Impact of IDH-1 Mutation status on outcome in clinical trials of recurrent glioblastoma
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Background
- Molecular profiling is now being utilized to separate diffuse gliomas including glioblastoma (GBM) into prognostic groups.
- A mutation affecting codon 132 of the isocitrate dehydrogenase 1 (IDH-1) gene occurs in 12% of GBMs.
- IDH-1 mutated tumors have been associated with an improved outcome compared to IDH-1 wild-type tumors.
- IDH-1 mutation has remained an independent favorable prognostic marker even after adjustment for age, grade, MGMT status, genomic profile, and treatment in multivariate analysis.

Despite IDH-1 mutated tumors being associated with an improved outcome, phase 2 single arm clinical trials for recurrent GBM currently do not typically stratify patients based upon IDH-1 status.

It remains unknown whether patients with IDH-1 mutated GBM on clinical trials for tumor recurrence have a higher 6-month progression free survival (PFS6) or radiographic response (RR) rate than IDH-1 wild-type tumors.

Methods
- We retrospectively identified 330 GBM patients treated at MD Anderson on clinical trials for recurrent disease from 2006-2012.
- 93 patients (28%) either had 6 month progression free survival (PFS6) or a complete or partial RR (radiographic response) per RANO criteria.
- 107/330 (32.7%) patients with PFS6 or a complete or partial RR were found to have tumor tissue available for IDH-1 testing.
- A matched cohort of pts on recurrent GBM clinical trials without PFS6 or RR (also with tissue for IDH-1 testing) was identified based on the specific clinical trial, age and sex.
- 49 pts were also identified for comparison.

Blinded neuropathologists then performed IDH-1 mutation testing by immunohistochemistry.

Clinical characteristics of patients on recurrent GBM trials

- IDH-1 status was obtained in 92 (94%) patients of which 17 (18%) had an IDH-1 mutation.
- Median overall survival from initial tumor diagnosis was 22 months for IDH-1 wildtype tumors vs. 13 months for IDH-1 mutated tumors (p=0.06).
- For all patients, median PFS on a recurrent trial was 3.68 months for IDH-1 wildtype GBM vs. 10.9 months for IDH-1 mutated GBM (p=0.66).
- Progression free survival (PFS6) or a complete or partial RR (radiographic response) per RANO criteria.

- Median time from GBM diagnosis to clinical trial was 8.4 months for IDH-1 wildtype tumors.
- Median overall survival from initial tumor diagnosis was 22 months for IDH-1 wildtype tumors.
- Median time from GBM diagnosis to clinical trial was 8.4 months for IDH-1 wildtype GBM vs. 10.9 months for IDH-1 mutated GBM (p=0.66).
- Median OS on recurrent trial was 8.64 months for IDH1- wildtype GBM vs. 9.59 months for IDH-1 mutated GBM (p=0.49).

Results
- Our study found that patients on clinical trials for recurrent GBM with PFS-6 and/or RR were not more likely to be IDH-1 mutated compared to a matched cohort of patients without PFS-6 or RR.
- Additionally, IDH-1 mutated tumors did not have a prognostic advantage compared to non-IDH-1 mutated tumors.
- Findings suggest that treatment response in recurrent GBM is likely dependent on more than just one genetic mutation.
- Lead time bias may also have been a factor in our study due to our inclusion of both secondary and primary GBM, as overall survival from initial tumor diagnosis was similar for IDH-1 mutated tumors regardless of whether they were in the cohort of patients with PFS-6 and/or RR or the matched cohort of patients without PFS-6 or RR (83.07 months vs. 86.07 months, p=0.22).
- Moreover, the high percentage of patients on clinical trials treated with an anti-VEGF therapy may have played a role in our studies findings.

Conclusions
- Further examination regarding the role of IDH-1 mutation and response on recurrent GBM clinical trials is needed in larger randomized prospective studies.

References