Background
Glioblastoma multiforme (GBM), the most aggressive CNS cancer, has limited effective therapeutic options, with underlying molecular heterogeneity contributing to the differential in treatment response. Our study was designed to interrogate biomarkers from a large cohort of GBM patients to seek potential therapeutic implications.

Methods
Data was analyzed from 648 GBM patients who underwent tumor profiling at Caris Life Sciences from 2008 to 2018. IHC (643), FISH (260), Sanger Sequencing (171), MGMT promoter methylation and NextGen (82) (Etuhaus-Tu) were performed. These studies were validated and performed by board-certified pathologists and molecular geneticists. Correlation studies were performed by two-tailed Fisher exact tests.

Results and Discussion

Four platforms (IHC, FISH, Methylation and Sequencing) reveal biomarker aberrations in GBM:

- The correlation of TS positive and RRM1 positive (p=0.006) indicates the potential benefit of a combination therapy of TS and RRM1 in GBM.
- In TS positive cohort, RRM1 is low in 52%, while in TS negative cohort, 75% shows low RRM1.
- The combination of TS positive and low RRM1 shows a trend for higher BCRP expression (p=0.0299), and a trend for a higher BCRP expression in the EGFR amplified patient cohort.
- TS negative and RRM1 negative patients are more frequently observed in IDH1 wild type and MGMT unmethylated patient cohorts. These correlation studies indicate potential resistance to temozolomide.
- Mutations on the MAPK, KIT and mTor pathways are more frequently seen in EGFR non-amplified patient cohorts. These correlation studies indicate potential resistance to temozolomide.
- EGFR amplification was seen in 41% of the EGFR non-amplified patient cohort with indicated PTEN, BRAF, PIK3CA, EGFR, KDR and CDKN2A mutations.
- The combination of IHC, FISH, Methylation and Sequencing tests identifies biomarker features of EGFR amplified patients:
  - 34% with SPARC, 26% with TS, 37% with Top2A, 19% with MGMT, 15% with cMYC, 10% with Ki67, 3% with MDM2, 3% with TLE3, 3% with TOP2A, 3% with CDKN2A.

Conclusions and Study Highlights

- Immunohistochemistry of 664 GBM patient tumors reveals the heterogeneous protein expression profile. Proportion of responders to standard and novel therapies are identified, examples include 49% for temozolomide, 10% for irinotecan, 23% for FISH and 29% for MGMT (p=0.0331).
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Correlated biomarkers in GBM may reveal novel combination therapies:

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