BACKGROUND: H3K27-altered diffuse midline gliomas (DMGs) have poor prognosis with no standard of care therapy beyond radiation (RT). While RT prolongs survival, not all patients respond. Prior work has shown somatic TP53 mutations predict radiation resistance, and poorer outcomes. We report on a multi-center retrospective cohort study to identify molecular biomarkers of RT response in DMG patients. METHODS: We performed retrospective chart reviews of patients with biopsy-proven H3K27M-altered DMG between 2013-2023 from six US medical centers and the DMG Center in Zurich. Patients with tumor genomic sequencing and completion of RT were eligible. Genomic alterations were evaluated for somatic mutations, fusions, and chromosomal instability. Cox proportional hazard models were used to evaluate associations between somatic alterations and survival. Multivariate analysis included all significant variables at P <0.1 in initial analysis, including age at diagnosis, tumor location, TP53 and PIK3R1 alterations.

RESULTS: 257 patients (135 female; median age 8.3 years; range 0.2-71.4 years) were included. Median progression-free survival (PFS) and overall survival (OS) was 7.6 months (95%-CI 6.9-8.6) and 14.0 months (95%-CI 12.9-15.7). Univariate analysis identified TP53 or PIK3R1 status to be associated with shorter OS (TP53-mutant 12.5 months vs. TP53-wildtype 15.2 months; HR=1.5; 95%-CI (1.1-2.0); P=0.005); (PIK3R1-mutant 12.6 months vs. PIK3R1-wildtype 14.5 months; HR=1.9, 95%-CI (1.1-3.4); P=0.03). Multivariate analysis corroborated TP53 status association with shorter OS (HR=1.5; 95%-CI (1.2-2.0); P=0.003). Subgroup univariate analysis of pontine DMG patients showed reduced OS with TP53, NF1, or TERT mutations (TP53-mutant 11.9 months vs. TP53-wildtype 15.2 months; HR=1.6; 95%-CI (1.2-2.0); P=0.02); (NF1-mutant 8.4 months vs. NF1-wildtype 13.6 months; HR=2.3; 95%-CI (1.1-5.0); P=0.03); (TERT-mutant 8.5 months vs. TERT-wildtype 13.6 months; HR=2.5; 95%-CI (1.1-5.7); P=0.03). Subsequent multivariate analysis corroborated the association of TERT mutations with shorter OS in pontine DMG (HR=2.5; 95%-CI (1.03, 5.9); P=0.03). CONCLUSIONS: This is one of the largest molecular characterized cohorts of H3K27M-altered DMG patients. DMGs with somatic TP53 or PIK3R1 mutations demonstrate inferior OS. Pontine DMG patients with somatic TP53, NF1 or TERT mutations demonstrate inferior OS.

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DIAG-77. SOMATIC TP53, PIK3R1, NF1 OR TERT MUTATIONS ARE ASSOCIATED WITH INFERIOR CLINICAL OUTCOME IN H3K27M-ALTED DIFFUSE MIDDLE GLIOMA

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