Abstract 111: Association of MGMT status with survival in low and high-grade IDH-mutant astrocytomas

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Background

How MGMT promoter methylation status affects survival in IDH-mutant astrocytomas is less understood than in IDH-wildtype GBM.

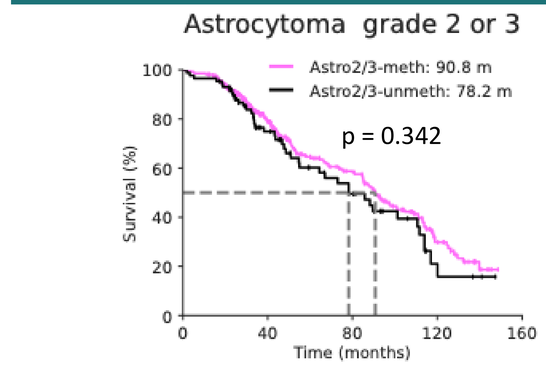
- MGMT is a DNA repair enzyme
  - Alleviates temozolomide damaged lesions
- **High MGMT expression** leads to **resistance** to **temozolomide**
- **Hypermethylation of MGMT promoter** leads to silencing of transcription, **increasing sensitivity to temozolomide**
- IDH mutants **lose** native enzymatic activity
- Acquires novel activity to promote epigenetic changes
- Leads to **G**lioma **C**pG **I**sland **M**ethylation **P**henotype (G-CIMP)
- Multiple techniques measure MGMT promoter methylation:
  - Pyrosequencing
  - Methylation-specific polymerase chain reaction (PCR)
  - Direct Sanger sequencing
- Limitations include low quantitative accuracy, short read length, and low sample throughput
- We used a large database of next-generation sequencing (NGS) and whole-transcriptome sequencing (WTS) performed in a single laboratory to determine the role of MGMT status on survival in IDH-mutant astrocytomas and in GBM.

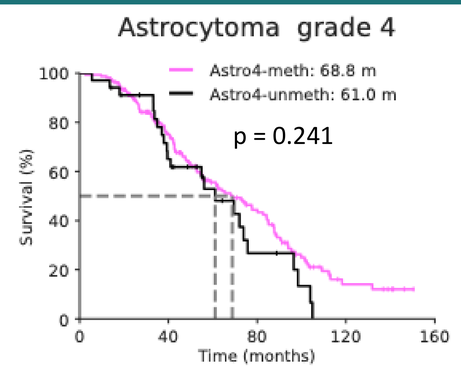
Methods

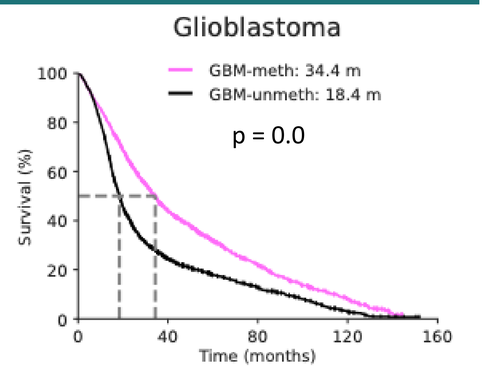
10,181 glioma samples were analyzed by NGS (592, NextSeq, or WES, NovaSeq) and WTS (NovaSeq) at Caris Life Sciences (Phoenix, AZ), including determination of methylation status of the MGMT promoter region by pyrosequencing. Real-world overall survival was obtained from insurance claims data and calculated from initial diagnosis to last contact. Hazard ratios (HRs) were analyzed using Cox proportional hazards model and p values (log-rank test). Multivariate regression analysis was performed on age, gender, radiation treatment, temozolomide treatment, and mutations in different biomarkers. Fisher's exact test was used at a significance level of 0.05.

MGMT status is not associated with survival in low or high-grade IDH-mutant astrocytoma.

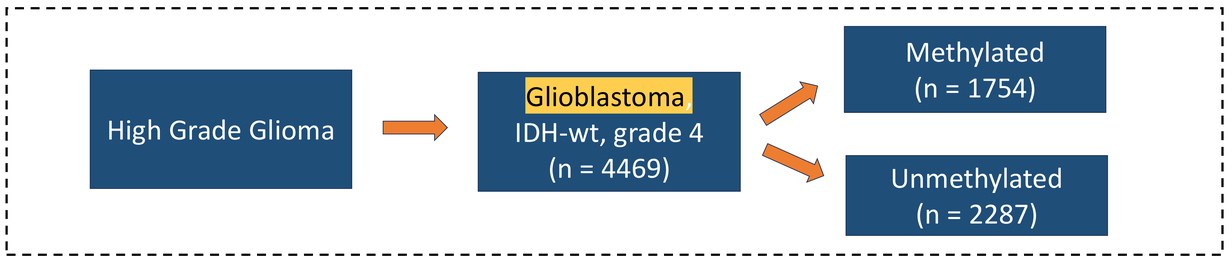
Results: Kaplan-Meier survival curves, initial diagnosis to last contact

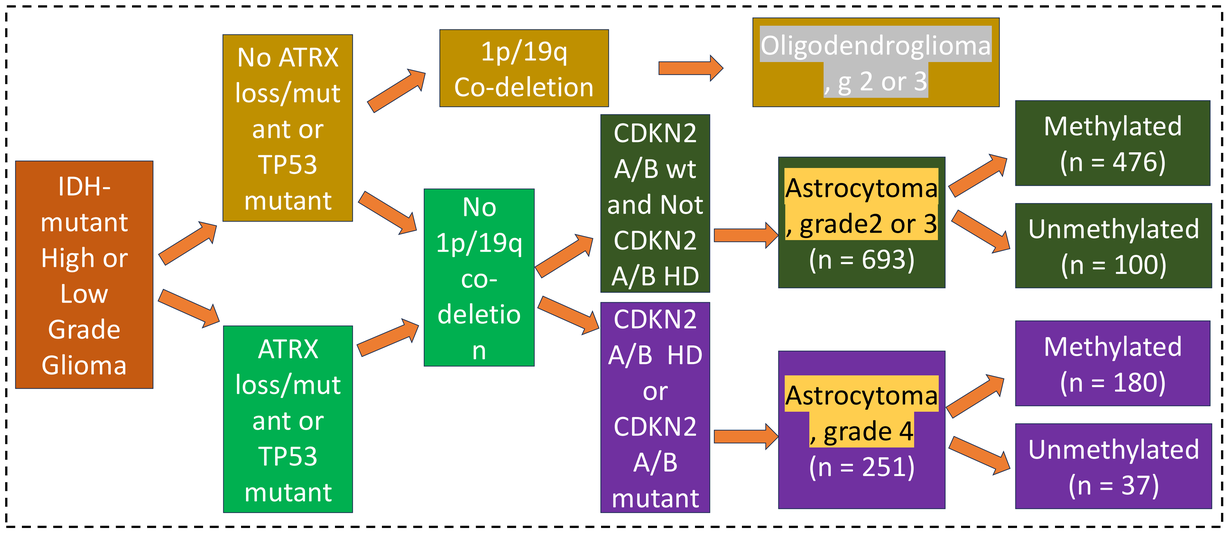






693 IDH-mutant astrocytomas grades 2 or 3 ("g2/3"), 251 IDH-mutant astrocytoma grade 4 ("g4"), and 4469 glioblastoma ("GBM") met inclusion criteria. Univariate and multivariate survival analysis showed that MGMT promoter methylation (mMGMT vs. unmethylated, uMGMT) was associated with improved overall survival only in GBM (HR = 0.62, 95% CI: 0.57 – 0.67, p < 0.00001), but not in astrocytoma-g2/3 or g4.





Future Directions

These results, derived from a large database and analyzed on a unified platform (next-generation sequencing at a single laboratory), support similar findings from recent, smaller cohort studies. Future investigation will focus on gene expression patterns and genetic alterations in IDH-mutant astrocytoma associated with morbidity and mortality to better identify actionable pathways and treatment targets.

Contact

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