Prognostic Impact of DDR Mutations (mt) in IDH mutant High-Grade Gliomas (HGG).

[1]John L. Villano, [2]Joanne Xiu, [2]Stephanie Rock, [2]Ninad Kulkarni, [2]Negar Sadeghipour, [1]Jill M. Kolesar, [1]Janna Neltner, [1]Trevor Morris, [3]Catherine R Garcia, Clyde Coleman, [1]David Spetzler, [4]Emil Lou, [5]Sonikpreet Aulakh, [6]Michael J. Glantz, [7]Eric T. Wong;

[1]University of Kentucky Markey Cancer Center, Lexington, KY; [2]Caris Life Sciences, Phoenix, AZ; [3]The University of Texas MD Anderson Cancer Center, Houston, TX; [4]University of Minnesota, Minneapolis, MN; [5]West Virginia University, Morgantown, WV; [6]Penn State Milton S. Hershey Medical Center, Hershey, PA; [7]Rhode Island Hospital, Providence, RI

Abstract

Background:

- The oncometabolite 2-hydroxyglutarate (2HG) produced by *IDH1/2* mt in HGG has profound effects on numerous pathways including DNA damage repair (DDR).
- We investigated the prognostic effect of DDR mt in *IDH* mutant vs. wild type (wt) tumors in a large cohort using a real-world database.

Methods:

- A total of 4894 HGG tumors tested at Caris Life Sciences (Phoenix, AZ) with NextGen sequencing of DNA (592-gene panel or whole exome sequencing) were included in the study.
- DDR alteration was defined as a pathogenic mutation in one of > 20 DDR genes (ATM, BARD1, BRCA1, BRCA2, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, MLH1, MSH2, MSH3, MSH6, PALB2, RAD50, RAD51, RAD51B, RAD51C, RAD51D
- Patient survival was obtained by insurance claims data and calculated from the initiation of tissue collection (rwOS).
- Cox proportional hazards model was used to calculate hazard ratios (HR) and log-rank tests to calculate p values, which were adjusted for multiple comparisons. Significance was set at p≤0.05.

Results

Patient Characteristics

Results

Figure 1. DDR mutations observed in the IDH MT cohort. A. Mutation frequencies B. Oncoprint of DDR mutation patterns in IDH MT tumors

	Mutated N	Total N	Prevalence
MSH6	27	115	23.5%
ATM	20	112	17.9%
MLH1	16	105	15.2%
MSH2	14	109	12.8%
MSH3	7	70	10.0%
BRCA2	11	111	9.9%
FANCA	9	106	8.5%
BRCA1	7	107	6.5%
BARD1	6	103	5.8%
RAD50	5	91	5.5%
PALB2	5	103	4.9%
FANCC	4	101	4.0%
FANCM	2	67	3.0%
RAD51D	2	67	3.0%
FANCL	2	103	1.9%
FANCD2	2	104	1.9%
FANCG	2	104	1.9%
FANCI	1	68	1.5%
RAD51C	1	70	1.4%
FANCE	1	87	1.1%
RAD51B	1	100	1.0%
FANCB	0	69	0.0%
FANCF	0	103	0.0%
RAD51	0	102	0.0%

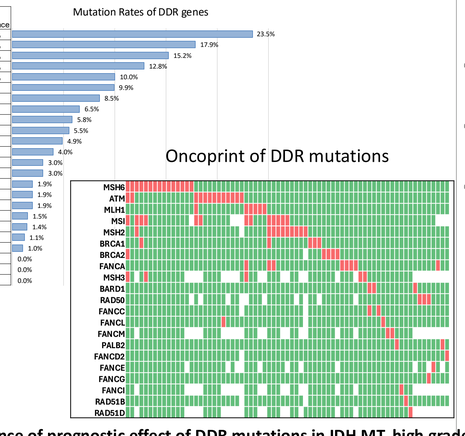
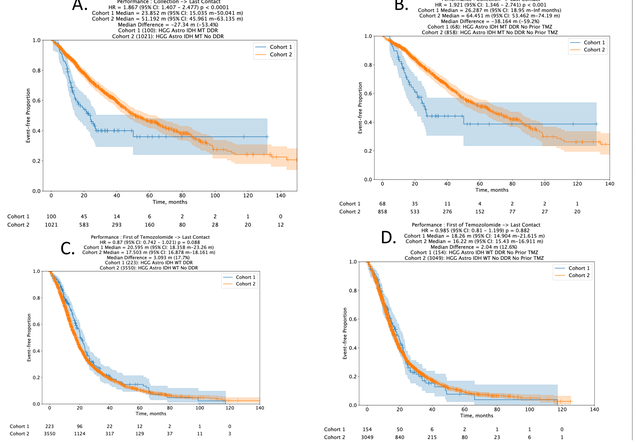
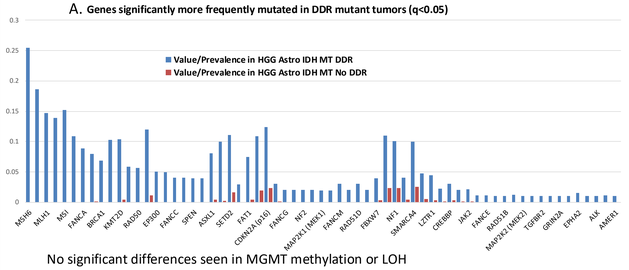


Figure 2. Drastic difference of prognostic effect of DDR mutations in IDH MT, high grade gliomas (A, B) and in ID WT (C, D) high grade gliomas. A, C: all tumors; B, D: restricted to tumors collected before temozolomide start; A, B: survivals calculated from tissue collection to last contact; C, D: survivals calculated from temozolomide start



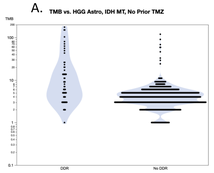
Results

Figure 3. Drastic difference of prognostic effect of DDR mutations in IDH MT, high grade gliomas (A, B) and in ID WT (C, D) high grade gliomas. A, C: all tumors; B, D: restricted to tumors collected before temozolomide start

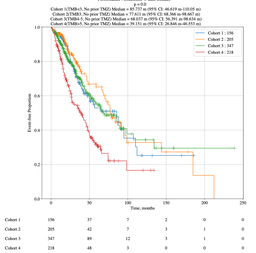


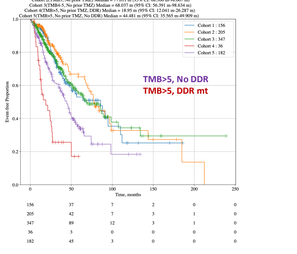
No significant differences seen in MGMT methylation or LOH

Figure 4. Tumor mutational burden (TMB) in DDR mutant vs. wild type tumors. A. Violin plot and statistics of TMB in HGG astrocytomas with or without DDR mutations.

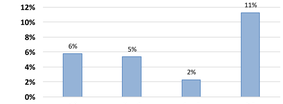


Level	Minimum	10%	25%	Median	75%	90%	Maximum
DDR	0	2	3	6	14	61.8	175
No DDR	0	2	3	4	5	7	119

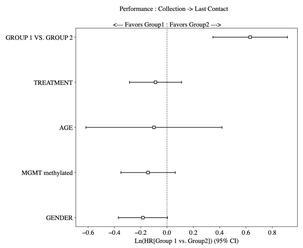


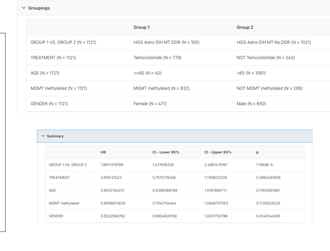


TMB Binned	DDR	No DDR	Total	Prevalence
< 3	9	147	156	0.05769231
3 — 4	11	194	205	0.05365854
4 — 5	4	171	175	0.02285714
≥ 5	44	346	390	0.11282051



Results





Conclusions

- In a large real-world database, we demonstrate IDH mt HGG with a DDR mutation exhibit significantly poorer survival compared to DDR wt.
- This is not seen in IDH wt, where survivals of the two groups are similar.
- These results stand in sharp contrast to reported prognostic effect of DDR mutation in many other solid tumors.
- The data suggest that DDR mutations in the context of 2HG accumulation in IDH mt HGG may be an indicator of profound genomic instability that confers severe negative impact on patient survival.
- Clinicians managing high-grade gliomas should consider the presence of DDR mutations in IDH mutant patients as a poor prognostic category in this overall favorable prognostic group and consider therapeutic approaches accordingly.

Prognostic Impact of DDR Mutations (mt) in IDH mutant High-Grade Gliomas (HGG).

[1]John L. Villano, [2]Joanne Xiu, [2]Stephanie Rock, [2]Ninad Kulkarni, [2]Negar Sadeghipour, [1]Jill M. Kolesar, [1]Janna Neltner, [1]Trevor Morris, [3]Catherine R Garcia, Clyde Coleman, [1]David Spetzler, [4]Emil Lou, [5]Sonikpreet Aulakh, [6]Michael J. Glantz, [7]Eric T. Wong;

[1]University of Kentucky Markey Cancer Center, Lexington, KY; [2]Caris Life Sciences, Phoenix, AZ; [3]The University of Texas MD Anderson Cancer Center, Houston, TX; [4]University of Minnesota, Minneapolis, MN; [5]West Virginia University, Morgantown, WV; [6]Penn State Milton S. Hershey Medical Center, Hershey, PA; [7]Rhode Island Hospital, Providence, RI

Abstract

Background:

- The oncometabolite 2-hydroxyglutarate (2HG) produced by *IDH1/2* mt in HGG has profound effects on numerous pathways including DNA damage repair (DDR).
- We investigated the prognostic effect of DDR mt in *IDH* mutant vs. wild type (wt) tumors in a large cohort using a real-world database.

Methods:

- A total of 7394 HGG tumors tested at Caris Life Sciences (Phoenix, AZ) with NextGen sequencing of DNA (592-gene panel or whole exome sequencing) were included in the study.
- DDR alteration was defined as a pathogenic mutation in one of > 20 DDR genes (ATM, BARD1, BRCA1, BRCA2, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, MLH1, MSH2, MSH3, MSH6, PALB2, RAD50, RAD51, RAD51B, RAD51C, RAD51D
- Patient survival was obtained by insurance claims data and calculated from the initiation of tissue collection (rwOS).
- Cox proportional hazards model was used to calculate hazard ratios (HR) and log-rank tests to calculate p values, which were adjusted for multiple comparisons. Significance was set at $p \leq 0.05$.

Results

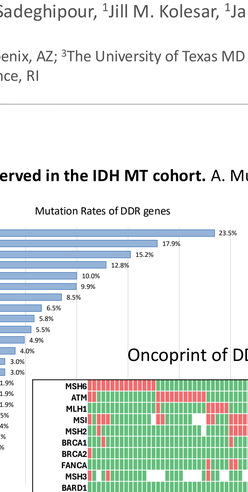
Patient Characteristics

		HGG Astro IDH MT DDR	HGG Astro IDH MT No DDR	HGG Astro IDH WT DDR	HGG Astro IDH WT No DDR	Total
Age	Median	40	38	60	62	
	Inter-Quartile Range	30-49	32-47	50-69	53-70	
Gender	Female	46	426	173	2396	**3041**
	Male	57	596	231	3469	**4353**
Race	Asian/Pacific Islander	1	24	9	123	**157**
	Black /African American	4	49	21	298	**372**
	Other	1	45	17	225	**288**
	White	61	530	230	3509	**4330**
	Unknown	36	374	127	1710	**2247**
Ethnicity	Hispanic or Latino	5	64	24	303	**396**
	Not Hispanic or Latino	73	646	269	4173	**5161**
	Unknown	25	312	111	1389	**1837**
	Total	**103**	**1022**	**404**	**5865**	**7394**

Results

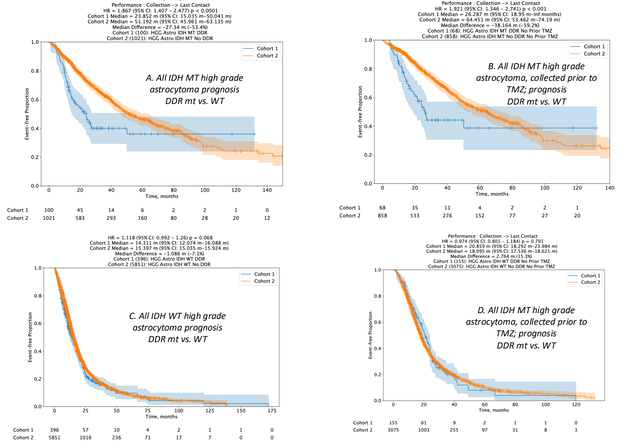
Figure 1. DDR mutations observed in the IDH MT cohort. A. Mutation frequencies

	Mutated N	Total N	Prevalence
MSH6	27	115	23.5%
ATM	20	112	17.9%
MLH1	16	105	15.2%
MSH2	14	109	12.8%
MSH3	7	70	10.0%
BRCA2	11	111	9.9%
FANCA	9	106	8.5%
BRCA1	7	107	6.5%
BARD1	6	103	5.8%
RAD50	5	91	5.5%
PALB2	5	103	4.9%
FANCC	4	101	4.0%
FANCM	2	67	3.0%
RAD51D	2	67	3.0%
FANCL	2	103	1.9%
FANCD2	2	104	1.9%
FANCG	2	104	1.9%
FANCI	1	68	1.5%
RAD51C	1	70	1.4%
FANCE	1	87	1.1%
RAD51B	1	100	1.0%
FANCB	0	69	0.0%
FANCF	0	103	0.0%
RAD51	0	102	0.0%



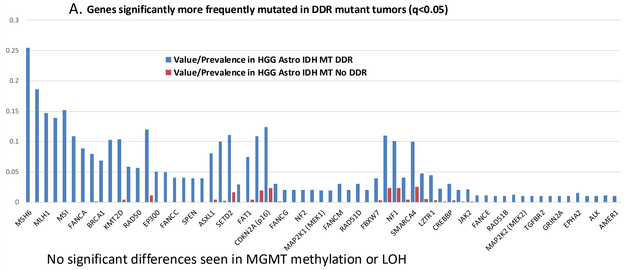
B. Oncoprint of DDR mutation patterns in IDH MT tumors, showing that a lot of the DDR mutations are largely mutually exclusive

Figure 2. Drastic difference of prognostic effect of DDR mutations in IDH MT, high grade gliomas (A, B) and in ID WT (C, D) high grade gliomas. A, C: all tumors; B, D: restricted to tumors collected before temozolomide start; A, B: survivals calculated from tissue collection to last contact; C, D: survivals calculated from temozolomide start



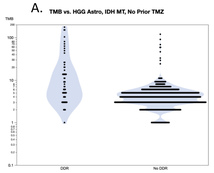
Results

Figure 3. Drastic difference of prognostic effect of DDR mutations in IDH MT, high grade gliomas (A, B) and in ID WT (C, D) high grade gliomas. A, C: all tumors; B, D: restricted to tumors collected before temozolomide start



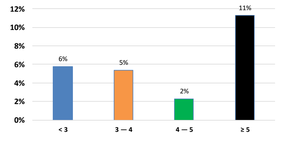
No significant differences seen in MGMT methylation or LOH

Figure 4. Tumor mutational burden (TMB) in DDR mutant vs. wild type tumors. A. Violin plot and statistics of TMB in HGG astrocytomas with or without DDR mutations.

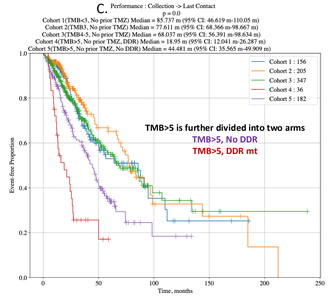


Level	Minimum	10%	25%	Median	75%	90%	Maximum
DDR	0	2	3	6	14	61.8	175
No DDR	0	2	3	4	5	7	119

B. Prevalence of DDR mutations in different TMB buckets C. Prognosis of TMB buckets in HGG not previously treated with TMZ. TMB>5 tumors were further stratified by DDR mutation and shows significant survival differences

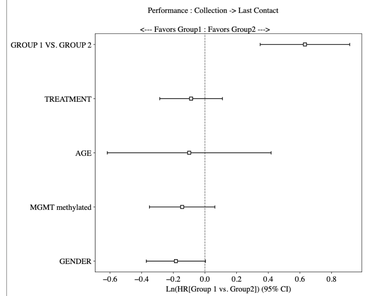


TMB Binned	DDR	No DDR	Total	Prevalence
< 3	9	147	156	5.8%
3 — 4	11	194	205	5.4%
4 — 5	4	171	175	2.3%
>5	44	346	390	11.3%



Results

Figure 5. Multivariate Analysis confirms that DDR mutation is associated with unfavorable prognosis after corrected for gender, age, temozolomide treatment and MGMT promoter methylation.



	Group 1	Group 2	HR (95% CI)	P value
Group 1 vs. Group 2 (N=1121)	HGG Astro IDH MT DDR Mt (N=100)	HGG Astro IDH MT DDR WT (N=1021)	1.88 (1.42-2.5)	1.12 E-05
Treatment (N=1121)	Temozolomide (N=779)	NO Temozolomide (N=342)	0.92 (0.75-1.12)	0.39
Age (N=1121)	>=65 (N=40)	<65 (N=1081)	0.91(0.54 -1.52)	0.71
MGMT Methylated (N=1121)	MGMT methylated (N=832)	NOT MGMT methylated (N=289)	0.87 (0.70-1.06)	0.17
Gender (N=1121)	Female (N=471)	Male (N=650)	0.83 (0.69-1.00)	0.054

Conclusions

- In a large real-world database, we demonstrate IDH mt HGG with a DDR mutation exhibit significantly poorer survival compared to DDR wt.
- This is not seen in IDH wt, where survivals of the two groups are similar.
- These results stand in sharp contrast to reported prognostic effect of DDR mutation in many other solid tumors.
- The data suggest that DDR mutations in the context of 2HG accumulation in IDH mt HGG may be an indicator of profound genomic instability that confers severe negative impact on patient survival.
- Clinicians managing high-grade gliomas should consider the presence of DDR mutations in IDH mutant patients as a poor prognostic category in this overall favorable prognostic group and consider therapeutic approaches accordingly.

Contact: Dr. John L. Villano jlvillano@uky.edu
University of Kentucky