Abstract # 2019: Biological and prognostic relevance of epigenetic regulatory genes in high-grade gliomas (HGGs).

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Background

- Gliomagenesis is regulated by dynamic epigenetic modifications of DNA methylation, deregulation of histones and alteration of the human Switch/Sucrose Non-Fermentable (SWI/SNF) chromatin remodeling complexes.
- These epigenetic genes are responsible for treatment resistance by inducing stemness of glioma cells and immune cells within the tumor microenvironment (TME).
- We evaluated the key chromatin remodeling (CR) genes and their interactions with other regulatory genes that are of prognostic importance.

Methods

- A total of 1856 HGGs underwent molecular profiling at Caris Life Sciences (Phoenix, AZ).
- Molecular analyses included next-generation sequencing of DNA (592 Genes, NextSeq or WES, NovaSeq) and RNA (WTS, NovaSeq).
- Cell infiltration in the TME was estimated by quanTIseq.
- X2/Fisher's-exact/Mann-Whitney U tests were used for comparison, and significance was determined as p-value adjusted for multiple comparison by the Benjamini-Hochberg method (q < 0.05).
- Overall survival (OS) was calculated from the start of temozolomide (TMZ) to last contact using insurance claims data.

Results

Table 1: Patient Characteristics

	Total	Wildtype	Mutant
Count (N)	1856	1264	181
Median Age (range)	59.0 (2 - >89)	59.0 (2 - 89)	57.0 (11 - 87)
Male	59.9% (1112/1856)	61.5% (777/1264)	58.0% (105/181)
Female	40.1% (744/1856)	38.5% (487/1264)	42.0% (76/181)

Table 2: Mutation frequency of chromatin remodeling genes in the 1856 high grade glioma tumors

	Features	Positive (Cohort)	Negative (Cohort)	Mutation Percentage (the cohort of 1856 HGG)
DNA MeT	NGS-DNMT3A	17	1800	0.94
His AceT	NGS-EP300	5	1836	0.27
Histone demethylase	NGS-KDM6A	4	1826	0.22
	NGS-KDM5C	2	1835	0.11
Histone methyltransferase	NGS-SETD2	62	1750	3.42
	NGS-KMT2D	18	1823	0.98
	NGS-KMT2C	11	1827	0.60
	NGS-KMT2A	9	1824	0.49
	NGS-EZH2	6	1836	0.33
	NGS-NSD1	3	1838	0.16
SWI/SNF	NGS-ARID1A	32	1804	1.74
	NGS-ARID2	15	1824	0.82
	NGS-SMARCA4	14	1823	0.76
	NGS-ARID1B	12	1815	0.66
	NGS-PBRM1	10	1832	0.54
	NGS-SMARCB1	5	1837	0.27
	NGS-SMARCE1	3	1828	0.16
Transcription coactivator	NGS-ASXL1	16	1616	0.98

Results

Figure 1: molecular differences in CR-mutated vs. wild types in high grade glioma. 1a: comparison in all tumors (all shown differences significant); 1b: comparison in IDH WT/MSS tumors (green: significant (q<0.05); purple: trending (p<0.05 and q>0.05)

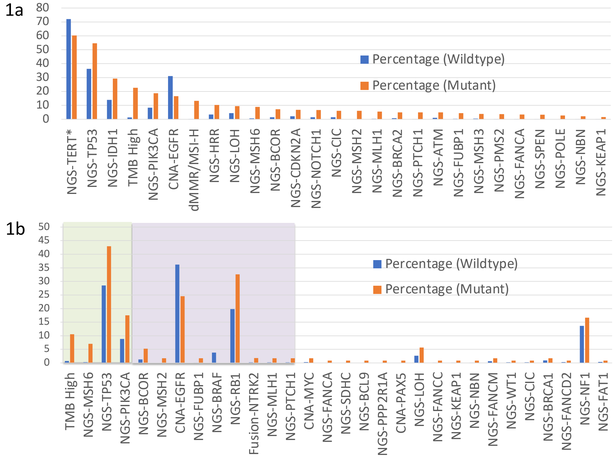
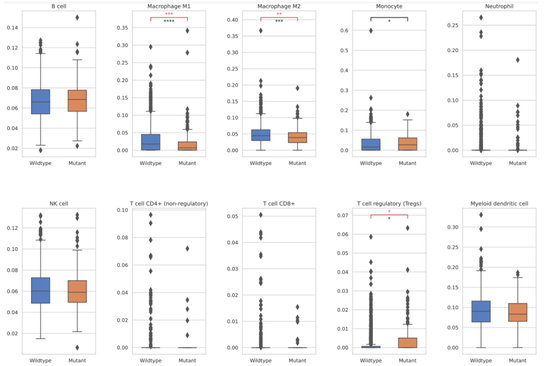


Figure 2: cell populations in the TME in CR-mutated vs. wild type in high grade glioma



Results

Figure 3: cell populations in the TME (3 a-b) and expression of selected immune-related genes (3c-d) in subgroups of CR mutations vs. wild type in high grade glioma

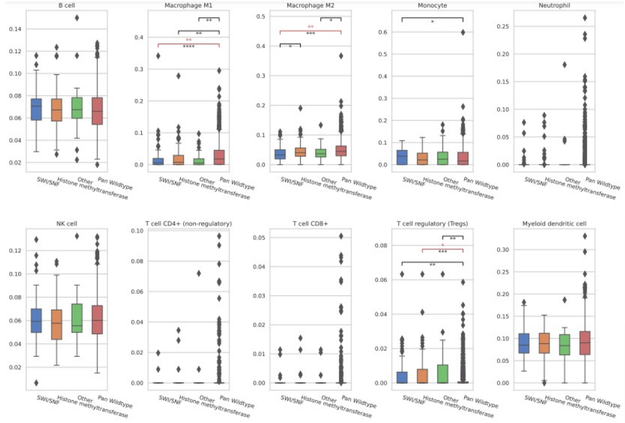


Figure 4: expression of selected immune-related genes in CR-mutated vs. wild type in high grade glioma.

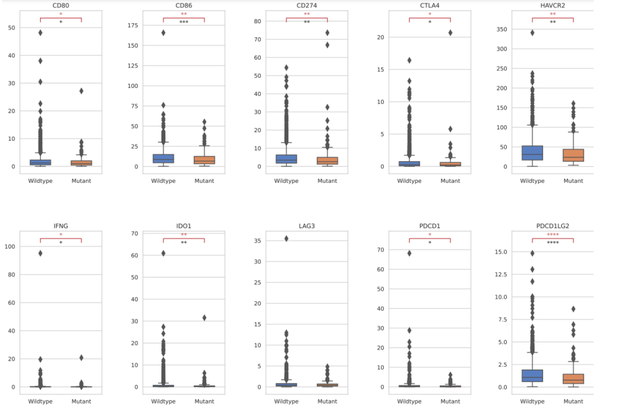
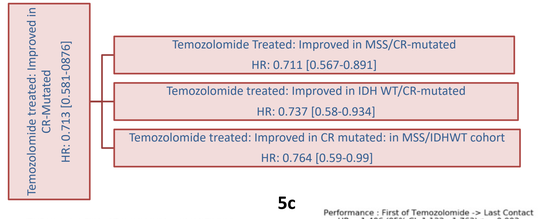
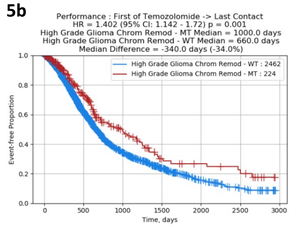


Figure 5: post-temozolomide survival in high grade glioma patients with or without chromatin remodeling mutations. 5a. Summary of Hazard Ratio (HR) in all HGG tumors and in molecular subgroups. 5b-e: Kaplan-Meier estimate of post-temozolomide survival in all HGG tumors(5b), in MSS-HGG tumors (5c), in IDH-WT HGG tumors (5d) and in IDH WT and MSS HGG tumors (5e)

5a



5b



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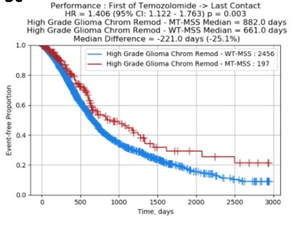

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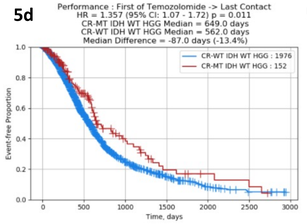

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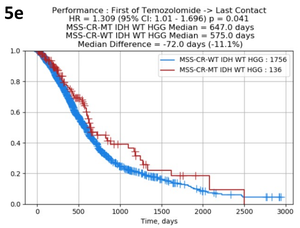

Conclusions

Nearly 10% of HGGs carry mts in CR genes. CR-mt HGGs possess significantly more favorable genetic alterations and colder TME compared to the CR-WT HGGs and showed better OS when treated with TMZ in univariate analysis. Multivariate modeling and analysis of associations with specific targeted therapies is underway.