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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.[1] 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.[2,3] 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.[4] 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.[5] 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 ($IDH^{wt}/TERT^{mut}$) and 70 patients without *TERT* promotor mutations ($IDH^{wt}/TERT^{wt}$). Diagnosis rested upon *IDH*-wildtype combined with histopathological findings in 372 $IDH^{wt}/TERT^{mut}$ (93.9%) and 65 $IDH^{wt}/TERT^{wt}$ patients (92.9%); and was established based on the molecular signature (*TERT* promotor mutation for $IDH^{wt}/TERT^{mut}$; *EGFR* amplification for $IDH^{wt}/TERT^{wt}$) in the absence of classical histological findings in the remaining patients. Three hundred and fifty-eight $IDH^{wt}/TERT^{mut}$ (90.4%) and 63 $IDH^{wt}/TERT^{wt}$ 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 $IDH^{wt}/TERT^{mut}$ and $IDH^{wt}/TERT^{wt}$ 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 ($IDH^{wt}/TERT^{mut}$ vs $IDH^{wt}/TERT^{wt}$: 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 ($IDH^{wt}/TERT^{mut}$ vs $IDH^{wt}/TERT^{wt}$: 7 vs 8 months; HR: 1.03, CI: 0.8–1.4) or overall survival ($IDH^{wt}/TERT^{mut}$ vs $IDH^{wt}/TERT^{wt}$: 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 $IDH^{wt}/TERT^{wt}$: 0.99, CI: 0.6–1.8), unmethylated *MGMT* promotor status (HR for $IDH^{wt}/TERT^{wt}$: 0.92, CI: 0.5–1.7), first-line radiochemotherapy *per* EORTC 26981/22981 (HR for $IDH^{wt}/TERT^{wt}$: 1.00, CI: 0.7–1.4), or classical histopathological findings of glioblastoma (HR for $IDH^{wt}/TERT^{wt}$: 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,[4,6,7] although these studies have either not controlled for clinical and molecular confounders[4,6] or were substantially limited in sample size.[4,7] Notably, $IDH^{wt}/TERT^{wt}$ glioblastomas may identify a subset with a distinct

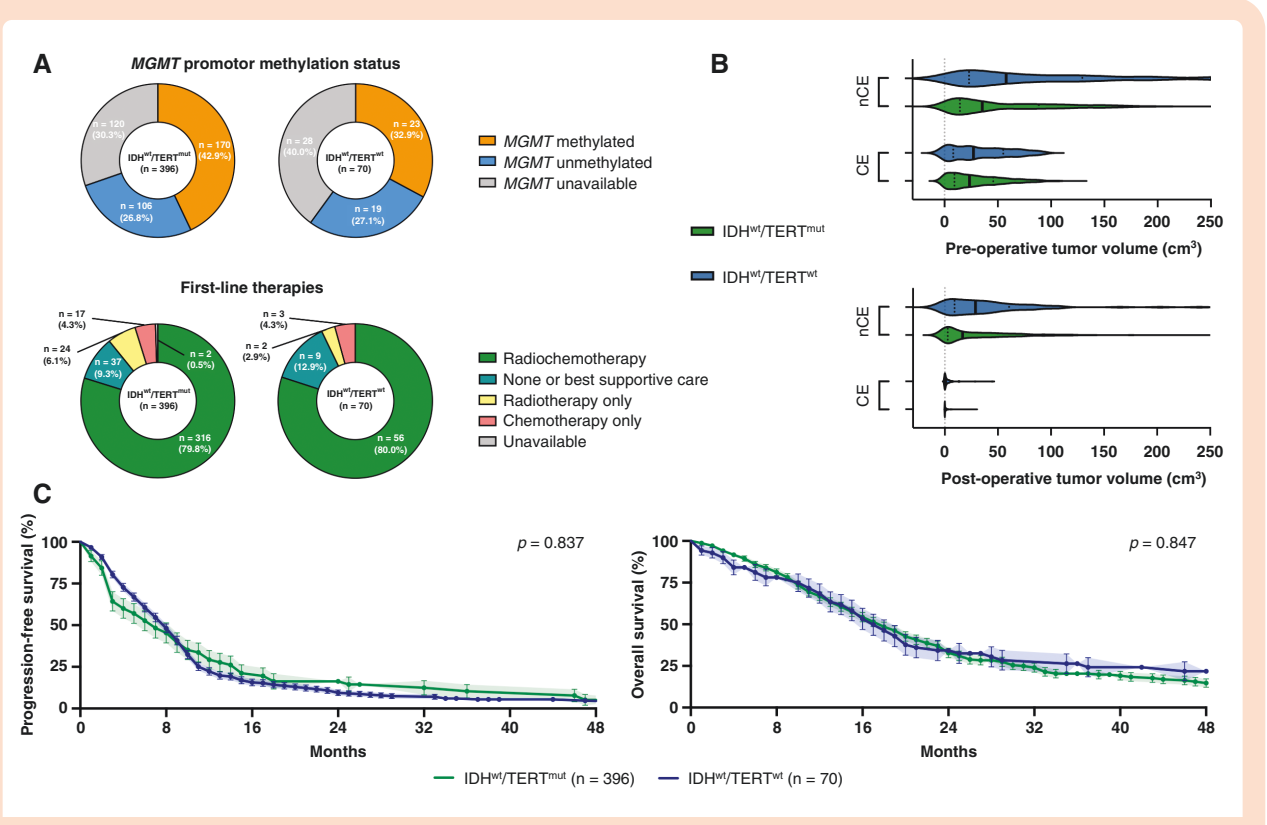

Figure 1. Clinico-molecular markers and outcome in *IDH*-wildtype glioblastoma with or without *TERT* promotor mutations. (A) Distribution of *MGMT* promotor methylation status (upper panel) and first-line therapies following surgery (lower panel) in *IDH*-wildtype glioblastomas with ($IDH^{wt}/TERT^{mut}$; $n = 396$) or without *TERT* promotor mutations ($IDH^{wt}/TERT^{wt}$; $n = 70$). (B) Pre- (upper panel) and postoperative tumor volumes (lower panel) in cm^3 among *IDH*-wildtype glioblastomas undergoing microsurgical tumor resection with ($IDH^{wt}/TERT^{mut}$; $n = 358$; green) or without *TERT* promotor mutations ($IDH^{wt}/TERT^{wt}$; $n = 63$; blue). Volumes are indicated for contrast-enhancing (CE) and noncontrast-enhancing (nCE) tumor tissue. Median ± 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^{wt}/TERT^{mut} tumors and may benefit from different, personalized treatment strategies.[2,4,6] 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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