p/19q Deleted Anaplastic Glioma) study on grade 3 non–1p/19q-codeleted tumors must answer this question. In this EORTC study conducted in Europe, Australia, and North America, patients are treated with various combinations of radiotherapy and temozolomide. The presence of an RT-only control arm will allow a further characterization of patients with grade 3 glioma who benefit from chemotherapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
Employment or Leadership Position: None **Consultant or Advisory Role:** Martin J. van den Bent, MSD (C); Alba A. Brandes, Roche (C), Schering-Plough (C) **Stock Ownership:** None **Honoraria:** Martin J. van den Bent, MSD; Alba A. Brandes, GlaxoSmithKline, Roche **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Martin J. van den Bent, Jean-Yves Delattre, Charles J. Vecht
Administrative support: Anouk Allgeier
Provision of study materials or patients: Martin J. van den Bent, Alba A. Brandes, Martin J.B. Taphoorn, Johan M. Kros, Mathilde C.M. Kouwenhoven, Jean-Yves Delattre, Hans J.J.A. Bernsen, Marc Frenay, Cees C. Tijssen, Wolfgang Grisold, László Sipos, Roelien H. Enting, Pim J. French, Winand N.M. Dinjens, Charles J. Vecht
Collection and assembly of data: Martin J. van den Bent, Anouk Allgeier, Denis Lacombe, Thierry Gorlia
Data analysis and interpretation: Martin J. van den Bent, Pim J. French, Denis Lacombe, Thierry Gorlia
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Cairncross G, Macdonald D, Ludwin S, et al: Chemotherapy for anaplastic oligodendroglioma: National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 12:2013-2021, 1994

2. van den Bent MJ, Kros JM, Heimans JJ, et al: Response rate and prognostic factors of recurrent oligodendroglioma treated with procarbazine, CCNU and vincristine chemotherapy: Dutch Neuro-Oncology Group. Neurology 51:1140-1145, 1998

3. van den Bent MJ, Carpentier AF, Brandes AA, et al: Adjuvant PCV improves progression free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: A randomized European Organisation for Research and Treatment of Cancer phase III trial. J Clin Oncol 24:2715-2722, 2006

4. Cairncross G, Berkey B, Shaw E, et al: Phase III trial of chemotherapy plus radiotherapy versus radiotherapy alone for pure and mixed anaplastic oligodendroglioma (RTOG 9402): Intergroup Radiation Therapy Oncology Group Trial 9402. J Clin Oncol 24:2707-2714, 2006

5. Cairncross JG, Ueki K, Zlatescu MC, et al: Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. J Natl Cancer Inst 90:1473-1479, 1998

6. van den Bent MJ, Looijenga LH, Langenberg K, et al: Chromosomal anomalies in oligodendroglial tumors are correlated with clinical features. Cancer 97:1276-1284, 2003

7. van den Bent MJ, Dubbink HJ, Sanson M, et al: MGMT promoter methylation is prognostic but not predictive for outcome to adjuvant PCV chemotherapy in anaplastic oligodendroglial tumors: A report from EORTC Brain Tumor Group Study 26951. J Clin Oncol 27:5881-5886, 2009

8. van den Bent MJ, Dubbink HJ, Marie Y, et al: IDH1 and IDH2 mutations are prognostic but not predictive for outcome in anaplastic oligodendroglial tumors: A report of the European Organization for Research and Treatment of Cancer Brain Tumor Group. Clin Cancer Res 16:1597-1604, 2010

9. Kleihues P, Burger PC, Scheithauer BW: Histological Typing of Tumours of the Central Nervous System. New York, NY, Springer-Verlag, 1993

10. Kouwenhoven MC, Gorlia T, Kros JM, et al: Molecular analysis of anaplastic oligodendroglial tumors in a prospective randomized study: A report from EORTC study 26951. Neuro Oncol 11:737-746, 2009

11. Idbaih A, Dalmasso C, Kouwenhoven M, et al: Genomic aberrations associated with outcome in anaplastic oligodendroglial tumors treated within the EORTC phase III trial 26951. J Neurooncol 103:221-230, 2011

12. Macdonald DR, Cascino TL, Schold SC Jr, et al: Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 8:1277-1280, 1990

13. Peto R, Peto J: A symptotically efficient rank invariant test procedures (with discussion). J R Statist Soc A 135:185-198, 1972

14. Taphoorn MJ, van den Bent MJ, Mauer ME, et al. Health-related quality of life in patients treated for anaplastic oligodendroglioma with adjuvant chemotherapy: Results of a European Organisation for Research and Treatment of Cancer randomized clinical trial. J Clin Oncol 25:5723-5730, 2007

15. van den Bent MJ: Interobserver variation of the histopathological diagnosis in clinical trials on glioma: A clinician's perspective. Acta Neuropathol 120:297-304, 2010

16. Giannini C, Burger PC, Berkey BA, et al: Anaplastic oligodendroglial tumors: Refining the correlation among histopathology, 1p 19q deletion and clinical outcome in Intergroup Radiation Therapy Oncology Group Trial 9402. Brain Pathol 18:360-369, 2008

17. Kros JM, Gorlia T, Kouwenhoven MC, et al: Panel review of anaplastic oligodendroglioma from EORTC trial 26951: Assessment of consensus in diagnosis, influence of 1p/19q loss and correlations with outcome. J Neuropathol Exp Neurol 66:545-551, 2007

18. Coons SW, Johnson PC, Scheithauer BW, et al: Improving diagnostic accuracy and interobserver concordance in the classification and grading of primary gliomas. Cancer 79:1381-1391, 1997

19. Burger PC: What is an oligodendroglioma? Brain Pathol 12:257-259, 2002

20. Rothwell PM: External validity of randomised controlled trials: "To whom do the results of this trial apply?" Lancet 365:82-93, 2005

21. Brandes AA, Tosoni A, Vastola F, et al: Efficacy and feasibility of standard procarbazine, lomustine, and vincristine chemotherapy in anaplastic oligodendroglioma and oligoastrocytoma recurrent after radiotherapy: A Phase II study. Cancer 101:2079-2085, 2004

22. Kouwenhoven MC, Kros JM, French PJ, et al: 1p/19q loss within oligodendroglioma is predictive for response to first line temozolomide but not to salvage treatment. Eur J Cancer 42:2499-2503, 2006

22a. Cairncross G, Wang M, Shaw E, et al: Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: Long-term results of RTOG 9402. J Clin Oncol 31:337-343, 2013

23. Parsons DW, Jones S, Zhang X, et al: An integrated genomic analysis of human glioblastoma multiforme. Science 321:1807-1812, 2008

24. Balss J, Meyer J, Mueller W, et al: Analysis of the IDH1 codon 132 mutation in brain tumors. Acta Neuropathol 116:597-602, 2008

25. Watanabe T, Nobusawa S, Kleihues P, et al: IDH1 mutations are early events in the development of astrocytomas and oligodendrogliomas. Am J Pathol 174:1149-1153, 2009

26. Hegi ME, Diserens AC, Gorlia T, et al: MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 352:997-1003, 2005

27. Noushmehr H, Weisenberger DJ, Diefes K, et al: Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma. Cancer Cell 17:510-522, 2010

28. van den Bent MJ, Gravendeel LA, Gorlia T, et al: A hypermethylated phenotype is a better predictor of survival than MGMT methylation in anaplastic oligodendroglial brain tumors: A report from EORTC study 26951. Clin Cancer Res 17:7148-7155, 2011

29. Laffaire J, Everhard S, Idbaih A, et al: Methylation profiling identifies 2 groups of gliomas according to their tumorigenesis. Neuro Oncol 13:84-98, 2011

30. Turcan S, Rohle D, Goenka A, et al: IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. Nature 483:479-483, 2012

31. Figueroa ME, Abdel-Wahab O, Lu C, et al: Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic differentiation. Cancer Cell 18:553-567, 2010

32. Lu C, Ward PS, Kapoor GS, et al: IDH mutation impairs histone demethylation and results in a block to cell differentiation. Nature 483:474-480, 2012

33. Wick W, Hartmann C, Engel C, et al: NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with procarbazine, lomustine, and vincristine or temozolomide. J Clin Oncol 27:5874-5880, 2009

34. Brada M, Stenning S, Gabe R, et al: Temozolomide versus procarbazine, lomustine, and vincristine in recurrent high-grade glioma. J Clin Oncol 28:4601-4608, 2010

35. Douw L, Klein M, Fagel SS, et al: Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: Long-term follow-up. Lancet Neurol 8:810-818, 2009

36. Abrey LE, Louis DN, Paleologos N, et al: Survey of treatment recommendations for anaplastic oligodendroglioma. Neuro Oncol 9:314-318, 2007

Support

Supported by a donation from the Kankerbestrijding/KWF from the Netherlands through the European Organisation for Research and Treatment of Cancer (EORTC) Charitable Trust. The study was further supported by the EORTC Translational Research Fund Grant No. TRF 01/02, by AstraZeneca EORTC Translational Research Grant No. AZ/01/02, and by the Dutch Cancer Society Grants DDHK 2005-3416 and EMC 2007-3932.

