**MGMT Promoter Methylation Status Independently Predicts Overall Survival in Anaplastic Astrocytoma in NRG Oncology/RTOG 9813: A Phase 3 Trial of Radiation Plus Nitrosourea Versus Radiation Plus Temozolomide**

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**Purpose/Objective(s):** This study sought to determine the proportion of patients with MGMT promoter methylation within NRG Oncology/RTOG 9813 and its prognostic significance in the setting of anaplastic gliomas (astrocytoma dominant) in a prospective phase III trial.

**Materials/Methods:** NRG Oncology/RTOG 9813 enrolled 196 eligible high-risk patients treated with RT + nitrosourea (NU) or RT + temozolomide (TMZ). The MGMT-STP27 prediction model was used to calculate MGMT promoter methylation status from Illumina HM-450K data. Univariate (UVAs) and multivariable analyses (MVAs) were performed using the Cox proportional hazard model, to analyze the effect of MGMT status on progression-free survival (PFS) and overall survival (OS). Patient pre- treatment characteristics and treatment assignment were included as covariates in MVAs.

**Results:** Of all the eligible and randomized patients in this trial, 58 currently have MGMT status available: 36 (62%) methylated and 22 (38%) unmethylated. Between the two groups, no significant difference was observed on age and performance status at baseline. Upon UVAs, MGMT promoter methylation trended toward better OS (HR = 1.78; 95% CI (0.93-3.40); P = 0.08). Upon MVAs, MGMT promoter methylation significantly correlated with better OS (HR = 2.28; 95% CI (1.15-4.45); P = 0.019), but not PFS (HR = 1.48; 95% CI (0.80-2.73); P = 0.22).

**Conclusion:** MGMT promoter methylation as determined by the MGMT- STP27 model was an independent prognostic biomarker of anaplastic astrocytomas treated with radiation plus nitrosourea or radiation plus temozolomide for OS. Importantly, this is the first study to validate the prognostic significance of MGMT promoter methylation on OS in a phase III study of grade III anaplastic glioma (astrocytoma dominant) patients treated with radiation plus TMZ or NU using rigorous MVAs with prospectively-collected, well-annotated clinical data. Analysis of the prognostic significance of MGMT promoter methylation relative to IDH and 1p/19q status is ongoing as well as efforts to increase sample size.