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Abstract

Purpose of review

Recent evidence suggests high tumor mutational burden (TMB-H) as a predictor of response to immune checkpoint blockade (ICB) in cancer. However, results in TMB-H gliomas have been inconsistent. In this article, we discuss the main pathways leading to TMB-H in glioma and how these might affect immunotherapy response.

Recent findings

Recent characterization of TMB-H gliomas showed that “post-treatment hypermutation” related to mismatch repair (MMR) deficiency is the most common mechanism leading to TMB-H in gliomas. Unexpectedly, preliminary evidence suggested no benefit with ICB as compared to chemotherapy in this population. In contrast, ICB response was reported in a subset of TMB-H gliomas associated with constitutional MMR or polymerase epsilon (POLE) defects (e.g., constitutional biallelic MMRd deficiency). In other cancers, several trials suggest increased ICB efficacy is critically associated with increased lymphocyte infiltration at baseline which is missing in most gliomas. Further characterization of the immune microenvironment of gliomas is needed to identify biomarkers to select the patients who will benefit from ICB.

Summary

Intrinsic molecular and immunological differences between gliomas and other cancers might explain the lack of efficacy of ICB in TMB-H gliomas. Novel combinations and biomarkers are awaited to increase immunotherapy response in these cancers.

Key words

Biomarkers; immune checkpoints; immunotherapy; chemotherapy; immune microenvironment.

Introduction

Gliomas are the most common primary tumors of the central nervous system (CNS) [1]. They can affect patients of any age. They are frequently aggressive and responsible for high morbidity and mortality. The treatment of gliomas varies depending on accessibility for surgical resection, tumor grade and molecular profile. It typically includes radiation therapy and chemotherapy with alkylating agents such as temozolomide (TMZ) [2–4]. Despite these treatments, relapse is almost inevitable, especially in high-grade gliomas (HGG). Recurrent HGGs are among the most challenging cancers to treat, commonly harboring resistance to conventional, targeted therapies and immunotherapies [5].

The development of immune checkpoint blockade (ICB) has recently transformed the care of various cancer types. Intensive efforts have focused on identifying predictive biomarkers for clinical response to ICBs. Among several markers under investigation, a number of studies showed a positive correlation between ICB response rates and the presence of a high tumor mutational burden (TMB-H), defined as the number of coding mutations per megabase (Mb) across the genome [6–11]. These data as well as promising results from the Keynote-158 study led to the tumor-agnostic approval of the anti-PD1 pembrolizumab for TMB-H tumors by the Food and Drug Administration (FDA) in 2020 [12]. However, the correlation between TMB and ICB clinical benefit was mainly driven by data from a limited number of cancers such as melanoma, lung carcinomas and known mismatch repair deficient (MMR-d) cancers, and it remains unclear whether TMB-H and MMR-d are universally predictive in rare cancers not represented in these studies [13,14]. Gliomas are one of such cancers, as these tumors typically harbor a strong immunosuppressive TME [15] and conflicting data has been reported regarding their benefit from ICB, even in the presence of TMB[16–28].

In this review, we discuss recent data on hypermutated gliomas, their mechanism of mutagenesis and the potential role of TMB-H as a prognostic and predictive biomarker for response to chemotherapy and immunotherapy.

TMB-H in gliomas: mechanisms and potential role in predicting prognosis and response to conventional therapies.

Cancer somatic mutations are caused by mutational processes of exogenous and endogenous origin which happen during development of each tumor cell and its progeny [29–32]. Each mutational process can involve components of DNA damage or modification, abnormal DNA replication or repair and generates a “mutational signature” (e.g., specific mutational pattern), which can include base substitutions, small insertions and deletions (indels), chromosome rearrangements and copy number abnormalities. Mutational signatures can be extracted from tumor sequencing data (e.g., exome or

genome sequencing) to infer the mutational processes responsible for mutations in individual samples. Mutations are sometimes associated with the production of foreign antigens (neoantigens) which are recognized by the immune system and can elicit T cell immunoreactivity.

The frequency of mutations and underlying mechanisms causing them varies greatly across cancers [13,33]. A small subset of cancers (<20% of cancers) show a markedly elevated mutation burden which is referred to as TMB-H (or hypermutation, often used for some cancers like gliomas). The mutation burden defining this varies across assays used but is generally higher than 10 mutations per Mb of genome sequenced. Exceptionally (<1% of cancers), an “ultra-hypermutated” (i.e. TMB higher than 100 mutations per Mb) is observed [13]. TMB-H is prevalent in melanoma [34] and lung cancer [35], where the increase in TMB is mainly related to environmental mutagens exposure (tobacco smoke, UV light), and associated with ICB response [36]. In gliomas, TMB-H is less common and observed in two distinct contexts associated with unique biology: de novo (i.e., hypermutation present in the newly-diagnosed tumor) and post-treatment (i.e. hypermutation only found at recurrence after treatment).

De novo hypermutation

De novo hypermutation is found in less than 2% of all newly-diagnosed gliomas [14]. De novo hypermutation in gliomas has been reported in tumors with inherited or somatic defects of the DNA polymerases ε (POLE) and δ (POLD1) or the MMR system, which lead to the loss of polymerase proofreading or DNA replication error repair, respectively (Figure 1). Given its rarity and lack of dedicated prospective trials focusing on these patients, the management of gliomas in patients with de novo TMB-H glioma is not well codified [37].

DNA replication fidelity is primarily governed by the DNA polymerases POLE and POLD1 catalytic and proofreading domains. Germline pathogenic mutations in the exonuclease domains of polymerases POLE and POLD1 predispose to adenomatous polyps, colorectal cancer (CRC), endometrial cancer, and more rarely to other malignancies including glioblastoma [26,38], all of which are typically harboring hypermutation or ultra-hypermutation [13]. Somatic POLE defects have also been reported in glioblastoma [39]. Very little is known about the phenotype of POLE/POLD1-deficient gliomas. Recent studies have suggested an association between POLE/POLD1 defects, increased inflammatory infiltrates, and longer survival in gliomas, but these data need further confirmation in larger datasets [40].

The MMR system - consisting mainly of MSH2, MSH6, MLH1 and PMS2 proteins - is responsible for recognizing base-base mismatches and indels occurring during DNA

replication and recruiting proteins which excise the newly-synthetized strand before DNA is resynthesized by DNA polymerases [33]. Germline - and less commonly somatic - MMR defects have both been reported in de novo hypermutated gliomas. Constitutional (Biallelic) mismatch repair deficiency (CMMR-d) is a rare autosomal recessive disorder caused by germline biallelic MMR mutations, most commonly affecting PMS2, and characterized by early-onset cancers. Gliomas are one of the tumors commonly seen in CMMR-d patients [26,41–45]. They develop at younger age (<10 years). The histology is most commonly glioblastomas which are wild-type for other common defining driver events such as *H3F3A*, *IDH1/2*, or infant-type receptor tyrosine kinase (RTK) aberrations. The prognosis of CMMR-d patients is poor, especially once patients develop brain tumors. In a subset of patients with CMMR-d glioma, secondary hits in the polymerase POLE/POLD1 are acquired, leading to a rapid burst in the mutational burden (ultra-hypermutation) (Figure 1) [13,46].

Lynch syndrome is an autosomal dominant disorder caused by germline heterozygous inactivating mutations of one of the MMR genes. Patients with Lynch syndrome can develop cancers after a second hit occurring in the remaining wild-type MMR allele leading to MMR loss of function, which typically occurs after the first decade of life. Patients with Lynch syndrome most commonly develop colorectal, urinary, or gynecological cancers but can also suffer from high-grade glioma [47,48]. Most gliomas arising in patients with Lynch syndrome are IDH1/2-wild-type glioblastomas and seem to have a poor prognosis, although IDH1/2-mutant astrocytomas with MMR-d have also been reported [47,49].

Post-treatment hypermutation

Post-treatment hypermutation is the most common cause of TMB-H in gliomas, ranging from 5-60% of gliomas depending on tumor subclass, genetics, and treatment history [50,51]. Post-treatment hypermutation is predominantly seen in gliomas which are known to be the most responsive to chemotherapy [14,50,52–56]. TMZ is an alkylating agent widely used to treat gliomas. Its mechanism of action is based on the production of an intermediate metabolite reaching high concentration in the brain and producing methyl groups in tumor cells DNA, particularly on N7 and O6 guanines residues [57]. The enzyme O6-methylguanine DNA methyltransferase (MGMT) removes the O6 guanine methyl groups (O6-meG) which are the most cytotoxic lesions [58]. The enzyme is a “suicide” protein and each MGMT protein can only repair one O6-meG residue on DNA, which means the levels of MGMT protein in cells is critical to DNA repair. MGMT promoter methylation, which silences its expression, leads to an MGMT-deficient state

(MGMT-d), and is associated with increased sensitivity to TMZ and improved prognosis in patients with glioma [59,60].

In the absence of O6-meG removal (e.g. in MGMT-d tumors), replication of O6-meG-containing DNA results in the insertion of a thymine opposite the O6-meG, creating a O6-meG:T mismatch that is recognized by the MMR machinery. Failed attempts to repair O6-meG:T mismatch by MMR generate DNA strand breaks, ultimately leading to cell cycle arrest and cell death. This means that TMZ cytotoxicity is critically dependent on a functional MMR pathway. Consequently, MMR-d cells (e.g. cells lacking MMR capacity due to mutations in genes encoding MMR proteins) display resistance to alkylating agents such as TMZ [14].

MMR-d cells have increased burden of mutations of several types. Single base substitutions are the most common and are the mutation type reported in “TMB” most commonly calculated from sequencing. In addition, MMR deficiency also results in mutations (e.g. indels) at tandemly repeated DNA motifs (microsatellites) which lead to microsatellite instability (MSI), a well-known and widely used marker to diagnose MMR deficiency in common MMR-d cancers such as colorectal cancer [61]. The degree to which the MSI/indel repair and MMR are linked in TMB-H cancers is not well understood and in the most common MMR-d cancers they co-occur in almost all cases.

In gliomas, TMZ-induced DNA damage and hypermutation is now known to be characterized by the acquisition of MMR-d mutations or other alterations but shows a lack of MSI or significantly increased indels. They also harbor a unique MMR-d mutational signature (signature 11) specific to TMZ in a setting of cells which cannot repair TMZ-related mismatches due to MMR deficiency. Interestingly, MMR-d gliomas with TMB-H also lack significant inflammatory $CD8^+$ infiltrates compared to the most common MMR-d cancers [14,62–64], even when the latter are located in the CNS [65,66].

Origins of MMR-d cells in post-treatment gliomas and clinical implications

The highest rates of TMB-H have been reported in the most chemosensitive subtypes where MGMT promoter methylation is more common (e.g., IDH1/2-mutant astrocytomas and oligodendrogliomas). While recent studies help to define post-treatment TMB-H gliomas as an MMR-d cancer, a question that remains unaddressed is whether pre-existing MMR-d cells are selected for after treatment response or whether the initial MMR mutations are induced by TMZ in cells and selected for during treatment, or a combination of both processes. Although it is difficult to ascertain the origins of post-treatment MMR deficiency in individual samples, indirect data suggests that in a subset of samples TMZ induces mutations which cause MMR-d in cells. This is for instance

showed by the fact that the MMR-d inducing hotspot mutation most frequently found in post-treatment hypermutated gliomas (~15%) is an MSH6 T1219I mutation with dominant negative effect found exceptionally in patients with Lynch syndrome [67–71]. This variant results from a C > T transition similar to TMZ-associated lesions and is inducible in in vitro models chronically exposed to TMZ [14].

Conflicting data has been reported regarding the prognosis of post-treatment hypermutation. While the GLASS study found no prognostic significance [56,72], two retrospective studies suggested that post-treatment hypermutated might have a worse prognosis from recurrence when compared to non-hypermutated recurrences. However, since secondary MMR defects occur in tumors most sensitive, and potentially with the greatest beneficial responses to TMZ, the deleterious effect of secondary MMR deficiency (poor prognosis after relapse) is unlikely to outweigh its positive effects. These results therefore do not argue for the use of TMZ vs nitrosourea-based protocols (e.g. PCV) in lower grade gliomas, especially given that randomized trial data demonstrated survival benefit with TMZ in both IDH1/2-wild-type and -mutant tumors [73,74].

Regarding treatment response, while data regarding radiation therapy or chemoradiation is currently insufficient [75], consistent evidence shows that MMR-d or TMB-H in gliomas are both predictive biomarkers for resistance to single-agent TMZ. Interestingly, experimental data from models and indirect evidence from clinical samples suggest that at least a subset of MMR-d tumors might retain sensitivity to nitrosoureas such as CCNU [14,57,76,77]. This observation might explain at least in part the superiority of the TMZ/CCNU combination with radiation compared to standard chemoradiation with TMZ recently reported in a randomized trial of newly-diagnosed MGMT-d glioblastomas [78]. Further research is needed to address whether the TMZ/CCNU combination or PCV might reduce the risk of post-treatment hypermutation and to characterize the unique resistance mechanisms associated with this combination. Another area of ongoing investigation is whether PARP inhibition might restore TMZ sensitivity in MMR-d glioma cells and therefore prevent the development of post-treatment hypermutation [79].

Treatment of hypermutated gliomas with ICB

The concept that TMB-H tumors are capable of presenting immunogenic neoantigens is well established [6]. Neoantigens are recognized and processed by dendritic cells which recruit lymphocytes against tumor neoantigens. In this context, ICB treatment enables lymphocyte proliferation (anti-CTLA-4) and prevents lymphocyte inactivation (anti-PD-1/PDL-1). Melanoma [80], NSCLC [81] and MMR-d tumors with MSI [82] are the classic examples of TMB-H benefiting from ICB, but clinical data in hypermutated glioma as well

as other cancer types has been so far inconsistent. Research for biomarkers predicting ICB response in the context of hypermutation is an area of intensive investigation [11,83,84]. A recent pan-cancer study was able to categorize TMB-H tumors in two groups with distinct pattern of ICB response [85]. The first group, enriched with ICB responders, consisted of tumors in which increased TMB was associated with a great number of $CD8^+$ lymphocytes infiltrates. In contrast, the second group showed no correlation between increased TMB and $CD8^+$ infiltration. Of note, the latter group represents the majority of cancers including TMB-H gliomas [16]. These important results clearly indicate TMB is not a universal predictive marker and suggests that additional biomarkers are required to appropriately select the patients most likely to benefit from immunotherapy.

Current data in de novo and post-treatment hypermutated gliomas

ICBs as a treatment has not shown improvement compared to standard of care in newly-diagnosed and recurrent glioblastomas, although the majority of patients included in these trials were TMB-low gliomas [86]. Unfortunately, similar results have been observed even in TMB-H gliomas now. Indeed, while reports suggested that a subset of hypermutated gliomas might benefit from ICB [17], recent retrospective analyses of hypermutated or MMR-d gliomas - mostly post-treatment - treated with anti-PD1 suggested that the use of ICB does not translate into clinical benefit (Table 1) [14,24]. Nevertheless, given their retrospective nature, further confirmation of these results in prospective studies is warranted (NCT03718767, NCT02658279, NCT04145115).

In contrast, in de novo TMB-H gliomas ICB has shown encouraging results reported in series studies [17,20] and in several case reports [17,19,21,22,26–28]. These findings were confirmed in a recent non-peer reviewed pre-print [20]. In this study, the authors analyzed the responses to ICBs of pediatric CMMR-d patients, including patients with glioma. Interestingly, in a subset of tumors with additional POLE/POLD1 defects, significant recruitment of inflammatory $CD8^+$ cells and ICB benefit was observed. Even though CMMR-d gliomas response to ICBs was lower than in other tumor types developed in the same patients, it remained in appearance superior to the one of TMB-low gliomas [20].

Potential explanations for the low response rates in gliomas

A number of unique characteristics of hypermutated gliomas with other MMR-deficient tumors could at least in part explain the lack of response to ICB. First, the lack of clonal MSI and predominantly subclonal mutational burden of gliomas with post-treatment hypermutation could be associated with the absence of effective immune responses

against tumor neoantigens [10,14,83,87]. Interestingly, patients with CMMR-d are more likely to harbor POLE/POLD1 defects which lead to ultra-hypermutation and accumulation of indels which are much more immunogenic neoantigens [88] (Table 1). This might explain the presence of $CD8^+$ cells expressing PDL-1 and increased rate of benefit from ICB in this setting. Furthermore, the absence of significant T lymphocyte infiltrates and ICB response even in some gliomas with de novo MMR-d gliomas (Lynch syndrome) suggest that beyond the nature of tumor neoantigens, specificities in the immunosuppressive microenvironment of gliomas - especially in the population of immunosuppressive microglial and macrophage cells which are the dominant immune TME cell types in glial tumors [15] - contribute significantly to gliomas ICB resistance. A proposed mechanism of resistance in non-responders derived from the study of preclinical models is the expansion of Treg ($FOX3P^+$) and macrophages in the tumor microenvironment [89]. In this study, increased $CD8^+$ infiltrates and INF-γ signaling was observed in the responders, suggesting that additional biomarkers might enable further subgrouping hypermutated gliomas and identifying ICB responders. The benefit of neoadjuvant PD1 inhibitors may support this as surgery is known to increase the levels of macrophages within the tumors.

Conclusions

Recent studies have improved our understanding of the mechanisms responsible for TMB-H in gliomas and its potential role as prognostic and predictive biomarker. Efforts are ongoing to determine the optimal strategy for use of radiation therapy and chemotherapy in the context of TMB-H. Areas of investigation include the development of non-invasive biomarkers to monitor hypermutation and the investigation of novel therapeutic strategies that will prevent MMR-d acquisition in the most chemosensitive such as oligodendrogliomas (e.g. by using CCNU or PARP inhibition in combination with TMZ) to determine whether preventing TMB-H development might improve patients outcome. As regard immunotherapy strategies, response and clinical benefit is driven by a sum of complex factors which cannot be explained only with the number of mutations in tumor exomes. Neoantigen quality seems determinant to responses as well as the presence of effectors immune cells in the TME. Approaches aimed at increasing both tumor infiltration by cytotoxic lymphocytes are therefore likely both necessary in order to improve the response to immunotherapy in gliomas. Among several current strategies under investigation, IL-12 gene therapy combined with ICB showed safety and biological efficacy (production of IFN-γ) in HGG patients including one patient with post-treatment hypermutation [22,90].

Key points

TMB-H in gliomas is observed in two distinct contexts associated with unique biology: de novo and post-treatment.

De novo TMB-H is observed in tumors with inherited or somatic defects of the DNA polymerases POLE/POLD1 or the MMR system.

TMZ together with MMR-d is responsible for TMB-H and resistance in post-treatment gliomas.

TMB-H MMR-d gliomas harbor unique characteristics (e.g., low lymphocyte infiltration) compared to other cancers where MMR-d is common.

ICBs response in TMB-H is uncommon except in rare contexts such as CMMR-d.

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Figures and tables legends

Figure 1. Characteristics associated with de novo (top) and post-treatment (bottom) TMB-H in gliomas. Frequency and distribution across ages represent adults/adolescents/infants. De novo TMB-H tumors are rare and related to young patients. In these tumors, the driver MMR/POLE mutations can be inherited or somatic. TMB-H is found in the newly-diagnosed tumor. The combination of increased TMB, increased indels burden (often observed in POLE-deficient tumors), and increased tumor infiltration by T cells make these tumors more likely to benefit from ICBs, although the relative contribution of each individual factor is unknown. Post-treatment TMB-H tumors are strongly related to the use of TMZ in chemotherapy sensitive tumors (eg MGMT-d). TMB-H is only found in the recurrent (post-chemotherapy) tumor. Increased tumor infiltration and ICB response in this context are both rare.

Table 1. Case reports and series of TMB-H gliomas and CNS tumors treated with ICB and other immunotherapy approaches.

§ Defined by prolonged disease control or radiological response as assessed by authors. A subset of patients in the Morgenstern et al. study [20] showed tumor control after initial flare.

† Post-nivolumab progression data from patient reported in the Bouffet et al. 2016 study [17].

†† POLE deficiency assessed based on mutational signature analysis. PFS of 9.9 months and OS of 21.6 months reported for the overall dataset.

* PFS and OS not available for POLE-deficient vs POLE-proficient cases. PFS of 9.9 months and OS of 21.6 months reported for the overall dataset.

Abbreviations: IDH1/2-mut, IDH1/2-mutant; MMR-d, MMR-deficient; POLE-d, POLE-deficient; TMZ, temozolomide; RT, radiation therapy; PFS, progression free survival; OS, overall survival; na, not available

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† Post-nivolumab progression data from patient reported in the Bouffet et al. 2016 study [17].

†† POLE deficiency assessed based on mutational signature analysis.

* PFS and OS not available for POLE-deficient vs POLE-proficient cases. PFS of 9.9 months and OS

Abbreviations: IDH1/2-mut, IDH1/2-mutant; MMR-d, MMR-deficient; POLE-d, POLE-deficient; TM

Study	IDH1/2-mut	MMR-d	Stage	Prior TMZ
POLE-deficient				
[17] Bouffet et al. 2016 (n=2)	0 (0%)	2 (100%)	Recurrence	1 (50%)
[26] Johanns et al. 2017 (n=1)	0 (0%)	NA	Recurrence	1 (100%)
[28] Larouche et al. 2018 (n=1) †	0 (0%)	1 (100%)	Recurrence	1 (100%)
[27] Anghileri et al. 2021 (n=1) ††	0 (0%)	1 (100%)	Recurrence	1 (100%)
[19] Sathornsumetee et al. 2021 (n=1)	0 (0%)	NA	Recurrence	1 (100%)
[20] Morgenstern et al. 2021 (n=19)	na	19 (100%)	na	na
POLE-proficient				
[14] Touat et al. 2020 (n=11)	3 (27.2%)	11 (100%)	Recurrence	11 (100%)
[22] McCord et al. 2021 (n=1)	1 (100%)	1 (100%)	Recurrence	1 (100%)
[20] Morgenstern et al. 2021 (n=8)	na	8 (100%)	na	na
POLE status na				
[24] Lombardi et al. 2020 (n=13)	4 (30.7%)	13 (100%)	na	13 (100%)
[21] Rittberg et al. 2021 (n=1)	1 (100%)	1 (100%)	Primary	0 (0%)
[27] Alharbi et al. 2018 (n=1)	na	1 (100%)	Recurrence	1 (100%)
[20] Morgenstern et al. 2021 (n=4)	na	4 (100%)	na	na

ɪmunotherapy approaches.

ɔf patients in the Tabori et al. study [20] showed tumor control after init

ɔf 21.6 months reported for the overall dataset.

Z, temozolomide; RT, radiation therapy; PFS, progression free survival; O

Prior RT	Clinical benefit §	PFS months	OS months
2 (100%)	2 (100%)	9; 11	NA
1 (100%)	1 (100%)	2	NA
1 (100%)	1 (100%)	30 months, ongoing	30 months, ongoing
1 (100%)	1 (100%)	13	80,4
1 (100%)	1 (100%)	15	20
na	13 (68.4%)	na *	na *
11 (100%)	0 (0%)	1,38	8,07
1 (100%)	0 (0%)	2	na
na	1 (12.5%)	na *	na *
13 (100%)	0 (0%)	2,2	5,4
0 (0%)	1 (100%)	20	NA
1 (100%)	1 (100%)	10	na
na	3 (75%)	na *	na *

ial flare.

)S, overall survival; na, not available

Notes
Both patients had combined MMR-d and POLE-d (CMMR-d); one of patients is included in Larouche et al. [86]
Patient with germline POLE deficiency
Response to combined nivolumab and ipilimumab after progression on nivolumab De novo TMB-H patient with high lymphocyte infiltration and high burden of clonal variants in both primary and recurrent tumor samples
Clinical benefit with combined bevacizumab and pembrolizumab
Higher TMB, indel burden, T-cell infiltration and PDL1 expression in tumors with combined MMR-d and POLE-d as compared to MMR-d only tumors
De novo (5) and post-treatment (6) TMB-H samples
Loss of MMR-d clones after local IL-12 and anti-PD-1 combination therapy
Significantly less response seen compared to POLE-deficient cases
Neither TMB nor CD8+ T-cell infiltration associated with pembrolizumab activity
CMMR-d patient
CMMR-d patient
Tumor sequencing data not available. 2 Lynch and 2 CMMR-d patients

De novo Hypermutated

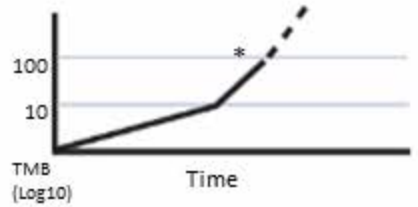
Gliomas associated with constitutional mismatch repair defects

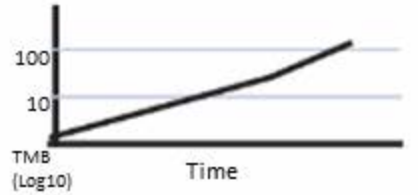
Frequency and distribution

bMMRD <1%
Lynch 1-2%

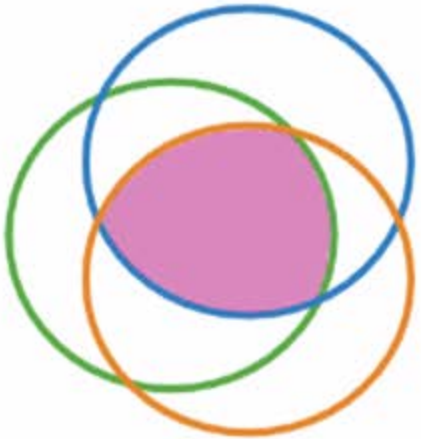
Children and young adults

Pattern of DNA replication repair deficiency and mutation gain



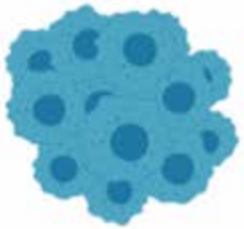


Response to ICI and putative predictive factors overlap



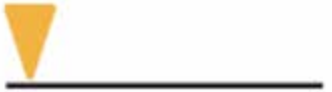
Hypermutation associated with an "inflamed" tumor microenvironment > frequent response to ICB

Gliomas associated with constitutional polymerase defects



<1%

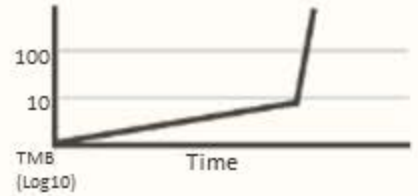
Children and young adults



Post-treatment Hypermutated

20%

All age



Hypermutation associated with a "cold" tumor microenvironment > uncommon response to ICB