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ORIGINAL REPORT

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NOA-04 Randomized Phase III Trial of Sequential Radiochemotherapy of Anaplastic Glioma With Procarbazine, Lomustine, and Vincristine or Temozolomide

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See accompanying editorial on page 5861 and article on page 5881

ABSTRACT

Purpose
The standard of care for anaplastic gliomas is surgery followed by radiotherapy. The NOA-04 phase III trial compared efficacy and safety of radiotherapy followed by chemotherapy at progression with the reverse sequence in patients with newly diagnosed anaplastic gliomas.

Patients and Methods
Patients (N = 318) were randomly assigned 2:1:1 (A:B1:B2) to receive conventional radiotherapy (arm A); procarbazine, lomustine (CCNU), and vincristine (PCV; arm B1); or temozolomide (arm B2) at diagnosis. At occurrence of unacceptable toxicity or disease progression, patients in arm A were treated with PCV or temozolomide (1:1 random assignment), whereas patients in arms B1 or B2 received radiotherapy. The primary end point was time to treatment failure (TTF), defined as progression after radiotherapy and one chemotherapy in either sequence.

Results
Patient characteristics in the intention-to-treat population (n = 274) were balanced between arms. All histologic diagnoses were centrally confirmed. Median TTF (hazard ratio [HR] = 1.2; 95% CI, 0.8 to 1.8), progression-free survival (PFS; HR = 1.0; 95% CI, 0.7 to 1.3, and overall survival (HR = 1.2; 95% CI, 0.8 to 1.9) were similar for arms A and B1/B2. Extent of resection was an important prognosticator. Anaplastic oligodendrogliomas and oligoastrocytomas share the same, better prognosis than anaplastic astrocytomas. Hypermethylation of the O^6-methylguanine DNA-methyltransferase (*MGMT*) promoter (HR = 0.59; 95% CI, 0.36 to 1.0), mutations of the isocitrate dehydrogenase (*IDH1*) gene (HR = 0.48; 95% CI, 0.29 to 0.77), and oligodendroglial histology (HR = 0.33; 95% CI, 0.2 to 0.55) reduced the risk of progression. Hypermethylation of the *MGMT* promoter was associated with prolonged PFS in the chemotherapy and radiotherapy arm.

Conclusion
Initial radiotherapy or chemotherapy achieved comparable results in patients with anaplastic gliomas. *IDH1* mutations are a novel positive prognostic factor in anaplastic gliomas, with a favorable impact stronger than that of 1p/19q codeletion or *MGMT* promoter methylation.

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INTRODUCTION

Common practice of care for patients with anaplastic astrocytoma (AA) is surgery followed by radiotherapy alone or radiochemotherapy.[1,2] It is unknown whether the survival benefit achieved with radiochemotherapy in glioblastoma[3] can and should be extrapolated to AA, as suggested in a meta-analysis of nitrosourea-based therapies.[1] Further, there are concerns regarding late neurotoxicity associated with concurrent radiochemotherapy, which manifests as cognitive decline, being possibly relevant for patients with AA with a long course of the disease.[4]

Since the early 1990s, initial therapy for newly diagnosed anaplastic oligodendrogliomas (AO) has become procarbazine, lomustine (CCNU), and vincristine (PCV), with or without radiotherapy, in many centers.[5] The Radiation Therapy Oncology Group study (R9402) compared radiotherapy with and without preceding PCV and the contemporaneous European Organisation for Research and Treatment of Cancer (EORTC) study (26951) compared

radiotherapy with and without adjuvant PCV in patients with anaplastic oligodendroglial tumors. Both trials showed improved progression-free survival (PFS) but not overall survival in patients receiving radiochemotherapy, but at the cost of significant toxicity from PCV.[6,7]

The 1p/19q deletion may predict a superior outcome in AO and anaplastic oligoastrocytoma (AOA) in response to cytotoxic treatments,[6-8] but not in patients with low-grade oligodendroglial tumors treated with surgery alone.[9] It has thus remained unclear whether the 1p/19q codeletion in AO and AOA reflects a favorable natural history or is mechanistically related to response. No prospective data are available to delineate the role of extent of resection or 1p/19q deletion in AA, or the hierarchy between putatively positive prognostic or predictive parameters. Furthermore, the role of novel prognostic markers like mutations in the isocitrate dehydrogenase (*IDH1*) gene emerging from a sequencing analysis of glioblastoma[10] and proposed as indicative of WHO grade 2 and 3 gliomas[11,12] needs to be delineated in controlled trials.

The NOA-04 trial compared the efficacy and safety of radiotherapy versus chemotherapy with either PCV or temozolomide (TMZ) as initial therapy in patients with newly diagnosed, supratentorial anaplastic gliomas (WHO grade 3) and examined the clinical relevance of 1p/19q codeletion, O^6-methylguanine DNA-methyltransferase (*MGMT*) promoter methylation, and *IDH1* mutations in codon 132 in these tumors.

PATIENTS AND METHODS

Patients

Adult patients with centrally confirmed diagnosis of a WHO grade 3 anaplastic glioma,[13,14] Karnofsky performance score (KPS) of ≥ 70, no prior systemic chemotherapy or radiotherapy to the brain, and adequate bone marrow reserve, liver and renal functions, and stable or decreasing corticosteroid dose within 14 days before random assignment were eligible.

Trial Design and Treatment

This phase III trial was approved by the ethics committee at the University of Tübingen and enrolled patients after written informed consent at 39 German sites. Patients were randomly assigned 2:1:1 to receive radiotherapy (arm A) or chemotherapy with either PCV (arm B1) or temozolomide (arm B2; Figs 1 and 2).

Radiotherapy consisted of fractionated focal irradiation to gross tumor volume (GTV) plus a 2-cm margin in 6-week courses of 1.8- to 2-Gy fractions to a total 60-Gy dose based on preoperative magnetic resonance imaging (MRI) with dedicated computed tomography or three-dimensional planning systems. Arm B1 chemotherapy consisted of four 8-week cycles of lomustine (110 mg/m^2 on day 1), vincristine (2 mg on days 8 and 29), and procarbazine (60 mg/m^2 on days 8 through 21). Dose modifications were based on weekly blood cell counts and polyneuropathy. Arm B2 chemotherapy consisted of eight 4-week cycles of temozolomide (200 mg/m^2 on days 1 through 5) with dose modifications based on blood cell counts. If toxicity in arms B1 and B2 resulted in delays longer than 4 weeks, radiotherapy was commenced. Treatment was stopped at disease progression or for unacceptable toxicity.

At disease progression after completion of primary treatment, patients in arm A were treated with PCV or temozolomide (1:1 random assignment). Patients in arms B1 or B2 who achieved an initial response or stable disease and completed the full course of chemotherapy were re-treated with the same chemotherapy for two (arm B1) or four (arm B2) additional cycles before radiotherapy was given at further progression (Fig 2).

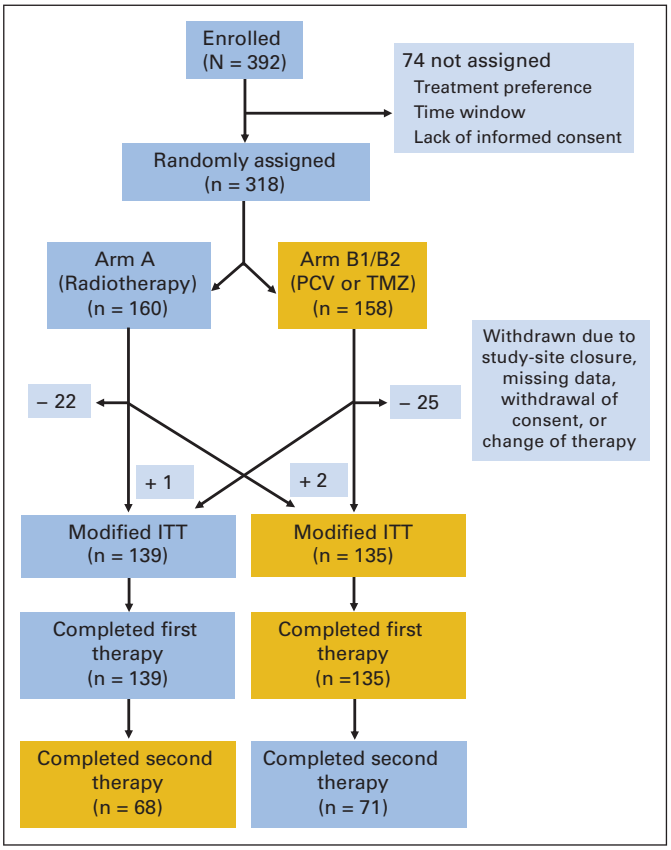

Fig 1. CONSORT diagram of patient disposition. Forty-four patients (21 in arm A; 23 in arm B1/B2) were excluded from the modified intention-to-treat (ITT) analysis because of study site closure, missing data, or withdrawal of consent. The analysis population was a modified ITT population because two patients assigned to radiotherapy received chemotherapy and one patient assigned to temozolomide (TMZ) received radiotherapy. Because treatment in the two groups was quite different, these three patients were analyzed in their treatment group rather than the group to which they were assigned. PCV, procarbazine, lomustine, and vincristine.

Evaluations

Baseline examinations included physical examination, MRI, full blood cell counts and blood chemistry, and Mini-Mental State Examination. Patients were seen weekly during radiotherapy, on days 1, 8, and 29 in arm B1, and every 4 weeks in arm B2. Patients received monthly clinical evaluations and comprehensive evaluations including MRI after cycles 2 and 4 in arm B1 and after cycles 4 and 8 in arm B2. Patients underwent a comprehensive evaluation including MRI 4 weeks after completing radiotherapy and every 3 to 4 months thereafter. Tumor response and progression were defined according to Macdonald criteria[15] and centrally confirmed. Patients with a complete resection had nonmeasurable disease, and their best response possible is stable disease (SD). Toxicity was assessed monthly according to the Common Terminology Criteria for Adverse Events, version 2.0.

Molecular Methods

Only tissue samples with a tumor cell content of 80% or more underwent molecular analysis. DNA was extracted from paraffin-embedded tumor tissue using the DNeasy blood and tissue kit (Qiagen, Hilden, Germany).

Detection of chromosome arms 1p and 19q deletions was performed by a multiplex ligation-dependent probe assay (Salsa MLPA, P088 lots 0305 and 0706, MRC Holland, Amsterdam, the Netherlands).[16] Chromosomal regions were scored as under- or overrepresented if two or more loci on 1p or 19q adjacent to each other exhibited a gene dosage ratio less than 70% or more than 130% relative to the reference value. In the 59 patients from whom leukocyte DNA was available, we additionally performed microsatellite-based loss of

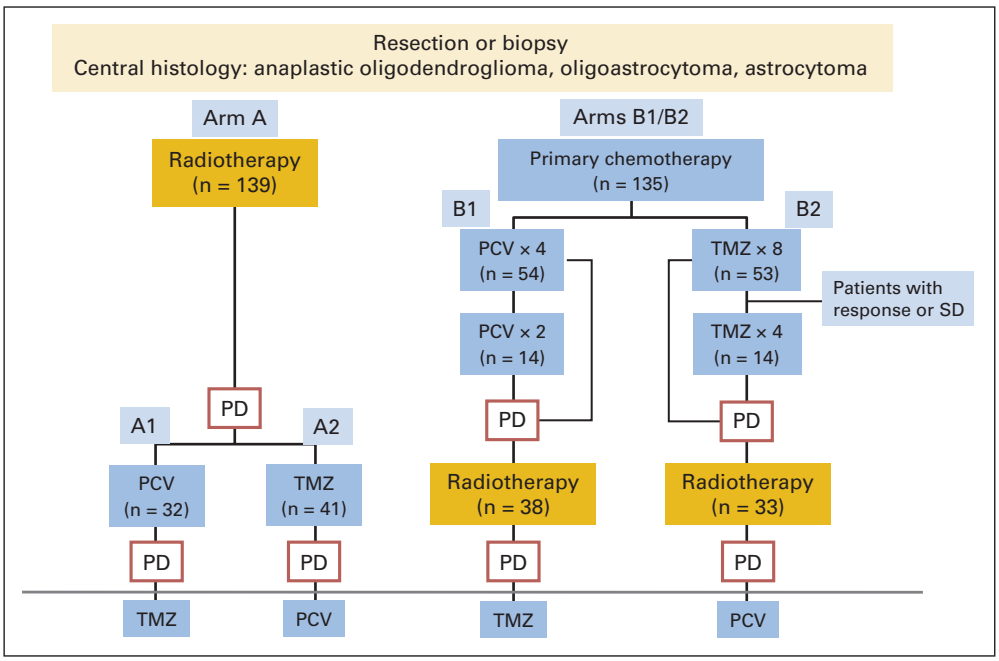

Fig 2. Trial design. Patients were randomly assigned 2:1:1 to receive radiotherapy (arm A) or chemotherapy with either procarbazine, lomustine, and vincristine (PCV; arm B1) or temozolomide (TMZ, arm B2) as initial therapy. Patient numbers represent the modified intention-to-treat population. At first disease progression, patients treated initially with radiotherapy (44 patients with anaplastic astrocytoma [AA; 63% of patients with AA treated in arm A], nine patients with anaplastic oligodendrogliomas [AO; 41%], and 20 patients with anaplastic oligoastrocytoma [AOA; 43%]) crossed over to treatment with chemotherapy and were randomly assigned 1:1 to PCV (arm A1) or TMZ (arm A2). Patients who experienced disease progression after initial chemotherapy (44 patients with AA [60% of patients with AA treated in arms B1/2], six patients with AO [35%], and 21 patients with AOA [48%]) crossed over to second-line treatment with radiotherapy. SD, stable disease; PD, progressive disease.

heterozygosity analyses for allelic losses on 1p and 19q. At least five microsatellite loci on each arm were analyzed.[17,18]

MGMT promoter methylation status was determined by methylation-specific polymerase chain reaction.[19,20] DNA from each tumor (200 ng) was treated with sodium bisulfite using the EZ DNA Methylation-Gold Kit (HISS Diagnostics, Freiburg, Germany).

A fragment of 129-bp length spanning the catalytic domain of *IDH1* including codon 132 was amplified using sense primer IDH1f CGGTCTTCAGAGAAGCCATT and antisense primer IDH1r GCAAAATCACATTATTGCCAAC, and a fragment of 150 bp for *IDH2* on chromosome 15q26.1 was amplified using sense primer IDH2f AGCCCATCATCTGCAAAAAC and antisense primer IDH2r CTAGGCGAGGAGCTCCAGT. Sequences were determined using a semiautomated sequencer (ABI 3100 Genetic Analyzer, Applied Biosystems, Foster City, CA) and the Sequence Pilot version 3.1 (JSI-Medisys, Kippenheim, Germany).[11]

Statistical Analysis

The primary end point was time from operation to treatment failure stratified for therapy in the intention-to-treat (ITT) population. Treatment failure was defined as withdrawal from therapy before second progression because of toxicity or poor general condition, second progression, or death. Patients without one of these events were censored at the end of their follow-up.

The protocol intended to re-expose patients who had undergone at least one postchemotherapy evaluation with SD or better to two more cycles of PCV (arm B1) or four more cycles of temozolomide (arm B2) at progression. Accordingly, 14 patients (20.6%) in arm B1 and 14 patients (20.9%) in arm B2 were re-exposed to chemotherapy. Nevertheless, the term "progression" in the protocol and in this article has been used as progression after chemotherapy or after radiotherapy, indicating the time point to switch treatments between these modalities. The interval of PFS was calculated as time between operation and first progression during or after either chemotherapy or radiotherapy.

Secondary end points included response rate, PFS, overall survival, time to treatment failure (TTF) stratified for histology, 1p/19q codeletion, *MGMT* promoter methylation status, and safety. Event times were examined using Kaplan-Meier estimates[21] and a Cox proportional hazard model for evaluating hazard ratios (HRs) and their 95% CIs. In the multivariate analyses, age (> 50 *v* ≤ 50 years), KPS (≤ 80 *v* > 80), Mini Mental Status (≤ 27 *v* > 27), resection (biopsy, incomplete, and complete), histology (AA *v* OA/AOA), *MGMT* promoter methylation (no *v* yes), 1p/19q codeletion (no *v* yes), and R132H mutation in *IDH1* (no *v* yes) were considered. When colinearity was observed, only one of the variables was included in the final model. Interactions were also investigated. Remission rates were analyzed using a nominal odds model. Histology and reference histology results were compared by calculating Cohens κ. Pearson product moment correlation coefficient, *r*, was calculated for the extent of a linear relationship between histology and *MGMT* promoter methylation.

Sample Size Considerations

Based on an expected median TTF of 30 months in arm A, 236 patients were required to achieve 80% power ($\alpha = 5\%$) to demonstrate a 50% superiority of the treatment in arm B for TTF. After a planned interim analysis (February 2002), this conservatively calculated patient number was recalculated to 318 patients on the basis of, among other reasons, the higher dropout rate. Analyses were performed with SAS 9.1.3 (SAS Institute, Cary, NC) on a modified ITT (mITT) basis. All participants included in the study formed the ITT population if they received any study treatment and did not belong to an excluded center.

Because the treatment-related documentation in the two groups was quite different, patients who changed their therapy were analyzed in the group in which they were treated, not in the group to which they were randomly assigned. According to the treatment schemes, this followed a more conservative approach. This concerned two patients in arm A and one patient in arm B and constituted the mITT population.

RESULTS

Patients

From June 1999 to February 2005, 318 patients with centrally confirmed anaplastic gliomas were randomly assigned to receive radiotherapy (160 patients) or chemotherapy (PCV, n = 78; temozolomide, n = 80; Fig 1). The mITT population included 139 patients in arm A and 135 in arms B1 and B2. Baseline characteristics between treatment groups were well balanced (Table 1). Central pathology review demonstrated a high concordance between local and central histologic diagnoses ($\kappa = 0.7$; 95% CI, 0.62 to 0.79).

Table 1. Baseline Patient Characteristics

Characteristic	Radiotherapy (n = 139)	PCV or Temozolomide (n = 135)
Age, years		
Median	44	42
Range	23-74	20-77
Sex, No.		
Female	55	61
Male	84	74
Histopathology, No.		
Anaplastic astrocytoma		
Local	65	66
Central	70	74
Anaplastic oligoastrocytoma		
Local	41	41
Central	47	44
Anaplastic oligodendroglioma		
Local	33	27
Central	22	17
κ-value	0.7	
Concordance between local and reference histopathology	0.62-0.79	
Karnofsky performance status, %		
Median	90	90
Range	70-100	70-100
Mini-Mental State examination score (of 30 possible points)		
Median	30	30
Range	21-30	21-30
Resection, No.		
Complete	53	47
Partial	61	57
Biopsy	25	31
Time from surgery to study treatment, days		
Median	46	28
Range	7-175	9-111
Corticosteroids, No.	27	33
Loss of 1p/19q, No.		
Yes	41	33
No	54	53
Missing	44	49
MGMT promoter, No.		
Methylated	59	64
Unmethylated	44	35
Missing	36	36
IDH-1, No.		
Wild-type	62	66
Mutated	36	31
Missing	41	38
IDH-2, No.		
Wild-type	94	95
Mutated	4	2
Missing	41	38

Abbreviation: PCV, procarbazine, lomustine, and vincristine.

Table 2. Toxicity in the First and Recurrence Treatments

Grade 2 to 3 AE According to CTCAE	Arm A, Radiotherapy (n = 139)	Arm B1/2, Chemotherapy (n = 135)
Any AE		
No.	19	61
%	12	39
Allergic reaction, No.	0	13 (PCV) 1 (TMZ)
Alopecia/local skin reaction, No.	5	0
Cephalgia, No.	3	0
Hematologic (grade 3 to 4), No.	2	14 (PCV) 3 (TMZ)
Herpes zoster infection, No.	0	1 (PCV) 1 (TMZ)
Polyneuropathy, No.	0	10 (PCV)
Pneumonia, pneumonitis, No.	2	1 (PCV) 1 (PCV)
Tumor bleed, thromboembolic events, No.	2	1 (TMZ) 1 (PCV)
Transaminase elevation	2	14 (PCV)
	Chemotherapy at Recurrence (n = 68)	Radiotherapy at Recurrence (n = 71)
Any AE		
No.	51	32
%	75	45
Alopecia/local skin reaction, No.	0	6
Cephalgia, No.	1 (TMZ)	3
Diarrhea	3 (TMZ)	0
Hematologic (grade 3 to 4), No.	8 (PCV) 3 (TMZ)	0
Herpes zoster infection, No.	3 (PCV) 1 (TMZ)	2
Infection (grade 2 to 4), No.	4 (PCV) 2 (TMZ)	2
Obstipation, No.	2 (TMZ)	0
Polyneuropathy, No.	6 (PCV)	0
Pneumonia, No.	2 (PCV) 2 (TMZ)	6
Radionecrosis, No.	1 (PCV)	2
Tumor bleed, thromboembolic events, No.	0 2 (PCV) 2 (TMZ)	16
Transaminase elevation (hepatic toxicity), No.	9 (PCV) 2 (TMZ)	4

Abbreviations: AE, adverse events; CTCAE, Common Terminology Criteria of Adverse Events; PCV, procarbazine, lomustine, and vincristine; TMZ, temozolomide.

Patient Disposition

Interruptions for toxicity in 3% of patients in arm A were usually brief (median, 3 days). Interruptions of chemotherapy from hematologic toxicity delayed 18% of cycles in arm B1 (median, 14 days) and 6% of cycles in arm B2 (median, 10 days). Fourteen patients (20.6%) in arm B1 and 14 patients (20.9%) in arm B2 were re-treated with chemotherapy at progression.

All patients in arm A completed treatment. The median number of completed cycles was four (range, one to five cycles) for PCV and eight (range, 0 to 12 cycles) for temozolomide. Discontinuations because of procarbazine allergy or hematologic toxicity occurred in 14 patients (9%). Dose reductions were necessary in 11 patients (16%) in arm B1 and four patients (6%) in arm B2. No patient developed pulmonary fibrosis. There was one case of possibly lomustine-related pneumonitis, and clinically relevant polyneuropathies occurred in 10% of patients treated with vincristine, which led to discontinuation in 7% of patients (Table 2).

Treatment Outcomes

At a maximal follow-up of 54 months, 117 patients (42.7%) have reached TTF. In the B1 and B2 arms, 77.8% of patients completed salvage radiotherapy, whereas only 48% completed salvage chemotherapy in arm A. Median TTF is 42.7 months with radiotherapy followed by chemotherapy and 43.8 months with chemotherapy followed by radiotherapy (Fig 3A and Table 3). The unadjusted HR for TTF in arms B1 and B2 versus arm A was 1.2 (95% CI, 0.8 to 1.8;

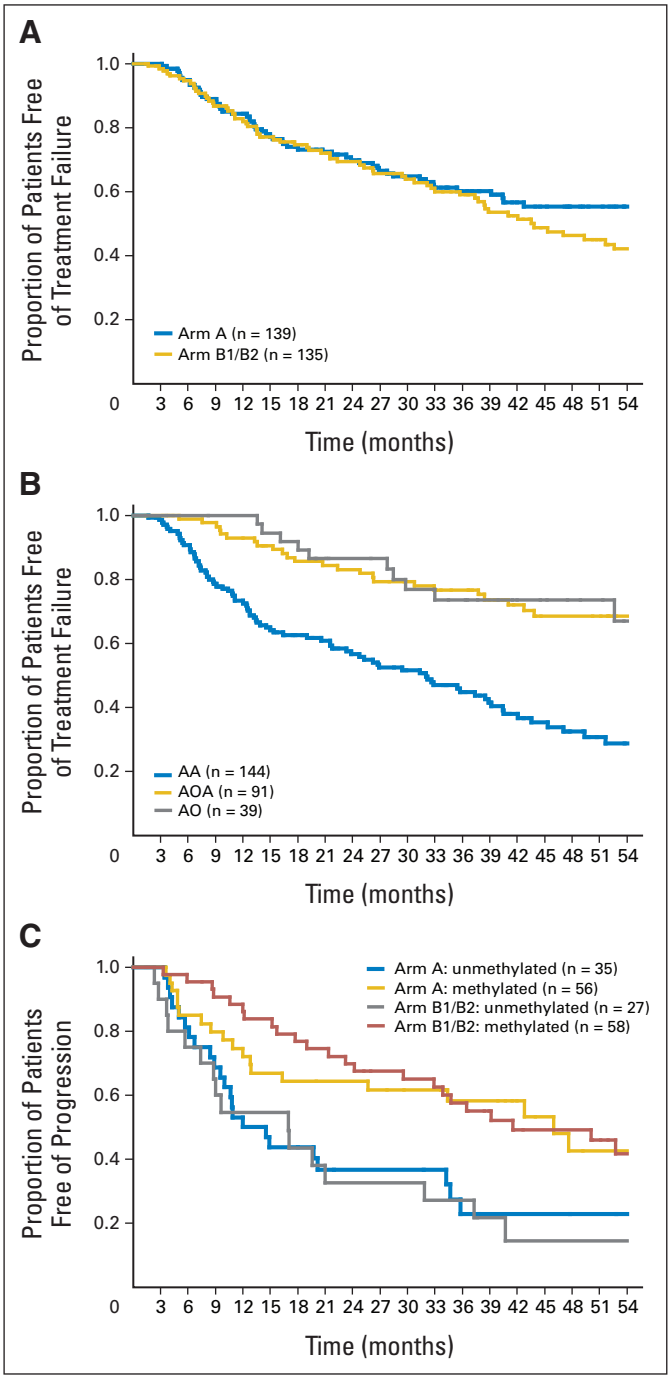

Fig 3. Kaplan-Meier estimates (modified intention-to-treat analysis). Data for time to treatment failure were analyzed by (A) treatment arm and (B) tumor histology. (C) Data for progression-free survival were analyzed for treatment arm and *MGMT* promoter methylation status. AA, anaplastic astrocytoma; AOA, anaplastic oligoastrocytoma; AO, anaplastic oligodendrogliomas.

log-rank $P = .28$). Within the different histologic groups, neither TTF nor PFS differed between treatments (Fig 3B and Table 3).

Median PFS was 30.6 months with radiotherapy and 31.9 months with chemotherapy (HR = 1.0, $P = .87$). No difference in PFS between patients treated with PCV versus temozolomide was observed. Median overall survival was not different between groups (Table 3).

Among 207 patients who received central neuroradiologic review, a response was achieved in 24.2% patients, including 36 complete responses and 14 partial responses. More patients receiving initial radiotherapy achieved a complete response (odds ratio [OR] = 1.2), a partial response (OR = 2.2), or stable disease (OR = 1.4) compared with chemotherapy ($P = .08$). SD as best response was achieved in 66% of patients. Patients with AA had a lower probability to achieve a complete response, partial response, or SD instead of progressive disease than patients with AO or AOA ($P = .005$).

Prognostic Factors

1p/19q codeletion was detected in 74 (40.9%) of 181 evaluable patients, including 13 (14.9%) of 87 patients with AA, 24 (77.4%) of 31 patients with AO, and 37 (58.7%) of 63 patients with AOA. Forty-eight (26.5%) of 181 evaluable tumors showed either partial or complete 1p deletions without concomitant 19q deletions. 19q deletions without 1p loss were found in 37 (20.4%) of 181 tumors. The incidences of 1p/19q codeletion and 1p or 19q deletions were balanced between study arms. *MGMT* promoter methylation was detected in 123 (60.9%) of 202 evaluable patients and was more common in AO (22 of 31 patients, 71%) and AOA (53 of 75 patients, 70.7%) than in AA (48 of 96 patients, 50%). *IDH1* codon 132 mutations resulting in an amino acid exchange from arginine to histidine (121 of 128 mutations), cysteine, (n = 5) guanine (n = 1), or serine (n = 1) in the isocitrate binding site were detected in 128 (65.6%) of 195 evaluable patients. The distribution between AO (22 of 31, 71%), AOA (55 of 75, 73%) and AA (51 of 89, 57%) was similar. *IDH2* mutations were detected in six (3.1%) of 195 evaluable patients, with one patients' tissue harboring both an *IDH1* codon 132 and an *IDH2* mutation (Table 1).

The univariate analysis for TTF and PFS are shown in Appendix Tables A1 and A2 (online only). Importantly, this trial did not support the hypothesis of an intermediate AOA prognosis, but rather defines a similar course of disease for AO and AOA regarding TTF and progression (HR = 1.0, 95% CI, 0.5 to 2.2; HR = 1.1, 95% CI, 0.6 to 2.0, respectively; Fig 3B).

Multivariate Cox regression analysis of prognostic factors for TTF showed that extent of resection ($P = .0006$), age less than 50 years ($P < .0004$), histology ($P < .0237$), *IDH*1 mutation ($P = .0128$), and *MGMT* promoter methylation status ($P = .0172$) were associated with TTF (Table 4). AA had a methylated *MGMT* promoter in 50% ($r = 0.17$, $P > .05$), whereas AO and AOA were methylated in 71% ($r = 0.82$, $P < .05$). Furthermore, *MGMT* promoter methylation was associated with 1p/19q loss in AO and AOA, but not in AA. Surprisingly, *MGMT* promoter methylation was associated with better PFS not only in arms B1 and B2, but also in arm A (Fig 3C; arm A, HR = 2.0, 95% CI, 1.1 to 3.6, $P < .03$; arms B1 and B2, HR = 2.7, 95% CI, 1.4 to 5.1, $P < .003$). Similar to TTF, *IDH1* mutation was positively associated with longer PFS irrespective of treatment arm, histology, 1p/19q status, or *MGMT* promoter methylation. In fact, in the multivariate model, *IDH1* mutation conferred a stronger risk reduction (HR = 0.47; 95% CI, 0.3 to 0.77; $P = .0021$) than 1p/19q codeletion (HR = 0.47; 95% CI, 0.3 to 0.83; $P = .0092$), *MGMT* promoter methylation (HR = 0.59; 95% CI, 0.37 to 1.1; $P = .0216$), or histology (HR = 0.63; 95% CI, 0.38 to 1.0; $P = .0425$; Appendix Table A3, online only).

Table 3. TTF, PFS, and OS

TTF, PFS, and OS	Radiotherapy (n = 139)		PCV or Temozolomide (n = 135)	
	Median	95% CI	Median	95% CI
TTF, months	42.7+		43.8	37.4 to not reached
Anaplastic astrocytoma	32.0	23.3 to not reached	29.4	19.0 to not reached
Anaplastic oligoastrocytoma	54+		54+	
Anaplastic oligodendroglioma	54+		54+	
Treatment failure at 48 months, %	55.5	46.3 to 64.6	46.4	36.7 to 56.2
PFS, months	30.6	16.3 to 42.8	31.9	21.1 to 37.3
Anaplastic astrocytoma	10.8	8.9 to 28.3	18.2	12.1 to 24.2
Anaplastic oligoastrocytoma/anaplastic oligodendroglioma	52.1	36.5 to not reached	52.7	33.9 to not reached
OS, months	72.1		82.6	
OS at 48 months, %	72.6	63.8 to 81.4	64.6	54.6 to 74.7

Abbreviations: TTF, time to treatment failure; PFS, progression-free survival; OS, overall survival; PCV, procarbazine, lomustine, and vincristine.

DISCUSSION

NOA-04 demonstrated the feasibility of initiating postoperative treatment with either chemotherapy or radiotherapy in patients with anaplastic gliomas, regardless of histologic subtype. No differences in TTF or PFS were demonstrated between initial radiotherapy and initial chemotherapy. Given the failure to improve survival with PCV-based radiochemotherapy and that improved PFS is only achieved at the cost of hematologic toxicity,[6,7] current standard of care for newly diagnosed anaplastic oligodendroglial tumors should probably be either radiotherapy or chemotherapy, but not their combination. New trials are examining the role of concomitant and/or adjuvant temozolomide in this setting.

In NOA-04, patients with AO and AOA showed virtually identical outcomes, although previous data indicated a less favorable prognosis for patients with AOA.[22] However, we used a rather restrictive central histologic AOA classification, whereby astrocytic tumors with just minute or ambiguous oligodendroglial differentiation features did not qualify for the diagnosis of AOA. This approach separated two prognostically distinct anaplastic glioma groups: AA versus AO and AOA. The findings argue that tumors with an unequivocal and quantitatively significant oligodendroglial component, in addition to astrocytic tumor parts, should qualify for a mixed oligoastrocytic glioma diagnosis. This approach may help to constrain the increase in oligodendroglial tumor diagnoses in recent years.[23]

Consideration has to be given to translation of trial results with central pathology review to the daily clinical routine, which is based on local histopathologic assessment. We noted a good concordance between local and central histopathology. Central re-evaluation of the EORTC 26951 trial histologies[7] disclosed that several patients with glioblastoma or low-grade gliomas had been included.[24]

It has been widely accepted that *MGMT* promoter methylation in gliomas is a predictor of response to alkylating chemotherapy.[25] With respect to PFS in *MGMT* unmethylated versus methylated tumors, this study confirms the prognostic relevance of *MGMT* promoter methylation. However, the present trial does not support the suggestion that *MGMT* promoter methylation is simply predictive for response to alkylating chemotherapy.[26] NOA-04 showed a striking difference in PFS between patients with versus without *MGMT* promoter methylation who were treated with radiotherapy alone. Thus *MGMT* promoter hypermethylation in anaplastic gliomas may be regarded as (1) a prognostic marker for good outcome in patients treated with radiotherapy or (2) predictive for response to radiotherapy itself. Interestingly, the EORTC 26981/22981 National Cancer Institute of Canada CE3 trial also showed better PFS in methylated (5.9 months) versus unmethylated (4.4 months) patients with glioblastoma treated with radiotherapy only.[26] 1p/19q-deleted and/or *MGMT* hyper-methylated anaplastic gliomas may carry a general defect in regulation of DNA methylation leading to epigenetic inactivation of multiple genes, including genes linked to radioresistance.

A novel prognostic marker, *IDH1* mutation,[11,12] emerged from this study, conferring a longer TTF independently of histology and treatment, as well as 1p/19q status or *MGMT* promoter methylation. Moreover, together with age, extent of resection, histology, and *MGMT* promoter methylation status, *IDH1* provides the best prognostic model. 1p/19q status emerged as prognostically relevant in the univariate analyses (Table 4 and Appendix Table A1). The R132 mutations in the *IDH1* gene represent a novel positive outcome marker in anaplastic gliomas that is independent from the classical 1p/19q deletion. The mutations are heterozygous and reduce the activity of the encoded protein.[12] Mechanistically, *IDH1* seems to function as a tumor suppressor that, when mutationally inactivated, contributes to tumorigenesis, in part through induction of the hypoxia inducible

Table 4. Complete Model of Major Prognostic Factors As Determined in a Multivariate Cox Regression Analysis for the Primary End Point of Time to Treatment Failure

Variable	Hazard Ratio	95% CI	*P*
Anaplastic astrocytoma *v* anaplastic oligoastrocytoma/ anaplastic oligodendroglioma	1.95	1.1 to 3.5	.0237
IDH1, wild-type *v* mutated	2.0	1.2 to 3.3	.0128
1p/19q retained *v* 1p/19q deleted	1.8	0.9 to 3.4	.0718
MGMT promoter, unmethylated *v* methylated	1.9	1.1 to 3.4	.0172
Age, > 50 *v* ≤ 50 years	2.6	1.5 to 4.3	.0004
Extent of resection			
Incomplete *v* complete resection	1.6	0.9 to 3.0	
Biopsy *v* incomplete resection	2.1	1.1 to 4.0	.0006
Biopsy *v* complete resection	3.5	1.8 to 7.0	

factor-1 pathway.[27] Practically, the determination of the *IDH1* mutation fills a gap in prognostic markers for AA, is easier to perform and interpret, and is more robust than the determination of 1p/19q status and especially *MGMT* promoter methylation.

In the AA subgroup, PFS was 10.8 months with radiotherapy and 18.2 months with chemotherapy. NOA-04 demonstrated that it is less likely that a patient will undergo treatment at recurrence when first treatment was radiotherapy as compared with chemotherapy. However, the incidence of relevant but manageable toxicity during chemotherapy (arm B1 and B2) was higher than during radiotherapy. These data may allow recommending chemotherapy as first-line treatment of patients with anaplastic gliomas, including patients with AA.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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