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Biomarkers of immunotherapy response in neuro-oncology

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Abstract

While immunotherapy has shown significant promise for many cancers, its translation into the treatment of brain tumors has been limited. While several immunotherapy trials have been negative in brain cancer, these studies have identified a subset of responders which has generated considerable excitement for the future of the field. In this review, we summarize promising immunotherapy response biomarkers for CNS tumors with a focus on brain metastases, glioblastoma, and meningioma. The potential value of genomic, transcriptomic, cellular, proteomic, radiologic, and liquid biopsy approaches are discussed in a tumor-specific fashion. We emphasize the need to validate and expand upon each of these purported biomarkers. Disease-specific immunotherapy response biomarkers may potentially lead to more efficacious clinical trial designs, ultimately leading to new treatment options for a subset of patients.

Key Points

1. Response biomarkers are needed for successful neuro-oncology immunotherapy trials.
2. Multiple molecular, cellular, and radiologic approaches have shown promise.
3. Validation is needed before these biomarkers can be used to inform clinical trials.

Introduction

Cancer immunotherapy has gained significant popularity in the last 2 decades. This was spurred in part by the seminal publication by Hodi et al. in 2010,[1] demonstrating in a phase 3 trial that inhibiting cytotoxic T-lymphocyte-associated antigen 4 (and therefore disinhibiting an anti-tumor T-cell response) was associated with improved survival in advanced melanoma. Since then, several immune checkpoint inhibitor (ICI) trials have been conducted across multiple cancer types with considerable success.[2] Additionally, other promising immunotherapeutic strategies have emerged including adaptive T-cell transfer (such as chimeric antigen receptor T cells, or CAR-T cells) and cancer vaccines.[3] Nevertheless, the same degree of benefit has not yet been realized in the field of neuro-oncology. This has been hypothesized to be due, at least in part, to the known heterogeneity and immunosuppressive microenvironment of CNS tumors.[4–6]

Traditionally, cancer biomarkers have consisted of molecules or substances produced by tumor cells that indicate certain characteristics such as subtype, grade, stage, or as we discuss here, response to therapy.[7–9] However, with increasing genetic and molecular characterization of cancers, modern biomarker definitions often extended to include genomic

markers.[10,11] Similarly, imaging characteristics of tumors are increasingly studied as radiomic "biomarkers."[12] Considerably efforts have been made to identify immunotherapy response biomarkers in CNS tumors spanning factors including soluble serum factors, genomic profiles, cellular factors, imaging characteristics, and many others.[7–9,12] Nevertheless, the role of both traditional and more advanced biomarkers of immunotherapy response for neuro-oncological applications has yet to be fully established. In this review, we explore purported immunotherapy biomarkers in CNS tumors, with a focus on brain metastases (BMs), glioblastoma (GBM), and meningioma. We suggest a need for biomarker-driven trials to address the heterogeneity which may have limited translational success in this field to date.

Brain Metastases

The development of metastatic brain tumors is a common and devastating event in cancer progression. Occurring in approximately one-quarter of all cancer patients, it carries a median overall survival (OS) of 10–16 months despite standard-of-care treatment with surgical resection and radiotherapy.[13] Traditionally, the role of chemotherapy been limited by constraints imposed by the blood–brain barrier.[14] More recently, the introduction of immunotherapy has dramatically altered the landscape of solid tumors, particularly those most associated with intracranial metastases such as lung and melanoma.[15] The most common form of immunotherapy utilized in BMs is ICIs. However, it is noteworthy that even in metastatic melanoma, wherein ICI treatment is highly efficacious, dual-ICI treatment was associated with intracranial efficacy in only 57% of patients[16]; while encouraging, this best-case result demonstrates the need for better treatment options and response biomarkers.

Tumor mutational burden (TMB) and microsatellite instability (MSI) are among the most studied biomarkers of ICI response in solid tumors overall, demonstrating a clear association with treatment response in multiple primary cancers.[17–22] However, their utility in BMs specifically remains poorly understood. Interestingly, 1 study examining the link between TMB and immunotherapy response in multiple advanced cancers found that BMs were more common in the "TMB-high" group of patients (>10 mutations/Mb based on the targeted Next-Generation Sequencing panel Tempus xT) than the "TMB-low" (<10 mutations/Mb) group,[20] though the ability of TMB to predict treatment response for intracranial disease specifically remains poorly understood and sequencing was not done on the BMs themselves. Indeed, another study demonstrated that TMB is not predictive of immunotherapy response across all solid tumors, postulating that this may in part be due to this observation that BMs are associated with elevated TMB but poor survival.[23] Similarly, while MSI has clear implications for immunotherapy patient selection in solid cancers, its role in intracranial response prediction has not been well studied. Notably, 1 study found colorectal cancer BMs had increased MSI compared to primary tumors,[24] which was also shown in 2 cases of metastatic endometrial cancer.[25] While elevated TMB and MSI in BMs compared to primary tumors for some cancers suggest a potential role for ICI therapy, additional dedicated work is needed to validate their value as biomarkers for intracranial response.

The expression of programmed death ligand 1 (PD-L1) has also been investigated as a potential response biomarker in BMs with some success. In lung cancers, ICIs can be added to platinum-based chemotherapies, or used as monotherapy for patients with tumors with over 50% PD-L1 expression.[26–28] An open-label phase 2 trial of pembrolizumab in adults with advanced non-small cell lung cancer (NSCLC) and at least 1 BM measuring 5–20 mm, which was either untreated or progressing after radiation, demonstrated that high expression of PD-L1 (>1%) in primary tumors predicted response to pembrolizumab therapy using the mRECIST framework,[29,30] though only 29.7% of cases fitting that criterion exhibited response.[31] The tumor proportion score (TPS) of PD-L1, defined as the proportion of tumor cells with positive membrane staining of PD-L1, may also serve as a response biomarker for BM treated with ICIs: 1 study found that high intracranial TPS (40%) significantly prolonged intracranial progression-free survival in a cohort of patients with NSCLC.[32,33] A strong trend toward increased OS was also noted in melanoma BMs with high expression of PD-L1.[34] However, this correlation between PD-L1 expression and treatment response was not seen in a phase 2 trial of atezolizumab (a PD-L1 inhibitor) with carboplatin and pemetrexed in a cohort of patients with nonsquamous NSCLC with untreated BM,[35] suggesting it may not be universally applicable. Additionally, PD-L1 expression is often discordant between systemic and intracranial diseases, and BMs are typically associated with a lower expression which may partially explain the challenge with ICI resistance in this subset of tumors.[33,36] Other genes that are related to PD-L1 signaling may also serve as potential biomarkers. Mutations in the KRAS (Kirset rat sarcoma viral oncogene homolog) genes can lead to high expression of PD-L1,[37] and indeed, patients with NSCLC BMs and KRAS mutations had had improved OS compared to those without mutations when treated with ICI therapy.[38]

In addition to common pan-tumor ICI biomarkers discussed earlier, some markers have been noted to be disease-specific. In melanoma, the third most common type of metastatic intracranial disease, there is some evidence to suggest that *BRAF* mutations, which are often targeted using precision approaches, confer some susceptibility to immunotherapies. For example, the TRICOTEL trial, a phase 2 study of melanoma patients with BM in which a combination of atezolizumab and cobimetinib +/– vemurafenib showed intracranial response rates in 42% of BRAF mutated patients and 27% in the non-mutated samples based on the mRECIST framework as assessed by an independent review committee.[39] Moreover, comprehensive analysis of the tumor microenvironment (TME) of melanoma-derived BMs demonstrated strong relationships between T-cell clonotypes both intracranially and peripherally, and that these clonotypes, as well as the overall number of tumor-infiltrating T-cells, were associated with ICI response.[40] In this study, single-cell RNA sequencing and TCR clonotyping were performed on 32 melanoma

BMs and clonotypes were compared to matched blood and extracranial lesions. The authors identified the fraction of FOXP3/CD4+ T cells, the degree post-ICI TCR clonal expansion, and the proportion of TCR clones which were private the BM (ie, not shared within the blood nor extracranial disease), as being associated with response to ICI. Interestingly, patients exhibiting response to ICI therapy had a greater proportion of T-cell clones that were private to the intracranial disease, and those private T cells were also more likely to be exhausted due to persistent antigen stimulation. Given the success of ICIs in melanoma overall, these markers give promise to increasing their utility in the setting of BMs.

Liquid biopsy approaches have also shown considerable promise in the ability to noninvasively and longitudinally monitor the efficacy of immunotherapies in BMs, and are often agnostic to the type of primary tumor. One emerging approach relies on the capture of circulating tumor DNA (ctDNA) released from tumor cells into blood, which may be used to measure MSI and RMB to predict and monitor response.[41–44] Applying these approaches to the cerebrospinal fluid (CSF), 1 study revealed that CSF has a high ctDNA detection rate (92.3%), and that TMB obtained from the CSF correlates well with that from tumor DNA.[45] Extracellular vesicles (EVs) have also been identified as a promising immunotherapy biomarker in BMs given their ability to cross the blood–brain barrier.[46,47] In metastatic melanoma, Chen et al. have shown that EVs carrying PD-L1 suppress the function of CD8 T cells, and that the levels of circulating exosomal PD-L1 correlates with that of IFN-γ and varies throughout the course of anti-PD-1 therapy. The magnitude of the increase in circulating exosomal PD-L1 with ICI therapy can stratify patients into responders and nonresponders, pointing to their potential use as a marker for immunotherapy response.[48] More traditional immunophenotyping in the context of BM immunotherapy may also lead to new biomarkers, as intracranial metastases have been shown to alter the CSF immune microenvironment.[49,50] Notably, 1 group demonstrated that the CSF-derived cytokine LAMP3 correlated with intracranial response to camrelizumab and pemetrexed in the setting of NSCLC, suggesting that CSF cytokines may serve as a useful tool for measuring clinical response to ICIs.[51] While soluble factors such as chemokines (CXCL8 and 10), cytokines (IL-6, IL-10, and PRAP1), and peripheral blood cell immunophenotyping have also been posited as potential ICI response biomarkers for solid tumors overall,[52] their value in the context of BMs remains unclear.

Glioma

Gliomas are the most common primary malignant brain tumor in adults with an incidence of 6 per 100 000 individuals annually.[53] GBM (defined as an IDH-wildtype, WHO grade 4 astrocytoma) accounts for over 50% of all gliomas and has a median survival of 14–18 months from diagnosis.[54] Current standard-of-care treatment consists of maximal safe resection followed by radiotherapy and concomitant/maintenance Temozolomide.[55] Despite this, patients invariably recur with a median progression-free survival of 7 months after treatment and 5-year survival of 6.8%[53] with limited treatment options at recurrence.[56] With the success of immunotherapy for non-CNS malignancies, several notable trials have applied similar strategies to gliomas and specifically GBM. A systematic review of immunotherapy trials in GBM found a total of 97 immunotherapy-related trials between 1995 and 2024. Of these, 51% were phase 1, 7% were phase 3, and the treatments included ICIs, cancer vaccines, CAR-T cells, oncolytic viruses, and combinatorial trials.[57] However, clinical responses to such therapies have been mixed.[58]

Imaging is associated with important challenges in the context of glioma immunotherapy, but also provides opportunities for biomarker discovery. Transient imaging changes have been described in glioma and other tumors when treated with immunotherapy, and MRI is often limited in its ability to discriminate pseudo-progression secondary to immune infiltration from true progression.[59,60] The Immunotherapy Response Assessment for Neuro-Oncology (iRANO) was introduced to help in part inform on radiological assessments for neuro-oncology immunotherapy clinical trials.[60] While these challenges are critical in the routine monitoring of patients, radiological biomarkers can also potentially be used to predict and monitor treatment efficacy. A recent systematic review by Ghimire et al.[61] examined 9 studies on GBM radiologic immunotherapy response biomarkers, demonstrating that several elements may correlate with treatment response including apparent diffusion coefficient (ADC), cerebral blood volume (CBV), presence of hemorrhage, and noninterpretable radiomics/texture-based features. This offers an exciting potential avenue for noninvasive disease and treatment-response monitoring, though this field remains in its infancy with additional validation needed prior to its routine applicability.

TMB is a widely used biomarker of ICI efficacy due to the link between high mutational load and the generation of immunogenic neoantigens. This is demonstrated in the rare subset of histologically defined GBM in the setting of germline mismatch repair deficiency, which portents a hypermutated tumor phenotype of which multiple cases have been associated with a robust response to ICI.[62] Notably, this study does not include IDH status, but these are very rare in the pediatric population being described. Similarly, some evidence suggests favorable responses to ICI therapy in patients with hypermutated GBM secondary to germline POLE mutations.[63,64] However, these represent a small minority of cases and the utility of TMB in GBM overall is limited due to the relatively low TMB of sporadic GBM. In a study of 198 IDH wildtype GBM samples, high TMB (defined as >10 mutations/megabase) was found in only 3.5% of cases and was not associated with increased PD-1+ T cells, CD8+ T cells, or tumor-expressed PD-L1.[65] Another study using data from The Cancer Genome Atlas similarly found that TMB was not meaningfully associated with ICI response in glioma overall.[23] Similarly, other biomarkers that have been predictive of response to ICIs in other cancers such as MSI, tumor-infiltrating lymphocytes (TILs), and PD-L1 expression have not been found to be useful in GBM.[66,67]

Attempts to target common GBM alterations such as EGFRvIII or IL13Rα2 overexpression with small molecule

inhibitors, vaccines, and CAR-T therapy have also been limited by tumor evolution and plasticity, wherein resistance develops due to loss of targeted mutation.[68] On the other hand, ERK1/2 phosphorylation, a marker of MAPK/ERK pathway activation, has been shown to be predictive of OS in 2 trials of adjuvant PD-1 blockade in GBM.[69] Additionally, Replication Stress Response Defect (RSRD), a gene expression signature correlating with defective replication stress response, has also been shown in multiple non-hypermutated solid tumors including GBM to be predictive of ICI sensitivity,[70] with an area under the receiver-operating characteristic curve of 0.81 for response prediction in 1 cohort[71] of GBM patients treated with programmed death 1 (PD-1) inhibitors. While its requirement for RNA sequencing is relatively resource-intensive for widespread clinical use, such whole-genome data can be used to generate new insights into treatment-specific changes to tumor biology. Moreover, targeted gene panels could be developed to significantly reduce costs if the translational value of this gene signature is ratified in prospective clinical trials.

Due to the known intratumoral heterogeneity within the GBMTME,[72] efforts have been made to identify molecularly distinct TME subtypes of GBM that inform a response to immunotherapies. Three distinct clusters of GBM microenvironment, termed TME^{low}, TME^{med}, and TME^{high}, have been identified using deconvolutional tools that infer the relative abundance of each immune cell type within a tumor from bulk transcriptomic (RNA sequencing) data.[73] In this approach, unsupervised clustering was done based on the inferred proportion of several immune cells including T cells, B cells, NK cells, monocytes, microglia, neutrophils, endothelial cells, and myeloid dendritic cells. According to this original description, TME^{high} tumors displayed elevated lymphocyte infiltration and PD-1/CTLA-4 expression, TME^{med} tumors had upregulated endothelial markers with a heterogeneous immune microenvironment, and TME^{low} cases were relatively immune-cold. Post-hoc analysis of 3 GBM ICI trials has found that TME^{high} patients had improved OS when treated with neoadjuvant anti-PD-1 and a trend toward improved survival in adjuvant anti-PD-1 and oncolytic virus (PVSPIR).[71,73–75] Responses to treatment, however, may be context and treatment-specific. A recent combinatorial oncolytic virus with PD-1 inhibition in recurrent GBM, motivated by the notion that oncolytic viral therapy can be used to transform the immunologically "cold" microenvironment of GBM into an immunologically "hot" microenvironment wherein ICIs could be more effective, showed improved OS in the TME^{med} group compared to TME^{low} and TME^{high}.[76] This suggests that the influence of TME on response prediction may be specific to trial parameters such as the specific virus being used, and highlights the complexity of the TME in the context of immunotherapy. Given that the TME group is inferred from RNA-sequencing, which can also be used to understand these treatment-driven shifts in TME and yield complementary biomarkers such as the aforementioned RSRD score, we believe that the continued use of genome-wide approaches for all CNS immunotherapy trials will hopefully yield validation of current findings and additional novel insights, though additional work is needed prior to applicability in routine clinical practice. This would allow for ongoing prospective validation of existing biomarkers prior to their eventual use in clinical trial design as well as the simultaneous identification of increasingly accurate molecular biomarkers.

Several host factors have also been correlated with the success of immunotherapy, particularly in the setting of cancer vaccines. For example, while PD-L1 expression in GBM has not been found to be a useful biomarker in the setting of ICI therapy, PD-L1 expression on myeloid cells was found to be important in a phase 2 trial of an autologous heat shock protein peptide vaccine in newly diagnosed GBM.[66] In this single-arm study that recruited 46 patients, the median OS among patients with high PD-L1 expression on myeloid cells (greater than the median) was 18 months compared to 44 months in patients with low PD-L1 expression on myeloid cells. Another similar phase 2 trial investigating a different heat-shock protein peptide vaccine in recurrent GBM found that peripheral lymphocyte count was associated with response, wherein patients with counts below the cohort median had significantly reduced OS (hazard ratio [HR] 4.0, $P = .012$).[67] The "GBM-Vax" phase 2 trial investigating a dendritic cell vaccine in GBM, while negative, also found that higher pretreatment levels of CD8+ lymphocytes and Granzyme B by ELISPOT were associated with improved survival.[77] Finally, a randomized, double-blind, placebo-controlled phase 2 study of the ICT-107 dendritic cell vaccine for patients with newly diagnosed GBM found that patients with the HLA-A2+ haplotype derived survival benefit regardless of MGMT methylation status, whereas patients with the HLA-A1+ haplotype derived benefit only in the setting of methylated MGMT.[78] Collectively, these findings suggest the critical importance of a patient's systemic immune state as a biomarker for immunotherapy success, particularly in the context of vaccines. For some patients, a multipronged immunotherapeutic strategy may therefore be required.

EVs, which play an important role in cell-to-cell interactions, have also recently been identified as potentially useful biomarkers in the context of cellular immunotherapies in GBM. Two early-phase CAR-T-cell-based clinical trials for recurrent GBM were simultaneously published earlier this year with promising results.[79,80] One of these studies, which treated 3 patients with next-generation CARv3-TEAM-ET cells targeting both the EGFR protein and the EGFRvIII tumor-specific antigen, used EV RNA from CSF and peripheral blood to monitor EGFRvIII and EGFR copy numbers post-treatment.[80] There appears to be some correlation of biofluid levels with treatment efficacy, and in 1 patient who underwent repeat resection after CAR-T-cell therapy, the tumor tissue was negative for EGFRvIII consistent with the liquid biopsy findings. While larger cohorts are needed, early evidence suggests the potential value of EV-based assays as a biomarker for cellular immunotherapy in GBM. A summary of the biomarkers identified in the aforementioned immunotherapy-related clinical trials is shown in Table 1.

Overall, glioma, specifically GBM, poses a formidable challenge and despite numerous efforts to improve survival, no approved immunotherapies exist to date. The molecular heterogeneity, immune escape mechanisms, and immunosuppressive microenvironment are a few of the challenges that have limited current immunotherapy

Table 1. Summary of Biomarkers Identified in Immunotherapy Trials of Recurrent Glioblastoma

Author	Year	Phase	Treatment	Biomarker
Weller	2017	3	Rindopepimut and Temozolomide	*EGFRvIII* expression
Desjardins (original), White (post hoc)	2018 (original), 2023 (post hoc)	1	PVSRIPO	TME subtyping
White (post hoc analysis of Zhao)	2019 (original), 2023 (post hoc)	n/a	Pembrolizumab/ Nivolumab	TME subtyping
McGrail (post hoc analysis of Cloughesy)	2019 (original), 2021 (post hoc)	pilot	Pembrolizumab	RSRD gene signature
McGrail (post hoc analysis of Zhao)	2019 (original), 2021 (post hoc)	n/a	Pembrolizumab/ Nivolumab	RSRD gene signature
Arrieta	2021	n/a	Pembrolizumab/ Nivolumab	ERK1/2 phosphorylation
Nassiri	2023	0/2	DNX-2401, Pemrbolizumab	TME subtyping
Choi	2024	1	CARv3-TEAM-E T Cells	CSF extracellular-vesicle *EGFRvIII* expression

trials.[56] However, the inclusion of biomarkers of response and monitoring into trials has the potential to drive the development of personalized and biology-driven therapeutics for glioma.

Meningioma

Meningioma is the most common primary brain tumor in adults,[81] but treatment options remain limited to surgery and radiation in the setting of symptoms or radiologic growth. Recent evidence has supported the potential role for immunotherapy in recurrent or aggressive disease.[82–86] To that end, the first open-label, single-arm trial of nivolumab, a PD-1 blocking antibody, in meningioma was published in 2022.[87] In this study, which enrolled 25 patients with recurrent, highly pretreated WHO grade 2 or 3 meningiomas, 6-month progression-free survival (PFS-6) was 42.4%. One patient did achieve sustained radiographic response based on the Radiologic Assessment in Neuro-Oncology (RANO) criteria and there were no unexpected adverse events. TMB and quantification of TILs were assessed as potential response biomarkers. Of 15 patients with sufficient tumor material to assess biomarker profiles, baseline TIL density was low but significantly increased in 3 patients, suggesting post-treatment immune activation. Importantly, only 2 tumors had elevated baseline TMB (>10/Mb) and both had increased immune infiltration post-treatment, suggesting a potential role for TMB as a biomarker for checkpoint blockade success in meningioma.

A similar phase 2 study was conducted simultaneously using pembrolizumab, another PD-1 inhibitor, and was also published in 2022.[88] This study also enrolled 25 patients and used the same design as the nivolumab study. This trial achieved a PFS-6 of 48% and 6 patients had growth stabilization on treatment, though no patients experienced complete or partial response by RANO criteria and 20% experienced at least one grade 3 or higher treatment-related adverse event. PD-L1 expression and MRI features were investigated as potential biomarkers. While no correlation between PD-L1 expression and outcome was noted, all 4 (of 9 patients with pre-enrollment progressive disease and sufficient available tumor tissue) cases with elevated PD-L1 expression had stabilization of their meningioma growth while on treatment. A nonsignificant trend was also noted between ADC values on MRI and outcome, with higher median ADC values among patients with PFS-6.

Overall, a subset of patients with meningiomas appear to respond to immunotherapy, and while nonspecific trends have been identified with traditional metrics such as TMB, PD-L1 expression, and imaging features, small cohorts limit a rigorous assessment of their translational value. Therefore, additional work is needed to validate these potential markers and, perhaps more importantly, explore additional biomarkers of response.[89] Additionally, other forms of immunotherapy have yet to be studied vigorously in human trials despite preclinical evidence of utility.[90–94] Notably, 1 case report found evidence of biological activity in a patient treated with B7-H3 targeted CAR-T cells,[95] and another observed radiographic meningioma necrosis in a patient treated with CD19-targeted CAR-T cells for diffuse large B-cell lymphoma,[96] but more data are needed to draw any conclusions regarding response biomarkers for these approaches. While considerable further work is needed, the role of immunotherapy in meningioma has shown early promise and the need for biomarker-driven approaches is clear.

Discussion

Immunotherapy has revolutionized the treatment paradigm of many cancers, but the same success has not been borne out for patients with CNS disease. Personalized, biomarker-driven care will be needed to homogenize future clinical trials and allow for useful translation of these

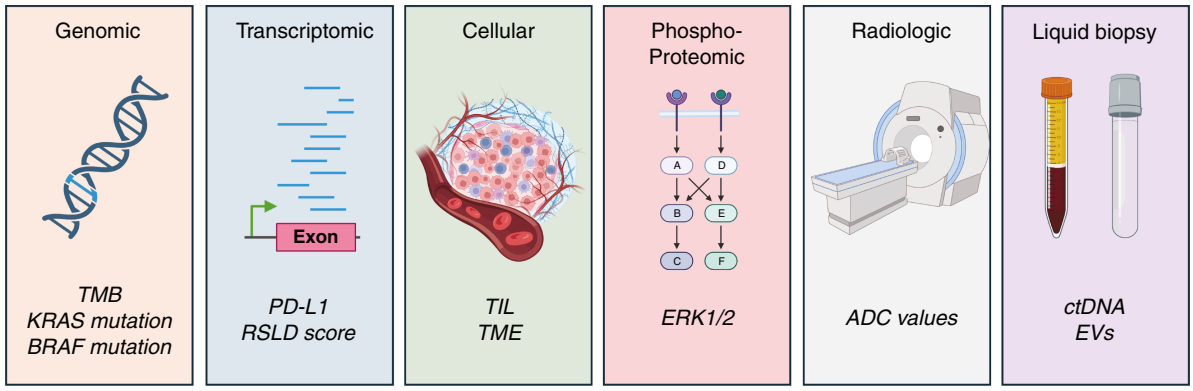

Figure 1. Graphical depiction of promising biomarkers of immunotherapy response in CNS tumors.

approaches into clinical practice. Emerging evidence has suggested the presence of multiple potential biomarkers (Figure 1), including specific mutations and TMB, gene expression (PD-L1, gene signatures), and TME which may play a role in predicting response to immunotherapy for some CNS tumors. While these markers could add some granularity to treatment response prediction for patients on immunotherapy for a CNS tumor, considerable additional work will be needed to ascertain their role in clinical trial design and ultimately clinical decision-making. Moreover, the value of other potential biomarkers such as DNA-methylation-based signatures, which have seen success in other predictive models of CNS tumor outcomes,[10,11] has yet to be explored. In addition, the majority of research thus far has been heavily focused on the role of immune checkpoint blockade in neuro-oncology, with a pressing need for further exploration of other immunotherapeutic avenues and their associated response biomarkers.

In addition to the need for increasingly accurate and robustly validated immunotherapy response biomarkers in CNS tumors, their eventual integration into a clinical trial design is equally important to consider. Biomarker-driven clinical trials offer an increasingly personalized approach and help address the heterogeneity of traditional clinical trial designs. Additionally, biomarker-driven "umbrella" or "basket" trial designs, which simultaneously target multiple molecular features across a single disease state or a single molecular feature across multiple disease states, respectively,[97,98] allow for this personalization to increase the efficiency of therapeutic discovery. As an example in the CNS, the Alliance A071401 umbrella phase 2 trial is actively investigating the role of targeted therapy in patients with meningiomas with somatic NF2, AKT, or SMO mutations or CDK pathway alterations.[99,100] Immunotherapy-specific biomarkers, of course, are considerably more challenging owing to multiple factors including the inducible and dynamic nature of many immunotherapy targets and the highly complex interactions within the TME which lead to treatment resistance via several immune-escape mechanisms.[9]

While considerable work is needed before biomarker-triggered immunotherapy trials become useful in the realm of neuro-oncology, recent studies are offering new reasons for hope and have begun to explore these new avenues and offer new hope for patients with resistant diseases. Identifying appropriate immunotherapeutic strategies for individual patients with CNS tumors represents the next frontier in personalized management and will be predicated on a biomarker-driven approach to clinical trial design.

Keywords

brain metastases | glioma | immunotherapy | meningioma | response biomarkers

Conflict of interest statement

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