New molecular targets in meningiomas: the present and the future

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Purpose of review
Meningiomas, the most common primary brain tumor, have historically been managed with surgery and radiation. Traditional chemotherapy has not been effective. Fortunately, recent advances in genetic sequencing have led to an improved understanding of the molecular drivers in meningioma. This article aims to discuss the diagnostic and therapeutic implications of recently discovered genetic alterations in meningiomas.

Recent findings
Many of the recently discovered genetic alterations correlate with distinct clinical phenotypes. *SMO*, *AKT* and *PIK3CA* mutations are enriched in the anterior skull base. *KLF4* mutations are specific for secretory histology, and *BAP1* alterations are common in progressive rhabdoid meningiomas. Alterations in *TERT*, *DMD* and *BAP1* correlate with poor clinical outcomes. Importantly, the discovery of clinically actionable alterations in a number of genes, including *SMO*, *AKT1* and *PIK3CA*, has opened up novel potential avenues for therapeutic management of meningiomas. Overexpression of PD-L1 in higher grade meningiomas also provides preclinical support for the investigation of checkpoint blockade.

Summary
The discovery of genetic alterations has improved our understanding of the natural history and classification of meningiomas. Clinical trials with several novel agents targeting driver mutations are currently accruing patients and they can lead to better treatment strategies.

Keywords
AKT, BAP1, checkpoint blockade, DMD, KLF4, meningioma, PD-L1, SMO, targeted therapies

INTRODUCTION

Meningioma is the most common intracranial malignancy. Meningothelial arachnoid cells are the presumed primary source of meningioma [1,2]. Approximately 90% of the meningiomas occur intracranially, and 10% in the spinal meninges [3]. The majority of meningiomas (up to 80%) are classified as WHO grade I and are consider to have so-called 'benign' histology. The remaining 20% of the meningiomas can exhibit a more aggressive course and include atypical meningioma (WHO grade II) or anaplastic meningioma (WHO grade III) [4]. Surgery is the mainstay of treatment, and in 70–80% of patients, a complete surgical resection is curative. The subgroup of patients with meningiomas that are in surgically challenging locations such as the skull base, that have undergone incomplete resections and/or that have histology consistent with WHO grade II or III meningiomas have higher rates of recurrences and might be candidates for radiation therapy or systemic therapy.

PRIOR STUDIES OF SYSTEMIC AGENTS IN MENINGIOMAS

Several systemic agents have been investigated in meningioma but have demonstrated limited benefit in numerous clinical trials. Chemotherapies such as temozolomide, irinotecan and combination of

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KEY POINTS

- Clinically actionable mutations in *AKT1*, *SMO* and *PIK3CA* have recently been discovered in meningiomas, with ongoing clinical trials investigating the efficacy of targeted therapies in this patient population.
- A subset of meningiomas express PD-L1, which has been associated with responses to checkpoint inhibitors in other tumor types.
- Anaplastic meningiomas can frequently harbor *CDKN2A* and *CDKN2B* mutations.
- Mutations in *TERT*, *BAP1* or DMD correlate with poor clinical outcomes.

cyclophosphamide, doxorubicin and vincristine have been largely ineffective [5]. Given the expression of somatostatin receptors in approximately 90% of meningiomas, somatostatin analogues have been evaluated in several small studies. Although a small pilot trial of 16 patients showed a 6-month progression-free survival (PFS6) of 40%, most other trials have not shown significant improvement in PFS6 [6,7]. Studies with other agents such as mifepristone, interferon-α, imatinib and hydroxyurea have failed to show consistent benefit [8–12]. Meningiomas are vascular tumors; however, attempts to target vascular endothelial proliferation receptors with bevacizumab and sunitinib have yielded modest results [13,14]. A single arm phase II study of sunitinib enrolled 36 patients with progressive WHO grade II or III meningiomas, and reported a PFS6 rate of 42%, and the median PFS was 4.2 months [13].

The challenges with interpreting these studies are that many are small underpowered studies with limited numbers of patients, often added as small cohorts to glioblastoma trials. Moreover, the preclinical data supporting the investigation of many of these agents in meningiomas have been limited. Furthermore, the endpoints for these trials have been variable, rendering it difficult to compare across studies. Recently, there has been a strong push to standardize response criteria in meningiomas. According to a recent meta-analysis of prospective clinical trials and retrospective case series of systemic therapies in meningioma, the weighted average PFS6 for WHO grade I meningiomas and WHO II/III meningioma was 29 and 26%, respectively [15]. To aid in standardizing response reporting in meningioma clinical trials, a PFS6 of 40% in WHO grade I meningioma and 30% in WHO grade II and III meningiomas are now considered reasonable endpoints for investigational agents in phase II trials [16]. This standardization of response criteria, along with our increased understanding of the molecular underpinnings of meningiomas, will likely lead to more effective systemic therapies in meningioma patients who cannot undergo resection safely and have exhausted radiation therapy options.

MOLECULAR TARGETS AND EMERGING SYSTEMIC THERAPIES IN MENINGIOMAS

With the advent of improved genomic technologies and analytic tools, our understanding of the molecular landscape in meningiomas has improved substantially. Generally, WHO grade I meningiomas have few chromosomal alterations. Higher rates of karyotype and copy number alterations are noted in WHO grade II, and grade III meningiomas like losses of 1p, 6q, 9p, 10, 14q, 18q and gains of chromosome 1q, 9q, 12q, 15q, 17q and 20q [17].

Mutations or loss of heterozygosity in *neurofibromin 2 (NF2)*, a tumor suppressor gene, are reported in approximately 60% of sporadic meningiomas [18]. *NF2* is located on chromosome 22 and encodes for a protein called Merlin (schwannomin). Merlin downregulates the mammalian target of rapamycin (mTOR) signaling complex 1 and upregulates the mTOR signaling complex 2, which leads to cell growth and motility [19,20]. Merlin also regulates various other pathways like the Hippo and Notch pathways, which play a role in the pathogenesis of meningioma [21]. Preclinical mouse models of *NF2* mutant meningiomas have shown overexpression of the mTOR signaling complex 1 pathway, which can be suppressed by mTOR inhibitors [22]. Temsirolimus and everolimus are two mTOR inhibitors in clinical use in advanced breast cancer and renal cell carcinoma [23,24]. A study of the combination of everolimus and bevacizumab in 17 meningioma patients who had progressed through surgery and radiation therapy demonstrated a median PFS of 22 months, with 88% of the patients having stable disease as the best response [25].

More recently, a phase 2 study investigated the combination of everolimus and octreotide, a somatostatin analog in 20 patients with progressive intracranial meningioma [26]. Although the study included patients with both *NF2* mutant and wild-type meningiomas, the PFS6 was 58.5%, showing preliminary evidence of activity of this combination in meningioma. A novel dual mTORC1 and mTORC2 inhibitor, AZD2014, inhibited the proliferation of meningioma cell lines, and these findings have led to two early phase clinical trials (NCT03071874 and NCT02831257) [27]. *NF2*-associated tumors like mesothelioma and serous ovarian

Table 1. Summary of ongoing clinical trials in meningioma

Clinical trial identifier (clinicaltrials.gov)	Drug being evaluated	Meningioma subgroups included in the study	Estimated enrollment	Mechanism of action
NCT02523014	GSK2256098 and vismodegib	Meningioma with *NF2*, *AKT1* *SMO* mutation	69	Combination of FAK and Hedgehog inhibitor
NCT03071874	Vistusertib (AZD2014)	Grade II and III	30	Dual mTORC1/mTORC2 inhibitor
NCT02831257	Vistusertib (AZD2014)′	Progressive meningioma in neurofibromatosis 2 patients	18	Dual mTORC1/mTORC2 inhibitor
NCT02933736	Ribociclib	Preoperative and postoperative treatment of meningioma	48	CDK4/6 inhibitor
NCT03279692	Pembrolizumab	Progressive high-grade meningioma	26	PD-1 inhibitor
NCT02648997	Nivolumab	Progressive high-grade meningioma	25	PD-1 inhibitor
NCT02234050	Trabectedin	Progressive high-grade meningioma	86	Preventing oncogenic factor from binding to DNA

carcinoma have shown to be sensitive to focal adhesion kinase (FAK) inhibition in merlin-deficient cells [28,29]. Phase 1 trials of the FAK inhibitors, GSK2256098 and VS-6063, were recently completed in other tumors [30,31]. GSK2256098 is being investigated in a phase 2 trial for NF2-altered meningioma (NCT02523014/A071401). Table 1 provides a list of currently active clinical trials of systemic therapies for meningioma.

Two pivotal studies with whole genome and whole exome sequencing of meningiomas were published in 2013 [32,33] which provided insights into the genetic and epigenetic drivers in *NF2* mutant and wild-type meningiomas. Interestingly, compared to many other adult brain tumors like glioblastoma, grade I meningiomas had relatively simple genomes. In *NF2* wild-type grade I meningiomas, mutations in *TRAF7*, *KLF4*, *AKT1* and *SMO* were noted. Interestingly, these studies revealed strong genotype and phenotype correlations with meningiomas harboring specific mutations enriched in certain histologic subtypes of meningiomas and in certain locations in the brain. For instance, NF2 mutant meningiomas commonly have fibroblastic histology and occur in the cerebral convexities or posterior skull base (Fig. 1A).

The *AKT1 E17K* mutation, which is recurrently found in 10–15% of meningiomas, activates the PI3K/mTOR pathway. AZD5363 is a pan-AKT inhibitor which has been safely tested in variety of malignancies, with responses observed in *AKT1*-mutated tumors [34]. Recently, a case report showed durable control of a multiply recurrent *AKT1* mutant metastatic meningioma with AZD5363 [35]. In addition to *AKT1 E17K* mutations, approximately 7% of *NF2* wild-type meningiomas have mutations in *PIK3CA* [36]. *AKT1* and *PIK3CA* mutations often co-occur with *TRAF7* mutations. *SMO* mutations, which activate the Hedgehog signaling pathway [37,38], are found in 3–5% of meningiomas. SMO inhibitors such as vismodegib are food and drug administration (FDA)-approved for the treatment of basal cell carcinoma which are also characterized by alterations in the Hedgehog signaling pathway. Anterior skull base meningiomas have a higher frequency of *SMO*, *AKT1* and *PIK3CA* mutations and these tumors generally display meningothelial histology [39] (Fig. 1B). Specifically, *SMO* mutations are highly enriched in olfactory groove meningiomas, and tend to present as larger meningiomas compared to those arising with *AKT1* mutations [39]. Given these data, Hedgehog inhibitors could have activity in *SMO* mutant meningiomas and such an approach warrants further investigation [40]. SMO and AKT1 inhibitors are now being evaluated in an ongoing Alliance-sponsored cooperative group phase II trial in the United States. This is the first precision medicine trial to be conducted in meningioma and is accruing patients with recurrent or progressive meningiomas with alterations in *SMO*, *AKT1*, *PIK3CA* and *NF2* (NCT02523014/A071401).

CDKN2A and *CDKN2B*, tumor suppressor genes located on chromosome 9p21 regulate the cyclin-dependent kinases which are critical for cell division. Loss of chromosome 9p and alterations in *CDKN2A* and *CDKN2B* are predominantly noted in anaplastic meningiomas and tend to co-occur with NF2 alterations [41] (Figure 1C). Patients with anaplastic meningiomas harboring *CDKN2A* loss have particularly poor outcomes [42]. Several CDK inhibitors are in clinical use for breast cancer, and these will be evaluated in higher grade meningiomas in Alliance A071401 (NCT02523014).

Immunotherapy is a promising investigational agent in meningiomas. Interferon-α has been used historically in meningioma with modest benefit. A phase 2 trial of 35 patients with progressive WHO

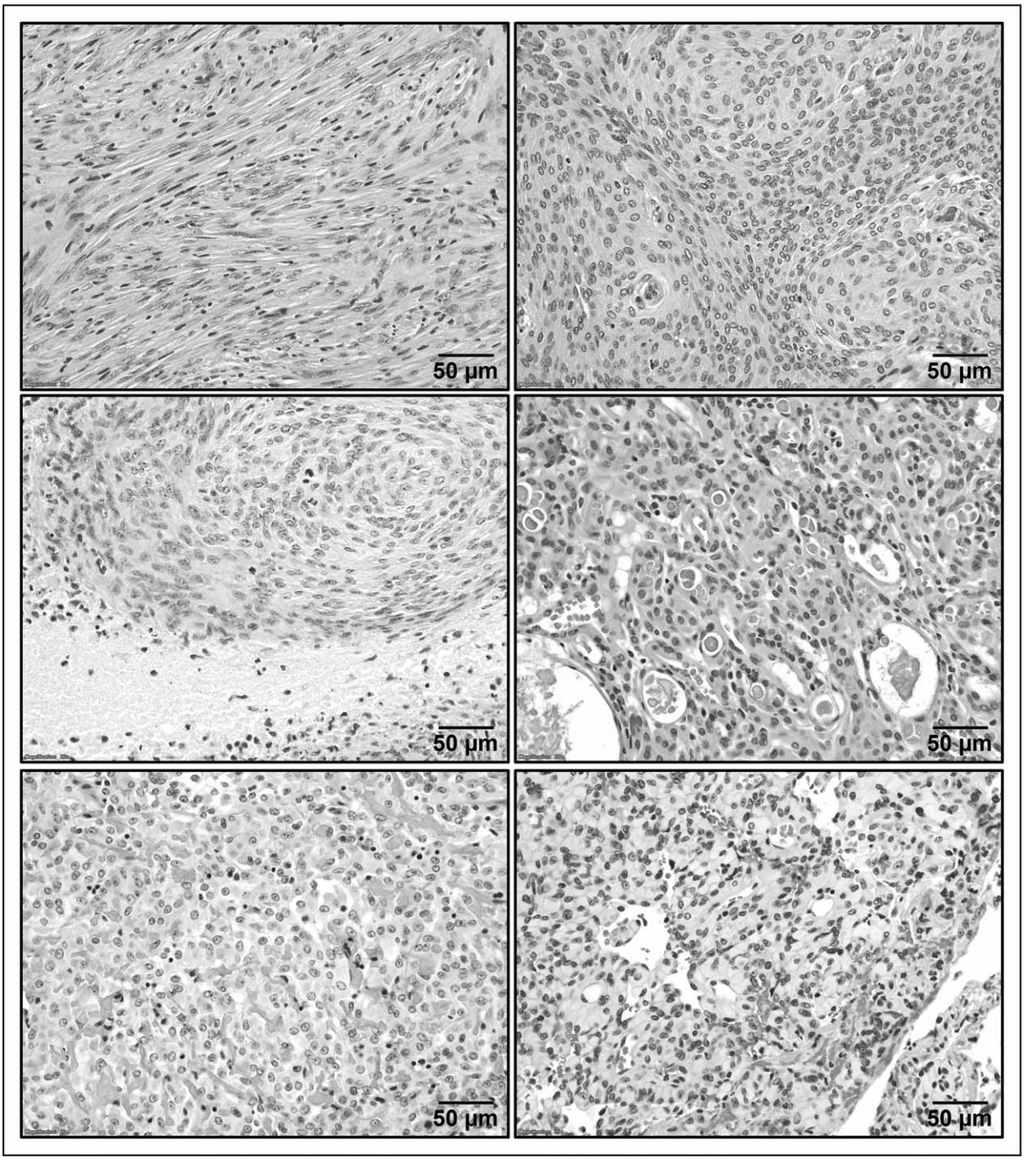

FIGURE 1. Representative images of H&E stained sections of meningiomas of various subtypes. (A) Fibrous (fibroblastic), (B) meningothelial, (C) anaplastic, (D) secretory, (E) clear cell and (F) rhabdoid/papillary.

grade I meningiomas treated with interferon-α showed a PFS6 of 54% [9]. However, given the adverse effects profile, interferon-α is not routinely used. There are several factors which support the investigation of anti-PD-1 (Programmed death-1) therapy in meningioma. A subset of meningiomas express PD-L1, with higher rates of expression in WHO grade II and III tumors [43]. Higher grade meningiomas have mutations that are predicted to generate neoantigens which have been linked to response to immunotherapies in other tumor types [44,45]. The tumor microenvironment in meningioma contains PD-L1 and PD-1 expressing immune cells including exhausted effector T cells which have been exposed to tumor antigens [46]. These findings have lead to several phase 2 clinical trials with anti-PD1 therapy enrolling patients with recurrent high-grade meningiomas.

Potential biomarkers of clinical phenotypes

A number of genetic signatures and mutations have been identified which correlate with prognosis and/or histopathologic phenotypes. Up to 25% of WHO grade I and II meningiomas have *TRAF7* mutations [36]. TRAF7 is a proapoptotic E3 ubiquitin ligase that has seven WD40 repeats in its carboxyl terminus which interacts with MAP Kinase signaling, NF-κB and antiapoptotic molecules like c-FLIP [33]. KLF4 (Kruppel like factor-4) is a transcription factor, critical for reprogramming somatic cells to pluripotent stem cells [47]. *KLF4* mutations frequently co-occur with *TRAF7* mutations and are specific for meningiomas of secretory histology [48,49] (Fig. 1D). *TRAF7* alterations can also occur in other meningioma histopathologic subtypes. Mutations in epigenetic modifiers such as *SMARCB1*, *KDM6A* and *KMD5C* have been discovered in approximately 8% of meningiomas [50]. Clear cell meningiomas which often occur in the spine harbor loss of function *SMARCE1* mutations, which are often present as germline mutations [51] (Fig. 1E). Such events indicate that targeting epigenetic modifiers could have therapeutic potential in meningiomas and should be investigated preclinically.

Polymerase (RNA) II (DNA directed) polypeptide A *(POLR2A)* mutations are seen in a small subset of WHO grade I meningiomas which do not harbor *NF2* or *TRAF7*-associated mutations. *POLR2A* encodes for the catalytic subunit of Pol II, known as RPB1 [50]. *POLR2A* mutant meningiomas usually have meningothelial histology and higher propensity to arise from the tuberculum sellae regions.

Although the mainstay of tumor prognostication remains histologic grading, genomic biomarkers are becoming increasingly useful for identifying patients who may have worse outcome. For instance, copy number alterations have been associated with increased risk of recurrence [52,53]. There is also growing evidence that DNA methylation profiling has prognostic significance in meningioma [54▪▪,55].

In addition, mutations in certain genes are associated with poor prognosis. In particular, mutations in the promoter of the telomerase reverse transcriptase (TERTp) gene are present in a small subset of meningiomas [56▪▪]. Unlike most of the other mutations present in meningiomas that were discussed above, *TERTp* mutations are seen more commonly in WHO grade III meningiomas and indicate increased malignancy. Even when detected in lower grade meningiomas, *TERTp* mutations indicate a shorter time to recurrence, and an increased risk of malignant transformation [57,58]. In a recent study of 252 meningioma patients, 16 carried *TERTp* mutations. The time to tumor progression in *TERTp* mutant meningioma was 10.1 months compared to 179 months in the rest of the cohort [58]. Another study showed that *TERTp* mutations occur later in the evolution to more aggressive meningiomas and are associated with decreased overall survival [56▪▪]. More recently, inactivating alterations in the muscular dystrophy-associated *(DMD)* gene were found to be common in progressive high-grade meningiomas and were associated with shorter overall survival [59▪▪].

The *BAP1* tumor suppressor gene (breast cancer type 1-associated protein), a ubiquitin carboxy-terminal hydrolase, is another biomarker of aggressive meningioma. *BAP1* mutations in meningiomas have been associated with a subset of tumors that show rhabdoid and papillary histology (WHO grade III) [60] (Fig. 1F). Germline mutations in *BAP1* are the hallmark of the *BAP1* tumor-predisposition syndrome, which is associated with an increased risk of uveal and cutaneous melanoma, mesothelioma and renal cell carcinoma and meningioma [61▪▪]. Strikingly, in a study of 27 rhabdoid meningiomas, *BAP1* inactivation predicted a reduced time to recurrence at 26 months compared to 116 months [60]. *BAP1* may also represent a potential therapeutic target because in preclinical studies of other tumor types, *BAP1* inactivation may increase the sensitivity of tumors to EZH2 and PARP inhibition [62]. Like *SMARCE1*-mutant clear cell meningioma, the identification of *BAP1*-mutant meningiomas should trigger genetic counseling and germline testing.

CONCLUSION

The paradigm of systemic therapy for meningioma is changing rapidly. Although older traditional chemotherapies have limited activity in meningiomas, improved technologies have led to a better understanding of driver mutations and potential therapeutic targets in meningioma. Some of these driver mutations, such as *BAP1* or *TERTp* mutations, have prognostic value and could change the classification system in the future. Novel clinical trials exploring targeted therapies and immunotherapies are ongoing, and could shift how meningiomas are clinically managed in the near future.

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Conflicts of interest

V.A.V. has no pertinent conflicts of interest.

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