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CODEL: phase III study of RT, RT + TMZ, or TMZ for newly diagnosed 1p/19q codeleted oligodendroglioma. Analysis from the initial study design

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Abstract

Background. We report the analysis involving patients treated on the initial CODEL design.

Methods. Adults (>18) with newly diagnosed 1p/19q World Health Organization (WHO) grade III oligodendroglioma were randomized to radiotherapy (RT; 5940 centigray) alone (arm A); RT with concomitant and adjuvant temozolomide (TMZ) (arm B); or TMZ alone (arm C). Primary endpoint was overall survival (OS), arm A versus B. Secondary comparisons were performed for OS and progression-free survival (PFS), comparing pooled RT arms versus TMZ-alone arm.

Results. Thirty-six patients were randomized equally. At median follow-up of 7.5 years, 83.3% (10/12) TMZ-alone patients progressed, versus 37.5% (9/24) on the RT arms. PFS was significantly shorter in TMZ-alone patients compared with RT patients (hazard ratio [HR] = 3.12; 95% CI: 1.26, 7.69; $P = 0.014$). Death from disease progression occurred in 3/12 (25%) of TMZ-alone patients and 4/24 (16.7%) on the RT arms. OS did not statistically differ between arms (comparison underpowered). After adjustment for isocitrate dehydrogenase (IDH) status (mutated/wildtype) in a Cox regression model utilizing IDH and RT treatment status as covariables (arm C vs pooled arms A + B), PFS remained shorter for patients not receiving RT (HR = 3.33; 95% CI: 1.31, 8.45; $P = 0.011$), but not OS ((HR = 2.78; 95% CI: 0.58, 13.22, $P = 0.20$). Grade 3+ adverse events occurred in 25%, 42%, and 33% of patients (arms A, B, and C). There were no differences between arms in neurocognitive decline comparing baseline to 3 months.

Conclusions. TMZ-alone patients experienced significantly shorter PFS than patients treated on the RT arms. The ongoing CODEL trial has been redesigned to compare RT + PCV versus RT + TMZ.

Key Point

Patients with newly diagnosed 1p/19q codeleted anaplastic oligodendroglial tumors treated with TMZ alone experienced significantly shorter PFS than the pooled group of patients treated with RT and RT + TMZ.

Importance of the Study

The initial CODEL phase III randomized trial for patients with newly diagnosed 1p/19q codeleted anaplastic oligodendroglial tumors compared survival outcome following RT alone (control arm) versus RT with concurrent and adjuvant TMZ. A third TMZ-alone exploratory randomization arm was included as well, based on common clinical practice at the time of design. The RT-alone control arm was changed to RT + adjuvant procarbazine/lomustine/vincristine (PCV) following reports from EORTC 26951 and RTOG 9402, which showed a survival benefit of added PCV for this cohort. In our analysis of the patients treated on the original CODEL design, we found that TMZ-alone treated patients experienced significantly shorter PFS than patients treated on the RT arms. When combined with prior reported data, our results suggest that the current standard of care for these patients should include both radiation and chemotherapy.

CODEL (North Central Cancer Treatment Group [NCCTG]/Alliance for Clinical Trials in Oncology N0577; European Organisation for Research and Treatment Center [EORTC] 26081-22086; NRG 1071; Canadian Cancer Trials Group [CCTG] CEC.6) is an ongoing National Cancer Institute (NCI)–sponsored, international intergroup, prospective randomized phase III trial for patients with newly diagnosed 1p/19q codeleted oligodendroglial tumors. The original design included randomization of patients to radiotherapy (RT) alone (arm A); RT plus concomitant and adjuvant temozolomide (TMZ) (arm B); or TMZ alone (arm C). The primary objective of the trial was to compare overall survival (OS) between patients on arms A and B. A secondary analysis compared OS and progression-free survival (PFS) between patients receiving RT (on the pooled arms A + B) versus arm C patients. After active enrollment began, results from RTOG 9402 and EORTC 26951 became available, which showed a survival benefit with the addition of procarbazine, lomustine, and vincristine (PCV) to RT versus RT alone.[1,2] Accordingly, CODEL was redesigned, replacing the RT-alone control arm with RT followed by adjuvant PCV, using the schedule utilized in EORTC 26951. Later, the TMZ-alone treatment arm was dropped, in part due to the findings from the current analysis. As the data from the initial patients enrolled in CODEL will not be utilized in the primary analysis for the redesigned CODEL study, the analysis is reported herein.

Methods

Eligibility

Eligible patients included adults (age ≥18 y) with newly diagnosed, 1p/19q codeleted World Health Organization (WHO) grade III anaplastic oligodendroglial tumors. In the North American patients, histologic diagnosis and 1p/19q status were centrally confirmed at the Alliance/NCCTG central laboratory at Mayo Clinic (C.G., R.J.); in EORTC, pathology was centrally confirmed and 1p/19q codeletion status determined in the process of screening for EORTC 26053-22054 (CATNON). Isocitrate dehydrogenase (IDH) status was not required for eligibility, but was retrospectively obtained in 35/36 (97%) patients, as determined by immunohistochemistry (IHC) for IDH-R132H, or by sequencing. If IDH status was not known, tumor tissue banked per protocol was evaluated by IHC for IDH in the Pathology Research Core, Mayo Clinic Rochester. For those found to be IDH wildtype (WT) by IHC and with tumor tissue available, sequencing for IDH 1 and 2 was performed at the Clinical Genomics Laboratory, Mayo Clinic Rochester.

Additional eligibility criteria included that patients: were ≤3 months from surgical diagnosis and recovered from effects of surgery; had acceptable hematologic parameters (absolute neutrophil count ≥1500/μL, platelet

count ≥100 000/μL, hemoglobin ≥9 g/dL, serum total bilirubin ≤3 times upper limit of normal [ULN], aspartate aminotransferase ≤3 times ULN, and creatinine ≤1.5 ULN); had Eastern Cooperative Oncology Group (ECOG) performance status 0–2; were willing to provide tissue samples for translational research studies; were able to complete neurocognitive testing and quality of life (QoL) questionnaire without assistance; and were able to provide informed, written consent. Women of child-bearing potential had a negative pregnancy test and expressed willingness to use contraception. Patients were ineligible if they had comorbid medical conditions compromising safety on this treatment; were immunocompromised (other than receiving steroids); had active serious infection or history of HIV infection; had recent (<6 mo) history of myocardial infarction or congestive heart failure; had another active malignancy, with the exception of non-melanomatous skin or cervical cancer; or were receiving other active therapies directed at the central nervous system neoplasm.

Study participants were required to sign institutional review board–approved, protocol-specific informed consent documents in accordance with federal and institutional guidelines. Site participation required protocol approval by local institutional review boards, in accordance with assurances filed with the US Department of Health and Human Services, or as required by the applicable national legislation of non-US countries. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The trial is registered in the public domain (clinicaltrials.gov: NCT00887146).

Study Design and Treatment

Patients were randomized to arm A, RT alone (5940 centigray [cGy] in 33 fractions); arm B, RT + concomitant TMZ (75 mg/m^2/day) followed by adjuvant TMZ (150–200 mg/m^2, days 1–5 every 28 days) for up to 12 cycles; or arm C, TMZ alone (150–200 mg/m^2, days 1–5 every 28 days for up to 12 cycles) (Fig. 1). The decision to extend TMZ treatment beyond 6 cycles, for up to 12 cycles, was left to the treating investigator, without protocol-defined progression or development of adverse events meeting criteria for discontinuation of therapy. Patients were randomized in a 1:1:1 fashion with the following stratification factors: age (≥50 vs ≤50 y), registering group (NCI/CCTG versus EORTC), and ECOG performance status (0–1 vs 2). Temozolomide was provided initially by Schering-Plough and later by Merck Pharmaceuticals. Prophylaxis for *Pneumocystis jirovecii* was required in patients receiving TMZ.

For North American sites, the radiation treatment volume was defined as the T2 hyperintensity on fluid-attenuated inversion recovery or T2-weighted MR images including the surgical cavity, with a 1.0 cm margin anatomically constrained, plus a 5 mm planning target volume (PTV) margin to account for daily setup variation. This volume received 5040 cGy in 28 daily fractions if a sequential boost technique was used or 5445 cGy in 33 daily fractions if a concomitant boost technique was used. If enhancing tumor was present, this represented the boost volume with the resection cavity, plus a 5-mm PTV margin. If no tumor enhancement, the boost was defined as the original volume, but with no extra margin, except for the 5-mm PTV margin. For sequential boost technique, 900 cGy was administered in 5 daily fractions

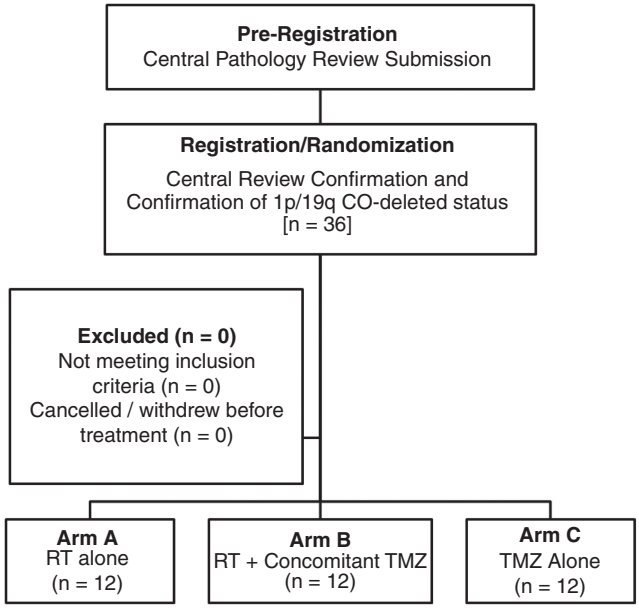


Fig. 1 CONSORT diagram.

(total dose 5940 cGy in 33 daily fractions). For concomitant boost technique, the total dose to the boost volume was 5940 cGy in 33 daily fractions. EORTC sites utilized a single gross tumor volume target (with no boost), defined as the entire region of T2 hyperintensity plus the region of enhancement on either the postoperative MRI (if available), or on the preoperative scan.

Endpoints

In the initial CODEL study, the primary endpoint was the comparison of OS between arm A versus arm B. OS was measured from the time of randomization until death. Secondary endpoints included comparison of PFS (arm A vs B) and time to neurocognitive progression (arm C vs arm B). However, this initial study was temporarily closed prematurely at the request of the Alliance Data Safety Monitoring Committee, in part due to the data observations regarding arm C patients, and due to reports from the late analyses of RTOG 9402 and EORTC 26951 which impacted the control arm of this initial CODEL study. Adequate events were not observed for the protocol-defined primary and secondary endpoint comparisons. Thus, we performed an initially unplanned secondary analysis to compare PFS of patients randomized to arm C with the pooled arm A and B patients. PFS was measured as the time from randomization until investigator-defined progression (earliest of either clinical progression or radiographic progression, protocol-defined per NCCTG criteria[3] (see Supplementary Material), or death without documented progression. Patients alive at the time of analysis (May 2020) were censored at their last follow-up date. Patients having biopsy or subtotal resection were evaluated for clinical and radiographic response utilizing NCCTG criteria and designated as either complete response (CR), partial response (PR), or regression (REGR) sustained at least 4 weeks; or as progression (PROG), as compared with the pretreatment baseline assessment.

Neurocognitive timepoints varied slightly by arm, and compliance with the schedule was limited. Thus, the only meaningful analysis that could be conducted compared baseline assessments with those competed within the first 3 months of treatment. A reliable change index (RCI), representing the 90% confidence interval (CI) for test-retest variability (RCI90) was utilized to compare baseline and 3-month subtests. Cognitive decline was defined as a worsening from baseline greater than the respective RCI90 normative values on any one of the following subtests: Hopkins Verbal Learning Test–Revised (HVLT-R)[4]; Total Recall, Delayed Recall, and Delayed Recognition; Controlled Oral Word Association (COWA)[5]; or Trail Making Test Part A and B.[6] Credentialing of site personnel was required for administration of cognitive testing (J.C., J.W. or M.K.). Quality of life was assessed via 2 instruments: the EORTC 30-item core QoL questionnaire (QLQ-C30, version 3) and the 20-item EORTC brain neoplasm module (QLQ-BN20). The protocol defined schedule for cognitive testing and QoL reporting was baseline, 4–6 weeks post RT (arms A and B), or at the beginning of every other treatment cycle (arm C), then 8 weeks for 18 months, then every 12 weeks until progression.

Adverse events were evaluated with the NCI Common Terminology Criteria for Adverse Events version 3.0. Arms A and B assessments (neurological exam, neuroimaging, and blood profiles) were performed at baseline, 4–6 weeks post RT, and at the beginning of every other treatment cycle (arm C), then every 8 weeks for 18 months, and then every 12 weeks until progression. Patients who progressed were followed clinically until death. Per protocol, MRI scans were required unless contraindicated (eg, presence of pacemaker), in which case CT scans were allowed; however, in review, all patients were followed by MRI. Sites were required in advance to meet credentialing standards for RT.

Statistical Considerations

The study was powered to detect OS hazard ratio (HR) of 0.67 or less when comparing arm B to arm A. A sample size of 219 patients per arm would have 80% power with a one-sided alpha = 0.05 using a log rank test,[7] assuming the median survival for the control arm (arm A) was 7.2 years. The final OS analysis was to be performed when 178 deaths were observed. The sample size for the secondary analysis, comparing PFS between arm C and arms A and B, was to include 50 patients in arm C and 100 patients in arms A and B, performed when 75 progression events were observed. All analyses were based on the intention-to-treat principle, with all eligible patients belonging to the treatment arm to which they were randomized. The distributions of OS and PFS were estimated using the Kaplan–Meier method,[8] along with median survival and corresponding 95% CIs. The differences between Kaplan–Meier survival curves were evaluated with a log rank test. Cox models were used to generate point estimates and HRs for comparisons between arms, comparisons between IDH mutation status, and comparisons between arms while adjusting for IDH mutation status. Differences in the proportions of patients with grade 3+ adverse events among/between treatment arms were evaluated with a chi-square test. Neurocognitive analysis across the 3 arms was based on the change from baseline to the 3-month evaluation. Differences in proportions of patients with cognitive decline among/between treatment were evaluated with a chi-square test. QoL analysis across all 3 arms was based on the change from baseline to the 3-month QLQ-C30 and QLQ-BN20 evaluations. Change-from-baseline values were compared across arms using the Kruskal–Wallis test. All analyses were completed with SAS version 9.4M5.

Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center. Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson following Alliance policies. The study was monitored by the Alliance Data and Safety Monitoring Board.

Results

Thirty-six patients with 1p/19q codeleted anaplastic glioma (WHO grade III) were randomized between November 2009 and December 2011 (arm A, n = 12; arm B, n = 12; arm C,

n = 12) and included in this analysis. The North American NCI-sponsored cooperative groups accrued 19 patients (53%) and EORTC accrued 17 patients (47%). The treatment arms were balanced for age, ECOG status, and extent of resection (Table 1).

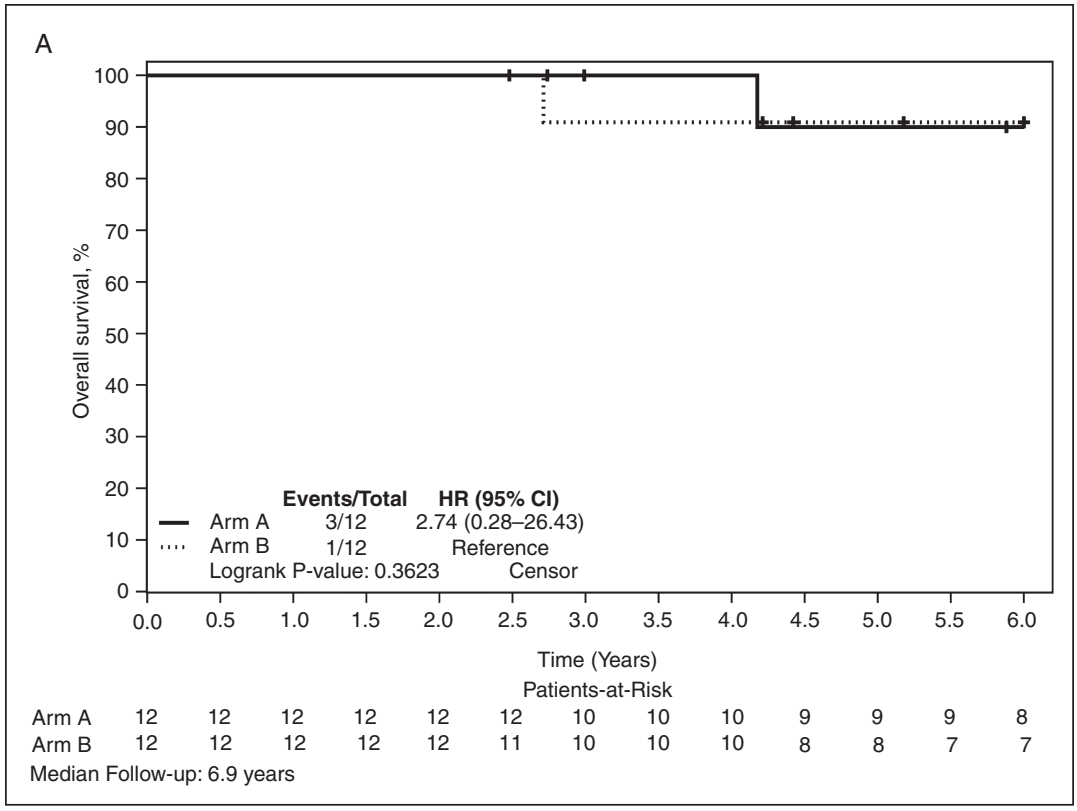
Patient Outcomes

There were 8 deaths: 3 on arm A, 1 on arm B, and 4 on arm C. The median follow-up was 7.5 years. Overall survival time (Fig. 2) was not statistically different between RT alone (arm A) and RT + TMZ (arm B) with median OS not reached in either arm (Fig. 2A); HR 2.74 (95% CI: 0.28 to 26.43 log rank *P*-value = 0.36); however, this comparison is significantly underpowered. OS difference also failed to reach statistical significance with regard to patients treated on arm C, compared with the patients on arms A and B combined (log rank *P*-value = 0.27; Fig. 2B). The median OS was not reached in either group, with observed HR 2.14 (95% CI: 0.53 to 8.61). The 3- and 5-year OS rates were 75% and 67%, respectively, for TMZ-alone arm C patients compared with 96% and 91% for patients treated with RT (arms A and B). When comparing patients treated without TMZ (arm A) versus those treated with TMZ (pooled arms B + C), there were no significant differences in PFS (median = 4.2 y vs 6.5 y, respectively; HR = 1.44, 95% CI: 0.58 to 3.60; log rank *P* = 0.43) or OS (neither reached median; HR = 1.12, 95% CI: 0.27 to 4.71; log rank *P* = 0.87).

With a median clinical follow-up of 6.6 years, there were 19 disease progression events; 10 on arm C on arm B, and 8 on arm A. Radiographic progression was listed in the case

Table 1. Patient demographics

	Arm A: RT Alone (*N* = 12)	Arm B: RT + Concomitant TMZ (*N* = 12)	Arm C: TMZ Alone (*N* = 12)
Group, *n* (%)			
EORTC	6 (50.0)	5 (41.7)	6 (50.0)
North America	6 (50.0)	7 (58.3)	6 (50.0)
Age, y			
N	12	12	12
Mean (SD)	48.3 (10.28)	48.3 (9.19)	42.5 (12.97)
Median	50.0	48.5	43.5
Range	29.0, 66.0	31.0, 64.0	18.0, 61.0
Sex, *n* (%)			
Female	3 (25.0)	6 (50.0)	2 (16.7)
Male	9 (75.0)	6 (50.0)	10 (83.3)
ECOG Performance Score, *n* (%)			
0	9 (75.0)	8 (66.7)	9 (75.0)
1	3 (25.0)	4 (33.3)	3 (25.0)
Previous Cancer, *n* (%)			
Yes	1 (8.3)	0 (0.0)	0 (0.0)
No	11 (91.7)	12 (100.0)	12 (100.0)
Site Primary Tumor, *n* (%)			
Right	6 (50.0)	8 (66.7)	9 (75.0)
Left	5 (41.7)	3 (25.0)	3 (25.0)
Bilateral	1 (8.3)	1 (8.3)	0 (0.0)
Corticosteroid Therapy at Entry, *n* (%)			
Yes	3 (25.0)	1 (8.3)	4 (33.3)
No	9 (75.0)	11 (91.7)	8 (66.7)
Extent Surgical Resection, *n* (%)			
Biopsy	0 (0.0)	1 (8.3)	2 (16.7)
Subtotal resection	6 (50.0)	6 (50.0)	4 (33.3)
Gross total resection	6 (50.0)	5 (41.7)	6 (50.0)
Prior History Brain Tumor, *n* (%)			
Yes	1 (8.3)	0 (0.0)	1 (8.3)
No	11 (91.7)	12 (100.0)	11 (91.7)



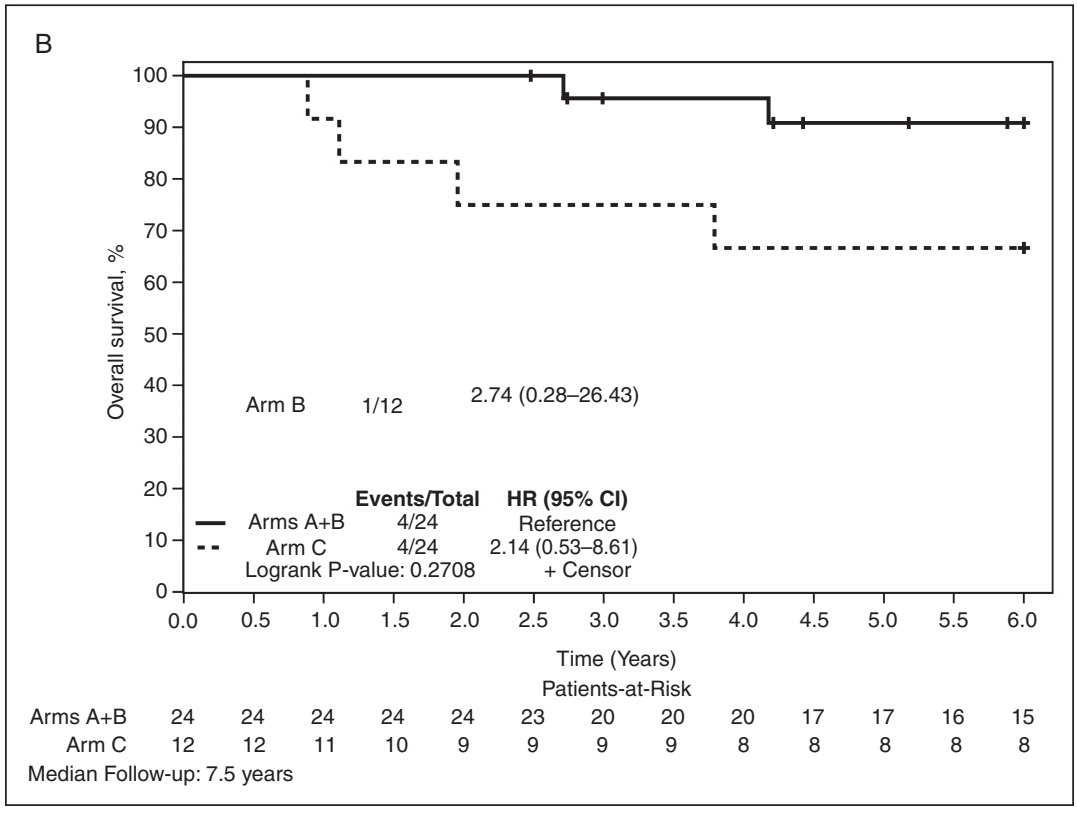


Fig. 2 (A) Overall survival arm A vs arm B. (B) Overall survival arms A + B vs arm C.

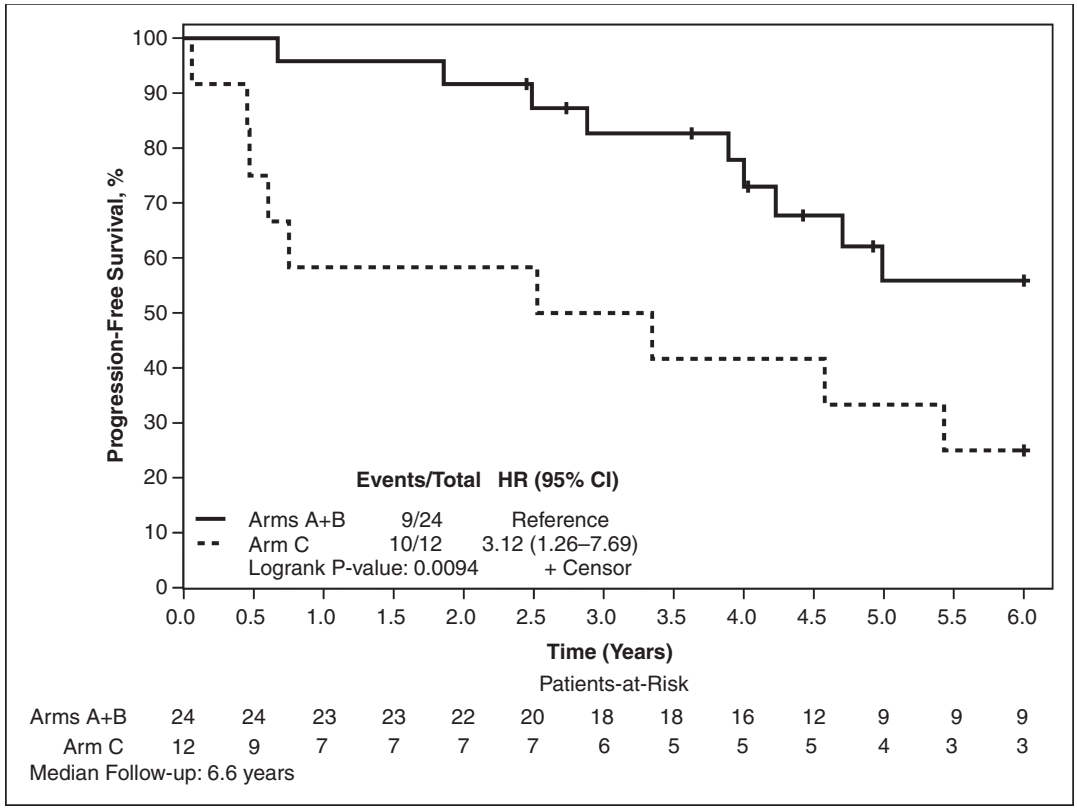


Fig. 3 Progression-free survival (arms A + B vs arm C).

report forms as the justification for determination of progression in 18 patients, with the remaining patient listed as "local brain failure and clinical progression." Median PFS (Fig. 3) was significantly shorter in TMZ alone-treated patients compared with those receiving RT (arm A + B) (2.9 y vs not reached, respectively; HR = 3.12, 95% CI: 1.26 to 7.69; log rank $P = 0.009$). The 3- and 5-year PFS rates were 50% and 33%, respectively, in the TMZ-alone treated patients compared with 83% and 56% in those receiving RT (arms A + B). There were 6 response-evaluable patients on each arm. No statistical difference ($P = 0.52$) was observed across arms for patients with a tumor response of REGR, PR, or CR lasting at least 4 weeks; there were no responses on arm A (0%), 2 responses on arm B (33%), and 1 response on arm C (17%).

All of the arm C patients who progressed on TMZ alone subsequently received RT or RT + TMZ, and 3 also underwent re-resection, all with pathologic confirmation of tumor progression. One progressing patient each on arm A and arm B underwent subsequent re-resection, both with pathologic confirmation of tumor progression.

IDH Status

Tissues from 35 of the 36 (97%) patients (arm A = 12; arm B = 11; arm C = 12) were available for IDH analysis. Of these, 30 (86%) were IDH mutated (arm A = 11; arm B = 10; arm C = 9) and 5 were IDH WT (arm A = 1; arm B = 1; arm C = 3). IDH 1 and 2 WT status was confirmed by sequencing of available tumor tissue from 2/5 of these patients; for the purposes of this analysis, the 3 remaining patients were considered IDH WT based on IHC results alone, When comparing the IDH mutated and nonmutated patients, PFS differed, but did not reach statistical significance (median = 5.4 y vs 0.8 y, respectively; HR = 0.35, 95% CI: 0.12 to 1.06; log rank $P = 0.052$), but OS differed significantly (median = not reached vs 2.0 y, respectively; HR = 0.07, 95% CI: 0.01 to 0.31; log rank $P < 0.01$). Cox regression was used to adjust for IDH mutation status. The model included IDH mutational status and radiation treatment status as covariables (arm C vs pooled arms A + B), as no significant interaction between these 2 variables was observed (OS, $P = 0.995$; PFS, $P = 0.068$). Again, PFS was shorter for patients who did not receive RT (HR = 3.33; 95% CI: 1.31, 8.45; $P = 0.011$). In the analysis of OS, RT status (arm C vs A + B) was not statistically associated with OS (HR = 2.78; 95% CI: 0.58, 13.22; $P = 0.200$).

Adverse Events

No statistical difference was observed across treatment arms with respect to the proportion of patients with at least one grade 3 or 4 adverse event (25%, 42%, and 33% on arms A, B, and C, respectively; $P = 0.69$). There was 1 patient in each arm that experienced a grade 4 event and

Table 2. Cognitive progression at 3 months

	Arm A: RT Alone (*N* = 9)	Arm B: RT + Concomitant TMZ (*N* = 11)	Arm C: TMZ Alone (*N* = 9)	Total (*N* = 29)	*P*-value
Median Days to Testing (range)	87 (84–105)	85 (73–130)	82 (59–97)	86 (59–130)	0.13[e]
Frequency of Deterioration[a]					
HVLT-R Immediate Recall, *n* (%)	1 (11.1)	1 (9.1)	1 (11.1)	3 (10.3)	0.93[d]
COWAT, *n* (%)	0 (0.0)	1 (9.1)	1 (11.1)	2 (6.9)	0.20[d]
Trail Making A, *n* (%)	1 (12.5)	0 (0.0)	3 (37.5)	4 (15.4)	0.18[d]
Trail Making B, *n* (%)	5 (71.4)	3 (33.3)	3 (42.9)	11 (47.8)	0.29[d]
HVLT-R Delayed Recall, *n* (%)	3 (33.3)	1 (9.1)	0 (0.0)	4 (14.3)	0.18[d]
HVLT-R Delayed Recognition, *n* (%)	2 (22.2)	2 (18.2)	1 (12.5)	5 (17.9)	0.24[d]
Progression Determination					
Neurocognitive Progression[b], *n* (%)	7 (77.8)	8 (72.7)	6 (66.7)	21 (72.4)	0.87[d]
Clinical Progression[c], *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	NA

RCI, reliable change index; HVLT-R, Hopkins Verbal Learning Test–Revised; COWAT, Controlled Oral Word Association Test.
[a]>RCI90 value decrease from baseline.
[b]Number deteriorating on any one subtest >RCI90 value decrease from baseline.
[c]Defined by clinical exam and/or radiographic progression at 3 months after registration.
[d]Chi-square.
[e]Kruskal–Wallis.

no grade 5 adverse events were observed. There were 2 patients on arm A, 4 patients on arm B, and 3 patients on arm C who experienced grade 3 adverse events. Two RT patients withdrew from treatment due to adverse events: 1 arm A patient with empyema requiring surgery, and 1 arm B with neutropenia. No arm C patients withdrew from treatment due to adverse events.

Cognitive Decline

Twenty-nine (81%) patients completed the full cognitive test battery assessments for the baseline and 3-month timepoints (Table 2B). Overall, there was deterioration in at least one test by >RCI90 at 3 months compared with baseline pretreatment testing in 21 patients (72%). Of the patients demonstrating cognitive decline at 3 months, none met protocol-defined criteria for clinical progression. There was no significant difference in proportions of patients who declined (arm C, 67%; arms A and B, 75% $P = 0.99$). Comparisons of individual subtests also did not yield statistically significant differences between arm C and arms A and B.

Quality of Life

QoL assessments for change from baseline to timepoint 1 (3 mo) were available for 21 patients in pooled arms A and B, and 9 in arm C. Changes from baseline to timepoint 2 were available from 14 patients in arms A + B and 6 patients in arm C. There was no statistical difference between arm A + B and arm C as measured by QLQ-C30 overall QoL. Slight increases from baseline were noted in the averages for both groups of patients at both timepoint 1 (arms A + B: 5.6 points, arm C: 4.6 points; $P = 0.89$) and timepoint 2 (arms A + B: 7.1 points, arm C: 4.2 points; $P = 0.67$). Two subscales showed statistically significant differences between arms A + B versus arm C for at least one timepoint: the QLQ-C30 subscale for constipation showed an average improvement at timepoint 1 for arm C and no change in arms A+ patients (18.5 points vs 0.0 points; $P = 0.002$). The QLQ-BN20 subscale for motor dysfunction showed an average improvement at timepoint 2 for arm C and a decline for patients in arm A + B combined (7.4 points vs –4.0 points; $P = 0.018$).

Discussion

From 1985 to 2000, many physicians recommended treatment of 1p/19q codeleted patients with RT alone, or RT + PCV. In the 2000s, there was a shift to recommendation of either chemotherapy (PCV or TMZ) or RT + TMZ,[9] which occurred in the absence of comparative data from randomized prospective trials. As of this writing, TMZ has not yet been approved by the US Food and Drug Administration for the specific indication of newly diagnosed WHO grade II or III oligodendroglioma.

The original CODEL study was designed with an RT-alone control arm, as at the time there were no conclusive data demonstrating OS benefit with the addition of PCV chemotherapy to RT compared with RT alone. At the time (2006), the initial analyses from RTOG 9402 and EORTC 26951 did not demonstrate superiority of RT + PCV (neoadjuvant or adjuvant) over RT alone.[10,11] Accordingly, the main objective of the original CODEL study was to determine whether the addition of TMZ to RT might result in superior survival compared with RT alone, when (at the time) the addition of PCV to RT had not.

The original CODEL design became obsolete after mature analyses from RTOG 9402 and EORTC 26951 showed inferior survival with RT alone compared with RT + PCV.[1,2] Both randomized trials suggested that 1p/19q codeletion predicted benefit to addition of chemotherapy. More recent reports suggest that O^6-methylguanine-DNA methyltransferase gene promoter hypermethylation and IDH mutation may be superior predictive factors.[12,13] The current WHO 2016 classification requires that both 1p/19q codeletion and IDH mutation be present for a diagnosis of oligodendroglioma.[14]

The authors acknowledge the limitations of this study. The current analysis involved a small sample size, and comparisons are likely underpowered. It is noted that central confirmation of radiographic progression was not performed, although the specific reasons for determination of progression were reviewed as documented in the protocol case report forms for each patient. We cannot completely exclude introduction of bias regarding timing of progression; however, this is felt unlikely. In review of the case report forms, radiographic progression was listed as the determining cause for all progressing patients except the latter progressing due to "local brain failure and clinical progression." Furthermore, the definition of progression was clearly protocol specified; the NCI Cooperative Group, CCTG, and EORTC site investigators are experienced in clinical trial conduct; and several different centers accrued patients to the different treatment arms.

With these caveats in mind, our data showed that treatment with TMZ alone was associated with earlier time to tumor progression and significantly shorter PFS compared with radiotherapy (RT and RT + TMZ). Although the observed median PFS of 2.9 years for newly diagnosed codeleted patients treated with TMZ alone appears shorter than expected, it is similar to that previously reported in retrospective or prospective studies involving 1p/19q codeleted patients treated with TMZ alone (Table 3).[15–19] Given our data and prior reports indicating median PFS of 8.4–12.8 years with RT + PCV,[1,2] the Alliance Data Monitoring Committee and NCI recommended closure of the TMZ-alone arm in CODEL as it was felt that it would be unlikely that patients treated with TMZ alone would experience superior survival than those treated on the RT arms. Although OS was longer on the RT-containing arms, it did not achieve statistical significance, but this comparison was underpowered. It is also possible that OS curves converged in part due to subsequent treatment, given that all patients treated with TMZ alone received RT-containing regimens at relapse. Based on these data and prior phase III results, the ongoing CODEL trial has been redesigned as a 2-arm comparison of RT followed by adjuvant PCV (control, based on RTOG 9402 and EORTC 26951) versus RT with concomitant and adjuvant TMZ, with PFS as the primary endpoint.

We did not find significant differences in cognitive function between treatment arms at 3 months, but the number of patients tested was small and hence comparisons are underpowered. The lack of later assessment points precludes meaningful conclusions. Comprehensive mandatory serial cognitive and QoL assessments are required in the ongoing CODEL study, which we hope will clarify the comparative toxicities of RT + PCV versus RT + TMZ. The comparative toxicities of PCV chemotherapy alone versus RT + PCV may also be clarified in the ongoing POLCA study (NCT02444000).

In the original CODEL design, IDH status was not required for eligibility. We were able to retrospectively identify IDH status in 35/36 (97%) patients; 30 (86%) were IDH mutated (arm A = 11; arm B = 10; arm C = 9) and 5 were IDH WT (arm A = 1; arm B = 1; arm C = 3). One might expect that IDH WT 1p/19q codeleted patients would show earlier progression than IDH mutated patients, but when adjusting for IDH mutation status (WT vs mut), treatment with RT (arms A and B vs C) remained significantly associated with longer PFS (HR = 3.33; 95% CI: 1.31, 8.45; $P = 0.011$), and no significant interaction was observed between IDH mutation status and treatment with RT ($P = 0.068$). One potential reason for this apparent discordance may be that only 2 of our 5 patients had confirmation of IDH WT status, as determined initially by IHC, with subsequent sequencing. It has been reported that almost all 1p/19q codeleted oligodendroglial

Table 3. Progression outcome following initial chemotherapy alone: patients with newly diagnosed, 1p/19q codeleted anaplastic oligodendrogliomas

Authors	Study Type	*N*	Initial Treatment	Median PFS or Median TTP, y
Lassman et al[15]	Case Series	124	TMZ	3.3
			PCV	7.6
Mikkelsen et al[16]	Case Series	36	TMZ	2.4
Thomas et al[18]	Phase II	33	TMZ → ASCT[b]	5
Wick et al[19,a]	Phase III	17	TMZ	4.5
		16	PCV	9.4

AO, anaplastic oligodendroglioma; AOA, anaplastic oligoastrocytoma; HDC-ASCT, high dose chemotherapy with autologous stem cell transplant; TTP, time to progression.
[a]1p/19q codeleted, CpG island methylator phenotype + patients.
[b]Responders to TMZ subsequently received ASCT.

tumors show IDH 1 or 2 mutations by sequencing, and thus it is theoretically possible that IDH WT, as determined by IHC, represented false negatives in our 3 patients. Nevertheless, we did observe significant differences in OS of codeleted patients as a function of IDH status. Given the 2016 WHO definition of oligodendroglioma now requires both 1p/19q codeletion and IDH mutation for diagnosis,[14] it is reasonable to consider the rare, 1p/19q codeleted, IDH WT patients as a separate cohort for future trials. In accord with the 2016 WHO definition, both 1p/19q codeletion and IDH mutation are now required as eligibility criteria in the ongoing CODEL study.

It is acknowledged that certain patients with 1p/19q codeleted, IDH mutated tumors, even when treated with TMZ alone, can exhibit indolent disease.[12,21,22] It has been postulated that such variation in biological behavior may in part be explained by additional genomic alterations within 1p/19q codeleted tumors. The presence of 9p21, loss, 14q loss, or *MYC* activation has been associated with unfavorable outcome in patients with 1p/19q codeleted tumors.[21] Conversely, overexpression of neuronal intermediate progenitor proteins has been associated with more indolent behavior.[22] It is expected that the comprehensive correlative multi-omics analyses which are part of the ongoing CODEL study might identify new biomarkers that delineate prognostic subgroups and identify important new potential therapeutic targets for future clinical trials involving this patient population.

Conclusions

We found that treatment with TMZ alone of newly diagnosed patients with 1p/19q codeleted WHO grade III oligodendroglial tumors was associated with significantly inferior PFS compared with RT. When combined with prior reported data,[1,2] our results support the assertion that the current standard of care for newly diagnosed patients with 1p/19q codeleted anaplastic gliomas should include both radiation and chemotherapy. The ongoing CODEL trial should establish the comparative efficacy and toxicity of RT plus adjuvant PCV versus RT plus concomitant and adjuvant TMZ, and the integrated correlative molecular analyses may identify prognostic subgroups and new therapeutic targets for this population.

Supplementary Material

Supplementary data are available at *Neuro-Oncology* online.

Keywords

CODEL | 1p/19q | codeleted | N0577 | oligodendroglioma

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