



# Advances in Molecular Classification and Therapeutic Opportunities in Meningiomas

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## Abstract

**Purpose of Review** Our understanding of the genetic and epigenetic alterations in meningioma and the underlying tumor biology of meningioma has significantly changed over the past decade and resulted in revision of prognostically relevant meningioma subclasses within and beyond the WHO classification of CNS tumors.

**Recent Findings** The 2016 WHO classification of CNS tumors recognizes WHO grade I, II, and III based on histopathological features. Recent work has identified genetic alterations with prognostic implications, including mutations of the *TERT* promoter, loss of function of the *DMD* gene, and inactivation of the tumor suppressor *BAP-1*. Studies of DNA methylation patterns in meningiomas have resulted in a novel and prognostically relevant meningioma subclassification schema.

**Summary** There have been major advances in our understanding of prognostically relevant genetic and epigenetic changes in meningioma which will hopefully allow for improvement in clinical trial design and the development of more effective therapies for meningioma.

**Keywords** Meningioma · Atypical · Anaplastic · WHO classification of CNS tumors · Radiation · Methylation class · Methylome · H3K27me3 · Molecular targets · *Neurofibromin 2* · *NF2* · *TERT* · *BAP-1* · *AKT1* · *SMO* · *TERT* · *SSTR2* · <sup>177</sup>Lu-DOTATATE · Lutathera · Trastectedin · Outcome · PFS-6 benchmark · Immunotherapy

## Introduction

Meningiomas represent 37.6% of primary intracranial and other central nervous system tumors, making them the most common histology of all [1]. They are thought to originate from arachnoid cap cells due to their histologic similarities [2]. In the USA, there are about 30,000 people diagnosed each year, and the incidence is increasing. In 2020, the incidence is projected to increase to 34,210 cases. The median age at diagnosis is 66 years. Females have a higher incidence than males, overall, particularly in non-malignant meningiomas. The 10-year relative survival rate for non-malignant and

malignant meningioma is 83.7% and 61.7%, respectively; differences are observed relative to tumor location with higher survival rates for spinal tumors compared to a cerebral location [1]. While the majority (~80%) of meningiomas are considered benign and can be observed or cured by surgical resection alone, a subset of up to 20% of meningiomas represent aggressive tumors that recur and continue to grow despite surgical resection and/or radiotherapy [3]. Once patients have failed surgical and radiotherapeutic options, prognosis is typically poor and there are currently no effective medical treatment options.

The development of medical therapies for meningiomas has long been difficult due to multiple and diverse reasons, including incomplete understanding of meningioma pathobiology and therefore lack of meningioma-specific therapeutic targets, the difficulties to develop representative animal models to evaluate novel therapeutic agents, and the significant heterogeneity in clinical trial design [4, 5]. With regard to clinical trials in meningiomas, one major challenge has been the lack of a standardized outcome measure used in these studies. However, a more recent detailed review and meta-analysis of the available clinical studies for progressive

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meningiomas determined the 6-month progression-free survival (PFS-6) to be the most reliable outcome measure. Based on the studies included in this analysis, the weighted average PFS-6 was 26% (95% CI 19.3–32.7%) for World Health Organization (WHO) grade II/III meningiomas and 29% (95% CI 20.3–37.7%) for WHO I meningiomas. The authors proposed to use these PFS-6 benchmarks for the design of future clinical trials in meningiomas [5]. To further improve and standardize meningioma-specific outcome measures for meningioma studies, the Meningioma Response Assessment in Neuro-Oncology (Meningioma-RANO) working group is working towards standardized radiographic assessment criteria [3, 5].

The past years have brought major advances in our understanding of the molecular underpinnings of meningiomas leading to updated and refined meningioma subclasses based on histopathological, genetic, and epigenetic determinants. This will hopefully spur the development of more effective and meningioma-specific therapies. This review focuses on the advances in meningioma genetics and epigenetics and will highlight potential therapeutic opportunities.

## Histopathological WHO Classification of Meningiomas

Various types of classification systems have been used for meningiomas, dating back to Virchow in the nineteenth century [6]. In 1979, the World Health Organization (WHO) published the “Histologic Typing of Tumours of the Central Nervous System,” known as the “blue book,” in order to establish a standardized grading system of CNS tumors, including meningiomas, based on histological features [7]. The WHO classification of CNS tumors has undergone several updates since then [8–11]. Based on their malignant potential, the WHO classifies meningiomas as grade I (benign), grade II (intermediate), and grade III (malignant) tumors. Based on the criteria used in the 2007 WHO classification, 80.5% of pathologically confirmed meningiomas were WHO grade I, 17.7% were WHO grade II, and 1.7% were WHO III, respectively [1, 10]. Despite several advances in the recent versions of the WHO classification, the current 2016 WHO classification of CNS tumors remains largely based on histological and cytomorphological criteria as well as mitotic rate. As such, 15 histological meningioma subtypes are recognized and categorized as WHO grade I, II, or III. One change to the previous 2007 WHO classification was that brain invasion was established as an independent histological criterion to justify the diagnosis of a grade II (atypical) meningioma [10, 11]. It is expected that this will result in a proportional increase in WHO grade II meningioma diagnoses.

Overall, a correlation between WHO histopathological grade and patient outcome has been documented in multiple studies

[12–15]. Nevertheless, the current histopathological assessment criteria allow for interrater variability, especially when considering WHO grade II meningiomas. A recent secondary analysis from the NRG Oncology RTOG 0539 trial assessed the concordance rates between histopathological meningioma diagnosis at the enrolling study subsite and at central pathology review. While the concordance rates for histopathological WHO grade I and III diagnoses were 93% and 93.6%, respectively, the concordance rate for WHO grade II meningiomas was only 87.8%. Of the 22 reclassified cases, all but one case involved a WHO grade II correction: 9 were upgraded from a WHO I to WHO II, 8 were upgraded from WHO II to WHO III, two were downgraded from WHO III to II, and two were downgraded from a WHO II to WHO I. Interestingly, the study found the highest concordance rates for the histopathological features of  $\geq 20$  mitoses/10 HPF (95.3%), anaplasia (93.6%), and brain invasion (92.4%) [16, 17]. Still, the histopathological WHO criteria appear to be insufficient to predict clinical course in some patients; i.e., up to 20% of patients with grade I meningiomas experience tumor recurrence [18–20], and some of the patients diagnosed with grade II meningiomas may experience a rather benign clinical course where radiotherapy might confer unnecessary risks [17, 21, 22].

## Current Clinical Management of Meningiomas

Surgical resection remains the initial step and mainstay of treatment for most symptomatic meningiomas as it leads to decompression of the affected areas of the CNS, symptom improvement, and allows for a histopathological diagnosis.

The extent of initial resection remains a strong predictor of outcome and is traditionally assessed according to the Simpson grade, a grading system which is based on the surgeon’s assessment of the extent of resection, ranging from Simpson grade I (complete removal of tumor, dura, and bone) to grade V (biopsy/decompression only) [23]. More recently, a number of studies have assessed the validity of the Simpson grading system in the modern era and found that maximum safe resection remains a positive predictor of survival, but only in conjunction with other factors such as histopathological grade, mitotic rate, and tumor location [24, 25]. A recent prospective study determined that statistically significant risk factors associated with incomplete meningioma resection were symptomatic presentation, skull-base location, and bone invasion. In contrast, patient gender, preoperative Karnofsky performance status, WHO grade, and patient age were not predictive of incomplete resection [26].

After initial resection, WHO grade I meningiomas are most often followed by clinical and radiographic observation, with re-resection and/or radiation being offered for any subsequent tumor progression. In the case of a WHO grade III diagnosis, radiation is recommended. For WHO grade II meningiomas, however, the role of radiation following initial resection is

controversially discussed with no consistent practice across the USA. Few studies investigate this question, including RTOG 0539 (NCT00895622) and NRG-BN003 (NCT03180268). The ongoing RTOG 0539 trial stratifies patients according to WHO Grade and extent of resection. In this study, gross-totally resected WHO grade II and recurrent WHO grade I meningiomas are considered intermediate risk, and these patients are stratified to receive radiotherapy to 54 Gray (Gy). Patients with recurrent grade II meningiomas, newly diagnosed subtotally resected WHO grade II meningioma, and all WHO grade III meningiomas are considered high-risk and receive radiotherapy to 60 Gy. The initial outcome report for the intermediate-risk group documented a favorable 3-year progression-free survival (PFS) of 93.8% and overall survival OS of 98% in 52 evaluable patients [17]. Additionally, the currently ongoing NRG-BN003 trial randomizes patients with gross-totally resected WHO grade II meningiomas to either observation or radiation to address the uncertainty of postsurgical treatment in this meningioma subgroup.

Once surgical and radiotherapeutic options have been exhausted, there are unfortunately no established medical treatment options or preferred regimens despite numerous clinical trials that have evaluated a number of agents including hydroxyurea, temozolomide, irinotecan, imatinib, erlotinib, gefitinib, and antiangiogenic drugs such as bevacizumab and sunitinib, with or without mTORC1 inhibitors such as everolimus. Unfortunately, these agents have been largely ineffective and there remains a dire need for novel treatment targets and improved medical therapy options for meningiomas [4, 5, 27, 28]. Patient enrollment into clinical trials is therefore strongly encouraged whenever possible.

One such clinical study recently evaluated trabectedin, a cytotoxic agent that is frequently used in sarcomas, in the prospective phase II EORTC-1320-BTG study. Patients with progressive WHO grade II and grade III meningiomas were randomized to either receive trabectedin or the investigator's choice of therapy. However, based on the recently presented preliminary results, there was no significant improvement in PFS or OS for patients receiving trabectedin, and notably, there was significantly higher toxicity in this group [29].

### Somatostatin Analogues

Somatostatin receptor type 2 (SSTR2) is overexpressed on the surface of 79–100% of meningiomas, regardless of grade, and represents a specific biomarker that can be applied diagnostically via immunohistochemical staining and radiographically via <sup>68</sup>Gallium (Ga)-DOTATATE PET-MR Imaging [30–32]. In addition, SSTR2 is a potential therapeutic target [31, 33], although several clinical trials evaluating somatostatin analogues in monotherapy have been disappointing so far [34, 35]. However, more recently, a single-arm phase II study using octreotide, a synthetic

somatostatin analog with affinity to SSTR2 and SSTR5, and everolimus in 20 adults with recurrent meningioma showed more encouraging results by reporting PFS-6 of 55%, and a 6- and 12-month OS of 90% and 75%, respectively. Most tumors on study (78%) demonstrated a decrease of over 50% in growth rate at 3 months on treatment. There was no association observed between SSTR2A expression and PFS or growth rate [36]. In contrast to the somatostatin analogues, <sup>177</sup>Lutetium (Lu)-DOTATATE (Lutathera) is a radiolabeled antibody that targets SSTR2 with high affinity and is independent from the downstream effects of the somatostatin-receptor pathways. <sup>177</sup>Lu-DOTATATE is used as peptide receptor radionuclide therapy (PRRT) and was recently approved for the treatment of advanced, somatostatin-receptor positive gastroenteropancreatic neuroendocrine tumors [37]. Several case series and small prospective clinical studies have evaluated the utility of <sup>177</sup>Lu-DOTATATE and other SSTR2-targeting radionuclide agents with encouraging results [38–41]. Based on these studies, <sup>177</sup>Lu-DOTATATE is now investigated for patients with progressive intracranial meningiomas in two ongoing prospective clinical studies (NCT03971461, NCT04082520). In addition to the potential therapeutic value of <sup>177</sup>Lu-DOTATATE, both of these studies also investigate <sup>68</sup>Ga-DOTATATE, another SSTR2 binding radionuclide, as a possible predictive imaging biomarker.

### Hallmark Molecular Alterations in Meningiomas and Potential Therapeutic Opportunities

The past decade has brought an emerging understanding of genetic, epigenetic, and other molecular alterations in meningiomas which will likely further enhance the accuracy of the pathological diagnosis and clinical risk assessment for individual patients (Table 1).

### Copy Number Alterations

Higher-grade meningiomas have been shown to contain more chromosomal alterations than lower grade tumors. One study showed that while chromosome 22q loss was the most prevalent copy number alteration in both WHO grade II and III meningioma, other variants were also common: 1p loss, 14q loss, and 10q loss. Interestingly, they identified 10q loss in four of the five WHO grade III meningiomas analyzed but in none of the WHO grade II tumors. The authors suggested that this could be one way to differentiate WHO grade II from grade III [42]. In work which we will describe later in this review, classification of meningioma by methylation rather than WHO grading identified patterns of copy alterations in different meningioma subclasses: MC ben-1 nearly always contained deletion 22q (95%), MC ben-2 had no recurrent

**Table 1** Overview of histopathological, molecular, and epigenetic characteristics of meningioma variants

Subtype (WHO grade)	Histopathological criteria	Genetic/molecular aberrations	Epigenetic subclass
Meningothelial (I)	Epithelioid tumor cells in lobules	<i>POLR2A, TRAF7, AKT1</i>	MC ben-2
Fibrous (I)	Spindle-shaped tumor cells, collagenous background		MC ben-1, MC int-A
Transitional (I)	Meningothelial and fibrous features, prominent whorls		MC ben-1, -2, -3, MC int-A
Psammomatous (I)	Prominence of psammoma bodies		
Angiomatous (I)	Numerous blood vessels		MC ben-3
Microcystic (I)	Thin microcysts		
Secretory (I)	Focal epithelial differentiation with PAS positive eosinophilic secretions called pseudopsammoma bodies	<i>KLF4 and TRAF7</i>	MC ben-2
Lymphoplasmacyte-rich (I)	Extensive chronic inflammatory infiltrates		
Metaplastic (I)	Contain mesenchymal components (bone, fat, or cartilage)		
Chordoid (II)	Cords or trabeculae of eosinophilic vacuolated cells		
Clear Cell (II)	Patternless architecture, Round cells with clear glycogen-rich cytoplasm	<i>SMARCE1</i>	
Atypical (II)	4–19 mitotic figures/10 HPF, or brain invasion, or required histologic features	<i>TERTp, TRAF7, AKT1</i>	MC ben-1, MC ben-3, MC int-A, and -B
Papillary (III)	Perivascular pseudopapillary pattern		
Rhabdoid (III)	Plump cells with eccentric nuclei, prominent nucleolus, eosinophilic paranuclear inclusions	<i>BAP1</i>	
Anaplastic (malignant) (III)	Overly malignant cytology and/or $\geq 20$ mitotic figures/10 hpf	<i>TERTp</i>	MC int-B, MC mal

copy number variations, MC ben-3 often contained chromosome 5 alterations (47%). Intermediate classes commonly had 1p (70% in group A, 89% in group B) and 22q loss (84% in group A and 89% in group B), as well as alterations in chromosome 10 (89% in group B). The malignant class, MC mal, often had *CDKN2A* deletion (70%) [43].

### Neurofibromin 2 and SMARCB1

Alterations in the *Neurofibromin 2 (NF2)* gene are the most commonly seen aberrations in meningiomas. The *NF2* gene is located on Chromosome 22 and encodes for a cell membrane-related protein called merlin or schwannomin that functions as a tumor suppressor [44–46]. Alterations in the *NF2* gene can be caused by mutation, allelic inactivation, splicing alterations, or Chromosome 22 loss and have been implicated in approximately 40–60% of sporadic meningiomas, making it the single most frequent gene alteration in this tumor [47–52]. Additionally, loss of *NF2* function is seen in nearly all meningiomas associated with neurofibromatosis type II, an autosomal dominant hereditary condition in which inherited loss of *NF2* function leads to development of bilateral vestibular schwannomas, intracranial and spinal meningiomas, and other spinal tumors such as ependymoma. Meningiomas with *NF2* mutations and/or chromosome 22 loss are more likely to be atypical and localize to the cerebral and cerebellar hemispheres [51]. In a

recent study of intraventricular meningiomas, loss of *NF2* function was confirmed to be the most common genetic alteration; loss of Chromosome 22 was seen in 89% of cases, and deleterious *NF2* mutations were seen in 44% of cases [53].

The mechanisms by which merlin loss of function leads to meningiomagenesis are insufficiently understood; however, it is speculated that merlin plays a role in contact-dependent inhibition of proliferation, mediated by mTORC1, with effects on the downstream PI3K-Akt-mTOR pathway [54–56].

The co-occurrence of *NF2* and *SMARCB1* mutations, the latter in close proximity to *NF2* on Chromosome 22, is seen in some of the meningiomas and schwannomas harboring *NF2* alterations [57]. An ongoing Alliance of Clinical Oncology Trial is currently evaluating the efficacy of the focal adhesion kinase (FAK) inhibitor GSK2256098 for meningiomas with *NF2* alterations (NCT02523014), which is exciting given that merlin deficiency has been shown to predict for FAK inhibitor sensitivity in tumor xenograft models [58].

### Alterations of the PI3K-AKT1-mTOR Pathway

A subset of meningiomas that do not harbor *NF2* alterations is characterized by dysregulation of the PI3K-AKT1-mTOR signaling pathway. One study detected the *AKT1 p.Glu17Lys* mutation in 13% of WHO grade I and II meningiomas which leads to constitutive activation of the AKT1 protein and

therefore overactivation of the PI3K-AKT1-mTOR pathway [59]. Other studies confirmed *AKT1* mutations as a hallmark alteration in meningiomas of the skull base and higher rate of tumor recurrence [51, 60, 61]. Most recently, the *AKT1* p.Glu17Lys mutation was also described as the hallmark mutation in meningiomas located at the foramen magnum [62].

The previously mentioned Alliance in Clinical Oncology trial is evaluating the AKT inhibitor capivasertib (AZD5363) for patients with progressive meningiomas characterized by an *AKT1* mutation (NCT02523014). One study evaluated the efficacy of the mTOR inhibitor everolimus with bevacizumab but was unfortunately disappointing [63]. The dual mTORC1 and mTORC2 inhibitor Vistusertib (AZD2014) is currently being explored in an ongoing phase II clinical trial in patients with sporadic grade II and III meningiomas (NCT03071874) and in *NF2*-associated progressive or symptomatic meningiomas of any grade (NCT02831257).

Other alterations of the PI3K signaling pathway have been described in several studies [64, 65], and the oncogenic *PIK3CA* mutation is found in up to 7% of non-*NF2* altered meningiomas [66]. While *PIK3CA* and *NF2*, *AKT1*, and *SMO* mutations are mutually exclusive, *PIK3CA* mutations appeared to co-occur with those in *TNF receptor associated factor 7 (TRAF7)*, which encodes for an E3 ubiquitin ligase that interacts with pro-apoptotic signaling pathways [67]. *TRAF7* mutations are seen in up to 24% of WHO grade I and II meningiomas, suggesting a potential cell cycle regulatory function in meningiomas [59].

### Alterations of the Hedgehog Signaling Pathway

Activation of the Hedgehog signaling pathway is a characteristic alteration in a subset of meningiomas that is not characterized by alterations in *NF2* or *AKT1*. Hotspot mutations in *Smoothed, Frizzled Class Receptor (SMO)*, are seen in 1–5% of meningiomas and are associated with anterior skull-base/olfactory groove location and higher potential for tumor recurrence [51, 59, 68, 69]. The SMO-inhibitor vismodegib is therefore evaluated in patients with progressive meningiomas characterized by alterations in *SMO* (NCT02523014).

### Genetic Alterations with Potential Prognostic Implications

#### Telomerase Reverse Transcriptase Promoter Mutations

The presence of either of the two hotspot *TERT* mutations C228T and C250T has been associated with more aggressive meningiomas [70, 71]. In a cohort of over 250 meningiomas, these *TERT* mutations were shown to occur in 6.4%, most

commonly in those with WHO Grade III. Clinical course in patients with *TERT* mutant meningiomas was notable for higher risk of recurrence and shorter time to progression, and this appeared independent from WHO grade. In the study, the median time to progression in those meningiomas possessing a *TERT* hotspot mutation was 10.1 months compared with 179 months in *TERT* wildtype meningiomas [72]. *TERT* mutations were confirmed as poor prognostic indicators in several recent studies [73–76].

### Loss of Function of the *Dystrophin-encoding and Muscular Dystrophy-associated Gene*

In a recent study of 169 meningiomas of 53 patients, *DMD* inactivation by genomic deletion or loss of protein expression was detected in 32% of patients with progressive meningiomas and associated with shorter overall survival. While *TERT* alterations co-occurred in 18.8% of these patients, multivariate analysis revealed *DMD* inactivation and *TERT* mutations as independent predictors of poor prognosis [74].

### Loss of *BRCA1* associated protein-1, Tumor Protein p53 (*TP53*) Mutations, and Loss of *CDKN2A/B*

*BAP-1* is a tumor suppressor gene encoding for a deubiquitylating enzyme, the ubiquitin carboxyl-terminal hydrolase BAP1. Inactivating *BAP-1* mutations have been associated with rhabdoid meningioma (WHO III) histology, heralding early meningioma recurrence and aggressive clinical course [77, 78]. Similar to other cancers and CNS tumors, mutations in the tumor suppressor gene *TP53* and loss of function of *CDKN2A/B* are found in higher-grade meningiomas (WHO II/III) and are associated with cell anaplasia and high risk of recurrence [79, 80]. In a study evaluating a total of 30 recurrent and non-recurrent meningiomas, identification of a new single nucleotide variant in *CDKN2A* was significantly associated with risk of recurrence. Additionally, the majority of recurrent tumors included in this study were noted to have one of three well-known *CDKN2A* alterations [71, 81].

### Forkhead Box M1

Another gene that appears to signal more aggressive behavior in meningioma is *Forkhead box M1 (FOXM1)*, which encodes for the FOXM1 transcription factor, a regulator of the cell cycle and therefore integral to tumor proliferation. Two studies have shown that *FOXM1* mRNA expression levels were highest in grade III, followed by grade II, and were lowest in grade I meningiomas [69, 82]. A FOXM1 inhibitor, siomycin A, has shown activity against cell proliferation in cell lines [82].

## Kruppel-like factor 4

In meningioma, the *KLF4* p.K409Q hotspot mutation nearly always co-occurs with *TRAF7* mutations and was in approximately 11% of non-NF2 meningiomas [59, 83, 84]. Like the other members of the large family of Kruppel-like factors, KLF4 is involved in regulation of gene transcription, inhibiting cell cycle progression by binding to the cell cycle inhibitor *p21<sup>Cip1/Waf1</sup>* promoter and recruiting p53 [85]. In addition, the Kruppel-like factors may play an important role in the induction and maintenance of pluripotent stem cells in cell cultures [86]. Interestingly, *KLF4* mutations have been primarily associated with WHO grade 1 secretory meningiomas—a meningioma subtype that is characterized by low risk of recurrence [59, 61, 83].

## RNA Polymerase II Subunit A

One study found recurrent somatic mutations in *POLR2A* in 6% of meningiomas and appeared mutually exclusive to any of the other known meningioma driver mutations. Presence of a

*POLR2A* mutation was associated with location in the tuberculum sellae and meningothelial (WHO I) histology, i.e., low risk of recurrence [87].

## Methylation Classification of Meningiomas

In a recent multicenter study, 497 meningiomas were analyzed for their genome-wide DNA methylation patterns and additionally characterized by DNA copy number analysis, mutational profiling, and RNA sequencing. The DNA methylation profiling led to segregation of six meningioma subclasses with distinct clinical behavior, i.e., methylation class (MC) benign 1–3, MC intermediate A and B, and MC malignant. Although WHO grade I tumors were enriched in MC benign 1–3, and grade III tumors were enriched in MC malignant, WHO grade II tumors were scattered throughout the six classes. In this analysis, the methylation subclasses were more accurately predictive of clinical course and risk of recurrence compared with WHO grade. In addition, the known hallmark molecular aberrations demonstrated enrichment in certain methylation

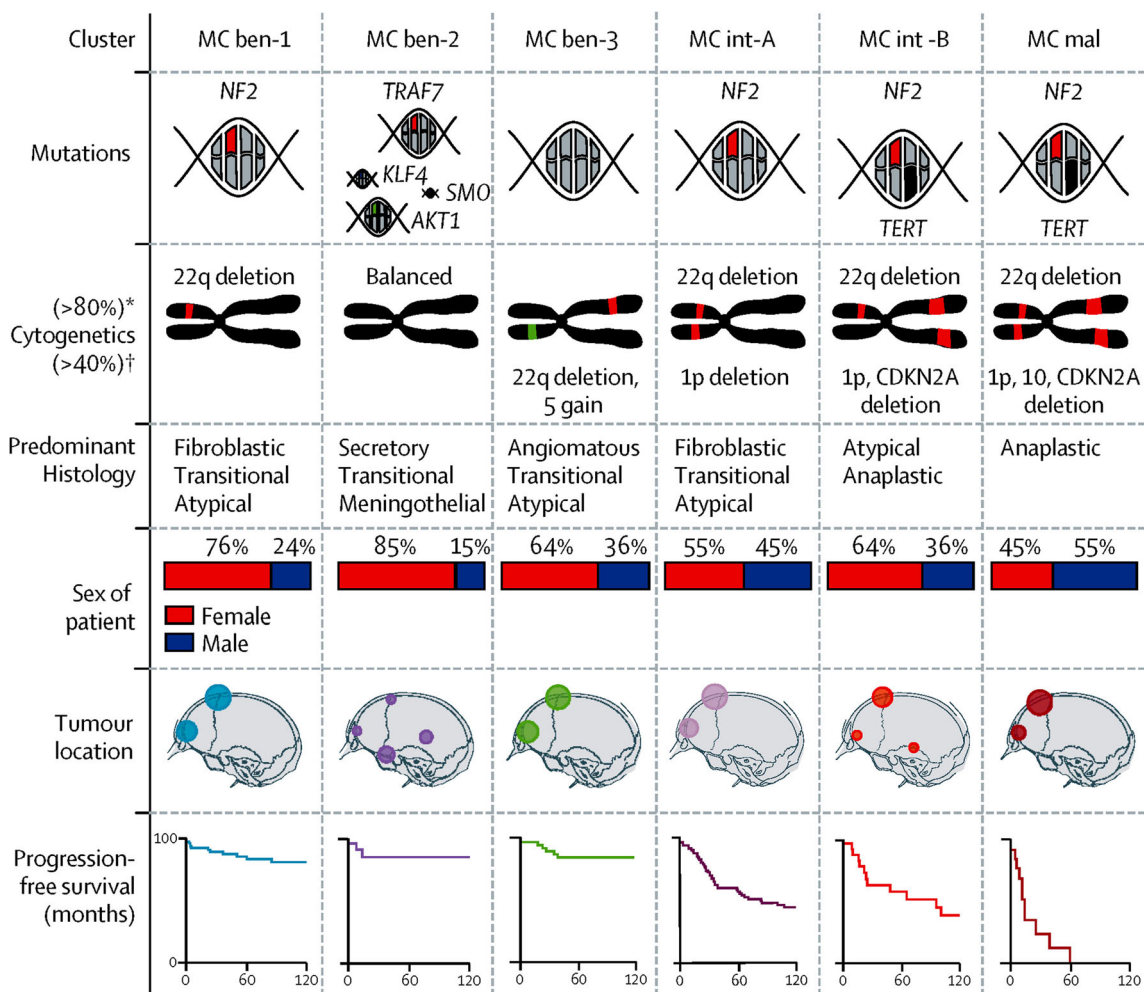


Fig. 1 Schematic overview of the six identified methylation classes and their molecular and clinical characteristics [43]

classes (Fig. 1) [43]. Another study established two distinct methylation subclasses based on analysis of 140 meningioma samples [88].

Most recently, a model of 5-year recurrence free survival (RFS) was developed to assess individual patient risk of meningioma recurrence, generating a probability score based on methylation results, extent of resection (Simpson grade), and WHO grade. The model was developed based on a discovery cohort of 282 meningiomas and validated in two independent validation cohorts comprising of 140 and 46 samples, respectively [89]. It is expected that these and other methylation classification schemata will be adopted to risk-stratify meningioma patients in future clinical trials.

### H3K27 Trimethylation

Beyond the epigenetic patterns of DNA methylation in the characterized meningioma subclasses [43], epigenetic modification on the level of histones, in particular trimethylation at the 27th lysine residue of Histone H3 (H3K27me3), was recently established to represent a poor prognostic biomarker in meningioma. In a study of 232 meningiomas, reduced staining for H3K27me3 by immunohistochemistry (IHC) was significantly associated with increased risk for more rapid progression and association with the MC-malignant methylation subclass mentioned previously [81]. In addition, H3K27me3 negative cases were enriched for tumors containing *NF2* and *SUFU* mutations. IHC staining for H3K27me3 may represent a useful adjunct diagnostic marker to refine the histopathological diagnosis of meningiomas; however, this needs to be validated in future prognostic studies [90].

### Meningiomas and Their Immunological Tumor Microenvironment

The immunological tumor microenvironment of meningiomas is insufficiently understood. In one study, 51 frozen meningioma samples were evaluated for tumor and non-tumor cell composition; this demonstrated that the majority ( $76 \pm 20\%$ ) of cells represented CD45(−) neoplastic cells, and the majority of tumor infiltrating CD45(+) immune cells were tissue macrophages ( $22 \pm 18\%$ ) with low numbers of tumor infiltrating lymphocytes ( $2 \pm 2\%$ ) [91]. Various studies have evaluated the degree of programmed death–ligand 1 (PD-L1) expression in meningiomas with highly variable expression levels ranging from anywhere between 0.9 and 40.9% in grade I, 2.6 and 60.5% in grade II, and 8.8 and 88.9% in grade III meningiomas [92–94]. This may, at least in part, be due to the various assays being used in clinical practice to test for PD-L1 expression [95]. In another study, immunogenic neoantigens were detected in the majority of the meningiomas tested [96]. However, tumor mutational burden (TMB) of meningiomas was generally low; one study

sequenced 228 meningioma samples and reported a mean TMB of 4.2 mutations/Mb only. In a pooled data set of 843 samples, only 21 (2.5%) had a total of TMB > 10 mutations/Mb which would be conventionally considered as high [97]. Nevertheless, of these 21 patients, the authors detailed one patient whose tumor had a documented *MSH2/MSH6* inactivation and TMB of 38 mutations/Mb and had a durable response to nivolumab. Another report documented treatment response of a presumed sphenoid wing meningioma in a patient receiving nivolumab for concomitant metastatic lung cancer although no biopsy was obtained [98].

In spite of these studies, which suggest that only a small subset of meningiomas may respond to immunotherapies, several clinical trials are underway that evaluate the efficacy of various checkpoint inhibitors for patients with progressive meningiomas (e.g., NCT02648997, NCT03279692, NCT03604978, NCT032667836).

### Conclusions

Meningiomas are the most common primary intracranial and spinal tumors, the majority of which are benign and will not recur. However, a subset of them represent aggressive brain tumors for which there are no effective medical therapies once surgery and radiation have failed. Currently, ongoing studies evaluate the efficacy of agents targeting *NF2*, *AKT1*, *SMO*, and *SSTR2*, as well as immunotherapies. There have been significant advances in the understanding of the genetic and epigenetic alterations in meningiomas, particularly in their characterization into prognostically relevant methylation subclasses. As with other intracranial tumors, histology and WHO grade may not be sufficient for accurate prediction of recurrence risk. Therefore, these advances will hopefully result in improved patient risk stratification for enrollment in future clinical trials and help to advance the field in the quest to find effective medical therapies for meningioma.

### Compliance with Ethical Standards

**Conflict of Interest** Christine Cordova is a co-investigator of NCT03971461. She did not receive research funding NCT03971461. Sylvia C. Kurz is study chair of NCT03971461, a study funded by Advanced Accelerator Applications evaluating Lutathera for advanced meningiomas.

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