Results of molecular profiling for recurrent malignant gliomas reveal significant changes in biomarkers compared to mostly treatment naïve tumors that could impact treatment decision
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Background
There have been few studies done in systemic malignancies to look for differences in molecular profiling in newly diagnosis versus recurrence.
Molecular genetic profiling of ovarian cancer comparing first and recurrent paired tissues revealed significantly high discordance rate (up to 40%) in some biomarkers which could impact the treatment strategy in recurrent setting.

The difference between treatment naïve and recurrent malignant gliomas profiling is not known.

Methods
• 10 patients (pt) were identified retrospectively with tumor profiling tests on multiple specimens.
• Molecular profiling was performed by Caris Life Sciences, Inc.
• Tests included immunohistochemistry (IHC), next generation sequencing, and fluorescence in situ hybridization.
• A total of 10 paired pt's results were obtained from March 2011 to May 2016.
• Male:Female 8:2 Age: 22-69 years old Median Age: 42 years old.
• 7/10 patients had tests performed at the time of 1st surgery and recurrence. Of 7 pts who had 1st test at the time of 1st surgery, 2pt had second test at the 1st recurrence, 3 pts at the 2nd recurrence, 2 pt at the 3rd recurrence and 2 pts at the 4th recurrence.
• 3 pts had the first test performed at the time of recurrence: 4 months (GBM pt) 8 months (GBM) and 8 years (AO pt) from the 1st diagnosis/surgery and the second test was performed after 2nd, 3rd and 3rd surgery 34 months, 6 months and 13 months later, respectively.
• Average time between two tests/time of recurrence was 32.6 mo for AA/AO and 26.1 mo for GBM respectively.

Results
Decreased expression of PD-L1 2/8 (25%), ERCC1 2/7 (29%), PTEN 3/9 (33%), RRM1 2/5 (40%), TLE3 4/8 (71%) and EGFR 2/6 (33%) were seen over, while no increase of expression were seen.
1 showed loss of EGFRvIII variant over time out of 5 pairs tested. In contrast, cMET expression and amplification, as well as TUBB3 expression were seen to increase over time in 1/5 (20%), 1/4 (25%), 2/10 (20%) samples, while no decrease was seen.
Expression of PD-1, TOP02A, TOP01, TS were seen to both increase and decrease over time.
In the 9 pairs with sequencing data available, acquisition of EGFR(V292L), FLT3(D324N), NOTCH1(G736R) and ATM (H231R) were seen in one tumor each.
In one case, Tp53 R175H mutation was seen in the first sample and an R158H mutation was seen in addition to R175H was seen in a sample collected 3.3 years later; in the same case, PDGFRA (R841_I843del) was seen in the first sample and D842V is seen in a sample collected later. In the 8 pairs with MGMT methylation tests done, two samples showed decreased MGMT methylation.

Discussion
• MGMT Methylation seems to confer improved time to tumor progression and overall survival compared to pts with Unmethylated MGMT.
• IDH1 mutations are seen in the GBM and anaplastic gliomas with the longest TTP, confirming its predictive value for a better survival.
• Changes of TS and expression may have potential to associate with patient’s outcome. decrease of protein expression vs. increase may suggest better patient outcome.
• Irinotecan treatment based on positive TOP01 expression is often adopted and generated favorable outcome: e.g., patient 3 was treated with irinotecan x 7 cycles at the third recurrence after patient has failed bevacizumab and achieved stable disease.
• Acquisition of variants of unknown significance by sequencing is seen as the tumor progresses, the therapeutic implication remains unknown.
• Further data analysis is ongoing.

Conclusions
• Although cohort is small, we show dynamic changes in recurrent malignant gliomas with high discordance rate of 29% compared to the first test.
• There was greater loss of targetable-biomarkers than gains over time (p=0.015).
• Frequent biomarker changes are seen when serial tumor samples are compared for biomarker aberrations; suggesting the need for a fresh specimen to guide next line of therapy.

References:
1) Treatment-Related Protein Biomarker Expression Differences between Primary and Recurrent Ovarian Carcinomas in Molecular Cancer Therapeutics 11(2):402-902 December 2011