Reference #1

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Biology Over Monotherapy: Mature Results From European Organisation For Research and Treatment of Cancer 22033-26033 Reaffirm Molecular Stratification, Not Treatment Sequence, Defines Prognosis in Low-Grade Glioma

Authors: Ariel E. Marciscano, MD, and Helen A. Shih, MD, MS, MPH, AM, FASTRO AUTHORS INFO & AFFILIATIONS

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ACCOMPANYING ARTICLE

ORIGINAL REPORTS

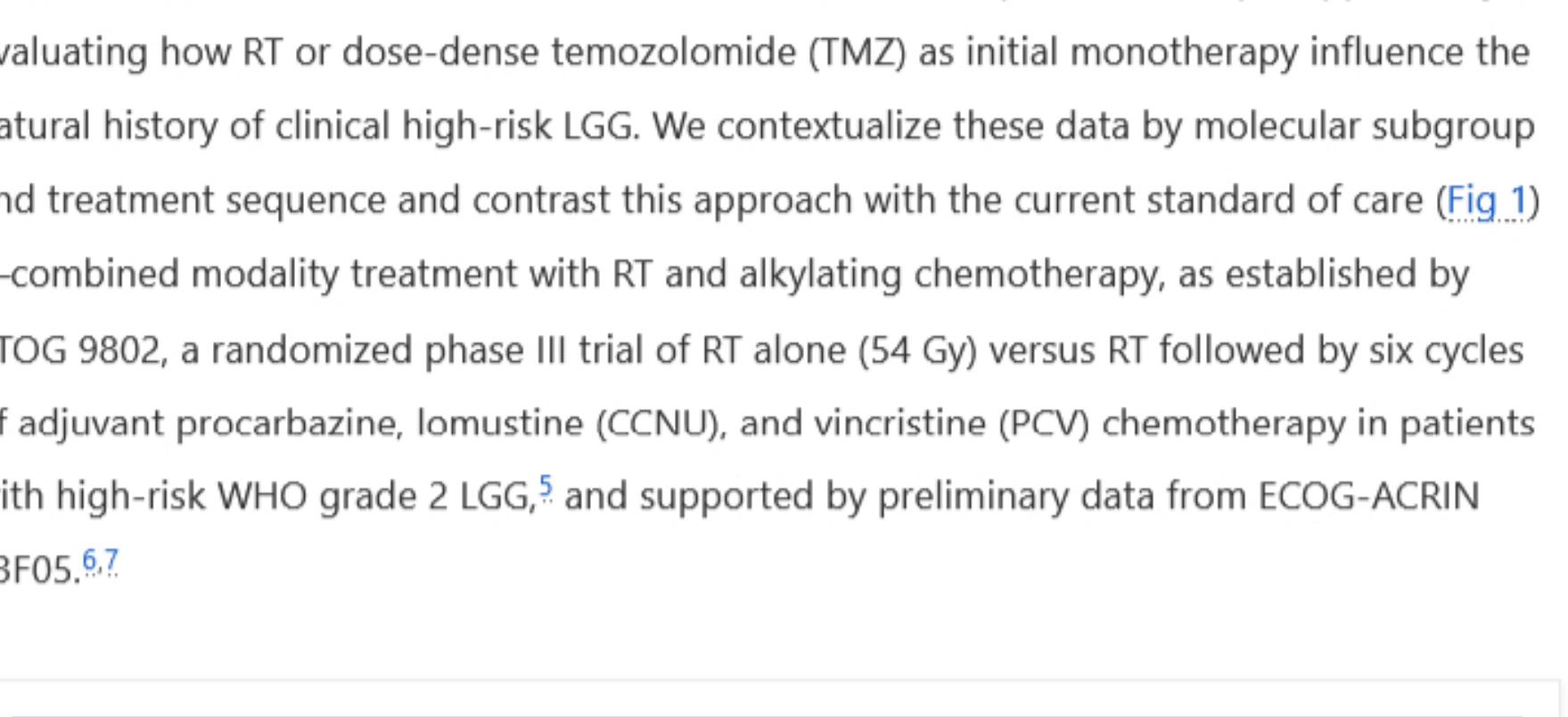
Temozolomide Versus Radiotherapy as First-Line Therapy for Low-Grade Glioma: Mature Results of a Randomized Phase III Trial (EORTC 22033-26033/NCIC-CTG/TROG/MRC-CTU)

Determining optimal treatment selection and timing for patients with low-grade glioma (LGG) remains one of the most complex clinical decision frameworks in neuro-oncology. This challenge stems from a heterogeneous patient population with generally favorable prognosis requiring careful balance of optimizing therapeutic efficacy and long-term survivorship with minimization of treatment-related toxicity. In parallel, advances in the understanding of glioma biology over the past two decades have prompted successive iterations of the WHO classification of CNS tumors. The landmark 2016 WHO CNS classification formally incorporated molecular genetic features—including isocitrate dehydrogenase (*IDH*) mutation and 1p/19q codeletion status—officially ushering in the molecular era of glioma.[1] The current 2021 WHO classification further leverages molecular stratification through integrated diagnostic criteria that define biologically and prognostically distinct subsets of LGG.[2] This progress also introduces complexity in the interpretation of trials designed and conducted before the molecular era.

The Takeaway

In the article that accompanies this editorial, Baumert et al[4] report the mature analysis of European Organisation For Research and Treatment of Cancer 22033-26033, a randomized phase III trial with a median follow-up of 13 years, that examined radiotherapy (RT) versus dose-dense temozolomide as up-front treatment in a cohort of 478 patients with clinical high-risk WHO grade 2 glioma and observed no significant difference in progression-free survival or overall survival in the intent-to-treat (ITT) population. Post hoc stratification by 2021 WHO criteria (available in 73% of ITT population) demonstrated that molecular classification was more prognostic of long-term survival than any predictive impact of either monotherapy which does not displace the currently established standard of combined modality treatment with RT and alkylating chemotherapy for these patients.

European Organisation For Research and Treatment of Cancer (EORTC) 22033-26033, a randomized open-label phase III trial comparing up-front dose-dense TMZ versus radiotherapy (RT; 50.4 Gy) among patients with clinical high-risk WHO grade 2 LGG (Fig 1), reflects this dynamic landscape as it was conceptualized in the early 2000s and accrued between 2005 and 2012 during a transitional period in which molecular classification was evolving and alkylating chemotherapy was reaffirmed as an active agent in glioma.[3] To this point, EORTC 22033-26033 was the first randomized glioma trial to prospectively incorporate a molecular feature (ie, 1p deletion) as a stratification factor. With a median follow-up of 13 years and mature survival data now available, Baumert et a[4] provide a unique opportunity for evaluating how RT or dose-dense temozolomide (TMZ) as initial monotherapy influence the natural history of clinical high-risk LGG. We contextualize these data by molecular subgroup and treatment sequence and contrast this approach with the current standard of care (Fig 1)—combined modality treatment with RT and alkylating chemotherapy, as established by RTOG 9802, a randomized phase III trial of RT alone (54 Gy) versus RT followed by six cycles of adjuvant procarbazine, lomustine (CCNU), and vincristine (PCV) chemotherapy in patients with high-risk WHO grade 2 LGG,[5] and supported by preliminary data from ECOG-ACRIN E3F05.[6,7]


EORTC 22033-26033
N = 478 | 78 sites | 19 countries
WHO grade 2 glioma (2000 criteria)
Astrocytoma, oligodendroglioma, OA
Clinical high-risk (≥1 EORTC high-risk features)
Clinically/radiographically progressive, uncontrollable seizures, requiring additional txt
1:1 random assignment
Stratification
1p loss
Contrast-enhancement on MRI
Age < v ≥ 40 yrs
Institution
Standard radiotherapy (n = 240)
50.4 Gy in 28 fractions
68% crossover at progression
Dose-dense temozolomide (n = 238)
each cycle of 75 mg/m² once daily for 21 days followed by 7 days of no treatment, ≤12 cycles
Current Standard of Care for High-Risk LGG→ Combined Modality = Radiotherapy + Alkylating Chemotherapy
RTOG 9802
RT vs RT→PCV (N = 251)
WHO grade II glioma (1993 criteria)
Astrocytoma, oligodendroglioma, OA
Clinical high-risk (RTOG definition)
Age <40 yr with STR/biopsy
Age ≥40 yr any EOR
ECOG-ACRIN E3F05ᵃ
RT v RT+TMZ→TMZ (N = 172)
WHO grade 2 glioma (2007 criteria)
Astrocytoma, oligodendroglioma, OA
Clinical high risk (≥1 high-risk feature)
Age >40 yr, uncontrolled symptoms/seizures, progression after initial observation

Molecular Reclassification 2021 WHO Criteria n = 351/478 (73% evaluable)		mPFS	mOS	10-yr OS
Oligodendroglioma (n = 109) IDHmt / 1p19q codeleted	RT	4.6 years	12.9 years	57.9%
	TMZ	5.4 years	14.9 years	64.3%
Astrocytoma (n = 178) IDHmt / 1p19q non-codeleted	RT	4.0 years	6.6 years	32.4%
	TMZ	3.0 years	6.7 years	27.6%
IDH-wildtype NOS (n = 64)	RT	1.6 years	2.5 years	5.9%
	TMZ	2.2 years	4.7 years	27.6%

ITT Population per High-Risk LGG RCT	mPFS	10-yr PFS	mOS	10-yr OS	mFUP
TMZ EORTC 22033-26033	3.1 yrs	13.4%	8.0 yrs	40.0%	13 yrs
RT EORTC 22033-26033	3.6 yrs	14.4%	6.6 yrs	35.1%	13 yrs
RT RTOG 9802	4.4 yrs	21%	7.8 yrs	40%	11.9 yrs
RT ECOG-ACRIN E3F05	NR	NR	NR	47%	9.75 yrs
RT+PCV RTOG 9802	10.4 yrs	51%	13.3 yrs	60%	11.9 yrs
RT+TMZ ECOG-ACRIN E3F05	NR	NR	NR	70%	9.75 yrs

RTOG 9802: post hoc analysis of IDH-mutant high-risk LGG benefit from RT→PCV regardless of codeletion status
ECOG-ACRIN E3F05: 10-yr OS: IDHmt / 1p19q non-codeleted, 39% (RT alone) vs 80% (RT+TMZ→TMZ) (HR = 0.15); IDHmt/1p19q codeleted, 68% (RT alone) v 90% (RT+TMZ→TMZ) (HR = 0.51)

Fig 1. EORTC 22033-26033 and the treatment landscape of high-risk low-grade glioma. [a]Only published in abstract form, closed because of RTOG 9802 interim analysis of RT → PCV benefit. EOR, extent of resection; EORTC, European Organisation For Research And Treatment of Cancer; Gy, Gray; HR, hazard ratio; *IDH*, isocitrate dehydrogenase; ITT, intention-to-treat; LGG, low-grade glioma; mFUP, median follow up; mOS, median overall survival; mPFS, median progression-free survival; MRI, magnetic resonance imaging; mt, mutant; NOS, not otherwise specified; NR, not reported; OA, oligoastrocytoma; OS, overall survival; PCV, procarbazine, lomustine (CCNU), vincristine; PFS, progression-free survival; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; STR, subtotal resection; TMZ, temozolomide; txt, treatment.

The EORTC 22033-26033 investigators successfully reclassified 73% of enrolled patients (351 of 478) per 2021 WHO criteria, generating the largest and most robust molecularly defined WHO grade 2 LGG cohort to date. For context, the high-risk arm of RTOG 9802 enrolled 251 patients, with only 42% of tumor specimens able to be reclassified for subsequent molecular analyses.[5,8] With mature survival data, the topline message from the intent-to-treat population remains consistent with the earlier report that there are no significant differences in progression-free survival (PFS) or overall survival (OS) for patients treated with up-front RT or TMZ.[9] A nuanced interpretation is warranted as the impetus for this study was to evaluate whether RT could be deferred in favor of chemotherapy without compromising survival in an attempt to mitigate neurotoxicity and other late sequelae related to RT. Importantly, at progression, approximately two thirds of patients in each arm crossed over to the other modality—specifically, 68% of up-front TMZ patients received salvage treatment with RT or chemoradiotherapy. The substantial proportion of patients with crossover confounds interpretation of OS, particularly given the availability of effective salvage therapy in a disease with a long natural history such as LGG. From a practical standpoint, it is reassuring for clinicians that each modality retains efficacy as a salvage option after progression on either chemotherapy or RT. This has led to a notion that selection of up-front treatment modality and sequencing may be individualized for patients appropriate for monotherapy. What remains unanswered by EORTC 22033-26033 is the relative limitation of monotherapy when compared with the superior outcomes achieved using combined modality approaches.

Acknowledging the caveats of cross-trial comparisons, RTOG 9802 demonstrated a clinically meaningful improvement in both PFS and OS with the addition of alkylating chemotherapy (PCV) to RT, establishing the contemporary foundation for management of higher-risk LGG.[5] Preliminary results from ECOG-ACRIN E3F05, a randomized phase III study of RT alone (54 Gy) versus RT with concurrent/adjuvant TMZ, presented in abstract form, suggest a similarly striking benefit of adding chemotherapy to RT. Notably, accrual for ECOG-ACRIN E3F05 was stopped early at 32% of the intended sample size for ethical considerations as RTOG 9802 contemporaneously established a clear survival benefit for combined modality therapy over monotherapy.[6,7] Collectively, these data support the concept that up-front treatment intensification with combined modality therapy is superior to sequential treatment delivered at time of progression. As we enter the molecular genetic era, it will be increasingly important to understand how each treatment alters the tumor ecosystem, how this influences the efficacy of subsequent lines of therapy, and what mechanisms underlie combinatorial efficacy.[10-12] This is particularly relevant to *IDH*-mutant glioma, where the recent regulatory approval of vorasidenib represents the first molecularly guided approach for this disease with ongoing efforts to define the optimal integration and sequencing with RT and chemotherapy in the clinic.[13]

The molecular subgroup analyses of EORTC 22033-26033 (Fig 1) provide the most instructive findings of this report. Across both *IDH*-mutant subgroups, initial treatment modality exerted no significant effect on OS, reinforcing that molecular biology is the primary determinant of outcome in *IDH*-mutant LGG. The established chemosensitivity and radiosensitivity of oligodendroglioma (*IDH*mt/codeleted) are reflected in the favorable median OS achieved with both RT and TMZ (12.9 *v* 14.9 years), confirming that initial treatment sequencing is of limited consequence in this population when combined modality therapy is not used. In astrocytoma (*IDH*mt/non-codeleted), the numerically longer PFS with up-front RT (4.0 *v* 3.0 years) despite equivalent OS likely reflects effective TMZ salvage after RT failure. Within the IDH-wildtype NOS subgroup, the apparent OS advantage with TMZ over RT (4.7 *v* 2.5 years) must be interpreted cautiously given the small sample size (n = 64) and biological heterogeneity.

Traditionally, age >40 years has been incorporated as a criterion to define clinical high-risk LGG, used in both the Pignatti scoring system[14] and the RTOG high-risk LGG criteria that defined eligibility for RTOG 9802. However, whether older age retains prognostic relevance in the molecular era or merely serves as a crude surrogate for *IDH*-wildtype biology remains an open question. When excluding this *IDH*-wildtype subset, age loses prognostic significance among *IDH*-mutant populations, with older patients demonstrating superior outcomes. Moreover, if the historical basis of age-based risk stratification reflects contamination by *IDH*-wildtype tumors rather than a true biological signal, then the RTOG high-risk definition and the trial populations defined by these criteria likely enrolled biologically and prognostically heterogeneous cohorts obscuring the treatment effect and outcome signals. Validation in independent molecularly annotated data sets is warranted and may facilitate development of novel definitions and criteria for high-risk *IDH*-mutant LGG for use in future trials.

A key hypothesis for testing up-front TMZ was that it may better preserve neurocognition and health-related quality of life (HRQoL) relative to RT. These investigators were highly attuned to these patient-centric considerations, which are of importance in LGG, a disease predominantly affecting younger adults with potential for decades of survivorship. Prior reports from this trial found no significant differences in HRQoL, memory, or global cognitive function within the first 3 years between arms and also noted that early HRQoL declines were more often associated with tumor progression rather than with volume of irradiated brain tissue.[15-17] More than 80% of patients received 3-dimensional conformal RT, whereas more modern techniques and modalities such as intensity-modulated RT, volumetric-modulated arc therapy, and proton RT are increasingly used in contemporary practice to mitigate neurotoxicity risks.[18] The available evidence from EORTC 22033-26033 therefore does not substantiate selection of up-front TMZ over RT on the basis of neurotoxicity concerns. Nevertheless, late cognitive effects remain a legitimate concern. A longitudinal study of LGG patients treated with RT demonstrated decline in attention and executive function at a median follow-up of 12 years—deficits that were not apparent at earlier time points and noting that RT techniques and treatment volumes reflect clinical practice in the 1990s.[19] With a median follow-up of 13 years, EORTC 22033-26033 is ideally positioned to evaluate long-term HRQoL and neurocognitive outcomes by modality; however, attrition of follow-up assessments limits conclusions beyond 3 years. Serious late effects were low in both arms, 1.3% with TMZ and 4.2% with RT, including high-grade hematologic toxicity (eg, lymphoma, myelodysplastic syndrome) with TMZ and predominantly neurocognitive/neurovascular (eg, cognition, memory impairment) toxicity with RT. Although preservation of neurocognition was a primary justification for up-front TMZ versus RT, the reporting of comprehensive long-term neurocognition remains an undercharacterized aspect of this mature data set.

The long-term update of EORTC 22033-26033 confirms that molecular subtype, rather than treatment sequence, is the chief determinant of clinical outcomes. The comparably inferior survival benchmarks of both monotherapy arms serve as a compelling reminder that combined modality therapy remains the standard against which future approaches should be measured for high-risk *IDH*-mutant LGG. As the field further refines molecular risk stratification and advances toward biology-guided treatment paradigms, the insights offered in this mature EORTC 22033-26033 data set will continue to shape how we select, sequence, and individualize treatment for patients with *IDH*-mutant LGG.

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Authors' Disclosures of Potential Conflicts of Interest

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Helen A. Shih

Employment: Mass General Brigham, Elliot Hospital, Manchester, NH (I)

Honoraria: UpToDate (less than $10,000 USD in a single calendar year), MedLink Neurology (less than $10,000 USD in a single calendar year)

Consulting or Advisory Role: Advanced Accelerator Applications/Novartis (less than $10,000 USD in a single calendar year), SERVIER (less than $10,000 USD in a single calendar year), Novocure (less than $10,000 USD in a single calendar year)

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Other Relationship: UpToDate, SERVIER, Cancer (journal)

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