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CORRESPONDENCE

Phosphorylated mTOR immunohistochemistry–guided use of temsirolimus in recurrent IDH-wildtype glioblastoma: a real-world retrospective series

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Glioblastoma (isocitrate dehydrogenase [IDH]–wild-type) almost invariably recurs, and evidence-based options at progression remain limited (Wen et al. 2020). After failure of temozolomide, lomustine (chloroethyl-cyclohexyl-nitrosourea [CCNU]) is commonly used, and benefit from alkylating chemotherapy is enriched in tumors with O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation (Wen et al. 2020; Hegi et al. 2005). In randomized trials, bevacizumab improves symptoms and progression-free survival (PFS) but not overall survival (OS) in recurrent glioblastoma (Wick et al. 2017). The phase 2 REGOMA trial reported longer OS with regorafenib than with lomustine (Lombardi et al. 2019). However, in the phase 3 adaptive Glioblastoma Adaptive Global Innovative Learning Environment (GBM AGILE) platform, the regorafenib arm was stopped for futility and did not improve OS in either newly diagnosed MGMT-unmethylated or recurrent glioblastoma, tempering the REGOMA signal (Wen et al. 2023). Against this backdrop, biomarker-guided inhibition of the mechanistic target of rapamycin (mTOR) is compelling: in the phase 1/2 N^2M^2 umbrella trial of newly diagnosed, MGMT-unmethylated glioblastoma, the temsirolimus subtrial met its primary endpoint (PFS at 6 months, 39.1%) under a prospectively defined mTOR-activation selection strategy (Wick et al. 2025). Safety findings in the temsirolimus subtrial were consistent with prior experience, with infections and hematologic events predominating (Wick et al. 2025).

To explore the clinical translation of these findings in recurrent glioblastoma (GBM), we conducted a single-center retrospective evaluation at the University Hospital Essen between 2017 and 2023. Tumor tissue from the primary or recurrent tumor was assessed for phospho-mTOR (Ser2448) expression by immunohistochemistry. Tumors with > 10% phospho-mTOR-positive tumor cells were considered eligible for individualized treatment planning with

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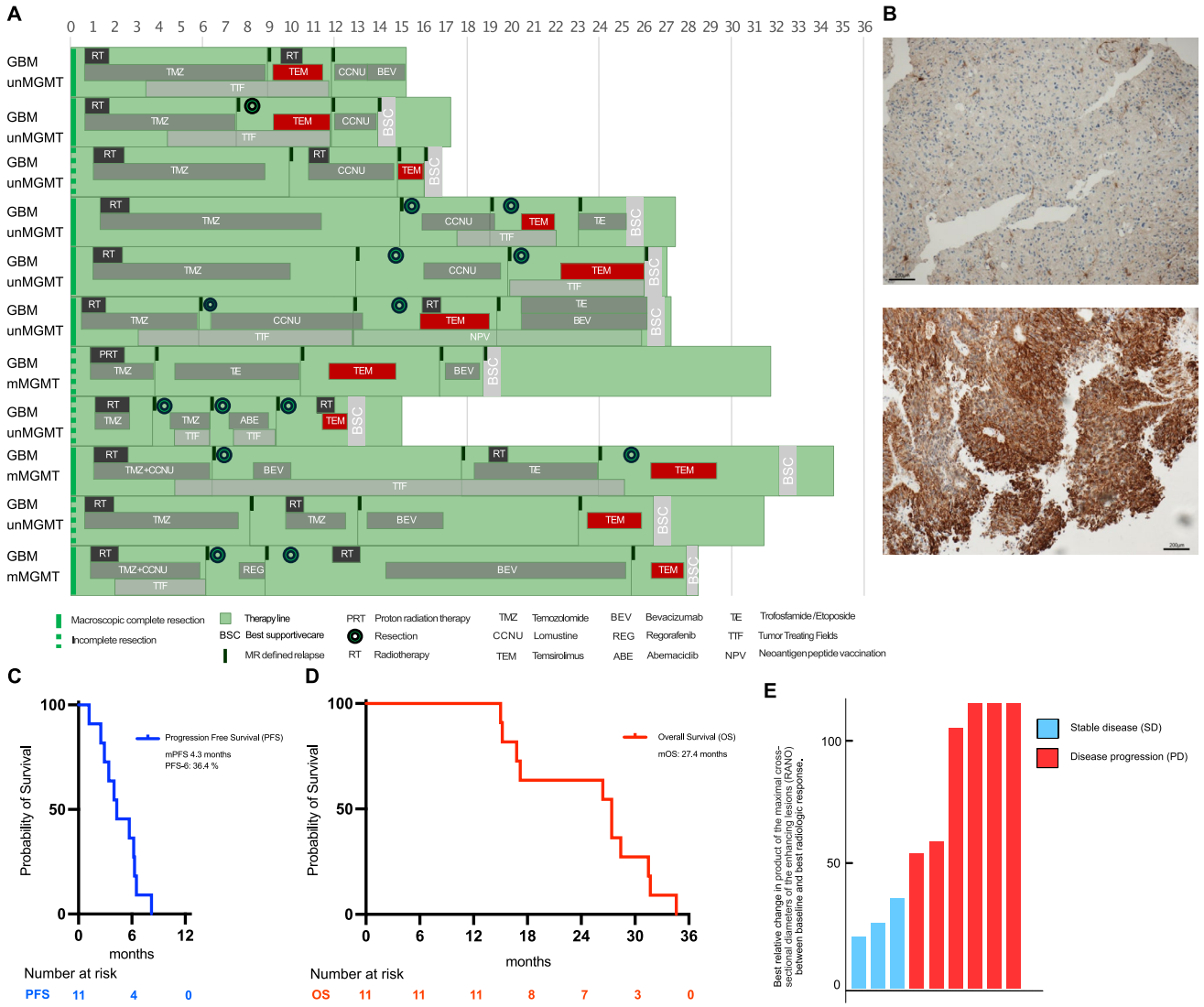

Fig. 1 Temsirolimus in recurrent glioblastoma **A** Treatment timelines for glioblastoma patients. **B** Immunohistochemistry staining with phospho-mTOR antibody Ser2448 (positivity cut-off: > 10%) demonstrating no phosphorylated mTOR activation (top) and positivity in 70% (bottom). **C** Kaplan–Meier analysis of PFS. **D** Kaplan–Meier analysis of OS. **E** Best radiologic response assessment during temsirolimus treatment

temsirolimus. Because this was a retrospective real-world study, the biomarker assessment should not be interpreted as a prospectively batch-standardized assay. Treatment was initiated only after approval of health insurance coverage. Temsirolimus was administered at 25 mg intravenously once weekly with standard premedication.

The endpoints were PFS, measured from temsirolimus initiation, and OS, measured from initial diagnosis, with radiologic assessment according to Response Assessment in Neuro-Oncology (RANO) criteria (Wen et al. 2010). The study was approved by the local ethics committee (23–11440-BO).

Eleven patients received temsirolimus at recurrence (Fig. 1A). The median age at initial diagnosis was 55.7 years (range, 28 to 64). Gross total resection was performed in 64% of cases (7 of 11 patients), and partial resection was performed in 37% (4 of 11 patients). MGMT promoter methylation was present in 3 of 11 patients (27.3%) by pyrosequencing in primary tumor tissue, using a prespecified cutoff of at least 9% methylation.

Temsirolimus was initiated as second-line therapy in two patients, as third-line therapy in five, and as fourth-line therapy in four. Temsirolimus was administered as monotherapy (n = 4) or in combination with surgery (n = 4), radiotherapy (n = 1), or both surgery and radiotherapy (n = 2; Fig. 1A). Figure 1B shows representative examples of low and high phospho-mTOR staining and should not be interpreted as a cohort-level screening distribution. The median

Karnofsky Performance Status (KPS) at treatment initiation was 70 (range, 50 to 90). The median PFS was 4.3 months (range, 1.2 to 8.2 months; Fig. 1C), PFS-6 of 36.45% and the median OS from initial diagnosis was 27.4 months (range, 15.0 to 34.6 months; Fig. 1D). By RANO criteria, the best radiologic response among nine evaluable patients was stable disease in three (33%) and progressive disease in six patients (67%); two patients had no evaluable imaging because source scans were unavailable (Fig. 1E) (Wen et al. 2010). Grade 3 or higher adverse events, assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, occurred in 7 of 11 patients (64%); most were hematologic—lymphocytopenia and thrombocytopenia—or cholestatic—elevation of gamma-glutamyltransferase—and were attributed to temsirolimus.

Despite the small size and single-center nature of this series, the findings support the feasibility and acceptable tolerability of temsirolimus in patients with recurrent glioblastoma. The observed median PFS of 4.3 months and a PFS-6 rate of 36.45% indicate a clinically meaningful signal of activity when viewed in the context of currently established therapies for recurrent disease. In cross-trial comparisons, these outcomes appear favorable relative to those reported for regorafenib in the REGOMA trial (PFS-6: 16.9%) and lomustine (PFS-6: approximately 6–25%), and fall within the range described for bevacizumab administered as monotherapy or in combination regimens (PFS-6: 25–63.7%) (Wick et al. 2017; Lombardi et al. 2019; Taal et al. 2014; Wen 2025).

Treatment decisions were guided by immunohistochemical evaluation of primary tumor tissue. The present retrospective series does not establish screening feasibility for a prospective biomarker-driven trial; this will require prospective reporting of the number assessed, biomarker prevalence, and reasons for non-treatment. In addition, potential temporal and treatment-related tumor evolution, including dynamic changes in mTOR pathway activation, were not assessed and warrant further investigation. The retrospective design precluded evaluation of intratumoral target engagement, including paired on-treatment assessment of phospho-mTOR signaling after temsirolimus exposure. Prospective window-of-opportunity studies with timed preoperative dosing, paired tumor sampling, and pharmacokinetic analyses are required to determine intratumoral pathway inhibition in recurrent glioblastoma. The frequent use of combination therapies may also have contributed to the observed outcomes.

While these limitations are inherent to the retrospective design and treatment heterogeneity, the present data provide a rationale for further prospective evaluation. Controlled clinical trials are needed to more definitively establish the role of temsirolimus in the treatment of recurrent glioblastoma.

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Data availability All data supporting the findings of this study are available within the article file and from the corresponding author upon reasonable request.

Declarations

Conflicts of interest Teresa Schmidt received honoraria and travel support from Novocure.
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Ethics approval The study was conducted in accordance with the Declaration of Helsinki, and the study was ap-proved by the local ethics committee, Ethics-Commission, Medical Faculty, University of Duisburg-Essen, 23–11440-BO, 8 November 2023.

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