

# Neuro-Oncology Advances

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## Brief Communication

### TERT promotor status does not add prognostic information in IDH-wildtype glioblastomas fulfilling other diagnostic WHO criteria: A report of the RANO resect group

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In *IDH*-wildtype glioblastomas which meet the histopathological or molecular diagnosis criteria, it remains unclear whether the presence of *TERT* promotor mutations provides additional prognostic information. Based on a multicenter cohort of 466 *IDH*-wildtype glioblastomas (including 396 with and 70 patients without *TERT* promotor mutations), we found that *TERT* promotor mutations were neither associated with progression-free survival nor overall survival. This held true in various treatment-based or molecular subgroups. This argues against standardized analysis for *TERT* promotor mutation status for the purpose of prognostic or therapeutic relevance in newly diagnosed *IDH*-wildtype glioblastoma that otherwise meets the histopathological and molecular diagnosis criteria.

The WHO 2021 classification restricts the diagnosis of “glioblastoma WHO grade 4” to *IDH*-wildtype astrocytic gliomas either with (1) classical histopathological hallmarks or (2) qualifying molecular features.<sup>1</sup> The latter include *EGFR* amplification, +7–10 genotype, and *TERT* promotor mutation which

are all associated with less favorable outcome when observed in combination with *IDH*-wildtype status.<sup>2,3</sup> The presence of one of these three markers allows the diagnosis of “molecular” glioblastoma even when tumors appear histologically lower grade, and 80% of glioblastomas exhibit *TERT* promotor mutations.<sup>4</sup> Whether *TERT* promotor mutations are of prognostic value in *IDH*-wildtype glioblastomas which otherwise yet fulfill the diagnostic (histopathological or molecular) criteria for glioblastoma is unclear. Here, we explored such an association based upon a well-annotated glioblastoma cohort from 7 international neuro-oncological centers participating in the RANO resect group.

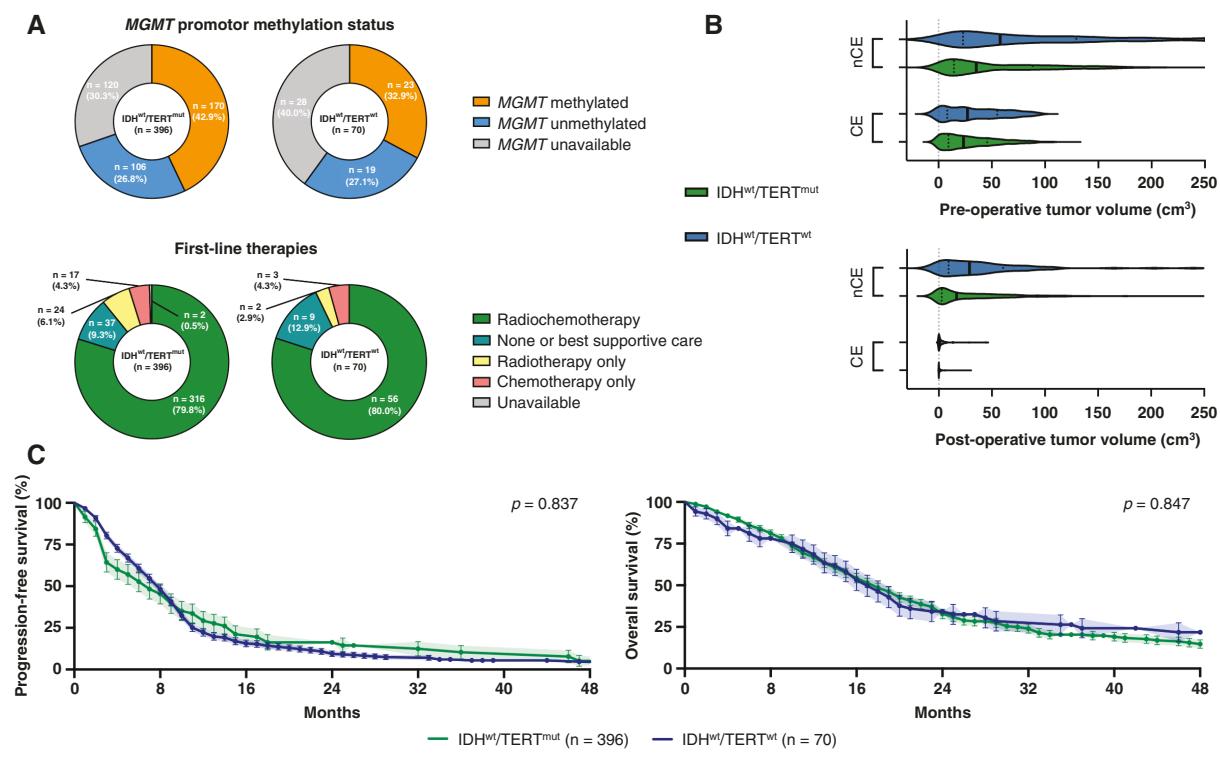
With approval of the ethics committee of the Ludwig-Maximilians-University (Munich, Germany; AZ-21-0996), the RANO resect group compiled a retrospective database of newly diagnosed *IDH*-wildtype glioblastomas treated between 2003 and 2022 with a follow-up of ≥3 months.<sup>5</sup> For the current study, individuals were selected when information on

*TERT* promotor mutation status was available for review. Demographics, molecular information, clinical data, and outcome were extracted; and date of progression was determined *per RANO* criteria.

Among 1008 *IDH*-wildtype glioblastomas WHO grade 4, *TERT* promotor status was available in 466 patients including 396 individuals with (*IDH*<sup>WT</sup>/*TERT*<sup>MUT</sup>) and 70 patients without *TERT* promotor mutations (*IDH*<sup>WT</sup>/*TERT*<sup>WT</sup>). Diagnosis rested upon *IDH*-wildtype combined with histopathological findings in 372 *IDH*<sup>WT</sup>/*TERT*<sup>MUT</sup> (93.9%) and 65 *IDH*<sup>WT</sup>/*TERT*<sup>WT</sup> patients (92.9%); and was established based on the molecular signature (*TERT* promotor mutation for *IDH*<sup>WT</sup>/*TERT*<sup>MUT</sup>; *EGFR* amplification for *IDH*<sup>WT</sup>/*TERT*<sup>WT</sup>) in the absence of classical histological findings in the remaining patients. Three hundred and fifty-eight *IDH*<sup>WT</sup>/*TERT*<sup>MUT</sup> (90.4%) and 63 *IDH*<sup>WT</sup>/*TERT*<sup>WT</sup> patients (90%) underwent microsurgical resection, whereas the remaining had biopsy for tissue-based diagnosis. There were no differences in *MGMT* promotor methylation status, first-line therapy, or pre- and postoperative tumor volumes (both for contrast-enhancing and noncontrast-enhancing tumor) between *IDH*<sup>WT</sup>/*TERT*<sup>MUT</sup> and *IDH*<sup>WT</sup>/*TERT*<sup>WT</sup> patients (Figure 1A and B). Median progression-free survival was 8 months and overall survival was 18 months at a median follow-up

time of 36 months (*IDH*<sup>WT</sup>/*TERT*<sup>MUT</sup> vs *IDH*<sup>WT</sup>/*TERT*<sup>WT</sup>: 33 vs 52 months; HR: 1.50, CI: 1.0–2.3). When patients were stratified according to *TERT* promotor mutation status, no outcome differences were detected for progression-free survival (*IDH*<sup>WT</sup>/*TERT*<sup>MUT</sup> vs *IDH*<sup>WT</sup>/*TERT*<sup>WT</sup>: 7 vs 8 months; HR: 1.03, CI: 0.8–1.4) or overall survival (*IDH*<sup>WT</sup>/*TERT*<sup>MUT</sup> vs *IDH*<sup>WT</sup>/*TERT*<sup>WT</sup>: 18 vs 17 months; HR: 0.97, CI: 0.7–1.3) (Figure 1C). Also, no association between survival and *TERT* promotor mutation status was found in the subgroups of patients with *MGMT* promotor methylation (HR for *IDH*<sup>WT</sup>/*TERT*<sup>WT</sup>: 0.99, CI: 0.6–1.8), unmethylated *MGMT* promotor status (HR for *IDH*<sup>WT</sup>/*TERT*<sup>WT</sup>: 0.92, CI: 0.5–1.7), first-line radiochemotherapy *per EORTC* 26981/22981 (HR for *IDH*<sup>WT</sup>/*TERT*<sup>WT</sup>: 1.00, CI: 0.7–1.4), or classical histopathological findings of glioblastoma (HR for *IDH*<sup>WT</sup>/*TERT*<sup>WT</sup>: 1.06, CI: 0.8–1.5).

We did therefore not find evidence that *TERT* promotor status adds prognostic information in *IDH*-wildtype glioblastomas exhibiting classical histopathological hallmarks (or other mutations) sufficient for glioblastoma diagnosis. This is in line with previous reports on *IDH*-wildtype glioblastomas,<sup>4,6,7</sup> although these studies have either not controlled for clinical and molecular confounders<sup>4,6</sup> or were substantially limited in sample size.<sup>4,7</sup> Notably, *IDH*<sup>WT</sup>/*TERT*<sup>WT</sup> glioblastomas may identify a subset with a distinct



**Figure 1.** Clinico-molecular markers and outcome in *IDH*-wildtype glioblastoma with or without *TERT* promotor mutations. (A) Distribution of *MGMT* promotor methylation status (upper panel) and first-line therapies following surgery (lower panel) in *IDH*-wildtype glioblastomas with (*IDH*<sup>WT</sup>/*TERT*<sup>MUT</sup>; *n* = 396) or without *TERT* promotor mutations (*IDH*<sup>WT</sup>/*TERT*<sup>WT</sup>; *n* = 70). (B) Pre- (upper panel) and postoperative tumor volumes (lower panel) in cm<sup>3</sup> among *IDH*-wildtype glioblastomas undergoing microsurgical tumor resection with (*IDH*<sup>WT</sup>/*TERT*<sup>MUT</sup>; *n* = 358; green) or without *TERT* promotor mutations (*IDH*<sup>WT</sup>/*TERT*<sup>WT</sup>; *n* = 63; blue). Volumes are indicated for contrast-enhancing (CE) and noncontrast-enhancing (nCE) tumor tissue. Median  $\pm$  interquartile range. (C) Kaplan–Meier estimates of progression-free survival (left) and overall survival (right) for *IDH*-wildtype glioblastomas with (green line) or without *TERT* promotor mutations (blue line). Points indicate deceased or censored patients; light shadings indicate SEM.

(epi-)genetic and molecular profile compared to *IDH*<sup>wt</sup>/*TERT*<sup>mut</sup> tumors and may benefit from different, personalized treatment strategies.<sup>2,4,6</sup> These biological findings, however, to date do not result in different clinical outcomes. Thus, up to now our retrospective data argue against standardized analysis for *TERT* promotor mutation status for the purpose of prognostic or therapeutic relevance in newly diagnosed *IDH*-wildtype glioblastoma that otherwise meets the histopathological and molecular diagnosis criteria. This might change in the future whenever *TERT*-directed therapies emerge.

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## References

1. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. *Neuro Oncol.* 2021;23(8):1231–1251.
2. Stichel D, Ebrahimi A, Reuss D, et al. Distribution of EGFR amplification, combined chromosome 7 gain and chromosome 10 loss, and *TERT* promoter mutation in brain tumors and their potential for the reclassification of *IDH*<sup>wt</sup> astrocytoma to glioblastoma. *Acta Neuropathol.* 2018;136(5):793–803.
3. Arita H, Yamasaki K, Matsushita Y, et al. A combination of *TERT* promoter mutation and MGMT methylation status predicts clinically relevant subgroups of newly diagnosed glioblastomas. *Acta Neuropathol Commun.* 2016;4(1):79.
4. Diplas BH, He X, Brosnan-Cashman JA, et al. The genomic landscape of *TERT* promoter wildtype-*IDH* wildtype glioblastoma. *Nat Commun.* 2018;9(1):2087.
5. Karschnia P, Young JS, Dono A, et al. Prognostic validation of a new classification system for extent of resection in glioblastoma: a report of the RANO resect group. *Neuro Oncol.* 2022. doi:[10.1093/neuonc/noac193](https://doi.org/10.1093/neuonc/noac193)
6. Liu EM, Shi ZF, Li KK, et al. Molecular landscape of *IDH*-wild type, p*TERT*-wild type adult glioblastomas. *Brain Pathol.* 2022;e13107.
7. Gramatzki D, Felsberg J, Hentschel B, et al. Telomerase reverse transcriptase promoter mutation- and O(6)-methylguanine DNA methyltransferase promoter methylation-mediated sensitivity to temozolomide in isocitrate dehydrogenase-wild-type glioblastoma: is there a link? *Eur J Cancer.* 2021;147:84–94.