Impact of IDH-1 Mutation status on outcome in clinical trials of recurrent glioblastoma

Jacob J. Mandel, David Cachia[2], Diane Liu[2], Charmaine Wilson[2], Ken Aldape[3] ,Greg Fuller[2] , and John de Groot[2]
Department of Neurology, Baylor College of Medicine, Houston TX
[2]Department of Neuro-oncology, The Brain Tumor Center, University of Texas M. D. Anderson Cancer Center, Houston TX
[3]Department of Pathology, Princess Margaret Cancer Centre, Toronto ON

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 wildtype 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.
- 49/93(53%) 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 KPS.
- 49 pts were also identified for comparison resulting in a total of 98 patients
- Blinded neuropathologist then performed IDH-1 mutation testing by immunohistochemistry.

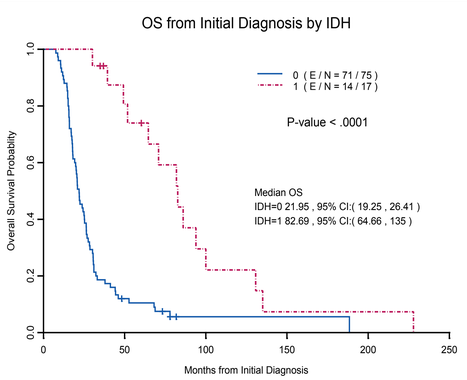
Results

- 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. 83 months for IDH-1 mutated tumors (p<0.0001).
- Recurrent GBM trial was at 1st-4th tumor recurrence from GBM diagnosis.
- Recurrent trials consisted of a bevacizumab containing regimen (38%), XL-184 (22%), temozolomide containing regimen (12%),carboplatin containing regimen (10%), lapatinib and pazopanib (8%), other (6%) and VEGF trap (4%).
- 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).
- PFS6 was seen in 26/49 (53%) patients. IDH-1 status was unknown in 2 of these patients. IDH-1 mutation was present in 5/24 (21%) patients with PFS6 compared to 5/24 (21%) patients of their matched cohort without PFS6.
- RR was found in 47/49 (94%) patients. IDH-1 status was unknown in 6 of these patients. IDH-1 mutation was present in 7/43 (16%) of the pts with a RR compared to 10/43 (23%) patients of their matched cohort without RR (p<0.49).
- For all patients, median PFS on a recurrent trial was 3.68 months for IDH-1 wildtype GBM vs. 3.52 months for IDH-1 mutated GBM (p<0.72).
- 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).

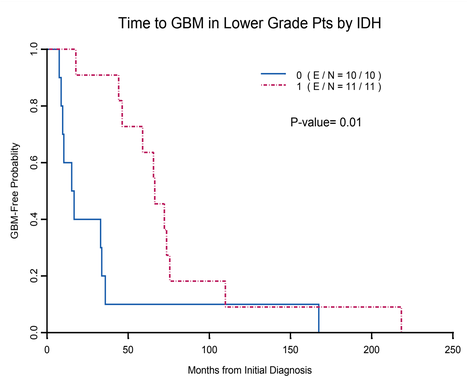
Clinical characteristics of patients on recurrent GBM trials

covariate	*levels*	*ALL*	*IDH*		*p_value*
			0	*1*	
Initial tumor grade	2	13(13.3%)	5(6.7%)	7(41.2%)	<.0001
	3	10(10.2%)	5(6.7%)	4(23.5%)	.
	4	75(76.5%)	65(86.7%)	6(35.3%)	.
Imaging response	0	49(50%)	37(49.3%)	10(58.8%)	.4797
	1	49(50%)	38(50.7%)	7(41.2%)	.
Number of recurrences prior to trial	1	61(62.2%)	54(72%)	5(29.4%)	.0039
	2	25(25.5%)	12(16%)	9(52.9%)	.
	3	8(8.2%)	6(8%)	2(11.8%)	.
	4	4(4.1%)	3(4%)	1(5.9%)	.
Extent of prior GBM resection	Gross total	23(23.5%)	12(16%)	8(47.1%)	.0052
	Near total	18(18.4%)	12(16%)	5(29.4%)	.
	Subtotal	10(10.2%)	8(10.7%)	0(0%)	.
	Biopsy	47(48%)	43(57.3%)	4(23.5%)	.
KPS at initial tumor diagnosis	Unknown	3(.%)			.
	60	1(1.1%)	1(1.4%)	0(0%)	.4124
	70	6(6.3%)	5(6.8%)	1(6.7%)	.
	80	14(14.7%)	13(17.6%)	0(0%)	.
	90	32(33.7%)	25(33.8%)	6(40%)	.
	100	42(44.2%)	30(40.5%)	8(53.3%)	
KPS at GBM diagnosis	60	1(1%)	1(1.3%)	0(0%)	1.000
	70	6(6.1%)	5(6.7%)	1(5.9%)	.
	80	14(14.3%)	11(14.7%)	2(11.8%)	.
	90	36(36.7%)	27(36%)	7(41.2%)	.
	100	41(41.8%)	31(41.3%)	7(41.2%)	
KPS at recurrent GBM trial	50	14(14.3%)	10(13.3%)	1(5.9%)	.7636
	60	6(6.1%)	4(5.3%)	1(5.9%)	.
	70	13(13.3%)	12(16%)	1(5.9%)	.
	80	31(31.6%)	23(30.7%)	6(35.3%)	.
	90	16(16.3%)	13(17.3%)	3(17.6%)	.
	100	18(18.4%)	13(17.3%)	5(29.4%)	

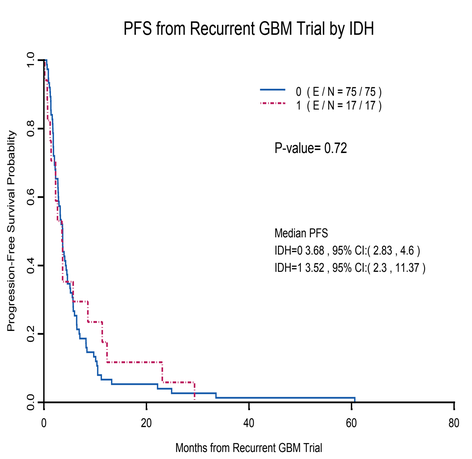
Overall Survival by IDH-1 mutation

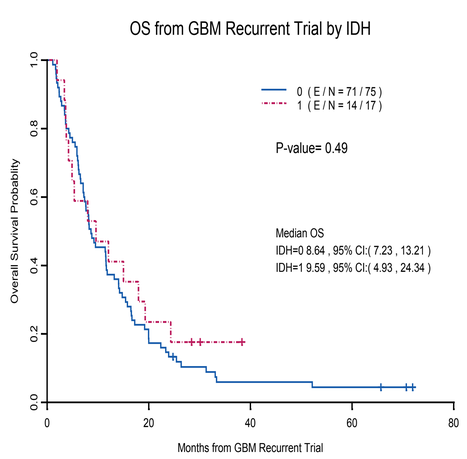


Time to GBM by IDH-1 mutation



Progression Free and Overall Survival of patients on recurrent GBM trials by IDH-1 mutation





Conclusions

- 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 prolonged progression free survival or overall survival on recurrent GBM trials compared to IDH-1 wildtype tumors.
- These results would seem to indicate that stratifying recurrent GBM trials based upon IDH-1 status may be unnecessary.
- Findings suggest that treatment response in recurrent GBM is likely dependent on more than just one genetic mutation.
- Lead time bias may have also 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
- Further examination regarding the role of IDH-1 mutation and response on recurrent GB clinical trials is needed in larger randomized prospective studies

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